

28 **Abstract**

29 Anosmia is common with respiratory virus infections, but loss of taste or
30 chemesthesis is rare. Reports of true taste loss with COVID-19 were viewed skeptically
31 until confirmed by multiple studies. Nasal menthol thresholds are elevated in some with
32 prior COVID-19 infections, but data on oral chemesthesis are lacking. Many patients
33 recover quickly, but precise timing and synchrony of recovery are unclear. Here, we
34 collected broad sensory measures over 28 days, recruiting adults (18-45 years) who were
35 COVID-19 positive or recently exposed (close contacts per U.S. CDC criteria at the time
36 of the study) in the first half of 2021. Participants received nose clips, red commercial
37 jellybeans (Sour Cherry and Cinnamon), and scratch-n-sniff cards (ScentCheckPro).
38 Among COVID-19 cases who entered the study on or before Day 10 of infection,
39 Gaussian Process Regression showed odor identification and odor intensity (two distinct
40 measures of function) each declined relative to controls (close contacts who never
41 developed COVID-19), but effects were larger for intensity than identification. To assess
42 changes during early onset, we identified four COVID-19 cases who enrolled on or prior
43 to Day 1 of their illness – this allowed for visualization of baseline ratings, loss, and
44 recovery of function over time. Four controls were matched for age, gender, and race.
45 Variables included sourness and sweetness (Sour Cherry jellybeans), oral burn
46 (Cinnamon jellybeans), mean orthonasal intensity of four odors (ScentCheckPro), and
47 perceived nasal blockage. Data were plotted over 28 days, creating panel plots for the
48 eight cases and controls. Controls exhibited stable ratings over time. By contrast,
49 COVID-19 cases showed sharp deviations over time. No single pattern of taste loss or
50 recovery was apparent, implying different taste qualities might recover at different rates.
51 Oral burn was transiently reduced for some before recovering quickly, suggesting acute
52 loss may be missed in data collected after acute illness ends. Changes in odor intensity
53 or odor identification were not explained by nasal blockage. Collectively, intensive daily
54 testing shows orthonasal smell, oral chemesthesis and taste were each altered by acute
55 COVID-19 infection, and this disruption was dyssynchronous for different modalities,
56 with variable loss and recovery rates across modalities and individuals.

57

58 **1. Introduction**

59 The COVID-19 pandemic caused by the SARS-CoV-2 virus is one of the most
60 devastating infectious disease outbreaks since the H1N1 avian flu of 1918 [1, 2]. By the
61 end of 2021, roughly two years after the start of the pandemic, there were over 281
62 million cases of COVID-19 globally, resulting in over 5.4 million deaths [3]. Early in the
63 pandemic, SARS-CoV-2 infection was associated with myriad symptoms, one of the
64 most common being anosmia [4-7]. Meta-analyses of dozens of early studies suggested
65 half to three-quarters of COVID-19 patients lost their sense of smell [8]. Further, smell
66 loss was the most predictive symptom of COVID-19 [9] in the first several waves.

67 In contrast to other respiratory illnesses that cause acute anosmia – including
68 those caused by rhinoviruses, influenza viruses, and common coronaviruses – both taste
69 and chemesthesis function were reportedly lost in some people with COVID-19 [10-12].
70 Taste loss in the absence of smell loss is rare [13], and many individuals may mistakenly
71 conflate the impaired flavor perception associated with anosmia with a true loss of taste
72 function. However, one large crowd-sourced study reported ~60% of COVID-19-positive
73 individuals had impaired perception of specific taste qualities (i.e., sweet, salty, sour or
74 bitter tastes), suggesting taste loss in these individuals is distinct from impaired flavor
75 perception accompanying smell loss [10, 14]. The findings of that study and others
76 based on self-reports (e.g., [15-17]), were confirmed by psychophysical tests of taste
77 function, suggesting ~47 to 64% of COVID-19 positive individuals experience taste loss
78 [18, 19]. As a result, taste dysfunction (distinct from impaired flavor perception due to
79 smell loss) is now also recognized as a common symptom of COVID-19 [20, 21].

80 Data on disruption of chemesthesis associated with COVID-19 remains quite
81 limited. Consistent with many patient anecdotes that chili and ethanol burn were
82 transiently depressed (e.g., [22]), studies relying on self-report suggested roughly half of
83 individuals with COVID-19 experienced disruptions of chemesthesis [10]. In a small
84 study of Italians with COVID-19-associated smell loss, 57% of patients had reported a
85 severe impairment of nasal chemesthesis at initial diagnosis, but over 90% reported full
86 recovery of chemesthesis six months later [23]. A Swedish study that used “olfactory”
87 stimuli known to concomitantly activate the trigeminal system (e.g., vinegar, chopped
88 garlic, vodka) provided evidence for impairment of nasal chemesthesis [24]. Thus, while
89 self-report and clinical assessment both suggest COVID-19 may associate with acute

90 impairment of chemesthesis in many individuals, the time course of loss and recovery is
91 lacking, as is any assessment of the impact on oral chemesthesis. We attempt to fill
92 these knowledge gaps here.

93 In approximately 85% of COVID-19 cases where chemosensation (smell, taste
94 and/or chemesthesis) has been affected, recovery of chemosensory function is typically
95 seen within ~6 weeks [6, 25, 26]. Unfortunately, some patients do not report
96 appreciable recovery after many months [13, 26-30]. However, without daily
97 chemosensory testing, the precise timing of recovery remains unknown [6, 25, 31].
98 Because patient anecdotes suggest the timing of recovery of different chemical senses
99 may be dyssynchronous [26], we assessed smell, taste, and chemesthesis function
100 acutely and transiently over 28 days by collecting longitudinal data using commercially
101 available chemosensory stimuli in a cohort of patients diagnosed with COVID-19 and
102 control participants without COVID-19 in early 2021. Here, we present a small case-
103 control series using temporally intensive data collection from remote daily testing. We
104 focus on a handful of COVID-19 cases that allow for visualization of loss and recovery of
105 chemosensory function as well as baseline ratings obtained prior to the onset of illness.

106 **2. Methods**

107 **2.1 Study design and recruitment**

108 This prospective study investigated COVID-19-related chemosensory dysfunction
109 in a community-derived sample of 18- to 45-year-old adults recruited on and around the
110 campus of a large public university in rural central Pennsylvania (i.e., the area
111 surrounding State College, PA). Enrollment began in February, 2021, on a rolling basis
112 using geotargeted ads on social media, and ended in May, 2021. Potentially interested
113 individuals were asked to contact a study team member (author EMW) via email if they
114 believed they were qualified for the study, who then emailed them a link to a brief
115 screening questionnaire. The screening questionnaire asked questions about
116 demographics, prior diagnosis of COVID-19, contact with a COVID-19-positive (COVID-
117 19+) individual, and any recent symptoms of COVID-19. Contact with a COVID-19+
118 individual was defined by the Centers for Disease Control (CDC) screening criteria in
119 use at the time of enrollment (specifically, 15 or more minutes within 6 feet of a
120 confirmed case of COVID-19). Due to the fluidity of the COVID-19 pandemic in early

121 2021, however, a strict timeline was not rigidly enforced and enrollment occurred on a
122 case-by-case basis. As vaccines were not available to non-health care workers at study
123 initiation in February, 2021, but became more widely available during the enrollment
124 window, we added a short retroactive questionnaire to the end of the study to gather
125 self-reported information on vaccination status and date. No attempt was made to
126 confirm these reports against medical records.

127 Participants with the following conditions were excluded: not diagnosed with
128 COVID-19 or not a close contact of a COVID-19+ individual, pregnant, food allergies (or
129 another reason they could not consume commercial jelly beans), prior history of a
130 disease of the central nervous system (including Alzheimer's disease, multiple sclerosis,
131 Parkinson's disease, Huntington's disease, brain tumor), nasal obstruction
132 (tumor/polyps), a history of nasal surgery, history of a severe head injury/concussion,
133 history of chronic sinus infections, history of radiation therapy to the head or neck
134 (ever), recent chemotherapy (within the last year), a prior diagnosis of smell or taste
135 loss, diabetes, history of lung/pulmonary disease or neurological disease, were unwilling
136 to create a PayPal account for compensation if they did not already have one, or were
137 below 18 years or above 45 years of age.

138 Data were collected using REDCap, a secure data capture platform for clinical
139 research [32, 33] on a server hosted and maintained by the Penn State College of
140 Medicine in Hershey, PA. The study was performed in compliance with the principles of
141 the Declaration of Helsinki, informed consent was obtained electronically, and the
142 specific protocol was approved by the Institutional Review Board at Penn State
143 (STUDY00016377). The subject identification numbers referenced below were known
144 only to our research staff and were not known to the participants or other individuals.

145 **2.2 Chemosensory stimuli and assessment**

146 The longitudinal design consisted of brief daily assessment every day for 28 days,
147 followed by four additional follow-up sessions every 2 weeks, for a total of 32 sessions
148 over a 12-week period. This report focuses on data from the first 28 days of testing. In
149 each daily session, participants were asked to complete questions on COVID-19 status or
150 symptoms that had changed since the last session, as well as self-administered
151 psychophysical smell and taste tests. They were instructed to minimize any distracting

152 smells or odors before any sensory testing and were also asked not to eat or drink
153 (anything other than water) or smoke for at least 30 minutes prior to testing.

154 Upon enrollment, the first author arranged contactless delivery of all research
155 materials in a large plastic zip-top bag. Specifically, participants were given 32
156 ScentCheckPro cards (Item #098515, Lot #0821) from Taylor Corp (North Mankato,
157 MN). Each ScentCheckPro card consisted of 4 microencapsulated scents in a scratch-n-
158 sniff format, with one scent located near each corner of the postcard sized card. The four
159 scents on a given card were some combination of the following: coconut, grape, coffee,
160 lemon, bubble gum, popcorn, pine, cinnamon, flowers, banana, or none of these.

161 Participants were also given 36 lidded plastic 2 oz souffle cups (Solo P200N; Lake
162 Forest IL) labeled with blinding codes. Individual cups contained one of two kinds of red
163 colored jellybeans (Jelly Belly, Fairfield, CA): either Sour Cherry (Lot #20200601) or
164 Cinnamon (Lot #200731). Each cup contained three jellybeans of a single flavor.
165 Jellybeans are a highly familiar confection in the United States that are made with
166 sweeteners (sugar, and/or corn syrup), corn starch, confectioners glaze, added color and
167 natural or artificial flavors. They have a shiny candy shell and a soft gel center, and come
168 in many different colors and flavors including fruit or spice flavors. With the nose
169 pinched closed, the Sour Cherry jellybean used here evoke both sweetness and sourness,
170 while the Cinnamon jellybean elicits sweetness and a mild warming/burning sensation.
171 Because of the glazed outer shell, jellybeans have little to no orthonasal smell, and both
172 jellybeans had a similar red color, so there were no obvious cues of the specific flavor in
173 each cup. Across days, jellybean presentation order was counterbalanced with pairwise
174 randomization, so that a participant who was presented with Sour Cherry on Day 1
175 would get Cinnamon on Day 2, while the next participant would start with Cinnamon on
176 Day 1 before receiving Sour Cherry on Day 2. This procedure was used to maximize the
177 range of chemosensory stimuli used in the study (i.e., taste, smell, and chemesthesis)
178 while minimizing participant burden on any given day of the study (i.e., a very brief test
179 time to enhance compliance). Individual lidded cups were labeled with random 3-digit
180 blinding codes, and these codes were programmed into REDCap prompts for each
181 session to help ensure participants sampled the correct jellybean on the correct day. We
182 also provided a disposable foam padded nose clip (A-M Systems; Sequim WA; Model

183 #166500, Lot #189615) to allow ratings of oral sensation to be collected with occluded
184 nostrils to minimize olfactory input.

185 Once a day, participants were asked to rate how blocked their nose was using a
186 horizontal 0-100 visual analog scale (VAS) scale anchored with ‘Not blocked at all’ to
187 ‘Completely blocked’. Participants were then asked to scratch the spot containing the
188 encapsulated odorant on each postcard sized smell card with a coin or fingernail for 5-10
189 seconds before sniffing; they were then asked to bring the card one inch from their nose
190 and sniff the odor. For each odor spot, participants were asked to first identify the odor
191 they smelled from four multiple choice options presented in REDCap before rating the
192 perceived intensity of the odor on a 0-100 VAS anchored with labels of ‘None’ to ‘Very
193 intense’. This process was repeated for the four different odorants on a given card.

194 Next, participants were asked to pinch their nose closed using the provided nose
195 clip and put all three jellybeans from the cup into their mouth. With their nose *pinched*
196 *closed*, they were asked to chew the jellybeans slowly, and rate the perceived intensity of
197 various qualities on five different horizontal 0-100 VAS scales labeled ‘None’ to ‘Very
198 intense’. These qualities included: *sourness*, *sweetness*, *warming/burning*, *cherry*
199 *flavor*, and *cinnamon flavor*. Participants were then asked to *unpinch* their nose and
200 exhale (while still chewing the jellybeans) and rate the same five intensity scales with
201 their nose *unpinched* (data not shown). All five scales were presented in both conditions
202 (nose closed / nose open) to minimize any “dumping” artifacts [34]. To decrease daily
203 test time and participant burden on days 1 through 28, participants assessed only one
204 jellybean flavor per day (either Sour Cherry or Cinnamon, counterbalanced as described
205 above). In four follow up sessions at weeks 6, 8, 10 and 12, a longer assessment was
206 deemed reasonable, so participants were presented with two cups of jellybeans, one with
207 each flavor. These data are not reported here.

208 **2.3 Categorization of participants as COVID-19 cases versus controls**

209 For the purposes of this study, a *COVID-19 contact* was defined as a participant
210 who had been exposed to a COVID-19+ individual (e.g., 15 or more minutes within 6 feet
211 of a confirmed case of COVID-19, per US CDC guidelines at the time), but never
212 developed any symptoms or received a positive diagnosis in subsequent testing.
213 Conversely, a *COVID-19 case* was defined as a participant who was either formally
214 diagnosed with COVID-19 *or* began having symptoms while enrolled in the study

215 following their recent exposure. By studying close contacts who later became cases while
216 enrolled in our study, we were able to observe acute changes in chemosensation using
217 controlled stimuli from the earliest days of their infection. When COVID-19 symptoms
218 started prior to the participant receiving a positive COVID-19 diagnosis via clinical
219 testing (typically a positive PCR test), an *estimated day of infection (Day 0)* was defined
220 as the first day of symptoms. When a positive test preceded COVID-19 symptoms, the
221 date of the positive test was used as *Day 0 of infection*. Data from controls were not
222 centered on the day of infection, as these participants enrolled at their discretion. For
223 these individuals, the *day of rating (Day 0)* is defined as the first day of their
224 participation in the study.

225 **2.4 Data analysis**

226 Between February and May of 2021 (i.e., in the months prior to the Delta and Omicron
227 waves in North America), a total of 55 participants were enrolled in the study. For this
228 analysis, 39 participants with confirmed COVID-19 infection were identified as *COVID-*
229 *19 cases* (Figure 1). Of these 39, 15 participants were identified as having an active
230 COVID-19 infection and enrolled in the study prior to or during the first 10 days of
231 infection. Of these 15 participants, four COVID-19 cases entered the study on or before
232 day 1 of their infection, allowing us to capture acute changes in their symptoms
233 throughout their entire infectious period, including early onset of symptoms. As shown
234 in Figure 1, three more cases enrolled on days 2-4 of infection, and nine enrolled on day
235 5-10 of their infection. An additional 24 participants who had enrolled were identified as
236 COVID-19 cases, but only after their initial 10-days of infection had passed. Because we
237 were not able to enroll these subjects early enough to capture potential changes in
238 chemosensory function during acute illness, data from these subjects were not included
239 in the present analyses. We plan to analyze and publish these data elsewhere to better
240 understand recovery over time, but the focus of the current report is initial loss during
241 early illness. Finally, in this analyses, 15 participants were identified as *controls* (i.e.,
242 they did not develop COVID-19 during the duration of the study).

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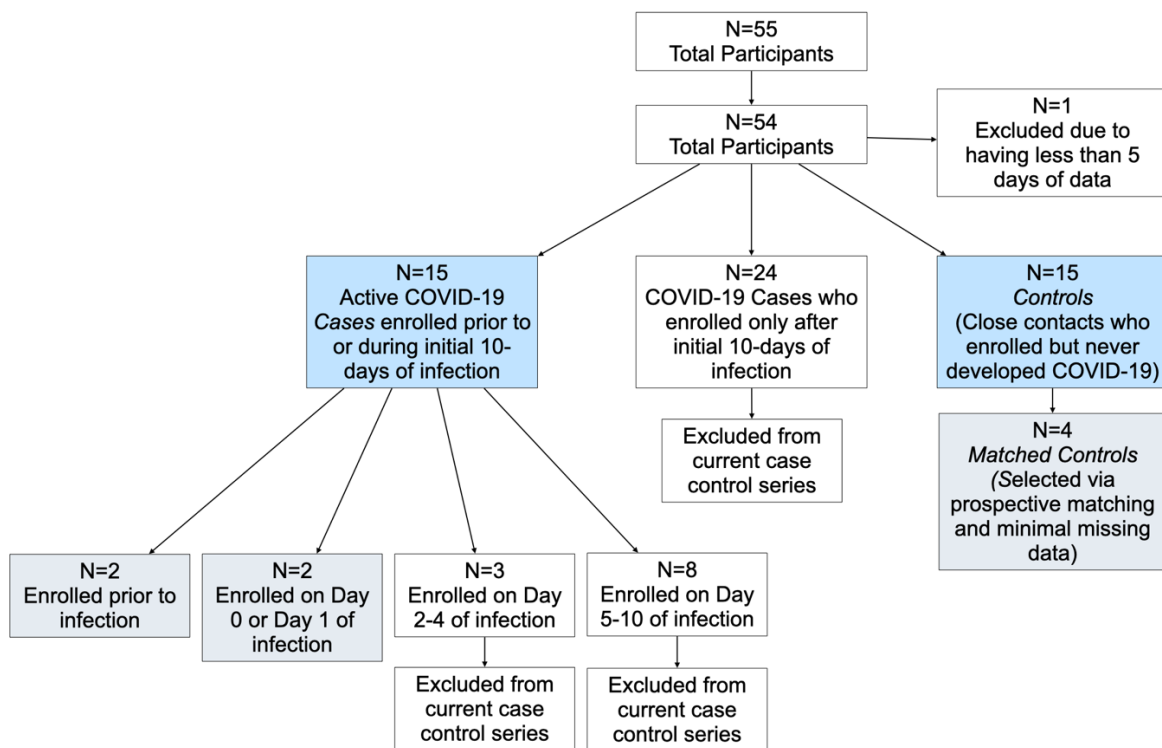


Figure 1: Flow diagram summarizing selection of cases and controls for this case series. Blue boxes indicate the 30 participants included in the Gaussian Process model regression, and gray boxes indicate the 8 individuals shown in the in-depth panel plots.

245 Here, we wanted to assess whether deviation of smell intensity in the cases differed from
246 controls, so we identified the fifteen COVID-19 cases in our study who had enrolled on
247 or before day 10 of either infection and tested if their average deviation in smell
248 intensity over time differed from the 15 participants who were controls. To do this, a
249 grand mean of smell intensity was calculated for the controls across all days and
250 individuals. Deviation scores (deltas) for the 15 COVID-19 cases were then calculated by
251 subtracting that individual's ratings from the grand mean of the 15 controls, resulting in
252 a deviation score for smell intensity. Similarly, for the controls, we subtracted each
253 control's *individual* rating from the *grand mean* of all controls, to get a deviation score
254 for that rating relative to performance of the group. We used a Gaussian Process

255 Regression model to analyze the deviation (delta) scores for *cases* and *controls* over
256 time (both individually and as a group). A Gaussian Process model is a probabilistic
257 unsupervised machine learning concept used for regressions in which the model makes
258 predictions by utilizing prior knowledge about the smoothness of plausible time series
259 and provides uncertainty measures for such predictions [35]. COVID-19 cases were
260 normalized on Day 0 of infection and missing values were extrapolated via the Gaussian
261 Process Regression model. Controls were normalized on Day 0 of rating. To be
262 conservative and avoid overfitting sparse data, ratings of the two jellybean flavors were
263 not modeled via Gaussian Process Regressions, as the counterbalancing of flavors across
264 days meant only half as many data points were available for analysis. Analyses and data
265 visualization were conducted using SAS software (Version 9.4), R using RStudio
266 software (Version 2021.09.0), Python software (Version 3.9.10), or DataGraph version
267 4.7.1 (Visual Data Tools, Inc; Arlington TX).

268 Elsewhere, it has been suggested smell and taste changes occur within the first
269 four days of disease onset [36], and the median incubation period for symptom onset is
270 approximately five days [37]. We observed the same overall pattern within our data; as
271 reported below, it became clear the confidence interval of cases did not include zero in
272 the first week of infection. Given the unique opportunity to explore acute and early
273 changes in chemosensation in a small number of participants who had been enrolled
274 prior to acute illness, we also performed an in-depth analysis of these individuals, in
275 hopes of better understanding the initial trajectory of changes in chemosensation.

276 **2.4 Selection of participants for in-depth case control series**

277 Here, we describe a very small case series restricted to four specific cases who
278 enrolled in the study prior to or on Day 1 of infection (Figure 1). Studying these four
279 participants in detail allowed us to capture changes in symptoms throughout their entire
280 infectious period, including early onset of symptoms. More specifically, this prospective
281 approach maximizes the potential to capture baseline ratings, loss, and recovery of
282 chemosensory function that would not be possible with patients recruited only after they
283 were ill. This is a distinct and unique feature of this case series, as most other studies
284 have assessed chemosensory function multiple days into a participant's isolation period,
285 which does not allow for visualization of initial loss [30, 38-43]. For the other 12

286 participants who entered on or before Day 10 of infection (see Figure 1), we did not
287 capture their initial loss, so they are not included in this analysis.

288 From the 15 *controls*, four were selected as *matched controls* for the four COVID-
289 19 *cases*, based on age, gender, and race (Figure 1). To be considered for matching with
290 a specific COVID-19 case, potential candidates were required to (a) provide data on a
291 minimum of 80% of days, and (b) remain active for the full 28-day data collection
292 period (to avoid bias from dropout over time). If more than one potential candidate met
293 the age, gender, and race criteria to be included in a matched pair, the control used here
294 was randomly selected. Matching was performed manually by an experienced
295 epidemiologist (author CE). This process resulted in a final analysis of four *cases* and
296 four *matched controls* (Figure 1; Table 1).

Table 1: Participant demographics from COVID-19 case-control series identifying cases and matched controls.

ID	Status	Race (Self-Identified)	Gender (Self-Identified)	Age Range	Estimated Day of Infection relative to Day 0 of the Study
35	Case	White/Caucasian	Female	18-23	-4
3	Control	White/Caucasian	Female	18-23	n/a
45	Case	White/Caucasian	Female	18-23	0
10	Control	White/Caucasian	Female	18-23	n/a
62	Case	White/Caucasian	Male	18-23	1
10	Control	White/Caucasian	Male	18-23	n/a
63	Case	White/Caucasian	Female	38-43	-14*
22	Control	White/Caucasian	Female	38-43	n/a

* Follow up via email revealed this participant was exposed twice. Based on symptoms, the first exposure resulted in enrollment as a close contact, but not infection. The participant only became ill following the second exposure.

297 For these four *cases* and their *matched controls*, we plotted six key variables
298 related to smell, taste, and chemesthesis. Specific outcomes were selected *a priori* by
299 two authors (EMW and JEH) as being the most salient and theoretically interesting
300 variables. These were: perceived *nasal blockage*, mean orthonasal *smell intensity* of the
301 four odorants on a given ScentCheckPro card, *sourness* and *sweetness* (from the Sour

302 Cherry jellybeans), and oral *burn* (from the Cinnamon jellybeans). Also, we included
303 *daily number correct* on the odor identification task. These seven variables were then
304 plotted across all 28 days to create a series of panel plots for all eight individuals.

305 In summary, ratings were collected on 101 point VAS, and variables summarized
306 here were: daily ratings of *nasal blockage*; a daily measure of orthonasal *smell intensity*
307 derived from the mean of four scratch-n-sniff spots on a ScentCheckPro card for a given
308 day; oral *burn* ratings collected every other day from a Cinnamon jellybean; and
309 *sweetness* and *sourness* ratings collected every other day from a Sour Cherry jellybean.

310 **3. Results and Discussion**

311 **3.1 Odor identification scores and ratings of orthonasal intensity from a** 312 **commercial scratch-n-sniff card**

313 For controls, the grand mean correct on the daily odor identification (OdorID)
314 across the entire study period was 3.32 out of 4 possible (Figure 2, Supplemental
315 Figures 1, 2). There was some evidence of a learning effect, as controls got slightly better
316 at the task over time (see upward slope, Figure 2A and 2B). For OdorID, the delta score
317 for cases deviates from zero, with a maximal dip occurring around days 5 to 8 (Figure
318 2A and 2B). Conversely, this dip was not observed in the controls, indicating that the
319 drop in OdorID performance was limited to COVID-19 cases.

320 After performing the OdorID task for 4 days, the median number correct for
321 controls increased by ~ 0.5 , and after 14 days (two weeks), the median number correct
322 for controls increased by $\sim 0.7-0.8$ above the grand mean; that is, there was nearly
323 perfect performance on a 4 item OdorID task. Based on odor intensity ratings (discussed
324 below), smell loss for cases appears to be maximal near Day 5 (see Figure 2C and 2D).
325 Accordingly, we would also expect OdorID performance to be lowest on Day 5. However,
326 this is just when the first increase due to the learning effect appears to occur (Figure 2A
327 and 2B). If we assume cases (at least those who are not totally anosmic) show similar
328 ability to learn as the controls, this offsetting bump upward would minimize the
329 apparent dip in OdorID performance seen around Day 5. Thus, the COVID-19-
330 associated drop in identification performance may appear smaller than it actually is due
331 to a simultaneous offsetting increase in performance due to learning (or practice).
332 Evidence of such learning is also seen in Supplemental Figures 1 and 2.

333 Regarding suprathreshold odor intensity, the grand mean of perceived intensity ratings
334 for controls across time was 59.47 on 0 to 100 VAS. The mean on Day 0 was used to
335 calculate daily deviation scores for cases and controls (Figure 2C and 2D). Data were
336 centered using Day 0 means so the delta could be more easily compared across the data
337 set. For the cases (Figure 2C and 2D), the delta score of smell intensity clearly deviates
338 from zero, and this difference was maximal in the first week of infection, as noted above.
339 In sharp contrast, this pattern is not seen in the controls, with a score of zero falling
340 inside the interquartile range across the entire study period (Figure 2D). This indicates
341 there was a significant drop in smell intensity for cases but not controls for ratings of the
342 scratch-n-sniff spots on commercial ScentCheckPro cards. In contrast with the learning
343 seen for the OdorID data, we failed to observe any evidence of a learning effect for smell
344 intensity ratings. Collectively, these data suggest OdorID tasks may be less sensitive to
345 acute changes in smell with COVID-19, relative to odor intensity ratings, at least in
346 repeated testing situations that encourage learning or practice effects.
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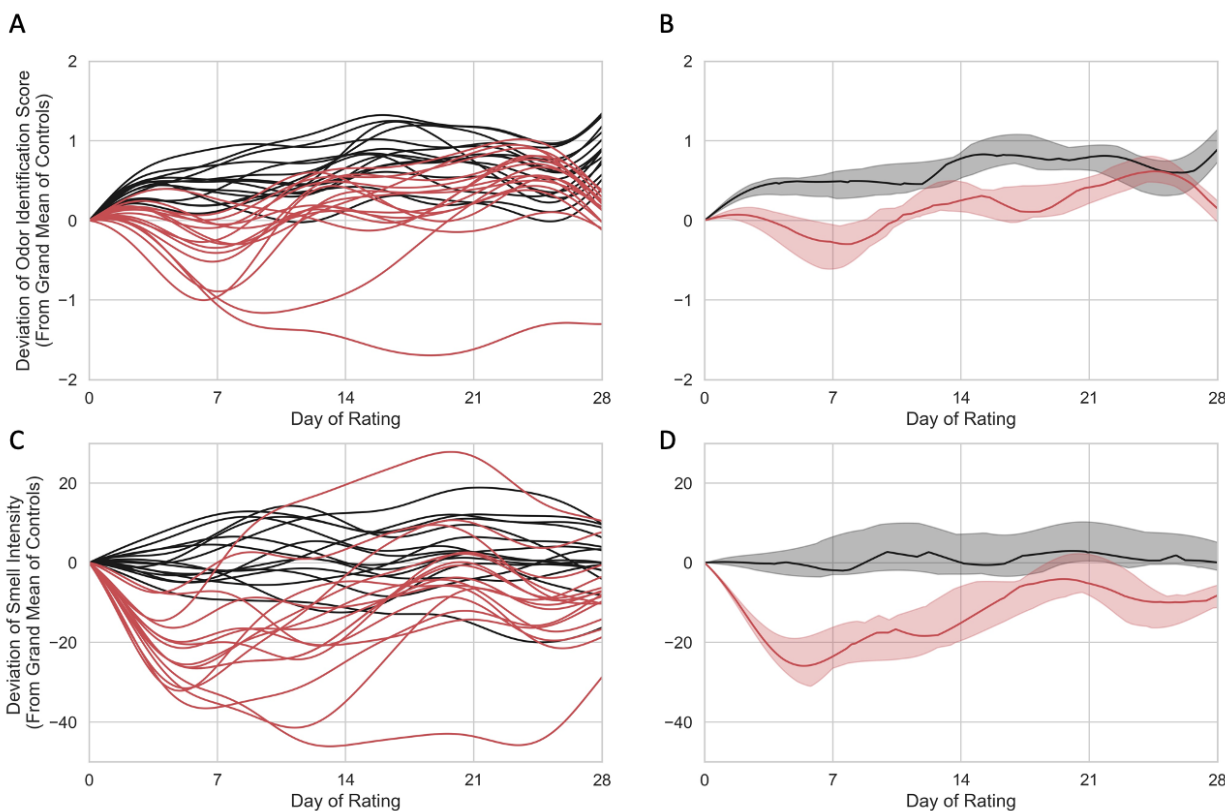


Figure 2. Individual (left) and group level (right) Gaussian Process Regression models for 15 controls (red) and 15 COVID-19 cases (black) who entered the study on or before day 10 of their infection. For cases, Day of Rating is centered on estimated day of infection. Odor identification scores (top) and odor intensity ratings (bottom) are shown as deviation scores calculated from a grand mean of controls across time. **(A)** Individual odor identification data in a Gaussian Process Regression model of deviation scores from 15 COVID-19 cases (red) and 15 controls (black). **(B)** Group level odor identification data in a Gaussian Process Regression model for COVID-19 cases (red) and controls (black). **(C)** Individual deviation scores for smell intensity ratings for 15 COVID-19 cases (red) and 15 controls. **(D)** Group level smell intensity data in a Gaussian Process Regression model for 15 COVID-19 cases (red) and 15 controls (black). In panels B and D, the solid line represents the group median, and the shaded region shows the interquartile range. Panels A and C show maximal loss roughly around day. Panel B shows some evidence of a learning effect for the OdorID task in the controls; no evidence of learning is seen for controls in the intensity task shown in panel D.

349 **3.2 Demographics of participants in case control series**

350 Given the maximal deviation in smell early in acute illness, we chose to explore the
351 specific changes in multiple chemosensory modalities in the handful of cases who
352 enrolled *prior* to onset of acute illness in greater detail. Demographics of four COVID-19
353 cases and four matched controls are summarized in Table 1. The mean age of
354 participants with COVID-19 was 26 years of age (range 21-43) and the mean age of
355 matched controls was 25.5 years of age (range 22-38).

356

357 **3.3 Controls**

358 Throughout the course of the study, controls exhibited normal function for smell,
359 taste, and chemesthesis (Figure 3). Specifically, mean scores on odor identification,
360 orthonasal smell intensity ratings, and ratings of perceived nasal blockage were
361 relatively constant across days, although some participants were more variable than
362 others. A few patterns deserve comment. For example, with Subject 1 we see a clear
363 learning effect for odor identification where they became better at the task over time
364 (Figure 3). Separately, controls may vary in perceived nasal blockage from day to day.
365 For example, with Subject 3, we see a slight decrease in orthonasal smell intensity and a
366 slight increase in nasal blockage in the last four days of testing (Figure 3). Such mild
367 transient hyposmia would be wholly consistent with conductive smell loss due to nasal
368 blockage typically seen with allergies or the common cold. Similarly, for taste, ratings of
369 sweetness and sourness remained relatively constant throughout the course of the study
370 for controls, although ratings were noisier for some participants than others. One rating
371 for Subject 22 deserves comment: in the third week of testing, we observed a sharp drop
372 in sour taste intensity and sharp increase in burn intensity, but only for a single day
373 (Figure 3). While we cannot be sure, we suspect they simply picked the wrong cup from
374 the bag of samples, as Sour Cherry jellybeans should not burn and should be sour.
375 Subject 22 may have misread the 3-digit blinding code, or our research team may have
376 mislabeled the cup. Either way, this single datum does not alter their overall pattern.
377 Also, we note Subject 22 tends to give Cinnamon jellybeans a relatively high amount of
378 oral burn relative to the other participants; we might speculate they eat spicy food
379 infrequently, as large variation in burn ratings due to dietary exposure is very common
380 (e.g., [44-47]).

381 In summary, daily data from these four *controls* suggest individuals without
382 COVID-19 are able to correctly identify the odors from the ScentCheckPro cards, and to
383 consistently rate the various attributes from the cards (orthonasal intensity) and the
384 jellybeans (taste, burn). While some minor variation is observed over time and across
385 participants, the ratings are generally stable over the study period, in sharp contrast to
386 the COVID-19+ cases (Figure 4).
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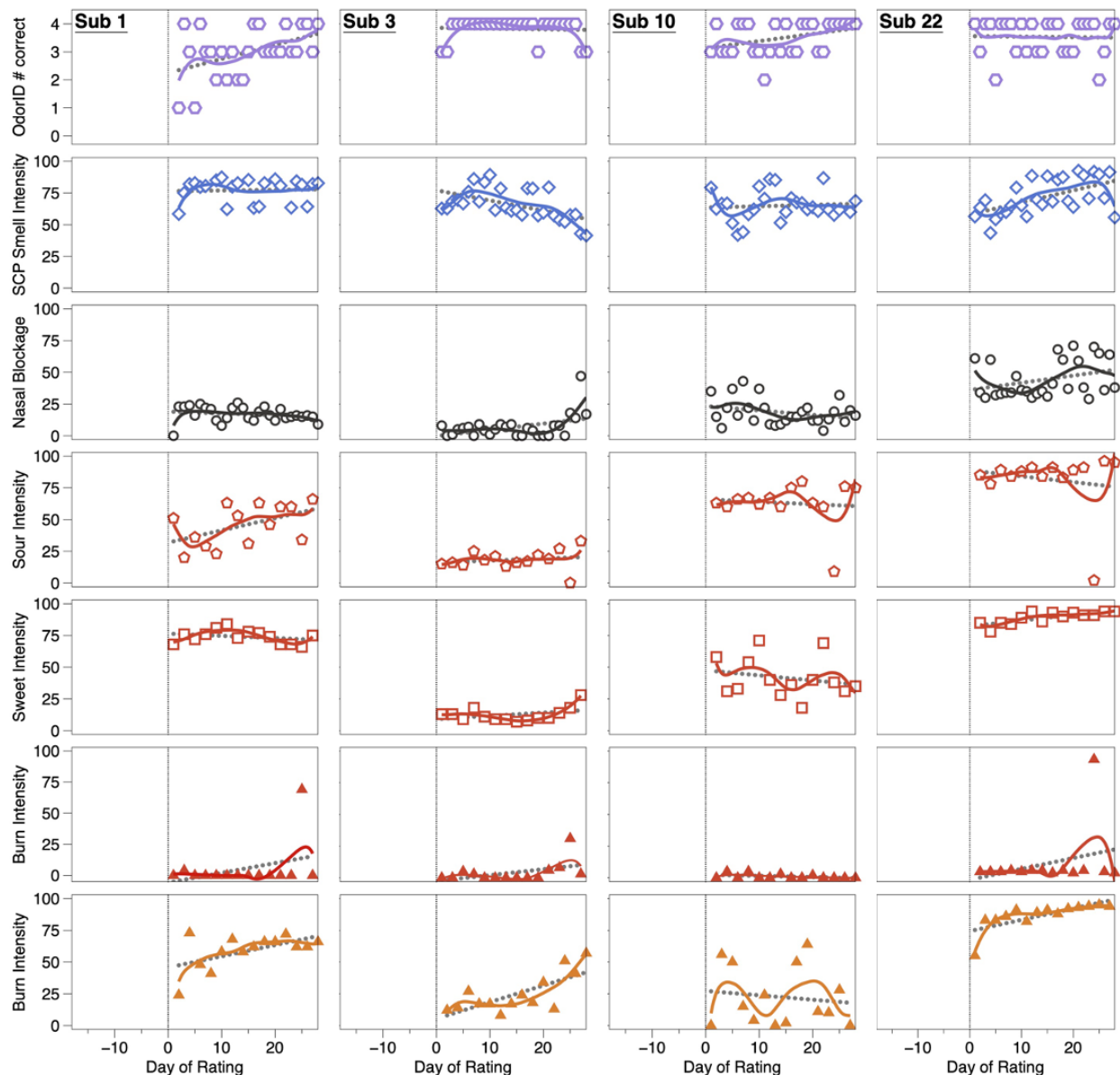


Figure 3: OdorID scores, and intensity ratings from matched controls over time. These participants (Subjects 1, 3, 10, and 22) show generally consistent ratings across the study. To help illustrate uniformity across the observation period, solid (colored) lines were fit via LOESS regression and dotted lines (gray) were fit via linear regression. A vertical line on Day 0 highlights the start of the 28-day study. Open hexagons (1st row) are the number correct on a ScentCheckPro card, while open diamonds (2nd row) are the mean daily smell intensity ratings from the same card. Open circles (3rd row) reflect ratings of perceived nasal blockage. Red symbols (rows 4, 5, and 6) reflect specific quality ratings from Sour Cherry jellybeans collected with a pinched nose. Orange triangles (row 7) indicate burn ratings from Cinnamon jellybeans collected with a pinched nose.

388 **3.4 Cases**

389 All four cases converted from being close contacts to being COVID-19+ while
390 enrolled in the study, enabling visualization of changes in their responses over time
391 (Figure 4). For brevity, we only highlight a few notable points here and a more detailed
392 account is provided in the supplemental materials. When smell loss was observed, it was
393 largely unrelated to nasal blockage, consistent with prior reports [4-7, 10] and the idea
394 that COVID-19-associated smell loss arises from ACE2 receptor-mediated disruption of
395 the olfactory epithelium, rather than the conductive losses typically seen with the
396 common cold. Regarding chemesthesis, the lack of burn from the Sour Cherry jellybeans
397 served as a negative control, suggesting participants were successful in discriminating
398 between burn from a Cinnamon jellybean and a lack of burn from a Sour Cherry
399 jellybean. From this, we can assume changes in burn observed here for the Cinnamon
400 jellybeans was not merely a failure to understand the task.

401 **3.4.1 Subject 35**

402 Symptoms for Subject 35 included cough, runny nose/congestion, sore throat,
403 and headache. Odor intensity ratings dropped through day 15 before recovering; her
404 OdorID scores showed a similar pattern, but her data were noisier given the learning
405 effect noted previously. Her nasal blockage resolved around Day 8, but she still showed
406 impaired smell. Sourness ratings declined until ~Day 15 while sweetness declined until
407 ~Day 6, before each began to recover. This was not merely a taste/flavor semantic
408 confusion, as ratings were obtained while wearing nose clips. Her data also suggest
409 sweet and sour taste are each transiently affected with an active COVID-19 infection,
410 and loss and recovery may be dyssynchronous (i.e., sweetness did not recover as swiftly
411 as sourness). Separately, she showed large changes in burn from Cinnamon jellybeans,
412 suggesting oral chemesthesis is affected by COVID-19 infection, and this may be
413 dyssynchronous from altered taste or smell function.

414 **3.4.2 Subject 45**

415 Subject 45 reported no symptoms despite becoming an active COVID-19 case
416 while enrolled. Notably, despite being nominally asymptomatic, she clearly showed
417 altered smell function that was reflected in both in OdorID performance and orthonasal
418 intensity ratings, with maximal loss around Day 5. This highlights that some COVID-
419 19+ individuals may be unaware of altered smell function, consistent with meta-analysis

420 by Hannum and colleagues [8, 48]. As above, this transient disruption could not be
421 attributed to nasal blockage. Regarding taste ratings, she also exhibited temporal
422 dyssynchrony for different qualities. For the Cinnamon jellybeans, she showed a
423 monotonic increase in burn over ~3 weeks, before showing a small drop at the end of
424 the study. Elsewhere, some patients reported an increase in the ability to feel sensations
425 in the mouth (including burning) during recovery from COVID-19 [49], so her temporal
426 pattern may potentially reflect acute hypoalgesia, followed by hyperalgesia, before
427 eventually returning to normal. In any case, her data support the idea that oral
428 chemesthesis can be affected acutely by SARS-CoV-2 infection.

429 **3.4.3 Subject 62**

430 Like Subject 45, Subject 62 failed to report any symptoms, but unlike the prior
431 cases, his orthonasal intensity ratings and OdorID performance remained relatively
432 constant over time, and nasal blockage was generally low. This highlights that while
433 many individuals with COVID-19 experience smell loss, some do not (e.g., [8, 48]).
434 Regarding taste, noisy data preclude any strong conclusions, but tentatively, it seems he
435 may have experienced large changes in both sweetness and sourness. That said, there is
436 a sharp drop in sour taste intensity and sharp increase in burn intensity on two separate
437 days (Figure 4). We suspect Subject 62 may have simply tasted the wrong sample on
438 these days, as Sour Cherry jellybeans should be sour without any burn. Still, despite
439 these caveats, his panel plots also suggest he experienced acute changes in oral
440 chemesthesis without concomitant smell loss. If true, this would highlight that
441 mechanisms of loss across all three chemosensory modalities are likely to be distinct.

442 **3.4.3 Subject 63**

443 Subject 63 enrolled 2 weeks before becoming a case. This greatly exceeds the
444 expected incubation period (5 to 7 days) [37, 50], so we contacted her via email and she
445 reported a second exposure to a COVID-19+ individual. Thus, we assume she became ill
446 upon her second exposure rather than the initial exposure that caused her to enroll. Her
447 data reveal changes in smell, taste, and chemesthesis. However, the 28-day observation
448 period only captures initial illness without recovery, as she initially enrolled after an
449 exposure that did not cause infection. Consistent with this interpretation, she did not
450 report any symptoms for the first 2 weeks, before reporting many symptoms (sore
451 throat, fever or chills, dry cough, body aches, fatigue, diarrhea, nausea or vomiting,

452 headache, and dry cough). Notably, her mean orthonasal ratings began to decline
453 somewhat a few days before the estimated day of infection, in the absence of nasal
454 blockage. Further, her intensity data suggest she experienced hyposmia, rather than full
455 anosmia, so it is not surprising that her OdorID performance remained relatively
456 constant across the study period. This suggests rated smell intensity might provide more
457 nuanced assessment of smell function versus odor identification (as discussed above).
458 Her taste data were somewhat noisy, but it seems sourness may have been more affected
459 than sweetness. Tentatively, her plots suggest she lost taste function in a quality specific
460 manner, along with partial smell loss and loss of oral chemesthesis, with staggered
461 timing of each.
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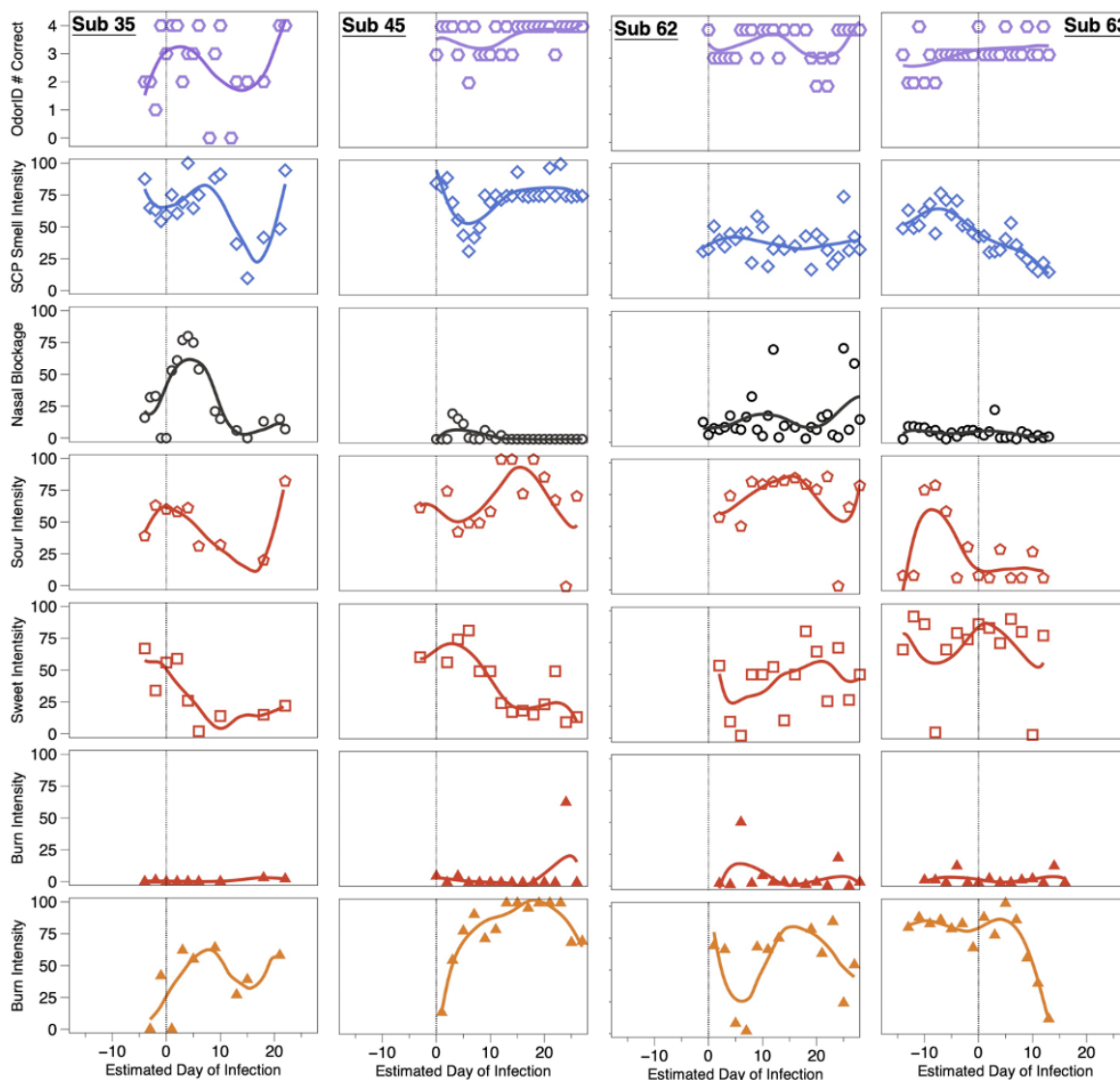


Figure 4: OdorID scores and VAS ratings from four COVID-19 positive individuals. COVID-19 cases (subjects 35, 45, 62, and 63) tended to show transient alterations of smell, taste, and/or chemesthesis during the observation period. To help illustrate uniformity across the study days, solid lines were fit via LOESS regression. A vertical line at Day 0 was added to highlight the estimated day of infection. Symbols and rows match those used in Figure 3: row 1 is daily number correct, and row 2 is orthonasal intensity of four scratch-n-sniff patches from a ScentCheckPro card, row 3 is ratings of perceived nasal blockage, rows 4-6 are sour, sweet, and burn ratings for Sour Cherry jellybeans with the nose pinched, and row 7 is burn for Cinnamon jellybeans with the nose pinched.

464 **3.4 General Discussion**

465 By using intensive longitudinal data collected daily for 28 days, we were able to
466 assess COVID-19-associated changes over time. Further, by leveraging enrollment of
467 individuals upon exposure rather than waiting until they were already ill, we were able
468 to create a small case control series that captured both initial loss and recovery. We can
469 draw several conclusions from the results described here. First, number correct on a
470 short odor identification task may potentially miss dysfunction in hyposmic individuals
471 who have clearly depressed perceived intensity, but who still retain enough function to
472 successfully complete an identification task. Longer tests, such as the 40-question
473 University of Pennsylvania Smell Identification Test (Sensonics), may be better at
474 differentiating these levels of smell loss, though their greater cost and time-to-complete
475 make them impractical for this type of intensive longitudinal study. Second, we find
476 smell loss appears maximal around Day 5, but this varies somewhat across participants.
477 Third, COVID-19 related chemosensory dysfunction can manifest as reduced oral
478 chemesthesis, reduced taste, and/or reduced orthonasal smell with little to no nasal
479 blockage, with temporally staggered onset and time course. Collectively, these results,
480 although limited in scope, extend prior work by providing direct assessment of multiple
481 sensory modalities repeatedly over time using stable, commercially-available products
482 as stimuli.

483 A strength of this study involved the use of commercial stimuli like jellybeans to
484 collect ratings while the nose was blocked with nose clips. First, because of their glazed
485 candy shell, jellybeans have little to no orthonasal scent and the odorant is only released
486 from the food matrix upon chewing. For our purpose, this gave us a convenience way to
487 deliver consistent shelf stable stimuli safely during a pandemic. All jellybeans of the
488 same flavor came from the same lot; given routine quality control measures in
489 commercial manufacturing, we are confident participants received consistent stimuli
490 even if we do not know the exact formulation of the jellybeans. Second, our use of
491 similarly colored jellybeans with different flavors minimizes potential biases
492 participants may have from prior experience or knowledge with other foods (e.g., this is
493 a lemon, and I know lemons tend to be sour [51]). When this lack of expectation is
494 coupled with the use of nose clips, we believe the data shown here reflect true
495 differences in taste and chemesthesis and not merely they result of a flavor taste

496 confusion. Other studies have also reported loss in function when using taste stimuli
497 that do not have an olfactory component [52].

498 Currently, there is disagreement regarding whether different types of taste cells
499 are differentially affected by SARS-CoV-2 infection. Indeed, several studies have showed
500 quality-specific differences (i.e., [27, 43, 53-56]), while others have not (i.e., [18, 40-42,
501 57-61]). Here, sourness and sweetness from consistent stimuli were lost and recovered
502 at similar rates for some participants, but this was not uniformly true. This implies
503 specific taste qualities may recover at different rates, although additional work is needed
504 to confirm this. Also, our data indicate taste qualities may be differentially affected,
505 consistent with other reports [19, 62]. While the specific mechanisms underlying taste
506 dysfunction with SARS-CoV-2 infection remain unclear, several mechanisms have been
507 proposed. For example, ACE2 could allow for the infection of Type 2 (sweet, bitter and
508 umami) taste receptor cells by SARS-CoV-2. Saliva could affect gustation as salivary
509 glands express high levels of ACE2 and TMPRSS2. SARS-CoV-2 may even affect the
510 central nervous system, as the virus has been detected in the cerebrospinal fluid [63-67].

511 Anecdotal reports and preliminary psychophysics suggest loss of chemesthesis
512 with SARS-CoV-2 infection is real [10, 23, 30, 68]. We extend prior reports here by
513 showing oral chemesthesis, not just nasal chemesthesis, may be altered by COVID-19.
514 This effect appears to be highly transitory, which could cause underreporting, especially
515 when assessment occurs multiple days after illness has started. Definitionally,
516 chemesthesis includes both thermal and tactile percepts like warming, cooling, and
517 buzzing, and these sensations occur via distinct and specialized receptors. Even if
518 focusing solely on burn, multiple receptors like TRPV1 and TRPA1 are involved. Despite
519 multiple advantages of commercial stimuli (high consistency, low cost, shelf stability,
520 etc.), use of commercial jellybeans here limits interpretation somewhat. That is,
521 cinnamon flavored candies presumably contain cinnamaldehyde, a well-known TRPA1
522 agonist [69, 70]. However, we cannot rule out whether they contain capsaicin (or
523 another TRPV1 agonist), as food labeling laws in the United States allow manufacturers
524 to declare such ingredients as natural or artificial flavors on the package without being
525 more specific, so we cannot make strong inferences about which specific chemesthetic
526 mechanisms might be affected by SARS-CoV-2 infection. Nonetheless, present data
527 extend prior work by clearly showing oral burn can be transiently affected by COVID-19.

528 **4. Limitations and Conclusions**

529 Our data suggest intensive cohort study designs are imperative for understanding
530 and tracking symptoms of COVID-19 patients. Through intensive daily ratings we were
531 able to examine and follow participants from initial exposure to catch symptoms as the
532 emerged, allowing for the visualization of symptom onset, not just recovery. Thus, a
533 strength of this study is the nature of the cohort examined, and it exemplifies a need for
534 more cohort studies to catch patients before and during the most infectious period of
535 their illness. A few limitations should be briefly noted. First, all sensory testing in this
536 study was performed remotely at home, due to pandemic related safety restrictions
537 meant to protect both participants and our research team. Because participants made
538 daily ratings at their leisure without direct supervision, we cannot obtain the same level
539 of stimulus control we would have with an in-person lab-based study. Also, while all
540 study materials were clearly labeled, we cannot preclude whether participants may have
541 occasionally chosen the incorrect blinding codes on some days or that our staff might
542 have mislabeled these samples. Further, we should note the commercial ScentCheckPro
543 scratch-n-sniff cards used here were not validated as a clinical smell test; also, they were
544 originally designed as an odor identification task, rather than a smell intensity task, so
545 we cannot assume all stimulus concentrations were precisely matched for intensity. This
546 concern is partially offset however by the randomization of odorants on any given card,
547 and the use of daily means. Finally, we fully acknowledge this study had a very small
548 number of participants (albeit with many data points per participant), so present
549 findings should be taken as tentative until confirmed. Attempts to generalize the
550 incidence or prevalence of distinct types of loss or dysfunction should not be made from
551 this small case-control series. Despite these limitations, this dataset is highly unique in
552 that it captures changes very early in COVID-19 illness with intensive daily sampling.

553 Here, we extend current knowledge by showing oral chemesthesis, taste, and/or
554 orthonasal smell function can each be acutely affected by COVID-19. Further, we find
555 such disruption may be dyssynchronous for the different chemical senses, with differing
556 rates of loss and recovery across modalities and individuals. Also, odor intensity ratings
557 revealed potentially hyposmic individuals who might be missed if smell function is only
558 assessed via odor identification scores. Finally, disrupted chemosensation, especially for

559 chemesthesis, appears to be highly transient, suggesting studies that collect a single
560 snapshot in time, often retrospectively, may underestimate the true prevalence of loss.

561

562 **5. Acknowledgements**

563 The authors wish to thank our participants for their time and critical contribution to this
564 work.

565

566 **6. Funding / COI disclosure**

567 EMW, SM, JEH and RCG each receive partial salary support from a competitive grant

568 [1U01DC019573] from the National Institutes of Deafness and Communications

569 Disorders (NIDCD); JEH also receives salary support from the United States

570 Department of Agriculture (USDA) via the National Institute of Food and Agriculture

571 (NIFA) Hatch Act Appropriations [Project PENo4708 and Accession # 1019852]. Drs.

572 Munger, Hayes, and Gerkin each hold equity in Redolynt, LLC, which they co-founded

573 in 2021. This financial interest has been reviewed by the Individual Conflict of Interest

574 Committee at each of their respective universities and is being actively being managed

575 by each university. None of the other authors have any conflicts to disclose.

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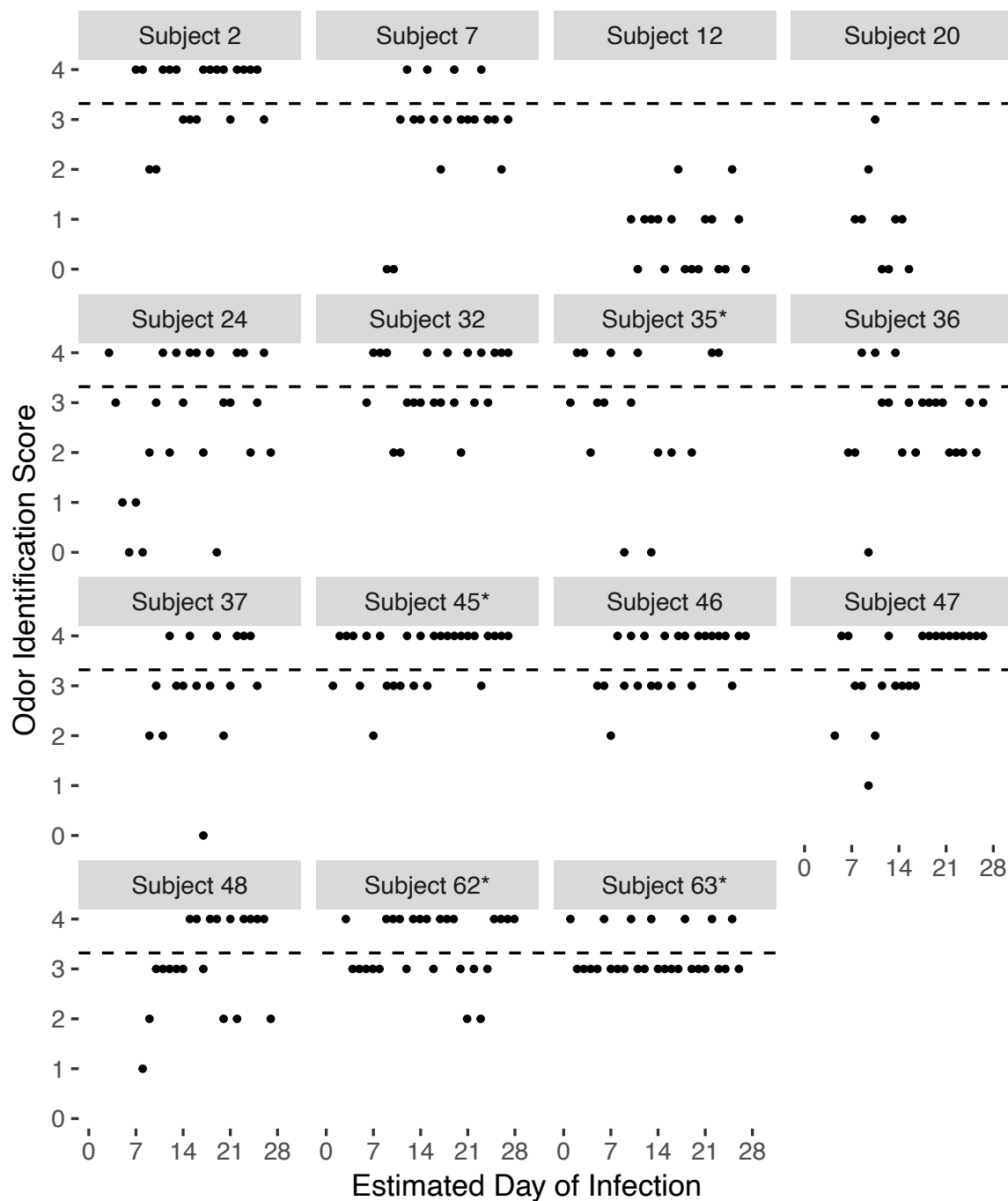
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578 **Supplemental Materials**

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580 *Supplemental Figure 1*

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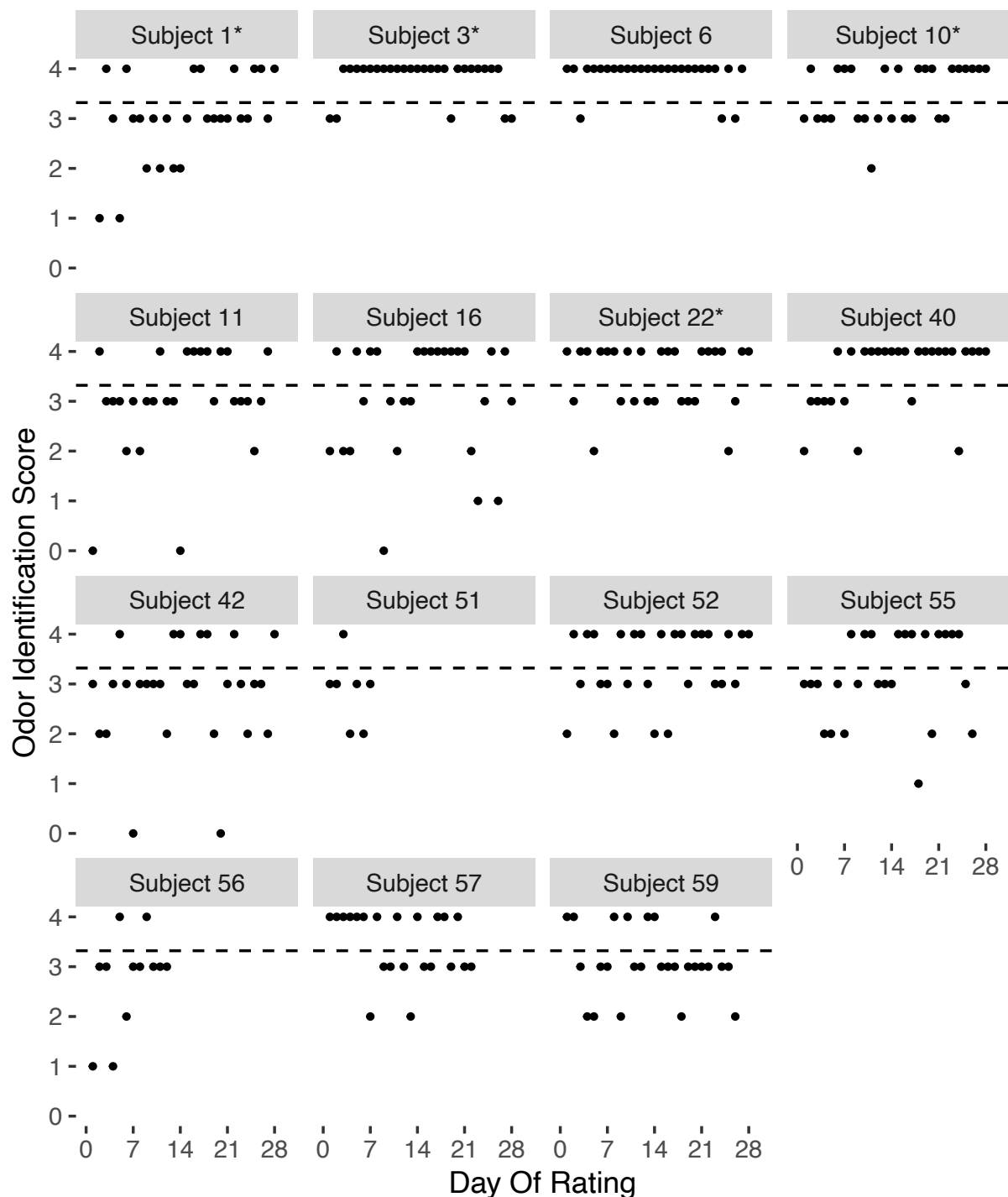
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583 Raw daily odor identification scores from the ScentCheckPro cards over time for the

584 COVID-19 cases (n=15) who entered the study on or before day 10 of their infection.

585 *Supplemental Figure 2*

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588 Raw daily odor identification scores from the ScentCheckPro cards over time for the 15

589 controls.

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591 **Supplemental narrative and discussion of symptoms for the 4 cases**

592 ***Subject 35***

593 Subject 35 became a case during the study, enabling visualization of the falling
594 and rising phases of her responses (see Figure 4). Her symptoms included cough, runny
595 nose/congestion, sore throat, and headache. Regarding orthonasal scratch-n-sniff
596 intensity ratings, daily means decreased through day 15 before recovering. OdorID
597 scores showed a similar pattern, but data were noisier given the learning effect
598 described above. Together, this suggests her orthonasal olfaction was transiently
599 affected during active COVID-19 infection, as expected (e.g., [19, 71, 72]). Notably, she
600 showed impaired smell even after nasal blockage resolved around Day 8, and her
601 maximal smell loss and maximal nasal blockage were dyssynchronous. This is consistent
602 with other reports showing COVID-19 smell loss is not associated with nasal blockage
603 [4-7, 10], presumably because COVID-19-associated loss arises from ACE2 receptor-
604 mediated disruption of the olfactory epithelium, and not the conductive losses seen with
605 the common cold.

606 Her sourness ratings from the Sour Cherry jellybean declined until ~Day 15,
607 when ratings began to increase, while sweetness declined until ~Day 6, before beginning
608 to recover. The decline and subsequent rise of sweet and sour taste likely signifies
609 normal recovery, although Figure 4 also shows dyssynchronous recovery of these tastes
610 (i.e., sweetness did not recover as swiftly as sourness). These data indicate sweet and
611 sour taste are each transiently affected with an active COVID-19 infection, and this was
612 *not* merely a taste/flavor semantic confusion, as ratings were obtained while wearing
613 nose clips. Subject 35 also showed large changes in burn from the Cinnamon jellybeans,
614 suggesting oral chemesthesis is affected by COVID-19. The lack of burn from the Sour
615 Cherry jellybeans serves as a negative control, indicating she was successful in
616 discriminating between burn from a Cinnamon jellybean and a lack of burn from a Sour
617 Cherry jellybean (a pattern also seen in the three other cases shown in Figure 4). These
618 data indicate perception of oral burn can be affected by an active COVID-19 infection
619 dyssynchronously from taste or smell. While patient anecdotes (including social media
620 posts) have previously suggested nasal and/or oral chemesthesis may be affected by
621 SARS-CoV-2 infection [39, 49, 73], the daily assessment and prospective design used
622 here provide quantitative evidence of altered oral chemesthesis with COVID-19.

623 **Subject 45**

624 Subject 45 converted from being a close contact to an active COVID-19 case
625 during the study, but unlike Subject 35, Subject 45 never reported any symptoms during
626 her infection. Yet, despite being nominally asymptomatic, she still showed a clear drop
627 in both OdorID performance and ratings of orthonasal intensity around Day 5 (with a
628 bigger effect size for intensity). This highlights that some individuals infected with
629 SARS-CoV-2 may be unaware of the impact on their sensory abilities, consistent with
630 recent meta-analysis by Hannum and colleagues [8, 48]. Nor was this transient
631 disruption in smell due to nasal blockage (as reported elsewhere [4-7, 10]). As her
632 infection progressed, sourness from the Sour Cherry jellybean was variable, and
633 sweetness from this jellybean steadily declined over the course of infection, again
634 indicative of temporal dyssynchrony for different taste qualities. In contrast to burn
635 rating from the Sour Cherry jellybean (which stayed near 0 across the study period, as
636 expected), burn from the Cinnamon jellybean steadily increased in a monotonic fashion
637 until a small drop was observed at the end of the study. Taken together with data from
638 Subject 35, this indicates suggests oral chemesthesis is altered by active SARS-CoV-2
639 infection. Another study noted that during recovery from COVID-19, some patients
640 report an increase in the ability to feel sensations in the mouth, including burning [49].

641 **Subject 62**

642 Subject 62's infection began 1 day before enrollment. Like Subject 45, he failed to
643 self-report any symptoms, but unlike Subjects 35 and 45, his orthonasal intensity
644 ratings and OdorID performance remained relatively constant throughout the study
645 period, and his nasal blockage was generally low – while many individuals experience
646 smell loss with COVID-19, some do not (e.g., [8, 48]). Regarding taste, noisy data make
647 it hard to draw any strong conclusions, but it still seems he may have experienced
648 substantial changes in sour and sweet taste. Regarding burn, he rated the burn from
649 Sour Cherry jellybeans near zero for the entire study, suggesting he successfully
650 distinguished burn from the Cinnamon jellybean from the lack of burn from the Sour
651 Cherry jellybean (like the other cases). Two other values merit comment: in the 1st and
652 3rd week of testing, a sharp drop in sour taste intensity and sharp increase in burn
653 intensity can be seen on two separate days; we suspect he may have misread the
654 blinding codes, tasting the wrong sample on these days, as Sour Cherry jellybeans

655 should be sour without any burn. Still, despite noise in his ratings, his panel plots for
656 burn suggest he experienced transient changes in oral chemesthesis. If this case did in
657 fact experience altered burn and altered taste without concomitant smell loss, this
658 would emphasize that mechanisms of loss across all three modalities are distinct, with
659 the caveat that the noise in these data should temper any strong inferences.

660 ***Subject 63***

661 Subject 63 enrolled 2 weeks days before becoming a case. Because this greatly
662 exceeds the expected incubation period of 5 to 7 days [37, 50], our study team contacted
663 her via email. At that point, she reported a second exposure to an individual with
664 COVID-19 – we assume this second exposure was the source of the infection
665 documented here. Her data reveals changes in smell, taste, and chemesthesis as she
666 transitioned from being a close contact to being a case, but the observation period only
667 captures her initial illness without any recovery as she had enrolled after her first
668 exposure that did not cause an infection. Consistent with this interpretation, she did not
669 report any symptoms for the first 2 weeks, but then began reporting many symptoms
670 (sore throat, fever or chills, dry cough, body aches, fatigue, diarrhea, nausea or
671 vomiting, headache, and dry cough). Notably, her mean orthonasal ratings began to
672 decline somewhat a few days before the estimated day of infection, but she indicated
673 little to no nasal blockage, as expected [4-7, 10]. Also, her intensity ratings suggest she
674 experienced hyposmia, rather than full anosmia, so it is unsurprising that her OdorID
675 performance remained relatively constant across the study period, with some evidence
676 of a slight learning effect near the beginning of the study. As discussed previously, this
677 suggests rated smell intensity might provide more nuanced assessment of smell function
678 versus odor identification. We have no obvious explanation for her unexpectedly low
679 sourness ratings on the first two days of the study. Still, if her peak ratings during this
680 initial (uninfected) period are tentatively treated as a baseline, we see a subsequent
681 decline in sourness around the time her other symptoms appeared. For the rest of the
682 study, her sour ratings remained relatively depressed, at least relative to the maximal
683 values she reported pre-infection. In contrast, sweetness, while noisy, appeared more
684 constant across the entire study. Tentatively, these plots suggest Subject 63 lost some
685 taste function in a quality specific manner, as well as partial smell loss and loss of oral
686 chemesthesis, with staggered timing of each, during her infection.

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