The analysis of three-dimensional facial dysmorphology

A grant proposal to the Wellcome Trust

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Responses to reviewers' comments: January 10th 2009

For convenience, we have collated the issues raised by the reviewers into a single list under the headings below.

1. The validation of the algorithms (Referees 1, 3, 4 and 5)
2. Dealing with surface defects (Referee 4)
3. Adjusting for age and other factors (Referees 4 and 5)
4. The number and poses of images for each patient (Referee 5)
5. A clear hypothesis for the orthognathic surgery application (Referee 5)
6. The sample size for orthognathic surgery (Referee 4)
7. Data management and sharing (Referee 1)

1. The validation of the algorithms (Referees 1, 3, 4 and 5)

All of our previous studies based on three-dimensional images have been preceded by assessment of the variability and reproducibility of the manual landmarking process. In addition to the use of human subjects, we have a set of plastercast models with landmarks whose positions have been independently identified to a high degree of accuracy. This process will be repeated with the equipment and operators to be used in the new investigations.

In assessing the performance of automatic landmarking procedures, we now have the benefit of a very substantial database of more than 800 facial images from these earlier studies, with manually identified landmarks for each case. We propose to carry out initial development of automatic procedures on a relatively small subset of these images, supplemented by data simulated from a principal components description of the database. A larger subset of the database will then be used for more systematic evaluation and fine-tuning of the proposed algorithms. However, the size of the database allows a further subset to be retained for final assessment of the algorithms on independent cases. In addition, the data to be collected under the new medical studies of the project will extend the range of the data available for development and independent assessment.

The differences between manually and automatically located landmarks will be analysed carefully to identify those landmarks where the latter can be regarded as acceptable equivalents for manual location. However, the variability and reproducibility of the automatically located landmarks are also of interest in their own right. Even where systematic differences between the locations identified by these two approaches are detected, the automatic solution may still prove to be an excellent basis for subsequent analysis, if the consistency with which the location is identified is sufficiently good. The clinical interpretation of such landmarks may need to be adjusted, but the removal of the need for laborious manual identification provides a significant advantage.

2. Dealing with surface defects (Referee 4)

With the current generation of capture equipment, we have found serious surface defects to be relatively rare. Our standard protocol for image capture involves building models at low

resolution during the capture session, which usually identifies any occasional problems and allows further imaging to be undertaken. However, we recognise that distortion can occur. Where major difficulties arise, we will investigate the effectiveness of excision and interpolation algorithms. However, we expect that exclusion of such cases will also be a feasible option, in view of the very small numbers involved. For more minor defects, we have available a variety of filtering algorithms designed to remove noise while retaining underlying discontinuities or other important structures.

A significant amount of facial hair is certainly a difficulty. For the purposes of developing and evaluating algorithms to extract shape information automatically, we plan simply to exclude cases where facial hair obscures the required information. Although interpolation algorithms could be investigated here, the technical challenge in developing automatic forms of shape extraction are sufficiently strong, and of sufficient potential benefit, that restriction to images without facial hair is justifiable. In orthognathic surgery, 70% of patients are female and the majority of studies on cleft lip and palate involve children. Facial hair should not prove a major difficulty in either of these settings.

For the specific medical applications to be pursued in this proposal, landmarks will be identified by both manual and automatic approaches, as part of the validation of the automatic methods. For cases with significant facial hair, it is possible that more information can be extracted by the manual approach and used as the basis of subsequent analysis on the primary questions of medical interest. However, restriction to cases without facial hair provides a further opportunity to compare the automatic and manual methods, this time by comparing the results of the analyses based on these differently generated types of information.

3. Adjusting for age and other factors (Referees 4 and 5)

Control cases will be collected across the range of ages represented by patients, in both medical applications, and any models used to compare patients and controls will certainly need to include an appropriate adjustment for change in soft tissue shape with age. Since the change in mean shape can be assumed to be smooth, we plan to construct a multivariate regression model. We expect that the response information on shape will be coded most effectively through principal component scores derived from the full dataset. This reduces the dimensionality involved, without substantial loss of information if a reasonable number of components is used. Regression modelling for multivariate response information is a well established statistical tool which can be applied with age as a covariate. A linear model will be used as the starting point but appropriate forms of non-linear age effects will also be investigated, if required. Separate models will be constructed for males and females.

The medical studies proposed are not of sufficient size to allow ethnic effects to be estimated well. These will therefore be avoided by restricting attention to white British and Irish subjects. For orthognathic surgery, the operations are all of the same type, involving surgical correction of maxillo-mandibular position in relation to the base of skull. The degree of shift, and the surgeon involved, will be recorded and effects examined by inclusion in the statistical model.

4. The number and poses of images for each patient (Referee 5)

It is our standard practice to take multiple images of each patient, with the highest quality image subsequently selected for analysis. This is simple to do, once a subject has been positioned appropriately, and it overcomes any occasional technical difficulties with the mechanics of image capture. As mentioned above, the creation of low resolution models during the capture sessions

allows problematic images to be identified and replacement images to be collected.

Subjects will be asked to adopt a neutral facial expression, with mouth lightly closed. This single pose will be used for all patients. We do not plan to investigate animation in these particular medical studies.

5. A clear hypothesis for the orthognathic surgery application (Referee 5)

In the schizophrenia study, we plan to test the hypothesis that the mean craniofacial shape of patients differs from that of age and sex matched controls and to investigate the further hypothesis that this difference is characterised primarily by abnormalities of the frontonasal prominences, with narrowing and lengthening of the anterior mid-face. Differences of this type would overlap with, but be distinct from, those evident in bipolar disorder.

For orthognathic surgery, our proposal has been formulated in terms of the quantification and assessment of change. However, we recognise the value of expressing this more clearly in hypothesis form. We therefore propose to examine the hypothesis that there is no difference between the mean post-surgical facial shape and that of age and sex matched controls. If post-surgical deformity is identified, we will examine whether this is related to the severity of pre-surgical deformity. We also plan to examine each individual post-surgical shape to identify whether it lies within the normal range of control facial shape, to provide a more patient-specific method of analysis.

6. The sample size for orthognathic surgery (Referee 4)

The sample size for orthognathic patients is determined by the scheduling of appropriate operations in local hospitals and the need to postpone post-surgical assessment until soft tissue swelling has fully subsided, which is usually six months after the operation. However, we have re-examined patient recruitment and we are pleased to say that we now believe that the number of patients can be increased to at least 60. We believe we can achieve this with the assistance of Dr. Balvinder Khambay, a consultant orthodontist at Glasgow Dental Hospital, plus some assistance from postgraduate students funded from other sources. In view of this, we would like to add Dr. Khambay as a co-investigator on the project.

With this increased level of resource, we have also re-assessed the recruitment of controls and we now believe that we will be able to collect one hundred controls in both Ireland and Scotland. This doubles the proposed number of controls.

7. Data management and sharing (Referees 1 and 5)

All collected data will be held on secure, password-protected servers in the University of Glasgow and Dublin City University. The data in both locations will be protected by back-up facilities provided by these institutions. The Department of Statistics in the University of Glasgow has particularly extensive experience in data preparation and management through involvement in a wide variety of clinical trials and other scientific investigations. There is also substantial collective experience in the management and archiving of image data.

On completion of the project, the data will be made available to other researchers who wish to analyse the information for scientific purposes. Researchers will be asked to register, to state the purposes of their analysis and to undertake not to pass the data on to third parties, before the data will be released, to prevent inappropriate use. Derived data, such as landmarks, curves and asymmetry scores, will be made available in anonymised form. Image data cannot, by its nature, be fully anonymised. This form of data will therefore be released only when patients and controls have given permission to do so, at the time of recruitment.