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Switching from sucrose to saccharin: Extended successive negative contrast is not maintained
by hedonic changes.

Simone Rehn¹, Robert A. Boakes¹ & Dominic Dwyer²

1. School of Psychology, University of Sydney, Australia.

2. Department of Psychology, Cardiff University, UK.

Correspondence:

Prof. R.A. Boakes,

School of Psychology (A18),

University of Sydney, NSW 2006,

Australia.

Tel: +612 9351 3347

Email: bob.boakes@sydney.edu.au

23

Abstract

24 Previous experiments found that acceptance of saccharin by rats was reduced if they had
25 prior experience of sucrose or some other highly palatable solution. This reduction in
26 saccharin consumption was particularly extended after a switch from sucrose. On the
27 surface, this seems to correspond to a successive negative contrast (SNC) effect – a term
28 coined by C. F. Flaherty to describe the situation where consumption of a target solution is
29 reduced by prior experience of a more valuable solution (typically a more concentrated
30 version of the target solution). However, SNC effects are typically transient and assessed
31 relative to a non-shifted control. Here, we confirm that the reduction in consumption seen
32 when shifting from sucrose to saccharin is persistent and is seen relative to the traditional
33 unshifted control. In addition, an analysis of licking microstructure showed that the shift
34 from sucrose to saccharin suppressed the hedonic value of saccharin relative to controls, but
35 this effect was far less persistent than consumption suppression. Interestingly, a similar
36 dissociation is observed in extinction of conditioned taste aversion (CTA): suppression of
37 consumption produced by CTA is far more persistent than suppression of hedonic value. The
38 comparison of results across procedures suggests that persistent SNC produced by a
39 qualitative downshift from sucrose to saccharin appears different from quantitative
40 downshifts in the concentration of a single solution, and qualitative downshift effects may be
41 based on CTA.

42

43 230 words

44 *Key words:* sucrose; saccharin; negative contrast; hedonic value; licking microstructure; rats.45 *Running head:* Successive negative contrast and hedonic value

46 Rats allowed to consume concentrated sucrose solutions for extended periods show
47 cognitive and metabolic impairments (Kendig, Boakes, Rooney, & Corbit, 2013; Kendig et
48 al., 2018). These impairments decline in severity over time if the rats are switched to a
49 saccharin solution but intriguingly consumption of saccharin remain persistently low and
50 similar to intakes of water (Kendig et al., 2018) even though rats generally prefer saccharin
51 and drink more than water (Mook, 1974). Subsequent experiments designed to investigate
52 this effect confirmed that, following an initial stage in which rats were given access to highly
53 palatable solutions, including glucose and maltodextrin solutions as well as 10% w/v sucrose,
54 acceptance of saccharin was reduced relative to controls (Boakes, Rehn, Badolato, &
55 Rooney, 2020).

56 Described in these general terms, it seems reasonable to assume that these results might
57 reflect a form of successive negative contrast (SNC). This refers to an abrupt drop in
58 consumption of some normally palatable solution following a 'downshift' from a higher
59 valued one or a drop in performance after a downshift in reward (Flaherty, 1996). For
60 example, in a downshift that was widely used in Flaherty's laboratory and by other
61 researchers, rats were switched from 32% sucrose to 4% sucrose (32-4 condition); this results
62 in lower consumption of the 4% solution than that of an unshifted group (4-4 condition)
63 maintained on 4% sucrose throughout (Flaherty & Largen, 1975; Pellegrini, Muzio, Mustaca,
64 & Papini, 2004). However, the effect of shifting from sucrose to saccharin in the studies
65 noted above (Boakes et al., 2020; Kendig et al., 2013; Kendig et al., 2018) differed in two
66 main respects from the example from Flaherty's laboratory of what we will term a
67 *quantitative downshift*, that is, one involving a reduction in the amount or the concentration

68 of some incentive¹. First, the effect of the latter is normally short-lived. Recovery to the
69 level of controls is normally rapid in SNC experiments measuring consumption (Flaherty,
70 1996), as well as for running speeds in runway experiments such as Crespi's (1942) classic
71 study. The second major difference is that a shift from sucrose to saccharin involves the
72 introduction of a new taste as well as an unexpected decrease in palatability. We refer to
73 these relatively rare examples as *qualitative downshifts*. An example is a shift from a highly
74 palatable mixture of glucose and saccharin to glucose alone; the resultant low acceptance of
75 the glucose solution, compared to controls, persisted over eight post-shift sessions (Mitchell
76 & Flaherty, 2005; see Figure 1).

77 In addition, our previous studies shared a limitation with many prior investigations of
78 SNC, namely that they relied entirely on endpoint measures of behavior such as the total
79 amount consumed or the total number of licks. While intake measures are certainly
80 informative, it has long been recognized that overall intake reflects the combination of a
81 variety of processes (e.g. Davis, 1998; Dwyer, 2012; Spector, Klumpp, & Kaplan, 1998).
82 Analyzing the microstructure of licking displayed by rats during the consumption of fluids
83 has allowed researchers to assess some of the mechanisms contributing to overall
84 consumption in more detail. A cluster is defined as a series of licks that occur prior to some
85 pause criterion (e.g., a series of licks separated by < 0.5 s). The number of licks per cluster is
86 used as an index of hedonic value (Davis, 1989; Dwyer, 2012). For example, when a

¹ There are also two potentially important practical differences: our prior studies used long (up to 24 h/day) exposures, while most studies of consumption-based SNC have used relatively short (5-30 min) daily sessions; and the typical controls for SNC studies have been “unshifted” groups receiving the lower-valued solution throughout, while our prior studies have typically used controls exposed to water alone.

87 palatable solution is consumed, there is a positive monotonic relationship between lick cluster
88 size and solution concentration; and pairing a taste with an aversive outcome such as LiCl has
89 been reliably found to reduce lick cluster size (e.g. Arthurs, Lin, Amodeo, & Reilly, 2012;
90 Baird, St John, & Nguyen, 2005; Dwyer, Boakes, & Hayward, 2008). Thus, higher lick
91 cluster sizes are indicative of greater hedonic value (and vice versa).

92 Three previous SNC studies used microstructural analysis of licking behavior. Grigson,
93 Spector, and Norgren (1993) reported a SNC effect that persisted throughout the four-day
94 post-shift period in rats shifted from 1.0 M (~ 34.2% w/v) to 0.1 M (~3.42% w/v) sucrose
95 solution. The shift was followed by consistent reductions in the number of licks per cluster
96 (i.e., lick cluster size), relative to unshifted controls, which suggests a reasonably persistent
97 reduction in the hedonic value of the downshifted sucrose solution. Conversely, Mitchell and
98 Flaherty (2005) only found lower lick cluster size on the first post-shift day in rats switched
99 from a 2% glucose+0.15% saccharin mixture to 2% glucose. Lick cluster size did not differ
100 between shifted and unshifted groups in this experiment for the remaining seven post-shift
101 days, although a SNC effect on solution intake persisted. In a study with mice, a reduction in
102 cluster size was found in a 32%-4% sucrose shift group; however, this effect was very
103 transient, in that no differences between this group and an unshifted control were found after
104 the first 2 min of a single 10-min test session and no overall SNC effect was detected in terms
105 of total intake of 4% sucrose during this session (Austen, Strickland, & Sanderson, 2016).

106 The design of the present experiment involved two stages and is outlined in Table 1. In a
107 10-session Stage 1 rats received daily 30 min drinking sessions with access to either 10%
108 sucrose, 10% maltodextrin, 0.4% saccharin or water. This was followed by a 12-session
109 Stage 2, during which all rats received 0.4% saccharin, and a final 2-session two-bottle
110 choice test between 0.4% saccharin and 2% sucrose. The inclusion of a group given 10%
111 maltodextrin in Stage 1 (*Malto-Sacch*) was to test whether any effects found in the *Suc-Sacch*

112 group would also be found when rats were given access to this other highly palatable, energy-
113 dense solution, one far less sweet than either sucrose or saccharin (Davis, 1996; Dwyer,
114 2008; Sclafani, 2004), prior to the shift to saccharin.

115 The more general aim of this study is to extend our understanding of *qualitative* contrast
116 effects as opposed to the much more extensively studied *quantitative* effects.

117

118 **Method**

119 **Subjects.** Sixty-four female Sprague-Dawley rats were purchased from Envigo
120 (Blackthorn, United Kingdom). On arrival they were 6 weeks old, with an average weight of
121 187 g (range, 165-213 g). The rats were housed in pairs throughout the experiment. The
122 colony room was maintained on a 12:12 h light/dark cycle with lights turning off at 1900 h.
123 All experimental procedures occurred during the light phase of the cycle and only on
124 weekdays. Rats were handled for three days prior to the start of experimental procedures.
125 They were maintained on *ad libitum* access to chow and water, except on experimental days
126 when water bottles were removed 1 h prior to drinking sessions and replaced after the
127 session. Rats were weighed twice a week. All procedures reported here were conducted in
128 accordance with the Animals Scientific Procedures Act (1986) requirements for animal
129 experimentation in the United Kingdom.

130 **Solutions.** All solutions were prepared on a weight/weight (w/w) basis using distilled
131 water on the same day that it was provided to the rats. Sucrose solutions (2%, 10%) were
132 prepared using commercially available white sugar (17 kJ/g, Silver Spoon, UK). A 10%
133 maltodextrin solution was prepared using maltodextrin (16.2 kJ/g, C*Dry MD 01904,
134 Cerestar-UK, Manchester, UK). A 0.4% saccharin solution was prepared using saccharin
135 sodium salt hydrate (S6047, Sigma-Aldrich).

136 **Apparatus.** All drinking sessions took place in a separate testing room from the colony
 137 room. The testing room contained 16 custom-made automated drinking chambers, measuring
 138 $32 \times 15 \times 12$ cm, with acrylic walls, steel mesh flooring and wire mesh lids. Two 50 mL
 139 drinking bottles with metal spouts could be inserted 8 cm apart at one end of each box. A
 140 contact-sensitive lickometer registered the licks made by rats to the nearest 0.01 s once the
 141 bottle was available. MED-PC software (Med Associates, Inc) was used to control the
 142 equipment and record the data.

143 **Table 1. Design of the experiment.**

Groups ($n = 16$)	Stage 1 (10 x 30-min sessions)	Stage 2 (12 x 30-min sessions)	Preference tests (2 sessions)
Suc-Sacch	10% sucrose		
Malto-Sacch	10% maltodextrin		0.4% saccharin
Sacch-Sacch	0.4% saccharin	0.4% saccharin	vs 2% sucrose
Water-Sacch	Water		

144

145 **Procedure.** The experiment design is outlined in Table 1.

146 *Stage 1* (Sessions 1-10). Rats were allocated to one of four groups ($n = 16$), matched for
 147 body weight, that differed only in terms of the solution they received during Stage 1: *Suc-*
 148 *Sacch*, *Malto-Sacch*, *Sacch-Sacch*, and *Water-Sacch*. Sessions took place on five days each
 149 week. They were conducted in four runs of 16 rats each ($n = 4/\text{group}$) starting at 1000 h.
 150 Rats were transferred from home cages to individual drinking chambers where they received
 151 30-min access to their respective solutions. There was no pre-training period to acclimatize
 152 the rats to drinking in the experimental boxes, and so initially the spouts were inserted to
 153 protrude by 1cm into the box. While this facilitated initial drinking, it also allows non-lick
 154 contact with the spout which can interfere with lick-recording. Thus, the spouts were

155 progressively retracted over Sessions 1-4 until presented flush with the front of the cage
156 allowing consumption with minimal lick recording artefacts. The position of the solutions
157 alternated between left (Sessions 1, 3, 5, 7) and right (Sessions 2, 4, 6, 8) to habituate rats to
158 the two positions for future preference tests. Bottles were weighed before and after each run
159 to measure consumption and lick data were recorded in each session throughout the
160 experiment.

161 *Stage 2* (Sessions 11-22). For twelve sessions all groups received 30 min daily access to
162 0.4% saccharin in the licking chambers. As in Stage 1, solutions were presented on the left
163 (Sessions, 11, 13, 15, 17, 19, 21) and right (Sessions 12, 14, 16, 18, 20, 22) in alternate
164 sessions.

165 *Preference tests* (Sessions 23-24). On Session 23 all rats received 15 min access to 0.4%
166 saccharin solution in the left bottle and access to 2% sucrose in the right bottle. On Session
167 24 rats received a second preference test with the positions of the solutions exchanged.

168 **Data analysis.** Lick cluster size, the mean number of licks per cluster, was extracted from
169 MED-PC data. A cluster was defined as a series of licks separated by pauses no longer than
170 0.5 s, a criterion used by Davis (1989) and in previous studies of licking microstructure and
171 contrast effects (Grigson et al., 1993; Mitchell & Flaherty, 2005). Only cluster size data from
172 Stage 1 Session 5 onwards were analysed, as this was when spouts were positioned for
173 optimal lick recording.

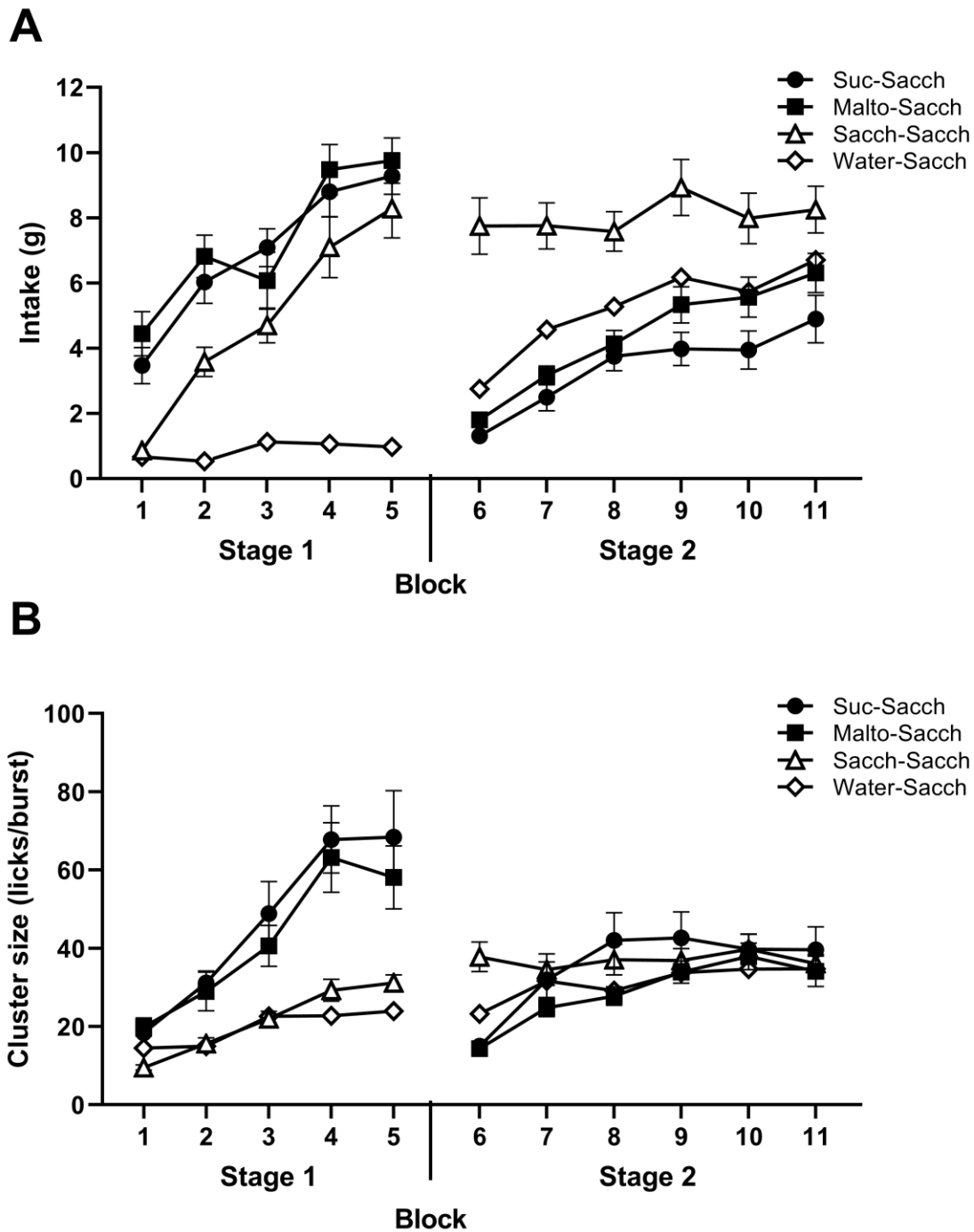
174 Intake and licking data were excluded for rats on days in which observable bottle
175 malfunctions were noted (e.g., blocked spout, leaking bottle). Licking data were also
176 excluded when malfunctions in licking apparatus or recordings were observed (e.g., no licks,
177 short circuit in licking chamber). Licking and intake data were then averaged across two-
178 session blocks to account for potential position preferences as bottle positions alternated
179 between left and right on consecutive sessions. In the single instance where licking data were

180 missing on both days in a two-session block for one rat, it was replaced with an average of
181 the previous and following two-session blocks for that rat (note this occurred on training
182 sessions 5 and 6 and so does not affect the critical test-phase data).

183 Data were analyzed using IBM SPSS (V25) and statistical significance was set at $p < .05$.
184 Intakes and cluster size data were analyzed using separate mixed-ANOVAs in Stages 1 and 2
185 with Group as the between-subjects variable and two-session Blocks as a repeated measures
186 variable. Significant effects and interactions were followed up using simple main effects
187 with two-tailed pairwise comparisons implemented using the “compare” command in SPSS
188 with a common standard error derived from the relevant ANOVA using Fisher's protected least
189 significant difference methods. Preference for saccharin relative to sucrose was calculated as a
190 percentage for each rat by taking total intakes of saccharin across both preference tests and
191 dividing it by total solution intakes (saccharin + sucrose) across both preference tests.
192 Percentage preference data were then analyzed using one-way ANOVA with Group as the
193 between-subjects variable. Greenhouse-Geisser corrections were applied when Mauchly's
194 test of sphericity was violated in mixed-ANOVAs.

195 **Data Transparency and Openness**

196 This experiment was not pre-registered. The data are available upon request to the
197 corresponding author.



200 *Figure 1.* Average (\pm SEM) (A) intakes and (B) lick cluster size for the *Suc-Sacch*, *Malto-*
 201 *Sacch*, *Sacch-Sacch* and *Water-Sacch* groups ($n=16$) during Stage 1 (2-session blocks 1-5),
 202 when rats received their respective solutions, and during Stage 2 (2-session blocks 6-11),

203 when all rats received 0.4% saccharin solution. NB: Error bars for the Water-Sacch group are
204 hidden behind the symbols because they are small.

205 *Stage 1*

206 **Intakes.** Figure 1A shows the average solution intakes over Stages 1 and 2. In Stage
207 1 (left hand panel), *Suc-Sacch* and *Malto-Sacch* rats initially had higher solution intakes than
208 *Water-Sacch* or *Sacch-Sacch* rats, indicating some neophobia to saccharin. By the end of
209 Stage 1 intakes remained low in the *Water-Sacch* group compared to all other groups. This
210 description was confirmed by the results of the mixed ANOVA which indicated that there
211 were significant main effects of Block, $F(2.76, 165.7) = 67.81, p < .001, \text{MSE} = 4.96$, and
212 Group, $F(3, 60) = 49.1, p < .001, \eta^2_p = .71, \text{MSE} = 14.19$, plus a significant Block by Group
213 interaction in solution intakes, $F(8.29, 165.7) = 7.46, p < .001, \eta^2_p = .27, \text{MSE} = 4.96$.

214 Regarding the interaction, in Block 1 intakes were not different between the *Suc-Sacch* and
215 *Malto-Sacch* groups, $t(60) = 1.56, p = .125, \text{Std. Error} = 0.62$, nor between the *Water-Sacch*
216 and *Sacch-Sacch* groups, $t(60) = 0.32, p = .754, \text{Std. Error} = 0.62$, while both the *Suc-Sacch*
217 and *Malto-Sacch* groups displayed higher intakes than both the *Water-Sacch* and *Sacch-*
218 *Sacch* groups, smallest $t(60) = 4.16, p < .001, \text{Std. Error} = 0.62$ (for the *Suc-Sacch* vs *Sacch-*
219 *Sacch* comparison). However, by Block 5 the *Water-Sacch* group had lower intakes than all
220 other groups (smallest $t(60) = 8.11, p < .001, \text{Std. Error} = 0.90$, for the comparison to group
221 *Sacch-Sacch*), and the other three groups did not differ (largest $t(60) = 1.63, p = .108, \text{Std.}$
222 $\text{Error} = 0.90$, for the *Suc-Sacch* vs *Sacch-Sacch* comparison).

223 **Lick cluster size.** Lick cluster size data are shown in Figure 1B. Lick cluster sizes
224 were generally higher in Stage 1 (left hand panel) for groups *Suc-Sacch* and *Malto-Sacch*
225 than groups *Water-Sacch* and *Sacch-Sacch*, with this difference becoming larger along with
226 the general increase in lick cluster sizes across Stage 1. However, because the inferential
227 analysis focused only on blocks 3-5 (due to the fact that Blocks 1 and 2 had the spouts

228 extending into the cages and thus allowed non-lick contacts to be recorded) the ANOVA
 229 analysis revealed only main effects of Block, $F(2, 120) = 9.78, p < .001, \eta^2_p = .14, \text{MSE} =$
 230 $317.60,$ and Group, $F(3, 60) = 12.98, p < .001, \eta^2_p = .39, \text{MSE} = 1354.61,$ but no significant
 231 interaction between them $F(6, 120) = 1.57, p = .163, \eta^2_p = .07, \text{MSE} = 317.60.$ Regarding the
 232 group effect, lick cluster sizes were not significantly different between the *Suc-Sacch* and
 233 *Malto-Sacch* groups, $t(60) = 1.03, p = .308, \text{Std. Error} = 7.51,$ nor between the *Water-Sacch*
 234 and *Sacch-Sacch* groups, $t(60) = 0.58, p = .562, \text{Std. Error} = 7.51,$ while both the *Suc-Sacch*
 235 and *Malto-Sacch* groups displayed higher lick cluster sizes than both the *Water-Sacch* and
 236 *Sacch-Sacch* groups (smallest $t(60) = 3.53, p < .001, \text{Std. Error} = 7.51,$ for the *Malto-Sacch*
 237 vs *Sacch-Sacch* comparison).

238 **Stage 2**

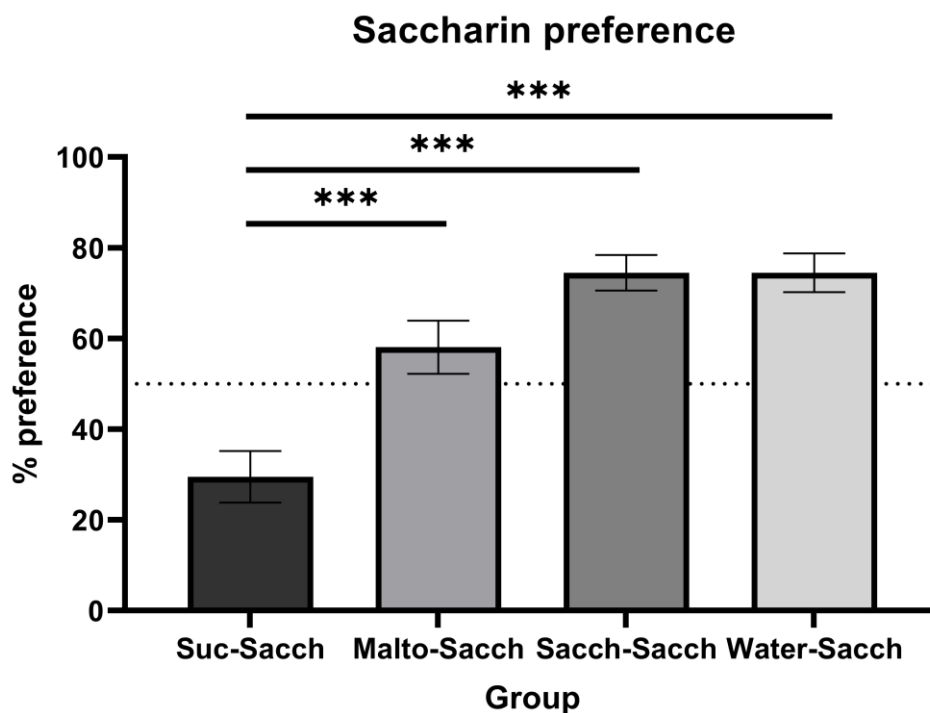
239 **Intakes.** Inspection of the right-hand panel of Figure 1A shows that intake of
 240 saccharin was initially lower, but later recovered, in the *Water-Sacch* group compared to the
 241 *Sacch-Sacch* group. This is consistent with the suggestion from Stage 1 of a neophobic
 242 reaction to saccharin. Importantly, in the *Suc-Sacch* group intake of saccharin was
 243 suppressed relative to the unshifted *Sacch-Sacch* group as well as the *Water-Sacch* group
 244 (with the former effect persisting across testing), suggesting that the suppression of intake in
 245 the *Sacch-Sacch* group is not simply neophobia. The patterns of intake in group *Malto-Sacch*
 246 were similar to those of group *Suc-Sacch* but were numerically smaller.

247 Consistent with the description above, mixed ANOVA revealed main effects of
 248 Block, $F(3.98, 239.0) = 41.24, p < .001, \eta^2_p = .41, \text{MSE} = 2.61,$ and Group, $F(3, 60) = 15.13,$
 249 $p < .001, \eta^2_p = .43, \text{MSE} = 25.33,$ as well as a Block by Group interaction, $F(11.95, 239.0) =$
 250 $3.48, p < .001, \eta^2_p = .15, \text{MSE} = 2.61.$ Pairwise comparisons revealed that *Suc-Sacch* rats
 251 had lower intakes than *Sacch-Sacch* rats in all blocks of Stage 2 (smallest $t(60) = 3.37, p <$
 252 $.001, \text{Std. Error} = 1.00,$ for the final block 6). *Suc-Sacch* rats also had significantly lower

253 intakes than *Water-Sacch* rats in Blocks 1, 2, and 4 (smallest $t(60) = 2.07, p = .043$, Std. Error
 254 = 0.69, for block 1), while on the remaining blocks the difference did not reach standard
 255 levels of significance on two-tailed tests (smallest $t(60) = 1.80, p = .077$, Std. Error = 1.00,
 256 for block 5) but would have been significant using one-tailed tests. In addition, *Water-Sacch*
 257 rats had lower intakes than *Sacch-Sacch* rats in Blocks 1-5 of Stage 2 (smallest $t(60) = 2.26, p$
 258 = .028, Std. Error = 1.00, for block 5), but not Block 6 ($t(60) = 1.55, p = .127$, Std. Error =
 259 1.00). *Malto-Sacch* rats had lower intakes than *Sacch-Sacch* rats in Blocks 1-5 of Stage 2
 260 (smallest $t(60) = 2.43, p = .018$, Std. Error = 1.00, for Block 5), this difference was not
 261 significant on a two-tailed test on Block 6 ($t(60) = 1.95, p = .056$, Std. Error = 1.00). While
 262 intake in *Malto-Sacch* rats was numerically lower than *Water-Sacch* rats in all blocks, this
 263 difference was never significant on two-tailed tests (largest $t(60) = 1.90, p = .062$, Std. Error
 264 = 0.74, for Block 2).

265 **Lick cluster size.** Inspection of the right-hand panel of Figure 1B shows that lick
 266 cluster sizes in groups *Suc-Sacch* and *Malto-Sacch* were suppressed relative to both *Sacch-*
 267 *Sacch* and *Water-Sacch* on Block 1 but not thereafter. Consistent with this description, mixed
 268 ANOVA revealed main effects of Block, $F(3.67, 220.0) = 22.39, p < .001, \eta^2_p = .27$, MSE =
 269 128.03, and a Block by Group interaction, $F(11.00, 220.0) = 4.36, p < .001, \eta^2_p = .18$, MSE =
 270 128.03, but no significant effect of Group, $F(3, 60) = 1.39, p = .253, \eta^2_p = .07$, MSE =
 271 955.21. Pairwise comparisons revealed that in Block 1 lick cluster sizes in group *Suc-Sacch*
 272 were smaller than those in group *Sacch-Sacch* ($t(60) = 6.08, p < .001$, Std. Error = 3.85) and
 273 group *Water-Sacch* ($t(60) = 2.30, p = .036$, Std. Error = 3.85), but not in any subsequent
 274 block (largest non-significant $t(60) = 1.53, p = .131$, Std. Error = 5.83, for the comparison
 275 with *Water-Sacch* on block 4; although group *Suc-Sacch* did have significantly *larger* lick
 276 cluster sizes than group *Water-Sacch* on block 3 $t(60) = 2.02, p = .048$, Std. Error = 6.33).
 277 Similarly, in Block 1 lick cluster sizes in group *Malto-Sacch* were smaller than those in group

278 *Sacch-Sacch* ($t(60) = 5.93, p < .001$, Std. Error = 3.85) and group *Water-Sacch* ($t(60) = 2.30$,
 279 $p = .025$, Std. Error = 3.85), but not in any subsequent block (largest $t(60) = 1.70, p = .095$,
 280 Std. Error = 5.73, for the comparison with *Sacch-Sacch* on Block 2). Group *Suc-Sacch* did
 281 have significantly larger lick cluster sizes than group *Malto-Sacch* on Block 3 $t(60) = 2.25, p$
 282 $= .028$, Std. Error = 6.33, and there were no other significant differences between groups
 283 (largest $t(60) = 1.51, p = .137$, Std. Error = 5.83, for the comparison between *Malto-Sacch*
 284 and *Suc-Sacch* on Block 4).



285

286

287 **Figure 2.** Average (\pm SEM) preference for 0.4% saccharin relative to 2% sucrose as a
 288 percentage of total fluid intake during two-bottle choice tests conducted after the final post-
 289 shift session in Stage 2. $n = 16$ for *Suc-Sacch*, *Malto-Sacch*, *Sacch-Sacch* and *Water-Sacch*
 290 groups, *** $p < .001$.

291

292 **Preference tests.** Average percentage preference data for 0.4% saccharin over 2% sucrose
293 in two-bottle choice tests are shown in Figure 2. Group *Suc-Sacch* displayed a preference for
294 sucrose, group *Malto-Sacch* appeared indifferent, which groups *Sacch-Sacch* and *Water-*
295 *Sacch* showed a preference for saccharin. A one-way ANOVA revealed a main effect of
296 Group, $F(3, 60) = 18.0, p < .001, \eta^2 = .47, \text{MSE} = 0.04$. Post-hoc pairwise comparisons
297 revealed that *Suc-Sacch* rats had lower preferences for saccharin relative to sucrose than rats
298 in the other three groups (smallest $t(60) = 4.04, p < .001, \text{Std. Error} = 0.071$, for the
299 comparison to group *Malto-Sacch*); group *Malto-Sacch* had lower preferences for saccharin
300 relative to sucrose than rats in groups *Sacch-Sacch* and *Water-Sacch* (smallest $t(60) = 2.31, p$
301 $= .024, \text{Std. Error} = 0.071$, for the comparison to group *Sacch-Sacch*), which were not
302 significantly different from each other ($t(60) = 0.09, p = .992, \text{Std. Error} = 0.071$).

303 One-sample t-tests which compared each group's preference against 50% (i.e. indifference)
304 confirmed that *Sacch-Sacch* ($t(15) = 6.27, p < .001, \text{Std. Error} = 0.039$) and *Water-Sacch* rats
305 ($t(15) = 5.77, p < .001, \text{Std. Error} = 0.043$) showed a significant preference for saccharin over
306 sucrose. *Suc-Sacch* rats had a significant preference for sucrose over saccharin, $t(15) = 3.61,$
307 $p = .003, \text{Std. Error} = 0.057$. *Malto-Sacch* rats did not show a significant preference for either
308 sucrose or saccharin, $t(15) = 1.38, p = .19, \text{Std. Error} = 0.058$.

309

310 Discussion

311 Following extended exposure to sucrose, switching to saccharin resulted in persistently
312 lower consumption relative to controls receiving prior exposure to either water or saccharin.
313 The switch also produced a reduction in the hedonic value of saccharin indicated by lower
314 lick cluster sizes, but this effect was transient compared to the suppression of consumption.
315 Exposure to maltodextrin had similar effects but to a lesser extent. In addition, following 12
316 days of post-switch saccharin access, controls showed a preference for saccharin over dilute
317 sucrose that was reversed in animals previously exposed to sucrose and absent in animals
318 previously exposed to maltodextrin. This confirms our prior observation that prior exposure
319 to sucrose (or maltodextrin) results in persistent suppression of consumption after a switch to
320 saccharin and extends this observation to the situation in which exposure is limited to a single
321 30-min session per day as opposed to the almost 24-h access in earlier studies. The fact that
322 the suppression of consumption and reduction in hedonic value was observed relative to both
323 water-exposed and unshifted saccharin-exposed controls demonstrates that the effects cannot
324 be attributed simply to neophobia. Moreover, the persistence of consumption suppression
325 over extended testing, and the terminal preference test results, are inconsistent with the effect
326 being attributed to the same processes involved in quantitative SNC because that effect is
327 typically short lived.

328 While the present demonstration that the persistent reduction in saccharin consumption
329 resulting from prior sucrose exposure cannot be explained by a long-term change in the
330 hedonic value of saccharin, neophobia, or “standard” quantitative SNC is informative, it
331 leaves open the question of what mechanism(s) may be responsible. In this light, it is
332 interesting that studies of extinction of conditioned taste aversion display a similar
333 dissociation between long-term changes in consumption and transient effects on hedonic
334 value (e.g. Cantora, López, Aguado, & Rana, 2006; Dwyer, 2009; Dwyer, Gasalla, & López,

335 2013). For example, when saccharin was paired with lithium chloride-induced malaise, rats
336 subsequently showed suppressed saccharin intakes which did not fully extinguish whereas
337 reductions in lick cluster size did. The similarity in the pattern of results raises the possibility
338 that the downshift from sucrose to saccharin results in an aversion to saccharin. There are
339 multiple possible sources of such an aversion, but perhaps the two most obvious are linked to
340 metabolic effects of extended sucrose exposure and the frustrative effects of reward
341 downshift.

342 Previous experience with sucrose may establish a conditioned physiological response such
343 as insulin release. When non-caloric saccharin is encountered, its sweet taste may also
344 produce this inappropriate insulin response and cause illness, thus producing an aversion to
345 saccharin which fails to extinguish. In support of this idea, pairing insulin administration with
346 a flavor has been shown to produce an aversion to that flavor in rats (Vanderweele, Deems, &
347 Kanarek, 1990), and we have observed impaired insulin regulation following extended
348 exposure to sucrose in the studies that motivated the current experiment (Kendig et al., 2018;
349 Kendig, Martire, Boakes, & Rooney, 2021). Alternatively, given that SNC is widely assumed
350 to involve a negative emotion – 'disappointment' or frustration (e.g. Papini, 2003) –
351 encountering a novel taste following a qualitative downshift could become associated with
352 frustration to produce an aversion. Although based on simultaneous contrast rather than
353 SNC, there is already evidence for contrast-produced changes in solution value supporting
354 learning (Dwyer, Figueroa, Gasalla, & López, 2018). The fact that extended maltodextrin
355 exposure produces similar metabolic (and cognitive) effects to sucrose (Kendig, Lin,
356 Beilharz, Rooney, & Boakes, 2014) with less apparent consumption suppression effects in the
357 current experiment, may seem to favour the frustration conditioning possibility, but this
358 neglects the possibility that the overlap in sweet taste between sucrose and saccharin might
359 better support conditioned insulin release. Although speculative, the potential link between

360 fear and frustration (Gray & McNaughton, 2003; Papini, 2003) may also suggest ways to
361 investigate these different putative mechanisms because aversions based on nausea and
362 avoidance based on fear have differing behavioural effects (e.g. Dwyer, Gasalla, Bura, &
363 López, 2017; Parker, 2003).

364 Setting aside the exact mechanisms involved, the qualitative downshift from sucrose to
365 saccharin examined here had more persistent effects than quantitative shifts that have been
366 the mainstay of SNC research. In turn, this is consistent with the possibility of the effects
367 being driven by the development of an aversion given that quantitative-only shifts would
368 mean that the putative CS (i.e., post-shift solution) would have received extended pre-
369 exposure that would produce latent inhibition to reduce any conditioning effect (Lubow,
370 1989, 2009).

371 It will be recalled that a previous quantitative SNC using lick cluster analysis found a
372 relatively persistent effect on cluster size (Grigson & Norgren, 1993). However, in a
373 qualitative SNC study that also employed lick cluster analysis the size effect was short-lived,
374 even though the depression of intakes persisted (Mitchell & Flaherty, 2005). In the light of
375 such apparent inconsistencies and the present results, it would be valuable to carry out a
376 direct comparison between quantitative and qualitative SNC effects.

377 In summary, shifting rats from sucrose to saccharin exposure results in transient
378 reductions in hedonic value and extended suppression of consumption. The prolonged
379 suppression of saccharin consumption cannot be attributed to either a persistent change in the
380 hedonic value of saccharin or to neophobia, and it also differs from quantitative SNC. The
381 effect may be due to the qualitative downshift from sucrose to saccharin producing (perhaps
382 due to inappropriate conditioned metabolic responses or frustration) an aversion to the
383 saccharin solution.

384

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