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Functional Outcomes of Cleft Lip Surgery. Part IV: Between- and Within-Participant Variables Affecting Lip Vermilion Sensory Thresholds

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Abstract

Objective—Compare neurosensory assessments for participants with and without a cleft lip; identify between- and within-participant variables affecting sensory thresholds on the vermilion of participants with cleft lip.

Design—A parallel group, nonrandomized clinical trial.

Subjects—There were 56 participants with cleft lip and 37 noncleft participants.

Analysis—Two-point perception and warmth and cool detection thresholds were measured on the right and left sides of the upper and lower vermilion. A cotton-tip stick, stroked across the skin, was used to identify altered sensation. Linear mixed effects modeling was used to examine the effects of between-and within-participant variables on the thresholds.

Results—Threshold values on the upper and lower vermilion were similar for cleft and noncleft participants and were unaffected by the presence of a cleft on the side tested. Participants with cleft lip who reported hyposensitive altered sensations had higher two-point thresholds on the upper lip than those who reported hypersensitivity. Participants with cleft lip who reported altered midface sensation had lower warmth detection, but higher cool detection thresholds, on the lower vermilion than participants with cleft lip who did not report altered sensation. Participants with bilateral cleft lip had lower warmth detection thresholds on the upper vermilion than participants with unilateral cleft lip.

Conclusions—Although participants with cleft lip and noncleft participants exhibit similar thermal and two-point discrimination, on average, differences exist among subgroups of participants with cleft lip that may reflect central disturbances in the processing of somatosensory stimuli.

Keywords

cleft lip; craniofacial defects; impairment; sensation; sensory testing

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Previous investigations employing conventional sensory testing methods to evaluate specific anatomical sites on the face and in the mouth have concluded that patients with cleft lip have normal sensory function (Posnick et al., 1994a, 1994b; Uchiyama et al., 1998; Akal et al., 2000); patients with repaired cleft lip and palate, however, exhibit uniquely different repaired and scarred tissues, and the specific sites selected for testing in these studies might not have included the individual patients' areas of altered sensory function. Indeed, patients with cleft lip, when carefully questioned, often report altered sensation on the upper lip (Essick et al., 2005). Based on the patients' verbal responses to stroking the ends of a cotton-tip applicator stick lightly across the face, 56% experienced hyposensitivities (negative symptoms such as numbness), whereas 38% experienced hypersensitivities (active symptoms such as "tingling" or "tickling"). For many patients, the altered sensation was mild and was restricted to the tissues traumatized during primary and secondary revision surgeries. For other patients, however, the altered sensation extended to the contralateral, noncleft side of the upper lip or onto the philtrum.

This paper is one of four in a series describing initial findings of participants enrolled in the study titled "Functional Outcomes of Lip Revision" (NIDCR DE13814). One aim of this study was to determine whether abnormalities in facial (lip) form and function can be attributed to impaired sensorimotor integration (Trotman et al., 2007b). The purpose of the analyses reported below was to determine if prior to any additional revision surgery, participants with cleft lip have abnormal sensory function that could negatively impact sensorimotor integration. By evaluating between- and within-participant variables, three key questions were addressed: (1) Do neurosensory assessments (two-point perception and thermal thresholds) on upper and lower vermilion sites differ for participants with and without a cleft lip? (2) Do neurosensory assessments differ when a cleft is present on the side tested? (3) Do neurosensory assessments differ when sensation is perceived to be altered?

Method

The data reported below were obtained at baseline from 56 cleft lip (21 female and 35 male) and 37 noncleft (18 female and 19 male) participants of a total of 100 participants in a longitudinal study of the functional outcomes of lip-revision surgery (C.-A.T., principal investigator). All participants with cleft lip had received prior lip revision surgery, but no participant had undergone any surgery to the lips, face, or mouth within 2 years of testing. Individuals with a medical history of diabetes, collagen vascular disease, or systemic neurological impairment were excluded from participation (Trotman et al., 2007b). Data were obtained from each participant during a half-day appointment. For all participants, data were obtained 3 months later at a second visit using the same testing methods. The study was approved by the Committee on Investigations Involving Human Subjects at the University of North Carolina School of Dentistry.

General Protocol

At each appointment and for each participant, estimates were obtained at each of four sites on the vermilion border of the lips (upper right, upper left, lower right, and lower left vermilion) for (1) the two-point perception threshold (2-Point), (2) the warmth detection threshold (Warm), and (3) the cool detection threshold (Cool). Each site was located halfway between the midline and commissure of the lips at rest. The sequence of sites to be tested was randomized for each procedure. Repeated estimates for a single site and visit, when available, were averaged. For four participants, testing was terminated early due to the participants' lack of attention or inability to understand instructions, resulting in missing data for one or more procedures. The participant kept his or her eyes closed during estimation of the thresholds.

After the two-point perception and thermal thresholds had been estimated, a sensory mapping procedure was used to determine if the participants with cleft lip experienced altered sensation (Essick et al., 2005). None of the noncleft participants reported any area of altered sensation on the face.

Two-Point Perception Threshold

The two-point perception threshold was estimated at each test site using a tracking procedure based on maximum likelihood estimation (Chen et al., 1995; Feldman et al., 1997). The stimuli were provided by a disk-shaped Disk-Criminator™ (Neuro Regen LLC, Lutherville, MD), which supported multiple sets of two small metal prongs at 16 different separations ranging from 2 to 25 mm (Chen et al., 1995). On each trial, the experimenter pressed the two prongs perpendicularly into the skin for 2 to 3 seconds without producing discomfort or lateral movement. The prongs were oriented horizontally along the vermilion site under study. After the stimulus was removed, the participant responded either “yes” (“two touches” were felt) or “no” (only “one touch” was felt). The threshold-tracking algorithm specified the separation to be used based on the participant’s previous responses. Fifteen trials were administered, after which the algorithm estimated the threshold (i.e., the separation predicted to result in the perception of two points 50% of the time). The threshold was $\log_{10}$-transformed prior to analysis.

Warmth Detection and Cool Detection Thresholds

A modification of the Marstock protocol was used to estimate the detection thresholds for warmth and cool at each site (Fruhstorfer et al., 1976; Essick et al., 2004). The thermal stimuli were delivered by a TSA II Neurosensory Analyzer (Medoc Advanced Medical Systems U.S., Durham, NC). A special intraoral transducer probe, 6 mm in diameter, was used to apply thermal stimuli to the discrete sites on the vermilion. A single layer of cling film was stretched tightly across the end of the probe to maintain clinical asepsis. The film was replaced between subjects. Prior to measuring the thermal thresholds, the temperature of the vermilion was estimated using a remote sensing infrared thermometer held above the test sites (SenseLab Tempett; Somedic Sales AB, Horby, Sweden). This temperature defined the baseline vermilion temperature. If needed, cotton rolls were placed in the labial vestibule to improve access to the vermilion.

To test each site, the transducer probe was set to the baseline vermilion temperature and applied perpendicularly to the skin with consistent and comfortable pressure (the probe indented the vermilion skin 1 to 2 mm). After about 7 seconds, warming pulses were produced at 0.3°C/sec. Each was terminated by the participant’s response to signify that the transducer began to feel warmer. The temperature returned to the baseline temperature and the next stimulus was initiated at a randomly chosen time between 4 and 6 seconds. Four stimuli were delivered at each test site. If the participant’s responses to the first two stimuli appeared inappropriate to the experimenter (e.g., the participant responded before the warming pulse was delivered), the testing was restarted at that site. The warmth detection threshold was calculated as the difference between the mean of the four response temperatures and the baseline vermilion temperature. The cool detection threshold was estimated in a similar manner. The stimulus temperature decreased at 0.3°C/sec until the participant responded to signify that the transducer began to feel cool. The warmth and cool detection thresholds were $\log_{10}$-transformed prior to analysis.

Sensory Mapping

Because none of the noncleft participants reported any areas of altered sensation on the face, the mapping procedure was not applied. For the participants with a cleft lip, areas of altered sensation were identified by stroking the cotton tip and the wooden ends of a cotton-tip applicator stick lightly across the face, midcheek to midcheek, along parallel paths from the inferior nose to the mentolabial groove (Essick et al., 2005). The participant was asked to concentrate and to tell the examiner of any unusual or different feelings in the face and lips from midcheek to midcheek (Essick et al., 2005). The participant was asked to tell the examiner if the stimulus felt weaker, stronger, smoother, rougher, duller, sharper, scratchier, or less scratchy. The examiner outlined the identified areas with a washable-ink marker and photographed the patient's face with a digital camera.

Using photographs and participants' comments, the cleft lip participants were categorized as (1) whether there was evidence of any altered sensation on the upper lip or midface, (2) whether the altered sensation was more indicative of losses in sensitivity (hyposensitivity) or increased sensitivity (hypersensitivity), and (3) whether the outlined area of sensory alteration encompassed the specific test sites on the upper vermilion.

Data Analysis

Linear mixed effects models were used to examine the effects of between-participant and within-participant variables on the $\log_{10}$-transformed values of the thresholds. Between-participant variables included presence of cleft lip, presence of bilateral cleft, presence of cleft palate, presence of altered sensation on midface, nature of altered sensation (hyposensitivity or hypersensitivity), age, and sex. Within-participant variables included presence of cleft on side tested, altered sensation at site tested, and visit (first or second). The effect of each variable was estimated by a regression coefficient (the beta given in the data tables). Further details of the statistical models can be found in the Appendix. The relationships between altered sensation and the sensory thresholds were analyzed only for the participants with cleft lip, because none of the noncleft participants reported any alteration. These analyses were considered exploratory, because mappings were not completed for five participants with cleft lip due to the lack of attention or the participant's visits had been completed before the mapping procedure had been implemented in the study. Separate analyses were conducted for the upper and lower lip data: An aim of the study was to determine the impact of the presence of a cleft on the threshold measures, and the lower lip that did not ever have a cleft.

Results

A total of 56 participants with cleft lip (average age = 12.7 years; SD = 3.54; range = 6.9 to 21.5 years) and 37 noncleft participants (average age = 13.1 years; SD = 3.6; range = 6.6 to 22.1 years) provided data for this report (Table 1). Ten of the participants with cleft lip had bilateral clefts, and 39 had cleft palate in addition to cleft lip. During the mapping procedure, areas of altered sensation were identified on the midface of 32 participants with cleft lip. The alteration was consistent with hyposensitivity (i.e., stimulus-evoked sensations were less intense, duller, lighter, or less ticklish than elsewhere on the face) for 16 participants whose alterations were classified. The perceived alteration for the other 14 participants was consistent with hypersensitivity (i.e., the stimulus-evoked sensations were more intense, stronger, or more ticklish). Of those mapped, type of alteration could not be classified and/or the side could not be ascertained for three participants.

All of the participants with bilateral cleft lip who perceived altered sensation reported this alteration on only one side of the upper vermilion. For 20 of the participants with unilateral cleft lip who perceived an alteration, the altered sensation encompassed the test site on the clefted side.

Differences Between Participants With Cleft Lip and Noncleft Participants

Descriptive statistics are shown for the two-point, cool, and warmth detection thresholds for the upper vermilion in Figure 1 and the lower vermilion in Figure 2. The values are averaged over right and left sides. On average, the thresholds did not differ for the two groups of participants on either the upper or lower vermilion sites (p values > .17; Tables 2 and 4).

Differences Within and Between Participants With Cleft Lip

Differences were detected within and among subgroups of participants with cleft lip. These differences were unrelated to the presence of a cleft on the side tested (Tables 2 and 4); rather, they were associated with differences in the reports of altered sensation and the bilaterality of the clefts. Differences are illustrated for the two-point perception threshold, the warmth detection threshold, and the cool detection threshold in Figures 3 to 5, respectively.

Figure 3 shows descriptive statistics for the two-point threshold for the participants with cleft lip who had altered sensation. The thresholds were greater on the upper vermilion of those participants with hyposensitive altered sensations ($\bar{X}$ = 3.5 mm) compared with participants with hypersensitive altered sensations ($\bar{X}$ = 2.7 mm, p = .01; Table 3). No other variable accounted for variability in the two-point thresholds on the upper vermilion (Tables 2 and 3) or on the lower vermilion (Tables 4 and 5).

The results for the thermal thresholds were more complex, involving differences among subgroups of participants in sensitivity on the upper and lower lips. The differences were always in the same direction for the upper and lower vermilion sites, although the effects did not always attain statistical significance at the .05 level at both sites. For example, participants with cleft lip who reported altered sensation on the mid-face tended to have lower warmth detection thresholds on both the lower ($\bar{X}$ = 1.9°C versus 2.6°C, p = .03) and upper ($\bar{X}$ = 2.3°C versus 3.0°C, p = .08) vermilion compared with participants who did not report altered sensation (illustrated by the left panel of Fig. 4). In contrast, the cool detection thresholds on the lower vermilion were higher for those same participants with altered sensation than for those who did not report altered sensation ($\bar{X}$ = 1.4°C versus 1.0°C, p = .01; Fig. 5). A trend in the same direction was observed on the upper vermilion ($\bar{X}$ = 1.5°C versus 1.3°C, p = .26).

Participants who had a bilateral cleft lip exhibited lower warmth detection thresholds on the upper vermilion than did those who had a unilateral cleft lip ($\bar{X}$ = 1.9°C versus 2.8°C, p = .04). A trend in the same direction was observed on the lower vermilion ($\bar{X}$ = 1.7°C versus 2.2°C, p = .14). This result is illustrated in the right panel of Figure 4. No other variables accounted for variability in the thermal thresholds with the exception of visit (Tables 2 and 4): The thresholds for warmth detection tended to be slightly lower at visit 2 than on visit 1 (p = .01).

Differences Within Noncleft Control Participants

Differences in the threshold values for the upper and lower vermilion were detected for all three threshold measures (Fig. 6 and Table 6). The noncleft participants were found to have lower thresholds for two-point discrimination on the upper vermilion (mean threshold = 3.0 mm) than on the lower vermilion (3.2 mm; p = .01). There was also a significant difference between males and females (p = .02): female patients had an adjusted mean two-point threshold of 2.83 mm, whereas male patients had an adjusted mean threshold of 3.33 mm.

For cool detection, location was significant (p = .03), but unlike the two-point thresholds, the upper vermilion (mean threshold = 1.27°C) was less sensitive than the lower vermilion

(1.15°). Similarly for warmth, the detection threshold was higher on the upper vermilion (2.3°C) than on the lower vermilion (2.0°C; $p = .001$). Similar to the participants with cleft lip, the mean threshold for warmth detection decreased slightly from visit 1 to visit 2 (by 0.26°C; $p = .004$).

The noncleft participants were more sensitive to cool than to warm stimuli ($p = .0001$; Table 7). On average, the cool detection thresholds were 1.8°C lower than the warmth detection thresholds for the upper lip and 1.7°C lower than the warmth detection threshold for the lower lip.

Discussion

Most neurosensory studies published to date suggest that patients with cleft lip and palate exhibit normal or near normal orofacial sensory function. For example, tactile sensitivity (pressure detection thresholds) and acuity (two-point discrimination) on the upper lip, midface, and hard and soft palates have been found to be comparable for groups of patients and control subjects (Posnick et al., 1994b; Uchiyama et al., 1998; Akal et al., 2000). Consistent with this previous work, the current study found that threshold values of two-point perception, warmth detection, and cool detection for the participants with cleft lip, on average, did not differ from those of the noncleft group. However, recent neurocognitive studies have demonstrated that patients with nonsyndromic clefts constitute a heterogeneous group of individuals in their ability to process and respond to sensory stimuli (Čeponienė et al., 1999, 2002; Laasonen et al., 2004). The investigators of these studies hypothesized that the developmental defects, visibly observed in the orofacial region, extend to patterns of neuronal disorganization that are specific to distinct cleft subtypes (e.g., cleft lip only versus cleft lip and palate). Although the underlying mechanisms are not known for certain, developmental errors associated with signaling molecules, such as the neural cell adhesion molecule, are strongly implicated. These molecules are involved not only in the fusion of the labial and palatal shelves but also in the formation of neural connections and neurotransmitter systems that critically determine the central representations of sensory stimuli (Rutishauser et al., 1988; Melnick, 1992; Čeponienė et al., 1999).

Differences in neurocognitive function among subgroups of patients with clefts have been demonstrated both neurophysiologically and psychophysically. For example, cortical evoked potential studies have found electrophysiological evidence of impairment in auditory short-term memory in patients with cleft palate only (Čeponienė et al., 1999). The impairment is graded in severity with the posterior extent of the cleft. These studies further showed that pooling data from patients with cleft lip (or cleft lip and alveolus) with data from patients with cleft lip and palate can mask deficits in the latter group of patients (Čeponienė et al., 2002).

Psychophysical testing of temporal processing acuity (i.e., the ability to process rapidly changing sequential information in the auditory, visual, and tactile modalities) also has identified cleft subtype-specific deficits (Laasonen et al., 2004). Overall, patients in the cleft lip and palate subgroup of Laasonen et al. exhibited the best temporal acuity—better even than noncleft subjects in the tactile modality—and patients with only submucosal palatal clefts exhibited the worst performance. However, the thresholds, when pooled and averaged across the different subgroups of patients with clefts, did not differ from those of the noncleft subjects.

Differences Within and Among Patients With Cleft Lip

In recognition of the possibility that participants with cleft lip in the current study might not represent a homogenous group with respect to their neurosensory function, statistical models were developed to account for differences in the participants' reports of altered sensation, as well as for anatomical differences in their clefts (Appendix). Subgroups of participants with cleft lip were found to exhibit differences in neurosensory thresholds that could not be explained easily by a simple loss of innervation in and around the healed surgical sites. For example, lower thresholds for warmth detection were observed on the upper vermilion in participants with bilateral cleft lip compared with participants with unilateral cleft lip (Fig. 4, right). Increased innervation of the tissue surrounding the scar by warming thermoreceptive afferents might be postulated as the basis for this finding. The explanation, however, seems unlikely because for participants with unilateral cleft lip, the warmth threshold was not lower on the clefted side than on the nonclefted side.

Lower thresholds for warmth detection also were observed on the vermilion in participants with cleft lip who reported altered sensation on the midface region compared with those who did not (Fig. 4, left). This finding was attributed initially to a difference in response bias: Specifically, those patients who were more attuned to the presence of altered sensation on the face might be expected to be more attuned to detecting subtle increments and decrements in the temperature of the stimulus probe (Essick et al., 2004). However, this simplistic explanation seems unlikely, because the same participants who reported altered sensation exhibited higher (rather than lower) thresholds for cool detection compared with participants who did not (Fig. 5).

In contrast to thresholds for warmth or cool perception, qualitative differences in participants' reports of altered sensation were found to predict differences in two-point perception thresholds on the upper vermilion. Specifically, patients whose altered sensations were more consistent with hyposensitivities exhibited higher thresholds than patients whose altered sensations were more consistent with hypersensitivities (Fig. 3). This pattern is consistent with that expected for impaired mechanoreceptive function after peripheral nerve injury (Chen et al., 1995; Feldman et al., 1997; Essick et al., 2002), as well as for impaired tactile function secondary to central neural dysfunction in children (Bolanos et al., 1989; Krumlinde-Sundholm and Eliasson, 2002). However, given that the thresholds did not differ between the cleft and noncleft sides of the upper lip, the higher thresholds observed in participants who reported hyposensitivities may not be explained solely by greater tissue and nerve injury.

All considered, the sensory differences observed between subgroups of participants with cleft lip are complex and are not explained by any simple model purporting higher thresholds at less innervated sites. The differences may reflect central disturbances in the representation and processing of sensory stimuli, disturbances that have been reported previously to underlie neurocognitive differences between subgroups of patients with cleft lip and palate (Čeponienė et al., 1999, 2002; Laasonen et al., 2004). The generality of the developmental disturbance would additionally explain why the alteration in sensory function extends to the lower lip (Iwata et al., 2004; Jääskeläinen et al., 2005). Indeed, our investigative team has found that fine motor control is impaired in the lower lip, as well as in the upper lip, of many cleft patients (D'Antonio et al., 1994, 1995; Trotman et al., 2007a). Thus, neither sensory nor motor dysfunction in participants with cleft lip can be attributed solely to the morphological defects in their upper lip or maxilla.

Differences Within Noncleft Control Participants

Findings from the noncleft participants were in general accord with those from adult noncleft populations. For example, the two-point perception thresholds were not only roughly similar in value to those from adults, but similar test site and gender differences were found. In the present study, the two-point threshold, on average, on the upper vermilion (3.0 mm) was 94% of the value on the lower vermilion (3.2 mm; $p = .01$), and the threshold for females (2.8 mm) was 85% of the value for males (3.3 mm; $p = .02$). A study of young adult subjects (median age = 22 years; Chen et al., 1995) found that the value on the upper vermilion (2.4 mm) approximated 85% of the value on the lower vermilion (2.8 mm), and the threshold for women (2.3 mm) was 82% of the value for men (2.8 mm; $p = .04$). The procedure used by Chen et al. (1995) for estimating the two-point threshold was similar to the one used in the present study. Other investigators also have found that children older than 6 years of age can perform tests of two-point discrimination with an acceptable degree of reliability and that values from children and adults are roughly comparable (Cope and Antony, 1992; Menier et al., 1996).

Similarly, investigators have found that children in this age range can reliably perform tests of warmth and cool detection (Hilz et al., 1998; Meier et al., 2001). Although similar testing procedures were used in these previous studies and in the current study, sites on the upper and lower limbs were tested with thermal transducer probes that were 12.5 to 42 times greater in area than those used in the current study, making any comparison of threshold values between studies uninterpretable. However, studies of adult subjects have found that the face is more sensitive to cool than to warmth (reviewed in Essick et al., 2004), substantiating the similar finding from the control children in the current study. The slight decrease in the warmth detection threshold from visit 1 to visit 2 is suggestive of a learning effect. It is unclear why only this threshold exhibited such an effect, although the exquisite sensitivity of warmth detection to subtle changes in sensory function and in experimental conditions is well documented (Van Boven and Johnson, 1994; Hilz et al., 1998; Meier et al., 2001; Essick et al., 2004; Jääskeläinen et al., 2005).

To the authors' knowledge, no previous study has demonstrated lower thresholds for warmth and cool detection on the lower vermilion compared with the upper vermilion. However, thermal thresholds are particularly sensitive to innervation density, and other equally sensitive neurosensory measures of innervation density are lower in value on the lower vermilion than on the upper vermilion (Van Boven and Johnson, 1994; Patel et al., 1997). Alternatively, the miniature transducer probe used in the current study stimulated less tissue and could be placed more precisely on the vermilion test sites compared with the larger probes used in previous studies. These features might have revealed a sensory difference that was obscured in previous studies by use of larger probes that could not be positioned so precisely.

Limitations and Future Directions

Collection of the data in the present study required the cooperation, concentration, and active participation of young individuals in a clinical environment. As such, the data may have been biased by the anxieties and cognitive skills of the individual patients. Moreover, relatively small numbers of participants provided data for some of the subgroup analyses (e.g., only 10 participants had bilateral clefts), and membership in the subgroups was often an outcome of the participant's evaluation (e.g., presence of altered sensation). Given these limitations, we cannot rule out the possibility that some of the neurosensory differences detected within and among participants with cleft lip were due to biases and variables unrelated to those under investigation or to chance alone. However, given that differences in neurocognitive function among subgroups of similarly aged individuals with cleft lip and palate have been identified by other investigators, the results of the present study cannot be dismissed.

The rather subtle differences in the sensory thresholds between subgroups of participants with cleft lip bring into question the role of altered sensory function in the motor disability of the perioral region with cleft lip (e.g., see parts I and II of this series of papers). However, sensory function of hairy skin regions may be of greater importance to motor control

(Trulsson and Essick, 1997), regions that were not evaluated in this study. Future work should aim to confirm and extend the neurosensory observations of the present study and to determine if/how they may be related to neurocognitive abnormalities or altered motor control.

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Appendix

Description of Statistical Models

Covariates

Given the possibility that sensory testing data from younger participants might not be as reliable as data from older participants and that males might differ from females in their threshold values, both age and sex were included as covariates. Age was centered on the mean value of age in order to aid model interpretation (i.e., the model estimate specifies an increase or decrease in threshold related to a 1-year difference from the average age of all participants). The variable visit (first or second) was included to evaluate consistency in the threshold measures over the 3-month period.

Explanatory Variables

The data set consisted of information from both between- and within-participant variables. These explanatory variables are presented in Table 8. Effect coding was used to provide a cell mean interpretation for all variables with two exceptions. Reference cell coding was used to differentiate cleft lip and control groups (Presence of Cleft Lip); and for patients with a cleft, to differentiate those with versus without altered sensation (Presence of Altered Sensation).

Model Specification

Each of the outcome measures (the $\log_{10}$-transformed values of the two-point threshold, the warmth detection threshold, and the cool detection threshold) was analyzed separately for the upper vermilion and the lower vermilion. The aim was to examine the effects of between-participant variables and within-participant variables on each of the sensory thresholds.

The first analysis sought to compare the noncleft participants and the participants with cleft lip. The basic linear model of interest was

$$Y_{ij}=\beta_0+b_i+\beta_1 X_{1i}+\beta_2 X_{2i}+\beta_3 X_{3i}+\beta_4 X_{4i}+\beta_5 X_{5i}+\beta_6 X_{6ij}+\beta_7 X_{7ij}+e_{ij}$$

where Y_{ij} is the jth threshold measurement from the ith participant. The covariates (X) are defined in Table 8A; between-participant covariates have the subscript i, whereas covariates that may vary within participants have the additional subscript j. The intercept term β_0 represents the overall mean threshold response for noncleft participants, b_i is a random participant-specific effect, and e_{ij} are independent random error terms. The model is estimated using maximum likelihood as implemented by SAS Proc Mixed (Version 9.1; SAS Institute, Inc., Cary, NC).

The choice of model parameterization provides the following expected responses depending upon the presence of a cleft lip (and dropping on the $\beta_3 X_{3i} + \beta_4 X_{4i} + \beta_5 X_{5i} + \beta_6 X_{6ij}$ right-hand side of the equation without loss of generality):

$$\text{Control:} \quad E(Y_{ij})=\beta_0$$

Unilateral (same side as test site):

$$E(Y_{ij})=\beta_0+\beta_1-0.5\beta_2+0.5\beta_7$$

Unilateral (opposite side to test site):

$$E(Y_{ij})=\beta_0+\beta_1-0.5\beta_2-0.5\beta_7$$

$$\text{Bilateral:} \quad E(Y_{ij})=\beta_0+\beta_1+0.5\beta_2$$

From these equations, certain interpretations of the regression coefficients are apparent: The difference in the expected mean for those participants with a cleft lip (regardless of the type of cleft) and the noncleft participants is β_1; the difference between unilateral (regardless of test site: same or opposite side) and bilateral is β_2; and the difference between a cleft lip on the side tested and a cleft lip on the opposite side among unilateral cleft participants is β_7. Additionally, the difference in expected means between cleft lip with cleft palate and cleft lip without cleft palate is β_3; the difference due to a 1-year increase in age is β_4; between females and males is β_5; and between second and first visit is β_6.

A similar approach was used for the exploratory assessment of altered sensation in the participants with a cleft (Table 8B). Altered sensation was not reported for the lower vermilion sites; however, data from each lower vermilion site was coded “altered” if altered sensation was reported on the opposing upper vermilion site. The basic linear model of interest was

$$Y_{ij}=\beta_0+b_i+\beta_8X_{8i}+\beta_9X_{9i}+\beta_{10}X_{10i}+\beta_{11}X_{11i}+\beta_{12}X_{12ij}+\beta_{13}X_{13ij}+e_{ij}$$

The difference in the expected mean for participants with cleft lip who had altered sensation on the midface and those without is β_8; the difference between those with hyposensitivity and those with hypersensitivity is β_9; and the difference between those who perceived the alteration to be on the side tested and those who perceived it to be on the opposite side is β_{13}.

Additional analyses were conducted on the data from the noncleft participants. Linear models were used to determine whether the upper and lower vermilion differed in sensitivity for the three threshold measures and whether the lips differed in sensitivity to cold versus warmth. The between-participant covariates in these analyses were age (centered), sex, and visit; and the within-participant covariate was location. Using effect coding, a value of .5 was assigned to the upper vermilion and −.5 to the lower vermilion.

TABLE 8

Explanatory variables considered for inclusion in the model and the manner in which they were coded.

A) Comparison of Controls and Children with Cleft Lip					
Between-Subject Variables				**Levels and Values**	
Presence of Cleft Lip	X_1	No	0	Yes	1
Bilateral Cleft Lip	X_2	Control	0	Unilateral	−0.5
				Bilateral	0.5
Cleft Palate	X_3	Control	0	Cleft lip without cleft palate	−0.5
				Cleft lip with cleft palate	0.5
Age	X_4	Continuous – centered prior to modeling			
Sex	X_5	Male	−0.5	Female	0.5
Within-Subject Variables					
Visit	X_6	First	−0.5	Second	0.5
Cleft Present on Side Tested	X_7	Control	0	Bilateral cleft present	0
				Unilat. Cleft, opposite side	−0.5
				Unilat. Cleft, tested side	0.5

B) Effect of Altered Sensation for Children with Cleft Lip					
Between-Subject Variables					
Presence of Altered Sensation	X_8	No	0	Yes	1
Nature of Alteration	X_9	None	0	Hyposensitivity	−0.5
				Hypersensitivity	0.5
Age	X_{10}	Continuous – centered prior to modeling			
Sex	X_{11}	Male	−0.5	Female	0.5
Within-Subject Variables					
Visit	X_{12}	First	−0.5	Second	0.5
Alteration Present at Site Tested	X_{13}	No Alteration	0	Not on tested side	−0.5
				On tested side	0.5

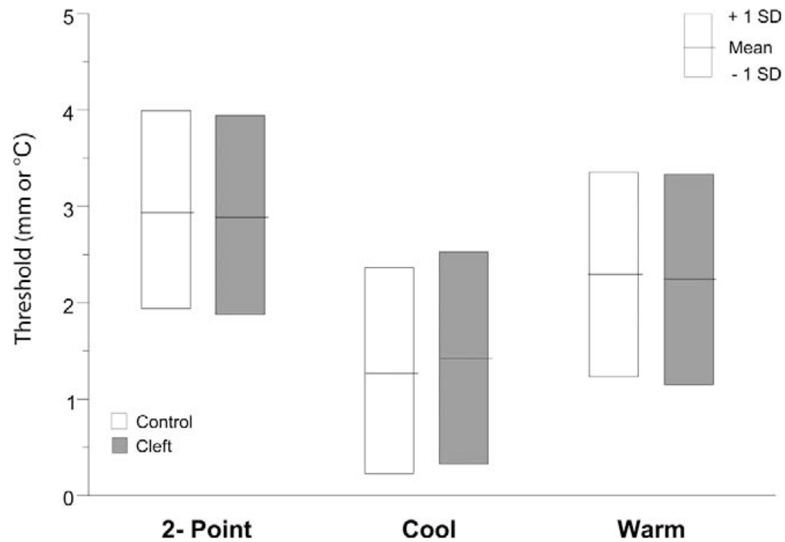

FIGURE 1.
Adjusted mean (±1 standard deviation) values for the two-point, cool, and warm detection thresholds on the upper vermilion. Data shown separately for patients with cleft lip and noncleft control subjects.

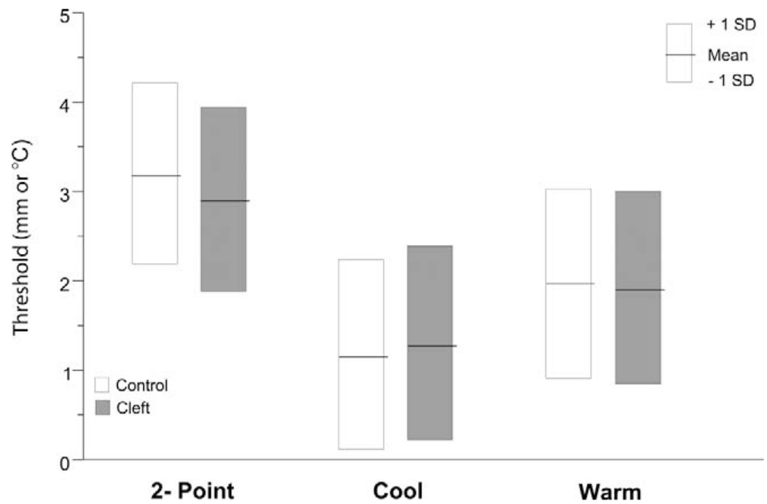

FIGURE 2.

Adjusted mean (±1 standard deviation) values for the two-point, cool, and warm detection thresholds on the lower vermilion.

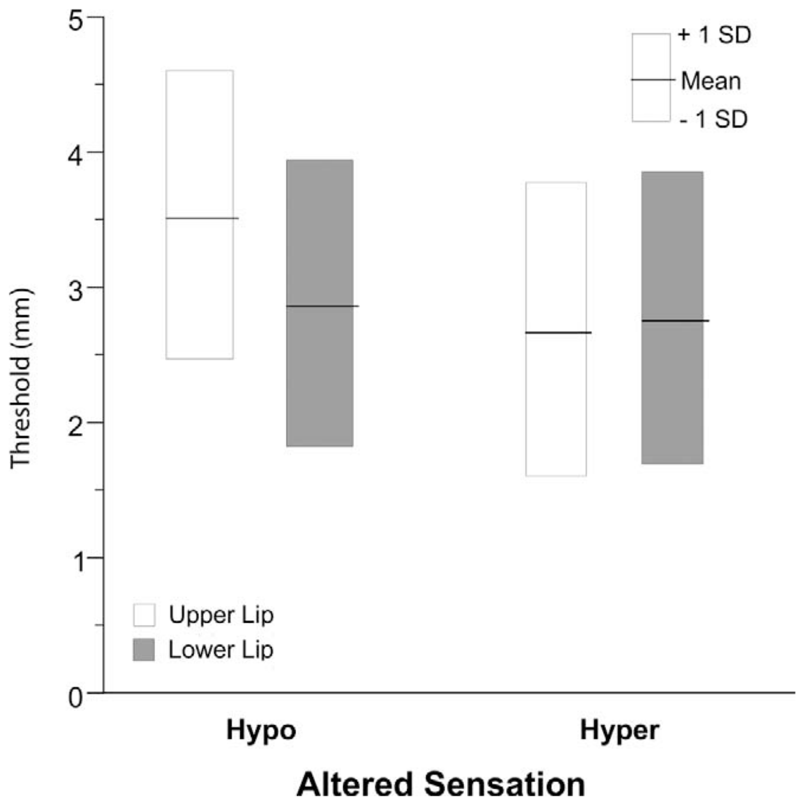

FIGURE 3.

Adjusted mean (±1 standard deviation) values for the two-point thresholds from the upper and lower vermilion of patients with cleft lip. Values for testing unilateral and bilateral cleft patients with hyposensitive versus hypersensitive altered sensations are shown.

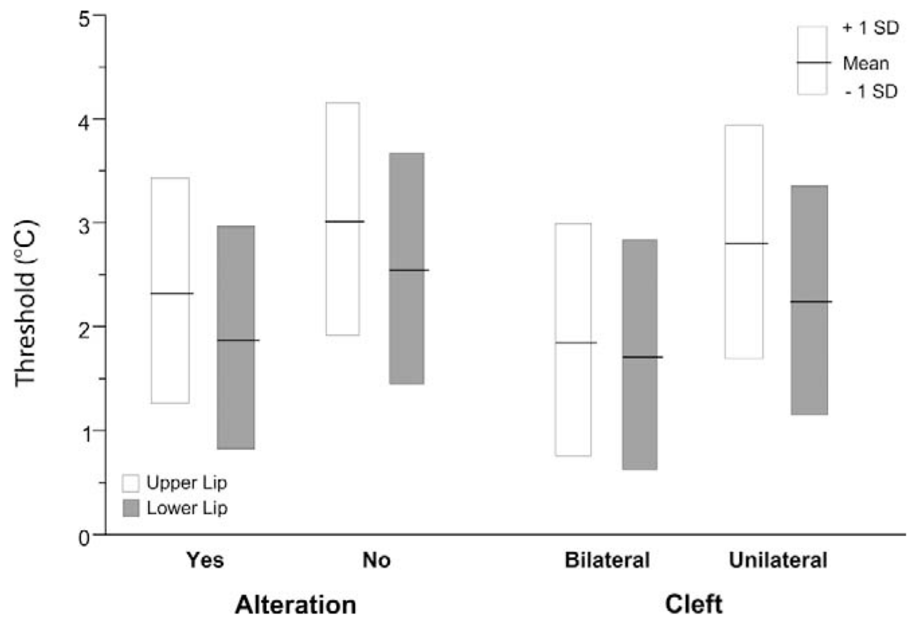

FIGURE 4.
Adjusted mean (±1 standard deviation) values for the warmth detection thresholds from the upper and lower vermilion of patients with cleft lip. Values for testing patients with versus without altered sensation are shown to the left. Values for testing patients with bilateral versus unilateral clefts are shown to the right.

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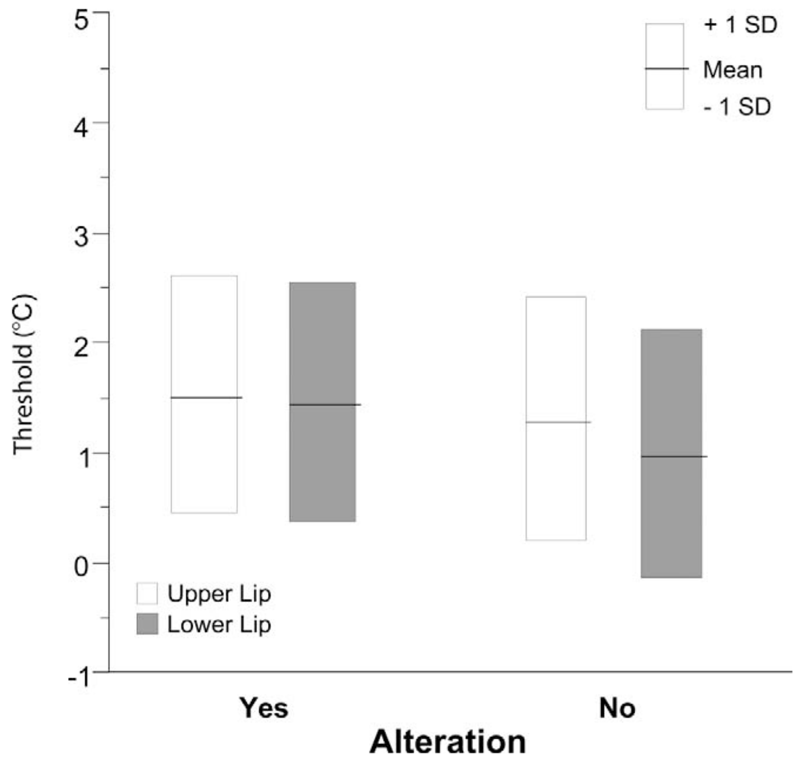

FIGURE 5.
Adjusted mean (±1 standard deviation) values for the cool detection thresholds from patients with cleft lip. Values for testing patients with versus without altered sensation are shown separately for the upper and lower vermilion.

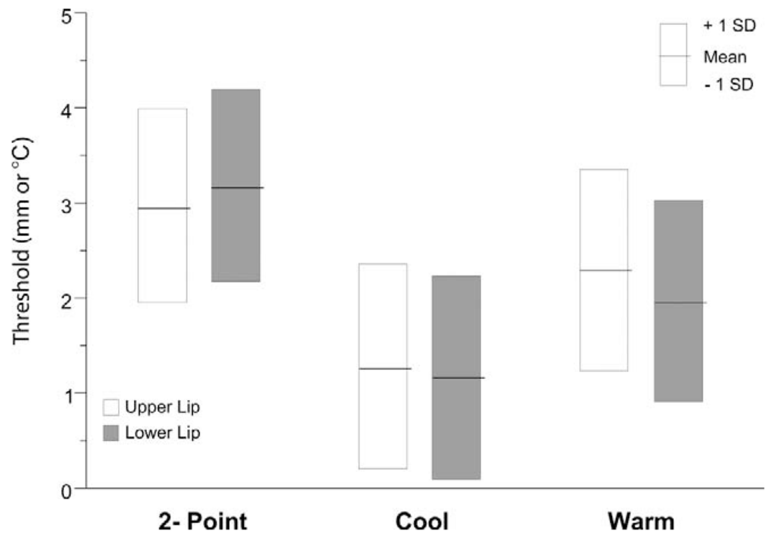

FIGURE 6.
Adjusted mean (±1 standard deviation) values for the two-point, cool, and warm detection thresholds for noncleft control subjects only. Data shown separately for the upper and lower vermilion.

TABLE 1

Demographic Characteristics of the Subjects Without and With Cleft Lip

		Age (y)	
	n	**Mean**	**SD**
Without cleft (control)	37	13.1	3.60
Cleft lip without cleft palate	17	12.7	4.58
Cleft lip with cleft palate	39	12.7	3.05
All cleft lip	56	12.7	3.54
Unilateral	46	12.7	3.69
Sensation not altered	16	11.9	2.77
Sensation altered on midface	26	13.2	4.13
Hyposensitive	14	14.6	4.44
Hypersensitive	11	11.5	3.31
Sensation altered at test site (cleft side)	20	13.6	3.75
Sensation altered at test site (noncleft side)	4	13.6	5.87
Mapping not completed*	4	12.6	4.2
Bilateral	10	12.6	2.93
Sensation not altered	3	13.4	3.16
Sensation altered on midface	6	11.6	2.61
Hyposensitive	2	11.7	0.61
Hypersensitive	3	11.8	4.03
Sensation altered one side only	6	11.6	2.61
Mapping not completed*	1	16.5	—

*Based on the responses from the young subjects, it was not possible to determine if sensation was altered.

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TABLE 2

Parameter Estimates* (Standard Errors) and *p* Values Associated With Between- and Within-Subject Variables for the Assessment of 2-Point, Cool, and Warm Detection Thresholds for the Upper Vermilion of Controls and Subjects With Cleft Lip

	Detection Thresholds								
	2-Point			Cool			Warm		
	Beta	**SE**	**p Value**	**Beta**	**SE**	**p Value**	**Beta**	**SE**	**p Value**
Intercept	.47	(.02)	<.001	.11	(.04)	.01	.36	(.04)	<.001
Between-subject variables									
Presence of cleft	−.01	(.03)	.81	.04	(.06)	.51	−.01	(.06)	.90
Presence of bilateral cleft	−.05	(.05)	.31	−.06	(.09)	.49	−.18	(.08)	.04
Presence of cleft palate	−.01	(.04)	.70	−.06	(.07)	.38	.04	(.07)	.54
Age (per year)	.002	(.004)	.66	.004	(.01)	.57	.005	(.01)	.45
Female	−.02	(.03)	.49	.02	(.05)	.72	−.07	(.05)	.18
Within-subject Variables									
Second visit	.006	(.01)	.57	−.005	(.02)	.78	−.08	(.02)	<.001
Cleft present on side tested	.02	(.01)	.27	.009	(.03)	.73	.01	(.03)	.64

*Model regression coefficients (Beta) evaluating differences in the threshold values for participants with versus without cleft lip (Presence of Cleft), female versus male (Female), second versus first visit (Second Visit), and so on. See Appendix for further details.

TABLE 3

Parameter Estimates (Standard Errors) and *p* Values Associated With Between- and Within-Subject Variables for the Effect of Altered Sensation in Subjects With Cleft Lip on the 2-Point, Cool, and Warm Detection Thresholds for the Upper Vermilion

	Detection Thresholds								
	2-Point			Cool			Warm		
	Beta	SE	p Value	Beta	SE	p Value	Beta	SE	p Value
Intercept	.49	(.03)	<.001	.11	(.05)	.06	.48	(.06)	<.001
Between-subject variables									
Presence of altered sensation	−.02	(.04)	.49	.07	(.06)	.26	−.11	(.06)	.08
Nature of altered sensation	−.12	(.04)	.01	−.12	(.08)	.12	.04	(.08)	.59
Within-subject variables									
Alteration present at site tested	.01	(.02)	.77	−.03	(.04)	.36	−.002	(.04)	.96

TABLE 4

Parameter Estimates (Standard Errors) and *p* Values Associated With Between- and Within-Subject Variables for the Assessment of 2-Point, Cool, and Warm Detection Thresholds for the Lower Vermilion of Controls and Subjects With Cleft Lip

	Detection Thresholds								
	2-Point			Cool			Warm		
	Beta	**SE**	**p Value**	**Beta**	**SE**	**p Value**	**Beta**	**SE**	**p Value**
Intercept	.50	(.02)	<.001	.06	(.04)	.15	.29	(.04)	<.001
Between-subject variables									
Presence of cleft	−.05	(.03)	.17	.05	(.07)	.49	−.01	(.06)	.84
Presence of bilateral cleft	−.02	(.05)	.73	−.06	(.09)	.52	−.12	(.08)	.14
Presence of cleft palate	−.03	(.04)	.41	−.12	(.07)	.08	.06	(.06)	.35
Age (per year)	.001	(.004)	.99	.007	(.01)	.35	.001	(.01)	.84
Female	−.03	(.03)	.27	−.006	(.05)	.90	−.08	(.05)	.09
Within-subject variables									
Second visit	.01	(.01)	.14	.006	(.02)	.72	−.04	(.02)	.01
Cleft present on side tested	.01	(.01)	.30	.008	(.02)	.75	−.002	(.02)	.95

TABLE 5

Parameter Estimates (Standard Errors) and *p* Values Associated With Between- and Within-Subject Variables for the Effect of Altered Sensation in Subjects With Cleft Lip on the 2-Point, Cool, and Warm Detection Thresholds for the Lower Vermilion

	Detection Thresholds								
	2-Point			Cool			Warm		
	Beta	SE	p Value	Beta	SE	p Value	Beta	SE	p Value
Intercept	.45	(.03)	<.001	−.02	(.06)	.78	.41	(.05)	<.001
Between-subject variables									
Presence of altered sensation	−.003	(.03)	.92	.17	(.07)	.01	−.13	(.06)	.03
Nature of altered sensation	−.02	(.04)	.68	−.14	(.08)	.10	.04	(.07)	.63
Within-subject variables									
Alteration present at site tested	.01	(.02)	.71	−.01	(.04)	.72	−.001	(.04)	.99

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TABLE 6

Parameter Estimates (Standard Errors) and *p* Values Associated With Between- and Within-Subject Variables for the 2-Point, Cool, and Warm Detection Thresholds for the Noncleft Control Subjects Only

	Detection Thresholds								
	2-Point			Cool			Warm		
	Beta	**SE**	**p Value**	**Beta**	**SE**	**p Value**	**Beta**	**SE**	**p Value**
Intercept	.49	(.02)	<.001	.08	(.04)	.04	.32	(.03)	<.001
Between-subject variables									
Age (per year)	.004	(.01)	.37	.01	(.01)	.45	.0001	(.01)	.99
Female	−.07	(.03)	.02	−.03	(.07)	.60	−.07	(.06)	.21
Within-subject variables									
Second visit	.01	(.01)	.49	.01	(.02)	.69	−.05	(.02)	.004
Upper vermilion	−.03	(.01)	.005	.04	(.02)	.03	.07	(.02)	<.001

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TABLE 7

Parameter Estimates (Standard Errors) and *p* Values Associated With Between- and Within-Subject Variables for the Difference Between Warm and Cold Thresholds in the Control Subjects Only

	Difference in Detection Thresholds (Warm–Cold)		
	Beta	**SE**	**p Value**
Intercept	.24	(.03)	<.0001
Between-subject variables			
Age (per year)	−.01	(.01)	.26
Female	−.04	(.05)	.45
Within-subject variables			
Second visit	−.06	(.02)	.005
Upper vermilion	.02	(.02)	.26