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Time–Intensity Ratings of Nasal Irritation from Carbon Dioxide

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Abstract

In three experiments, subjects tracked intensity of nasal irritation during sustained presentation of carbon dioxide in the nose. Experiment 1 showed that: (i) functions of peak intensity vs. concentration and latency to first non-zero ratings agreed with published literature, thereby supporting the validity of the technique; (ii) on average, rated intensity peaked ~3–4 s after stimulus-onset and began to fall rapidly thereafter; (iii) large and stable individual differences in temporal dynamics occurred. Experiment 2 replicated experiment 1 with some methodological refinements. In experiment 3, application of the technique revealed that the nose regains sensitivity with very brief (300–500 ms) interruptions in presentation of carbon dioxide. In short: (i) the method developed here provides a temporally fine-grained tool to study the time-course of nasal irritation, and (ii) nasal irritation from carbon dioxide shows relatively rapid temporal dynamics.

Key words: chemesthesis, desensitization, perceptual dynamics, trigeminal

Introduction

Subjects have rated nasal irritation from continuous presentation of volatile chemicals at discrete, successive time-points (Elsberg *et al.*, 1934; Cain *et al.*, 1986). Irritation may grow over several seconds to many minutes, depending on the chemical, concentration and method of stimulation. After peaking, irritation fades slowly, relative to odor, which is consistent with the notion that pungency helps protect organisms from extended exposure to harmful vapors (Cain, 1990).

Carbon dioxide (CO_2) may prove an exception. For example, recordings from neurons in the brainstem of the rat during 8 s presentations of CO_2 reveal that almost all units responded vigorously for ~2 s, but most activity diminished greatly well before stimulus-offset (Peppel and Anton, 1993). Mustard oil, on the other hand, elicited sustained responses. Further, results from psychophysical studies suggest that pungency from CO_2 builds and fades within a few seconds (e.g. Anton *et al.*, 1992). No study has examined the time-course of nasal irritation from sustained presentation of CO_2 with formal time–intensity ratings.

The current studies provide the first formal time–intensity ratings of nasal irritation from CO_2. Subjects tracked intensity of nasal irritation during continuous (7–10 s) presentation of CO_2 (0–70%). We examined the effects of concentration, since pungency from some chemicals tends to build and fade more quickly as concentration increases (Elsberg *et al.*, 1934; Cain *et al.*, 1986). We also examined the degree and stability (over three sessions) of individual differences in temporal dynamics. The paucity of data on individual differences in time-course of nasal irritation, indeed, the paucity of data on differences in nasal irritation in general (Shusterman, 2002), prompted an emphasis on individual differences. Finally, we examined the rate at which the nose recovers sensitivity with brief, i.e. 500 ms or less, interruptions in stimulation. Although studies have examined the effects of longer (2–90 s) intervals between presentations of CO_2 (Hummel *et al.*, 1994, 1996; Hummel and Kobal, 1999), no one has examined the earliest parts of the recovery curve.

If nasal irritation from CO_2 does wax and wane within a few seconds, single ratings at successive time-points might lack sufficient temporal resolution to characterize time–intensity profiles. Methods in which subjects continuously track perceived intensity exist (Lawless and Heyman, 1998), and have been used to track chemical irritation over relatively long periods of time (Hudnell *et al.*, 1992; Hemple-Jørgensen *et al.*, 1999). However, these techniques have seen relatively little use in the study of nasal irritation, particularly with a focus on short durations. Subjects have tracked nasal irritation from an initial, 200 ms presentation of a single concentration of nicotine (Hummel *et al.*, 1992). On average, ratings of stinging began 2.3 s after stimulus-onset, peaked at 4.6 s and ended at 11.1 s. These data suggest that subjects might be able to track relatively rapid changes in nasal irritation, but the fact the authors used only one concentration makes it difficult to evaluate the validity of the ratings. Since the current experiments employed more than one concentration of CO_2, they allowed comparisons with psychophysical functions and functions of detection-latency vs. concentration. Hence, the current experiments examined the validity of temporally fine-grained measurements of nasal irritation in a way that no one has previously attempted.

Experiment 1

Purpose

Study 1 provides the first data on time-intensity profiles for nasal irritation from CO_2. Subjects continuously tracked intensity for several concentrations. To assess stability of individual differences in time-course of rated intensity, selected subjects returned for multiple sessions.

Materials and methods

Apparatus

An air-dilution olfactometer (OMb6, Burghart Instruments, Wedel, Germany) delivered stimuli. Devices of this type have been described elsewhere (Kobal, 1985; Kobal and Hummel, 1988). Between stimulus-presentations, the device delivered, birhinally, a steady (5 l/min) stream of warm (38°C), humidified (97% RH) air (control-flow). During presentations, a mixture of medical grade CO_2 and air (38°C) replaced the control-flow (via vacuum-switching). One aspect of the functioning of the device deserves note: During 7 s presentations of CO_2, flow rates began to drop during the sixth second. By the end of the seventh second, flows dropped from 5 l/min to ~4 l/min. This occurred because CO_2 has greater density than air, and the mass flow controllers that regulate flow through the olfactometer began to compensate.

Output-ports of the olfactometer consisted of 3 cm lengths of Teflon tubing (1/16 in. i.d., 1/8 in. o.d.) inserted into Teflon nosepieces. The nosepieces fit loosely over the tubing (tubing ended ~1.0 mm before the end of the nosepieces). A flow-meter (Gillibrator 2; Gillian Instrument Corp., Wayne, NJ) and a CO_2-monitor (GD444; CEA Instruments, Emerson, NJ) verified key stimulus-parameters daily.

Subjects rated intensity by moving a slider (~6 cm of travel) that modulated a voltage-signal to a multifunction data acquisition card (PCI-6023E; National Instruments, Austin, TX). Software linearized the analog voltage-signal with respect to the position of the slider and continuously recorded the linearized signal at a rate of ~12 readings/s. A counter-timer on the same multifunction card monitored timing of voltage-readings and stimulus-events. At the end of a trial, ratings were saved in 200 ms bins, i.e. the final resolution was 5 ratings/s. A digital channel on the same card provided trigger-signals for outputs to both nostrils. Another routine superimposed a blue bar, the height of which was proportional to the linearized voltage from the slider) on a labeled magnitude scale, or LMS (Green *et al.*, 1996), that appeared on a monitor positioned in front of the subject.

Subjects

Sixteen (7 female) healthy adults participated. University students (ages 18–26 years) comprised the majority; one 48 year old male, and one 50 year old female, and an author (PW, designated S14 in Figure 3) comprised the remainder. The author was blind to the order of the stimuli (NB: no group analyses differed substantially with the author excluded, and the author did not show a unique response pattern). Subjects were assigned numbers according to order of participation.

Stimuli

Subjects received four concentrations of CO_2: 0% (to prevent anticipation and determine the effects of stimulus-switching without chemical stimulation), 35.5% (above localization threshold for a 500 ms stimulus for most subjects tested in this laboratory (Wise *et al.*, 2002), 53% (well above threshold) and 70% (clearly painful).

Training

After practicing with the slider, subjects received instructions on the LMS similar to those used previously (Green *et al.*, 1996). However, subjects were asked to rate sensations relative to the strongest imaginable sensation rather than the strongest previously experienced sensation (Bartoshuk *et al.*, 2002). Instructions identified the stimulus and included the example of holding the nose over a freshly opened can of soda. Instructions stated that sensations might include, but might not be limited to, tickling, tingling, burning or stinging. In part, the range of qualities CO_2 can elicit prompted the use of the LMS, which can allow subjects to rate the magnitude of different sensory qualities on a common scale (Green *et al.*, 1996).

Subjects were then acclimated to the olfactometer. Each subject inserted the nosepieces firmly enough to form seals at the nostrils. Subjects were instructed to perform velopharyngeal closure, i.e. to breath only through the mouth (Kobal and Hummel, 1991). The base of the nosepieces did not form a seal with the output port of the olfactometer, allowing flow to escape from the nose. We did not verify velopharyngeal closure, but instructions had subjects rate only sensations in the nose (not in the throat or mouth, in case stimuli reached beyond the nasal cavity). Finally, subjects completed 6–10 practice trials (random concentrations). Subjects remained still during trials and continuously tracked any increases or decreases in nasal sensation. In total, training lasted ~30 min.

Procedure

Subjects indicated readiness with a keystroke to begin each trial. After 1 s, the LMS appeared with the blue bar set at zero, or 'no sensation'. From that point on, subjects continuously tracked nasal sensation for 13 s. Control-flow continued for 3 s, was replaced by a dilution of CO_2 for 7 s, then switched back to the control flow for 3 s. A prompt then indicated completion of the trial. Three minutes separated successive trials. Not including practice, subjects completed 12 trials in three blocks of four (all four concentrations in random order).

Nine subjects (4 female), chosen to differ widely in time-course of ratings, returned for two more sessions. Procedures were identical, except that a reminder to focus on sensations in the nose and three practice trials (35.5, 53 and 70%, in random order) replaced the more extensive, initial training. All but one of the subjects completed all three sessions within two weeks (1–5 days between sessions); subject 11 returned after 2 months. Testing occurred at about the same time of day for each subject.

Data analysis (general notes)

Repeated-measures analysis of variance (ANOVA) tested most effects. A Greenhouse–Geisser correction (Greenhouse and Geisser, 1959) adjusted degrees of freedom for violations of sphericity. Bonferroni-corrected, matched-pairs *t*-tests (on data averaged across other conditions) evaluated simple effects.

Ratings and response-latency (see below) both followed roughly log-normal distributions, hence analyses of peak intensity and response-time were performed on log-transformed data. However, since ratings of zero often occurred late in trials, a simple log-transform could not serve; hence, for complete curves, analyses were performed on (i) untransformed values, and (ii) values log-transformed after adding 1% of maximum to all scores. For the most part, both analyses supported the same conclusions, and only analyses on untransformed data appear.

For ANOVA, ratings were averaged in bins of 1 s. Larger bins failed to clearly preserve patterns in the data; smaller bins yielded many degrees of freedom, leading to unjustifiably small p-values for some very weak (in terms of sums of squares) effects. Since subjects gave ratings of zero during the 3 s before stimulus-onset, only ratings made after stimulus-onset served as input. Likewise, 0% CO_2 generated zero-ratings (on one trial, one subject gave a rating of ~0.5% of maximum); hence, only ratings of concentrations greater than zero served as input.

Results and discussion

Peak intensity

Peak intensity was submitted to a three-way, repeated-measures ANOVA: Gender × Concentration × Block. Only the effect of Concentration reached significance, $F(1.4,19.4) = 92.37$, $P < 0.0001$. Linear functions best fit plots of log rated intensity vs. log concentration (Figure 1). Thus, peak intensity rose as a power function of concentration. Further, exponents of power functions (slopes in log–log coordinates) agreed well with published psychophysical functions for nasal pungency from CO_2 (see General Discussion), thereby supporting the validity of the time-intensity ratings.

Response time

Time from stimulus-onset (log-transformed) to the first non-zero rating served as input to a three-way (Gender × Concentration × Block) ANOVA. Only the effect of Concentration reached significance, $F(1.3,18.3) = 37.77$, $P < 0.001$. Contrasts ranked latency as follows: 35.5% > 53% > 70%. Geometric mean, with 95% confidence intervals, were 1.63 (1.34–1.98), 1.03 (0.94–1.13) and 0.84 (0.79–0.90) s, respectively. Further, latencies agreed well with published detection-latencies for CO_2 (see General Discussion), again supporting the validity of the time-intensity ratings.

Time–intensity curves

A four-way ANOVA (Gender × Concentration × Elapsed Time × Block) on rated intensity confirmed some obvious features (Figure 2) of time–intensity curves: ratings increased with concentration and changed over time ($P < 0.0001$ for both main effects). The effect of Gender failed to reach significance, but the Gender × Concentration interaction did [$F(1.4,19.0) = 4.06$, $P < 0.05$]: ratings rose more sharply with concentration for females; according to Bonferroni-corrected contrasts, women gave higher ratings for 70%. Block and all interactions involving Block failed to reach significance. One other effect reached significance, namely the Time × Concentration interaction, $F(3.8,52.9) = 15.54$, $P < 0.0001$.

To tease apart the Time × Concentration interaction, slopes for both the ascending and descending portions of curves were calculated. The ascending portion included points between the first non-zero rating and the peak. The

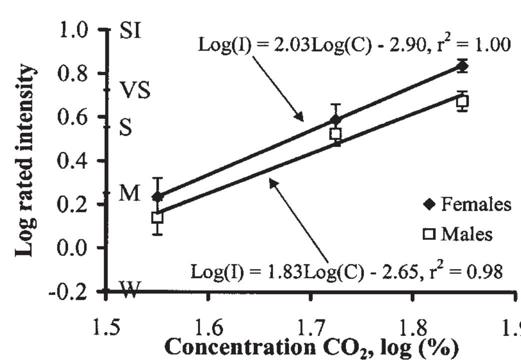

Figure 1 Psychophysical functions for experiment 1. LMS descriptors also appear on the *y*-axis (inside): W = weak, M = moderate, S = strong, VS = very strong, and SI = strongest imaginable. Filled diamonds and opens squares: means (± SEM) for males and females, respectively. Lines represent least squares linear fits (equations on figure).

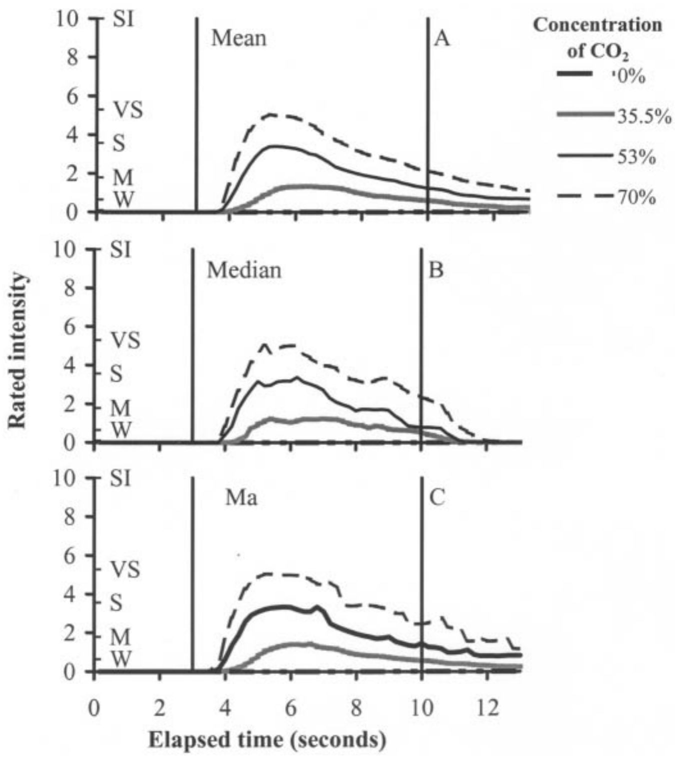

Figure 2 Time–intensity curves for experiment 1 (*x*-axis: elapsed time from trial-onset; y-axis: rated intensity in units of linearized voltage from the slider). LMS descriptors (see caption for Figure 1) also appear on the *y*-axis. Vertical lines at 3 and 10 s represent stimulus onset and offset, respectively. **(A)** Arithmetic mean, **(B)** median, **(C)** Ma, an estimate of the mean for lognormal distributions that may contain zeros (Owen and De Rouen, 1980). Since, for the most part, all three statistics (plus the geometric mean, not shown), support the same general conclusions, only the arithmetic mean will appear in subsequent figures.

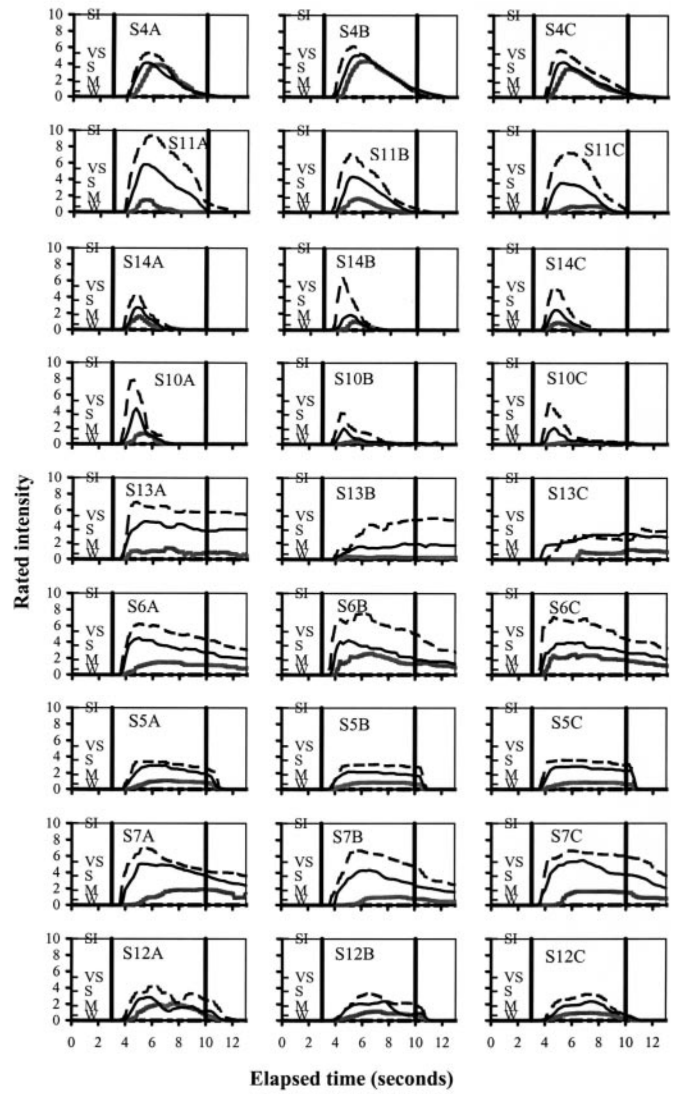

Figure 3 Time–intensity curves (experiment 1) for individuals (rated intensity in units of linearized voltage). LMS descriptors (see caption for Figure 1) also appear on the *y*-axis. Vertical lines at 3 and 10 s represent stimulus onset and offset, respectively. Coarsely hatched line: 70%; solid black line: 53%; grey line: 35.5%; hatched and dotted line: 0%. Data for individuals appear in rows; Data for sessions (1–3) appear in columns (i.e. S4A: data from the first session subject 4 completed).

descending portion included points between the peak and either (i) the rating at stimulus-offset, or (ii) the first zero-rating after peak, whichever came first. Log-transformed slopes served as the dependent variable for a two-way ANOVA: Portion (ascending or descending) × Concentration. The effect of Portion reached significance, $F(1,15) = 90.61$, $P < 0.0001$. Curves rose faster than they fell. The effect of Concentration also reached significance, $F(1.6, 23.8) = 49.77$, $P < 0.0001$. Contrasts ranked average (across Portion) slopes as follows: 70% > 53% > 35.5%. Finally, the Portion by Concentration interaction reached significance, $F(1.5,22.0) = 5.45$, $P < 0.02$. Contrasts ranked the difference in log slope (ratio in linear slope) between rising and falling portions as follows: 73% and 53% > 35.5% (although, again, slope increased with concentration for both portions).

In summary, on average, the data confirmed relatively rapid temporal dynamics of nasal irritation from CO_2 (intensity peaked within a few seconds, and fell considerably by stimulus-offset). Further, curves became more sharply peaked (slopes of rising and falling portions increased) as concentration rose.

Stability of individual differences

Individual differences in shapes of time–intensity curves appeared stable (Figure 3). To confirm this, slopes of descending portions, computed from data normalized to equate peak height across subjects but retain ratios between time-points, served as input for correlation. Out of 36 possible correlations among the three concentrations and sessions (35.5, 53 and 70% for sessions 1, 2 and 3), 35 Spearman correlations reached significance ($P < 0.05$); the other reached marginal significance ($P < 0.10$). This confirmed a degree of stability in descending slopes. Rising slopes of functions (normalized data) again showed a degree of stability, though correlations proved less robust: 20 out of 36 reached significance at the 0.05 level; another four reached significance at the 0.10 level. Differences in latency from stimulus onset to first non-zero response, on the other hand, showed little evidence of stability. Here, limited range (few individual differences), perhaps due in part to temporal averaging (200 ms bins), probably contributed to the weak correlations. In short, data revealed substantial, and stable, individual differences in the time-course of rated sensation. The next study examined some possible methodological causes of individual differences.

Experiment 2

Purpose

Two concerns prompted a partial replication of experiment 1. First, as noted previously, flow dropped somewhat from the sixth second of stimulation due to the response of mass flow controllers. Subjects reported no drop in pressure, but the decrease in flow might have contributed to rapid fading of irritation. Accordingly, manual needle valves replaced mass flow controllers to produce a stable stimulus (verified with a rotameter). Second, as also noted previously, velopharyngeal closure was not verified during training. Perhaps 'slow adapters' failed to maintain closure, thereby allowing the stimulus to elicit taste (Hummel, 2000) or irritation in the throat (Anderson *et al.*, 1990), whereas 'rapid adapters' eliminated such cues to the continued presence of the stimulus by maintaining closure, thereby keeping the stimulus in the nasal cavity. Accordingly, before providing ratings, subjects practiced closure until they could breathe without fogging a mirror held under the nose.

Materials and methods

Nineteen (8 female) subjects, age-range similar to the first sample, participated (five from the first sample returned). Subjects rated five concentrations of CO_2 (0, 35.5, 44, 53 and 70%; the additional concentration facilitated analyses of dose–response functions). Two minutes separated successive trials. Apart from these aspects and training in velopharyngeal closure, procedures matched those of experiment 1.

Results and discussion

Results agreed well with those of experiment 1. Functions of peak intensity versus concentration showed reasonable agreement (Figure 4), though the effect of Gender reached significance, $F(1,17) = 4.56$, $P < 0.05$. Latency of first non-zero response decreased as concentration increased: 35.5% > 44% > 53% > 70%. Geometric mean latencies, with 95% confidence intervals, were 1.74 (1.52–2.01), 1.36 (1.17–1.57), 1.11 (0.95–1.30) and 0.96 (0.83–1.11) s, respectively. Time–intensity curves again showed rapid temporal dynamics (Figure 5A); unlike experiment 1, the effect of Gender reached significance, $F(1,17) = 9.36$, $P < 0.01$. Again, both

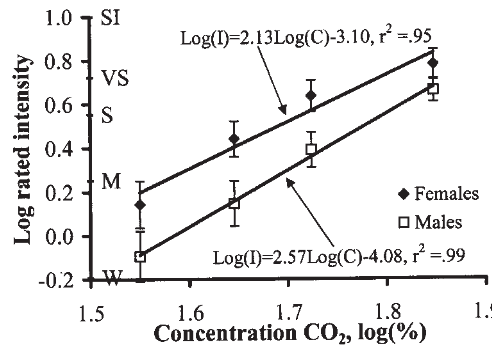

Figure 4 Psychophysical functions for experiment 2. Filled diamonds and opens squares: means (± SEM) for males and females, respectively. Lines represent least-squares linear fits (equations on figure).

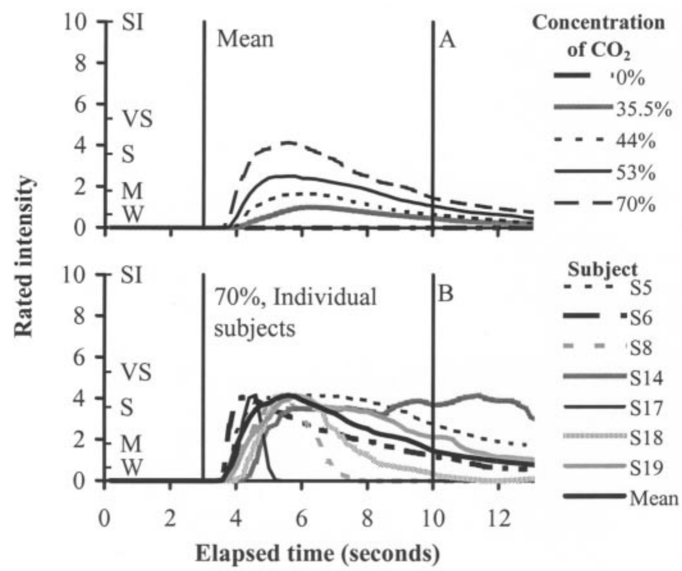

Figure 5 Time–intensity ratings from experiment 2 (rated intensity in units of linearized voltage). LMS descriptors (see caption for Figure 1) also appear on the *y*-axis. Vertical lines at 3 and 10 s represent stimulus onset and offset, respectively. **(A)** Arithmetic mean. **(B)** Time–intensity curves (70% CO_2) for representative individuals, normalized to equate peak height across subjects but preserve relative values within subjects.

ascending and descending slope tended to rise with concentration. Finally, substantial individual differences occurred (Figure 5B). The strong agreement with experiment 1 allays both of the concerns that prompted this replication: data still show rapid temporal dynamics with a stable stimulus, and large individual differences still occur with training in velopharyngeal closure.

The experiment still had two possible problems. First, although ability to maintain velopharyngeal closure was confirmed during training, it was not verified during actual trials. To explore this issue, nine subjects (three who reported rapid fading, six who reported slower fading) made further ratings with continuous monitoring of intranasal pressure (verification of closure). For these subjects, differences in ability to maintain closure during trials failed to account for differences in time-course of reported irritation. Second, because the olfactometer humidified the control flow and air used to dilute the CO_2, but not the CO_2 itself, humidity dropped during stimulus-presentation. To test the notion that subjects who reported slow fading were really rating sustained dryness, six subjects who previously reported slow fading made further ratings where both concentration and humidity varied. For these subjects, concentration clearly affected ratings, but humidity had little or no effect. Further work with larger samples would help settle the matter with more certainty, but these results suggest that individual differences in tendency to rate dryness and ability to maintain velopharyngeal closure fail to account for all individual differences in time-course of rated irritation.

Experiment 3

Purpose

Hummel and colleagues (Hummel *et al.*, 1994, 1996; Hummel and Kobal, 1999) examined the effect of inter-stimulus interval (ISIs between 2 and 90 s) on the perceived intensity of repeated pulses of CO_2. That intensity decreases over time with ISIs as long as 90 s suggests that irritation from CO_2 may have a relatively long recovery-curve. However, no one has examined recovery over very brief periods (i.e. <1 s). In part, researchers may have failed to examine shorter recovery-periods because individual ratings of successive pulses would prove difficult with very brief ISIs. The time–intensity method developed above offers a possible alternative: Subjects can track intensity both with and without brief gaps in stimulation. If subjects do not recover during a gap, ratings might look the same as those made with continuous stimulation. If subjects do recover, we might expect a second peak after the gap.

Materials and methods

Twenty (9 female) subjects (aged 19–49 years) participated. Seven, including S14 (an author, blind to the order of presentation; again, group analyses did not change with the author excluded) had served in previous studies. Subjects received a fixed concentration (35.5%, to avoid unreasonable discomfort given the relatively large number of judgments in a session), and time-course of stimulation varied: 3 s of control air, 5 s of CO_2, an interruption (restoration of control air for 0, 100, 200, 300, 400 or 500 ms), 5 s of CO_2, and finally 3 s of control air (total length 16–16.5 s). Study 1 suggested the position of the gaps (for most subjects, ratings fell substantially by 5 s) and pilot data suggested the length of gaps. Subjects completed at least two blocks of six trials for practice. Next, subjects completed five blocks for analysis. Blocks consisted of all delays (0–500 ms) in random order. One minute, which pilot work suggested would ensure reasonable independence with 35.5% CO_2, separated trials.

Results and discussion

Visual inspection suggests all ratings match until ~2 s after gap-onset; after that, second peaks occur for some gaps (Figure 6). For average data, starting with the 200 ms gap, height of the second peak increased with gap-length. To confirm this, ratings were submitted to a four-way ANOVA: Gender × Block (first two vs. last three) × Time (4th–16th s) × Gap (0–500 ms). The effect of Gender, Block and all interactions involving Gender and Block failed to reach significance. As one might expect, the effect of Time did reach significance [$F(2.6,48.1) = 28.51$, $P < 0.001$]. More importantly, the effect of Gap [$F(2.3,42.0) = 7.87$, $P < 0.001$] and the Time × Gap interaction [$F(8.1,146.5) = 6.42$, $P < 0.001$] also reached significance. Further, an ANOVA on the first 7 s after stimulus-onset (before second peaks) yielded no significant effects involving gap, whereas an ANOVA on the last 6 s yielded a significant effect of Gap [$F(2.2,40.3) =$

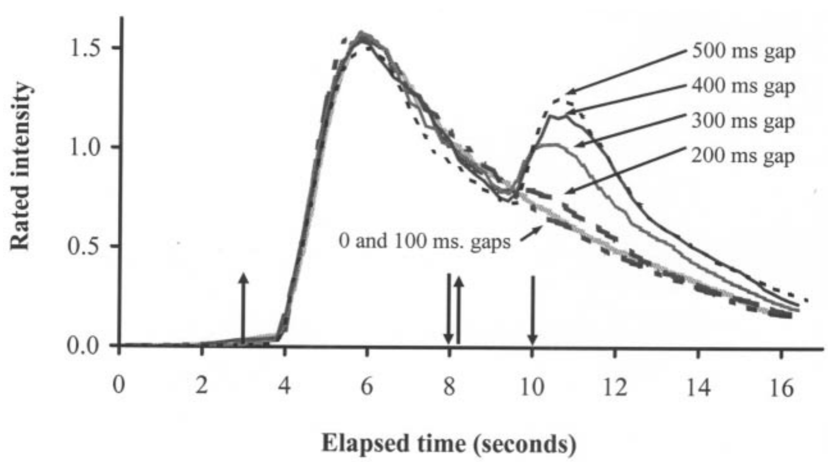

Figure 6 Time–intensity curves (35.5% CO2) from experiment 3 (arithmetic mean). Perceived intensity is in units of linearized voltage. Arrows represent onset (up) or offset (down) of CO_2.

13.82, $P < 0.001$] and a significant Time × Gap interaction [$F(3.6,67.3) = 10.28$, $P < 0.001$]. Contrasts showed that 300, 400 and 500 ms all differed significantly from 0 ms, whereas 100 and 200 ms did not differ from 0 ms.

In debriefing, subjects reported that they failed to perceive gaps, though their ratings clearly reflected the presence of gaps of sufficient length. These results suggest that subjects recovered somewhat with gaps as brief as 300 ms. In fact, with a gap of 500 ms, the second peak reached ~80% of the height of the first peak (as in previous studies, subjects differed in how rapidly sensation faded, but analyses revealed no clear relationship between descending slope of time–intensity curves and degree of recovery). Thus, whatever mechanisms govern the early phase of recovery operate rapidly. The time–intensity method has demonstrated its utility by facilitating this discovery, and could prove useful in further investigations of recovery.

General Discussion

Agreement with existing psychophysical data

With any new technique, or in this case, an existing technique applied in a new setting, comparisons with results from established methods can help evaluate validity. Published studies have examined, among other issues, (i) slopes and shapes of perceived-intensity vs. concentration (psychophysical) functions and (ii) reaction time.

Using magnitude estimation or magnitude matching, various researchers report psychophysical functions roughly linear in log–log coordinates (power functions) with slopes between about 1.55 and 2.2; females tended to emit higher ratings when differences in gender received attention (e.g. Cain and Murphy, 1980; Cometto-Muñiz and Cain, 1982; Cometto-Muñiz and Noriega, 1985; Stevens and Cain, 1986). Functions of peak intensity vs. concentration from the current studies, collected with the LMS, agree well with past findings (power functions, slopes between 1.8 to 2.5, and significantly higher ratings from females in one dataset). Other researchers, using Ekman's modified psychophysical function (Stevens, 1975), report slopes for nasal and ocular irritation from CO_2 closer to unity (Anton *et al.*, 1992; Chen *et al.*, 1995; Belmonte *et al.*, 1999). Application of this analysis to the current data yielded slopes that ranged from 0.75 to 1.29 (r^2 values from 0.99 to 1.00). In short, functions of peak intensity from the current studies proved consistent with published psychophysical functions, thereby supporting the validity of the ratings.

One can also compare latency of first non-zero response with response times to CO_2 (since subjects also received blanks, the tracking procedure includes some features of a classic detection paradigm). Investigators (Cain and Murphy, 1980), using a different stimulation-technique, found that latency to detect CO_2 increased monotonically as concentration decreased from ~0.8 s for high concentrations to ~1.4 s for low concentrations. In the current studies, latency increased as concentration decreased, from 0.84 to 1.63 s and from 0.96 to 1.74 s in experiments 1 and 2, respectively. In short, latency of first non-zero responses proved roughly consistent with published response-times, thereby supporting the validity of the ratings.

Dynamics of nasal irritation from CO_2

Sensation generally waxes and wanes more slowly for nasal irritation than for odor (Cometto-Muñiz and Cain, 1984; Cain, 1990). In fact, irritation may persist for many minutes with steady presentation (Elsberg *et al.*, 1934; Cain *et al.*, 1986). However, physiological and psychophysical studies (see Introduction) suggest that CO_2 may exhibit more rapid dynamics than other nasal irritants, waxing and waning within seconds. The studies reported above support this notion with the first formal time–intensity ratings of nasal irritation from CO_2: on average, rated intensity peaked ~3–4 s after stimulus-onset, then began to fade rapidly.

Since responses to CO_2 fade quickly in neurons of the brainstem (Peppel and Anton, 1993), and even in recordings from the ethmoid nerve (H. Alimohammadi, personal communication), the mechanism(s) that underlies rapid fading probably lie at or close to the periphery. The action of CO_2 in the periphery, which is fairly well characterized, has been reviewed recently (Hummel, 2000; Hummel *et al.*, 2003). In brief, CO_2 diffuses through the mucosa, where carbonic anhydrase catalyses a reaction with water to form carbonic acid, which in turn stimulates free endings of the trigeminal nerve.

Could the peripheral endings rapidly desensitize? In this regard, the finding that very high acidity can suppress neural activity (Carpenter *et al.*, 1974) seems relevant, and time–intensity curves became more peaked (more rapid onset and fading) as concentration increased. On the other hand, the findings that continuous infusion of an acidic solution under the skin evokes sustained pain (Steen and Reeh, 1993), and that nociceptors *in vitro* can show sustained responses (minutes-long) to steady perfusion with CO_2-saturated fluid (Steen *et al.*, 1992), suggests that dynamic regulation of acidity in the peri-receptor environment might also play a role in fading under natural conditions (Steen and Reeh, 1993). Recordings of mucosal pH (Shusterman and Avila, 2003) combined with time–intensity ratings, whole-nerve recordings (Silver, 1990) or recordings of gross potential (Kobal, 1985) could help determine the extent to which changes in trigeminal activity over time mirror changes in pH over time. Studies of other chemicals (including other acids, bases, and chemicals that do not stimulate via changes in pH) could also prove instructive.

Individual differences in temporal dynamics

Large and stable individual differences in time-course of reported irritation occurred. These findings extend the literature on individual differences in nasal irritation (Shusterman, 2002) to include differences in time-course of sensation, and parallel reports of large individual differences in time-course of oral irritation (McBurney *et al.*, 2001). Any of the factors discussed above (particularly in dynamic regulation of pH) could differ among individuals, as could condition of the mucosa (e.g. differences in the amount or composition of mucous secreted). What other factors might prove important?

Gender

As noted above, females gave higher ratings than males, consistent with reports of lower thresholds (Shusterman *et al.*, 2001) and higher perceived intensity (Cometto-Muñiz and Noriega, 1985). In experiment 2, average heights of time–intensity curves also grew more rapidly with concentration for females, consistent with steeper slopes of psychophysical functions for women. Did females also differ in time-course of ratings? In general, the distributions of descending slopes of time–intensity curves looked quite similar for the two genders (Figure 7), though males comprise most (all but one) of the fastest desensitizers. We currently have no explanation for this result, though we note that rats display sexual dimorphism in carbonic anhydrase activity (Jeffery *et al.*, 1986). Future studies might clarify the role of gender and other factors, e.g. allergic status and age (Shusterman and Balmes, 1997; Shusterman *et al.*, 2001).

Differences in neural response

Differences in central integration might occur. Hummel, and colleagues (Hummel *et al.*, 1994, 1996) found that pain from repeated (200 ms) pulses of CO_2 actually increased over the first few pulses with 2 s (but not longer) ISIs. All subjects reported that stinging decreased, but most also reported that burning increased with successive pulses. Hummel and colleagues suggested that central integration ('wind-up': see Handwerker and Kobal, 1993) might be responsible for the build-up of burn. Consistent with a central locus, simultaneous recordings of negative mucosal potential, which reflect peripheral activity, decreased with successive pulses for all ISIs, even when ratings of pain did not (Hummel *et al.*, 1996). Further, some research (Peppel and Anton, 1993) suggests that at least some neurons in the brain stem increase activity during prolonged presentation of CO_2. Future work might determine whether subjects who report slower fading during steady presentation also experience a build-up of burning with repeated (short ISI) stimulation. If so, individual differences in integration, rather than individual differences in desensitization, might account for at least some individual differences in dynamics.

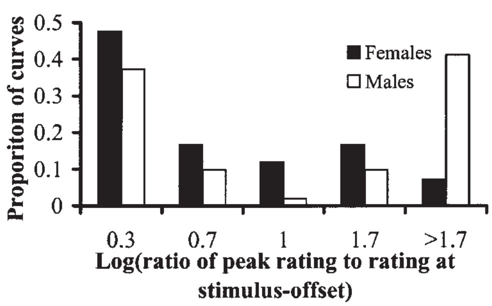

Figure 7 Histogram of log ratio of peak rating to rating at stimulus-offset. Filled and open bars represent females and males, respectively. Figure represents data pooled across subjects and concentrations (one value per subject and concentration when multiple replications of a given concentration occur).

Cognitive factors

Future studies could examine the extent to which individual differences in expectations, beliefs about stimuli, and personality factors influence the irritation subjects report at different time-points (Stevens, 1990; Dalton *et al.*, 1997). Future studies could also determine whether subjects differ substantially in their interpretation of instructions; e.g. did some subjects who reported rapid fading ignore low-level, residual sensations and report only frank pain? Finally, future studies might also compare time–intensity ratings to more objective measures, e.g. a measure of pungency based on deformation of skin around the eye (Jalowayski *et al.*, 2001). Such studies might prove valuable in the quest to untangle real individual differences in dynamics of sensation from individual differences in tracking style (Lawless and Heyman, 1998) and use of the scale (Bartoshuk *et al.*, 2002).

Recovery of sensitivity with gaps in stimulation

Experiment 3 presumably constitutes the first psychophysical work on the earliest phases of recovery from nasal irritation, made possible by application of the time–intensity method developed in experiments 1 and 2. Gaps in stimulation as brief as 300 ms (experiment 3) allowed significant recovery of sensitivity. This extremely rapid recovery might suggest that some biochemical mechanism, like carbonic anhydrase activity or buffering, might play a particularly important role in the early phase of recovery (as opposed to dilution and clearance through vasodilatation and plasma extravasion, which would presumably reset on a slower time-scale). Future studies might provide further insights into the mechanisms that underlie phases of recovery by examining (i) the effects of concentration on speed of recovery, and (ii) differences between chemicals.

Summary

With formal time–intensity ratings, the experiments confirmed relatively rapid dynamics of nasal irritation from CO_2, at least on average. However, substantial individual differences in time-course of reported irritation occurred. Future studies can explore the causes of those differences. The experiments also demonstrated that the nose recovers a substantial amount of sensitivity with gaps of just 500 ms; whatever mechanisms govern the earliest phase of recovery from stimulation must operate on a fairly rapid time-scale. Finally, the experiments support the validity of fine-grained time–intensity ratings of nasal pungency, since functions of peak intensity versus concentration and latency of first non-zero response show good quantitative and qualitative agreement with published psychophysical data. Application to the study of recovery of sensitivity illustrated the potential utility of the method. Thus far, the time–intensity method developed in the current work shows promise as a tool to investigate the temporal microstructure of nasal pungency (Cain, 1990).

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