Pathways of Sensory Recovery after Face Transplantation

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Background: Severely disfiguring facial injuries have a devastating impact on the patient's quality of life. The advent of facial allotransplantation has allowed optimal anatomical reconstruction to be achieved; however, the need for lifelong immunosuppression and unpredictable functional outcomes preclude it from routine acceptance in clinical practice. Evidence from published reports on the first four face transplant recipients indicates improved and accelerated return of sensation to the facial allograft despite suboptimal repair of the sensory nerves.

Methods: The authors performed a comparative analysis of the sensory outcomes following face transplantation with the sensory recovery achieved after conventional nerve repair, autologous face and scalp replantation, and vascularized free tissue transfer.

Results: Sensory recovery following face transplantation, even when the sensory nerves were not repaired, was comparable to the outcome of microsurgical repair of the peripheral branches of the trigeminal nerve and innervated free flaps.

Conclusions: Nearly normal sensory recovery can be expected following facial allotransplantation with or without repair of the sensory nerves. The mechanisms responsible for this surprising outcome include preservation of normal density of the receptors within the facial allograft, regeneration from the recipient bed and allograft margins, transmission of the sensory inputs through afferent fibers contained in the facial nerve, nerverorum of the facial nerve, or trigemino-facial communicating rami. Furthermore, immunosuppressive therapy with tacrolimus contributes to the accelerated nerve regeneration. The minimum requirements for quantitative sensory testing and timing of the follow-up assessments are outlined to facilitate comparison of sensory outcomes after face transplantation. (Plast. Reconstr. Surg. 127: 1875, 2011.)

In recent years, composite tissue allotransplantation has offered a unique opportunity for optimal restoration of facial anatomy and function in patients presenting with massive and disfiguring facial defects. Return of normal function is a critical determinant of transplant success and is essential to justify a favorable risk-to-benefit balance in view of the long-term side effects of immunosuppression and concerns about integration and psychological acceptance of the donor face. It should be further emphasized that recovery of fine facial movements is fundamental for sphincteral control, prevention of ectropion and drooling, and facilitation of normal speech; whereas normal sensation is critical for interaction with the environment, initiation of defense mechanisms, and deriving pleasure and satisfaction from the external stimuli. The motor and sensory pathways of the human face interact closely, and these interactions are essential for normal facial functions. Although the recovery of facial motor function has been studied extensively, the mechanisms of sensory return are not well established because of the lack of standard methods of assessments of facial sensory recovery after trauma. The available reports on the first four face transplant patients confirm a steady and consistent improvement of sensation, despite suboptimal repair of the sensory nerves.

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To fulfill the existing gap in the literature, the focus of this review is to present different mechanisms and pathways of sensory recovery and factors that contribute to optimal sensory outcomes after face transplantation. Understanding of sensory recovery pathways in the setting of face transplantation should be of value to all physicians involved in counseling and care of potential candidates for facial transplantation.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

We considered the following clinical conditions that could bring insight to the mechanisms of facial sensory recovery: (1) repair of the severed peripheral branches of the trigeminal nerve, (2) autologous vascularized tissue transfers commonly used in head and neck reconstruction, and (3) autologous scalp and face replantation. Access to the International Registry on Hand and Composite Tissue Transplantation was obtained. A comprehensive PubMed and Ovid MEDLINE search was performed in the English literature for peer-reviewed articles published between 1940 and 2010. The keywords used in the search are listed in Table 1. Articles relevant to the topic were selected from the reference list of the reviewed articles as well. In addition, a Google search was performed using “face transplantation” and “allo-transplantation” as key words.

Statistical Analysis

To compare the sensory outcomes in different clinical conditions, the sensory return was graded using the Medical Research Council Scale as modified by Mackinnon and Dellon1 based on the evaluation of light touch, pain, and two-point discrimination (Table 2). The Wilcoxon sum of ranks test was used to detect significant differences in the sensory recovery of innervated and noninnervated free flaps, innervated and noninnervated free fasciocutaneous flaps, and innervated and noninnervated free radial forearm flaps.

Table 1. Key Words Used for Literature Search

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Key Words</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve repair</td>
<td>“Trigeminal nerve,” “supraorbital nerve,” “infraorbital nerve,” “mental nerve,” “lingual nerve,” “inferior alveolar nerve” plus nerve repair, “microsurgery,” “neurotomy”</td>
</tr>
<tr>
<td>Autologous vascularized tissue transfer</td>
<td>“Innervated,” “noninnervated free flaps plus sensory reinnervation,” “sensory recovery plus facial,” “orofacial,” “oral” “oropharyngeal reconstruction”</td>
</tr>
<tr>
<td>Scalp and face replantation</td>
<td>“Scalp replantation,” “scalp avulsion plus sensory recovery”</td>
</tr>
<tr>
<td>Face transplantation</td>
<td>“Face transplantation,” “face allodtransplantation plus sensory recovery”</td>
</tr>
</tbody>
</table>

Table 2. Medical Research Council Scale as Modified by Mackinnon and Dellon*

<table>
<thead>
<tr>
<th>Score</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0</td>
<td>No recovery</td>
</tr>
<tr>
<td>S1</td>
<td>Recovery of deep cutaneous pain</td>
</tr>
<tr>
<td>S2</td>
<td>Return of some superficial pain/tactile sensation</td>
</tr>
<tr>
<td>S2+</td>
<td>Return of some superficial pain/tactile sensation with overreaction</td>
</tr>
<tr>
<td>S3</td>
<td>Return of some superficial pain/tactile sensation without overreaction and the presence of static two-point discrimination &gt; 15 mm</td>
</tr>
<tr>
<td>S3+</td>
<td>As per S3 with good localization of stimulus, static two-point discrimination = 7-15 mm</td>
</tr>
<tr>
<td>S4</td>
<td>As per S3+, static two-point discrimination = 2-6 mm</td>
</tr>
</tbody>
</table>


RESULTS

Sensory Recovery after Repair of Peripheral Branches of the Trigeminal Nerve

Thirteen publications summarizing assessment of neurosensory outcomes following repair of the peripheral branches of the trigeminal nerve were relevant to the study. These reports addressed the outcomes after repair of the inferior alveolar, lingual, infraorbital, and mental nerves that were damaged during orthognathic surgery or facial trauma. The population of patients in most of the studies was not uniform for either the type of nerve repaired or the type of procedure used for nerve repair. These procedures included external neurolysis, internal neurolysis, and nerve repair using either direct neurotomy or interpositional nerve grafting. The presented outcomes were not based on the method of nerve repair. Although all reports used quantitative sensory testing as a method of sensory assessment, the outcomes were mainly expressed as a “degree of improvement” in the global sensation in contrast to the expected quantitative results. Only four studies, presenting detailed results of objective neurosensory tests, were available following repair of a completely transected nerve (Table 3). The Medical Research Council Scale could be applied
Table 3. Sensory Recovery following Repair of the Sensory Nerves of the Face

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Cases</th>
<th>Age (yr)</th>
<th>Injured Nerve</th>
<th>Procedure</th>
<th>Surgical Delay (mo)</th>
<th>MRC Scale Score</th>
<th>Follow-Up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson and Smith, 1996</td>
<td>13</td>
<td>51</td>
<td>Lingual</td>
<td>Direct suture</td>
<td>16</td>
<td>S3+</td>
<td>17</td>
</tr>
<tr>
<td>Robinson et al., 2000</td>
<td>53</td>
<td>30</td>
<td>Lingual</td>
<td>Direct suture</td>
<td>15</td>
<td>S3+</td>
<td>12</td>
</tr>
<tr>
<td>Hillerup and Stolze, 2007</td>
<td>67</td>
<td>30</td>
<td>Lingual</td>
<td>Direct suture</td>
<td>8.5</td>
<td>NA</td>
<td>13</td>
</tr>
<tr>
<td>Tay et al., 2008</td>
<td>3</td>
<td>27</td>
<td>Inferior alveolar</td>
<td>Direct suture</td>
<td>0</td>
<td>S4</td>
<td>12</td>
</tr>
</tbody>
</table>

MRC, Medical Research Council; NA, not applicable.

to three series. These clinical studies confirmed that after an average of 14 months, direct repair of facial sensory nerves results in a functional sensory recovery ranging between S3+ and S4 on the Medical Research Council Scale.

Sensory Recovery after Free Tissue Transfer

Of 20 reviewed studies, 13 described noninnervated flaps, including radial forearm, lateral thigh, anterolateral thigh, latissimus dorsi, trapezius, rectus abdominis muscular cutaneous, fibula osteocutaneous, jejunal, and gastroomental flaps (Table 4). 6-18 In contrast, seven studies reported results of innervated free flaps, including radial forearm, anterolateral thigh, and rectus abdominis muscular cutaneous flaps (Table 5). 7,8,12,13,15,17,19,20 For scoring, the Medical Research Council Scale was applicable to 11 series of patients in the noninnervated flap group and six series of patients in the innervated flap group. Considering the median Medical Research Council Scale values in

Table 4. Sensory Recovery following Reconstruction of Defects in the Head and Neck Region with Noninnervated Free Flaps

<table>
<thead>
<tr>
<th>Reference</th>
<th>Free Flap</th>
<th>No. of Cases</th>
<th>Average Age (yr)</th>
<th>Indication, Site</th>
<th>Radiotherapy</th>
<th>MRC Scale Score</th>
<th>Average Follow-Up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laitenmaki et al., 1999</td>
<td>Dorsalis pedis flap</td>
<td>1</td>
<td>31</td>
<td>ND, face</td>
<td>ND</td>
<td>S3</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Latissimus dorsi flap</td>
<td>2</td>
<td>40</td>
<td>ND, face</td>
<td>ND</td>
<td>S2</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Trapezius flap</td>
<td>1</td>
<td>25</td>
<td>ND, face</td>
<td>ND</td>
<td>S0</td>
<td>28</td>
</tr>
<tr>
<td>Boyd et al., 1994</td>
<td>Radial forearm flap</td>
<td>10</td>
<td>56</td>
<td>Cancer, oral cavity</td>
<td>10</td>
<td>S2</td>
<td>14</td>
</tr>
<tr>
<td>Kato et al., 1995</td>
<td>Radial forearm flap</td>
<td>9</td>
<td>62</td>
<td>Cancer, oral cavity</td>
<td>ND</td>
<td>NA</td>
<td>25</td>
</tr>
<tr>
<td>Close et al., 1995</td>
<td>Radial forearm flap</td>
<td>4</td>
<td>62</td>
<td>Cancer, oral cavity</td>
<td>3</td>
<td>S3+</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Lateral thigh flap</td>
<td>4</td>
<td>55</td>
<td>Cancer, oral cavity</td>
<td>3</td>
<td>S3+</td>
<td>7</td>
</tr>
<tr>
<td>Shindo et al., 1995</td>
<td>Radial forearm flap</td>
<td>9</td>
<td>ND</td>
<td>Cancer, oro facial</td>
<td>8</td>
<td>S3</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Fibula osteocutaneous flap</td>
<td>9</td>
<td>ND</td>
<td>Cancer, oro facial</td>
<td>ND</td>
<td>S2</td>
<td>13</td>
</tr>
<tr>
<td>Vriezen et al., 1996</td>
<td>Radial forearm flap</td>
<td>40</td>
<td>60</td>
<td>Cancer, oral cavity</td>
<td>28</td>
<td>S3+</td>
<td>38</td>
</tr>
<tr>
<td>Kimata et al., 1999</td>
<td>Anterolateral thigh flap</td>
<td>6</td>
<td>58</td>
<td>Cancer, oral cavity</td>
<td>ND</td>
<td>S1</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Rectus abdominis muscular cutaneous flap</td>
<td>10</td>
<td>57</td>
<td>Cancer, oral cavity</td>
<td>ND</td>
<td>S1</td>
<td>27</td>
</tr>
<tr>
<td>Yu, 2004</td>
<td>Anterolateral thigh flap</td>
<td>5</td>
<td>60</td>
<td>Cancer, tongue</td>
<td>5</td>
<td>S1</td>
<td>15</td>
</tr>
<tr>
<td>Avery et al., 2006</td>
<td>Subfascial radial forearm flap</td>
<td>20</td>
<td>68</td>
<td>Cancer, oral cavity</td>
<td>ND</td>
<td>S3</td>
<td>≥6</td>
</tr>
<tr>
<td>Suprafascial radial forearm flap</td>
<td>20</td>
<td>58</td>
<td>Cancer, oral cavity</td>
<td>ND</td>
<td>S3</td>
<td>≥6</td>
<td></td>
</tr>
<tr>
<td>Kerawala et al., 2006</td>
<td>Osteofascial radial forearm flap</td>
<td>12</td>
<td>65</td>
<td>ND, mandible</td>
<td>7</td>
<td>S2</td>
<td>38</td>
</tr>
<tr>
<td>Shibahara et al., 2006</td>
<td>Radial forearm flap</td>
<td>38</td>
<td>60</td>
<td>ND, oral cavity</td>
<td>17</td>
<td>S3</td>
<td>12</td>
</tr>
<tr>
<td>Kim et al., 2008</td>
<td>Radial forearm flap</td>
<td>12</td>
<td>55</td>
<td>Cancer, oral and oro pharyngeal</td>
<td>ND</td>
<td>S2</td>
<td>6</td>
</tr>
<tr>
<td>Sabesan et al., 2008</td>
<td>Radial forearm flap</td>
<td>24</td>
<td>57</td>
<td>Cancer, oral cavity</td>
<td>ND</td>
<td>S3</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Jejunal flap</td>
<td>10</td>
<td></td>
<td>Cancer, lateral pharyngeal wall</td>
<td>S3</td>
<td>S3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastroomental flap</td>
<td>6</td>
<td></td>
<td>Cancer, tongue base</td>
<td>S2</td>
<td>S2</td>
<td></td>
</tr>
</tbody>
</table>

ND, not determined; NA, not available.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Nerves Repaired</th>
<th>Free Flap</th>
<th>MRC Scale</th>
<th>Average Follow-Up (mo)</th>
<th>Sensation, Site</th>
<th>Sensory Recovery after Scalp and Face Replantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyd et al., 1994</td>
<td>Lateral antebrachial cutaneous, lingual</td>
<td>Radial forearm</td>
<td>S4</td>
<td>11</td>
<td>Cancer, oral cavity</td>
<td>Sensory Recovery was graded S2 at a mean follow-up of 33 months. In contrast, coaptation of sensory nerves of the flaps with sensory nerves at the recipient site improved significantly (p = 0.0004) the quality of sensation, and functional sensation (S3+) was achieved at a mean follow-up of 15 months. A similar outcome was observed when innervated and noninnervated fasciocutaneous flaps (p = 0.002) or innervated and noninnervated radial forearm flaps (p = 0.013) were used for reconstruction.</td>
</tr>
<tr>
<td>Kato et al., 1995</td>
<td>Lateral antebrachial cutaneous, lingual</td>
<td>Radial forearm</td>
<td>S4</td>
<td>13</td>
<td>Cancer, oral cavity</td>
<td></td>
</tr>
<tr>
<td>Shiomi et al., 1998</td>
<td>Lateral antebrachial cutaneous, lingual</td>
<td>Radial forearm</td>
<td>S4</td>
<td>18</td>
<td>Cancer, oral cavity</td>
<td></td>
</tr>
<tr>
<td>Kurosaka et al., 1999</td>
<td>Lateral antebrachial cutaneous, lingual</td>
<td>Radial forearm</td>
<td>S3+</td>
<td>18</td>
<td>Cancer, oral cavity</td>
<td></td>
</tr>
<tr>
<td>Rocular et al., 2001</td>
<td>Lateral antebrachial cutaneous, lingual</td>
<td>Radial forearm</td>
<td>S4</td>
<td>14</td>
<td>Cancer, oral cavity</td>
<td></td>
</tr>
<tr>
<td>Kim et al., 2004</td>
<td>Lateral antebrachial cutaneous</td>
<td>Anterolateral thigh</td>
<td>ND</td>
<td>23</td>
<td>Cancer, oral cavity</td>
<td></td>
</tr>
<tr>
<td>Kim et al., 2008</td>
<td>Lateral antebrachial cutaneous</td>
<td>Anterolateral thigh</td>
<td>S3+</td>
<td>16</td>
<td>Cancer, oral cavity</td>
<td></td>
</tr>
<tr>
<td>ND, not determined.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensory Recovery after Facial Transplantation

The results of sensory recovery were published for four face transplant recipients. Relevant patient data are detailed in Table 7.25-37 Sensory nerves were repaired directly in only one patient.25,33 In one patient, repair of the sensory nerves was technically difficult because of the shortness of the recipient's nerve stumps: the repair of the infraorbital nerves required fibrin glue and the mental nerves were not repaired.35 In two patients, repair of sensory nerves of the allograft (infraorbital nerves) was not feasible because of trauma-related nerve damage.36,37

The first face transplant patient25,33 (Fig. 1) followed an early sensory reeducation and cortical
reintegration protocol. The initial signs of sensory recovery were recorded at 2 weeks for thermal stimuli. At 10 weeks, sensory return was present at the lateral part of the upper lip and lateral area of the chin on both sides of the graft. At 14 weeks, sensory recovery was found over the entire facial graft, including the tip of the nose, and response to painful stimuli was registered as well. After 6 months, pressure thresholds were normal in the upper half of the graft, whereas in the lower half, the patient reported diminished light touch. Heat and cold sensation was nearly normal at 4 months and normal at 6 months.

In the second transplant patient (Fig. 2), sensory discrimination was restored at 3 months, whereas heat and cold sensations were recorded over the entire graft at 8 months following transplantation.

The third patient had return of thermal and mechanical sensation 3 months after transplantation and improvement of the sensory thresholds at 12 months.

The fourth patient (Fig. 4) started sensory reeducation 48 hours after surgery, once per day for the first 6 weeks, then 3 times per week during follow-up. She recovered pain discrimination over a period of 5 months, and at 6 months the sensation returned to the entire transplanted face, with an average two-point discrimination of 7 mm (S3+) (Fig. 5).

Factors Contributing to Sensory Recovery

Recipient and Donor Characteristics

Clinical studies of vascularized autologous tissue transfer have shown that several factors can affect sensory recovery in the facial region. Anatomical location of the recipient site plays an important role, because sensory recovery within the orofacial region is better as opposed to trunk and lower extremity reconstruction. Several studies have shown that sensory upgrading (improved two-point discrimination compared with the donor site) can occur when flaps harvested from regions of lower innervation density are transferred to the orofacial regions. This has been explained by wider cortical representation of the human face.

Scarring of the recipient bed delays and hinders nerve regeneration. Composition of the flaps could either facilitate or delay sensory return. Presence of a skin component within the flap has been associated with improved sensory return, whereas muscle or bone components have been found to create a barrier for potential neurotization.

Table 6: Sensory Recovery following Scalp Replantation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases</th>
<th>Mean Age (yr)</th>
<th>Site</th>
<th>No. of Nerve Repair</th>
<th>Mean</th>
<th>Follow-Up (mo)</th>
<th>Outcome, Function Sensitivity</th>
<th>Acceptable Recovery of Sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung et al., 1994</td>
<td>7</td>
<td>26</td>
<td>Scalp, forehead</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>Recovery of sensibility</td>
<td></td>
</tr>
<tr>
<td>Ueda et al., 2003</td>
<td>6</td>
<td>51</td>
<td>Scalp, forehead</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>Light touch (forehead)</td>
<td></td>
</tr>
<tr>
<td>Nii et al., 1985</td>
<td>5</td>
<td>25</td>
<td>Scalp, forehead</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>Light touch</td>
<td></td>
</tr>
<tr>
<td>Yin et al., 2008</td>
<td>4</td>
<td>39</td>
<td>Scalp, forehead</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>Light touch</td>
<td></td>
</tr>
<tr>
<td>Cho et al., 2006</td>
<td>2</td>
<td>41</td>
<td>Scalp, forehead</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>Light touch</td>
<td></td>
</tr>
<tr>
<td>Fengaustian and Liji, 1996</td>
<td>1</td>
<td>35</td>
<td>Scalp, forehead</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>Light touch</td>
<td></td>
</tr>
<tr>
<td>Zho et al., 2004</td>
<td>1</td>
<td>35</td>
<td>Scalp, forehead</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>Light touch</td>
<td></td>
</tr>
<tr>
<td>Xie et al., 2009</td>
<td>1</td>
<td>35</td>
<td>Scalp, forehead</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>Light touch</td>
<td></td>
</tr>
<tr>
<td>Sabatino et al., 2004</td>
<td>5</td>
<td>24</td>
<td>Scalp, forehead</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>Light touch</td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Summarized Clinical Data of the Four Face Transplant Patients with Documented Long-Term Follow-Up

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Status before Transplantation</th>
<th>Donor Age, Sex</th>
<th>Repaired Nerves</th>
<th>Postoperative Sensory Reeducation</th>
<th>Outcome Measure</th>
<th>Follow-Up, Function</th>
<th>MRC Scale Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>38, F&lt;sup&gt;20&lt;/sup&gt; Distal nose, full-thickness upper and lower lips, chin, adjacent parts of right and left cheek (dog bite)</td>
<td>Preserved integrity of the proximal stumps of the zygomatic and levator anguli oris muscles; mouth opening 19 mm, surgical delay 6 mo; no previous reconstruction</td>
<td>46, F</td>
<td>Facial nerve: mandibular branch (left side) end to end; right side unrepaird because of scar</td>
<td>Yes</td>
<td>Pressure thresholds (Semens-Weinstein test) Heat and cold sensation (method not reported)</td>
<td>2.5 mo, lateral part upper lip, lateral mental area; 3.5 mo, whole skin surface including tip of nose; 4 mo, heat and cold sensation almost normal (normal at 6 mo)</td>
<td>NA</td>
</tr>
<tr>
<td>30, M&lt;sup&gt;14&lt;/sup&gt; Extensive skin and soft-tissue loss in the right buccal division, upper lip, total nose, front wall of the right maxillary sinus, lateral right orbital wall, infraorbital wall, right zygomatic bone, and large portion of right parotid gland (bear attack)</td>
<td>Severe cicatricial contracture deformity; first reconstruction radial forearm free flap, waited 17 mo before definitive reconstruction</td>
<td>25, male</td>
<td>Facial nerve: repair reported not satisfactory</td>
<td>ND</td>
<td>Pressure thresholds (Semens-Weinstein test) Heat and cold sensation (method not reported)</td>
<td>3 mo, sensory discrimination; 8 mo, heat and cold sensation</td>
<td>NA</td>
</tr>
<tr>
<td>29, M&lt;sup&gt;16&lt;/sup&gt; Massive plexiform neurofibroma middle and lower part of face</td>
<td>Complete facial paralysis (right side), partial paralysis (left side); immediate reconstruction</td>
<td>ND</td>
<td>Facial nerve: both nerves sutured and glued</td>
<td>ND</td>
<td>Not reported</td>
<td>3 mo, sensory reinervation of skin for thermal, mechanical sensation; 4 mo, pain sensation; 12 mo, improvement in sensory thresholds</td>
<td>NA</td>
</tr>
<tr>
<td>45, F&lt;sup&gt;20,27&lt;/sup&gt; Absence of nose, nasal lining, and underlying bone; contracted remnants of upper lip; loss of orbicularis oris and orbicularis oculi muscle functions; distorted and scarred lower eyelids (close-range shotgun blast)</td>
<td>23 previous reconstructive procedures; surgical delay to face transplantation, 51 mo</td>
<td>ND</td>
<td>Facial nerve: interpositional nerve graft from donor vagus nerve (right side); interpositional nerve graft from donor hypoglossal (left side)</td>
<td>Yes</td>
<td>Pressure thresholds (Pressure-Specified Sensory Device; Sensory Management Services, LLC, Baltimore, Md.) Two-point discrimination (Disc-Criminator; Kom Kare Company, Middletown, Ohio) Temperature (Hot and Cold Discrimination Kit; TRIRICE, Oak Park, Mich.)</td>
<td>5 mo, sensation to pinprick; 6 mo, sensory discrimination over entire flap</td>
<td>S3+</td>
</tr>
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Fig. 1. (Above, left) Drawing depicting the first face transplant patient. The outline of the allograft is shown. (Above, right) Different tissue components of the allograft are highlighted. (Below) Schematic representation of the details of sensory and motor nerve repair. jON, infraorbital nerve; FN, facial nerve; MN, mental nerve; DAO, depressor anguli oris; LLS, levator labii superioris; LLSAN, levator labii superioris alaeque nasi; N, nasalis; OOr, orbicularis oris; QLI, quadratus labii inferioris; R, risorius; ZMM, zygomaticus major; ZMI, zygomaticus minor. (Reprinted with permission from the Cleveland Clinic Center for Medical Art & Photography © 2010. All rights reserved.)
Fig. 2. (Above, left) Drawing depicting the second face transplant patient. The outline of the allograft is shown. (Above, right) Different tissue components of the allograft are highlighted. (Below) Schematic representation of the details of sensory and motor nerve repair. FN, facial nerve; DAO, depressor anguli oris; LLS, levator labii superioris; LLSAN, levator labii superioris alaeque nasi; N, nasalis; OOr, orbicularis oris; QLI, quadratus labii inferioris; R, risorius; ZMi, zygomaticus major; ZMn, zygomaticus minor. (Reprinted with permission from the Cleveland Clinic Center for Medical Art & Photography © 2010. All rights reserved.)
Fig. 3. (Above, left) Drawing depicting the third face transplant patient. The outline of the allograft is shown. (Above, right) Different tissue components of the allograft are highlighted. (Below) Schematic representation of the details of sensory and motor nerve repair. iON, infraorbital nerve; FN, facial nerve; DAO, depressor anguli oris; LLS, levator labii superioris; LLSAN, levator labii superioris alaeque nasi; N, nasalis; OOC, orbicularis oculi; OOR, orbicularis oris; QLI, quadratus labii inferioris; R, risorius; ZMJ, zygomaticus major; ZMI, zygomaticus minor. (Reprinted with permission from the Cleveland Clinic Center for Medical Art & Photography © 2010. All rights reserved.)
Fig. 4. (Above, left) Drawing depicting the fourth face transplant patient. The outline of the allograft is shown. (Above, right) Different tissue components of the allograft are highlighted. (Below) Schematic representation of the details of sensory and motor nerve repair. FN, facial nerve; DAO, depressor anguli oris; LLS, levator labii superioris; LLSAN, levator labii superioris alaeque nasi; N, nasalis; OOC, orbicularis oculi; OOR, orbicularis oris; R, risorius; ZM, zygomaticus major; ZMI, zygomaticus minor. (Reprinted with permission from the Cleveland Clinic Center for Medical Art & Photography © 2010. All rights reserved.)

...tion coming from the recipient bed. 42 Thickness of the flap could impair sensory return, even in the absence of muscular or bony components. 38 In thin flaps such as the noninnervated radial forearm flap used for orofacial reconstruction, remarkable spontaneous return of sensation has been observed 36; however, significantly better results have been recorded for innervated versus noninnervated flaps. 7 In noninnervated vascularized tissue transfers, reinnervation seems to occur...
by ingrowth of the nerves from the recipient bed and from the flap's margins and along the neural sheaths within transferred tissues.\textsuperscript{33,41}

**Immunosuppressive Therapy with Tacrolimus**

The immunosuppressive protocol with tacrolimus confers a potential advantage for nerve regeneration, as observed in limb allografts. It was reported that tacrolimus increased the rate of axonal regeneration in a dose-dependent manner\textsuperscript{33} and influenced collateral sprouting of peripheral nerve fibers.\textsuperscript{44} It was also confirmed that tacrolimus doubles the number of regenerating axons after nerve injury, increases the number of myelinated axons by 40 percent, and significantly augments myelin thickness.\textsuperscript{45} In addition, tacrolimus reduces by half the time needed for neuronal recovery after repair of nerve lesions.\textsuperscript{46,47}

The immunosuppressive treatment protocol used in the first successful hand transplantation...
included tacrolimus, which facilitated median and ulnar nerve regeneration and promoted sensory and motor recovery.\textsuperscript{48} The rate of nerve regeneration as indicated by an advancing Tinel sign was faster than expected, and it was estimated to progress at approximately 2 to 3 mm/day.\textsuperscript{49}

Pathways of Sensory Recovery

Trigemino-facial Communications

Afferent fibers found in the communicating rami between trigeminal and facial nerves appear to contribute to the deep sensibility or proprioception of the face\textsuperscript{50} (Fig. 6, 2). The impulses conveying cutaneous sensation, which travel with the trigeminal nerve, contribute to the appreciation of facial movements.\textsuperscript{51} Therefore, there is a close relationship between the two systems. In the absence of impulses from the trigeminal nerve, the afferents of the facial nerve could contribute to the return of perception of position and deep pressure sensation and thus may directly play a role in transmission of superficial touch and pain sensation.

Nervi Nervorum of the Facial Nerve

The third neural pathway that may contribute to sensory recovery of the face is represented by nervi nervorum (Fig. 6, 3). All cranial nerves are richly innervated by their own nerves, known as nervi nervorum, which are derived from the nerve trunk fibers and are known to have nociceptive function.\textsuperscript{52} It was confirmed that stimulation of the nervi nervorum of the facial nerve trunk can be transmitted to the trigemino-cervical complex.\textsuperscript{53} However, whether these nerves can mediate somatic or referred pain has to be confirmed.

Somatic Afferents of the Facial Nerve

The facial nerve contains somatic fibers, collecting the sensation of the external auditory meatus and posterior surface of the ear. Distal to the level where these components have left the nerve trunk, the sensory fibers are sparse. However, a sensory component within the facial nerve is still present, which is mediating deep facial sensation such as pressure, pressure pain, and muscle sense (Fig. 6, 4). The presence of this component explains preservation of deep facial sensation after trigeminal neurectomy.\textsuperscript{54,55} This was confirmed in physiologic studies using a cat model.\textsuperscript{56} In the same model, the existence of purely sensory fibers was confirmed in three major peripheral facial nerve branches.\textsuperscript{57}

The pattern of sensory recovery in noninnervated free flaps occurs usually from the periphery to the center,\textsuperscript{7,58-60} whereas in innervated flaps the reverse occurs, with reinervation proceeding along the distribution of the sensory nerve.\textsuperscript{61} In face transplants, the observed direction of sensory return was from the periphery to the central portion of the allograft, and it paralleled the direction of facial nerve regeneration. Therefore, this directional may be consequent to sensory reinervation along the somatic afferents of the facial nerve as well.

Adrenergic Plexus of the Vascular Pedicle

The adrenergic fibers present in the skin innervate the erector pili muscles and form an extensive network around the vessels. After transfer of free vascularized tissues, there is an ingrowth of the adrenergic fibers from the graft margins, from the wound bed, and along the artery and the vein, forming a rich neural plexus around the vascular pedicle of the flap (Fig. 6, 5). The number of single nerve fibers invading the flap around the margins decreases over time, whereas more nerves
have been observed around the arteries and arterioles. The restoration of sympathetic innervations of the skin contributes to restoration of thermal regulation mechanisms of the graft.

DISCUSSION

Face transplantation is a novel experimental procedure and as such it is still reserved for a highly selected population of patients who have exhausted all conventional means of reconstruction and are left with severe facial disfigurement. Therefore, the first reported face transplantations have been performed in the setting of distorted facial anatomy and function. The functional outcome of these first cases will have an important impact on the future development of this complex procedure. In three of four cases with long-term follow-up, repair of the sensory nerves was less than optimal or could not be performed because of the severity of original trauma or disease. Because many candidates for face transplantation present with extensive facial injury where damage of the recipient nerves is irreversible, it was our aim to estimate how sensory recovery will progress under these unfavorable conditions and how this will impact the final functional outcome.

Based on the results of our comparative analysis, we can conclude that, in the absence of extensive soft-tissue injury, simple repair of facial sensory nerves leads to restoration of nearly normal sensation. After tissue avulsion or extensive trauma, despite repair of the sensory nerves, the outcomes are suboptimal, although some sensory return can be expected (e.g., face and scalp re-plantation). When tissues other than facial tissues are transferred to the facial region from different anatomical sites of the body, good functional sensory recovery can be achieved only when the sensory nerves of the transferred flaps are connected to the sensory nerves of the recipient site. Interestingly, face transplantation is the only clinical condition where, in the absence of sensory nerve repair, good functional outcome is achieved despite severe trauma causing soft-tissue and sensory nerve damage.

An important issue that emerged from the comprehensive review of the literature is an evident lack of universal methods of neurosensory assessment and an urgent need for establishment of guidelines that will help with comparative analysis of the sensory recovery data. This applies to the reported cases of face transplantation, where documentation of sensory recovery is either marginal or overlooked.

We found that the Medical Research Council Scale as modified by Mackinnon and Dellon provided an objective and simple method that allows for assessment and comparative analysis of results from different centers. Therefore, to facilitate comparison of results of sensory recovery, we propose that investigators working with face transplant patients will routinely assess the following measures: pressure thresholds, pain thresholds, and two-point discrimination. The follow-up visits for quantitative sensory testing should be scheduled at least once per month for the first 6 months, every 3 months during the first year, and every 6 months thereafter or until a plateau of sensory recovery is reached. Finally, because inclusion of a sensory training program during postoperative care has proved to affect significantly the outcomes following orthognathic surgery and toe-to-hand transfer, sensory rehabilitation protocols should be included in the postoperative management of face transplant patients, and the details of results should be disclosed. Establishment of unified standards of sensory assessment will aid in the functional evaluation of future cases of face transplantation.

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Discussion: Pathways of Sensory Recovery after Face Transplantation

Tae Chong, M.D.

Dallas, Texas

On December 9, 2008, the reconstructive transplant team at the Cleveland Clinic realized several decades of preparation and performed the first face transplantation in the United States. More importantly, the patient ended 4 years of failed partial reconstructions and was able to begin rehabilitating after complete restoration of her soft-tissue and bony defect. In this article, Siemionow et al. detail the sensory recovery achieved with this transplant despite the lack of a direct nerve repair. They compare this return of function with the outcomes reported in the literature for autologous reconstruction. Moreover, they highlight the outcomes in the reported cases of face transplantation, all of whom had different sensory nerve reconstructions.

Their patient was a 45-year-old woman who had a composite defect of her midface after a shotgun injury. She had what is considered the state-of-the-art reconstruction using autologous flaps. Despite this, she continued to have functional limitations and remained disfigured. She underwent a composite facial allotransplantation, which was based on a Le Fort III template. Bilateral facial nerves were anastomosed using interpositional grafts, but the sensory branches of the trigeminal nerve could not be anastomosed.1

She received sensory reeducation 48 hours after surgery. At 5 months, she had pain perception and was able to discriminate 7 mm by 6 months. Progression of sensory nerve recovery was graded using the Medical Research Council Scale, which evaluates light touch, pain, and two-point discrimination. Based on their literature review, innervated reconstructions using autologous tissue did not approach the sensory return that was achieved with their transplant. In fact, these patients could at best feel only superficial pain and tactile sensation, with no true ability to discriminate two points. Moreover, the transplant recipient's recovery compared favorably and even exceeded the sensory return in patients who had repair of an injured trigeminal nerve, an innervated free flap, or even an innervated scalp replant.

The authors propose several possible mechanisms that may contribute to their findings. There may be sensory upgrading caused by placement on the face because of its higher cortical representation. This may not apply to a facial allograft. However, tacrolimus may have some beneficial effect on nerve regeneration and recovery. Because their sensory return paralleled the recovery of the facial nerve, the authors postulate that trigemino-facial nerve communications and the complex interplay between the facial nerve afferents and the trigeminal complex may contribute to their findings. In several animal models, facial motor nerve recovery has been shown to be dependent on an intact sensory system.2,3 It would be interesting to compare the motor recovery of the transplant recipients who have had reconstruction of their sensory branches and received early sensory rehabilitation.

Each face transplant has been different. This is attributable to the nature and extent of the initial injury and the numerous reconstructive procedures performed before transplantation.4-6 Consequently, many of these patients have not had their sensory nerves repaired. In the series presented, the only direct sensory nerve repair for the entire allograft was performed in the first transplant patient from France. However, the others have all shown remarkable return of sensation. Each group has reported pain and temperature sensation and return of light touch demonstrated by cutaneous pressure thresholds. Dr. Siemionow's group reports their outcomes based on the Medical Research Council Scale, a system that facilitates ready comparison between groups based

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on established metrics. Given the intrinsic variability in the technical aspects of these operations, it is critical to adopt a grading system with fixed time points to advance the field.

Another factor limiting comparison and study of face transplant recipients is the differences in the postoperative protocols. For instance, the therapeutic range of tacrolimus, which has beneficial effects on nerve regeneration, varies between the groups. Differences in the maintenance immunosuppression and induction protocols may also affect acute rejection episodes, and this may limit overall graft function and delay rehabilitation. Face and hand transplant recipients, unlike solid organ transplant patients, have the ability to affect the functional outcome of their allograft. Consequently, an early and aggressive program may facilitate improved graft function. The Cleveland Clinic patient underwent aggressive speech therapy, range-of-motion exercises, and sensory reeducation as early as 48 hours after the transplantation. This contributed to her excellent return of function and acceptance of the graft. It would be instructional if the group could publish a detailed protocol for their rehabilitation program. Also, it would be interesting to follow changes in the functional magnetic resonance imaging studies with their program.

This is an exciting time for the field of reconstructive transplantation, with at least 10 face transplants in the world performed thus far. The authors have shown excellent recovery of sensory function to a greater extent and earlier than conventional reconstructive procedures. This in addition to the unmatched motor and cosmetic reconstruction argues for consideration of face transplantation earlier in the reconstructive algorithm of these disfigured patients. The morbidity of immunosuppression, however, continues to limit the widespread acceptance and use of face transplantation. Advances in the field will depend on the minimization of these drugs or the development of novel immunosuppressive agents.

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