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July 3, 2008

Wellcome Trust  
Gibbs Building  
215 Euston Road  
London

Dear Sir/Madam,

## **The analysis of three-dimensional facial dysmorphology**

A grant proposal to the Wellcome Trust, June 25th 2008

### **Investigators:**

*University of Glasgow:* Prof. Adrian Bowman (Statistics), Prof. Ashraf Ayoub (Dental School), Dr. Paul Siebert (Computing Science)  
*Royal College of Surgeons in Ireland:* Prof. John Waddington (Neuroscience)  
*Dublin City University:* Prof. Paul Whelan (School of Electronic Engineering)  
*University of Limerick:* Dr. Kevin Hayes (Statistics)  
*Institute of Technology, Tralee:* Dr. Brendan Guilfoyle (Mathematics)

I have submitted a revised version of a grant proposal for a project entitled 'The analysis of three-dimensional facial dysmorphology'. This is an interdisciplinary project involving scientists at the University of Glasgow and at several locations in Ireland.

The feedback received on the original submission was supportive of the proposal but identified a number of issues requiring attention. These issues are listed below, together with a description of how they have been addressed in the revised submission. The references in square brackets indicate the section of the Research Details of the proposal where corresponding changes have been made.

### **Issues raised by Referee 1**

We understand that the committee placed most emphasis on the issues raised by this reviewer. We have taken particular care in addressing all of these issues in the new proposal.

*The weakness is that some critical information is missing. This includes, spatial and depth resolution of the face image and what landmarks, that are currently manually marked, the investigators plan to extract automatically. An illustration of 3D facial image with landmarks marked on it would have been useful. Some details of landmark extraction algorithm the investigators plan to use would have been nice too. Finally, I would have liked to know what is the correlation has been found between facial measurements/shape and schizophrenia?*

Information on the resolution of the captured images has been provided [(a) para. 4]. This has changed markedly over the years in which we have been working in this area,

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as a result of the substantial increase in the number of pixels available in modern digital cameras and the resolution of modern laser scanners. The numbers quoted in the proposal make it clear that the spatial resolution is now very high.

We have also identified the specific landmarks which we plan to extract automatically [(c) 1]. It is important to achieve a satisfactory compromise between landmarks which are informative anatomically and are also able to be extracted in a robust and reliable manner. The point at which this compromise should be made will not be clear until our research has been conducted and the results evaluated.

An illustration of a facial image with the relevant landmarks has been included in the proposal. [(c) 1]

Further details of the landmark extraction algorithm have been provided [(c) 1]. In broad terms, we plan to characterise locations through the nature of the surrounding surface curvature, classified as peak or cap, ridge, saddle, valley or rut, pit or cup, and plane. Standard methods are described in Koenderink, J. J. (1990, Solid Shape, MIT Press) and an adaptive algorithm will be constructed to match these characterisations to each landmark of interest. This will extend to the face work which has proved to be successful in other anatomical regions such as the colon.

We have provided further information on the differences between the facial shapes of schizophrenic patients and controls which existing work, such as Hennessy *et al.* (2007), has been able to identify [(c) 5, para. 1]. This includes large scale facial characteristics as well as differences in more detailed facial features. Interestingly, while differences were found in patients of both sexes, these appeared to be more prominent in females. The challenge which we plan to tackle in the new proposal is to build on these initial findings in order to resolve the topography of facial dysmorphogenesis in greater detail and extend the analysis to new characteristics of shape such as asymmetry.

## Issues raised by Referee 2

*However, if the applicants want to model the three-dimensional data, then FDA can be hard to use in term of intensive computation load. Because FDA usually represents functions as linear combinations of basis functions. The three-dimensional basis functions are hard to construct, and usually a large number of basis functions are required to model the three-dimensional data especially the applicants here want to do shape analysis for complicated facial data. This weakness can be a minor issue to implement their method.*

We plan to tackle the specific case of anatomical curves, as an effective compromise between the need to extend the representation of shape beyond simple landmarks and the need to retain a degree of simplicity and interpretation in characterising features of interest. Functional data analysis is particularly appropriate for this setting as it allows each three-dimensional curve to be represented by three separate functions  $\{x(t), y(t), z(t)\}$  of the dummy variable  $t$ , representing the distance travelled along the curve. Each of

these three functions is one-dimensional and can be represented through a simple set of basis coefficients. The dimensionality of the information required to represent each three-dimensional curve is therefore likely to be less than 100. We are therefore able to reassure then reviewer that this can easily be handled without difficulty, in both computational and statistical terms. The wording of the revised proposal has been changed to clarify this.

### Issues raised by Referee 3

*There is extremely wide variation in normal human face shapes, and so it will be important to be able to assess the differences in the schizophrenia group from the controls. Is 30 controls enough for assessing this variability? It may be worth taking some more if possible.*

*One minor weakness of the proposal is that it is not clear how a significant difference in schizophrenia will be used in practice. Could it be used for prediction at younger ages, or is it more to offer further understanding of the broad condition?*

We fully recognise the importance of sample size and its effect on power and precision. We are encouraged by the fact that the earlier work of Hennessy *et al.* (2007) was able to identify differences between schizophrenic patients and controls with sample sizes close to 30. However, we accept that larger sample size would be preferable and this has been increased to 100, split evenly between and females [(c) 5, para. 2].

In the schizophrenia study, the principal aim is to understand the nature of brain dysmorphogenesis. Because the developmental biology of facial morphogenesis is considerably better understood than is brain morphogenesis, abnormalities in facial shape therefore have the potential to inform incisively on this. Such findings could potentially guide future molecular genetic and neuropathological studies. Furthermore, the ability to make comparisons of facial shape across diagnoses, for example between schizophrenia and bipolar disorder (formerly known as manic-depressive psychosis) will allow us to address directly the long-standing conundrum of whether these disorders involve similar, distinct or overlapping dysmorphogenic processes [(c) 5, para. 3].

### Reviewers

The names of the suggested reviewers from the first submission are listed below. We recognise, of course, that other reviewers may have been used. We also understand that the revised proposal will formally have the status of a new one. However, we hope that it might be possible to send the revision back to the original reviewers, so that they will be able to comment directly on the effectiveness with which the issues which have been addressed.

Professor Peter Hammond  
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(computing science and facial analysis)

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None of these reviewers has been approached about the grant proposal.

Yours sincerely,

A handwritten signature in black ink that reads "Adrian Bowman". The signature is written in a cursive, flowing style.

Prof. Adrian Bowman