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Comparison Between Two Types of Behavioral Variables of Non-Evoked Facial Pain after Chronic Constriction Injury to the Rat Infraorbital Nerve

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Background and Purpose: **Chronic constriction injury to the rat infraorbital nerve (IoN-CCI) was reported to induce asymmetric face grooming directed to the territory of the injured nerve, and localized mechanical allodynia. The model has been used for pharmacologic testing; responsiveness to mechanical stimulation has been used as outcome measure, but face grooming behavior was not studied in this context.**

Methods: **Face grooming data from a series of four experiments using the IoN-CCI model were retrospectively analyzed, and two types of face grooming were identified: on the one hand, isolated face grooming (i.e., face grooming that is neither preceded nor followed by body grooming); and on the other hand, face grooming during body grooming (i.e., face grooming that is part of more general body grooming behavior).**

Results: **In all four experiments, amount of isolated face grooming was found to be significantly increased after IoN-CCI. In contrast, the amount of face grooming during body grooming was not significantly altered after IoN-CCI in any of the four experiments.**

Conclusions: **The amount of isolated face grooming is a more sensitive outcome measure of neuropathic pain than is the total amount of face grooming, which includes face grooming during body grooming.**

Animal grooming serves a variety of adaptive functions. On the one hand, it is the principal means of caring for the external body surface, ridding it of surface debris and parasites (1, 2). Further, grooming has also been documented to be involved in counter-irritation, thermoregulation (3-5), spreading of pheromones for social signaling (6-8), and de-arousal and stress reduction (9-11). On the other hand, its function as an adaptive response to noxious stimulation has been extensively used in experimental pain research.

Grooming that is not evoked by noxious stimulation consists of prolonged and organized episodes of care and attention to the pelage (12). This type of stereotyped grooming behavior has been described as starting with a set of small bilateral face wash strokes, appearing as precise elliptic strokes over the mystacial vibrissae, followed by a series of slower, downward strokes of successively larger amplitude over the face, followed by head tucking and turning, and terminated by a bout of body licking (13, 14). A different pattern of grooming is observed after localized irritation. In contrast to the complete grooming observed after mild irritation by a water mist spray on the rat's back (12, 15, 16), more intense irritation of a body region (e.g., rubbing mineral oil into the fur) and painful irritation caused by biological factors or physical objects that damage the skin, were reported to evoke short episodes of grooming specifically directed to the irritated or painful body area (11, 12). Directed grooming actions also have been observed after formalin-induced inflammation in the face (17).

Chronic constriction injury (CCI) to the rat's infraorbital nerve (IoN) was reported to induce increased face grooming activity, directed to the territory of the injured nerve, for up to two months after such injury (13). Considering the phenomenologic similarity between face grooming patterns observed after IoN-CCI and those of normal rats in response to noxious facial stimulation (17-22), or to chemical irritation of the trigeminal nucleus caudalis (23, 24), it was proposed that asymmetric face grooming after IoN-CCI is a behavioral manifestation of "spontaneous," strongly aversive, and probably painful sensations in the injured nerve territory (13). The fact that the increase and asymmetry in face grooming behavior in IoN-CCI-treated rats persisted for a prolonged postoperative period further suggested presence of painful sensory dysfunction. Habituation to abnormal non-painful sensations and extinction of the face grooming response were expected to develop much earlier. Non-painful sensory disturbances in the territory of the infraorbital nerve (unilateral vibrissae clipping, anesthetic infraorbital nerve blockade, application of mineral oil on vibrissae) induced an initial bout of directed face grooming, but this response was transient and short lasting (25). Only formalin-injected rats manifested significantly more face grooming activity directed to the affected infraorbital nerve territory than did unstimulated control rats.

A number of researchers have used the IoN-CCI model to

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Table 1. Differences in conditions among the experiments

Experiment	No. of rats	Surgery	Injections	Arrival weight (g)	Arrival	Habituation	Pre-op testing	Post-op testing
		(1)	(2)		(3)	(4)	(5)	(6)
1	10	A	+5 and +7	220 - 240	-9	-3 and -2	-1	+5 and +7
2	5	B	None	220 - 240	-14	-4 and -3	-1 and -2	+6
3	50	A	All	220 - 240	-8	-4 and -3	-2	+5
4	68	B	None	220 - 240	-13	-7 and -5	-1	+6

(1) = IoN-CCI surgery was performed by two people.
(2) = Rats of experiment 1 were given saline on postoperative days +5 and +7, 15 min prior to testing; rats of experiment 3 were given saline 30 min before all testing points; and rats of experiments 2 and 4 were not given any injections.
(3) and (4) = Pre-operative times at which the rats arrived at the colony and were habituated to the testing procedure.
(5) and (6) = Pre- and postoperative times at which face grooming behavior was observed.

evaluate use of various pharmacologic treatments of neuropathic pain (26, 27) or to examine changes in neuronal activity after nerve constriction injury (28, 29). In all studies, testing was limited to assessment of changes in responsiveness to mechanical stimulation of von Frey hairs. Studies in which changes in face grooming behavior were quantified were not found. By contrast, in the original report documenting the IoN-CCI model (13) both behavioral variables were evaluated. Moreover, use of asymmetric face grooming as a sign of localized, facial pain in freely moving rodents was further validated in a second report (25).

In a series of experiments, changes in face grooming patterns following IoN-CCI were retrospectively quantified and analyzed. Two types of face grooming behavior were compared: face grooming that was neither preceded nor followed by body grooming versus face grooming that was part of a more general body grooming behavior. The aim of the study reported here was to examine which behavioral variable yields the most sensitive assessment of the changes observed after IoN-CCI: total amount of face grooming, amount of face grooming without body grooming, or amount of face grooming with body grooming.

Materials and Methods

Subjects. Male Sprague-Dawley rats (Charles River, 220 to 240 g at arrival and specific pathogen free according to FELASA guidelines [30]) from four different studies were used. In these experiments, they served to provide baseline values for either subsequent pharmacologic testing (experiments 1, 3, and 4) or histologic examination (experiment 2). This means that all data reported here were obtained before the animals were subjected to manipulations in the context of the subsequent experimental protocol. Some differences in experimental conditions between experiments existed and are described in Table 1. In experiment 1, rats were treated with one drug immediately after surgery. Therefore, in that experiment, only data from control rats, treated with saline, were used. Experiment 2 was a histologic experiment using a small number of animals. In experiments 3 and 4, on the other hand, baseline data were obtained before the rats were allotted to the various drug groups. This explains why the number of rats varies so much among the four experiments.

Rats were housed in solid-bottom polycarbonate cages (Tecniplast Gazzada S.a r.l., Buguggiate, Italy) in a room with constant degree of humidity and temperature of 21 ± 1°C. Tap water and rodent chow (Pavan Service PVBA, Oud-Turnhout, Belgium) were available at libitum. Rats were kept under a reversed 12:12-h dark:light cycle (lights on at 8 p.m.). Animals were treated and cared for according to the guidelines of the International Association for the Study of Pain (I.A.S.P.) (31).

Rats were allowed to acclimate to the housing facilities for at least six days before pre-operative testing. Rats were habituated to the test procedure at two pre-operative time points. Habituation and testing were conducted in a darkened room (light provided by a 60W red light bulb suspended one meter above the observation area) with 45-dB background noise. In addition to these similarities in experimental conditions, some differences among the four experiments were present, most importantly the number of rats used, the person performing surgery on the infraorbital nerve, and the presence or absence of intraperitoneal injection with saline (10 ml/kg of body weight) before testing.

Surgery. Unilateral ligation of the IoN was performed essentially according to the method described by Vos (21). Briefly, rats were anesthetized with pentobarbital (60 mg/kg, i.p.), then were given atropine (0.1 mg/kg, i.p.). All surgery was performed under direct visual control, using a Zeiss operation microscope (10 to 25×). The head of the rat was fixed in a stereotaxic frame and a mid-line scalp incision was made, exposing skull and nasal bone. The infraorbital part of the IoN was exposed by use of a surgical procedure similar to that described by Gregg (32) and Jacquin and Zeigler (33). The edge of the orbit, formed by the maxillary, frontal, lacrimal, and zygomatic bones, was dissected free. To give access to the IoN, the orbital contents were gently deflected, using a cotton-tipped wooden rod. The IoN was dissected free at its most rostral extent in the orbital cavity, just caudal to the infraorbital foramen. Two chromic catgut ligatures (5-0) were loosely tied around the IoN (2 mm apart). To obtain the desired degree of constriction, a criterion formulated by Bennet and Xie (34) was applied: the ligatures reduced the diameter of the nerve by a just noticeable amount and retarded, but did not interrupt circulation through the superficial vasculature. The scalp incision was closed, using polyester sutures (4-0).

Behavioral testing. Testing consisted of observation of free behavior in a transparent plastic cage (40 × 40 × 30 cm [l × w × h]) with a mirrored back. Rats were kept in a smaller plastic cage (24 × 14 × 17 cm) for 10 min to acclimate them to the test room, then were put in the larger observation cage. The behavior was videotaped for 10 min on postoperative days +5 and +7 (experiment 1), +6 (experiments 2 and 4), and +5 (experiment 3). These time points were chosen according to the time course of changes in face grooming behavior following IoN-CCI described by Vos (13). Videotaped behavior was analyzed by an experimenter who was blind to what procedures had been done on the rat.

Video analysis focused exclusively on face grooming behavior. The amount of time rats spent on face grooming was determined, using a stopwatch. Although asymmetry in face grooming behavior as well as increased face grooming activity following IoN-CCI were described by Vos and co-workers (13), the former was not determined in these experiments. Unpub-

lished data indicated that the asymmetry in face grooming behavior persisted in rats treated with an analgesic substance despite the fact that a significant decrease in the amount of face grooming activity was observed in these animals. Apparently, ipsilateral face grooming was so overwhelming, compared with that observed on the contralateral side, that the changes in face grooming behavior due to the analgesic medication were not sufficient to inverse this asymmetric behavior.

Distinction was made between isolated face grooming and face grooming during body grooming. If a sequence was neither preceded nor followed by body grooming, the episode was categorized as isolated face grooming (13). Amount of isolated face grooming was calculated as the sum of isolated face grooming episodes recorded during the observation period. If body grooming was present before or after a sequence of face grooming actions, the episode was categorized as face grooming during body grooming (13). Amount of face grooming during body grooming was calculated in the same way as that for isolated face grooming. Total amount of face grooming was defined as the sum of the amount of isolated face grooming plus the amount of face grooming during body grooming.

Analysis of data. Lilliefors tests are used on difference scores (postoperative minus preoperative scores) to test whether the data are normally distributed. If a significant difference from a normal distribution was not detected, paired Student *t* test were used to analyze the differences between pre- and postoperative data; if a significant *P*-value was found for the Lilliefors test, Wilcoxon signed rank tests were used. Differences between the four experiments were analyzed, using factorial analysis of variance (ANOVA) with post-hoc comparisons according to Fisher's protected least significant difference (PLSD) method, if the distribution of the measured behavioral variable was normal according to the Lilliefors test; if not, Kruskal Wallis tests with Mann Whitney U test post-hoc comparisons were done.

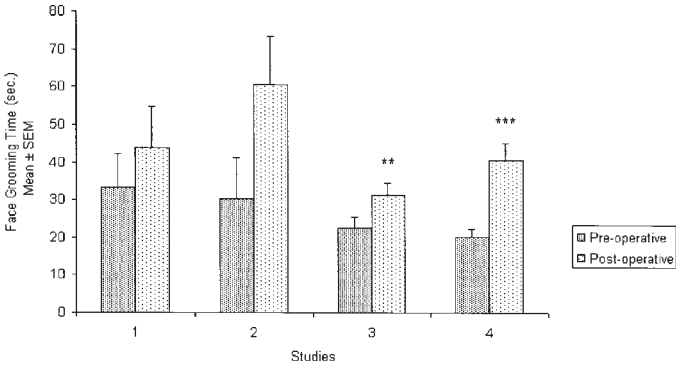

Figure 1. Changes in total amount of face grooming activity. Histograms representing the number of seconds of face grooming (mean ± SEM) observed in the four experiments (1-4) during a 10-min observation session before the operation (Pre-operative) and 5 to 7 days after the operation (Post-operative). Asterisks indicate significant differences between pre- and postoperative data (Students *t*-tests: $^{*}P < 0.05$; $^{***}P < 0.001$).

Results

Postoperative increases in total amount of face grooming were observed in all four experiments (Fig. 1), but statistical significance was reached only in experiments 3 and 4 (Table 2). Significant postoperative changes in amount of isolated face grooming were observed in all four experiments (Fig. 2). In contrast, significant postoperative changes in amount of face grooming during body grooming were not observed in any of the four experiments.

According to the results of Goodness of fit testing to a normal distribution (Table 3), differences among the four experiments were analyzed, using the Kruskal Wallis test. For total amount of face grooming, neither pre-operative ($P = 0.36$) nor postoperative ($P = 0.23$) differences among experiments were found. Sig-

Table 2. Comparison of pre- and postoperative amount of face grooming behavior

			Mean	SD	Range	Lilliefors test	Student's *t*-test	Wilcoxon signed rank test
	Exp. 1	Pre-op	31.44	29.64	0 - 98.90	> 0.20	0.2706	0.2604
		Post-op	21.84	22.37	0 - 54.58			
Face grooming	Exp. 2	Pre-op	28.05	23.65	0 - 58.72	> 0.20	0.6404	0.5002
during body		Post-op	19.20	18.03	0 - 45.16			
grooming	Exp. 3	Pre-op	21.21	20.40	0 - 99.48	> 0.20	0.4085	0.454
		Post-op	18.91	18.76	0 - 80.79			
	Exp. 4	Pre-op	12.46	16.38	0 - 69.45	< 0.01*	0.0293*	0.0781
		Post-op	19.66	28.70	0 -120.56			
	Exp. 1	Pre-op	1.65	3.38	0 - 10.43	> 0.20	0.0078*	0.0117*
		Post-op	22.01	18.68	0 - 59.10			
Spontaneous	Exp. 2	Pre-op	2.33	2.70	0 - 6.59	> 0.20	0.0052*	0.0431*
face		Post-op	41.38	13.97	29.04 - 63.88			
grooming	Exp. 3	Pre-op	1.28	2.70	0 - 10.30	< 0.01*	< 0.001*	< 0.001*
		Post-op	12.45	11.57	0 - 40.10			
	Exp. 4	Pre-op	7.63	9.21	0 - 39.69	< 0.01 *	< 0.001*	< 0.001*
		Post-op	21.09	21.73	0 - 93.22			
	Exp. 1	Pre-op	33.09	28.70	0 - 98.90	> 0.20	0.2187	0.2135
		Post-op	43.85	34.29	0 - 90.40			
Total amount	Exp. 2	Pre-op	30.39	24.06	2.82 - 60.97	> 0.20	0.2275	0.2249
of face		Post-op	60.58	28.80	29.04 - 90.57			
grooming	Exp. 3	Pre-op	22.50	20.82	0 -103.72	> 0.20	0.0046*	0.0124*
		Post-op	31.36	22.14	0 - 95.83			
	Exp. 4	Pre-op	20.08	17.96	0 - 86.68	< 0.01*	< 0.001*	< 0.001*
		Post-op	40.75	36.52	0 -169.81			

Goodness of fit to a normal distribution is tested for the difference scores (postoperative score – preoperative score), using the Lilliefors test. Post-operative changes in amount of face grooming were analyzed, using paired Student's *t* test (when no significant *P*-value was obtained for the Lilliefors test [column 7]) and Wilcoxon signed rank tests (if a significant *P*-value was found for the Lilliefors test); appropriate *P*-values are underlined. Additional descriptive statistical data include mean, SD, and range (minimum score – maximum score). Values of $P < 0.05$ are indicated by an asterisk.

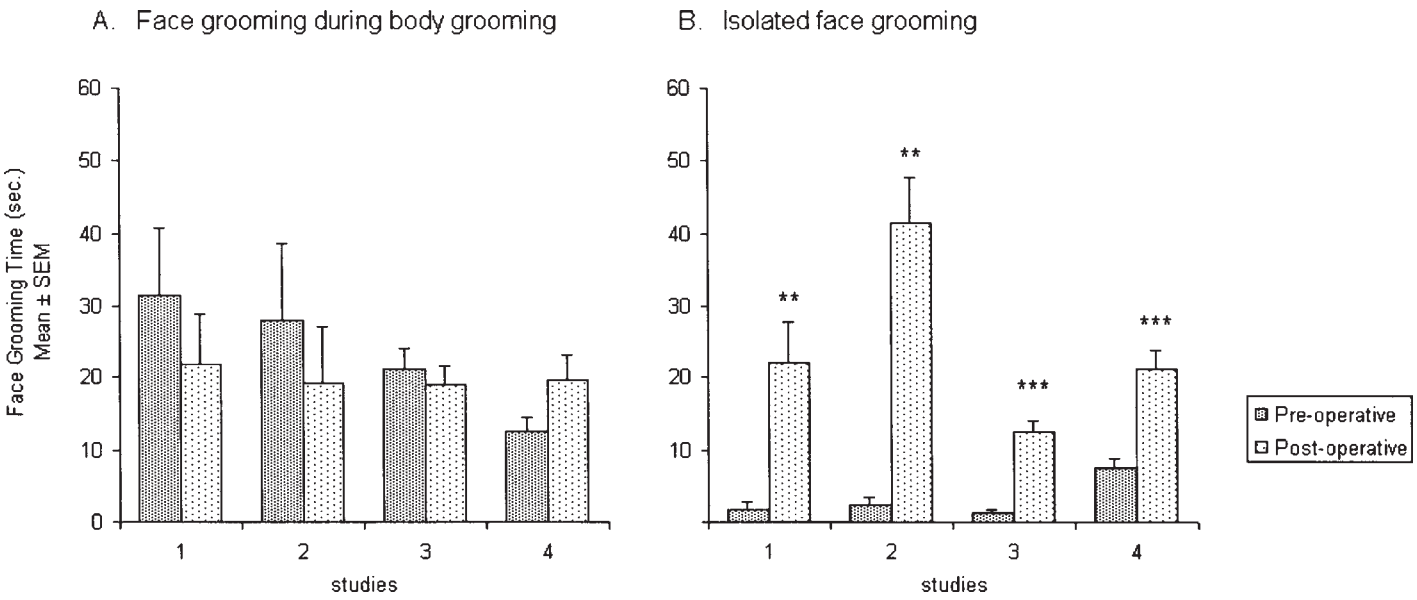

Figure 2. Comparison of two types of face grooming behavior. Histograms representing the number of seconds (mean ± SEM) of face grooming during body grooming (A) and isolated face grooming (B) observed in the four experiments (1-4) during a 10-min observation session before (Pre-operative) and 5 to 7 days after (Post-operative) the operation. Asterisks indicate significant differences between pre- and postoperative data (Students *t*-tests: $^{**}P < 0.01$; $^{***}P < 0.001$).

Table 3. Goodness of fit to a normal distribution

	Face grooming during body grooming		Spontaneous face grooming		Total amount of face grooming	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Experiment 1	> 0.20	> 0.20	< 0.01*	> 0.20	> 0.20	> 0.20
Experiment 2	> 0.20	> 0.20	> 0.20	> 0.20	> 0.20	> 0.20
Experiment 3	< 0.01*	< 0.01*	< 0.01*	< 0.01*	< 0.01*	> 0.20
Experiment 4	< 0.01*	< 0.01*	< 0.01*	< 0.01*	< 0.01*	< 0.01*

Data are *P*-values resulting from goodness of fit testing to a normal distribution, using the Lilliefors test. Values of $P < 0.05$ are indicated by an asterisk.

nificant differences for amount of isolated face grooming were found before ($P < 0.001$) and after ($P < 0.01$) surgery. Significant differences also were found for amount of face grooming during body grooming before ($P < 0.01$), but not after ($P = 0.48$) surgery.

Results of post-hoc comparisons are shown in Table 4. In experiment 4, there was a different distribution in pre-operative face grooming than in the other experiments. More isolated face grooming was observed and less face grooming during body grooming, but the total amount of face grooming in experiment 4 was not different from that of the other experiments. In experiment 2, there was a greater amount of post-operative isolated face grooming than that in the other three experiments, although the *P*-value resulting from a Mann Whitney U test comparison between experiments 2 and 1 was of borderline significance ($P = 0.05$).

Discussion

When describing the IoN-CCI model, Vos (13) reported postoperative increases in total amount of face grooming. We also found postoperative increases in all four of our experiments, but only the results of experiments 3 and 4 reached statistical significance. This lack of statistical significance, due to excess variability or insufficient postoperative increases, impaired the assessment of (pharmacologic) treatments of neuropathic pain, especially when the high number of animals used in experiments 3 and 4 was taken into account. Moreover, only the results of experiment 4, with 68 animals, seemed to have sufficient discriminatory power for pharmacologic testing. It is evident that this number of required animals is too high. The lack of significance may have been caused by variation in rats, variation in surgery, variation in test-

Table 4. Post-hoc comparisons between experiments

	Face grooming during body grooming		Spontaneous face grooming	
	Pre-op	Post-op	Pre-op	Post-op
Experiments 1 & 2	0.7501 0.9512	0.8453 0.9512	0.8571 0.3913	0.0525 0.0500
Experiments 1 & 3	0.1302 0.2459	0.7322 0.6130	0.8792 0.9525	0.1290 0.1422
Experiments 1 & 4	0.0045* 0.0145*	0.7943 0.1884	0.0119* 0.0214*	0.8805 0.6009
Experiments 2 & 3	0.4533 0.4914	0.9801 0.8262	0.7471 0.2659	< 0.001* < 0.001*
Experiments 2 & 4	0.0849 0.1184	0.9681 0.4984	0.1011 0.3366	0.0168 0.0218*
Experiments 3 & 4	0.0167* 0.0040*	0.8711 0.2713	< 0.001* < 0.001*	0.0114* 0.1046

*Data are *P*-values resulting from post-hoc comparisons according to Fisher's PLSD method (top of cell) and Mann Whitney U test post-hoc comparisons (bottom of cell). Appropriate *P*-values are underlined according to the results from goodness of fit testing to a normal distribution shown in Table 3. Values of $P < 0.05$ are indicated by an asterisk.

ing conditions, and by sensitivity of the observed variable for behavioral changes following IoN-CCI.

Considering the clear differences in postoperative changes found between isolated face grooming and face grooming during body grooming, it is proposed that the total amount of face grooming is not as sensitive a measure for pharmacologic testing as is isolated face grooming. Significant postoperative changes in face grooming during body grooming were not observed in any of the four experiments. Therefore, including this behavioral element in the analysis of the changes after IoN-CCI caused a serious decrease in the sensitivity of face grooming as a measure of neuropathic pain following IoN-CCI. Analysis of isolated face grooming on the other hand revealed significant postoperative changes in an experimental group of only five animals. These differences in postoperative changes between face grooming during body grooming and isolated face grooming correspond to the differences described between grooming that is not evoked by painful irritation, consisting of prolonged and organized episodes starting with face grooming and terminated by body licking (12-14), and grooming after localized irritation, consisting of short episodes of grooming specifically directed to the irritated or painful body area (11, 12).

Interestingly, despite the differences in experimental conditions among the four experiments (Table 1), similar results were obtained concerning the distinction that is made between isolated face grooming and face grooming during body grooming. On the other hand, some differences in face grooming behavior were found among the experiments. In experiment 4, a slightly different pattern of pre-operative face grooming behavior was observed (i.e., more isolated face grooming and less face grooming during body grooming), compared with that of the other experiments. The retrospective nature of this report does not allow for statistical analysis to investigate the cause of this effect. Still, it is proposed that possibly the longer period between the habituation sessions and actual pre-operative testing was responsible for this observation (*cf.* Table 1). It is likely that the animals of experiment 4 were less adequately habituated to the testing conditions because of this more prolonged time interval, and therefore, they experienced more stress. Furthermore, although a simple relationship does not exist between stress and face grooming behavior, some authors have reported fragmented grooming (short episodes of incomplete and variable grooming sequences) as an arousal-reducing activity (35). This could explain why rats of experiment 4 performed more isolated face grooming. However, other researchers have reported observations of complete and stereotyped "displacement grooming" (i.e., grooming in relation to apparently irrelevant stimuli that induce moderate to strong levels of fear and anxiety and in the absence of experimentally induced irritation or pain) and without apparent need for maintenance of the pelage (36-38).

Another difference among the experiments was the higher amount of isolated face grooming observed in experiment 2. It remains unclear which variables (e.g. surgeon, presence or absence of saline injections) may have caused this effect. However, it is important to stress that face grooming behavior was compared before and after surgery within each experimental group, and pooling of data from the four experiments was not done for the analysis. It is even more important that, despite the differences in experimental conditions and the observed differences in face grooming behavior among the experiments, the final conclusion with regard to the distinction that is made between isolated face grooming and face grooming during body grooming is valid. In fact, it indicates that the observed difference between the two types of face grooming is robust.

Isolated face grooming as a measure of neuropathic pain is a unique behavioral variable, considering the fact that this behavior is a spontaneous response to the nerve lesion that is not evoked by the experimenter and can be freely observed. Furthermore, it is virtually non-existent in healthy control animals and only becomes apparent under pathologic conditions. In contrast, face grooming during body grooming is part of the natural behavior of the rat. As such, it constitutes a good control measurement for non-specific drug effects (e.g. sedation) in pharmacologic testing.

Movements of the forelimbs during isolated face grooming episodes and face grooming episodes during body grooming are similar. Therefore, if a difference in isolated face grooming is found between drug-treated and control animals, and this effect is not accompanied by a difference in face grooming during body grooming, it is likely that the change in isolated face grooming is due to a specific drug effect. If both forms of face grooming are affected, this may rather suggest that, at least to some extent, it is due to a non-specific effect.

It is concluded that isolated face grooming is a more sensitive outcome measure than is total amount of face grooming for studies on the effects of infraorbital nerve constriction and this suggests that its alleviation by analgesic medication can be studied more accurately.

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