Effects of Acute Tryptophan Depletion on Human Taste Perception

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Abstract (Max 250 words)

Taste perception has been reported to vary with changes in affective state. Distortions of taste perception, including blunted recognition thresholds, intensity and hedonic ratings have been identified in those suffering from depressive disorders. Serotonin is a key neurotransmitter implicated in the aetiology of anxiety and depression; systemic and peripheral manipulations of serotonin signalling have previously been shown to modulate taste detection. However, the specific effects of central serotonin function on taste processing have not been widely investigated. Here, in a double-blind placebo-controlled study, acute tryptophan depletion was used to investigate the effect of reduced central serotonin function on taste perception. 25 female participants aged 18-28 attended the laboratory on 2 occasions at least 1 week apart. On one visit they received a tryptophan depleting drink and on the other a control drink was administered. Approximately 6 hours after drink consumption they completed a taste perception task which measured detection thresholds and supra-threshold perceptions of the intensity and pleasantness of four basic tastes (sweet, sour, bitter and salt). While acutely reducing central levels of serotonin had no effect on the detection thresholds of sweet, bitter or sour tastes it significantly enhanced detection of salt. For supra-threshold stimuli, acutely reduced serotonin levels significantly enhanced the perceived intensity of both bitter and sour tastes and blunted pleasantness ratings of bitter quinine. These findings show manipulation of central serotonin levels can modulate taste perception and are consistent with previous reports that depletion of central serotonin levels enhances neural and behavioural responsiveness to aversive signals.

Keywords (up to 6, avoid terms in the title): Serotonin (5-HT), Depression, Anxiety, Chemosensation, Gustation, Perception

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Abbreviations:

Introduction

The sense of taste serves to guide us towards nutritious foods and away from potentially harmful toxins (Breslin, 2013). Changes in taste perception can have significant consequences for health and well-being, altering food choices, diminishing the pleasure derived from eating and shifting levels of caloric consumption (Deems et al., 1991; Heckmann, Heckmann, Lang, & Hummel, 2003). Taste perception has been widely reported to vary with changes in mood and affective state (Bergdahl & Bergdahl, 2002; Hur, Choi, Zheng, Shen, & Wrobel, 2018). Distortions of taste perception, including blunted recognition thresholds, intensity, and hedonic ratings have been identified in those suffering from depressive disorders (Miller and Naylor 1989; Amsterdam et al. 1987; Steiner, Rosenthal-Zifroni, and Edelstein 1969; Arbisi et al. 1996; Berlin et al. 1998). Generally, these normalise upon recovery (Arbisi et al., 1996; Steiner et al., 1969). In contrast, stress induction, in humans and animals, has been reported to increase sensitivity to bitter, sweet, and sour tastes, as well as heightening motivation for highly palatable sweet foods and aversion to bitter tastes (Dess & Edelheit, 1998; Ileri-Gurel, Pehlivanoglu, & Dogan, 2013; Macht, 2008; Platte, Herbert, Pauli, & Breslin, 2013; Spence, 2017) though see (Al'absi et al. 2012). This suggests long and short-term changes in emotional state have differential effects on taste sensitivity.

In evolutionary terms, enhanced preference for high calorie foods under negative affective states has been interpreted as a drive for energy, through glucose ingestion, under demanding conditions (Markus 2007; Spence 2017). However, an alternative hypothesis is that high carbohydrate, sugar rich, low protein foods enhance plasma concentrations of the essential amino acid tryptophan, the chemical precursor of serotonin (5-HT). This transient increase in the ratio of tryptophan compared to other large neutral essential amino acids confers an advantage in competition to cross the blood brain barrier, where it is biosynthesised to 5-HT

(Fernstrom, Larin, and Wurtman 1973; Markus 2007; Wurtman and Wurtman 1996). Given the importance of 5-HT in the regulation of stress and affect, such changes in dietary behaviour can be interpreted as reflecting an instinctive drive to enhance circulating 5-HT (Kikuchi, Tanabe, & Iwahori, 2020; Macht, 2008). In support of this hypothesis, carbohydrate intake has been found to have a positive effect on mood and cognitive performance in subjects under stressful conditions (Markus et al. 1998, 1999; Markus 2008). Both genetic and pharmacology studies implicate reduced serotonin function as a key factor in the pathology of depression & anxiety (Adkins, Daw, Mcclay, & Van Den Oord, 2012; Hamet & Tremblay, 2005; Lesch et al., 1996; Schildkraut, 1995). Furthermore, affective and stress disorders are commonly treated with medications which modulate 5-HT levels. Thus, changes in the function of this neurochemical may underlie reported changes in taste perception and eating behaviour in affective disorders.

Gustatory behaviour is shaped by sensory signals from peripheral taste organs as well as by the central nervous system. 5-HT has potential to modulate taste perception at all stages of processing, from sensation to action (Cools, Roberts, & Robbins, 2008; Roper, 2013). Peripherally, 5-HT is released from cells in taste buds following gustatory stimulation (Roper, 2013). In isolated mouse taste buds, 5-HT was found to have an inhibitory effect during taste stimulation, with acute administration of an SSRI reducing and a 5-HT_{1A} receptor antagonist enhancing taste evoked activity (Huang, Dando, & Roper, 2009). While in rats, 5-HT manipulations did not have significant effects on behavioural responses to peri-threshold tastants (Mathes & Spector, 2011, 2014), in humans both lingual and systemic administration of an SSRI had rapid inhibitory effects on taste recognition thresholds for bitter quinine but not salt (O'Driscoll. et al., 2006). In contrast, 2 hours after systemic SSRI administration, recognition thresholds for both sweet and bitter tastants were found to be enhanced (Heath, Melichar, Nutt, & Donaldson, 2006). The importance of timing to

peripheral effects of 5-HT on gustation is further confirmed by studies in animals, with short and long term 5-HT stimulation inhibiting and enhancing taste sensitivity respectively (Esakov, Golubtsov, & Soloveva, 1983; Katushi Morimoto & Sato, 1977). Furthermore, in humans, male participants possessing two copies of the long (L) allele of the 5-HT transporter (5-HTTLPR) polymorphism, which is associated with increased expression of the serotonin transporter (SERT) and enhanced 5-HT function, showed enhanced detection thresholds for sucrose compared to others with at least one copy of the short (S)-allele (Andersen et al., 2014). Thus indicating, lifelong differences in 5-HTT gene transcription modulate gustatory processing.

Centrally, serotonin modulates numerous processes underlying mood and reward evaluation through its action on brain regions involved in emotion and cognition (Cools et al., 2008; Kranz, Kasper, & Lanzenberger, 2010). Low levels of central 5-HT are implicated in the enhanced threat detection associated with stress and anxiety disorders. For example, acute lowering of central 5-HT levels enhanced the amygdala response to threatening visual stimuli (Cools et al. 2005; Van Der Veen et al. 2007; Harmer et al. 2003; Browning et al. 2007) whereas long term SSRI treatment, thought to enhance 5-HT transmission, is associated with decreased neural responses to visual threats (Harmer et al. 2006), as well as to rewarding taste stimuli (McCabe, Mishor, Cowen, & Harmer, 2010). 5-HT is also known to modulate sensory systems according to the current behavioural and motivational context. In general it has an inhibitory effect on evoked activity in primary sensory regions (Hurley, Devilbiss, & Waterhouse, 2004; Jacob & Nienborg, 2018), which manifest behaviourally as decreased responses to sensory simulation (Costa, Kakalios, & Averbeck, 2016; Davis, Astrachan, & Kass, 1980; Dugué et al., 2014). Yet, despite the established effects of affective state and mood on taste perception, direct effects of central 5-HT manipulation on taste processing have not been widely investigated.

Here, using a well-established technique of acute tryptophan depletion (ATD) (Evers, Sambeth, Ramaekers, Riedel, & van der Veen, 2010; Roiser et al., 2008a; Weltzin, Fernstrom, McConaha, & Kaye, 1994), we investigated the effect of transiently lowered central 5-HT levels on detection, perceived intensity, and hedonic ratings of sweet, sour, salt and bitter tastes. While ATD results in substantial declines in central 5-HT synthesis (Bell, Hood, & Nutt, 2005; Hood, Bell, & Nutt, 2005), evidence to date indicates peripheral levels of 5-HT synthesis and metabolism are unaffected by a transient decrease in precursor availability (Geeraerts et al., 2011; Keszthelyi et al., 2012). Furthermore, the primary source of 5-HT within mammalian taste buds does not appear to be *de novo* synthesis from L-tryptophan but rather through absorption and conversion of the intermediate 5-HT precursor 5-hydroxy-L-tryptophan, which is abundant in the plasma and peripheral nerve fibres (Pan et al., 2018). Thus, unlike oral administration of SSRIs, using ATD we can selectively investigate the effects of 5-HT on central taste perception in the absence of changes in peripheral taste signalling. We hypothesise that ATD will have no effect on taste detection thresholds as they should largely reflect peripheral taste function. In contrast, given the established inhibitory effects of 5-HT on affective and sensory processing, we hypothesise ATD will enhance the perceived intensity of our most pleasant (sucrose) and aversive (aversive) tastants, as well as increasing hedonic ratings of sucrose while increasing aversion to bitter quinine. Given the lack of existing data, we make no direct predictions on the effect of ATD on perceptions of salt and sour.

Materials & Methods

Participants

Twenty-five healthy female participants aged 18 - 28 (M= 20.92, SD = 0.44) were recruited via Liverpool John Moores University. Only female participants were included in this study as they are twice as likely as males to be affected by depression (Hamet & Tremblay, 2005) and have been reported to be more susceptible to the effects of the Acute Tryptophan Depletion (ATD) (Bell et al., 2005; Nishizawa et al., 1997).

Participants attended a screening session during which the structured clinical interview to diagnose DSM-IV-TR Axis I disorders (SCID) (First, Spitzer, Gibbon, & Williams, 2002) and the Beck depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) were administered to exclude participants with a history of psychiatric illness. A score of less than nine on the BDI was required to participate. Additional inclusion criteria were no history of any neurological disorders, no heart abnormalities or heart conditions and normal or corrected to normal vision. Participants were excluded if they were using any medication except non-steroidal asthma inhalers or hormonal contraceptives and if they were pregnant. They were also excluded if they had used any street drugs, consumed more than 30 units of alcohol per week, or 6 strong cups of tea/coffee per day in the 4-week period prior to testing. During screening, participants were provided with details of the low-protein diet they were to follow the day before each experimental session. They were asked not to eat from midnight onwards on the day of the experimental session, not to drink alcohol for 24 hours before each experimental session and not to drink any caffeinated drinks on the morning of each experimental session.

Prior to recruitment, the study was approved by the LJMU research ethics committee. The study complied with the Declaration of Helsinki for Medical Research involving Human Subjects.

Tryptophan Manipulation

Acute Tryptophan Depletion (ATD) inhibits serotonin synthesis by reducing the availability of the essential amino acid and serotonin precursor, tryptophan. An amino acid load devoid of tryptophan is administered, inducing hepatic protein synthesis which depletes circulating tryptophan. Furthermore, the increase in large neutral amino acids competes with the transport of reduced levels of tryptophan across the blood–brain barrier via the large neutral amino acid transporter (Evers et al., 2010; Hood et al., 2005). The control condition is identical except the amino acid load contains tryptophan. This increases plasma tryptophan, but the ratio of tryptophan to other large neutral amino acids is still reduced, the reduction being significantly greater following ATD (Roiser et al., 2008a; Weltzin et al., 1994).

The amino acids were purchased from Nutricia (Liverpool, UK) and Fagron (Rotterdam, Netherlands). The ratios of amino acids used in the drinks were based on that of Young, Smith, Pihl, & Ervin (1985), but were 80% of the original quantities due to the lower average body weight of females than males (Hood et al., 2005). The amounts used are standard for ATD studies (Bilderbeck et al., 2011; Evers, Van Der Veen, Jolles, Deutz, & Schmitt, 2006; Trotter et al., 2016). The control drink contained all the amino acids in the quantities listed in Table 1, while the tryptophan depleting drink did not contain the 1.92g of tryptophan.

The amino acids for each drink, totalling 77.02g for the control drink and 75.10g for the tryptophan depleting drink, were weighed out in advance of the experimental session. The drink was made just before consumption on the morning of the testing session. Using a blender, the amino acids were mixed with 150 ml of water and ~45 ml of flavouring (chocolate or strawberry ice cream syrup), which is added to make the drink more palatable.

Every participant carried out two experimental sessions on separate laboratory visits separated by at least 1 week. During one session they received the tryptophan depleting drink and during the other session they received the control drink. Drink order delivery was

randomized and double blinded. This followed the protocol recommended by Hood et al (2005).

Measures

Taste Rating Task

The experimental protocol utilised was an adaptation of Heath *et al*., (2006). Four basic tastants were each presented at a range of concentrations: sweet (0.3mM to 1M sucrose), sour (0.3mM to 1M citric acid), salt (3.16mM to 3.16M sodium chloride) and bitter (0.003mM to 3mM quinine). At the start of each trial, due to the potential for low concentrations of tastants to be misidentified (Pilková, Nováková, & Pokorný, 1991), participants were informed which stimulus they were receiving. On a given trial a single taste solution was applied to the tip of the tongue using a cotton bud for approximately 5 seconds (Prutkin, Fast, Lucchina, & Bartoshuk, 1998). For a given tastant, the first concentration experienced was always midrange and supra-threshold. Thereafter concentrations were presented in a pseudorandom order 3 times each.

Immediately after presentation of each stimulus participants were asked to respond to three questions presented consecutively on a laptop computer running E-Prime (Psychology Software Tools, Pittsburgh, PA). The first asked if they could perceive a taste and response options were: Y (yes) or N (no). The second asked the participant to rate the intensity of the taste on a labelled magnitude scale (LMS). The LMS was a replica of that developed by Green, Shaffer, & Gilmore (1993) for use specifically in examining oral somatosensation and gustation. The final question asked participants to rate on a visual analogue scale (VAS) the pleasantness of the taste with -50 (very unpleasant) as the left anchor, 0 (neutral) in the centre and +50 (very pleasant) as the right anchor. Where the answer to the question regarding detection was No, the answers to the questions regarding intensity and pleasantness were by default zero.

Participants were given a cup of water and asked to sip some or swill their mouth between trials. The entire taste testing protocol took between 45 minutes and 1 hour, dependent upon the length of time participants needed to refresh their mouth.

Procedure

Participants entered the laboratory between 8.30am and 9am. They confirmed that they had followed the low protein diet the day before and not eaten since midnight. They then had their blood pressure and blood glucose levels taken. They also completed the Profile of Mood States (POMS) (McNair, Lorr, & Droppelmann, 1971). The first of two blood samples were then taken via venepuncture and the participant was given the amino acid drink to consume. They were instructed that the entire drink must be consumed within 15 minutes. Participants then rested for four hours. During this time their height and weight were measured, and participants completed a series of questionnaires and a short touch perception task (reported elsewhere) three times; immediately post drink, 2 hours after drink and 4 hours post drink. Three hours post drink participants were given a snack consisting of 4 crackers, 8g of jam and a jelly pot, the total protein contents were <2g. Approximately four hours after drink consumption, the participant's blood pressure, blood glucose and mood were measured again, and the second blood sample taken. Approximately 4.5 hours after drink consumption participants began the experimental phase of the study. They first completed a somatosensory protocol (reported elsewhere). Then, the taste protocol took place approximately 6 hours after drink consumption. At the end of the testing day, at approximately 5pm, all participants were given a protein-rich meal to replete their endogenous tryptophan levels. Their blood pressure, blood glucose and mood were assessed before they could leave the laboratory. Session 2 took place a minimum of 1 week after session 1. Participants returned to the laboratory, following the low protein diet the day before. The experimental protocol was the same as in session 1, with the exception that the amino acid drink was the one they had not yet consumed.

Data Analysis

Data were analysed using SPSS version 25. A repeated-measures ANOVA with 2 factors: Time (pre-drink/post-drink) and Treatment (Control/Tryptophan Depletion) was used to analyse changes in total plasma tryptophan and changes in self-reported mood before and after the amino acid drinks. Taste data was assessed for outliers, and skewness and kurtosis by z scoring and dividing by the SE. This indicated the data were within allowable limits for parametric testing (Field, 2009). Levene's test for homogeneity of variance also indicated that the majority of group variances were equal. Mauchly's tests of sphericity were examined and, where appropriate, Greenhouse Geisser correction was applied. The average percentage of positive detections was plotted against the log concentrations for each tastant. The effects of concentration and ATD treatment on detection were assessed using a repeated measures ANOVA. Taste threshold was assessed as the concentration at which positive detection occurred 50% of the time. Further repeated measures ANOVAs were conducted on above threshold concentrations of each taste to examine the role of treatment and concentration on perceived intensity and pleasantness. Post-hoc tests using pairwise comparisons of the estimated marginal means were run with Sidak correction for multiple comparisons.

Results

Plasma Tryptophan Analysis

Four participants were not included in this analysis due to missing data.

There was a significant interaction between Treatment and Time ($F_{1,20}$ = 150.64, $p < 0.001$, η_p^2 = 0.88, Power = 1.00). Analysis of simple main effects identified total plasma tryptophan concentrations significantly decreased 4 hours after administration of the Tryptophan Depleting Drink ($F_{1,20}$ = 128.721, $p < 0.001$, η_p^2 = 0.87, Power = 1.00) and significantly increased following the Control drink ($F_{1,20}$ = 64.75, $p < 0.001$, η_p^2 = 0.76, Power = 1.00). Total plasma tryptophan concentrations before amino acid drink consumption were comparable ($F_{1, 20}$ = 0.297, p = 0.59, η_p^2 = 0.02, Power = 0.08), but were significantly greater 4 hours after administration of the Control compared to the Tryptophan Depleting Drink ($F_{1,20}$ = 144.34, $p < 0.001$, η_p^2 = 0.88, Power = 1.00). Following the Tryptophan Depleting Drink, plasma tryptophan concentrations decreased (M = 68.1%, S.E. = 0.60%); while they increased (M = 160.8%, S.E. = 4.89%) following the Control drink (see Table 2). Average total plasma tryptophan concentrations reported for this study before and after consumption of the amino acid drinks were similar to those reported in previously published studies using ATD (eg Trotter et al., 2016).

Mood

Total scores on the POMS were examined and no significant main effect of Treatment ($F_{1, 23}$ = .014, p = .91, η_p^2 =.01, Power = .05) and no significant interaction between Treatment and Time ($F_{1, 46}$ = .195, p = .82, η_p^2 =.008, Power = .078) was identified. Thus, mood was unaffected by the amino acid consumption.

Taste Detection

Using separate repeated measures ANOVAs for each tastant, a significant main effect of concentration was identified in all four cases. As would be expected, detectability increased significantly as concentration increased (see Figure 1): Sucrose, (Figure 1**A**: $F_{2.16, 51.79}$ = 60.10, p <.001, η_p^2 = .72, Power = 1.00), Citric Acid (Figure 1**B**: $F_{2.21, 53.14}$ = 46.33, p <.001, η_p^2 = .66, Power = 1.00), Sodium Chloride (Figure 1**C**: $F_{1.78, 42.81}$ = 75.27, p <.001, η_p^2 = . 76, Power = 1.00) and Quinine (Figure 1**D**: $F_{2.67, 64.06}$ = 38.56, p <.001, η_p^2 = .62, Power = 1.00).

A significant effect of Treatment on taste Detection was identified for Sodium Chloride ($F_{1, 24}$ = 6.83, p = .015, η_p^2 = .22, Power = .71), with significantly better detection following Tryptophan Depletion (M = 67.40%, S.E = 3.30%) compared to the Control treatment (M = 61.90%, S.E. = 4.10%). Treatment had no effect on detection of Sucrose, Citric Acid and Quinine (Fs < 1). Post-hoc pairwise comparisons identified that the log -1, threshold concentration of Sodium Chloride was significantly different between Treatments (p <.05). The concentration at which a given tastant was detected at least 50% of time during the control condition were taken to be the detection threshold, that log level and over were used in subsequent analysis of intensity and pleasantness ratings.

Taste Intensity

As would be expected, there was a significant main effect of concentration on perceived intensity of all 4 tastants (Sucrose: ($F_{1.72, 41.33}$ = 74.28, p <.001, η_p^2 = .76, Power = 1.00), Citric Acid: ($F_{2.26, 54.25}$ = 109.21, p <.001, η_p^2 = .82, Power = 1.00), Sodium Chloride: ($F_{1.82, 43.58}$ = 119.66, p <.001, η_p^2 = .83, Power = 1.00) and Quinine: ($F_{1.59, 36.48}$ = 60.61, p <.001, η_p^2 = .73, Power = 1.00).

A significant main effect of Treatment was identified for the sour tastant, Citric Acid ($F_{1, 24}$ = 5.41, p < .05, η_p^2 = .18, Power = .61) and the bitter Quinine ($F_{1, 23}$ = 9.65, p <.01, η_p^2 = .30, Power = .85). As can be seen in Figure 2**B** and 2**D,** this reflects the fact intensity ratings were higher following Tryptophan Depletion than the Control treatment (Sour: Tryptophan Depletion: M = 34.74 S.E. = 2.79, Control: M = 29.83, S.E = 2.42; Bitter: Tryptophan Depletion: M = 35.55 S.E. = 3.39, Control: M = 27.17, S.E = 3.18). There was no effect of treatment on intensity ratings of either of the other two tastants (ps > .05).

Taste Pleasantness

As can be seen from Figure 3, there was a significant main effect of concentration on mean pleasantness ratings for each of the 4 tastes, sweet ($F_{1.35, 32.39}$ = 30.28, p <.001, η_p^2= .56, Power = 1.00), sour ($F_{1.41, 33.76}$ = 4.77, p < .05, η_p^2 = .17, Power = .66), salt ($F_{1.48, 35.42}$ = 3.49, p =.055, η_p^2 = .13, Power = .53) and bitter ($F_{1.31, 30.10}$ = 55.42, p <.001, η_p^2 = .71, Power = 1.00). While, for sucrose, pleasantness ratings increased with increasing concentration, perceived pleasantness decreased with increased concentrations of the other three tastants.

There was a significant effect of Treatment on pleasantness ratings of the bitter quinine ($F_{1, 23}$ = 11.75, p <.01, η_p^2 = .34, Power = .91) but no effect of Treatment on hedonic ratings of any of the other three tastants (ps > .05). As can be seen in Figure 3**D**, bitter quinine was rated as significantly less pleasant following Tryptophan Depletion (M = -1485, S.E. = 1.67) compared to the Control treatment (M = -10.59, S.E. = 1.30).

Discussion

Our data show that perceptions of pure tastants can be altered by acute manipulation of central serotonin levels. Detection thresholds primarily reflect peripheral sensory function and here, consistent with our hypothesis, transient lowering of central 5-HT levels had no

impact on the detection of sweet, sour or bitter tastes. However, contrary to expectation, we did see a significant effect of treatment on detection of salt, reflecting the fact that in the control condition at the threshold concentration, a taste was reported to be detected 70% of the time, whereas in the ATD condition this rose to 87% detection. Converging evidence to date supports the fact ATD exerts its effects via depletion of central 5-HT levels (Crockett et al., 2012) due to the competitive uptake of large neutral amino acids across the blood brain barrier (Hood et al., 2005). Though peripheral effects have received little direct attention, previous studies indicate ATD manipulations do not affect the synthesis and metabolism of 5-HT within enterochromaffin cells of the intestinal mucosa (Geeraerts et al., 2011; Keszthelyi et al., 2012) which synthesise and secrete around 90% of peripheral 5-HT (Martin et al., 2017). Additionally, in contrast to its relatively short half-life in the brain, in the blood and epithelial cells the half-life of 5-HT is least 3 days (Kema, De Vries, & Muskiet, 2000; Szeitz & Bandiera, 2018; Welford et al., 2016). Thus, it seems unlikely an acute decrease in precursor availability will have significantly affected 5-HT signalling in taste bud cells. Furthermore, the present finding is inconsistent with previous reports that systemic changes in 5-HT level following acute SSRI administration alter detection of bitter and sweet but not salt or sour (Heath et al., 2006). Thus, it seems probable that this finding reflects a centrally mediated positive response bias following ATD treatment (Linker, Moore, & Galanter, 1964; Potts, Bennett, Kennedy, & Vaccarino, 1997), though that cannot be determined definitively with the present protocol design. Salt detection thresholds have previously been reported to be enhanced following exposure to acute stress, though in that study sweet detection thresholds were also enhanced (Ileri-Gurel et al., 2013). However, consistent with previous studies (Roiser et al., 2008; Trotter et al., 2016), here we found no change in mood following ATD and if a response bias does underpin this finding, it is not clear why it was only apparent to the salt taste and not any of the other three tastants.

Considering supra-threshold rating of intensity and pleasantness, consistent with our hypothesis, reduced central 5-HT function led to enhanced perception of the intensity and unpleasantness of the bitter tastant, quinine. In evolutionary terms, bitter tastes signal potential toxins so enhanced sensitivity to such stimuli likely reflect an attentional bias to threat induced by centrally lowered 5-HT (Breslin, 2013; Browning et al., 2007; Fox, Zougkou, Ridgewell, & Garner, 2011). Given 5-HT generally has an inhibitory effect in sensory systems, this enhanced response may reflect increased neural responsiveness in gustatory cortex (Hurley et al., 2004; Jacob & Nienborg, 2018). However, the finding is also consistent with previous neuroimaging studies which have reported acute lowering of central 5-HT levels enhanced the amygdala response to threatening visual stimuli (Cools et al. 2005; Van Der Veen et al. 2007; Harmer et al. 2003; Browning et al. 2007). Thus, future neuroimaging studies are required to determine the neural basis of the observed effect.

ATD also enhanced perceived intensity, but not unpleasantness, in ratings of the sour tastant, citric acid. Sour acid tastes are typically experienced in combination with sweet tastes, for example within fruits rich in vitamin C. A sour taste in the absence of sweetness is suggestive of unripe fruit (Breslin, 2013). So increased intensity ratings following ATD depletion may well also reflect a negative attentional bias (Browning et al., 2007; Fox et al., 2011). Even at the strongest concentration used, the sour taste was only rated as mildly unpleasant and this may explain the lack of effect of ATD on hedonic ratings. In contrast to the enhanced sensitivity to salt detection induced by ATD, there was no impact of central serotonin depletion on ratings of either the intensity or hedonics of supra-threshold concentrations of sodium chloride.

Contrary to our hypothesis, the ATD manipulation did not affect ratings of either the intensity or pleasantness of sucrose. This is inconsistent with previous findings that 5-HT deficiency, including following ATD, significantly increases the intake of sweet foods (Pagoto et al., 2009; Wagner, Ahlstrom, Redden, Vickers, & Mann, 2014). Nor is it consistent with previous reports that enhanced 5-HT function decreased neural responses to rewarding sweet flavours (McCabe et al., 2010). These differences may reflect the use of pure tastants in the present study versus the more ecologically relevant flavours participants have been exposed to in previous studies. Although humans show innate responses to sweet and bitter tastes, it is multimodal flavour percepts which people learn to use to evaluate food (Breslin, 2013; Spence, 2017).

These differential findings may also reflect the varying methodologies used. Low levels of central serotonin have previously been reported to enhance the incentive salience of rewards, including highly palatable foods, driving consumption (Pagoto et al., 2009; Roiser et al., 2006). However, models of incentive motivation distinguish between wanting, that is motivation to obtain a food stuff, and liking, the sensory experience of consuming it (Berridge, Robinson, & Aldridge, 2009). Here our hedonic ratings of pleasantness, given immediately after administration of the taste, probe this latter sensory component. The lack of effect of serotonin liking is consistent with previous reports in rats that acute systemic administration of the SSRI paroxetine had no effect on hedonic responses to sucrose during a brief access test but did induce state dependent modulation of appetitive approach behaviour (Mathes & Spector, 2011). Finally, though differences in 5-HT function have previously been reported to impact neural and behavioural responses to both positive and negative affective stimuli (Browning et al., 2007; Fox et al., 2000, 2011), motivation to avoid bad outcomes is stronger than the drive to pursue good ones (Baumeister, Bratslavsky, Finkenauer, & Vohs,

2001) and negative material has a stronger draw on attention (Fox et al., 2000). This difference can further explain why we saw enhanced perceptions of unpleasant bitter and sour tastes without any corresponding enhancement in the perceived intensity or pleasantness of sucrose.

Given the established role of 5-HT function in the aetiology of mood disorders, changes in taste perception and eating behaviour frequently reported in these conditions have been linked to changes in the functioning of this neurotransmitter system (Macht, 2008; Mantantzis, Schlaghecken, Sünram-Lea, & Maylor, 2019; Markus, 2008). Furthermore, dietary changes associated with depression, specifically enhanced intake of sugar rich 'comfort' foods, have been interpreted as a drive to enhance mood, since carbohydrate intake in the absence of other macronutrients has been shown to enhance both plasma tryptophan levels and central 5-HT (Fernstrom et al., 1973; Markus, 2007; Wurtman & Wurtman, 1996). While a recent meta-analysis found no evidence of mood enhancement in healthy participants following carbohydrate consumption, the authors acknowledge effects may only be observed in specific clinical groups or following acute stress manipulations (Mantantzis et al., 2019).

Though the literature is mixed, affective disorders are generally associated with blunted sensitivity to both pleasant and unpleasant tastes (Amsterdam et al., 1987; Arbisi et al., 1996; Berlin et al., 1998; Miller & Naylor G J, 1989; Steiner et al., 1969). The enhanced taste sensitivity following ATD depletion reported here is more consistent with previous reports of the effects of acute stress induction on perception of and responses to a variety of tastes (Dess & Edelheit, 1998; Ileri-Gurel et al., 2013; Macht, 2008; Platte et al., 2013). However, in the present study participants had no history of psychiatric illness and consistent with previous studies, the ATD manipulation itself had no effect on mood (Evers et al., 2006; Roiser et al.,

2008; Trotter et al., 2016). Thus, the present findings cannot be interpreted as reflecting serotonin induced changes in affective state. Noradrenaline is another monoamine which plays a central role in modulating autonomic nervous system responses to stress (Chrousos, 2009) and has long been known to modulate peripheral taste perception (Heath et al., 2006; Katsushi Morimoto & Sato, 1982), as well a central responses to sensory stimuli (Jacob & Nienborg, 2018), thus further work is needed to fully determine the neurochemical basis of previously reported affective state induced changes in taste processing and eating behaviour.

In conclusion, our findings show that manipulations of central serotonin levels modulate perception of hedonically aversive bitter and sour tastes. The present study has added to existing knowledge by showing that central, as well as peripheral changes in 5-HT signalling impact taste perception. However, further work is needed to determine whether this reflects changes in the modulation of sensory and / or affective brain regions. Furthermore, how these findings relate to changes in dietary habits frequently reported in individuals suffering from affective and anxiety disorders remains to be determined.

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Table 1: Quantities of amino acids contained in the Control drink. The Tryptophan depleting drink was the same, except for the omission of l-Tryptophan.

Table 2: Total plasma tryptophan and mood before and after amino acid drink consumption for both tryptophan depletion and control sessions. Mean values (with SE) are presented.

Figure 1: The effects of tryptophan depletion on detection thresholds for each of the 4 tastants (A Sweet; B Sour; C Salt; D Bitter). The solid line represents the Control treatment and the dashed line represents the Tryptophan Depletion treatment, with the x-axis representing the concentration steps and the y-axis the percentage of responses confirming detection of the concentration. Significant effects for concentration were identified for all tastants (ps<.001). There was a significant effect of Treatment on (C) NaCl detection (**p < .02), but there was no significant effect of treatment on detection of any of the other tastants (ps>.05). Post-Hoc pairwise comparisons indicated that the threshold concertation of (C) NaCl at the log -1 was detected significantly more frequently in the Tryptophan Depletion than the Control condition (*p<.05).***

Figure 2: Mean intensity ratings +/- S.E. of the above threshold concentrations for each of the 4 tastants (A: Sweet; B: Sour; C: Salt; D: Bitter). Significant main effects for concentration of all 4 tastants was identified (ps<.001) and main effects for treatment on intensity ratings were identified for (B) Sour (*p<.05) and (D) Bitter tastes (**p <.01).***

Figure 3: Mean pleasantness ratings +/- S.E. of the above threshold concentrations for each of the 4 tastes (sweet (A), sour (B), salt (C) or bitter (D). A significant main effect of concentration was identified for all 4 tastants (*p<.05 & ***p<.001). A significant effect of treatment was identified on the pleasantness ratings of the (D) bitter quinine (**p < .01) but there was no effect of Treatment on hedonic ratings of any of the other tastes (ps > .05).