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TITLE: Using Emotional Expression as a Novel Indicator of Functional Outcomes and Facial Rehabilitation Following Face Transplantation via Software-Based Video Analysis

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14. ABSTRACT

Face transplantation (FT) outcomes have traditionally been defined by improvement of motor and sensory function. However, FT recipients seek to reintegrate into society, where ability to express emotions is integral to success. The ability to generate identifiable emotional expressions has not been yet successfully used as a quantitative outcome assessment in FT. Human observers use information from different areas of the face to successfully recognize expressed emotion. To the best of our knowledge, there is currently no established method to objectively assess expressed emotion the way human observers do in FT. Additionally, detection of immune rejection still poses challenges in the early stages after FT, and especially for visually impaired patients. There exists an unmet need for non-invasive, high-precision assessment of visual changes related to immune rejection of facial allografts. Aim 1: Quantitatively assess the ability to form identifiable facial emotional expression as a functional outcome of face transplantation. Aim 2: Develop software further for clinical monitoring of facial allograft rejection. Retrospective, matched-cohort study using 6 VCA recipients and 6 healthy subjects. Noldus video-analysis software will be used to detect emotional expression of all subjects.

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Contents

1. Introduction

Many individuals lose parts of their faces, their limbs or their abdomen in traumatic incidents such as active combat, burns, gunshot wounds, violent attacks, and motor vehicle accidents, amongst others. People with these types of traumatic injuries have decreased quality of life and are often disabled. Although they may receive the best of the available conventional reconstruction therapies, they continue to suffer from chronic pain, psychological distress, social isolation, and limitations in their ability to perform daily activities such as bathing, dressing, ambulating, and eating without substantial help.

Face transplantation is a viable reconstructive option for patients with severe facial deformity showing promising long-term results in improving functionality and quality of life. Outcome measures of face transplantation have traditionally assessed the recovery of vital functions (ability to breathe, eat, and speak) and independent functions (motor movement, protective and discriminative sensation); as well as the procedure's functional psychological impact on quality of life and mental health. Measuring the restoration of these functions is necessary to determine the value of face transplantation to the individual patient, but their recovery alone is not sufficient to achieve or explain societal reintegration after face transplant.

Non-verbal communication via facial emotional expression – a social function of the face – has evolved under the pressures of interacting in a social environment. Six specific emotional expressions – happiness, sadness, anger, surprise, fear, and disgust – are recognized across cultures and are the focus of social psychology research. Despite high relevance, limited quantitative data is available on restoration of facial emotional expression after face transplantation. Existing evidence comes from methods such as facial surface electromyography, a sensitive measure but one that requires painstaking placement of several electrodes on the skin; and appearance-based facial feature extraction, which is similar to facial recognition technology but requires significant data processing that limits reproducibility. These methods are obtrusive and prone to human instrumentation error. Their clinical implementation would be time-consuming and bind patients to laboratory settings, which could impact medical adherence over time. The need to find a less obtrusive and more reliable method for evaluating emotional expression as an outcome measure of face transplantation remains.

Software-based video analysis, a merger of facial recognition technology and deep learning, has proven capable of assessing facial motor movement functions after face transplantation. Our objective is to recognize emotional expression as a novel indicator of functional outcomes and rehabilitation following face transplantation via objective, non-invasive, and non-obtrusive software-based video analysis. We will complete a retrospective, matched-cohort study using 6 face transplant recipients and 6 healthy subjects. Noldus video-analysis software will be used to detect emotional expression of all subjects. Imaging data will be used to quantitatively assess the ability to form identifiable facial emotional expression as a functional outcome of face transplantation. Images and videos taken of 8 face transplant recipients during rejection episodes will be shared with Noldus to develop the software further for clinical monitoring of facial allograft rejection. We believe this video-analysis software can provide useful clinical information and aid rehabilitation after face transplantation.

2. Key Words:

Face transplantation, facial allograft, emotional expression, rejection detection

3. Accomplishments.

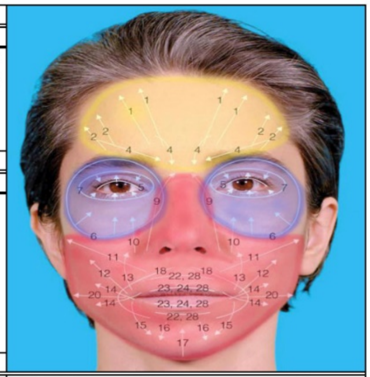
Specific Aim 1 of our study was to quantitatively assess the ability to form identifiable facial emotional expression as a functional outcome of face transplantation. This involved completing sub-tasks that included: calibration and optimization of emotional expression detection for patients with face transplants, recruiting matched healthy controls for comparison, and analyzing emotional expressions of both patients with face transplants and healthy controls.

Upper Third

Action Units	Description	Associated Muscle
1	Inner Brow Raiser	Frontalis, pars medialis
2	Outer Brow Raiser	Frontalis, pars lateralis
4	Brow Lowerer	Depressor Glabellae Depressor Supercilli Currugator

Orbital

Action Units	Description	Associated Muscle
5	Upper Lid Raiser	Levator palpebrae superioris
6	Cheek Raiser	Orbicularis oculi, pars orbitalis
7	Lid Tightener	Orbicularis oculi, pars palpebralis
9	Nose Wrinkler	Levator labii superioris alaquae nasi



Midface + Lower Two-Thirds

Action Units	Description	Associated Muscle	Action Units	Description	Associated Muscle
10	Upper Lip Raiser	Levator labii superioris Caput infraorbitalis	22	Lip Funneler	Orbicularis oris
			23	Lip Tightener	Orbicularis oris
11	Nasolabial Deepener	Zygomatic minor	24	Lip Pressor	Orbicularis oris
12	Lip Corner Puller	Zygomatic major	25	Lips part	Depressor Labii inferioris Orbicularis oris
13	Cheek Puffer	Levator anguli oris			
14	Dimpler	Buccinator			Relaxation of Mentalis
15	Lip Corner Depressor	Depressor anguli oris	26	Jaw Drop	Masetter
16	Lower Lip Depressor	Depressor labii inferioris			Relaxation of Temporal Pterygoid
17	Chin Raiser	Mentalis			Relaxation of Internal Pterygoid
18	Lip Puckerer	Incisivii labii superioris Incisivii labii inferioris	27	Mouth Stretch	Pterygoids
			28	Lip Suck	Orbicularis oris
20	Lip Stretcher	Risorius			

Figure 1

We used FaceReader facial expression recognition software version 6.1 (Noldus) to detect and track faces, extract facial features, and analyze facial expressions. The video analysis software achieves this by relying on the Facial Action Coding System which taxonomizes visibly different facial movements on the basis of underlying anatomical structures into individual action units (**Figure 1**).

The video analysis software determines the magnitude of vector variation between neutral and simulated facial expressions using a trained artificial neural network and then compares them with prototypical features of 6 basic emotions to produce an intensity score for each. The 6 emotions are happy, sad, angry, surprised, fear, and disgust. The intensity score value ranges from 0 to 1, depending on whether the emotional expression is entirely absent or fully present, respectively.

We found that the software could detect the faces of patients with face transplants after calibration. The calibration corrected for participant specific biases toward certain facial expressions. Baseline emotional expressions were set to 0 (ie, intensity score equal to 0) using a neutral resting face.

Thus, a retrospective case-control study was performed using 44 videos from 6 patients with face transplants (representing 15%of patients with face transplants worldwide) taken at regular intervals over a maximal post-transplant period of 9.5 years. Also used were 12 videos from 6 healthy controls who were matched according to the age of the donor and sex and cultural ethnicity of the recipient and who had no history of previous reconstructive or cosmetic facial procedures.

All study participants were recorded performing commands from 2 different protocols to either indirectly or directly evaluate emotional expression. All study participants performed a series of 12 facial movements: smile, frown, purse lips, open mouth wide, shut mouth tight, open eyes wide, close eyes tight, wrinkle nose, pucker lips, wink with right eye, wink with left eye, and puff cheeks. For direct evaluation, all healthy controls performed a series of 6 simulated faces for when they feel happy, sad, angry, surprised, scared, and disgusted. For both protocols, all study participants were asked to return to their neutral resting face between commands.

Each video was less than 2 minutes long, and we attempted to standardize the background and lighting implemented. For indirect evaluation, maximum intensity score values for each emotion were used, and the possibility of expression was verified by correlating the protocol command, with correspondent action units, to the emotional state detected for consistency. For direct evaluation, the maximal intensity score values were extracted from the video sequence dedicated to the performed emotion. Data from all study participants were used for analysis of happiness. For all other emotions, patients with partial face transplants were excluded because not all action units necessary for the emotional expression were transplanted. For indirect evaluation, the highest intensity score value after the first year was chosen for each patient with face transplant to allow comparison with healthy controls.

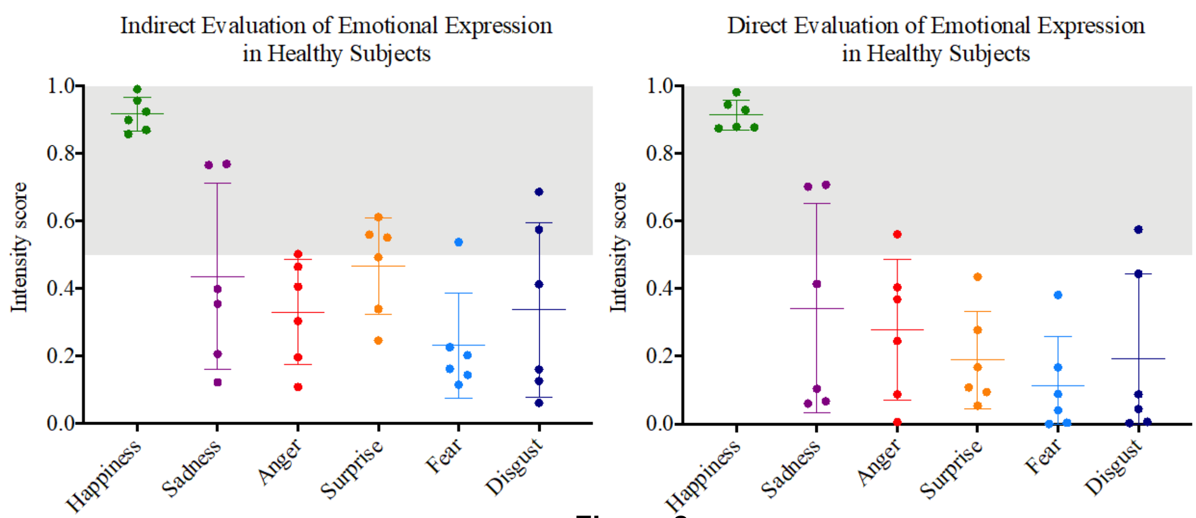


Figure 2

The healthy control videos were analyzed first to validate the sensitivity and specificity of both protocols and the video analysis software (**Figure 2**). Only the emotion of happiness could be reliably detected, with mean (SD) intensity score values of 0.92 (0.05) for indirect evaluation and 0.91 (0.04) for direct evaluation. All other emotions were detectable, but mean intensity score values did not pass the threshold for objective observer detection during both indirect and direct evaluation.

Figure 3

We found that the emotional expression of happiness, sadness, anger, surprise, fear, and disgust was possible after face transplant with nonzero intensity score values detectable in all patients with face transplants. The mean (SD) group intensity score values were 0.38 (0.24) for happiness, 0.34 (0.16), for sadness, 0.17 (0.21) for anger, 0.28 (0.23) for surprise, 0.24 (0.16) for fear, and 0.09 (0.10) for disgust.

The emotion of happiness was the most reliable expression to detect and could be restored after face transplant to a mean of 43% (range, 14% to 75%) of that of healthy controls (**Figure 3**).

During posttransplant year 1, the intensity score values for happiness decreased non-significantly by 0.06 point per year (95%CI, −0.34 to 0.23 point per year; P = .66) (**Figure 4, Panel A**). Afterward, intensity score values for happiness increased significantly by 0.04 point per year (95%CI, 0.02 to 0.06 point per year; P = .002). The software detected this improvement in happiness at a sub-clinical level which highlights the potential for this tool to be used in rehabilitation of patients with face transplants.

The intensity score values for sadness decreased significantly by 0.53 point during posttransplant year 1 (95%CI, −0.82 to −0.24 point per year; P = .005), with negligible changes afterward (0.01 point per year; 95%CI, −0.01 to 0.03 point per year; P = .48) (**Figure 4, Panel B**).The remaining emotions of anger, surprise, fear, and disgust had intensity score values with non-significant changes (P > .05) after transplant (**Figure 4, Panel C-F**).

Completion of Specific Aim 1 occurred by July 2019. Work from this portion of the project was presented either in part or completely at a meeting of the American Society for Reconstructive Transplantation 2018 and published as an original investigation in a Journal of the American Medical Association.

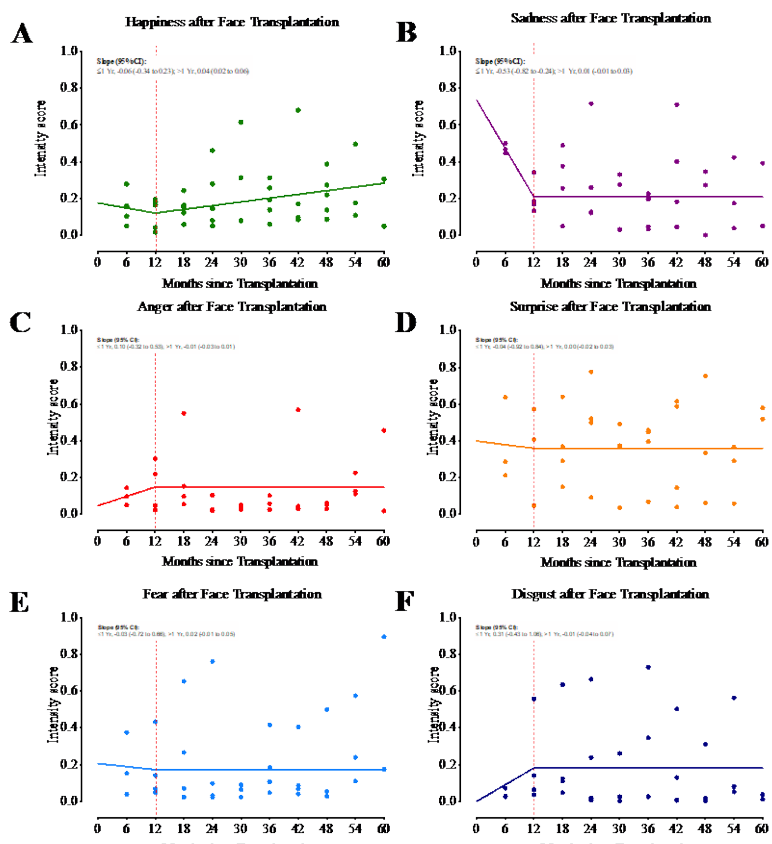


Figure 4

Simultaneously, Specific Aim 2 of our study was being worked on to develop the software further for clinical monitoring of facial allograft rejection. This involved completing sub-tasks that included: development of a software to detect redness on face transplant allografts, validating the software, and analyzing images of patients with face transplants to determine if rejection episodes can be detected. Our collaborators were able to create a software that met our indications by September 2019. We then proceeded to validate the software by performing a retrospective cohort study using 688 standardized images from 7 patients with face transplants and 7 healthy controls.

The software measures the redness of user-defined areas on an image and compares the average pixel color of labeled areas to absolute red. This yields R, a variable that corresponds inversely with redness. R values from labels on the allograft were averaged to have one average allograft redness value per timepoint. All images were each individually labelled and processed by four investigators. Linear mixed models were used to study effects of acute rejection on R value. Rejection state (determined by tissue biopsy and Banff Grade rejection) was considered a fixed effect, individual patients as random effects. Estimated marginal means of fitted models were calculated and *p-values* from pairwise comparisons among estimated marginal means were adjusted. Interrater reliability was measured using Cronbach's alpha test. Cut-off R value separating non-rejection (Banff Grade 0/1) and clinical rejection (Banff Grade 2/3) state determined from receiver operating characteristic curve analysis.

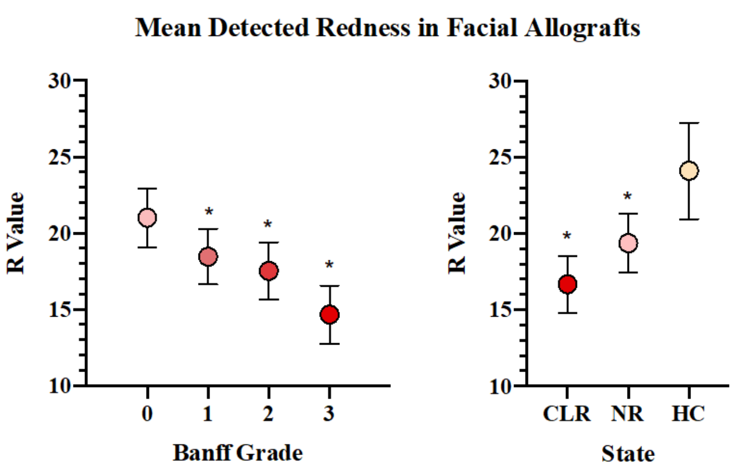


Figure 5

With a high interrater reliability (Cronbach's α=0.967), the estimated change in R value of facial allografts significantly decreased due to increasing Banff Grade (*p*=0.0001); see **Figure 5**. The estimated marginal mean R value decreases from 21.00 (95%CI, 18.90-23.10) at Grade 0, to 18.46 (95%CI, 16.48-20.43, *p*=0.048), 17.53 (95%CI, 15.50-19.56, *p*=0.009) and 14.65 (95%CI, 12.58-16.73, *p*=0.0001) at Banff Grade 1, 2, and 3, respectively.

Collectively, the R value of clinical rejection (CLR) images (16.67, 95%CI 14.79-18.58) was significantly lower (*p*=0.005) than non-rejection (NR) images (19.38, 95%CI 17.43-21.33), with R value of 17.97 (AUC=0.66, 95%CI 0.55-0.77) suggestive of CLR with sensitivity 60.8%, specificity 68.9%, positive predictive value (PPV) 68.9% and negative predictive value (NPV) 60.8%. Both R values for NR and CLR are significantly lower (*p*=0.0001) than healthy controls (HC) (24.12, 95%CI, 20.96-27.28). These results suggests that the developed software is capable of detecting clinical rejection in 2 out of 3 patients with face transplants that are actively in allograft rejection.

Work from this portion of the project was submitted for presentation, in part or completely, to the meeting of the American Society for Reconstructive Transplantation 2020 and submitted for publication as a research idea and innovation study in the Plastic and Reconstructive Surgery journal.

4. Impact

Active combat is inflicting devastating injuries to the face with alarming incidence, resulting in facial disfigurement. Conventional reconstructive surgery is limited in its ability to restore form and function after these injuries. Considering the high incidence and devastating consequences of these complex injuries to American Service members, there is a clear need to improve their treatment outcomes. Non-verbal communication via facial expression is a vital aspect of human communication. If successful, software-based video analysis will allow clinicians to more accurately assess the outcomes of facial transplantation. Additionally, the software could be used to define and treat transplant rejection more accurately than conventional methods. This will lead to improvements in medical outcomes, quality of life, mental health, social participation, and the American economy for transplant recipients.

5. Changes/Problems

We were unable to start the development of the rejection detector module on schedule due to both administrative and logistical setbacks. We strengthened our communication with Noldus, the collaborators, in order to clarify their position on required materials to begin development. From a logistical standpoint, we increased our dedicated time spent on working with collaborators to get back on schedule.

6. Products

Nothing to report at this time.

7. Publications, Abstracts and Presentations

- Oral presentation, “Recognizing Emotional Expression in the Face Transplant Patient”, at the American Society for Reconstructive Transplantation 6th Biennial Meeting 16-11-2018

- Scientific manuscript published in JAMA Network Open, an open-access academic journal:

  Miguel I. Dorante, MD, MBE, Branislav Kollar, MD, Doha Obed, Valentin Haug, MD, Sebastian Fischer, MD and Bohdan Pomahac, MD. Recognizing Emotional Expression as an Outcome Measure after Face Transplant. *JAMA Network Open. Jan 2020.* DOI: 10.1001/jamanetworkopen.2019.19247

- Abstract submitted for presentation, “Emotions After Face Transplant: First International Face Transplant Cohort Comparison”, at the American Society for Reconstructive Transplantation 7th Biennial Meeting

- Abstract submitted for presentation, “Software-based Detection of Redness Changes in Face Transplants Over Time”, at the American Society for Reconstructive Transplantation 7th Biennial Meeting

- Abstract submitted for presentation, “Detection of Redness Changes in Face Transplants During Rejection Episodes”, at the American Society for Reconstructive Transplantation 7th Biennial Meeting

- Scientific manuscript submitted to Plastic and Reconstructive Surgery, an academic journal:

  Miguel I. Dorante, MD, MBE, Branislav Kollar, MD, Marian Bittner, MSc, Alice Wang, BS, Yannick Diehm, MD, Sina Foroutanjazi, BS, Neil Parikh, BS, Tim M. den Uyl, MSc, Valentin Haug, MD, and Bohdan Pomahac, MD. *Software-based Detection of Redness Changes in Face Transplant.*

8. Inventions, Patents and Licenses

Nothing to report at this time.

9. Reportable Outcomes

For Specific Aim 1, a commercially available software, FaceReader produced by Noldus IT, was used to analyze emotional expression in patients with face transplants. Our study was the first to study its effectiveness in face transplant.

For Specific Aim 2, we collaborated with the engineers at VicarVision who designed the software in Specific Aim 1 to produce a software that could detect redness in facial allografts of patients with face transplants. The software titled, deltaR measure, is a prototype that we are still validating. Our study using the software found redness changes with allograft rejection.

10. Other Achievements

Nothing to report at this time.

11. Participant and other collaborating organizations

We collaborated with Noldus.

12. Special Reporting Requirements

None.

13. Appendices

List of Personnel Receiving Pay:

1. Valentin Haug (September 2018 – September 2019)
2. Bohdan Pomahac (November 2018 – October 2019)

3. Branislav Kollar (October 2019 and June 2020)
4. Jessica Detmerlillard (May-June 2019)