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Effects of Acute Tryptophan Depletion on Human Taste Perception

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19 **Abstract (Max 250 words)**

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

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

46 **Author Contributions:** SS conceived the study, all authors contributed to the design of the
47 study, SS & PT conducted the data collection, SS analysed the data, SS & SW wrote the
48 manuscript. All authors read and revised the manuscript before submission.

49 **Abbreviations:**

50

51 **Introduction**

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

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

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

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

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

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

126 Here, using a well-established technique of acute tryptophan depletion (ATD) (Evers,
127 Sambeth, Ramaekers, Riedel, & van der Veen, 2010; Roiser et al., 2008a; Weltzin,
128 Fernstrom, McConaha, & Kaye, 1994), we investigated the effect of transiently lowered
129 central 5-HT levels on detection, perceived intensity, and hedonic ratings of sweet, sour, salt
130 and bitter tastes. While ATD results in substantial declines in central 5-HT synthesis (Bell,
131 Hood, & Nutt, 2005; Hood, Bell, & Nutt, 2005), evidence to date indicates peripheral levels
132 of 5-HT synthesis and metabolism are unaffected by a transient decrease in precursor
133 availability (Geeraerts et al., 2011; Keszthelyi et al., 2012). Furthermore, the primary source
134 of 5-HT within mammalian taste buds does not appear to be *de novo* synthesis from L-
135 tryptophan but rather through absorption and conversion of the intermediate 5-HT precursor
136 5-hydroxy-L-tryptophan, which is abundant in the plasma and peripheral nerve fibres (Pan et
137 al., 2018). Thus, unlike oral administration of SSRIs, using ATD we can selectively
138 investigate the effects of 5-HT on central taste perception in the absence of changes in
139 peripheral taste signalling. We hypothesise that ATD will have no effect on taste detection
140 thresholds as they should largely reflect peripheral taste function. In contrast, given the
141 established inhibitory effects of 5-HT on affective and sensory processing, we hypothesise
142 ATD will enhance the perceived intensity of our most pleasant (sucrose) and aversive
143 (aversive) tastants, as well as increasing hedonic ratings of sucrose while increasing aversion
144 to bitter quinine. Given the lack of existing data, we make no direct predictions on the effect
145 of ATD on perceptions of salt and sour.

146 **Materials & Methods**

147 **Participants**

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

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

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

171 **Tryptophan Manipulation**

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

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

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

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

196 randomized and double blinded. This followed the protocol recommended by Hood et al
197 (2005).

198

199 **Measures**

200 **Taste Rating Task**

201 The experimental protocol utilised was an adaptation of Heath *et al.*, (2006). Four basic
202 tastants were each presented at a range of concentrations: sweet (0.3mM to 1M sucrose), sour
203 (0.3mM to 1M citric acid), salt (3.16mM to 3.16M sodium chloride) and bitter (0.003mM to
204 3mM quinine). At the start of each trial, due to the potential for low concentrations of
205 tastants to be misidentified (Pilková, Nováková, & Pokorný, 1991), participants were
206 informed which stimulus they were receiving. On a given trial a single taste solution was
207 applied to the tip of the tongue using a cotton bud for approximately 5 seconds (Prutkin, Fast,
208 Lucchina, & Bartoshuk, 1998). For a given tastant, the first concentration experienced was
209 always midrange and supra-threshold. Thereafter concentrations were presented in a
210 pseudorandom order 3 times each.

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

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

225 **Procedure**

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

247 **Data Analysis**

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

263

264 **Results**

265 **Plasma Tryptophan Analysis**

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

267 There was a significant interaction between Treatment and Time ($F_{1,20} = 150.64, p < 0.001, \eta_p^2 = 0.88, \text{Power} = 1.00$). Analysis of simple main effects identified total plasma tryptophan
268 = 0.88, Power = 1.00). Analysis of simple main effects identified total plasma tryptophan
269 concentrations significantly decreased 4 hours after administration of the Tryptophan
270 Depleting Drink ($F_{1,20} = 128.721, p < 0.001, \eta_p^2 = 0.87, \text{Power} = 1.00$) and significantly
271 increased following the Control drink ($F_{1,20} = 64.75, p < 0.001, \eta_p^2 = 0.76, \text{Power} = 1.00$).
272 Total plasma tryptophan concentrations before amino acid drink consumption were comparable
273 ($F_{1,20} = 0.297, p = 0.59, \eta_p^2 = 0.02, \text{Power} = 0.08$), but were significantly greater 4 hours after
274 administration of the Control compared to the Tryptophan Depleting Drink ($F_{1,20} = 144.34, p$
275 $< 0.001, \eta_p^2 = 0.88, \text{Power} = 1.00$). Following the Tryptophan Depleting Drink, plasma
276 tryptophan concentrations decreased ($M = 68.1\%, \text{S.E.} = 0.60\%$); while they increased ($M =$
277 $160.8\%, \text{S.E.} = 4.89\%$) following the Control drink (see Table 2). Average total plasma
278 tryptophan concentrations reported for this study before and after consumption of the amino
279 acid drinks were similar to those reported in previously published studies using ATD (eg
280 Trotter et al., 2016).

281

282 **Mood**

283 Total scores on the POMS were examined and no significant main effect of Treatment ($F_{1,23}$
284 = .014, $p = .91, \eta_p^2 = .01, \text{Power} = .05$) and no significant interaction between Treatment and
285 Time ($F_{1,46} = .195, p = .82, \eta_p^2 = .008, \text{Power} = .078$) was identified. Thus, mood was
286 unaffected by the amino acid consumption.

287

288 **Taste Detection**

289 Using separate repeated measures ANOVAs for each tastant, a significant main effect of
290 concentration was identified in all four cases. As would be expected, detectability increased
291 significantly as concentration increased (see Figure 1): Sucrose, (Figure 1A: $F_{2,16, 51.79} =$
292 $60.10, p < .001, \eta_p^2 = .72, \text{Power} = 1.00$), Citric Acid (Figure 1B: $F_{2,21, 53.14} = 46.33, p < .001,$
293 $\eta_p^2 = .66, \text{Power} = 1.00$), Sodium Chloride (Figure 1C: $F_{1,78, 42.81} = 75.27, p < .001, \eta_p^2 = .76,$
294 $\text{Power} = 1.00$) and Quinine (Figure 1D: $F_{2,67, 64.06} = 38.56, p < .001, \eta_p^2 = .62, \text{Power} = 1.00$).

295

296 A significant effect of Treatment on taste Detection was identified for Sodium Chloride ($F_{1, 24}$
297 $= 6.83, p = .015, \eta_p^2 = .22, \text{Power} = .71$), with significantly better detection following
298 Tryptophan Depletion ($M = 67.40\%, S.E = 3.30\%$) compared to the Control treatment ($M =$
299 $61.90\%, S.E. = 4.10\%$). Treatment had no effect on detection of Sucrose, Citric Acid and
300 Quinine ($F_s < 1$). Post-hoc pairwise comparisons identified that the log -1, threshold
301 concentration of Sodium Chloride was significantly different between Treatments ($p < .05$).
302 The concentration at which a given tastant was detected at least 50% of time during the
303 control condition were taken to be the detection threshold, that log level and over were used in
304 subsequent analysis of intensity and pleasantness ratings.

305

306 **Taste Intensity**

307 As would be expected, there was a significant main effect of concentration on perceived
308 intensity of all 4 tastants (Sucrose: ($F_{1,72, 41.33} = 74.28, p < .001, \eta_p^2 = .76, \text{Power} = 1.00$),
309 Citric Acid: ($F_{2,26, 54.25} = 109.21, p < .001, \eta_p^2 = .82, \text{Power} = 1.00$), Sodium Chloride: ($F_{1,82,$
310 $43.58 = 119.66, p < .001, \eta_p^2 = .83, \text{Power} = 1.00$) and Quinine: ($F_{1,59, 36.48} = 60.61, p < .001, \eta_p^2$
311 $= .73, \text{Power} = 1.00$).

312

313 A significant main effect of Treatment was identified for the sour tastant, Citric Acid ($F_{1, 24} =$
314 $5.41, p < .05, \eta_p^2 = .18, \text{Power} = .61$) and the bitter Quinine ($F_{1, 23} = 9.65, p < .01, \eta_p^2 = .30,$
315 $\text{Power} = .85$). As can be seen in Figure 2B and 2D, this reflects the fact intensity ratings were
316 higher following Tryptophan Depletion than the Control treatment (Sour: Tryptophan
317 Depletion: $M = 34.74$ S.E. = 2.79, Control: $M = 29.83, \text{S.E} = 2.42$; Bitter: Tryptophan
318 Depletion: $M = 35.55$ S.E. = 3.39, Control: $M = 27.17, \text{S.E} = 3.18$). There was no effect of
319 treatment on intensity ratings of either of the other two tastants ($ps > .05$).

320

321 **Taste Pleasantness**

322 As can be seen from Figure 3, there was a significant main effect of concentration on mean
323 pleasantness ratings for each of the 4 tastes, sweet ($F_{1.35, 32.39} = 30.28, p < .001, \eta_p^2 = .56,$
324 $\text{Power} = 1.00$), sour ($F_{1.41, 33.76} = 4.77, p < .05, \eta_p^2 = .17, \text{Power} = .66$), salt ($F_{1.48, 35.42} = 3.49, p$
325 $= .055, \eta_p^2 = .13, \text{Power} = .53$) and bitter ($F_{1.31, 30.10} = 55.42, p < .001, \eta_p^2 = .71, \text{Power} = 1.00$).
326 While, for sucrose, pleasantness ratings increased with increasing concentration, perceived
327 pleasantness decreased with increased concentrations of the other three tastants.

328 There was a significant effect of Treatment on pleasantness ratings of the bitter quinine ($F_{1, 23}$
329 $= 11.75, p < .01, \eta_p^2 = .34, \text{Power} = .91$) but no effect of Treatment on hedonic ratings of any
330 of the other three tastants ($ps > .05$). As can be seen in Figure 3D, bitter quinine was rated as
331 significantly less pleasant following Tryptophan Depletion ($M = -1485, \text{S.E.} = 1.67$)
332 compared to the Control treatment ($M = -10.59, \text{S.E.} = 1.30$).

333

334 **Discussion**

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

338 impact on the detection of sweet, sour or bitter tastes. However, contrary to expectation, we
339 did see a significant effect of treatment on detection of salt, reflecting the fact that in the
340 control condition at the threshold concentration, a taste was reported to be detected 70% of
341 the time, whereas in the ATD condition this rose to 87% detection. Converging evidence to
342 date supports the fact ATD exerts its effects via depletion of central 5-HT levels (Crockett et
343 al., 2012) due to the competitive uptake of large neutral amino acids across the blood brain
344 barrier (Hood et al., 2005). Though peripheral effects have received little direct attention,
345 previous studies indicate ATD manipulations do not affect the synthesis and metabolism of 5-
346 HT within enterochromaffin cells of the intestinal mucosa (Geeraerts et al., 2011; Keszthelyi
347 et al., 2012) which synthesise and secrete around 90% of peripheral 5-HT (Martin et al.,
348 2017). Additionally, in contrast to its relatively short half-life in the brain, in the blood and
349 epithelial cells the half-life of 5-HT is least 3 days (Kema, De Vries, & Muskiet, 2000; Szeitz
350 & Bandiera, 2018; Welford et al., 2016). Thus, it seems unlikely an acute decrease in
351 precursor availability will have significantly affected 5-HT signalling in taste bud cells.
352 Furthermore, the present finding is inconsistent with previous reports that systemic changes
353 in 5-HT level following acute SSRI administration alter detection of bitter and sweet but not
354 salt or sour (Heath et al., 2006). Thus, it seems probable that this finding reflects a centrally
355 mediated positive response bias following ATD treatment (Linker, Moore, & Galanter, 1964;
356 Potts, Bennett, Kennedy, & Vaccarino, 1997), though that cannot be determined definitively
357 with the present protocol design. Salt detection thresholds have previously been reported to
358 be enhanced following exposure to acute stress, though in that study sweet detection
359 thresholds were also enhanced (Ileri-Gurel et al., 2013). However, consistent with previous
360 studies (Roiser et al., 2008; Trotter et al., 2016), here we found no change in mood following
361 ATD and if a response bias does underpin this finding, it is not clear why it was only
362 apparent to the salt taste and not any of the other three tastants.

363 Considering supra-threshold rating of intensity and pleasantness, consistent with our
364 hypothesis, reduced central 5-HT function led to enhanced perception of the intensity and
365 unpleasantness of the bitter tastant, quinine. In evolutionary terms, bitter tastes signal
366 potential toxins so enhanced sensitivity to such stimuli likely reflect an attentional bias to
367 threat induced by centrally lowered 5-HT (Breslin, 2013; Browning et al., 2007; Fox,
368 Zougkou, Ridgewell, & Garner, 2011). Given 5-HT generally has an inhibitory effect in
369 sensory systems, this enhanced response may reflect increased neural responsiveness in
370 gustatory cortex (Hurley et al., 2004; Jacob & Nienborg, 2018). However, the finding is also
371 consistent with previous neuroimaging studies which have reported acute lowering of central
372 5-HT levels enhanced the amygdala response to threatening visual stimuli (Cools et al. 2005;
373 Van Der Veen et al. 2007; Harmer et al. 2003; Browning et al. 2007). Thus, future
374 neuroimaging studies are required to determine the neural basis of the observed effect.

375

376 ATD also enhanced perceived intensity, but not unpleasantness, in ratings of the sour tastant,
377 citric acid. Sour acid tastes are typically experienced in combination with sweet tastes, for
378 example within fruits rich in vitamin C. A sour taste in the absence of sweetness is
379 suggestive of unripe fruit (Breslin, 2013). So increased intensity ratings following ATD
380 depletion may well also reflect a negative attentional bias (Browning et al., 2007; Fox et al.,
381 2011). Even at the strongest concentration used, the sour taste was only rated as mildly
382 unpleasant and this may explain the lack of effect of ATD on hedonic ratings. In contrast to
383 the enhanced sensitivity to salt detection induced by ATD, there was no impact of central
384 serotonin depletion on ratings of either the intensity or hedonics of supra-threshold
385 concentrations of sodium chloride.

386

387 Contrary to our hypothesis, the ATD manipulation did not affect ratings of either the intensity
388 or pleasantness of sucrose. This is inconsistent with previous findings that 5-HT deficiency,
389 including following ATD, significantly increases the intake of sweet foods (Pagoto et al.,
390 2009; Wagner, Ahlstrom, Redden, Vickers, & Mann, 2014). Nor is it consistent with previous
391 reports that enhanced 5-HT function decreased neural responses to rewarding sweet flavours
392 (McCabe et al., 2010). These differences may reflect the use of pure tastants in the present
393 study versus the more ecologically relevant flavours participants have been exposed to in
394 previous studies. Although humans show innate responses to sweet and bitter tastes, it is
395 multimodal flavour percepts which people learn to use to evaluate food (Breslin, 2013;
396 Spence, 2017).

397

398 These differential findings may also reflect the varying methodologies used. Low levels of
399 central serotonin have previously been reported to enhance the incentive salience of rewards,
400 including highly palatable foods, driving consumption (Pagoto et al., 2009; Roiser et al.,
401 2006). However, models of incentive motivation distinguish between wanting, that is
402 motivation to obtain a food stuff, and liking, the sensory experience of consuming it
403 (Berridge, Robinson, & Aldridge, 2009). Here our hedonic ratings of pleasantness, given
404 immediately after administration of the taste, probe this latter sensory component. The lack of
405 effect of serotonin liking is consistent with previous reports in rats that acute systemic
406 administration of the SSRI paroxetine had no effect on hedonic responses to sucrose during a
407 brief access test but did induce state dependent modulation of appetitive approach behaviour
408 (Mathes & Spector, 2011). Finally, though differences in 5-HT function have previously been
409 reported to impact neural and behavioural responses to both positive and negative affective
410 stimuli (Browning et al., 2007; Fox et al., 2000, 2011), motivation to avoid bad outcomes is
411 stronger than the drive to pursue good ones (Baumeister, Bratslavsky, Finkenauer, & Vohs,

412 2001) and negative material has a stronger draw on attention (Fox et al., 2000). This
413 difference can further explain why we saw enhanced perceptions of unpleasant bitter and sour
414 tastes without any corresponding enhancement in the perceived intensity or pleasantness of
415 sucrose.

416

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

428

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

437 2008; Trotter et al., 2016). Thus, the present findings cannot be interpreted as reflecting
438 serotonin induced changes in affective state. Noradrenaline is another monoamine which
439 plays a central role in modulating autonomic nervous system responses to stress (Chrousos,
440 2009) and has long been known to modulate peripheral taste perception (Heath et al., 2006;
441 Katsushi Morimoto & Sato, 1982), as well a central responses to sensory stimuli (Jacob &
442 Nienborg, 2018), thus further work is needed to fully determine the neurochemical basis of
443 previously reported affective state induced changes in taste processing and eating behaviour.
444

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

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461

462

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

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

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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 ($*p < .001$). 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 concentration of (C) NaCl at the log -1 was detected significantly more frequently in the Tryptophan Depletion than the Control condition ($*p < .05$).**

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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 ($*p < .001$) and main effects for treatment on intensity ratings were identified for (B) Sour ($*p < .05$) and (D) Bitter tastes ($**p < .01$).**

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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 ($ps > .05$).**

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