CLINICAL CONSIDERATIONS IN FACIAL TRANSPLANTATION

by

Anthony Renshaw

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Department of Plastic and Reconstructive Surgery,

Academic Division of Surgical & Interventional Sciences,

University College London

Declaration

I, Anthony Renshaw, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis

…….

Abstract

Facial transplantation has emerged as the next step on the reconstructive ladder for severe facial disfigurement. Clinical issues surrounding facial tissue donation are examined, comprising pre-transplant facial vessel delineation; pre-operative aesthetic matching; and attitudes towards donation. An anatomical study of 200 consecutive facial and transverse facial vessels was performed using colour Doppler ultrasound. Facial vessels were measured at three landmarks and their branching pattern documented. The facial artery main branch was detected at the lower mandibular border in 99.5% of cases, the accompanying facial vein in 97.5%. The transverse facial artery was present in 75.5% of cases, the vein found in 58%. When the facial artery was undetectable, there was transverse facial artery dominance. When the facial vein was absent it was replaced with a transverse facial vein. This provides valuable pre-operative information regarding vessel status. A quantitative eleven-point skin tonal matching scheme is described using digital analysis of facial imagery. Attitudes towards tonal mismatch in facial and hand transplantation are examined in two representative skin types. There was more scope for skin tonal mismatching in skin tone 2 (slightly tanned white) than in skin tone 6 (light golden brown) participants. Tonal mismatches were more tolerated in facial than in hand transplant simulations in both groups. More acceptable donor tonal groups exist for males than females. Targeted matching of skin tone is thus required. Attitudes and beliefs of 170 transplant professionals were examined. Areas of concern included the organ retrieval process; impact on the retrieval team and donor family. In-depth analysis of a transplant donor focus group was performed; provision of information, post-transplant contact, and post-retrieval donor facial appearance was deemed important. A method of fabricating a donor-specific artificial prosthesis within the time frame of

facial graft retrieval is described. Finally, a method of framing the informed consent process is described.

To my wife Rashi

for all her support, patience and understanding

Statement

I researched and wrote Chapter 1, collaborating with Dr Henry Stephens on aspects of tissue typing. I designed and performed the ultrasound studies, analysed the data and wrote Chapter 2, under the guidance of Mr Peter Butler. Dr Leslie Berger provided me with ultrasound training for this aspect of the study. Dr Kerrie Whitwell assisted in recruiting volunteers for the study. I designed and carried out all the studies in Chapter 3 and 4, including the creation of transplant simulations, questionnaire design, data collection and analysis. Statistical advice was obtained from Professor Paul White. Mr David Bishop assisted me in the photographic image procurement. In Chapter 5, I assembled and described the raw data from the meetings with the transplant co-ordinators obtained by Mr Peter Butler, Miss Fidelma Murphy and Dr Alex Clarke. Miss Fidelma Murphy participated in analysis of the data. The donor focus group data was obtained by Dr Alex Clarke; I analysed and described this data. I designed and carried out Chapter 6, with technical assistance from Mr Teerathraj Chooneea. All projects fulfilled the requirements of the Helsinki Agreement and received prior ethical approval either from the University College London Hospitals (UCLH) Ethics Committee or the Ethics Committee of the Royal Free Hospital, London. All human subjects gave prior written consent to publication of data within this thesis, which specifically included the publication of identifiable images.

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List of Abbreviations

ANOVA	Analysis of Variance
CDC	Complement-Dependent Lymphocytotoxic
Cm	Centimetres
CMV	Cytomegalovirus
CTA	Composite Tissue Allotransplantation
EBV	Epstein-Barr Virus
FA	Facial Artery
FAMM	Facial Artery Musculomucosal
FV	Facial Vein
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HHV	Human Herpes Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HTLV	Human T-cell Lymphotropic Virus
Hz	Hertz
ICU	Intensive Care Unit
IgG	Immunoglobulin G
JPEG	Joint Photographic Experts Group
LC	Lateral Canthus
MHC	Major Histocompatibility Complex
MHz	Megahertz
MIC	MHC Class I Chain-Related

Mm	Millimetres
MSE	Mean Standard Error
PLS	Psychosocial Levels System
PTLD	Post-Transplantation Lymphoproliferative Disorder
RGB	Red, Green, Blue
RNA	Ribonucleic Acid
SD	Standard Deviation
ST	Skin Tone
TERS	Transplantation Evaluation Rating Scale
TIFF	Tagged Image File Format
TFA	Transverse Facial Artery
TFV	Transverse Facial Vein
UCLH	University College London Hospitals
UVA	Ultraviolet A

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Chapter 1

1. The Evolution of Facial Transplantation

1.1. Facial Disfigurement and its Sequelae

Many great writers from Shakespeare ('to find the mind's construction in the face') to Oscar Wilde ('it is only shallow people who do not judge by appearance') have long held the view that the face gives insight into a person's character (Rumsey and Harcourt 2005a). History has often been unkind to those of an unusual appearance. Nineteenth-century paintings by Hogarth depicted people with mental health problems with unusual or unattractive faces (Munro 1981), and society continues to maintain that connections exist between inner character and outward appearance.

The face is regarded as our most defining and recognisable feature; facial recognition is an essential characteristic of human interaction, which begins when we are newborn babies and continues throughout life. Modern-day exploitation of the unique nature of facial identity has led to the explosion of facial recognition software as a method of identification. The face is not however simply an anatomical storage place in which the mouth, eyes, nose and ears reside. It is a unique identifier to all those with whom we interact. It provides us with expressions that can convey our innermost feelings. It is an important marker for sexual attraction and an indicator of social status and identity (Furr *et al.* 2007). There is evidence for example that facial attractiveness can favourably effect evaluation of job status, ability and earning power (Bull and

Rumsey 1988). Facial disfigurement therefore presents a rather unique challenge to the facial surgeon.

Facial disfigurement is surprisingly common. In the UK, facial disfigurement-related disability is estimated to affect approximately 391,000 people (0.7% of the population) (Khan *et al.* 2007). Facial disfigurement can occur following a variety of events, including surgery, trauma (including burns) and cancer. The stigma of facial disfigurement plays a role in the morbidity of certain severe skin diseases such as acne, and can occur with congenital defects such as port wine stain and cleft lip. Disfigurement of the face is a significant life event associated with considerable psychological morbidity, lack of social interaction, feelings of withdrawal, and a lower self esteem and self image (Levine *et al.* 2005).

Evidence suggests that the public treat the facially disfigured with less trust and respect (Furr *et al.* 2007). Patients with facial scarring are rated as less honest than non-scarred individuals (Rumsey and Harcourt 2005a). Social isolation and unhappiness in the facially disfigured can lead to anxiety, substance abuse, relationship breakdown and an increased risk of suicide (Robinson *et al.* 1996; Ye 1998). The facially disfigured can experience discrimination in their daily activities; evidence suggests that the facially disfigured can be treated adversely during the assessment of work-related skills in the job interview process (Stevenage and Mckay 1999). They experience bullying, staring, social avoidance and other more subtle forms of discrimination.

It has been suggested that facial disfigurement constitutes a 'social disability' in that it affects both the disfigured person and the people around that person with whom they interact (Rumsey and Harcourt 2005b). For example, strangers leave a greater distance between themselves and a person with facial disfigurement than with someone of 'normal' appearance (Rumsey *et al.* 1982). The inability to use muscles of facial expression can lead to difficulty 'reading' the non-verbal cues communicated by a disfigured face (Macgregor 1989). The facially disfigured can be pre-occupied with the effect that their appearance has on others, which can lead to shyness and defensiveness, or at the other extreme, overconfidence and hostility (Rumsey and Harcourt 2005b). The reconstruction of the severely disfigured face can lead to significant measurable improvements in an individual's well-being (McGrouther 1997).

1.2. Facial Reconstruction

The reconstruction of the face has fascinated surgeons for centuries. The face represents the ultimate challenge: a group of unique structural and functional subunits made up of a variety of tissues which are difficult to replicate and mimic. Traditional methods of facial reconstruction have included skin grafts, flaps and tissue expansion, but these methods often cannot replace lost tissue faithfully.

There are numerous historical accounts of methods of facial reconstruction. The chronicles of the ancient Indian physician Sushruta give the earliest recorded account of facial reconstruction, describing the use of facial cheek tissue to reconstruct the nose in around 600 BC (Singh and Kelly 2005). In the 15th century the Sicilian surgeon Antonio Branca reconstructed the nose using pedicled forearm tissue. In the

16th century the Italian physician Gaspare Tagliacozzi further popularised this method, subsequently describing the transplantation of a nose from a slave onto his master (Barker *et al.* 2007b). In the 18th century, the ancient Indian technique of forehead flap reconstruction (the 'Indian Method') was popularised in the 'Gentleman's Magazine of London' in 1794 (Singh and Kelly 2005). The subsequent work of Gillies and McIndoe reconstructing facial and other injuries during the early 20th century is well-documented (Barron 1985; Triana 1999).

1.3. The History of Composite Tissue Allotransplantation

Composite tissue allotransplantation (CTA) is the surgical transfer of grafts composed of multiple tissue types. Its origins pre-date even those of solid organ transplantation. The 'Legend of the Black Leg' recounts how in AD 348, twins Damian and Cosmos replaced a diseased leg of a sleeping man with the leg of a dead Ethiopian Moor (Kann *et al.* 2000). Bunger famously described allotransplantation of sheep skin in 1804 (Barker *et al.* 2007b). In the early 20th century Carrel successfully performed orthotopic hind limb and kidney transplants in dogs (Carrel 1983). In the early 20th century Guthrie described heterotopic allotransplantation of dog heads (Barker *et al.* 2007b).

Medawar and Gibson first described the problem of skin allograft rejection in 1943 (Gibson and Medawar 1943). It was later shown in a mouse model that it was possible to induce a selective state of tolerance to skin grafts (Billingham *et al.* 1953). Plastic surgery has thus been intricately associated with transplantation for many years; it is no coincidence that it was a plastic surgeon, Joseph Murray, who performed the first human kidney transplant in the 1950s (Friedrich 2004).

The first albeit unsuccessful human hand transplant was performed in Ecuador in 1963 (Barker *et al.* 2007b). In the late 1980s several more attempts were made at transplanting hands in primate CTA models, but the relative immunogenicity of the skin led to failure, with the limbs developing signs of rejection after only a few months. This was despite the introduction of cyclosporine A which had been shown to prolong survival, dropping acute rejection rates from 70% to 50% (Borel *et al.* 1994). A number of swine CTA models were developed (Ustuner *et al.* 2000); the use of prednisolone, tacrolimus and mycophenolate mofetil in experimental models helped ascertain that prevention of skin rejection was indeed possible (Barker *et al.* 2007b). The first successful human hand transplants were performed in 1998 in Lyon (Dubernard *et al.* 1999), Louisville (Jones *et al.* 2000) and Guangzhou (Francois *et al.* 2000) and there have been over 60 hand transplants (Schneeberger *et al.* 2011) including over 16 double hand transplants (Wysong 2010) performed to date. There have also been attempts at CTA reconstruction of non-skin containing tissue such as bone and joint (Hofmann and Kirschner 2000), penis (Hu *et al.* 2006), larynx (Strome *et al.* 2001), tendon (Guimberteau *et al.* 1992), nerve (Bain 2000), muscle (including abdominal wall) (Levi *et al.* 2003), tongue (Birchall 2004) and uterus (Fageeh *et al.* 2002).

1.4. The Recent History of Human Facial Transplantation

Attention has in more recent years turned to alternative methods of facial reconstruction which could mimic tissue more precisely and provide satisfactory functional recovery of muscular sub-units. The preliminary clinical work behind modern human facial transplant techniques began following a series of reports in the 1990s. In 1996 a series of scalp replantations was reported by Cheng *et al* (Cheng *et*

al. 1996), with replantation of the face following a degloving accident described in 1998 by Thomas *et al* (Thomas *et al.* 1998). In 2004 Jiang *et al* transplanted a cephalocervical skin flap and two ears onto a 72 year-old lady with malignant melanoma (Jiang *et al.* 2005), leading to some debate regarding patient selection (Siemionow and Agaoglu 2006).

From these experimental procedures it became clear that future human facial transplantation was technically possible from a microsurgical perspective. The previously considerable problem of skin rejection seemed to have been largely overcome using tacrolimus, prednisolone and mycophenolate mofetil combinations in both pre-clinical and clinical hand transplantation studies (Francois *et al.* 2000; Jones, Jr. *et al.* 1999).

The various aspects of facial transplantation still to be resolved were discussed in a widely publicized report authored by the Royal College of Surgeons of England in 2005 (Morris *et al.* 2004). Although work had shown that facial transplantation was technically feasible, it was felt by the group that a number of outstanding issues still remained.

Following further ethical debate (Banis *et al.* 2004; Barker *et al.* 2007a; Haughton 2004; Summerton and Agha 2004; Thorburn *et al.* 2004; Wiggins *et al.* 2004), the first human partial face transplant was performed in 2005 in Amiens, France, on a 38 year-old lady whose face was severely injured following a dog bite injury (Devauchelle *et al.* 2006). A central triangular-shaped area of the face from the nose

to the chin was transplanted from a cadaveric donor. The mouth and lips were badly disfigured and functionally redundant, and were thus included within the graft.

The second partial face transplant took place in Xi'an, China in 2006 on a 30 year-old farmer whose face was mauled by a bear (Burd 2007; Guo *et al.* 2008). The patient died two years later, after having stopped his immunosuppressive medication on the advice of his community doctor who substituted traditional medicines. Later in 2006, a third partial facial transplant was successfully performed in Paris, this time on a young man with severe plexiform neurofibromatosis (Lantieri *et al.* 2008). In the US, Siemionow performed a complex near-total facial transplant on a 54 year old woman following severe mid-face trauma (Siemionow *et al.* 2009).

A total of 16 facial transplants have now been performed to date (Schneeberger *et al.* 2011), including a full facial transplant performed in Spain in early 2010 (Eaton 2010) which included the nose, facial muscles and maxilla. Later in 2010, Lantieri *et al.* performed a full facial transplant, this time also including eyelids and lacrimal system (Schpoliansky 2010). A total of two mortalities have been reported thus far, one in a Chinese patient who stopped immunosuppression two years post-transplant, and the second a patient with extensive burns sequelae who underwent bilateral upper limb transplantation at the same sitting as the facial transplant (Gordon *et al.* 2009). Two months post-transplant, the patient developed overwhelming infection requiring surgical revisions, and subsequently died following a cardiac arrest. All transplants have been performed due to a lack of alternative surgical methods to reconstruct severe trauma, burns or congenital deformity.

1.5. Minimizing Rejection in Facial Transplantation

Several factors are involved in matching facial transplant donor to recipient. These include aesthetic considerations and donor-to-recipient matching for blood group and tissue-type to reduce rejection. Additionally, transmissible infections may be prevented or managed if the viral disease status of donor and recipient is known. The purpose of this section is to outline the rationale behind the components of the immunological matching system for facial transplantation.

1.5.1. Human Leucocyte Antigen Matching in Organ Transplantation

Human leucocyte antigen (HLA) molecules are encoded by a set of highly polymorphic genes located within the major histocompatibility complex (MHC) on chromosome 6. There are three classical class I molecules (HLA-A, -B and -C) which are ubiquitously expressed on most cell types and recognized by both $CD8^+$ T cells and natural killer (NK) cells (Lanier 2005; Zinkernagel and Doherty 1997). Similarly, three classical class II molecules (HLA-DR, -DQ and -DP) exist, expressed predominantly on B cells, activated T cells and macrophages, and recognized by $CD4^+$ T cells. HLA class I and II gene loci are the most polymorphic in the human genome, with the HLA-B locus encoding over 900 alleles (see http://www.ebi.ac.uk/imgt/hla). Functionally, HLA molecules present antigenic peptides to T cells that drive both humoral and cellular immune responses to foreign antigens, including allogeneic HLA molecules on transplanted tissues. Techniques used to type HLA molecules and their allelic variants have largely evolved from the field of human transplant immunology and the need to predetermine compatible tissue types that will reduce the risk of organ rejection. A variety of other class I (HLA-E, -F and -G) and class II (HLA-DO and -DM) molecules (considered “non-classical” by

their unusual functions, restricted expression and limited polymorphism) are not considered relevant in mediating transplant rejection. Conversely, non-classical MHC class I chain-related (MIC) molecules genes are polymorphic, expressed predominantly on epithelial cells, and may mediate transplant rejection (Stephens 2001; Zou *et al.* 2007). Rejection occurs when HLA antigens on donor cells are recognised by recipient lymphocytes or antibodies, leading to destruction of the antigen-bearing graft (Porter 1976; Tilney *et al.* 1979); rejection may be hyperacute (antibody-mediated) (Williams *et al.* 1968); acute (cell and antibody-mediated) (Porter 1976; Tilney *et al.* 1979); chronic; or a combination thereof.

Different HLA matching requirements exist for different organs. Renal transplantation in the UK is based on a matching for HLA-A, -B and -DR loci, because graft survival has been shown to progressively decrease with increasing number of HLA mismatches (Terasaki *et al.* 1996). Evidence suggests that within this group, HLA-B and -DR may be the most important (UK Transplant 2006). Conversely, donor-recipient HLA matching in liver transplantation is of less importance and is not routinely performed in the UK, as the liver is relatively resistant to antibody-mediated rejection (Navarro *et al.* 2006). In cardiac transplantation studies have been contradictory, with evidence for and against HLA matching (Almenar *et al.* 2005; Smith *et al.* 1995). Prospective matching is logistically difficult however, because of the short ischaemic time tolerated by cardiac grafts. These matching requirements contrast markedly with bone marrow transplantation, where all six loci must be matched precisely at a very high resolution (Flomenberg *et al.* 2004).

The primary role of the HLA or tissue-typing facility is to provide advice on the relative risk of immunological rejection. With kidney, pancreas and cardiothoracic transplants, high immunological risk is indicated by a high titre of circulating antibodies specific for mismatched donor classical HLA class I and II antigens, detectable at time of transplantation (British Transplantation Society 2004; Gebel *et al.* 2003). Such antibodies may form in potential recipients through sensitisation to allogeneic HLA molecules during pregnancy, previous transplants and blood transfusions. Intermediate immunological risk is considered if there are known historic donor-specific sensitisation events, but weak or undetectable antibodies to donor-specific allogeneic HLA mismatches at the time of the transplant. Low immunological risk occurs if a recipient is non-sensitised, or is sensitised but has irrelevant alloreactive antibodies to HLA types not present on the donor graft (British Transplantation Society 2004; Gebel *et al.* 2003).

1.5.2. HLA Matching in CTA

Composite tissue allografts are by definition histologically heterogeneous. A hand allograft, for example, contains elements of skin, muscle, cartilage, nerve, vasculature and bone, along with immunocompetent cells in lymphoid tissue or bone marrow. High-to-intermediate expression of donor HLA in transplanted skin, bone marrow and vasculature (Duquesnoy 1998) provides potential targets for alloreactive recipient responses.

1.5.3. HLA Matching in CTA Animal Models

Rodent models of CTA demonstrate a reduced immunological response to allografts of a closer histocompatibility match. A hierarchy of tissue rejection has been

described in rats as: skin > muscle > bone > cartilage (Buttemeyer *et al.* 1996). Both the intensity and timing of rejection of a vascularised bone transplant was found to be dependent on the genetic disparity between donor and recipient; allograft survival was significantly shorter when transplanted across major rather than minor histocompatibility barriers (Yaremchuk *et al.* 1985). The importance of matching varies between the different MHC sub-regions, with mismatches at the RT1-A sub-region having the greatest negative impact on allogeneic hindlimb transplant survival (Iwasaki *et al.* 2001). This finding is not limited to limb allografts. Compared with transplantation across a full MHC barrier, transplantation across a semi-allogeneic barrier is associated with immune hyporesponsiveness to donor antigen and increased graft survival in a rat hemi-facial allograft model (Siemionow *et al.* 2005).

Benefits of genetic matching for CTA have also been suggested by work in MHC-inbred miniature swine, which possess a defined genetic transplant barrier similar to human MHC. Lee *et al* (Lee *et al.* 2001) compared survival of a limb allograft after transplantation between MHC-matched and MHC-mismatched animals. In the MHC-mismatched group, there was gross and histological evidence of allograft rejection by 42 days post-transplant. In comparison, the MHC-matched group showed no evidence of rejection at time of sacrifice (25 to 47 weeks), suggesting ongoing graft tolerance. The transplant barrier in the MHC-matched group resembled that between human siblings sharing the same paternal and maternal haplotypes.

Significant differences between animal models and humans have been observed in the response to composite tissue allografts and immunosuppressive regimes, such as the relative ease of tolerance induction in animals compared to humans (Cahill T.J. *et al.*

2006). Despite animal studies in favour of MHC matching for CTA, whether the results are applicable to human transplantation remains uncertain at present.

1.5.4. HLA Matching in Human CTA Trials

Early composite tissue allografts in humans have been variably matched for HLA. In bone grafting, histoincompatibility between donor and recipient in animal models affects revascularization, graft union and new bone formation (Stevenson *et al.* 1996). All three human femoral transplants reported were not matched at the HLA-A,-B and -DR loci (222mm) (Hofmann and Kirschner 2000), but none were viable at 2 years (Hettiaratchy *et al.* 2004). In comparison, the successful human laryngeal transplant performed in 1998 involved a total HLA-A,-B and -DR match between donor and recipient (000mm)(Strome *et al.* 2001). HLA-A, -B and -DR matching for renal transplantation (111mm) was performed on six patients who underwent simultaneous renal and skin allograft transplantation from their respective donor (Wendt *et al.* 1994). All skin allografts survived, bar one who underwent renal graft rejection in the early stages; one skin allograft survived despite the discontinuation of immunosuppression after four weeks. However, it is the outcome of HLA matching in hand transplantation which is most informative, as this group represents the human CTA model most analogous to facial transplantation. The first two hand transplants performed in Lyon (France) and Louisville (USA) were poorly HLA-A, -B and -DR matched (222mm). The next two (in Guangzhou, China) were performed on patients with three HLA-A, -B and -DR matches (111mm) (Barker *et al.* 2002). In the large human hand transplant series so far there is currently no difference in allograft survival according to the number of HLA matches (Lanzetta *et al.* 2005). It is noteworthy that the first hand transplant failed largely due to patient non-compliance

with medication (Dubernard *et al.* 2001); the second documented failed hand transplant did so largely due to inadvertent intra-arterial steroid injection (Guoxian *et al.* 2004). A number of hand transplant recipients from China have had rejection episodes linked directly to non-adherence with immunosuppressive medication.

Interestingly the HLA matching of the series of facial transplants has not had a significant impact on survival. Of the two deaths, one facial transplant recipient had significant HLA mismatches, but his death was very likely multifactorial involving post-operative sepsis. The second facial transplant mortality (in China) had three HLA mismatches; his mortality is however thought to be directly linked to unilaterally stopping immunosuppressant therapy rather than as a result of uncontrollable acute rejection (Gordon *et al.* 2009).

It has been proposed that HLA matching might reduce the doses of immunosuppression required to control rejection, reducing the risk of side effects (Duquesnoy 1998). However, to date there have been no clear differences in immunosuppression required, number of acute rejection episodes, or functional outcome in the human hand transplant cohort relating to HLA mismatch.

Given that the recipient of a facial transplant is likely to be healthy, it is possible that the immunological response to a facial graft will be more robust than following liver or heart transplantation, where recipients may be immunologically-suppressed due to hepatic failure or cardiogenic shock respectively (Cendales and Hardy 2000). However, episodes of acute rejection in hand and facial transplantation have so far proved controllable, and it has been reported that immunosuppressive requirements

for some hand transplants are lower than renal allografts (Dubernard *et al.* 2002; Dubernard *et al.* 1999).

Both donor and recipient in the first partial face transplant shared five HLA antigens (recipient: HLA-A2,3; B8,44; DR3,7; donor: HLA-A2,3; B8,44; DR-15,3) (Devauchelle *et al.* 2006). An immunosuppressive protocol of antithymocyte globulins, tacrolimus, mycophenolate mofetil and prednisolone was used during the immediate transplant period. At least two biopsy-defined episodes of cellular rejection have been recorded (Dubernard *et al.* 2007; Kanitakis *et al.* 2006), with donor-directed cytotoxicity noted at an early stage, disappearing at a later stage. It is unclear whether this was accompanied by any induction of detectable antibodies to the mismatched donor HLA class II antigen (DR15). The relatively high level of HLA-A, -B and -DR matching may favour survival by reducing the overall risk of rejection episodes occurring. However, to date there is not enough evidence from the relative paucity of transplants performed to advocate a minimum level of HLA class I and II matching of donor-recipient pairs in facial transplantation. The less conventional procedure of post-transplant donor bone marrow infusion was also performed in the first partial face transplant with the aim of inducing immunological tolerance to the facial graft (Devauchelle *et al.* 2006), but this procedure has not been utilised in subsequent facial grafts (Paraskevas *et al.* 2007) performed elsewhere.

One obvious disadvantage of HLA matching would be a reduction in the size of the suitable donor pool, potentially leading to a prolonged wait for a suitable donor, or to compromise in other areas such as aesthetic matching. Invoking a full HLA match might therefore preclude widespread uptake of facial transplantation as an option in

the reconstruction of the severely disfigured face. It is nevertheless important for pre- and post-transplant research and monitoring purposes to determine the patient HLA type and antibody status. The candidate facial transplant recipient should therefore be HLA-typed pre-operatively to the highest resolution possible (using direct sequencing or bead-based Luminex technologies). Similarly, in the immediate pre-transplant period a potential donor could be rapidly HLA-typed using moderate-resolution phototyping or PCR-SSP (Bunce *et al.* 1995) which will provide information on the level of HLA matching available. Pre-transplant assessment of the potential recipients HLA-specific antibody status should also be performed, preferably with high resolution flow cytometric or Luminex microsphere-based methods (Gibney *et al.* 2006). Similarly, regular screening of post–transplant recipient sera enables monitoring of antibodies specific to all possible mismatched classical class I and II antigens on the facial graft (HLA-A, -B, -C, -DR, -DQ and -DP), as well as mismatched non-classical MICA molecules (Mizutani *et al.* 2005). Such screening is informative both in defining the recipient's immunological response and predicting potential rejection episodes, particularly in conjunction with biopsy-driven analysis of graft tissue histopathology (Kanitakis *et al.* 2006).

1.5.5. Crossmatching

The purpose of the crossmatch test is to determine whether a potential transplant recipient has circulating antibodies directed against mismatched donor HLA antigens. This test is considered a prerequisite to renal (Doxiadis *et al.* 2003), heart (Tambur *et al.* 2000), lung (Palmer *et al.* 2002) and intestinal transplantation (Ruiz *et al.* 2003), as a positive result is indicative of a high probability of hyperacute and vascular rejection. The crossmatch assay utilises donor spleen, lymph node or peripheral blood

as a source of T lymphocytes (expressing classical HLA class I antigens) and B lymphocytes (expressing both class I and II antigens). Fresh recipient sera collected within 24 hours of a potential transplant and selected historic sera are reacted with donor T and B cells in a complement-dependent lymphocytotoxic (CDC) test (Smith and Rose 2006) or flow cytometric crossmatch (Scornik 1995). The latter is considered the more specific and highly sensitive method of detecting donor HLA-specific antibodies, and can be conveniently performed on donor serum.

Flow cytometric crossmatching can also be adapted to detect different immunoglobulin subclasses, although most laboratories focus on IgG. Both methods of crossmatching can detect donor HLA and non-HLA specific antibodies. If the specificity of antibodies causing a positive crossmatch were against non-HLA molecules, this should not be a veto to proceeding with the transplant. However, the interpretation of a crossmatch result is multifactorial and needs to be performed by experienced personnel who are capable of considering any result in the context of both donor and recipient's HLA types, and the recipient's known antibody profiles as previously determined by screening.

If a potential transplant recipient has never experienced a sensitising event (e.g. blood transfusion, previous pregnancies or organ transplant) then theoretically the production of HLA-specific antibody may not occur and a crossmatch test may not be necessary. This theory has been tested in a number of renal transplant units where pre-operative crossmatching has been successfully omitted in a sub-group of highly-selected immunologically non-reactive patients (Kerman et al. 1998). However, given that the incidence of humoral rejection in facial CTA is not yet fully known,

pre-transplant crossmatching is prudent given the serious consequences of facial allograft rejection.

In the facial transplantation setting, we suggest that rapid flow cytometric allogeneic cross-matching using donor lymphocytes and recipient sera should be performed. This process will help determine the likely risk of rejection, and can be performed within a reasonable time frame in the context of facial graft harvesting to allow appropriate interpretation of the results (Figure 1.1). A summary of the matching procedures recommended in facial transplantation is given in Table 1.1.

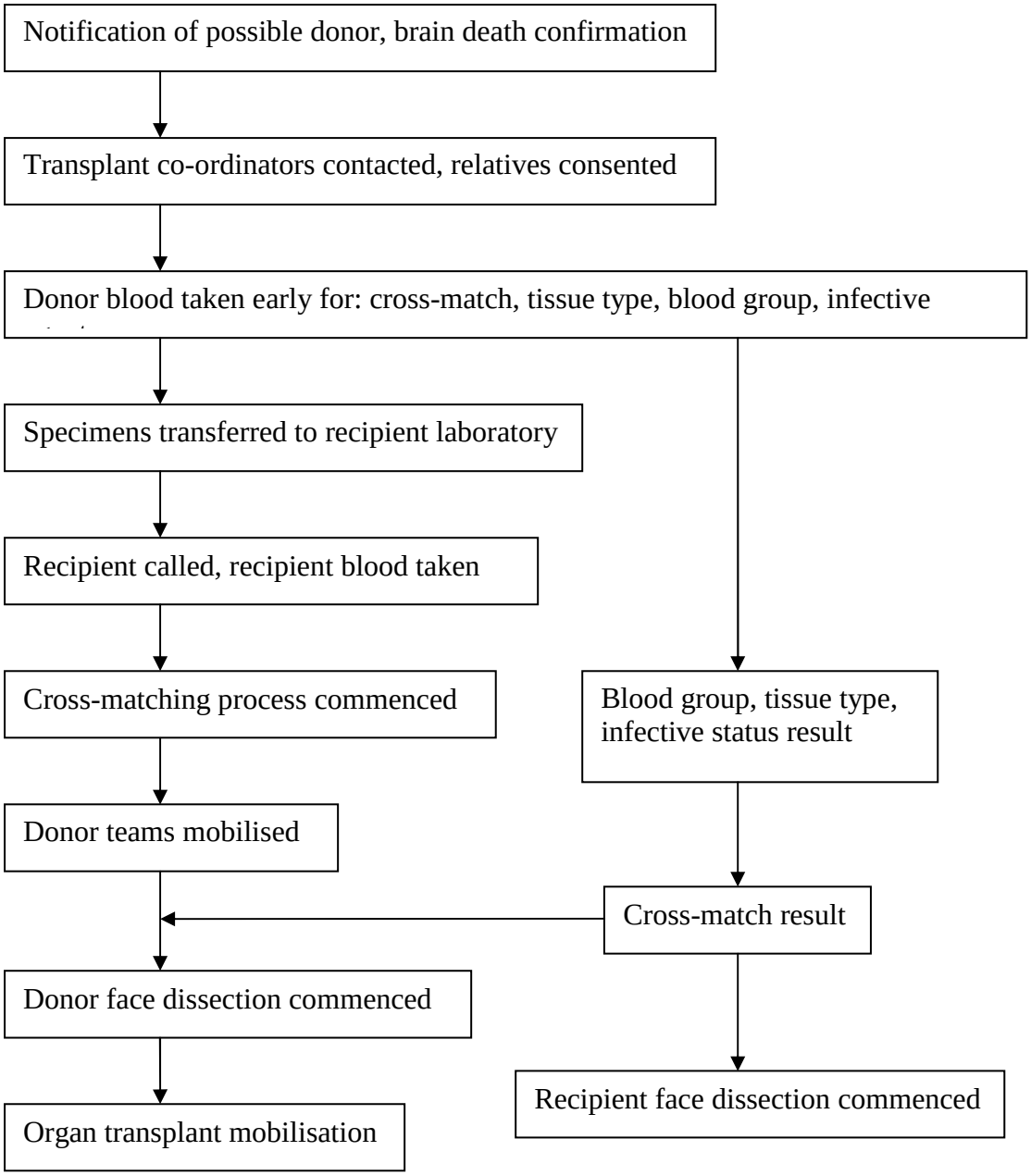


Figure 1.1. Proposed mechanism of donor face procurement: interaction with matching process.

Table 1.1. Summary of the process of immunological matching and monitoring required in facial transplantation.

Process	Method	Timescale	Essential (E) / Recommended (R) §
Recipient HLA typing: moderate-high resolution	Bead-based Luminex technology Direct sequencing	Pre-operative	R
Recipient screening for antibodies to HLA class I/II antigens: moderate-high resolution	Bead-based Luminex technology	Pre-operative three-monthly	R
Recipient & donor ABO matching	Standard blood typing	Pre-operative	E
Donor HLA typing: rapid assessment	Phototyping PCR-SSP*	Pre-operative	R
Cross-matching: allogeneic and autologous	CDC† Flow cytometry	Pre-operative Pre-operative Post-operative	E E R
Recipient screening for HLA-specific antibodies	Bead-based Luminex technology	Post-operative three-monthly	R
Graft tissue histopathology	Tissue biopsy monitoring	Post-operative	R

* PCR-SSP: polymerase chain reaction using sequence-specific primers; † CDC: complement-dependent cytotoxic cross-matching; § Recommended processes (R) are required mainly for monitoring and/or research purposes; essential processes (E) are required in order for the operation to proceed.

1.5.6. Blood Group Matching

In solid organ transplantation, donor-to-recipient matching for major (ABO) blood groups was traditionally considered important to prevent hyperacute rejection secondary to anti-A or anti-B antibody activation. Exceptions to this view generally include: liver transplantation (Gugenheim *et al.* 1990); after antibody removal by plasmapharesis or immunoadsorption (Higgins *et al.* 1996; Tyden *et al.* 2005; Winters *et al.* 2004); and following recipient immunomodulation of the immune system (Glotz *et al.* 2004; Vieira *et al.* 2004). The liver for example is considered a relatively immunoprivileged organ, the implanted liver adsorbing circulating antibodies. Hyperacute rejection is rarely seen, although there is a greater risk of acute rejection and poorer long-term survival in blood group incompatible transplants (Donaldson and Williams 1997). Such transplants are only considered in exceptional circumstances where delay to obtain a matched graft is of great risk to the recipient.

Such a clinical scenario clearly does not apply to facial transplantation. We consider that additional processes to modulate or remove antibodies from the recipient would overcomplicate the whole facial transplant process without a clear evidence base for its implementation. A low-risk strategy should therefore ideally be adopted. Both donor and recipient of the first partial face transplant shared the same blood group (O^+) (Devauchelle *et al.* 2006), and such an approach is probably prudent. Nevertheless, it is important to note that the fourth facial transplant was performed successfully (in Cleveland, USA) despite donor and recipient being blood group A and AB respectively (Siemionow *et al.* 2010). If shown to be reproducible, this could have significant impact on the availability of facial donor grafts globally.

1.6. The Matching of Infectious Disease Status

The rationale behind serological screening of the donor for infectious disease status is to minimise the risk of transmission of significant infections to the immunocompromised recipient. It is also important that a careful and detailed history of potential exposure and "at risk" behaviour is obtained, along with an accurate diagnosis of cause of death. In the UK, the practice is to routinely screen for the following: human immunodeficiency virus (HIV) -1 and -2; hepatitis B virus (HBV) surface antigen and core antibody; hepatitis C virus (HCV) antibody; human T-cell lymphotropic virus (HTLV) -1 and -2 antibody; cytomegalovirus (CMV) delta agent; toxoplasma antibody; syphilis; and Epstein-Barr virus (EBV) antibody (British Transplantation Society 1998).

1.6.1. Hepatitis and HIV

The transmission of HBV or HIV from an infected donor is high if the donor is positive for HBV surface antigen or for HIV antibody. The risk of transmitting HCV with an extrahepatic allograft from a donor who is positive for anti-HCV antibody is approximately 50%, with the risk approaching 100% if the donor's blood contains HCV RNA (British Transplantation Society 2003). In the US, an estimated 4.2% of cadaveric donors are positive for anti-HCV, with 1% positive in the UK (British Transplantation Society 1998). One approach has been to transplant organs from anti-HCV-positive donors only into critically ill patients awaiting heart, liver, or lung allografts, older patient with a limited expected life span, or patients awaiting renal transplantation who have been unable to find a suitable donor because of prior sensitization to MHC antigens, for whom a particular matched donor represents a unique opportunity. Organs from donors positive for anti-HCV are not used for

younger patients. Recent evidence shows that heart transplants from anti-HCV positive donors confer shorter survival to recipients (Gasink *et al.* 2006). Clearly, as a life-enhancing procedure, facial transplantation using a donor who is positive for HIV, HCV or HBV would be hard to justify. Therefore we propose that all donors should have negative virology results for these agents prior to graft harvesting. Donors with a history of possible exposure to HIV should also be excluded, as there is a time lapse after infection before the antibody appears.

1.6.2. Cytomegalovirus

Cytomegalovirus can be a devastating complication affecting long-term outcome in solid organ transplantation. At highest risk for developing primary CMV infection are CMV-negative recipients of a CMV-positive graft. Re-infection with a donor viral strain is more common than reactivation of a recipient viral strain, and is likely to produce more severe and frequent disease episodes. Serious CMV disease often depends on the total burden of immunosuppression (British Transplantation Society 2003). Knowledge of CMV status and immunosuppressive regimen therefore allows clinicians to adopt appropriate clinical strategies to prevent CMV infection. This can be via pre-emptive screening, prophylactic anti-viral medication or reduction of immunosuppressive intensity.

Of the first 18 hand transplants that were reported, 17 donors and 17 recipients received prior testing for CMV, although CMV status was not used as a criterion for donor selection (Schneeberger *et al.* 2005). Infection or disease due to CMV complicated the postoperative course in five of the nine recipients challenged with the virus. Importantly, in some cases a close time correlation between CMV replication

and episodes of acute rejection suggests a causative link (Schneeberger *et al.* 2005). Of the three femoral transplants reported, one recipient suffered from a transmitted CMV infection at seven weeks post-transplant (Hofmann and Kirschner 2000).

In the series of facial transplants performed so far worldwide, CMV remains a considerable issue, with severe valgancyclovir-resistant CMV viraemia complicating the course of the third transplant recipient and coinciding with a rejection episode – here the donor was CMV-positive, the recipient was negative and the patient suffered a severe viraemia episode coinciding with the timing of CMV seroconversion (Gordon *et al.* 2009). Many therefore feel that CMV remains the major infectious threat in facial CTA. Some authors advocate the avoidance of CMV-mismatch and mandatory prophylaxis with valgancyclovir and anti-CMV hyperimmunoglobulin in CTA (Schneeberger *et al.* 2005). Although CMV titres can be tightly monitored post-operatively, and pre-emptive treatment can be commenced if titres begin to climb, CMV matching of donor to recipient is ideal and should ideally be a performed in facial transplantation. Prophylaxis against CMV should certainly be considered if either the facial transplant donor or recipient is positive, as severe CMV viraemia is a predictor of mucosa rejection (Hui-Chou et al. 2010). In the fourth facial transplant case, CMV donor-positive/recipient-negative status meant that maintenance of a high level of ganciclovir was a priority post-operatively, and no CMV viraemia has been subsequently reported (Siemionow *et al.* 2009).

1.6.3. Epstein Barr Virus

In solid organ transplant populations, transmission of EBV to seronegative recipients is associated with several clinical scenarios including asymptomatic viraemia,

hepatitis and mononucleosis syndrome (Nicholson and Johnson 1994). In addition, the risk of post-transplantation lymphoproliferative disorder (PTLD) can increase as much as 20-30 fold (British Transplantation Society 1998). We suggest that EBV serology should be performed in both donor and recipient. Seronegative recipients at risk of EBV transmission from a seropositive donor should be monitored closely and the degree of immunosuppression modulated to minimise risk of development of PTLD.

1.6.4. Human Herpes Virus

In solid organ transplantation, transmission of human herpes virus 8 (HHV-8) from donor to recipient has been described, leading to an increased incidence of Kaposi sarcoma (Moore 2003). It would be prudent to test for this agent in donors from areas of increased prevalence (such as the Middle East or Africa). A type 1 human herpes simplex infection was reported on the lips of the first partial face transplant, and was successfully treated (Dubernard *et al.* 2007).

1.6.5. Human T-cell lymphoma virus (HTLV)

Donor screening for HTLV is not routine performed in the UK. Although the prevalence in the UK is very low for these viruses, HTLV-1 infection presents a serious threat to the recipient. Absolute lifetime risk of lymphoma in positive individuals approaches 5% in the immunocompetent, with the disease manifesting itself more rapidly in organ transplant recipients (British Transplantation Society 2003). There is scant data on HTLV incidence in CTA. Nevertheless, in areas where infection of potential donors with HTLV is endemic we suggest including it as part of the screening test for facial transplantation.

1.6.6. Syphilis

Syphilis is increasingly prevalent worldwide. Significantly the donor face in the third facial transplant performed worldwide was positive for *T. pallidum*; the *T. pallidum* negative recipient thus received treatment with methylpenicillin (Gordon *et al.* 2009).

1.7. A Rationale for Minimizing Rejection in Facial Transplantation

Experience from solid organ transplantation and CTA has demonstrated that matching of immunological and infectious disease status should be important considerations in facial transplantation. HLA tissue-typing is undertaken in a variety of solid organ transplant programs. Given the limited availability of facial transplant donors, and the paucity of evidence suggesting improved outcome following prospective donor-recipient HLA matching in comparable CTA groups (such as hand transplantation), it is difficult at present to invoke a prerequisite minimum level of HLA matching in facial transplantation. Nevertheless, it is imperative that as much relevant and meaningful information as possible should be collected for research purposes. Pre- and post- transplant crossmatching and screening for pre-formed and induced HLA specific alloantibodies (in conjunction with regular histopathology investigations) are likely to be highly informative to clinicians in the immediate and medium-term post-operative phase of a facial transplant, for this is when immunological rejection of donor tissue is most likely to occur. In addition, matching for infectious agents is required for some viruses (such as HIV and HTLV) but may not be quite as essential for others (such as CMV) where effective prophylaxis can be given post-operatively.

As the series of facial transplants performed so far have shown, it is no longer a question of how to perform a facial transplant, but rather a question of how to achieve the best possible outcome. Of course, parameters established prospectively for donor-recipient matching can only be validated once a larger cohort of facial transplant patients is established. Final outcome in facial transplantation will depend not just on technical accomplishment and immunological success. Psychological outcome and patient satisfaction will be related to the aesthetic endpoint. At present it is not fully clear which aesthetic properties of the allograft are of greatest importance and to what degree they need to be matched: it is likely to be of great importance for example to obtain a good skin tone match (Chapter 4). Tissue typing and matching of infectious agents must therefore be performed rationally in order to increase the potential facial donor pool. The matching process will also require careful collaboration between different units. Additional aesthetic matching requirements may necessitate the establishment of an international recipient database in order to maximise usage of potential donors. As the potential pool of facial transplant donors may be small, time may be better allocated to these aspects if we wish to fully optimise outcome in facial transplantation. As has been shown in hand transplantation (Banis *et al.* 2004), this can be a challenging endeavour, but an essential one.

1.8. Functional Outcome of Facial Transplantation

Transplanting skin and subcutaneous tissue in pan-facial injuries with a skin-only flap can often improve the mobility of deeper structures (and hence facial movement). Grafts have however so far required a number of combinations of skin, muscle, and bone (Siemionow *et al.* 2009), often incorporating complex maxillofacial subunits into the graft. How well the face transplants will ultimately function many years down the line is not fully known, yet the results are promising. Functional recovery of the upper lid is still likely to be difficult for example.

The evidence for full neurological recovery following reanastomosis of facial nerves is generally poor (Myckatyn and Mackinnon 2003). However, the results so far in the facial transplant group are promising; perhaps this is in part due to the effect of accelerated nerve regeneration associated with the administration of tacrolimus (Mackinnon *et al.* 2001). There have been notable exceptions within the facial transplant group however, such as the third facial transplant recipient whose facial nerve was more damaged than had been previously thought by the operating surgeon (Hui-Chou *et al.* 2010). Results for facial graft function on the whole compare favourably with the large group of hand transplants however (Wysong 2010). Reports of the first seven facial transplants performed claimed sensory recovery from between 3 and 6 months, with acceptable motor recovery commencing between 9 and 12 months (Gordon *et al.* 2009).

1.9. Attitudes to Risk in Facial Transplantation

In 2004 the Royal College of Surgeons of England suggested that the risks of facial transplantation outweighed the benefits (Morris *et al.* 2004). These risks pertained to psychological adaptation, allograft rejection, and the ethics of life-long immunosuppression for a non-lifesaving procedure. With increasing evidence from animal models and hand transplant data, and following partial face transplant cases in France and China, it became clear that these risks may not be as high as previously thought. In 2007 the Royal College issued an update in which they stipulated 15 measures which should be in place before facial transplantation can be considered (Morris *et al.* 2007).

How each individual professional views and frames each risk may actually differ. For example, when compared with facially disfigured or organ transplant recipient groups, plastic surgeons are less tolerant of the risks of facial transplantation (Vasilic *et al.* 2008). Although the majority of plastic surgeons in Mathes' study of 163 American plastic surgeons agreed that current techniques do not provide adequate reconstruction for severe facial injuries, only 26.2% were in favour of performing facial transplantation which includes immunosuppression (Mathes *et al.* 2009). Anecdotal evidence suggests that many reconstructive surgeons, when asked about whether they would undergo a face transplant at present, would refuse due to the risks of lifelong immunosuppression; if this were dramatically reduced however, most would go on to support it (Clarke 2006, personal communication).

1.10. Immunosuppressive Risks in Facial Transplantation

Immunosuppressive risks include increased predisposition to infection and cancer. Rejection is difficult to predict. Initial estimates were that up to 10% of face transplants will reject at 12 months, with 30-50% rejected within the first 5 years (Concar 2004). These estimates were made based on organ transplant populations, a group which is not directly comparable to composite tissue transplants.

The incidence of rejection following facial transplantation has been largely managed. However, in two of the transplants, rejection has at least partly contributed to patient mortality, albeit indirectly. The first facial graft recipient to die following the procedure did so most likely due to medication non-adherence, stopping his immunosuppressive drugs and replacing them with a traditional herbal remedy (Gordon *et al.* 2009).

Examining the one-year post-transplant data from the hand transplant cohort, 65% of patients experienced acute rejection (Barker *et al.* 2007b), with all episodes successfully reversed. In the series of 52 hand transplants performed so far (Wysong 2010), two particularly well documented cases were affected by immunological rejection: one due to patient non-compliance (Banis *et al.* 2004; Dubernard *et al.* 2001), and the other due to probable inadvertent intra-arterial steroid injection (Barker *et al.* 2007b). The increased visibility of a hand transplant probably contributes to earlier diagnosis of rejection and subsequent high survival rate. In acute rejection following hand transplantation, cutaneous manifestations present early, and correlate with pathological findings (Kanitakis *et al.* 2005). Time lag for the incidence of chronic rejection has been unpredictable in the hand transplant series, although when

compared to solid organ transplant groups this phenomenon may not be as important in composite tissue transplantation as previously thought. Chronic rejection is still however undefined in facial transplantation, and the likely incidence is not yet known (Hui-Chou *et al.* 2010).

The immunosuppressive protocols used for renal transplants (comprising prednisolone, tacrolimus and mycophenolate mofetil for example) have been used successfully in composite tissue allotransplants and are likely to be used for future face transplants; immunological tolerance will be the ultimate goal in the future (Siemionow and Agaoglu 2005).

Most of the facial transplant recipients reported so far encountered at least one episode of acute graft rejection: these have been successfully reversed. Anecdotal evidence suggests that many transplant physicians feel that the risks of immunosuppression are thus largely modifiable. We feel that these risks should not therefore preclude surgeons from considering facial transplantation.

1.11. Psychological and Societal Issues in Facial Transplantation

There should be methods in place to ensure patients selected for any facial transplantation programme are suitably adjusted psychologically and able to cope with the rigours of radical life-enhancing surgery (Clarke and Butler 2004; Clarke and Butler 2005). These include assessment of cognitive function, mental health status, pre-transplant compliance and an analysis of patient attitudes and beliefs. Some commentators view the psychological adjustment required in facial transplantation to be problematic; in fact, many psychologists would argue that many of these

psychological changes are also modifiable (Clarke and Butler 2005) and methods have been described to deal effectively with the psychological adaptation required (Brill *et al.* 2006).

There is need for open and careful public debate about the issues surrounding facial transplantation, and this has been addressed following a series of public engagement exercises (Clarke *et al.* 2006) in which societal issues towards facial transplantation were examined. The major barrier remained the risks associated with immunosuppression. When asked hypothetically whether they would accept or donate a face transplant, 70% of respondents agreed. Those that were staunchly opposed (11%) identified identity transfer as the main obstacle. The thought of a recipient adopting the donor's identity may also be disturbing for donor families.

In fact, experiments using free tissue transfer from cadaver-to-cadaver (Concar 2004), and with face exchange using laser scanning and photography (Clarke and Butler 2005), have shown that the resulting face consists of a donor craniofacial skeleton with an overlying recipient tissue 'envelope' - in effect a new identity altogether. This is supported by experimental work in simulated facial transplants where the transformed face is not perceived as completely novel, but is more commonly identified as the recipient (Pomahac *et al.* 2010). Some authors have commented that identity is an issue that a face transplant candidate will already be very familiar with following their injury (Brill *et al.* 2006). Indeed, adaptation has not been such an issue for facial transplant recipients as it has been for hand transplant recipients, probably because patients need to look into a mirror in order to see their face, whereas

their hands are in full view most of the time. If anything, aesthetic matching is perhaps of greater significance than identity transfer in facial transplantation.

1.12. Patient Selection Criteria for Facial Transplantation

Facial transplantation is major surgery and should not be undertaken lightly. One of the most important issues for the medical team is appropriate patient selection, which should be vigorous in its approach and draw on expertise from a range of relevant professionals. Surgeons, transplant physicians, psychologists and psychiatrists are likely to be involved in patient assessment and selection. Selection criteria should include physical assessment of the face and its functional deficit, general health assessment, and psychological profile. Even if a patient is felt to be appropriate, consideration should be given to alternative options such as psychosocial strategies to manage unusual appearance. These may already have been exhausted, but the patient should be fully aware of all options and counselled on advantages and disadvantages of each.

The reconstruction of form and function is now of such importance that it is no longer acceptable to produce a sub-optimal attempt at structural mimicry. In fact one can argue that the function of a limb or organ is of equal or greater importance to successful outcome. If we are ready and able to produce satisfactory functional reproductions of the larynx, the oesophagus and the hand, the next logical step should be to continue research on facial transplantation. In recognition of this, the Ethics Committee at the Royal Free Hospital gave its approval to commence patient selection for potential whole face transplantation in 2005 (Highfield and Hall 2005).

Working on the original Royal College of Surgeons Report on facial transplantation (Morris *et al.* 2004) the UK facial transplantation team has attempted to address each concern as a research question. In doing this they found that the barriers have been less substantial than previously thought. Ultimately, the risks of a procedure are never known until the procedure is actually performed – with partial and full facial transplantation now already a reality, the truest test of any selection criteria is time. How will the first facial transplant be reflected upon fifty years from now? We do not know. We do however know that fundamental principles of surgery will stand the test of time: research, preparation, planning, informed consent, and thorough pre-operative assessment. Only by incorporating these into a selection process can the likelihood of the most optimal patient outcome be maximised.

1.13. Summary of Chapters

In the following thesis, a number of the clinical considerations in facial transplantation will be explored and examined.

CHAPTER 2 deals with technical aspects of procurement of donor facial graft tissue. Clearly facial transplantation is major reconstructive surgery, and the surgeon harvesting the graft must be sure of the vascular configuration of the donor or recipient face. Estimates of technical failure in microsurgery are relatively easy to predict; the face has a robust blood supply and technical success rates in many microsurgical units can reach 96-98% (Kroll *et al.* 1996). Two cases have been reported of successful scalp and face replantation, one surviving on a single artery and two veins (Wilhelmi *et al.* 2003). Most plastic surgeons would therefore agree that the technical difficulties are significant but not insurmountable. However, the

definition of the facial vasculature can be tricky in the intensive care setting; this necessitates the development of an accurate, mobile and user-friendly method of defining the facial vessel anatomy.

CHAPTER 3 of this thesis described the development of a skin tonal matching system. This we hope will help in obtaining a satisfactory aesthetic end-point following facial transplantation.

CHAPTER 4 describes a system for assessing precisely which donor skin tone would be acceptable in some of the common recipient groups the UK facial transplant surgeon is likely to encounter.

CHAPTER 5 examines the attitudes of transplant professionals towards facial transplantation. For any face transplant programme to be successful, donor groups will need to be enlisted and every attempt should be made to do this in as sensitive a way as possible. The attitudes of health professionals dealing with the donor families and obtaining informed consent for donation are therefore of some significance, helping to pave the way towards the establishment of a national facial transplantation programme.

CHAPTER 6 describes the development of a system to restore form to the donor face following facial graft harvest. The donor face will exhibit a significant facial defect following facial graft harvest: this comprises the facial skeleton with or without muscle units. The reconstruction of such a significant defect should be carefully considered by any successful transplant programme. We have designed a system in

which a moulded silicone envelope can be fabricated during the graft harvesting process.

CHAPTER 7 explores the unique nature of informed consent in facial transplantation. This section of the thesis will review the process of informed consent in health settings, assessing how applicable the current standards are for facial transplantation. The factors which need to be assessed during the screening programme will be outlined, producing a new gold standard for ensuring informed consent in facial transplantation which categorises the procedure according to both individual and process factor. It is hoped that this can be extended to any consent process for radical new procedures.

Chapter 2

2. The Use of Colour Doppler Ultrasonography in the Assessment of Vessels for Facial Transplantation

2.1. Introduction

The majority of the facial skin is supplied by the paired facial, superficial temporal and transverse facial arteries (Figure 2.1). The facial artery is utilised widely in plastic surgery, such as in facial artery musculomucosal (FAMM) (Pribaz *et al.* 1992) and nasolabial flaps (Houseman *et al.* 2000). The facial artery has been examined in various cadaveric studies (Mitz *et al.* 1973; Niranjan 1988). These studies have shown wide variability, with few large studies (Lohn *et al.* 2004) outlining its course and terminal branching pattern. There is little data outlining the course of the facial vein, and scant data on the transverse facial vessels.

The facial artery arises from the external carotid artery, the main branch coursing above the submandibular gland. The artery traditionally has a tortuous course across the anterior face, the vein a more direct path (Houseman *et al.* 2000). The artery runs along the masseter muscle, where it becomes more superficial. It then moves gradually anteriorly until it gives off the two labial arteries near the angle of the mouth. Distally, the artery dives deep to the levator labii superioris and zygomaticus muscles, running towards the medial canthus whereupon it anastomoses with branches of the ophthalmic artery. The facial vein arises from the confluence of the supraorbital and supratrochlear veins in the medial canthus. It runs in a straight line

down to the angle of the mandible, lateral to the artery, before joining the anterior division of the retromandibular vein.

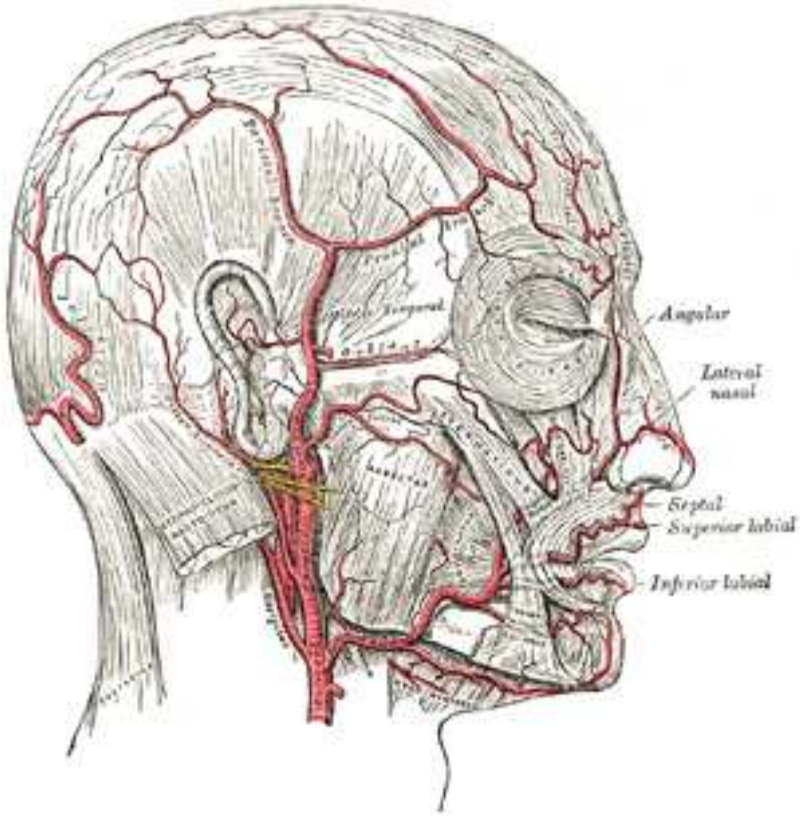


Figure 2.1. Blood supply to the face including facial artery and branches, reproduced with permission from *Gray's Anatomy: the Anatomy of Clinical Practice, 39th Ed, Churchill Livingstone, Edinburgh* (Standring 2005).

The transverse facial artery arises from the superficial temporal artery prior to its emergence from the parotid gland; there may alternatively be a direct origin from the external carotid artery (Standring 2005). The transverse facial artery crosses the parotid, passing masseter superficially between the parotid duct and the zygomatic arch, supplying masseter, the parotid gland and parotid duct. Anastomoses exist between the transverse facial artery and the facial, buccal, lacrimal and infraorbital arteries. The main transverse facial artery perforator occurs in a constant location (Whetzel and Mathes 1997), originating at the superficial musculo-aponeurotic system and coursing with the superior ligament of Furnas (Basar *et al.* 2004). This perforator is found approximately 3.1 cm lateral and 3.7 cm inferior to the lateral canthus (Basar *et al.* 2004).

Traditional methods used in pre-operative vascular evaluation of the face, such as manual palpation and Doppler probes, have limitations: they have no way of assessing flow direction or vessel diameter, and they have restricted capacity for venous evaluation. Colour Doppler sonography has been used to assess flow diameter, velocity and pulsatility in small blood vessels (Foley and Erickson 1991). Although there have been studies of the vasculature in cervical lymph nodes (Na *et al.* 1997), submandibular glands (Ariji *et al.* 1998) and masseter muscle (Ariji *et al.* 2001), there are few studies on colour Doppler sonography in delineating the blood supply to the anterior face (Nagase *et al.* 1997). Zhao *et al* (Zhao *et al.* 2002) used colour Doppler to assess the main trunk and labial and buccal branches of the facial artery in 46 volunteers, detecting 100% of facial artery main branches, and 92.4% of buccinator branches. In this chapter we clarify the distribution of the facial vessels and described

the transverse facial vessels in the anterior face using high-frequency colour Doppler ultrasound in a large series of healthy individuals.

2.2. Materials and Methods

A total of 200 facial arteries/veins, and 200 transverse facial arteries/veins were examined in 100 consecutive healthy volunteers (41 men, 59 women; 89 right-handed, 11 left-handed; 65 Caucasian, 16 Asian, 11 Afro-Caribbean and 8 Oriental; age 20 to 57 years, mean 32.3 years) recruited from two departments at the Royal Free Hospital (Department of Accident & Emergency and the Department of Plastic Surgery). The study was approved by the Royal Free Hospital Research Ethics Committee. All participants were informed of the study aims and gave written consent to participate.

Measurements were taken with the SonoSite MicroMaxx™ System 3.2 ultrasound machine (SonoSite Inc., Bothell, WA) furnished with an SLA 13.6 MHz wide-bandwidth linear active matrix transducer. All images were obtained in the superficial setting using a multifocus with an image depth of 2.2 cm for the facial and superficial temporal vessels and 3 cm for the transverse facial vessels. The settings were chosen to optimise colour Doppler flow measurements; artefact was minimised by altering the wall filter and pulse-repetition frequency. The linear transducer transmits parallel ultrasound beams in sequence, creating a field only as wide as the probe length. The short depth of field was chosen to maximise the potential pick-up rate of the small calibre vessels, which are found anatomically within the superficial facial tissues. The SLA probe is small, thin and held at an angle; this was chosen to allow examination to be most optimally applied around the contours of the face.

Colour gain was set at 2033 Hz. All measurements were made with the patient horizontal on the same couch in a room kept at a constant temperature of 20-22°C. Measurements of flow diameter were obtained when the vessel was maximally dilated. The probe was kept at right angles to the skin, and flow diameter measurements were taken perpendicular to the vessel. The machine's digital callipers were placed at the outer limit of the vessel wall, and a flow diameter measured vertically. All measurements were made at the same points on the face. Measurements were performed after confirming the presence of arteries or veins on the basis of their waveform in the audible Doppler mode (Figure 2.2).

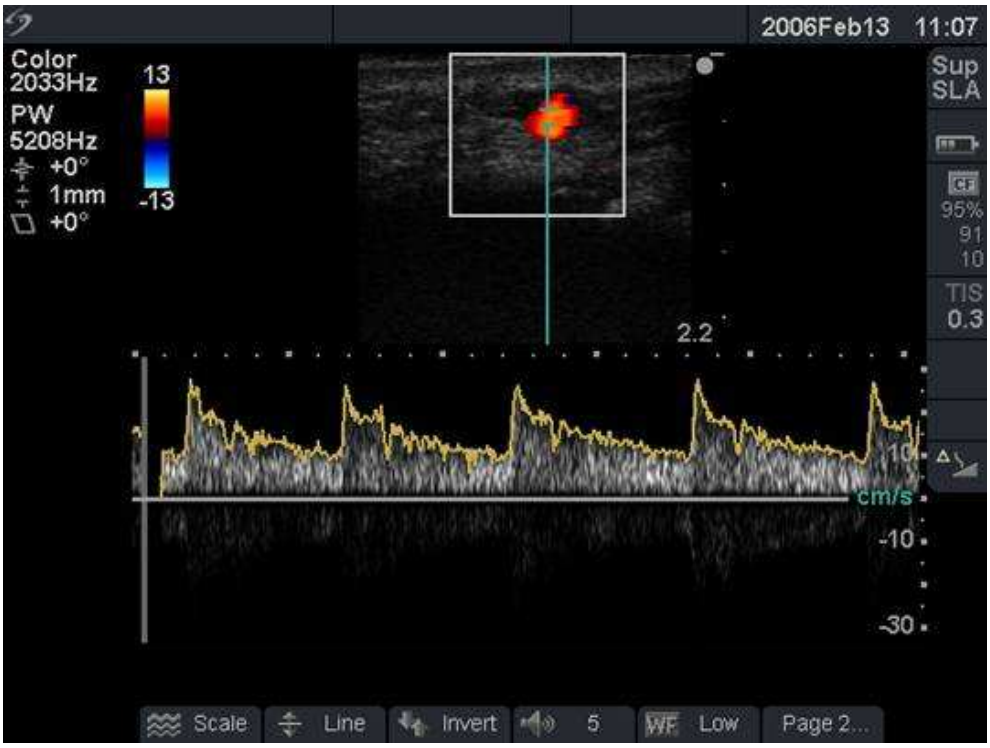


Figure 2.2. Doppler signal showing arterial wave pattern.

The facial artery and vein were scanned in three different positions (Figure 2.3). The landmarks used to measure distance from the facial artery or vein were: the mandibular crossing point (position 1), measured parallel and superior to the inferior border of the mandible; the laterality to the cheilion (position 2), measured horizontally from the angle of the mouth; and the point at which the facial vessel crosses a line drawn between the cheilion and the lateral canthus (position 3). Variation in branching of the facial vessels was documented up to the level of the nasal ala, corresponding with this final position. Anomalous drainage patterns were recorded.

The transverse facial vessels were found emerging from the superficial temporal vessels at the anterior border of the masseter muscle (position 4), travelling across the cheek in a reference line from the external auditory canal to the anterior nasal spine. Flow diameter was assessed perpendicular to the vessel. Distance was measured from the centre of the vessel to the lateral canthus. A flow diameter measurement of the superficial temporal artery and vein was taken concurrently. This was achieved by placing the probe perpendicular to the vessel 1 cm antero-superior to the tragus of the ear. All measurements were repeated bilaterally in all vessels.

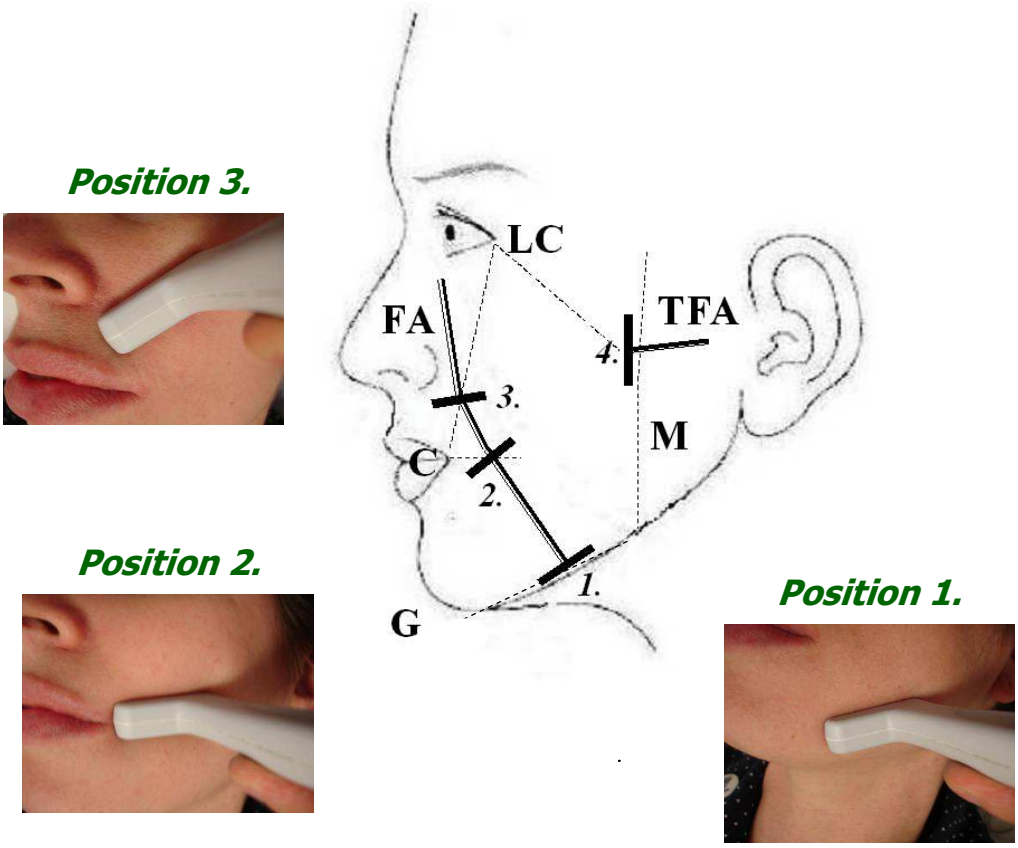


Figure 2.3. Landmarks for the measurement of the facial artery (FA) and transverse facial artery (TFA). Solid black lines represent probe application. Distances were recorded from: the mandibular crossing point (position 1), the point at which the vessel crosses a line drawn laterally from the gnathion (G); the laterality to the cheilion (position 2), the point at which the vessel crosses a line drawn laterally from the cheilion (C); and the approach to the nasal ala (position 3), representing the point at which the vessel crossed a line drawn from the cheilion to the lateral canthus (LC). The TFA was measured as it crossed the anterior border of the masseter (M), and the distance measured from this point (position 4) to the lateral canthus (LC).

The distribution patterns of the facial artery and vein were categorised according to the final branch of the facial artery that was detected up to and including the nasal ala (Figure 2.4). This was adapted from the system described by Koh et al (Koh *et al.* 2003) consisting of: angular, lateral nasal and alar (grouped together here as Types I-III), superior labial (Type IV), inferior labial (Type V) and undetected, or submental (Type VI).

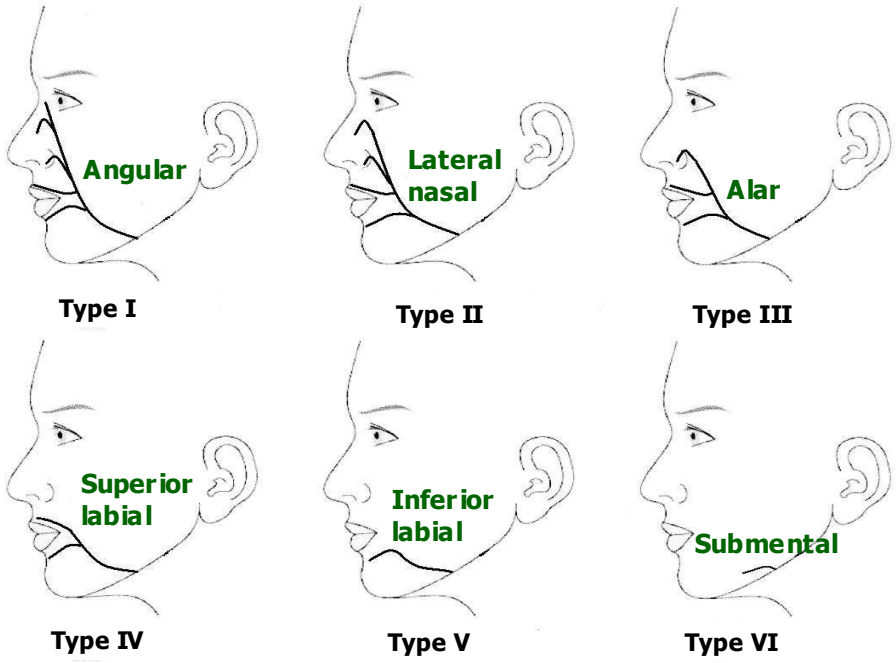


Figure 2.4. Distribution pattern of the facial artery: angular (type I); lateral nasal (type II); alar (type III); superior labial (type IV); inferior labial (type V); and submental (type VI).

2.3. Results

The main branch of the facial artery was detected at the lower mandibular border (Figure 2.5) in 99.5% (n=199) of cases. The accompanying facial vein was found in 97.5% (n=195) of cases, lateral to the artery in all cases.

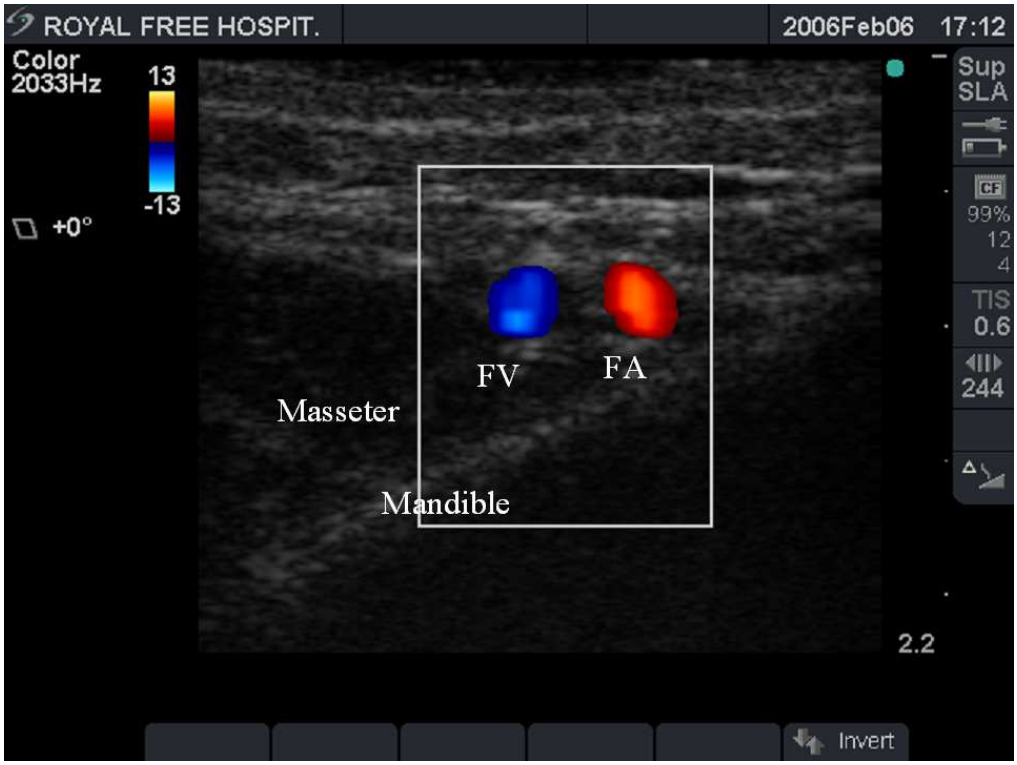


Figure 2.5. Right facial artery (FA) and vein (FV) at the mandibular crossing point (position 1).

At the mandibular crossing point (position 1: Figure 2.5) the flow diameter of the facial artery ranged from 1.1 to 3.7 mm (mean ± SD, 2.6 mm ± 0.45); the facial vein diameter ranged from 1.8 to 5.8 mm (mean ± SD, 3.1 mm ± 0.61). Lateral to the cheilion (position 2: Figure 2.6) the diameter of the facial artery ranged from 1.1 to 3.5 mm (mean ± SD, 2.1 mm ± 0.41); the facial vein diameter ranged from 1.2 to 4.5 mm (mean ± SD, 2.6 mm ± 0.55). Although the facial artery and vein were largely

located together at the mandibular crossing point (mean artery-to-vein distance 7.9 mm) the facial artery and vein diverged from each other more widely lateral to the cheilion (mean artery-to-vein distance 11.8 mm). At the nasal alar base, crossing the line drawn from the cheilion to the lateral canthus (position 3: Figure 2.7), the diameter of the facial artery ranged from 0.9 to 2.7 mm (mean ± SD, 1.8 mm ± 0.39); the facial vein diameter ranged from 1.2 to 4.9 (mean ± SD, 2.4 mm ± 0.64).

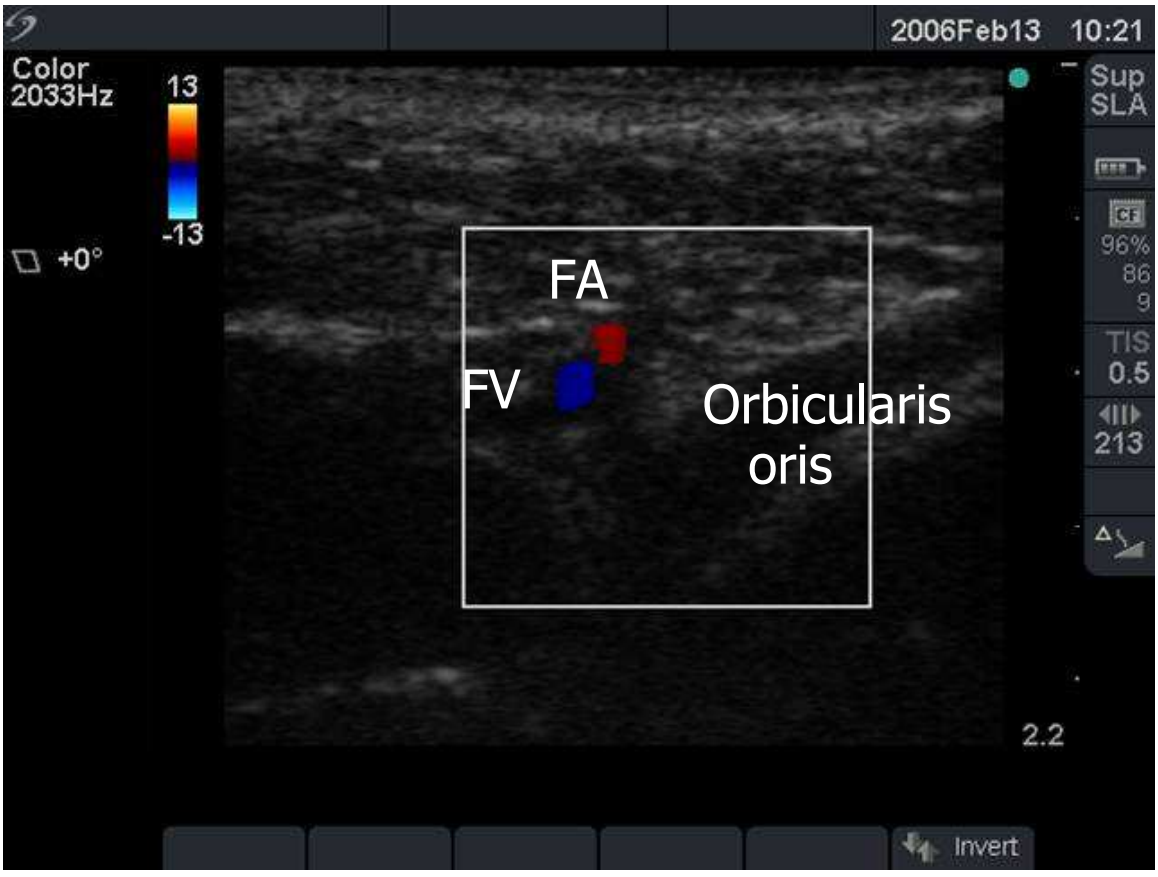
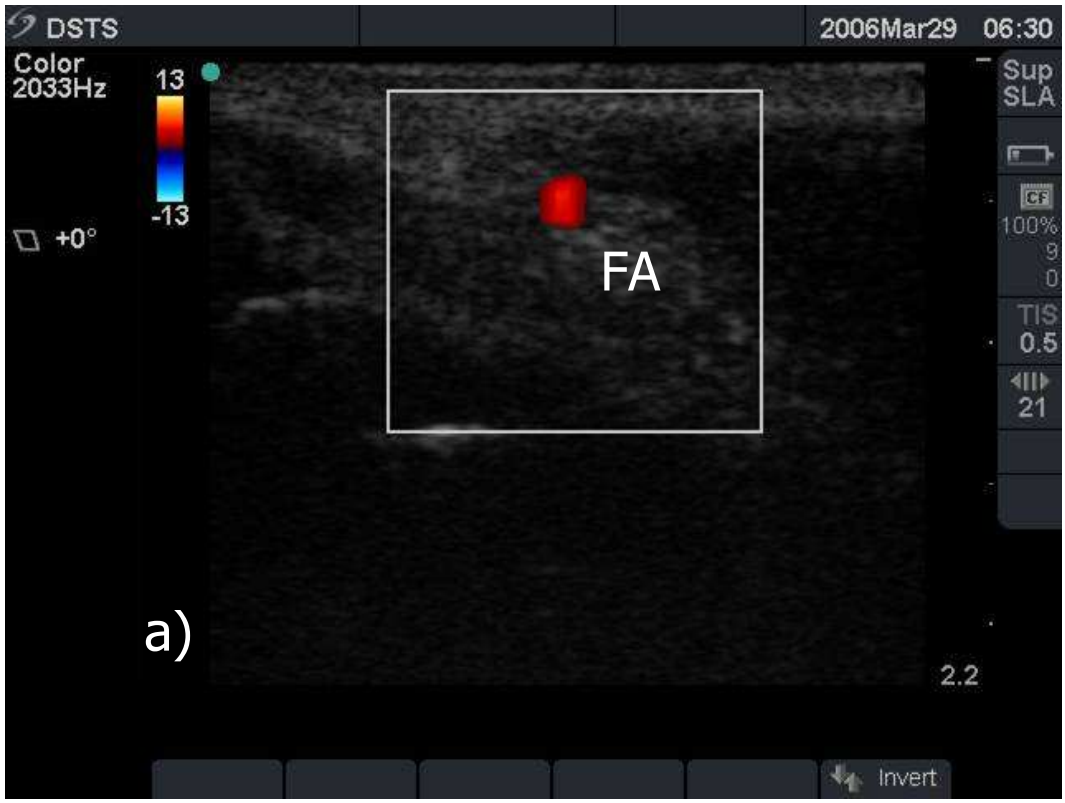
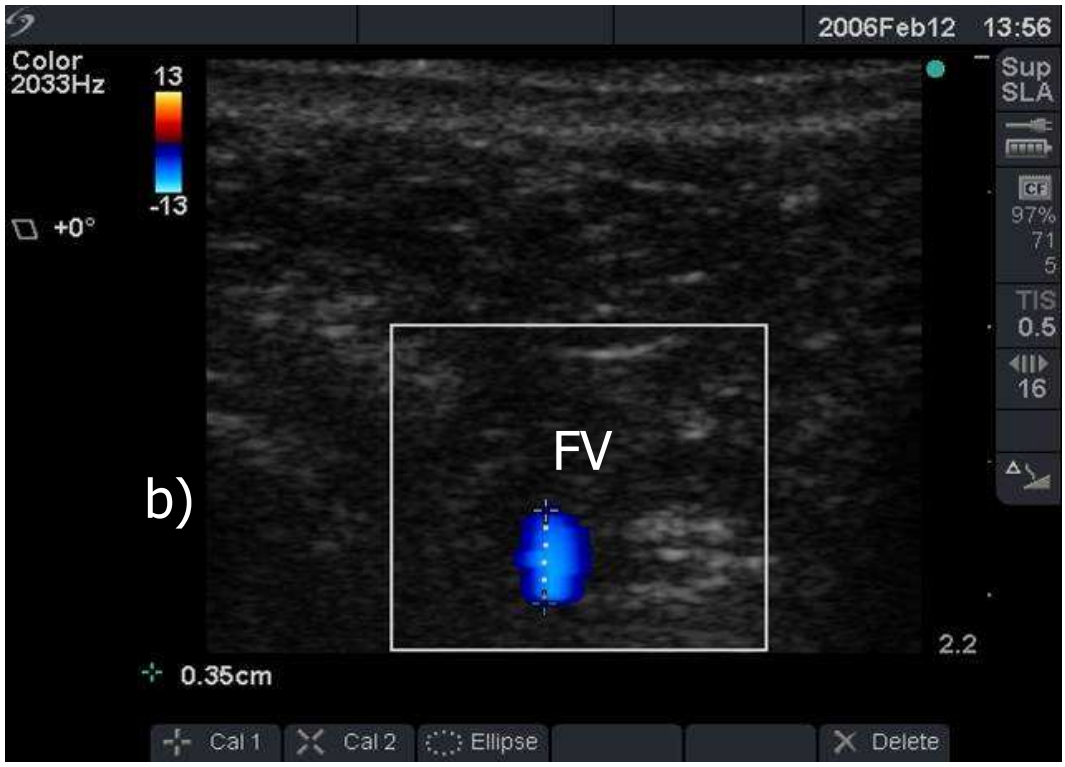


Figure 2.6. Laterality to the cheilion (position 2). FA = facial artery, FV = facial vein

Figure 2.7. Crossing the cheiliocanthal line (position 3). a) FA = facial artery, b) FV = facial vein.





The numbers of arteries in each distribution group (type I-VI, with type I-III grouped together) are summarised in Table 2.1. These are compared with distribution patterns from previous cadaveric studies.

Table 2.1. Distribution patterns of the facial artery.

	Number of facial arteries *(%)*			
	Type I-III	Type IV	Type V	Type VI
(Renshaw *et al.* 2007)* (n=200)	152 *(76)*	43 *(21.5)*	4 *(2)*	1 *(0.5)*
(Lohn *et al.* 2004) (n=200)	170 *(85)*	20 *(10)*	6 *(3)*	4 *(2)*
(Mitz *et al.* 1973) (n= 50)	42 *(84)*	5 *(10)*	4 *(8)*	0 *(0)*
(Niranjan 1988) (n=50)	48 *(96)*	2 *(4)*	0 *(0)*	0 *(0)*

* Current study

A total of 144 (72%) of all the facial arteries examined were symmetrical, with 56 (28%) of arteries asymmetrical. It is interesting to note that more of the symmetrical arteries were of Type I-III, and that the rarer variants, especially Type IV, were more likely to be asymmetrical (Table 2.2). One can thus extrapolate that if a type I-III facial artery is located on one side, the chances of finding a symmetrical arterial distribution is higher than had a type IV or V artery been found.

Table 2.2. Facial artery variation.

	No. of arteries, n=200 *(%)*	No. of symmetrical arteries, n=144 *(%)*	No. of asymmetrical arteries, n=56 *(%)*
Type I-III	152 *(76)*	126 *(87.5)*	26 *(46.4)*
Type IV	43 *(21.5)*	18 *(12.5)*	25 *(44.6)*
Type V	4 *(2)*	0 *(0)*	4 *(7.1)*
Type VI	1 *(0.5)*	0 *(0)*	1 *(1.8)*

The facial artery and vein distances from the three different points on the face described previously were used to calculate the mean position of the facial artery and vein, which are shown in Figure 2.8. The mean flow diameter of facial artery and facial vein, along with the distance from each of the three points on the face is shown in Tables 2.3 and 2.4.

Figure 2.8. The path of the facial artery (FA) and facial vein (FV) in the anterior face. Values (mm) represent distance (mean ± SD) of the vessel from three fixed landmarks, as shown from lateral to medial: the mandibular crossing point (1); laterality to the cheilion (2); and crossing a line drawn from the cheilion to the lateral canthus (3).

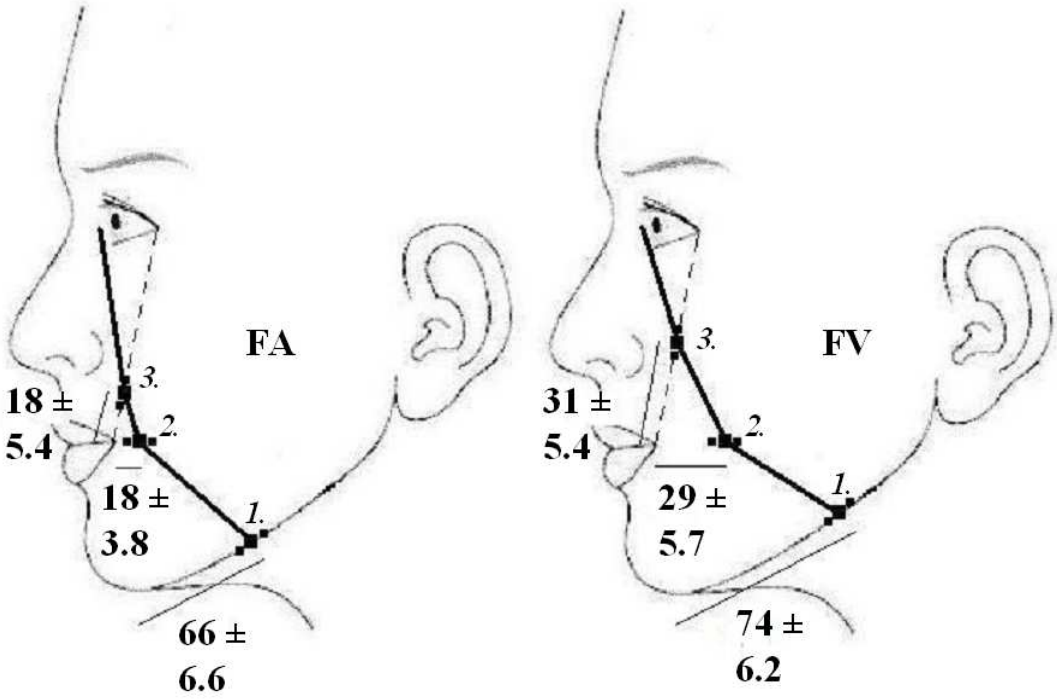


Table 2.3. Facial artery: mean flow diameter and mean distance from three fixed landmarks: the mandibular crossing point (position 1); laterality to the cheilion (position 2); and crossing a line drawn from the cheilion to the lateral canthus (position 3).

Position	Mean (± *SD*) diameter (mm)	Mean (± *SD*) distance (mm)
1	2.6 *(0.5)*	66 *(6.6)*
2	2.1 *(0.4)*	18 *(3.8)*
3	1.8 *(0.4)*	18 *(5.4)*

Table 2.4. Facial vein: mean flow diameter and mean distance from three fixed landmarks: the mandibular crossing point (position 1); laterality to the cheilion (position 2); and crossing a line drawn from the cheilion to the lateral canthus (position 3).

Position	Mean (± *SD*) diameter (mm)	Mean (± *SD*) distance (mm)
1	3.1 *(0.6)*	74 *(6.2)*
2	2.6 *(0.6)*	29 *(5.7)*
3	2.4 *(0.6)*	31 *(5.4)*

The transverse facial artery was present in 75.5% (n=151) of cases; the accompanying vein was found in 58% (n=116). The flow diameter of the transverse facial artery ranged from 0.7 to 3.1 mm (mean ± SD, 1.6 mm ± 0.46), with the transverse facial vein diameter ranging from 0.7 to 3.7 mm (mean ± SD, 1.8 mm ± 0.56). The mean distance from the lateral canthus to the transverse facial artery and vein was 58 mm ± 6.02 and 59.7 mm ± 6.59 respectively. The flow diameter of the superficial temporal artery ranged from 1.1 to 4.3 mm (mean ± SD, 2.3 mm ± 0.43), that of the vein ranging from 1.2 to 4.3 mm (mean ± SD, 2.7 mm ± 0.51).

In one case the facial artery was undetectable (Type VI), with a transverse facial artery dominance (diameter 2.3 mm, Figure 2.9). However, three out of four individuals with a short rudimentary facial artery (Type V) had an absent transverse facial artery. While the facial artery was more variable in its course, the facial vein was more predictable in position. On one occasion the facial vein was absent, replaced by a transverse facial vein which ran into the superficial temporal vein. This was in a hemiface with a normal arterial supply.

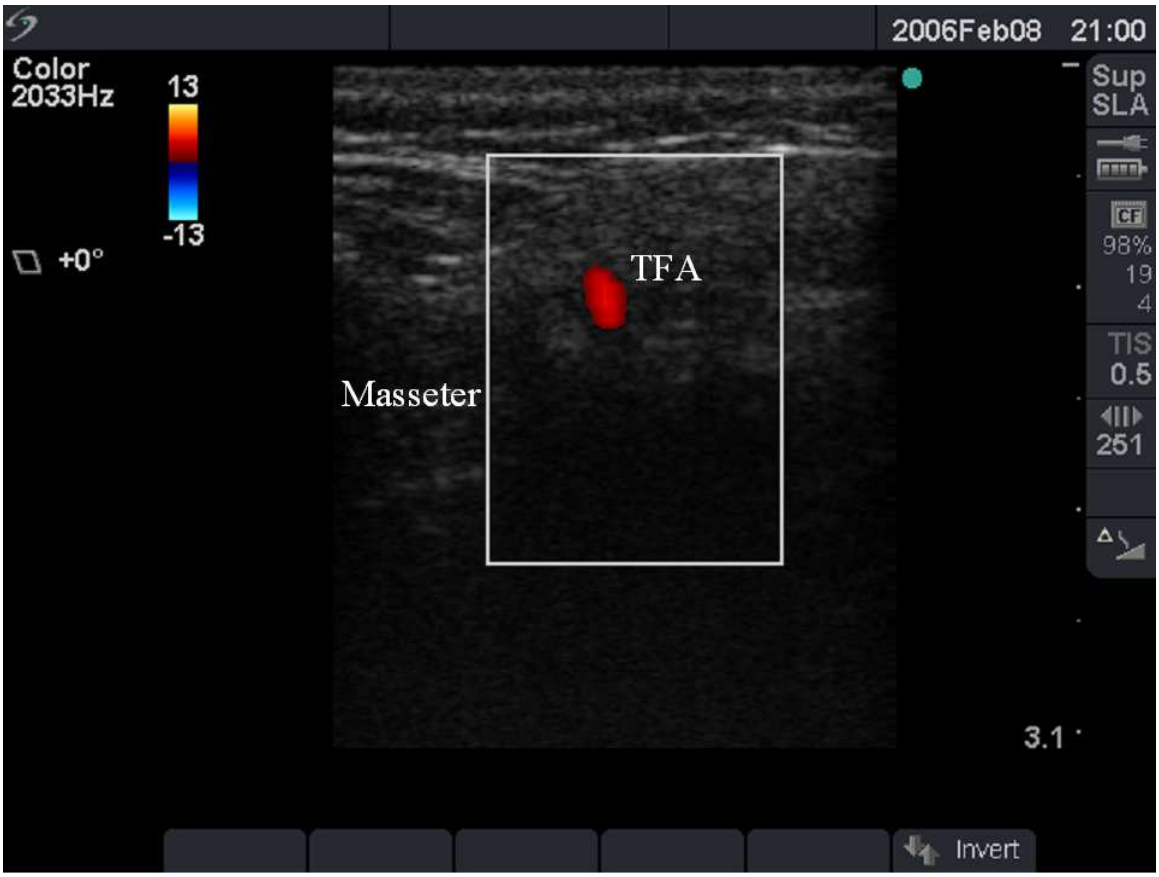


Figure 2.9. Large 2.3 mm right transverse facial artery (TFA) in a 23 year-old right-handed female with absent (Type VI) right facial artery.

Mean transverse facial artery flow diameter was significantly larger in females than males (one-way ANOVA test: 1.65 mm vs. 1.43 mm; $p=0.009$). A greater distance from the lateral canthus was noted in males than in females for both the transverse facial artery (60.59 mm vs. 56.7; $p=0.002$) and vein (63.46 mm vs. 57.99 mm; $p<0.001$). The facial artery was found further from the gnathion in males than in females (69.5 mm vs 63.42 mm; $p<0.001$), as was the facial vein (77.46 mm vs. 71 mm; $p<0.001$). At position 3 (approaching the nasal ala), the facial vein was found further away from the cheilion in males than in females (33.28 mm vs. 28.8 mm; $p<0.001$).

Only one significant difference was noted between racial groups (one-way ANOVA test, $p=0.001$), that of mean distance from the transverse facial vein to the lateral canthus (Caucasian 58.59 mm, Asian 61.77 mm, Oriental 68.36 mm, Afro-Caribbean 59.42 mm). Increasing age was associated with an increased mean distance of the facial artery from the cheilion at position 3 (bivariate correlation, $p=0.002$). Handedness was not associated with either increased flow diameter or distance from facial landmarks using the one-way ANOVA test.

2.4. Discussion

This is the first time such a large series of facial vessel scans using colour Doppler ultrasound has been described. The facial artery supplies the submandibular gland, masseter muscle and much of the anterior face including the lips. The assessment of facial vasculature is thus of particular importance when considering patient selection for facial transplantation (Diver *et al.* 2006), as the pan-facial injuries being considered by the UK facial transplantation team will likely include defects associated with severe functional deficits around this area.

The facial vessels were easily found in the anterior face, due to their superficiality to the skin. The mean facial artery diameter at the mandibular crossing angle (2.6 mm) correlates with previous studies (Pinar *et al.* 2005). The arterial diameter peters out as the artery reaches the nasal ala, as described in the cadaver (Lohn *et al.* 2004). The facial artery was found an average of 18 mm lateral to the mouth, compared with 15.5 mm quoted elsewhere (Pinar *et al.* 2005). The facial vein crossed the mandible at a predictable point, similar to that reported in the cadaver (7.4 cm vs. 7.5 cm) (Lohn *et al.* 2004). Importantly, in keeping with Nagase's study of facial vessels (Nagase *et al.* 1997) the artery and vein diverged widely from each other at the oral commissure. The surgeon should be wary of this when planning facial flaps.

This study confirms the branching patterns of the facial artery reported in other series (Lohn *et al.* 2004), although more individuals were reported to exhibit a Type IV artery than previously reported (21.5% vs. 10%) (Mitz *et al.* 1973). This may be due to the methodology used, or simply may represent the wider ethnic mix in our sample population. The main trunk was absent or rudimentary in a small minority of

individuals (2.5%), compared with between 0% and 8% quoted elsewhere (Foley and Erickson 1991; Lohn *et al.* 2004; Mitz *et al.* 1973; Niranjan 1988).

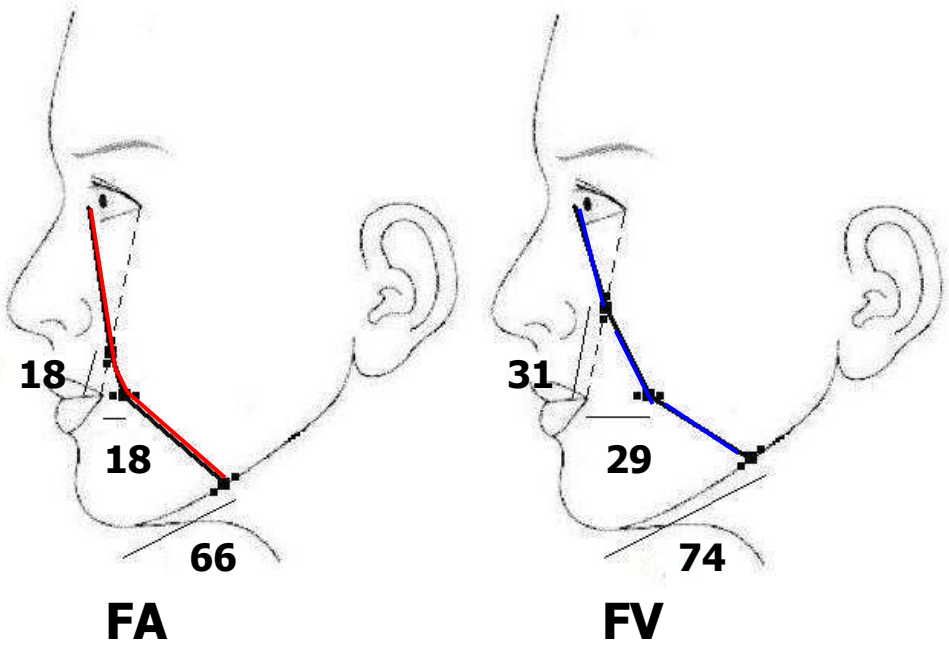
Importantly, this study verifies clinically the incidence of facial artery absence (Lohn *et al.* 2004): one individual with Type VI (submental variant) facial artery had reciprocal transverse facial artery dominance. This confirms previous observations that compensation for an underdeveloped facial artery may come from a more developed ipsilateral transverse facial or contralateral facial artery (Pinar *et al.* 2005), and that several arteries may contribute to this phenomenon (Mitz *et al.* 1973; Nakajima *et al.* 2002; Niranjan 1988).

The branches distal to the ala (Types I-III) were not specifically measured for two reasons. Firstly, our methodology meant that vessels became more difficult to detect the smaller they were, with probe application problematic at the side of the nose and at the medial canthus. Secondly, the terminal branching pattern of the facial artery is of little importance to a facial transplant graft, where proximal patterns are of more significance.

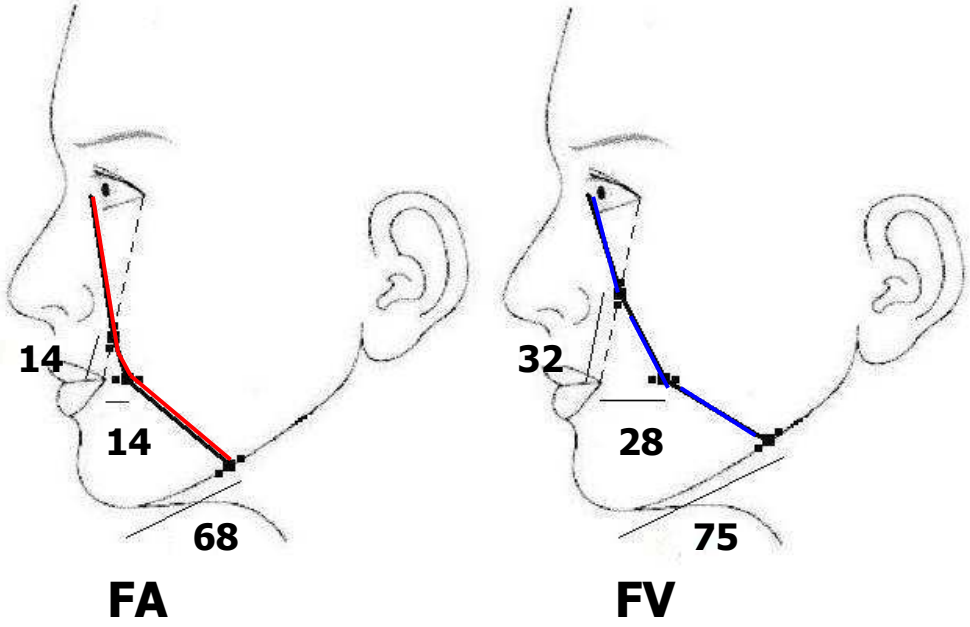
Handedness was investigated as it has been suggested as one of the factors that might influence arterial development: right-handed individuals have been reported to have higher flow rate in the right external carotid artery than in the left (Bogren *et al.* 1994). No significant associations were found in this study between handedness and flow diameter.

Figure 2.10. Mean path of 200 facial arteries and veins in the current study (a); mean path of 200 facial arteries and veins in the cadaver (b) (Lohn *et al.* 2004).

a)



b)



Increasing age had little effect on facial vessel diameter or distance. Gender differences in flow diameter of the main trunk of the facial artery have previously been found in some studies (Zhao *et al.* 2002) but not in others (Koh *et al.* 2003). In the current study there were often larger distances between vessel and fixed landmarks in males than females, probably due to the often larger facial proportions in males. Interestingly, flow diameter largely did not differ between sexes, apart from a larger mean transverse facial artery diameter in females. Racial differences in the origin and distribution of the facial artery have been reported previously (Mitz *et al.* 1973; Nakajima *et al.* 2002; Niranjan 1988) but other studies have shown quite different branching patterns within the same racial group (Koh *et al.* 2003). There was only one significant difference between racial groups in the current study: that of the position of the transverse facial vein, which was considerably further away from the canthus in Oriental faces.

There are many benefits to using colour Doppler sonography to assess facial vasculature. It is non-invasive, mobile, easily repeated and (importantly) has the ability to image veins. The facial vessels are easily found in the anterior face, due to their superficiality to the skin.

Disadvantages include uncertain reproducibility due to the 'fluid' nature of the measurements. Quantitative evaluation using digital callipers is also prone to variability (Zhao *et al.* 2000). The wide variation and tortuosity of the facial artery made visualisation occasionally difficult. The correct amount of pressure has to be maintained on the skin so as not to obliterate the vein wall. Vein flow varies with the respiratory cycle, especially closer to the thorax. No allowance was made for altered

fluid status: although this may be of potential importance in the assessment of the facial transplant donor in the acute clinical setting, all individuals in the present study were well-hydrated and received oral fluids prior to the assessment. Additionally, vessel flow diameter represents maximal inflation and gives little indication of the diameter when collapsed. The smaller-diameter transverse facial vessels (which lie deeper than the facial vessels) sometimes proved difficult to find, and indeed the smaller pick-up rate for the vein than for the artery (58% vs. 75.5%) may reflect this. Unlike the current study, patients selected for facial transplantation may not have normal anatomy. However, this method could still be used for assessment of the health of their vessels to ascertain which vessels remain intact after trauma.

The ability to locate and assess small vessel patency has many other applications in facial reconstruction. Colour Doppler ultrasound can be used in the planning of aesthetic procedures such as face lift procedures, since the transverse facial artery supplies a large portion of the lateral face lift flap (Whetzel and Mathes 1997).

Figure 2.11. MicroMaxx™ colour Doppler ultrasound system in use.

In the realm of facial transplantation, colour Doppler provides a good method of pre-operative vascular imaging to establish the feasibility of raising facial flaps based on the facial vascular pedicle. As part of this screening process, colour Doppler ultrasound could also help in establishing an operative contingency plan to delineate an alternative vascular pedicle should the facial artery be absent. The MicroMaxx™ system was chosen as it is mobile, hand-held, easily transported to the bedside, and rapidly boots up (Figure 2.11); its robust nature and use in other critical care settings, such as in the placement of central venous lines, means that it has particular application in the assessment of donor faces for facial transplantation. Colour Doppler ultrasound can be used by clinicians with some initial training in ultrasound technique to outline the course, diameter and relations of the facial and transverse facial vessels in the anterior face. This technique should therefore be considered a valuable adjunct to the facial reconstructive surgeon's armamentarium.

Chapter 3

3. The Development of a Skin Tonal Matching Scale for Facial Transplantation

3.1. Introduction

3.1.1. Human Skin Colour

Human skin acts as a physical barrier: it provides a first-line defence mechanism against infection; it protects against the damaging effects of ultraviolet radiation; and it acts as a locus for the ultraviolet-driven production of vitamin D (Jablonski 2004). Melanins are the skin's primary pigment. Two types of melanin exist: pheomelanin (a reddish-yellow colour) and eumelanin (a dark brown-to-black colour) (Thody *et al.* 1991). Eumelanin is characteristic of darker or tanned skin, with phaemelanin predominating in red-haired Caucasians for example (Thody *et al.* 1991).

Melanocytes (specialised dendritic cells residing in the epidermal stratum basale) produce melanins in specialized cytoplasmic organelles called melanosomes. These vary in size and amount of aggregation depending on skin type: darker individuals sport larger melanosomes which are dense and singly dispersed, deflecting more ultraviolet light than lighter individuals (Jablonski 2004). The epidermis of people with darkly pigmented skin contains a more tightly packed arrangement of cornified cells within the stratum corneum, thus conferring upon it superior barrier properties (Taylor 2002). Variation in pigmentation depends more on the distribution,

composition and size of melanocytes rather than their number, which remains constant in most individuals (Lin and Fisher 2007).

Human skin colour boasts a large multiplicity of shades. On average, women have slightly lighter skin than men (Jablonski and Chaplin 2000). Skin that is usually exposed to the sun has a more intense red component, due to increased vascularization (Andreassi *et al.* 1990; Kollias 1995). The quantity and type of melanin are determined by four to six genes operating under incomplete dominance. In addition there is an interplay between the environment and a few major genes accompanied by modifier genes (Jablonski 2004). With each gene manifesting several alleles, this results in a multitude of skin colours. Humans are able to distinguish a very large number of these shades.

3.1.2. The Fitzpatrick System of Skin Phototype Assessment

Skin type (and tone) can be assessed clinically but very imprecisely. Traditionally, skin phototype is determined by dermatologists and plastic surgeons using the Fitzpatrick system (Fitzpatrick 1988). This classifies skin into six skin phototypes, termed types I-VI (Table 3.1). Four categories are described for white-skinned persons (skin type I, II, III, IV), with brown skin classified as skin type V, and black skin as skin type VI. Later the system was modified to include three brown skin tones: type IV for light brown, type V for brown, and type VI for dark brown or black (Pathak and Fitzpatrick 1993). The clinical value of this system however lies in its ability to predict tanning or burning potential. This provides an indication of the potential for transformation of the skin into cancers caused by ultraviolet radiation (e.g. squamous cell carcinoma, melanoma). It provides the clinician with a quick

method of assessing patient skin phototype without the need for scientific instrumentation. However this rating is subjective and even efforts at objective measurement of Fitzpatrick type have been focussed on ultraviolet radiation and its sequelae (Ravnbak 2010).

Table 3.1. The Fitzpatrick system of skin phototyping.

Skin type	Colour	Reaction to UVA	Reaction to sun
Type I	Caucasian; blond or red hair, freckles, fair skin, blue eyes	Very sensitive	Always burns easily, never tans; very fair skin tone
Type II	Caucasian; blond or red hair, freckles, fair skin, blue eyes or green eyes	Very sensitive	Usually burns easily, tans with difficulty; fair skin tone
Type III	Darker Caucasian, light Oriental	Sensitive	Burns moderately, tans gradually; fair to medium skin tone
Type IV	Mediterranean, Oriental, Hispanic	Moderately sensitive	Rarely burns, always tans well; medium skin tone
Type V	Middle Eastern, Latin, light-skinned black, South Asian	Minimally sensitive	Very rarely burns, tans very easily; olive or dark skin tone
Type VI	Dark-skinned black	Least sensitive	Never burns, deeply pigmented; very dark skin tone

Melanin pigmentation is either constitutive (i.e. genetically determined) or facultative (i.e. secondary to ultraviolet light radiation exposure) (Quevedo *et al.* 1975); each component of the Fitzpatrick system attempts to assign skin either constitutive or facultative properties of colour.

Herein lies the problem with applying the Fitzpatrick system to facial transplantation. Facial transplantation is a rather unique scenario: the most optimal result will require a good aesthetic (or cosmetic) match. Skin colour is arguably one of the most obvious physical characteristics. Burning (or tanning) ability is of less significance than colour or tone *per se*. Additionally, although constitutive skin colour has been found to be a more meaningful parameter than facultative skin colour in assessing skin type, Fitzpatrick skin phototype does not correlate particularly well with measured constitutive colour (Andreassi *et al.* 1990). Finally, the darker skin types are notably underrepresented, leading to limited applicability in these groups.

3.1.3. The British Red Cross Skin Camouflage Matching System

The British Red Cross use a skin camouflage matching system which is more representative of the skin types present in the general population (Glennie and Tagg-Davis 2000).

The skin tones comprise 11 categories which are most representative of the wide variation of skin tone in the UK:

- Fair (e.g. red hair, freckles)
- Slightly tanned white
- Yellow (e.g. Chinese)
- Ivory/beige (e.g. Japanese)
- Olive (e.g. Spanish, Italian)
- Light golden brown (e.g. light Asian)
- Reddish brown (e.g. dark Asian)
- Light to mid-brown
- Mid brown
- Brown/black
- Black/black

Currently, this skin tone scale focussing on the cosmetic aspects of tonal matching is probably the closest to what is needed in facial transplantation. There are however problems with this system: it is a crude scale only; there is no definition of what constitutes each category; the photographs are not standardised and are poor quality. It is clear that a new system of skin tone matching is required.

3.1.4. Methods of Analyzing Skin Tone

Historically, a number of methods have been used to characterise skin tone. In the nineteenth century, von Luschan (von Luschan 1897) made one of the earliest attempts to match areas of unexposed skin using a scale comprised of a series of coloured tiles or tablets. This method remained popular until the emergence of spectrophotometry in the mid-twentieth century (Lasker 1954). Reflectance spectrophotometry remains in use for the assessment of skin pigmentation and tone,

as it has a number of benefits: there is a constant distance from the light source, and it is an objective measurement (Jablonski 2004). However, the different types of portable spectrophotometers available produce different skin reflectance measurements which are not directly comparable. Both skin pigmentation and reaction to ultraviolet radiation have been measured with the Derma-Spectrometer (Kollias 1995), the Datacolour International Microflash, and the Minolta Chroma Meter CR-200 (a colour analyser for measuring the reflective colour of surfaces by the tristimulus system) (Andreassi *et al.* 1990).

These methods are not readily available in most clinical environments. As the facial graft donor will be assessed initially in a high-dependency area, the portable assessment of donor facial skin tone using easily-accessible equipment should remain the goal of the facial transplant team.

Digital photography is one of the most widely available methods used to measure skin tone. The device can be set up at a fixed distance and at a fixed relative angle - in standardised light settings - in order to minimise light reflectance from the subject. Pixels within an image can be analysed using commercially available image analysis software (Adobe Photoshop CS2, Adobe Systems Incorporated, USA) to give a mean value for red, blue and green and luminosity. A single mean value for red, blue and green together can also be obtained: this is termed an 'RGB value'. Objective analysis of skin tone using such digital imagery has been used in a number of settings, such as examining burn depth (Roa *et al.* 1999), and scrotal skin colour changes in monkeys (Gerald *et al.* 2001).

3.2. Methods and Materials

3.2.1. Case Ascertainment

Volunteers were recruited from within staff in the Royal Free Hospital, London. Written informed consent was formally obtained in all volunteers. Ethical approval was obtained from the University College London Joint Hospitals Ethical Committee. No volunteers were ineligible unless they had previous facial disfigurement, facial discolouration or make-up, all of which might have skewed the results.

3.2.2. Photographic Studio Set-Up

Digital photographic images (anterior-posterior face, three-quarter view face, lateral face and right forearm/hand) were obtained by a senior medical photographer. All photographs were taken on the same Fuji S2 digital camera and 60 mm Nikon Nikkor lens at ISO-200 with a shutter speed of 1/125. All photographs were taken at a distance of two metres from the subject.

The same studio was used in order to allow standardisation of background light using electronic flash reflectors and diffusers. To minimize light drift, we used a tungsten bulb of the same wattage at a standard distance from subjects. Two lights and diffuser panels providing front key lighting were positioned at 60˚ two metres from subject; full power produced an aperture of f32. Two lights and diffuser panels providing rim lighting were positioned at 45˚ three metres from the subject; half power produced an aperture of f22. A custom white balance setting, using a background white card placed one metre behind the subject, was made to record the colour temperature of the lighting set up. The set-up of the studio is highlighted in Figures 3.1 and 3.2.

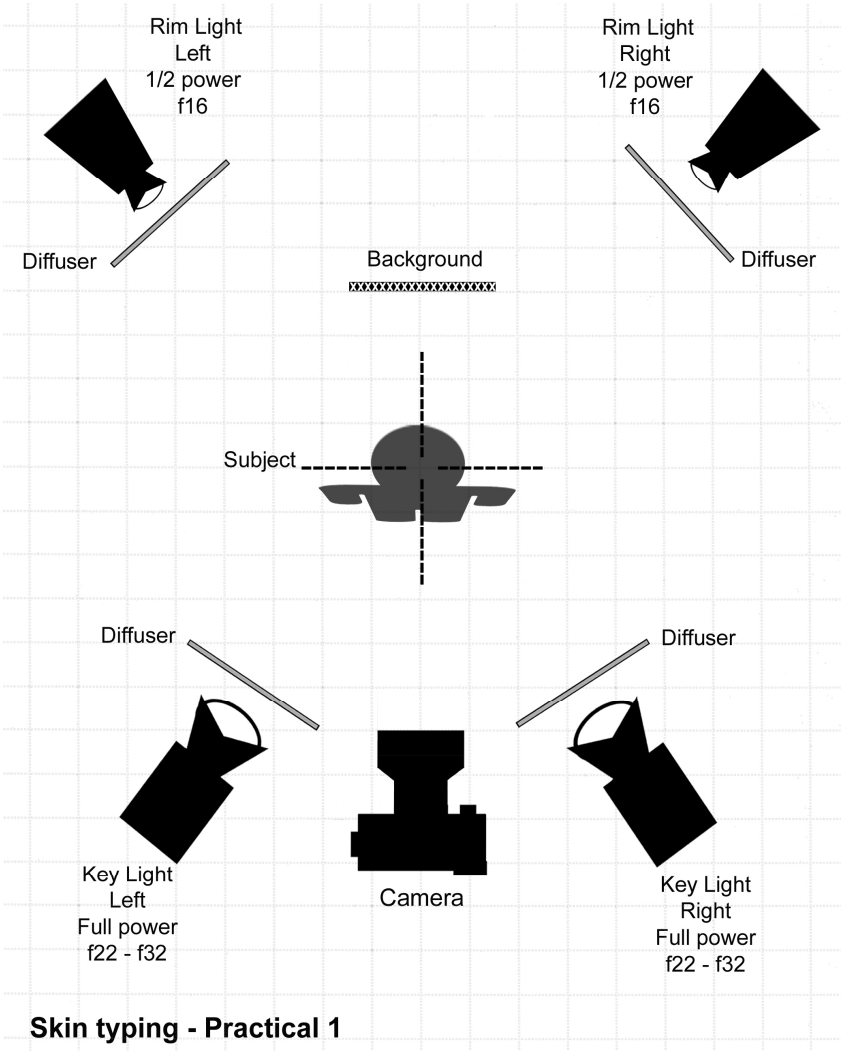


Figure 3.1. Photographic image procurement in a studio setting under standard, optimal and reproducible lighting conditions.

Figure 3.2. Photographic image procurement studio setting.

3.2.3. Monitor and Software Calibration

Image processing and assessment was conducted using a Dell Optiplex 3GHz PC/Nvidia-256Mb video display graphics card with a 21" Sony monitor. The calibration process involved the initial pre-setting of various monitor characteristics to specific standardised industry values. This was followed by a series of sequential steps using Gretag Macbeth Eye-One 2 software to ensure that tone and colour were displayed accurately (e.g. mid-grey should be displayed as Red=127, Green=127, Blue=127). The monitor-specific profile was then implemented and saved. To accommodate changes in the monitor over time the display profile was revised on a monthly basis.

A Gretag Macbeth Colour Checker Colour Rendition Chart™ (McCamy et al. 1976) and was used for objective standardization of images (Figure 3.3). This chart, measuring 83mm x 56mm in size, contains 24 coloured patches arranged in a 6-by-4 array, each colour reflecting light the same way in all parts of the visible spectrum.

This chart can be incorporated into photographs of the face without obstructing the selected target areas on the face (e.g. nose and forehead). A Pro-Photo RGB reference chart was accessed in order to provide reference values and a visual guide (www.colorremedies.com/realworldcolor/downloads.html).

Using the Adobe Photoshop CS2 ACR image converter, the images were converted using the ACR 2.4 camera profile. This profile was calibrated so that it matched the characteristics of the camera and lighting set-up, ensuring standardisation of image workflow. Each photographic image was taken in RAW image file type, containing raw untouched pixel information from the camera sensor. This was compared with the standardized Gretag Macbeth colour spectrum within the frame, and the image calibrated accordingly, thus creating a Tagged Image File Format (TIFF) file.

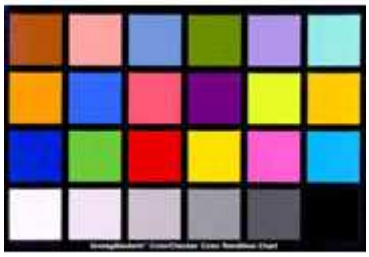


Figure 3.3. The Gretag Macbeth Colour Checker Colour Rendition Chart™.

When capturing sample images we also captured digital images of black and white standards for calibration. Photographic black and white reflection standards were used to maximize light absorption and minimize light reflectance, respectively.

3.2.4. Image Analysis

Images were analysed within the Adobe Photoshop CS2 software package (Adobe Systems Inc., USA). Captured image files were loaded into the software application, in which pixel intensity values (mean, standard deviation and median) were obtained for each of the RGB, red, green, blue and luminosity levels (normal range 0-220, where 0 = black and 220 = white) found within the histogram feature of the software package (Figure 4.4). The term 'RGB value' refers to an amalgamation of the individual values for red, green and blue; this value is calculated automatically within Adobe Photoshop CS2.

The RGB method characterizes colour by displaying numeric measures of the three basic colour components: 'hue', 'value', and 'chroma'. 'Hue' refers to the generally accepted interpretation of colour, and is measured by assessing pixel brightness in the three colour channels: red, green, and blue. Channel measures were graphically represented in a colour diagram (see Figure 3.4). 'Chroma' refers to the saturation of colour and this equates broadly to strength or purity of colour. The 'value', also known as brightness, refers to the relative darkness/lightness of the sample.

Faces were grouped into four separate regions: cheek, temple, forehead and nose. The dorsal hand was also analysed for comparison. A 300 x 300 pixel and 100 x 100 pixel fixed diameter area was used for analysis in the face and hand respectively. The points taken in the face for analysis remained constant.

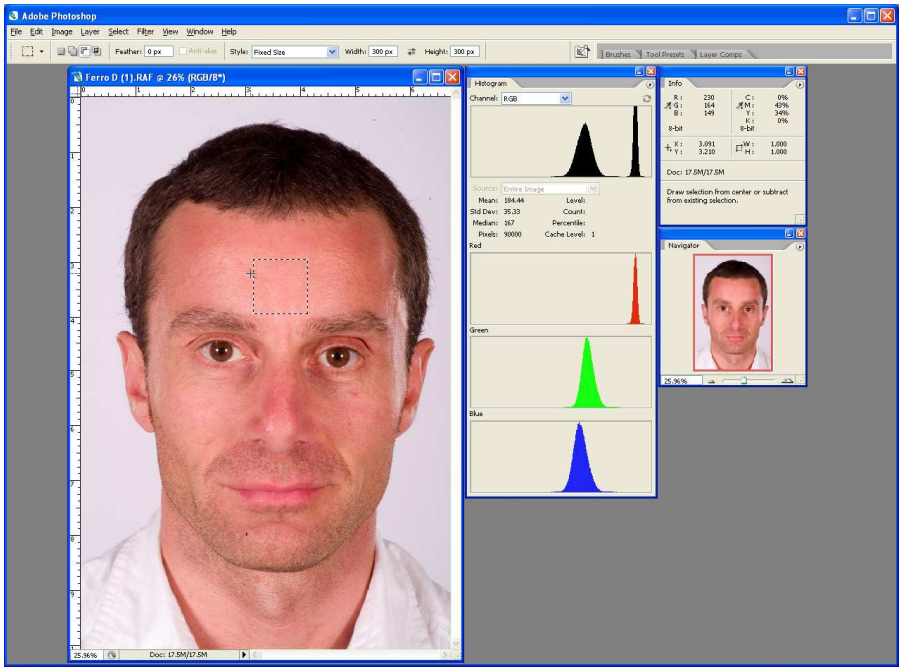


Figure 3.4. Anterior-posterior image of the forehead region. Histogram analysis of the RGB channel.

The four points used for analysis were defined as:-

a) 'Cheek': the point midway between the angle of the mouth and the root of the helix.

b) 'Temple': the point superior to the zygomatic arch, midway between the hairline and the lateral canthus;

c) 'Forehead': the central point midway between the glabella and the hairline;

d) 'Nose': the point midway from bridge to tip along the dorsum of the nose.

On the dorsal hand, the fixed diameter area was placed centrally, midway between the line of the metacarpophalangeal joints and the line of the radial and ulnar styloid processes. Each analysis was performed on the four facial images (and one dorsal hand image) taken in each volunteer.

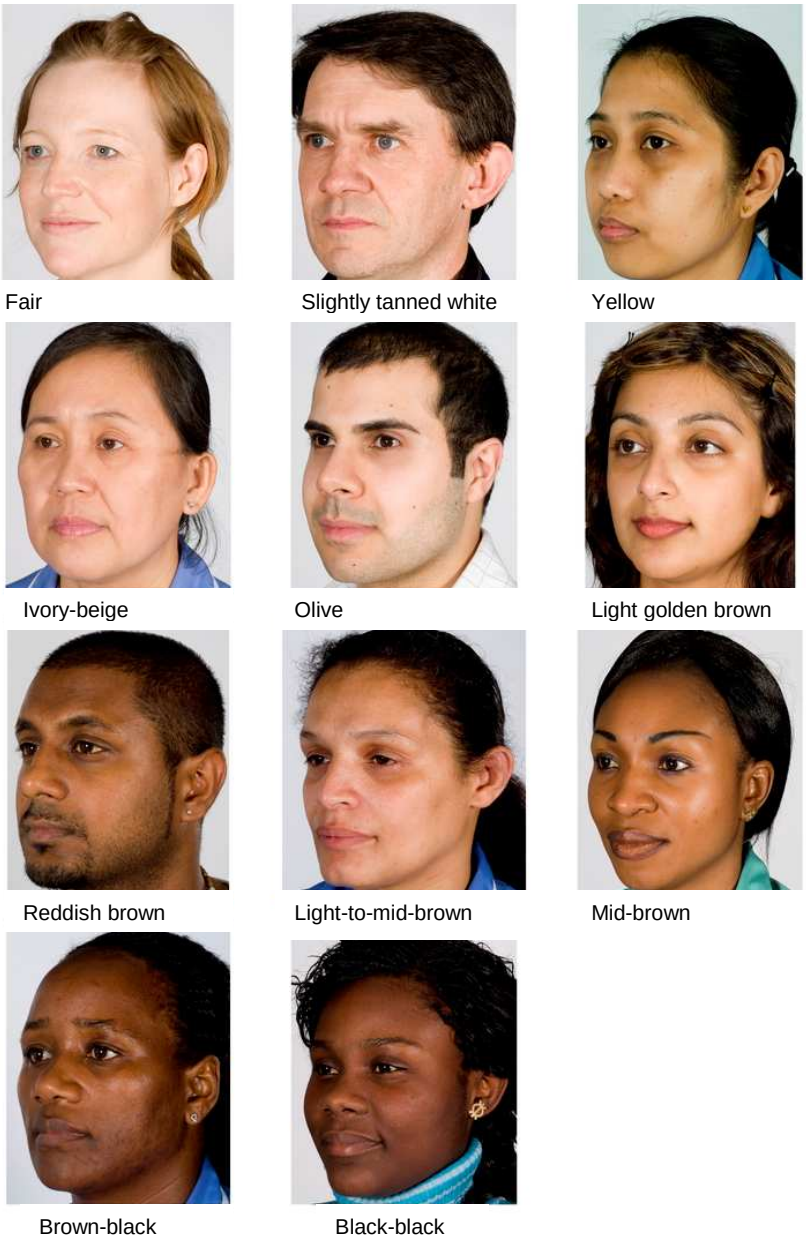
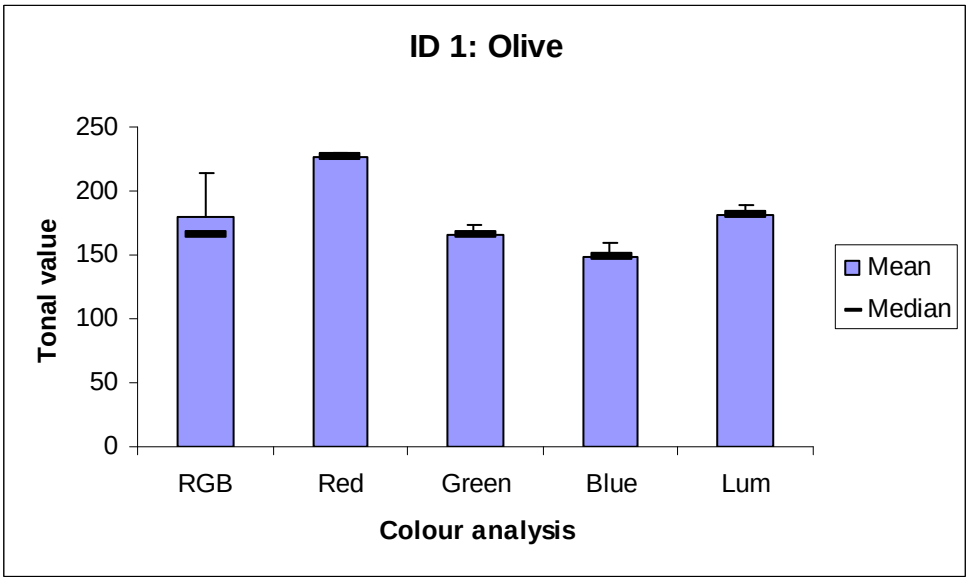


Figure 3.5. Red Cross skin types (ST). Fair; slightly tanned white; ivory-beige; ivory-beige; yellow; light golden brown; reddish brown; light-to-mid brown; mid-brown; brown-black and black-black.

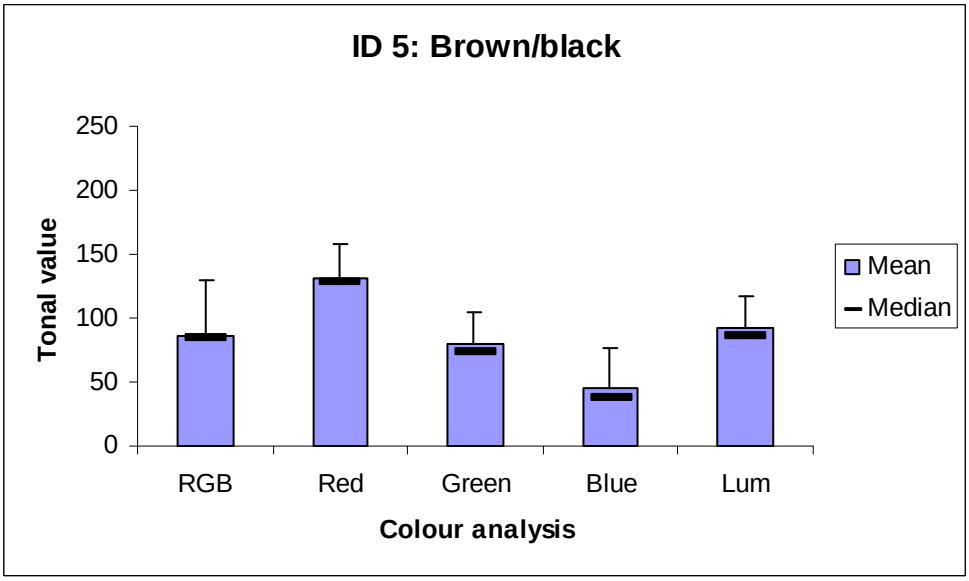
3.3. Results

A total of 108 individuals were photographed (42 men, 66 women; age range 19-62, mean age 35.5). Each participant was categorised into one of eleven different Red Cross skin types (Figure 4.5); there was a 95% independent observer correlation ($p<0.05$). Mean RGB, blue, green and luminosity values were obtained in each image (anterior-posterior face, lateral face and hand) in four areas: forehead, temple, cheek and dorsal hand. From this, a pattern emerged with mean RGB giving a representation of specific tonal variation. The mean values of three forehead images (ID 1 = olive, ID5 = brown/black, ID16 = fair) are shown as an example (Figure 3.6).

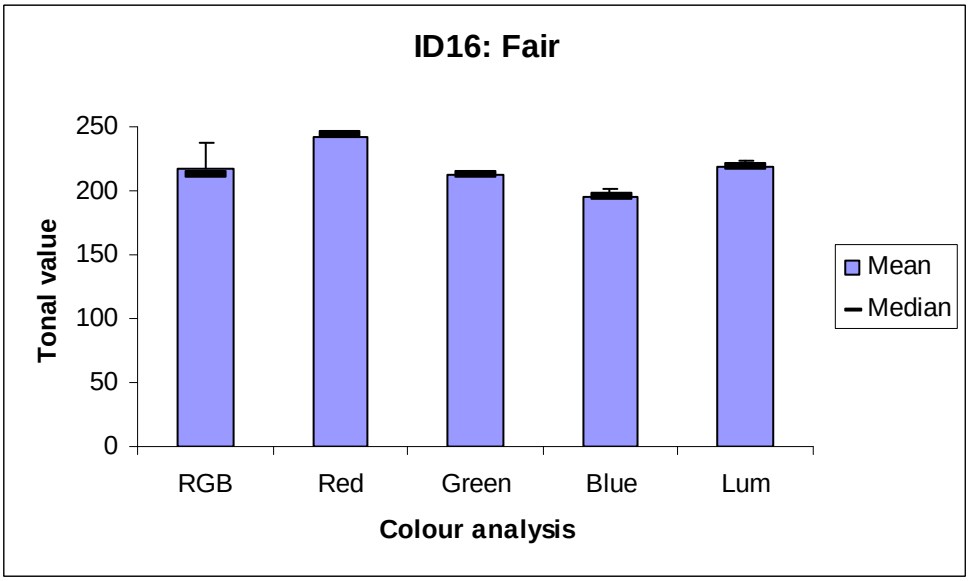
Figure 3.6. Colour analysis of the RGB spectrum showing variations in individuals from three different Red Cross skin types: a) olive; b) brown/black; and c) fair. Lum = luminosity.



a)



b)



c)

Eleven discrete skin tone types were categorised using analysis of standardised facial and hand images in the 108 volunteers as defined using mean RGB values within Adobe Photoshop CS2. Numbers of subjects examined in each tonal group are shown in Table 3.2.

Table 3.2. Numbers of photographic subjects examined (n=108).

Skin tone (ST1-11)	Number
Fair (ST1)	16
Slightly tanned white (ST2)	17
Ivory/beige (ST3)	6
Olive (ST4)	11
Yellow (ST5)	7
Light golden brown (ST6)	15
Light-to-mid brown (ST7)	8
Mid-brown (ST8)	11
Reddish brown (ST9)	4
Brown/black (ST10)	6
Black/black (ST11)	7

Mean RGB values in the four facial regions are shown in Table 3.3 and were categorised according to Red Cross skin tone. Values for the hand region are shown in Table 3.4. The forehead area was chosen as the most easily accessible and representative area for sampling, and due to the wider distribution pattern of mean RGB values. A graphical representation of the mean RGB values obtained in the forehead view is shown in Figure 3.7. The scale was then used to attribute skin tone to individuals. Mean RGB values for each Red Cross skin tone in each region in the face (forehead, temple, cheek and nose) are shown in Figures 3.8-3.11. Mean RGB values for the hand region are shown in Figure 3.12.

Table 3.3. Red Cross skin tones (termed ST1-11) in the forehead, temple, cheek and nose region of the face, categorised according to RGB value.

Skin tone (ST1-11)	Value (mean, *SE*)			
	Forehead	Temple	Cheek	Nose
Fair (ST1)	211.35	209.19	209.67	193.09
	(1.57)	*(2.4)*	*(2.37)*	*(2.11)*
Slightly tanned white (ST2)	206.90	203.48	204.47	186.17
	(2.00)	*(1.46)*	*(1.73)*	*(2.61)*
Ivory/beige (ST3)	191.97	200.12	202.40	178.99
	(3.48)	*(3.5)*	*(3.7)*	*(5.25)*
Olive (ST4)	191.88	190.18	189.00	174.18
	(3.09)	*(3.5)*	*(4.43)*	*(3.57)*
Yellow (ST5)	171.11	175.51	180.23	168.10
	(5.50)	*(7.39)*	*(5.96)*	*(6.92)*
Light golden brown (ST6)	172.31	171.24	170.35	162.42
	(3.73)	*(4.02)*	*(4.5)*	*(2.99)*
Light-to-mid brown (ST7)	155.57	158.26	161.65	152.68
	(6.58)	*(6.84)*	*(7.55)*	*(5.08)*
Mid-brown (ST8)	139.22	137.77	142.54	129.27
	(2.80)	*(3.65)*	*(3.83)*	*(2.65)*
Reddish brown (ST9)	124.33	133.05	134.07	119.22
	(13.27)	*(2.03)*	*(5.03)*	*(7.84)*
Brown/black (ST10)	102.56	102.66	106.87	95.13
	(5.51)	*(3.5)*	*(4.18)*	*(6.18)*
Black/black (ST11)	81.67	96.46	103.16	74.04
	(3.75)	*(7.09)*	*(4.79)*	*(3.42)*

Table 3.4. Red Cross skin tones (termed ST1-11) in the hand view, categorised according to RGB value.

Skin tone (ST1-11)	RGB value (mean, *SE*)
Fair (ST1)	208.1 *(3.21)*
Slightly tanned white (ST2)	202.21 *(3.88)*
Ivory/beige (ST3)	188.5 *(5.25)*
Olive (ST4)	182.7 *(3.74)*
Yellow (ST5)	179.05 *(8.00)*
Light golden brown (ST6)	166.94 *(4.64)*
Light-to-mid brown (ST7)	161.69 *(6.03)*
Mid-brown (ST8)	143.26 *(5.24)*
Reddish brown (ST9)	127.9 *(14.8)*
Brown/black (ST10)	118.85 *(3.36)*
Black/black (ST11)	109.73 *(7.48)*

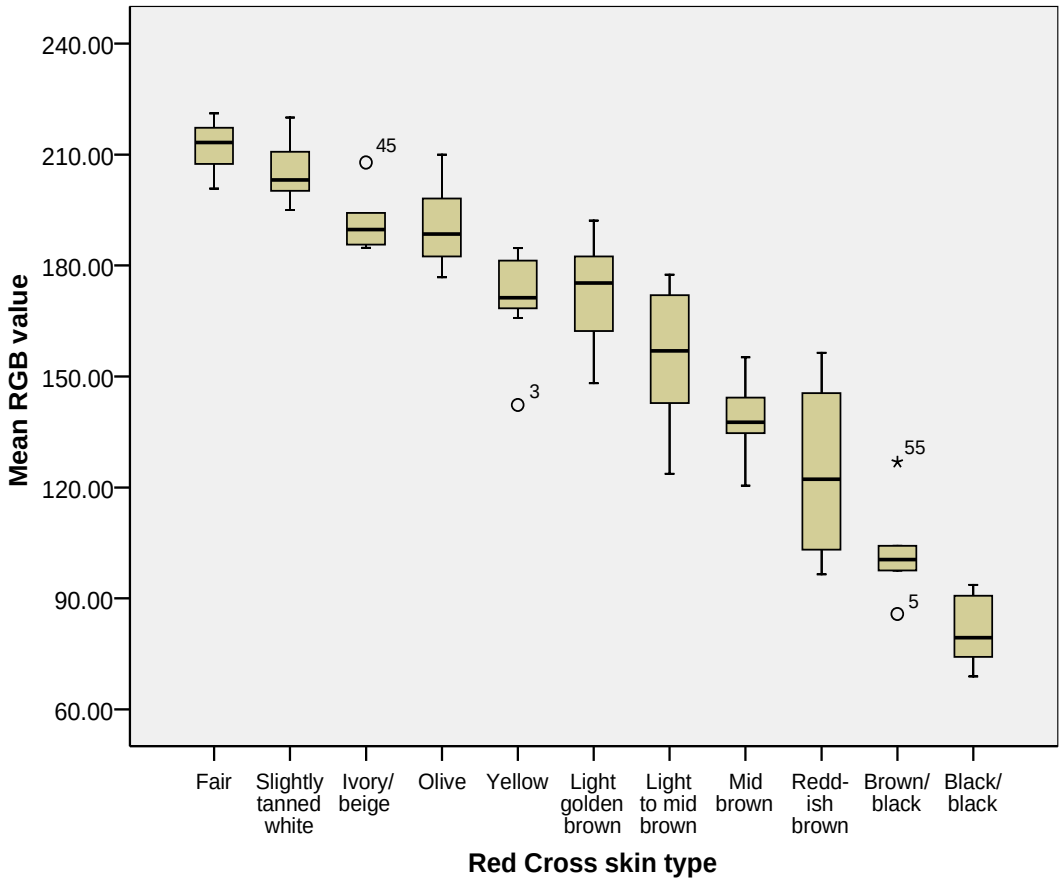


Figure 3.7. Mean RGB value, range and 95% confidence interval for each of the eleven Red Cross skin tones, in the anterior-posterior forehead view (n=108). A circle/star represents an outlying image with value outside range.

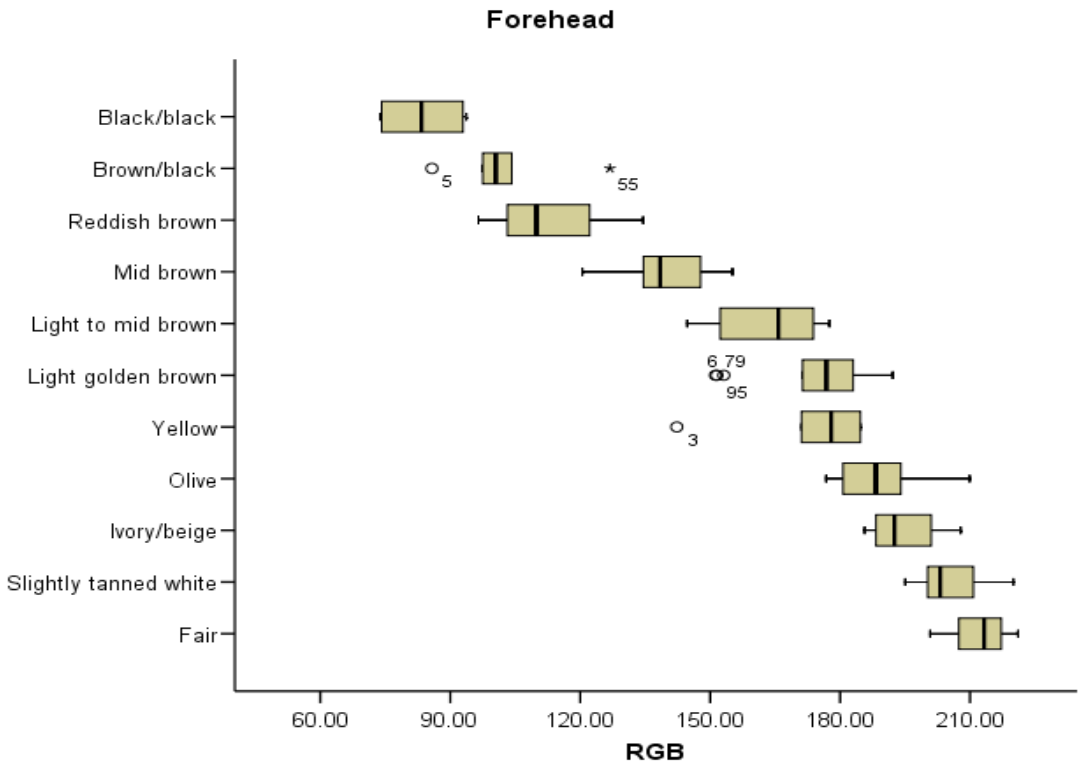


Figure 3.8. RGB values in each of the Red Cross skin tones, for the forehead region (mean, range and range and 95% confidence interval; n = 108).

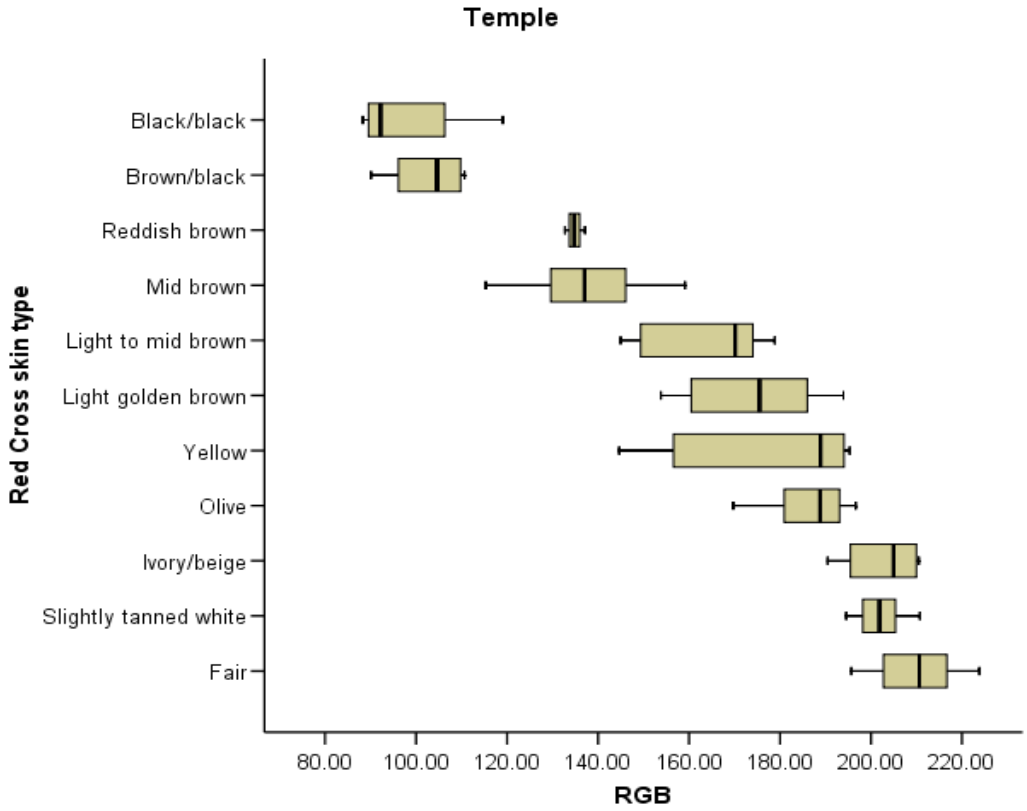


Figure 3.9. RGB values in each of the Red Cross skin tones, for the temple region (mean, range and 95% confidence interval; n = 108).

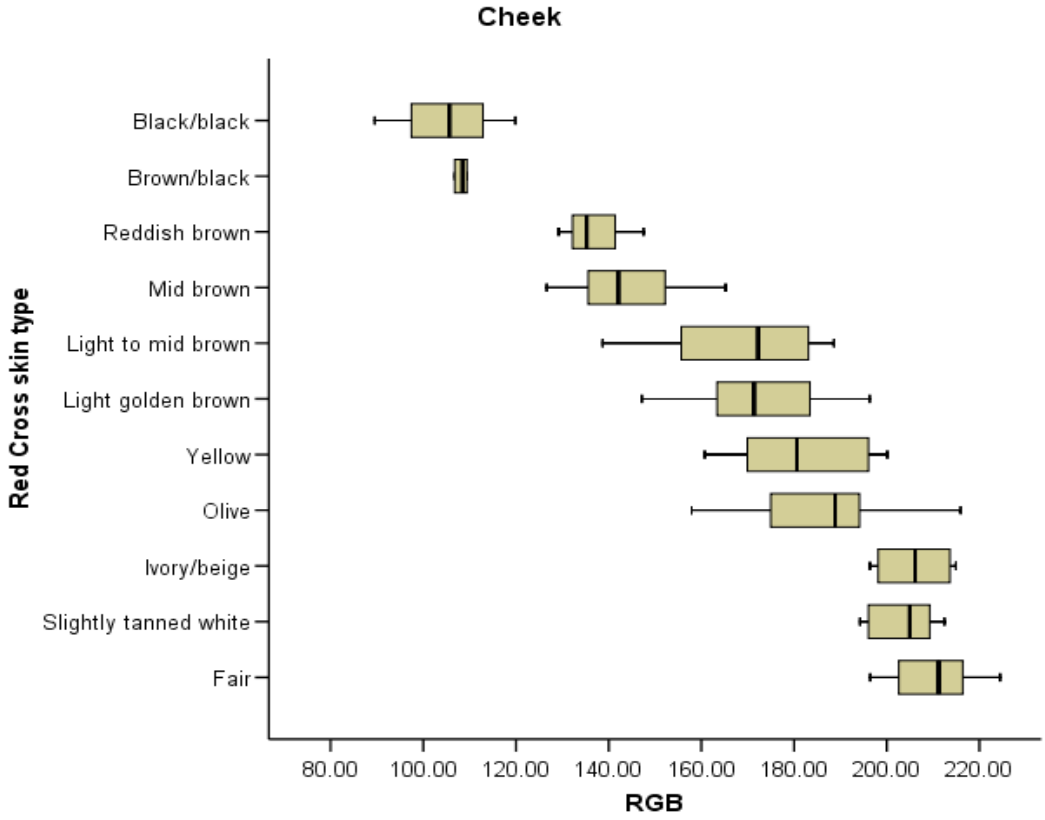


Figure 3.10. RGB values in each of the Red Cross skin tones, for the cheek region (mean, range and 95% confidence interval; n = 108).

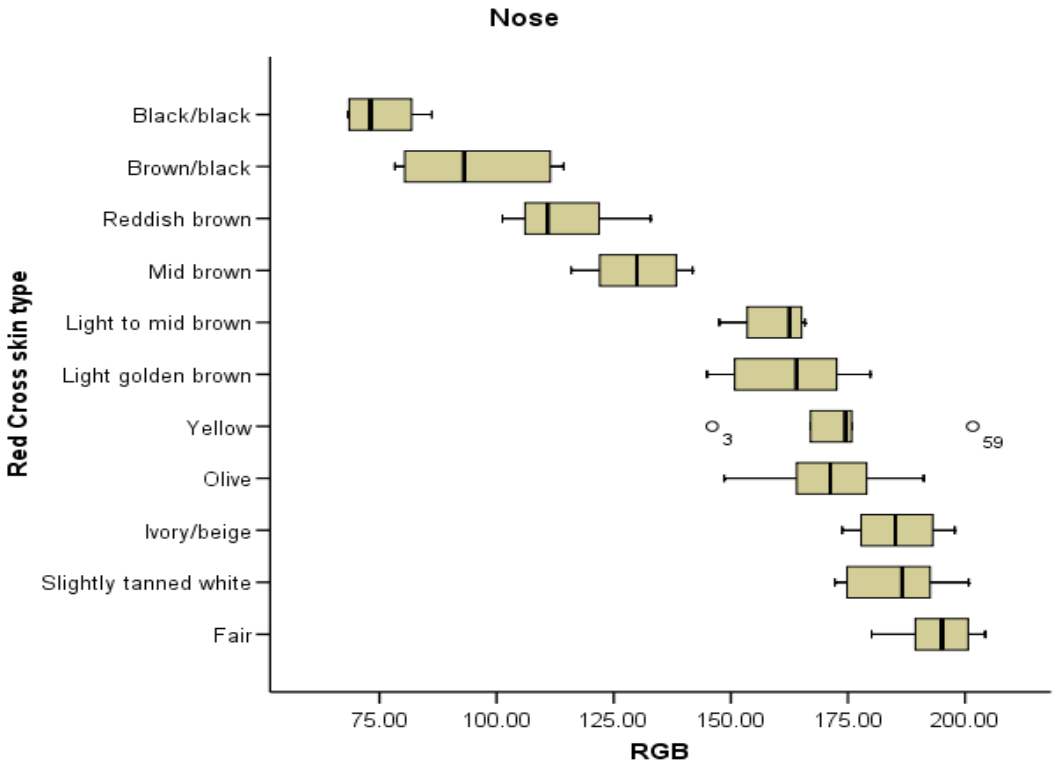


Figure 3.11. RGB values in each of the Red Cross skin tones, for the nose region (mean, range and 95% confidence interval; n = 108).

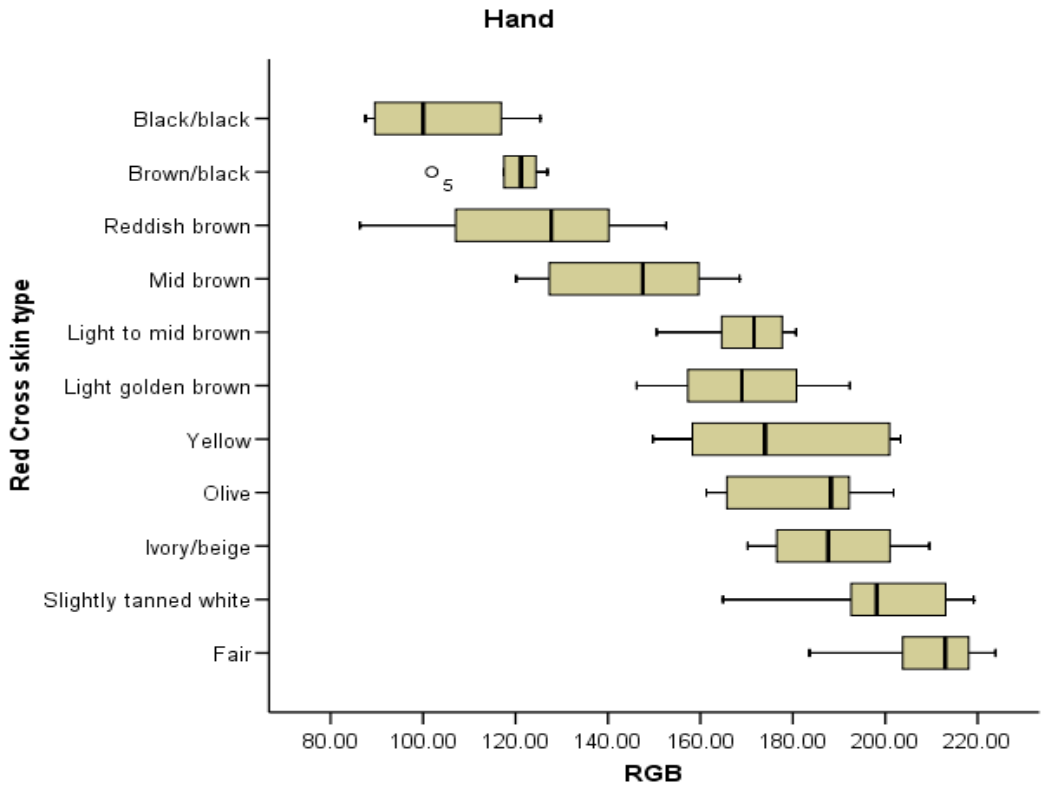


Figure 3.12. RGB values in each of the Red Cross skin tones, for the hand region (mean, range and 95% confidence interval; n = 108).

Using the data from representative forehead images we modified the order of Red Cross skin tones according to the assessments of mean RGB value, and compiled a scale of discrete skin tone groups which could be used for matching purposes as a quick reference chart (Figure 3.13). Each representative tone was taken from the image with the least deviation from the median RGB levels identified previously. All images were taken from the same forehead area described previously, to reduce tonal variability.

Figure 3.13. Colour scale of skin tones (ST) for use in matching for facial transplantation. ST1 = fair (F); ST2 = slightly tanned white (STW); ST3 = ivory-beige (IB); ST4 = olive (O); ST5 = yellow (Y); ST6 = light golden brown (LGB); ST7 = light-to-mid brown (LMB); ST8 = mid-brown (MB); ST9 = reddish brown (RB); ST10 = black-brown (Bl Br); ST11 = black-black (Bl Bl).

3.4. Discussion

Donor compatibility in facial transplantation has been substantially focussed on morphological or structural issues. Clearly this leaves a gap in terms of skin tone matching, something which cannot be easily and permanently altered. Using a series of standardised photographs we have thus sought to produce a bank of images with which we have created a graded system of assessing skin tone, with each skin tone assigned a number. This will allow transplant surgeons to better delineate which skin tones to use when performing facial transplant matching.

Accurate analysis of skin colour has been widely examined previously. Many different techniques of colour matching have relied on subjective means of analysis, such as the use of paint chips. There are a number of problems with using this in clinical practice (Gerald *et al.* 2001). First, ambient light affect all components of colour. Second, colour chips or cards are vulnerable to wear-and-tear and fading. Third, people vary with respect to 'normal' and 'abnormal' assessment, and various factors can further complicate colour assessment: these include fatigue, especially important in an after-hours assessment of a donor face by the treating surgeon, and the rather high incidence of colour blindness within the population. Colours adjacent to one another can also affect colour appearance. Spectrophotometry overcomes some of the subjective objections to using cards, however the considerable expense and the fact that there is a problem when multiple spectra are in adjacent distribution, mean that its use in this setting is somewhat limited. We thus sought to address these issues by using digital photographic corroboration of colour by means of RGB value analysis.

We chose the RGB method of image analysis due to its ease of accessibility, ease of use, and previous use in similar types of skin tone analyses (Gerald *et al.* 2001). All images were calibrated in their raw file format, and analysed within Adobe Photoshop CS2 as TIFF files. This was performed in order to preserve maximal image information. Although the JPEG format of photographic image has been used in the remote digital analysis of burn depth (Roa *et al.* 1999), this leads to the compression of colour. The greatest and most significant loss of image information occurs with colour more than spatial information (Neild and Davey 2001) so we sought to standardise this as much as possible. The human visual system can distinguish about hundreds of different saturation levels, and around 20 different shades, hence we can distinguish hundreds of thousands of colours. When perceiving coloured objects the characteristics of the illumination source also have an important influence, therefore a standardised photographic studio with reproducible illumination source was used.

Lastly, the concept of an individual's chronological age is important to the study of pigmentation and skin tone: the quantity of metabolically active melanocytes decreases over time and could affect whether or not the image is truly representative of each group. As winter months are correlated with lower skin pigmentation rates (Chaplin 2004), all photographic images were taken during the winter months in order to reduce the potential incidence of additive facultative colour (Quevedo *et al.* 1975).

It is important to note that for the potential facial graft donor, there is likely to be a loss of colour from the face following death. Therefore any assessment of facial skin tone must be done as early as possible following notification to the facial transplant team. In addition, the scale shows a grouping of values towards the fair end of the

RGB spectrum, and is thus less discriminating for distinguishing fairer skin types. This is easily explained by the more subtle changes in colour saturation values existing within these skin types.

We have defined an objective scale to categorise skin tone which we hope will be useful in assessing objectively to which category of skin tone a potential facial or hand transplant recipient would be assigned to. In creating this scale we thus hope to aid the assessment of the donor face, which could be occasioned remotely in the future.

Chapter 4

4. Skin Tonal Matching in Facial Transplantation

4.1. Introduction

4.1.1. Skin Type Assessment in Facial Transplantation

As facial transplantation becomes more commonplace, matching will become critically important to successful patient outcome. Donor compatibility in facial transplantation has been assessed previously in the cadaveric model; Baccarani *et al* (Baccarani *et al.* 2007) describe the morphological matching process as comprising evaluation of:-

- Gender
- Skin texture
- Features (nose, eyes, ears)
- Size of head

Many of the above factors are modifiable. As the graft is a pliable entity, head size discrepancy may be modified by draping or stretching of the facial graft for a small donor face, or by debridement of redundant tissue for a large donor graft. Skin texture differences might occur with a large age discrepancy, although such discrepancy may be small compared with other factors. Gender is included in this list but is not likely to be of such critical importance as might be expected, ethical considerations notwithstanding, as the facial graft will stretch and distort considerably

and any hair-bearing areas are likely to adapt to the recipient's hormonal environment. Pronounced and distinctive soft tissue features however - most notably the nose - can cause the chimeric face to resemble the donor to an unacceptable degree (Baccarani *et al.* 2007). In contrast, non-distinguishing soft tissue facial features are likely to mould to the recipients underlying facial skeleton, creating a hybrid chimeric face which primarily resembles the recipient. This has been confirmed by cadaveric studies on identity transfer in mock facial transplantation (Siemionow 2006).

The psychosocial sequelae associated with facial disfigurement should not be underestimated. These derive somewhat from a functional inability to send symbolic facial messages, which when coupled with altered aesthetic appearance can lead to psychological morbidity such as stigmatisation, social anxiety and avoidance, poor self-image and self-esteem, and substance abuse (Furr *et al.* 2007). Clearly unacceptable facial cosmesis plays a large role in the evolution of these sequelae.

A total of 52 hand and 13 face transplants have been performed worldwide (Wysong 2010). Although these have been matched for gender, and broadly by race, no indication has been given as to how precisely skin type matching was achieved, and no-one has yet described a system for assessing skin tone (an important component of the process) in either donor or recipient.

4.1.2. Importance of Skin Tonal Matching to Facial Transplantation

Skin colour distribution, independent of facial form and skin surface topography, seems to have a major influence on the perception of facial age and judgments of attractiveness and health (Fink *et al.* 2006). This is further supported by the fact that skin tonal mismatches following surgery (such as skin grafting) can cause psychological morbidity. We feel that robust system for aesthetic matching of skin tone is therefore required for any facial and hand transplantation programme for the following reasons:

a) Composite tissue transplantation is unique. Both the face and hand are visible to the naked eye, in direct contrast to solid organ transplants where aesthetic considerations are of no consequence.

b) The donor pool for facial transplantation will be restrained by the need for matching for gender and/or age. By ascertaining which skin tone donor/recipient matches are acceptable, we can increase our potential donor pool.

c) The outcome following facial transplantation needs to be considerably better than that achieved with standard plastic surgical reconstructive techniques in order to justify its choice as a reconstructive modality.

d) The impact of a facial graft may be lessened if the transplant looks similar to the recipient, or has minor discrepancies (Goering 2004).

4.2. Methods and Materials

4.2.1. Recipient Facial and Hand Transplant Images

A data set highlighting the distribution pattern in each of the RGB areas for each image was obtained as previously discussed in Chapter 3. A group of eleven antero-posterior facial images and dorsal hand images was chosen to represent each Red Cross skin tone according to mean RGB value (see Section 3.3). Using this data set, we chose two representative groups to act as recipient faces: skin tone 2 ('slightly tanned white') and skin tone 6 ('light golden brown'). The first group was chosen as it represented a common tonal group within the indigenous UK population; the second group represented a large minority group within the local population, which demonstrated contrasting RGB tonal values within the data set previously obtained. The two groups were chosen to provide sufficient contrast between light and dark recipient tones. A representative image for each skin tone was chosen by assessing which image lay closest to the mean RGB value for its group. In this way, both a male and female recipient face and hand were obtained for both recipient skin tones 2 and 6; appropriate donor face and hand tones were similarly obtained for types 1 to 11.

4.2.2. Creation of Simulated Face and Hand Transplant Images

Using the data set we obtained previously, we created a series of simulated facial and hand transplants, colour-matched to represent each skin tone identified. This was achieved in the following way. Areas likely to be grafted in a full facial transplant or a hand transplant were first delineated in the anterior-posterior facial and dorsal hand images respectively. In the face, this area extended laterally anterior to the ear to include the whole face and chin, mirroring the likely facial graft in a whole facial

transplant (Baccarani *et al.* 2007). The distinction between normal and altered skin inferiorly was made at the superior neck level. This was chosen to provide sufficient contrast to perform questionnaire analysis of a realistic tonal mismatch. Part of the neck was included to allow inclusion of the likely site of facial vessel anastomosis corresponding with the site reported from previous partial face transplants (Devauchelle *et al.* 2006). In the hand, the simulated transplant was designed at the mid-forearm level to coincide with the site of graft attachment in previous hand transplants.

The face and hand transplant simulations were performed using the 'Colour Match' facility within the Adobe Photoshop CS2 programme (Adobe Systems Inc., USA). In each image, the area of facial or hand transplant simulation was altered ten times in order to produce ten colour-matched images (giving eleven images in total, including the original). This reproduced the eleven skin tones identified in the previous photographic part of the study, providing eleven facial and hand transplant simulations. The order of hand or facial simulation images was randomised using true random generator techniques (www.random.org, Appendix B) and made into a customized flipchart booklet. Images were shown one-by-one, in a random order within a customized flip-chart. Each image occupied its own page on the flipchart, and each volunteer was shown the complete flipchart once to avoid repeated direct comparison between different shades. The process was repeated in both representative skin tone groups to make a series of simulated facial transplants (Figures 4.1 and 4.2). A sample of simulated hand transplant images is shown in Figure 4.3.

Each colour-matched image was compared with the original tone from which the colour was sampled. There were no significant differences between mean RGB values of each simulated image and mean RGB values of the original donor image for each of the images ($p>0.05$, two sided).

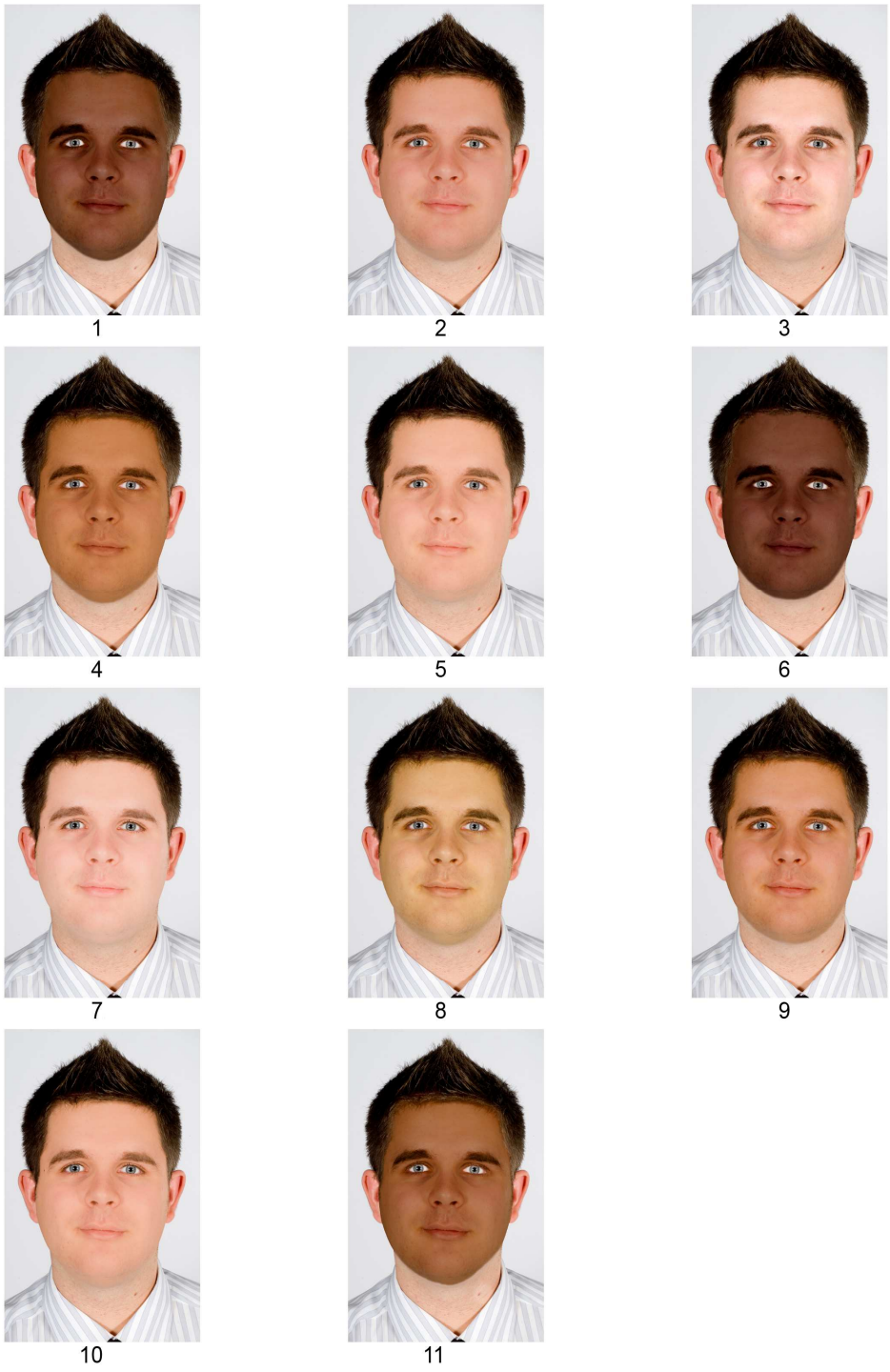


Figure 4.1. Facial transplant simulations using a skin tone 2 (slightly tanned white) male recipient with overlying sampled donor skin tones. Each image is presented in a randomised order (1 = brown-black skin tone overlay, 2 = olive skin tone overlay, and so on).

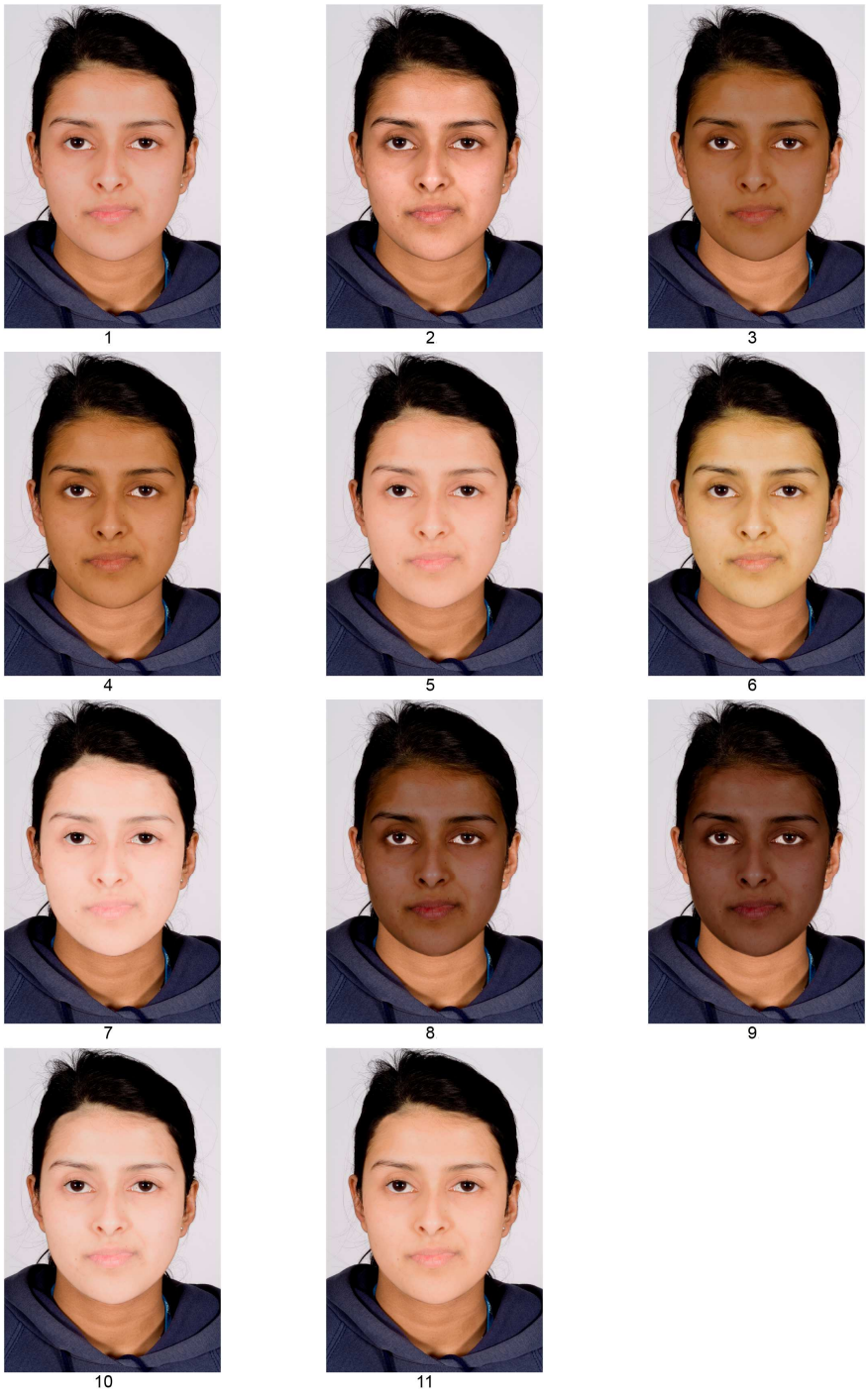


Figure 4.2. Facial transplant simulations using a skin tone 6 (light golden brown) female recipient with overlying sampled donor skin tones. Each image is presented in a randomised order (1 = slightly tanned white skin tone overlay, 2 = control image, no overlay, and so on).

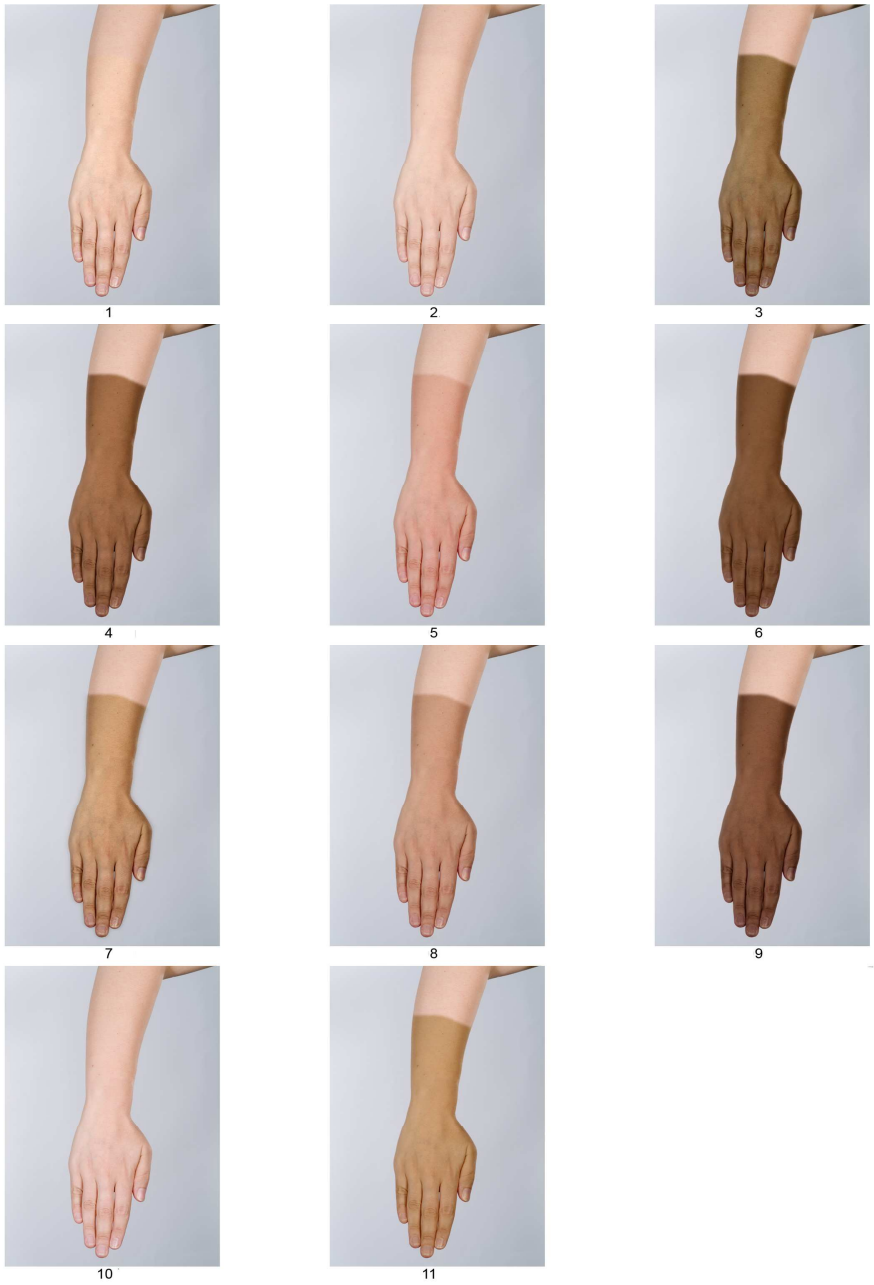


Figure 4.3. Hand transplant simulations using a skin tone 2 (slightly tanned white) female recipient with overlying sampled donor skin tones. Each image is presented in a randomised order (1 = ivory-beige skin tone overlay, 2 = fair skin tone overlay, and so on).

4.2.3. Case Ascertainment

A total of 122 volunteers were recruited into the study (61 males, 61 females) after correctly identifying their own facial skin tone type on a panel of images representing each of the eleven discrete skin tones previously identified (Figure 3.5). The volunteer's skin tonal type was recorded by two independent assessors. There was a 95% correlation between volunteer and assessor evaluation of volunteer skin tone (Pearson correlation, $p<0.05$). Volunteers who correctly assessed their own skin tone were recruited into the study, in order to eliminate responses based on potentially aberrant perceptions of skin tone. We chose to study observations made by two representative skin tone types: skin tone 2 ('slightly tanned white,' n=60) and skin tone 6 ('light golden brown,' n=62).

4.2.4. Questionnaire Study

For the questionnaire part of the study, volunteers were firstly asked to state which of the eleven facial images and eleven hand images represented the original non-altered image. They were then asked to state how confident they were in their choice, marked on a modified Likert scale (-7.0 to 7.0), ranging from 'not confident' to 'very confident' respectively. The volunteers then used the same scale to rate a series of randomised simulated face and hand transplant tonal mismatches in terms of:

a) Acceptability
b) Attractiveness
c) Normality

The Likert scale and questionnaire used are shown in Appendix C. For responses which required an estimation of whether simulations were deemed broadly acceptable, normal or attractive by participants, a response was termed 'positive' if it was above zero; a response was termed 'negative' if it was below zero.

'Acceptability' was defined as how socially acceptable the participant would find each of the simulated facial or hand transplants. 'Normality' was defined as how close to the average or normal face or hand each of the simulations appeared. 'Attractiveness' was defined as the perception of the physical traits of an individual as being aesthetically pleasing or beautiful. Each of these terms was clearly framed within the context of the participant appraising a simulated transplant of their own face.

Gender of participant was linked with the image viewed, such that all the men viewed the same 11 pictures created on one male recipient image, and all the women viewed the same 11 pictures based on one female image. All volunteers within the skin tone 2 (slightly tanned white) group viewed transplant simulations created on a skin type 2 recipient; similarly, all skin tone 6 (light golden brown) volunteers viewed simulations of a skin tone 6 recipient.

4.3. Results

4.3.1. Correlations between Acceptability, Attractiveness and Normality

There were significant correlations between acceptability, attractiveness and normality in all skin tones ($p<0.01$, Pearson correlation, two-tailed). This occurred in

both simulated hand transplant and facial transplant images, and in both skin tone 2 and skin tone 6 participant groups.

4.3.2. Skin Tone 2 (Slightly Tanned White) Participants

A total of 30 males (aged 23-60, mean 34) and 30 females (aged 22-59, mean 34) from skin tone 2 were recruited into the questionnaire part of the study. There was no gender difference in correct identification of the control face ($\chi 2 = 1.176$, $df = 1$, $p = 0.278$) or hand ($\chi 2 = 0.162$, $df = 1$, $p = 0.688$). When asked to make a choice over which simulation was the control image, there was no difference in confidence rating between facial ($p = 0.45$) or hand ($p = 0.693$) transplant images. There were no gender differences in the percentages of correct and incorrect responses, with no significant difference in mean confidence ratings given by male and female participants assessing simulated facial transplant ($t = 0.757$, $df = 57$, $p = 0.45$, two-sided) and hand transplant ($t = 0.397$, $df = 57$, $p = 0.693$, two-sided) control images.

i. Skin Tone 2 (Slightly Tanned White) Facial Transplant Simulations

The mean rates of acceptability for skin tone 2 (slightly tanned white) participants are shown in Table 4.1. There were statistically significant differences between mean levels of acceptability for each donor skin type simulation examined ($F(10, 590) = 238.183$, $MSE = 4.915$, $p < 0.001$, one-way repeated measures ANOVA) as shown in Figure 4.4.

There was a statistically significant interaction between gender and donor skin tone on acceptability ($F(10, 580) = 5.362$, $MSE = 4.577$, $p < 0.001$, one-way repeated measures ANOVA). Post hoc application of the independent samples t-test showed

mean acceptability ratings were significantly greater for males than females for light golden brown donor simulations (t = 3.894, df = 58, p < 0.001, two-sided); light-to-mid brown simulations (t = 4.893, df = 58, p < 0.001, two-sided); and mid-brown simulations (t = 2.997, df = 58, p = 0.004, two-sided). For this group of skin tone 2 participants, more groups were deemed acceptable (and thus potentially available for matching) for males than for females: a total of six donor skin tones for males, compared with three acceptable donor skin tones for females (excluding the control facial transplant simulation). Male participants stated that there were more numerous acceptable mismatches for facial transplant simulations than for the hand transplant simulations (six donor skin types compared with three donor skin tones, excluding the control simulation). The percentage of participants who rated the tonal mismatches acceptable is shown for both facial and hand transplant simulations (Figure 4.5).

Table 4.1. Mean (±*SD*) acceptability ratings of facial transplant simulations (skin tone 2 participants, n=60). Simulations were laid onto a skin tone 2 recipient face (scale ranged from most acceptable (7) to most unacceptable (-7)). * = Control image; § = Significant gender difference at the $p < 0.05$ level.

Donor skin tone (ST1-11)	**Mean acceptability *(±SD)***
Fair (ST1)	4.810 *(1.702)*
Male	3.04 *(1.499)*
Female	4.58 *(1.881)*
Slightly tanned white (ST2)	5.398 *(1.525)* *****
Male	5.5 *(1.314)*
Female	5.296 *(1.727)*
Ivory/beige (ST3)	4.248 *(2.151)*
Male	4.167 *(2.236)*
Female	4.330 *(2.097)*
Olive (ST4)	3.983 *(2.210)*
Male	4.137 *(2.038)*
Female	3.383 *(2.095)*
Yellow (ST5)	-.276 *(3.566)*
Male	.223 *(3.484)*
Female	-.776 *(3.635)*
Light golden brown (ST6)	-1.103 *(3.375)* **§**
Male	.420 *(3.428)*
Female	-2.627 *(2.572)*
Light-to-mid brown (ST7)	1.270 *(3.512)* **§**
Male	3.157 *(2.250)*
Female	.616 *(3.575)*
Mid-brown (ST8)	-4.188 *(2.234)* **§**
Male	-3.377 *(2.514)*
Female	-4.999 *(1.573)*
Reddish brown (ST9)	-5.128 *(1.810)*
Male	-4.737 *(1.947)*
Female	-5.520 *(1.599)*
Brown/black (ST10)	-5.420 *(1.582)*
Male	-5.217 *(1.742)*
Female	-5.623 *(1.405)*
Black/black (ST11)	-5.765 *(1.433)*
Male	-5.753 *(1.364)*
Female	-5.776 *(1.522)*

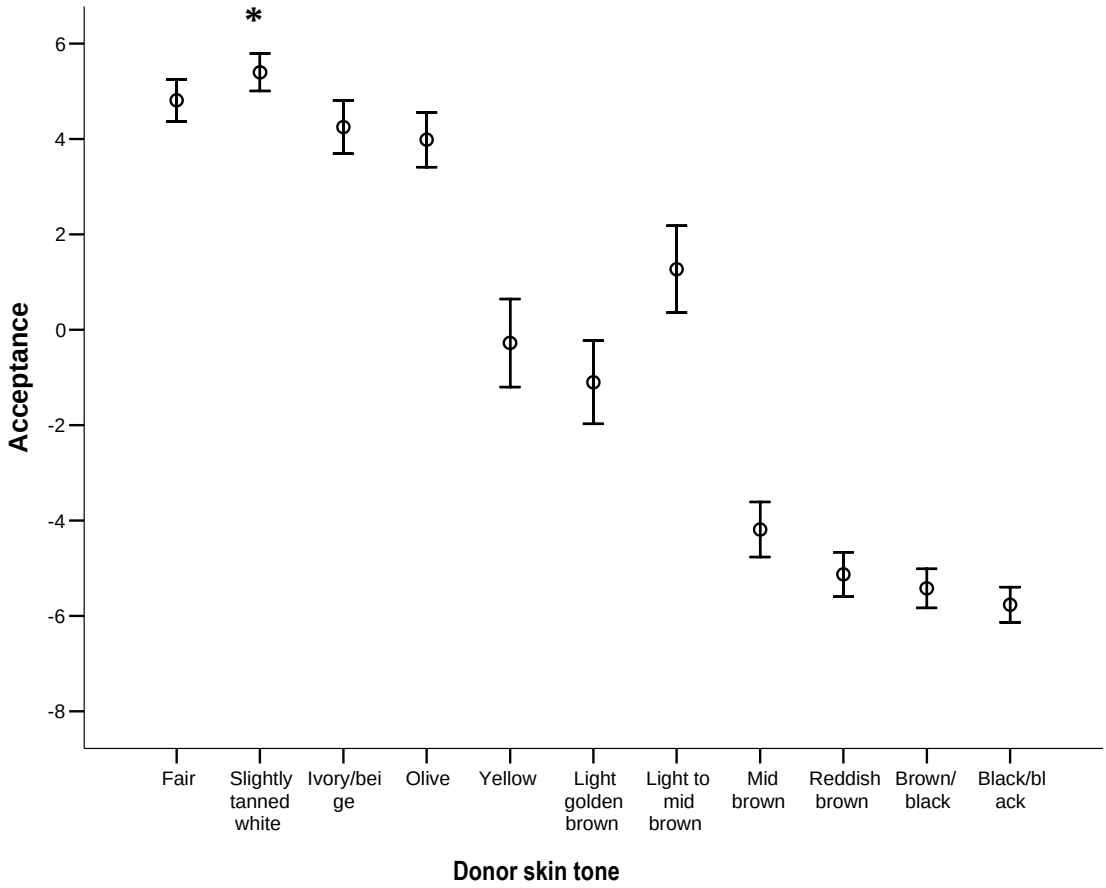


Figure 4.4. Donor skin tones for a simulated facial transplant performed onto a skin tone 2 (slightly tanned white) recipient; 95% confidence interval error bar graphic for mean acceptability (acceptance) values as rated by skin tone 2 participants. Error bars that do not overlap with one another indicate statistical significant differences.

* = Control image.

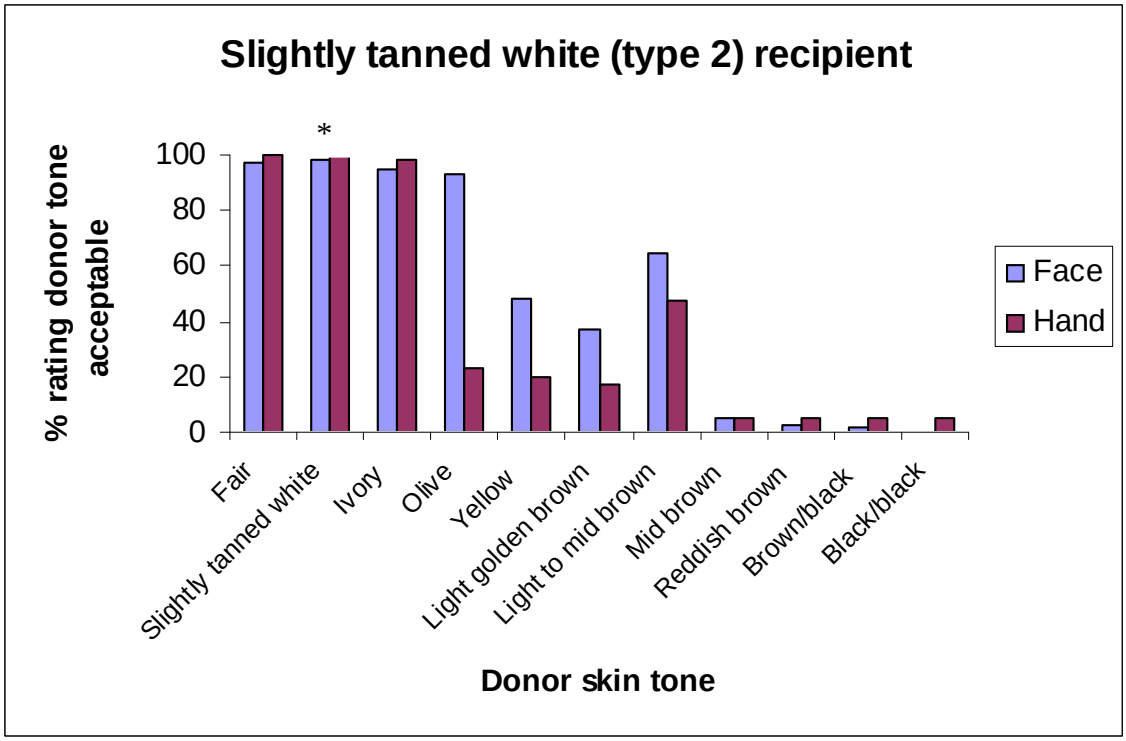


Figure 4.5. Percentage of skin tone 2 (slightly tanned white) respondents rating donor-recipient skin tonal matches acceptable in hand and face transplant simulations onto a skin tone 2 (slightly tanned white) recipient (n=60). * Control image.

In terms of perceptions of attractiveness, skin tone 2 (slightly tanned white) male participants were more likely to accept tonal mismatches than females, with a statistically significant interaction between gender and skin tone on attractiveness rating using independent sample t-test. Attractiveness ratings were higher in males for light golden brown donor simulations (t = 2.161, df = 58, p = 0.035, two-sided), for light-to-mid brown simulations (t = 5.187, df = 58, p < 0.001, two-sided), and for mid-brown simulations (t = 2.348, df = 58, p = 0.022, two-sided).

The interaction between donor skin tone and perceptions of normality was also significant, with males reporting higher rates of normality than females when viewing images of light golden brown simulations (t = 3.994, df = 58, p < 0.001, two-sided); light-to-mid brown simulations (t = 6.809, df = 58, p < 0.001, two-sided); mid-brown simulations (t = 3.627, df = 58, p - 0.001, two-sided); and reddish brown simulations (t = 2.07, df = 58, p = 0.043, two-sided). Mean values of acceptability, attractiveness, normality for the facial transplant simulations are shown in Figures 4.6 to 4.11.

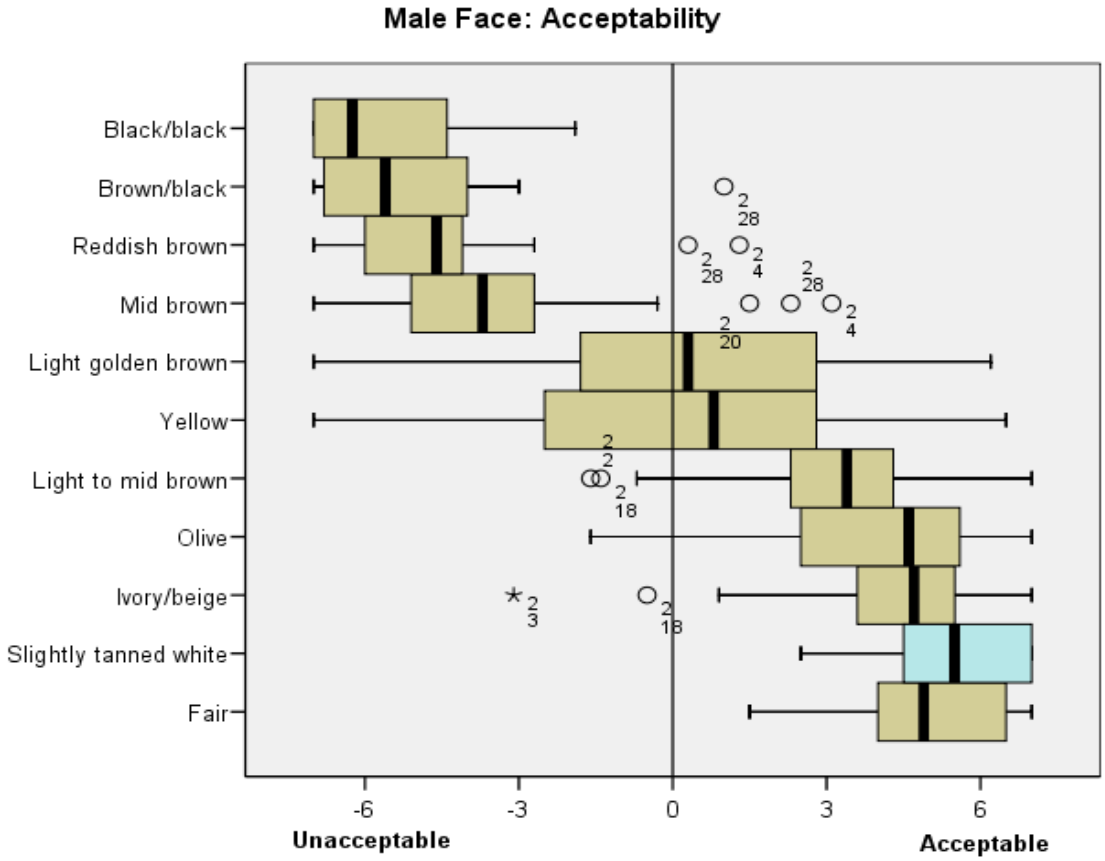


Figure 4.6. Mean, range and standard error of ratings of acceptability of facial transplant simulations, as assessed by skin tone 2 (slightly tanned white) males. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

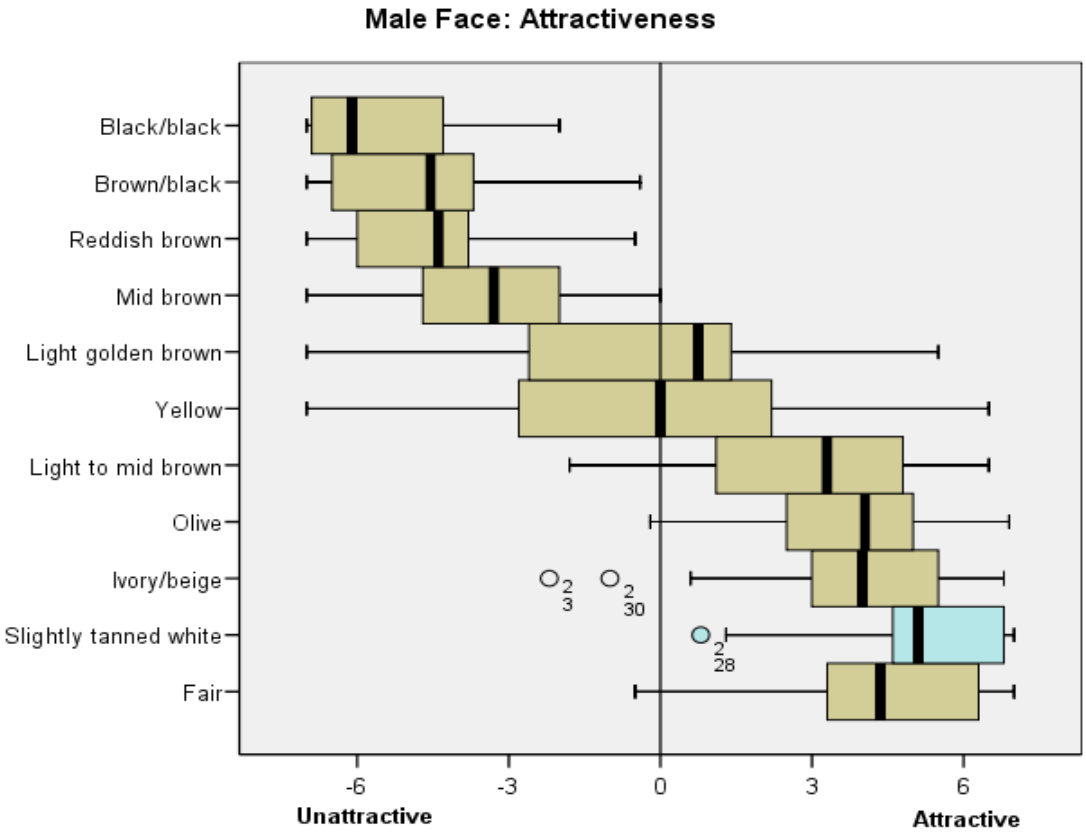


Figure 4.7. Mean, range and standard error of ratings of attractiveness of facial transplant simulations, as assessed by skin tone 2 (slightly tanned white) males. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle.

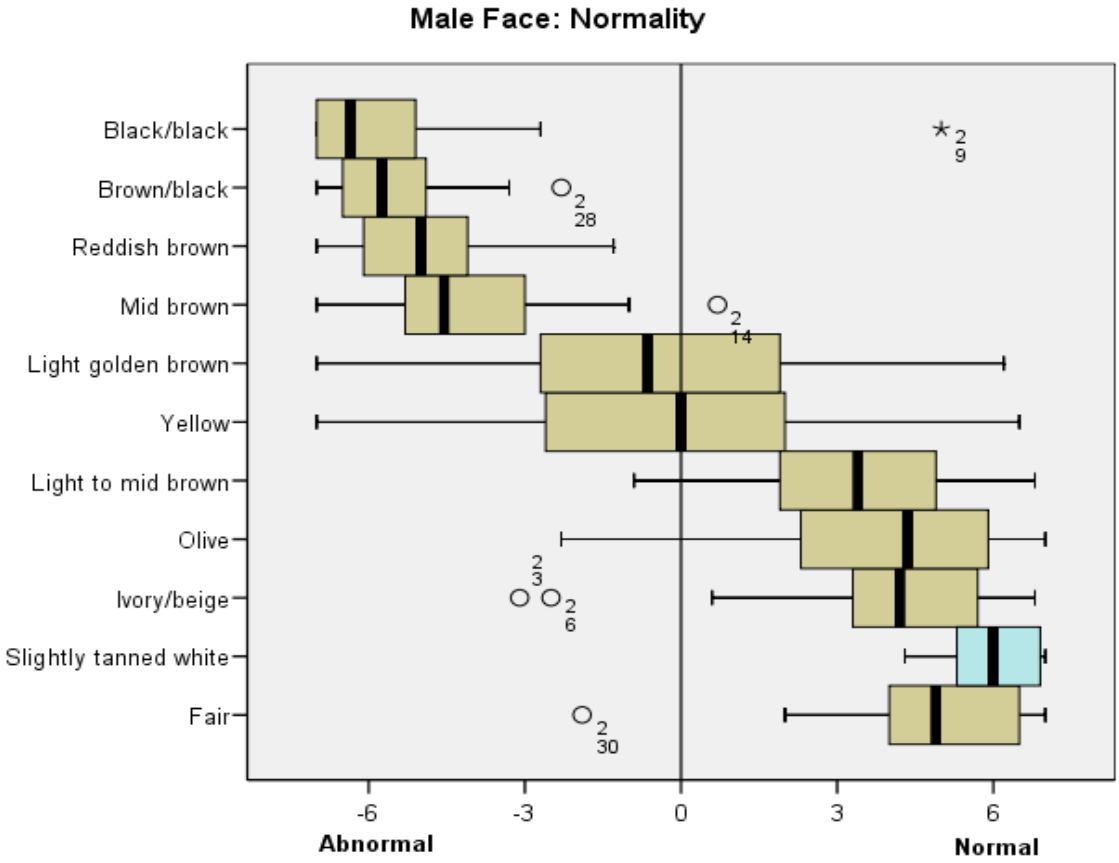


Figure 4.8. Mean, range and standard error of ratings of normality of facial transplant simulations, as assessed by skin tone 2 (slightly tanned white) males. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

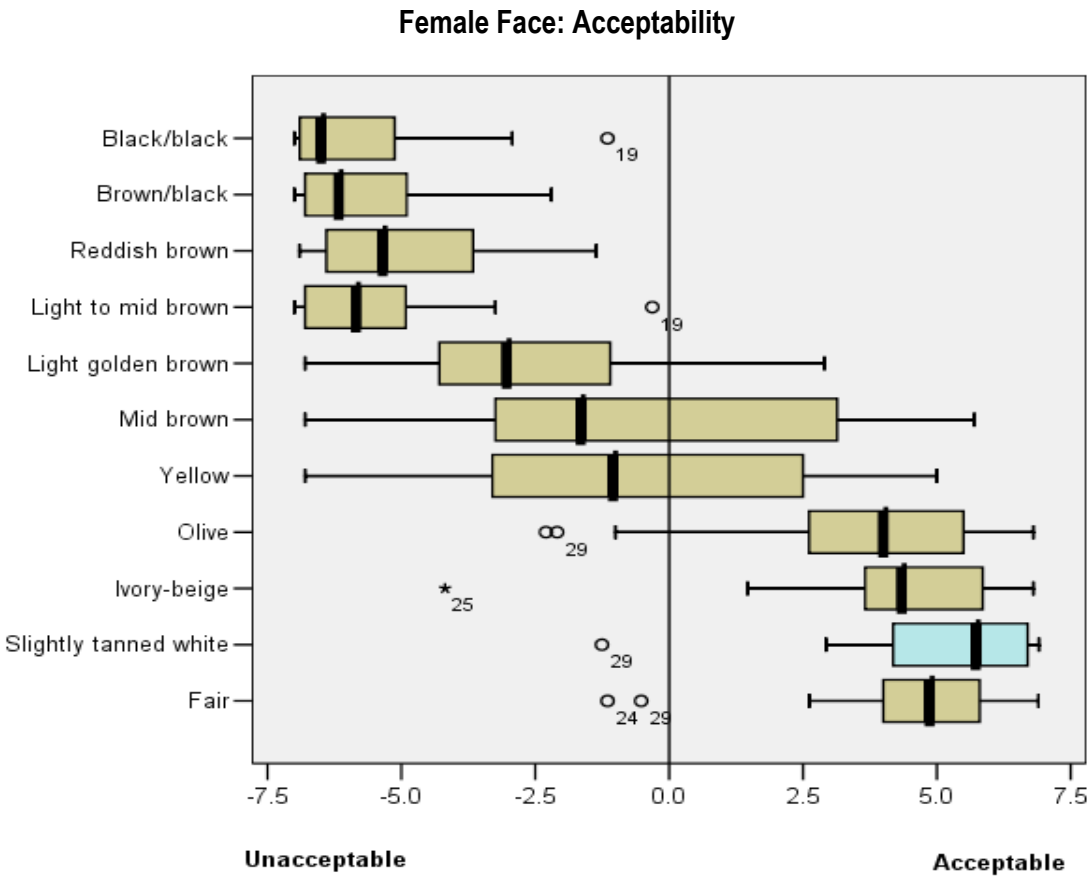


Figure 4.9. Mean, range and standard error of ratings of acceptability of facial transplant simulations, as assessed by skin tone 2 (slightly tanned white) females. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

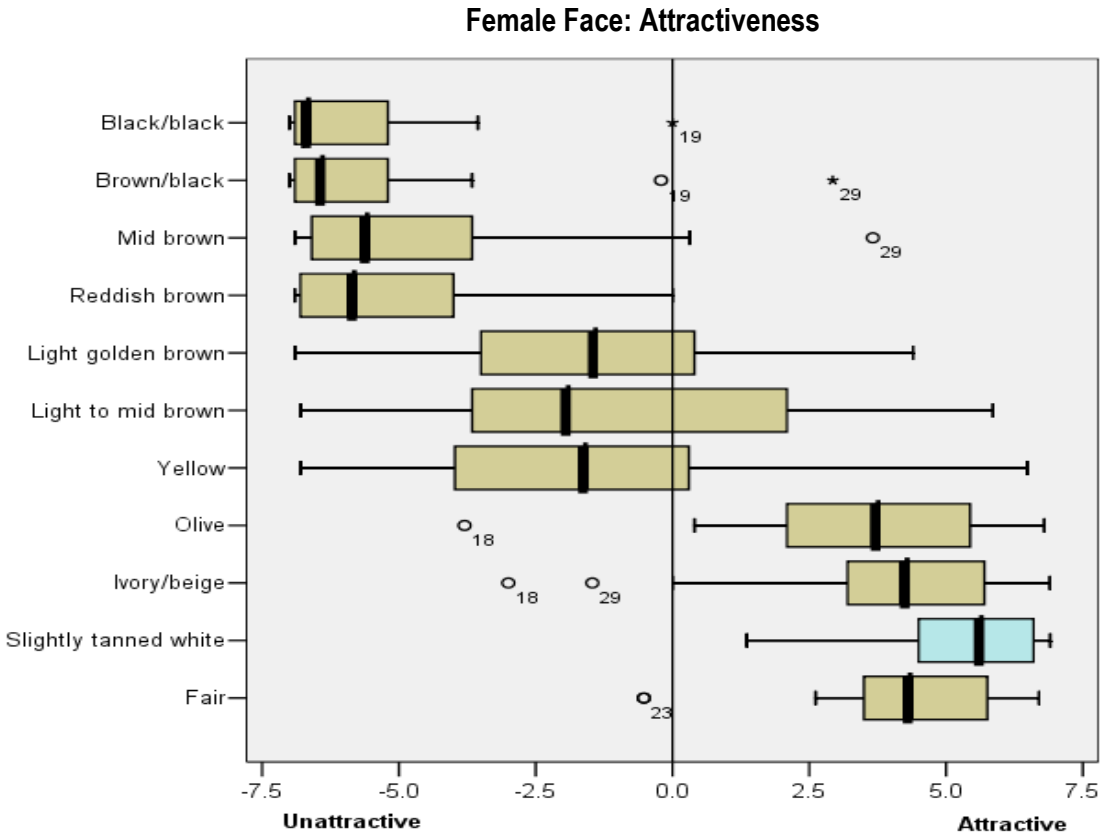


Figure 4.10. Mean, range and standard error of ratings of attractiveness of facial transplant simulations, as assessed by skin tone 2 (slightly tanned white) females. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

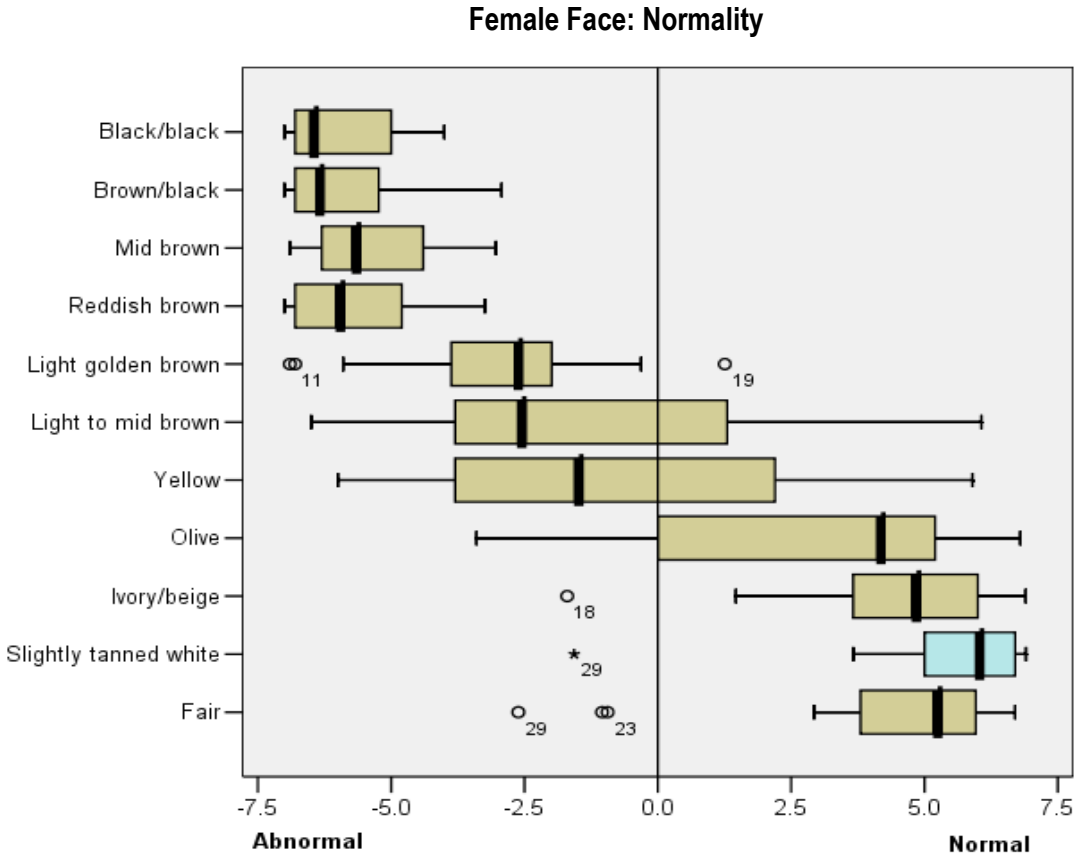


Figure 4.11. Mean, range and standard error of ratings of normality of facial transplant simulations, as assessed by skin tone 2 (slightly tanned white) females. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

ii. Skin Tone 2 (Slightly Tanned White) Hand Transplant Simulations

There were statistically significant differences between the mean levels of acceptability between the different donor skin tone simulations ($F(10, 590) = 237.96$, $MSE = 4.623$, $p < 0.001$, one-way ANOVA). There was a significant interaction between gender and donor skin tone on acceptability ($F(10, 580) = 5.131$, $MSE = 4.321$, $p < 0.001$) as highlighted in Table 4.2 and Figure 4.12.

Table 4.2. Mean (±SD) acceptability ratings of hand transplant simulations (skin tone 2 participants, n=60). Participants assessed simulations laid onto a skin tone 2 recipient hand (scale = acceptable 7, unacceptable -7). * = Control image; § = Significant gender difference at the $p < 0.05$ level.

Donor skin tone (ST1-11)	**Mean acceptability *(±SD)***
Fair (ST1)	4.489 *(1.577)*
Male	4.190 *(1.525)*
Female	4.788 *(1.596)*
Slightly tanned white (ST2)	.863 *(1.225)* *****
Male	5.903 *(1.178)*
Female	5.822 *(1.289)*
Ivory/beige (ST3)	4.644 *(1.612)*
Male	4.260 *(1.703)*
Female	5.028 *(1.439)*
Olive (ST4)	-2.026 *(3.475)* **§**
Male	-.990 *(3.395)*
Female	-3.063 *(3.289)*
Yellow (ST5)	-2.476 *(3.058)* **§**
Male	-1.297 *(2.977)*
Female	-3.655 *(2.7)*
Light golden brown (ST6)	-2.975 *(2.799)*
Male	-2.643 *(2.554)*
Female	-3.307 *(3.030)*
Light-to-mid brown (ST7)	-.319 *(3.692)* **§**
Male	.997 *(3.581)*
Female	-1.635 *(3.364)*
Mid-brown (ST8)	-4.947 *(2.149)*
Male	-4.917 *(2.037)*
Female	-4.977 *(2.291)*
Reddish brown (ST9)	-5.271 *(2.251)*
Male	-5.480 *(1.818)*
Female	-5.063 *(2.629)*
Brown/black (ST10)	-4.723 *(2.549)*
Male	-4.420 *(2.903)*
Female	-5.025 *(2.145)*
Black/black (ST11)	-5.409 *(2.024)*
Male	-5.457 *(1.794)*
Female	-5.361 *(2.261)*

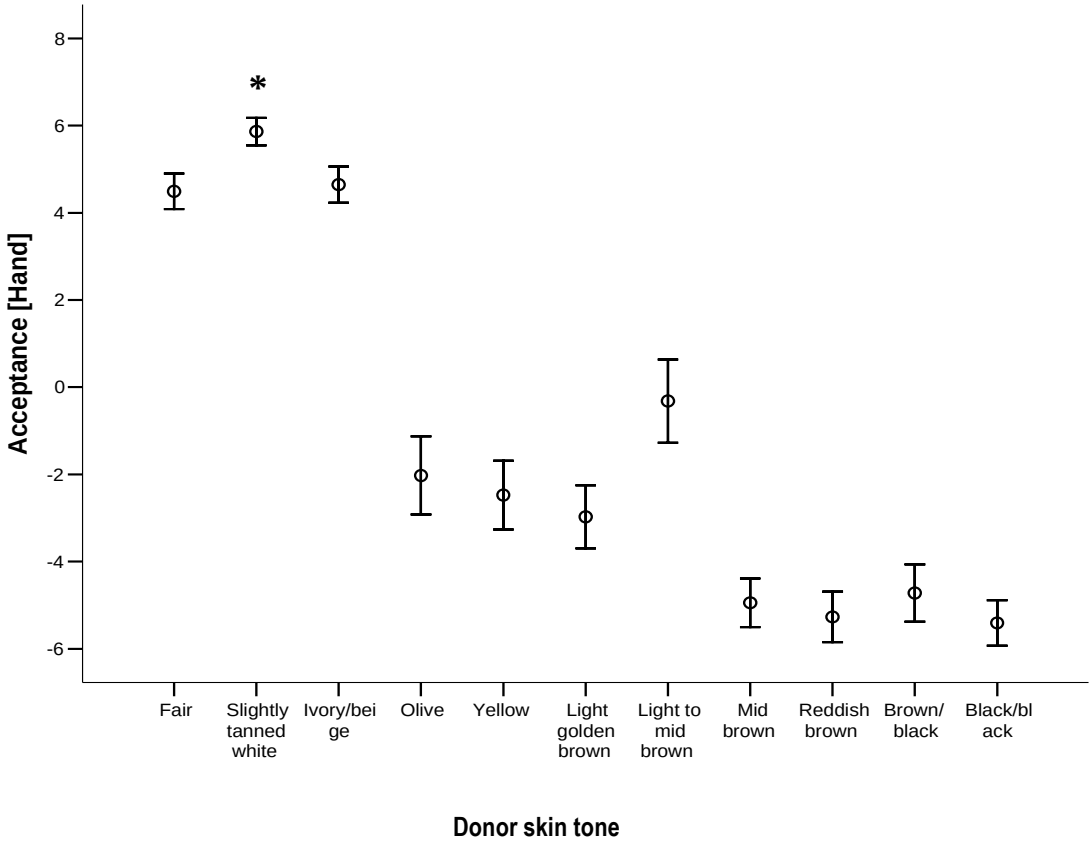


Figure 4.12. Donor skin tones for simulated hand transplants performed onto a skin tone 2 (slightly tanned white) recipient; 95% confidence interval error bar graphic for mean acceptability (acceptance) values. Error bars that do not overlap with one another indicate statistical significant differences.

* = Control image.

Independent samples t-test mean acceptability ratings for the hand simulations were significantly higher in males than females in three donor groups: olive (t = 2.402, df = 58, p = 0.020, two-sided), yellow (t = 3.214, df = 58, p = 0.002, two-sided), and light-to-mid brown (t = 2.934, df = 58, p = 0.005, two-sided). Mean attractiveness ratings were significantly higher for male participants looking at simulations of the following donor skin tones: olive (t = 2.284, df = 58, p = 0.026, two-sided), yellow (t = 3.156, df = 58, p = 0.003, two-sided), and light-to-mid-brown (t = 3.962, df = 58, p < 0.001,

two-sided). There was a significant interaction between gender and donor skin tone when looking at perceptions of normality in the hand transplant simulations ($F(10, 570) = 6.235$, $MSE = 3.360$, $p < 0.001$), with significantly increased ratings of normality reported by male participants when assessing the following donor skin tone simulations: olive ($t = 2.460$, $df = 58$, $p = 0.017$, two-sided), yellow ($t = 3.294$, $df = 58$, $p = 0.002$, two-sided), and light-to-mid brown ($t = 3.669$, $df = 58$, $p = 0.001$, two-sided). Acceptability, attractiveness and normality for the hand transplant simulations is shown graphically in Figures 4.13 to 4.15.

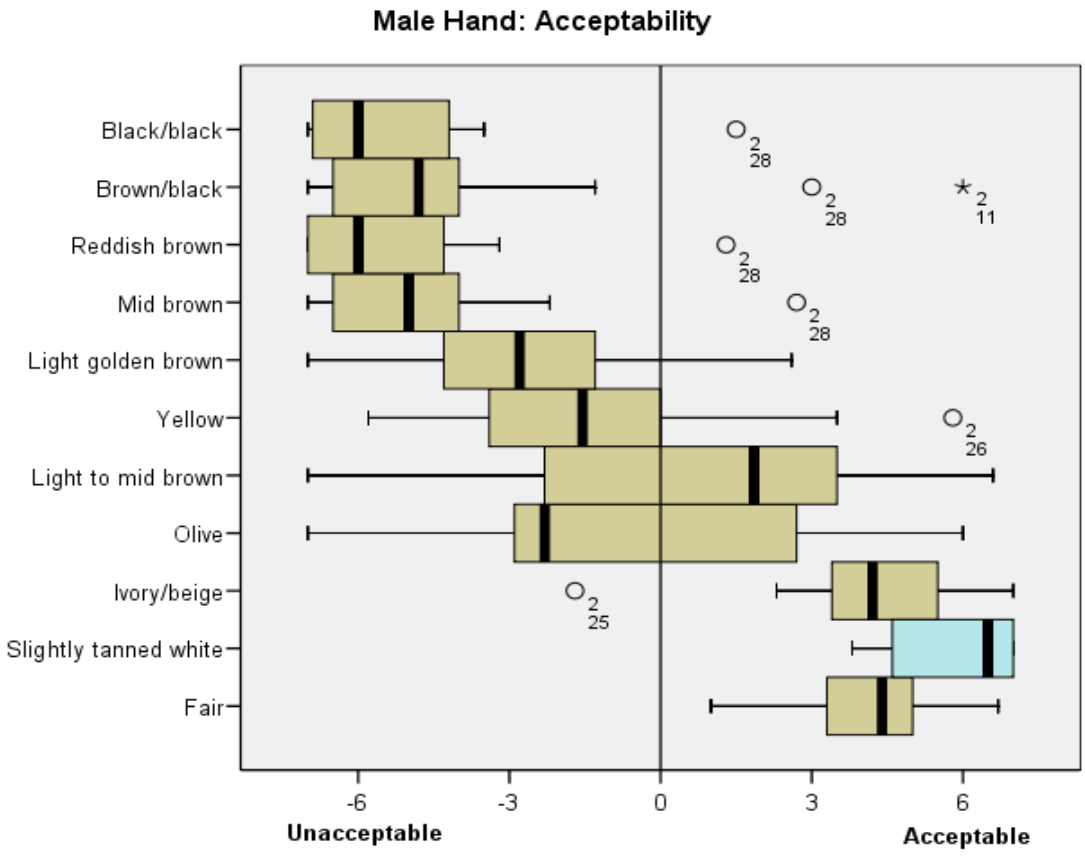


Figure 4.13. Mean, range and standard error of ratings of acceptability of hand transplant simulations, as assessed by skin tone 2 (slightly tanned white) males. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

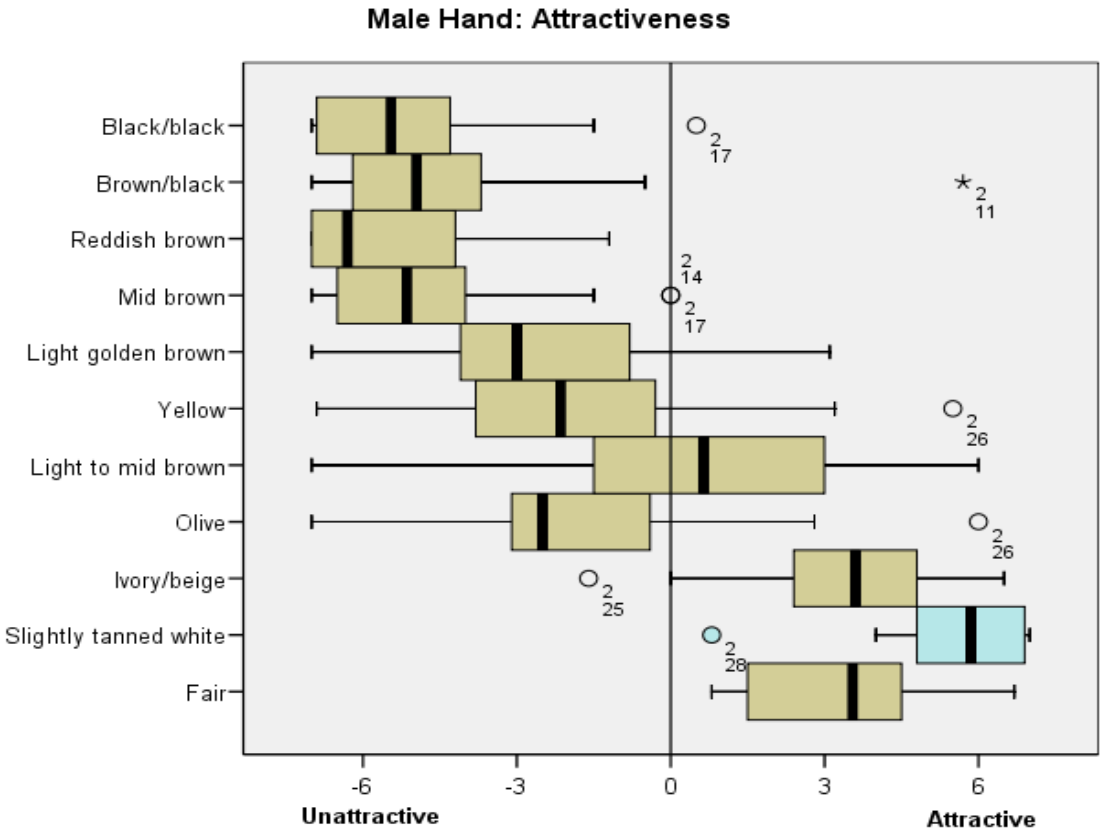


Figure 4.14. Mean, range and standard error of ratings of attractiveness in males of skin tone 2 (slightly tanned white) when assessing hand transplant simulations. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

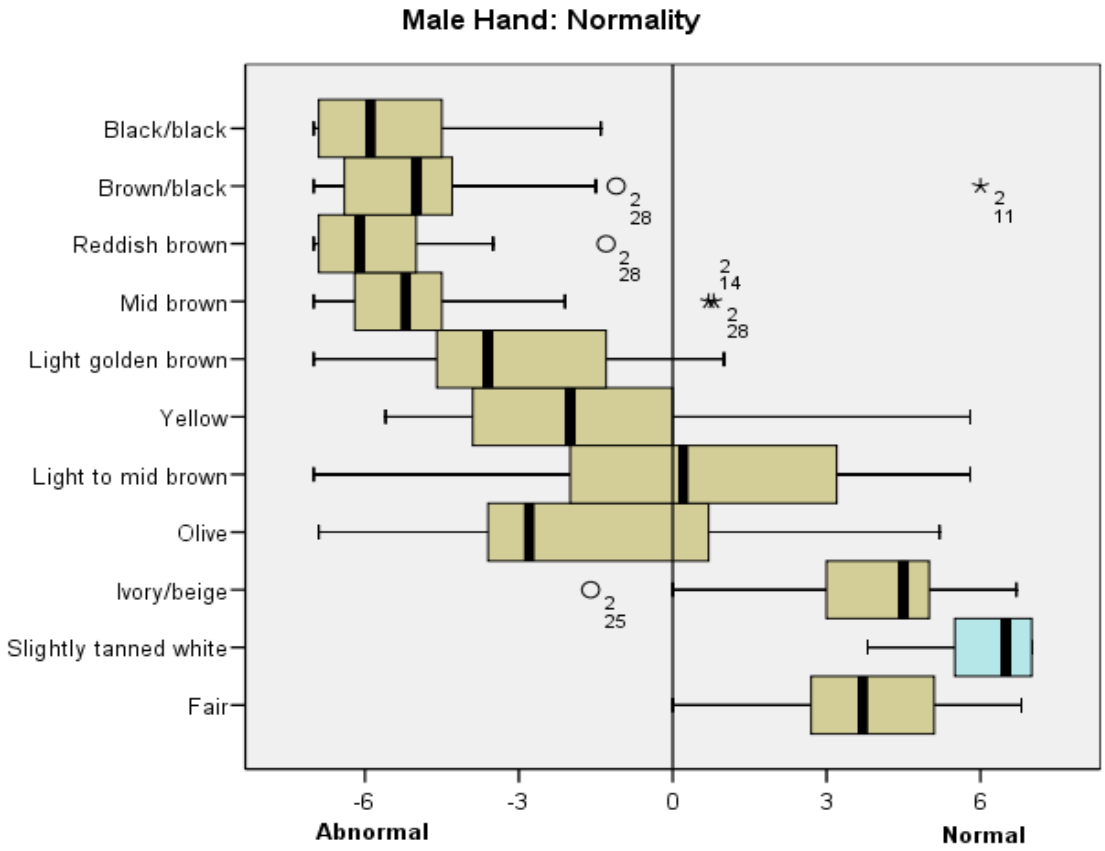


Figure 4.15. Mean, range and standard error of ratings of normality of hand transplant simulations, as assessed by skin tone 2 (slightly tanned white) males. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

4.3.3. Skin Tone 6 (Light Golden Brown) Participants

A total of 31 males (age 21-61, mean 28.3) and 31 females (age 21-60, mean 33.6) from skin tone 6 (light golden brown) were entered into the study. The majority of participants (females: face 25/31, hand 23/31; males: face 28/31, hand 26/31) could correctly identify the control image, with no gender difference in correct identification of the control face ($\chi 2 = 1.17$, $df = 1$, $p = 0.79$) or hand ($\chi 2 = 0.876$, $df = 1$, $p = 0.349$). For the male group, there was no significant difference between the mean confidence rating for identification of the control images (face 3.61, hand 3.752; $p = 0.45$), although for females there was a discrepancy (face 2.697, hand 2.213; $p = 0.02$). There was no significant difference in mean confidence ratings given by male and female participants assessing the simulated facial transplant control images ($t = 1.541$, $df = 60$, $p = 0.129$, two-sided). However, there were higher mean confidence ratings for males than females ($t = 2.755$, $df = 60$, $p = 0.008$, two-sided) in the hand transplant group.

iii. Skin Tone 6 (Light Golden Brown) Facial Transplant Simulations

There were statistically significant differences between mean levels of acceptance for each donor skin type simulation examined ($F(10, 600) = 125.886$, $MSE = 6.307$, $p < 0.001$, one-way repeated measures ANOVA). There was a statistically significant interaction between gender and donor skin tone on acceptability ($F(10, 590) = 11.192$, $MSE = 5.391$, $p < 0.001$, one-way repeated measures ANOVA) as shown in Table 4.3. Post hoc application of the independent samples t-test showed significantly greater acceptability ratings for male than female participants when viewing the following simulations: yellow ($t = 5.447$, $df = 60$, $p < 0.001$, two-sided); reddish brown ($t = 5.407$, $df = 60$, $p < 0.001$, two-sided); and mid-brown ($t = 4.517$, $df = 60$, $p < 0.001$,

two-sided). Interestingly however, females expressed significantly higher acceptability ratings than males when viewing slightly tanned white donor simulations (t = -2.099, df = 60, p = 0.04, two-sided).

Mean attractiveness ratings were significantly higher for male participants looking at facial transplant simulations using the following donor skin tones: yellow (t = 4.153, df = 60, p < 0.001, two-sided); reddish brown (t = 4.02, df = 60, p < 0.001, two-sided); and mid-brown (t = 3.872, df = 60, p < 0.001, two-sided). Interestingly males expressed higher attractiveness ratings than females when assessing the control light golden brown images (t = 3.67, df = 60, p = 0.001, two-sided). Females on the other hand expressed higher attractiveness ratings than males when looking at simulations using the fair donor skin tone (t = -2.136, df = 60, p = 0.037, two-sided).

There were significantly increased ratings of normality reported by male than female participants when rating the following donor skin tone simulations: yellow (t = 4.871, df = 60, p < 0.001, two-sided); mid brown (t = 3.482, df = 60, p = 0.001, two-sided); and reddish brown (t = 6.688, df = 60, p < 0.001, two-sided). Again, males rated the control light golden brown images more ‘normal’ than did females within the same skin tone group (t = 2.689, df = 58, p = 0.009, two-sided).

Table 4.3. Mean acceptability ratings of facial transplant simulations (skin tone 6 participants, n=62). Participants assessed simulations laid onto a skin tone 6 recipient face (scale = most acceptable 7, most unacceptable -7). * = Control image; § = Significant gender difference at the $p < 0.05$ level.

Donor skin tone (ST1-11)	Mean acceptability *(SD)*
Fair (ST1)	-4.318 *(1.769)*
Male	-4.710 *(1.469)*
Female	-3.926 *(1.972)*
Slightly tanned white (ST2)	-3.260 *(2.853)* **§**
Male	-4.000 *(2.010)*
Female	-2.519 *(3.368)*
Ivory/beige (ST3)	.885 *(3.539)*
Male	.268 *(3.413)*
Female	1.503 *(3.609)*
Olive (ST4)	-1.261 *(3.598)*
Male	-1.497 *(3.465)*
Female	-1.026 *(3.768)*
Yellow (ST5)	1.194 *(3.737)* **§**
Male	3.326 *(2.719)*
Female	-.939 *(3.407)*
Light golden brown (ST6)	5.237 *(1.879)* *****
Male	5.884 *(1.315)*
Female	4.590 *(2.127)*
Light-to-mid brown (ST7)	3.361 *(2.487)*
Male	3.560 *(2.414)*
Female	3.168 *(2.581)*
Mid-brown (ST8)	2.632 *(3.131)* **§**
Male	4.197 *(1.315)*
Female	1.068 *(3.446)*
Reddish brown (ST9)	-2.681 *(2.778)* **§**
Male	-1.103 *(2.797)*
Female	-4.258 *(1.652)*
Brown/black (ST10)	-4.737 *(1.683)*
Male	-4.716 *(1.887)*
Female	-4.758 *(1.482)*
Black/black (ST11)	-5.169 *(1.570)*
Male	-5.290 *(1.467)*
Female	-5.048 *(1.683)*

iv. Skin Tone 6 (Light Golden Brown) Hand Transplant Simulations

Application of the independent samples t-test showed significantly greater acceptability ratings for males than females when viewing yellow (t = 11.206, df = 60, p < 0.001, two-sided) and olive (t = 5.59, df = 60, p < 0.001, two-sided) donor simulations. However, females expressed significantly higher acceptability ratings than males when viewing slightly tanned white (t = -2.829, df = 60, p = 0.006, two-sided) and light-to-mid-brown (t = -11.669, df = 60, p < 0.001, two-sided) donor simulations (Table 4.4).

Mean attractiveness ratings were significantly higher for male participants assessing olive (t = 5.716, df = 60, p < 0.001, two-sided) and yellow (t = 11.75, df = 60, p < 0.001, two-sided) hand transplant simulations. Of note however, female ratings of attractiveness were much higher in the following donor skin tone simulations: light-to-mid-brown (t = -17.965, df = 60, p < 0.001, two-sided); ivory-beige (t = -3.036, df = 60, p = 0.004, two-sided); slightly tanned white (t = -4.225, df = 60, p < 0.001, two-sided); fair (t = -2.97, df = 60, p = 0.004, two-sided); and interestingly reddish brown (t = -2.588, df = 60, p = 0.012, two-sided).

There were significantly increased ratings of normality reported by male participants when assessing olive (t = 5.67, df = 60, p < 0.001, two-sided) and yellow (t = 11.881, df = 60, p < 0.001, two-sided) donor skin tone simulations. However, interestingly females expressed significantly higher ratings for normality in the light-to-mid brown simulations (t = -23.752, df = 60, p = 0.001, two-sided), along with lesser but still significantly higher ratings in the ivory-beige (t = -2.684, df = 60, p = 0.009, two-sided) and slightly tanned white (t = -3.583, df = 60, p = 0.001) donor group.

Table 4.4. Mean acceptability ratings of hand transplant simulations (skin tone 6 participants, n=62). Participants assessed simulations laid onto a skin tone 6 recipient hand (scale = most acceptable 7, most unacceptable -7). * = Control image; § = Significant gender difference at the $p < 0.05$ level.

Donor skin tone (ST1-11)	Mean acceptability *(SD)*
Fair (ST1)	-4.229 *(2.102)*
Male	-4.681 *(1.624)*
Female	-3.777 *(2.434)*
Slightly tanned white (ST2)	-2.261 *(3.233)* **§**
Male	-3.361 *(2.54)*
Female	-1.161 *(3.507)*
Ivory/beige (ST3)	-2.477 *(3.233)*
Male	-3.1 *(2.876)*
Female	-1.855 *(3.406)*
Olive (ST4)	1.303 *(4.139)* **§**
Male	3.697 *(3.164)*
Female	-1.09 *(3.603)*
Yellow (ST5)	1.208 *(4.501)* **§**
Male	4.881 *(1.546)*
Female	-2.465 *(3.306)*
Light golden brown (ST6)	5.294 *(1.563)* *****
Male	5.552 *(1.516)*
Female	5.035 *(1.591)*
Light-to-mid brown (ST7)	1.273 *(4.670)* **§**
Male	-2.587 *(3.337)*
Female	5.132 *(1.559)*
Mid-brown (ST8)	-4.439 *(1.648)*
Male	-4.426 *(1.75)*
Female	-4.45 *(1.568)*
Reddish brown (ST9)	-4.590 *(2.220)*
Male	-5.113 *(1.523)*
Female	-4.068 *(2.671)*
Brown/black (ST10)	-4.652 *(1.638)*
Male	-4.648 *(1.392)*
Female	-4.655 *(1.876)*
Black/black (ST11)	-5.042 *(1.583)*
Male	-5.3 *(1.33)*
Female	-4.784 *(1.785)*

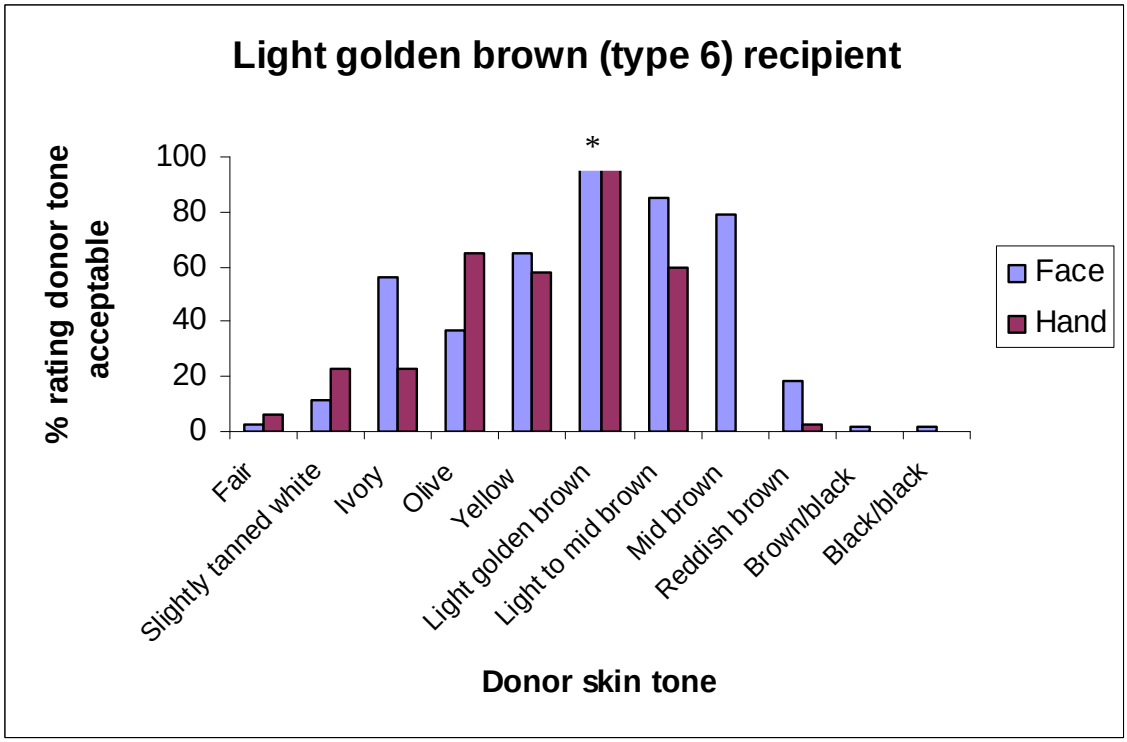


Figure 4.16. Percentage of skin tone 6 (light golden brown) respondents rating donor-recipient skin tonal matches acceptable in hand and face transplant simulations onto a skin tone 6 (light golden brown) recipient. * Control image.

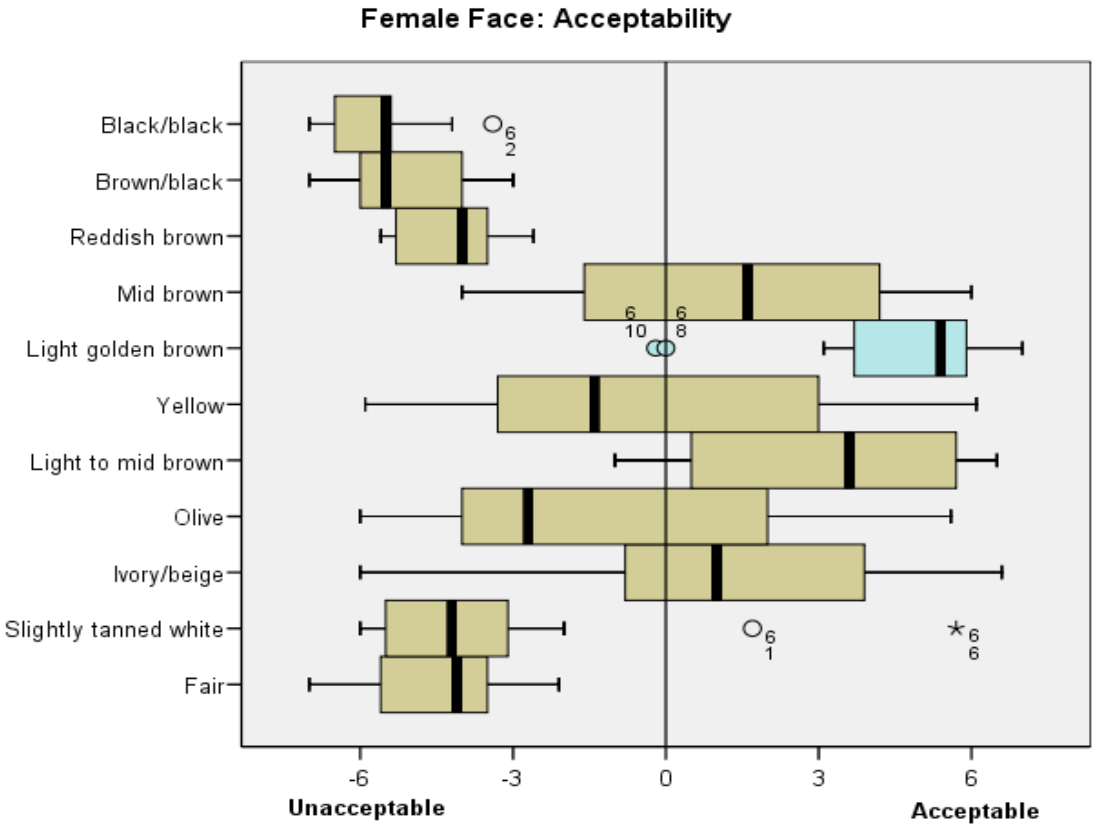


Figure 4.17. Mean, range and standard error of ratings of acceptability of facial transplant simulations, as assessed by skin tone 6 (light golden brown) females. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

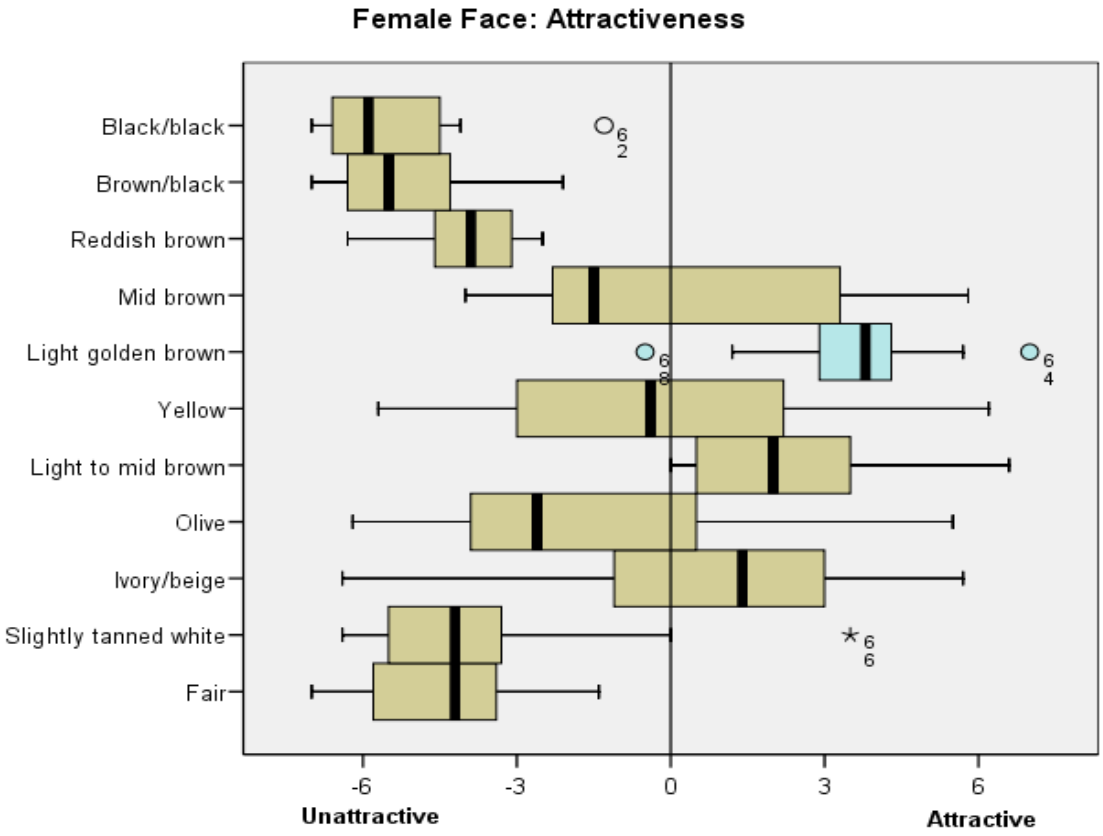


Figure 4.18. Mean, range and standard error of ratings of attractiveness of facial transplant simulations, as assessed by skin tone 6 (light golden brown) females. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

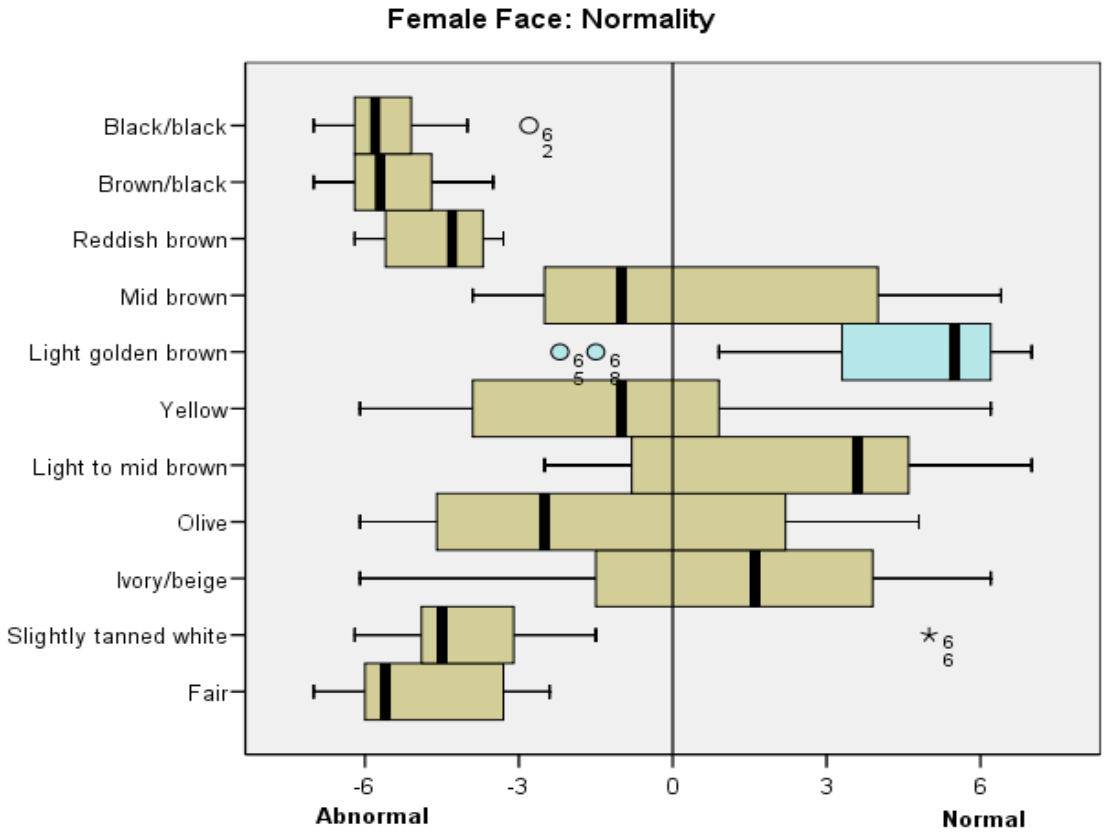


Figure 4.19. Mean, range and standard error of ratings of normality of facial transplant simulations, as assessed by skin tone 6 (light golden brown) females. Simulated donor skin tone is listed on the left. The control image is highlighted in blue; values which lie outside the range are highlighted with a circle or star.

For the skin tone 6 respondents, there were more acceptable groups available for males than for females (males, four groups; females, three groups). In the skin tone 2 group, more acceptable groups were available for males than for females (males, six groups; females, three groups). There was generally more scope in variability of tonal matching in skin tone 2 than skin tone 6 individuals (Table 4.5). Skin tonal mismatches were often more tolerated in facial than in hand transplant simulations, as highlighted in Figures 4.20-4.23.

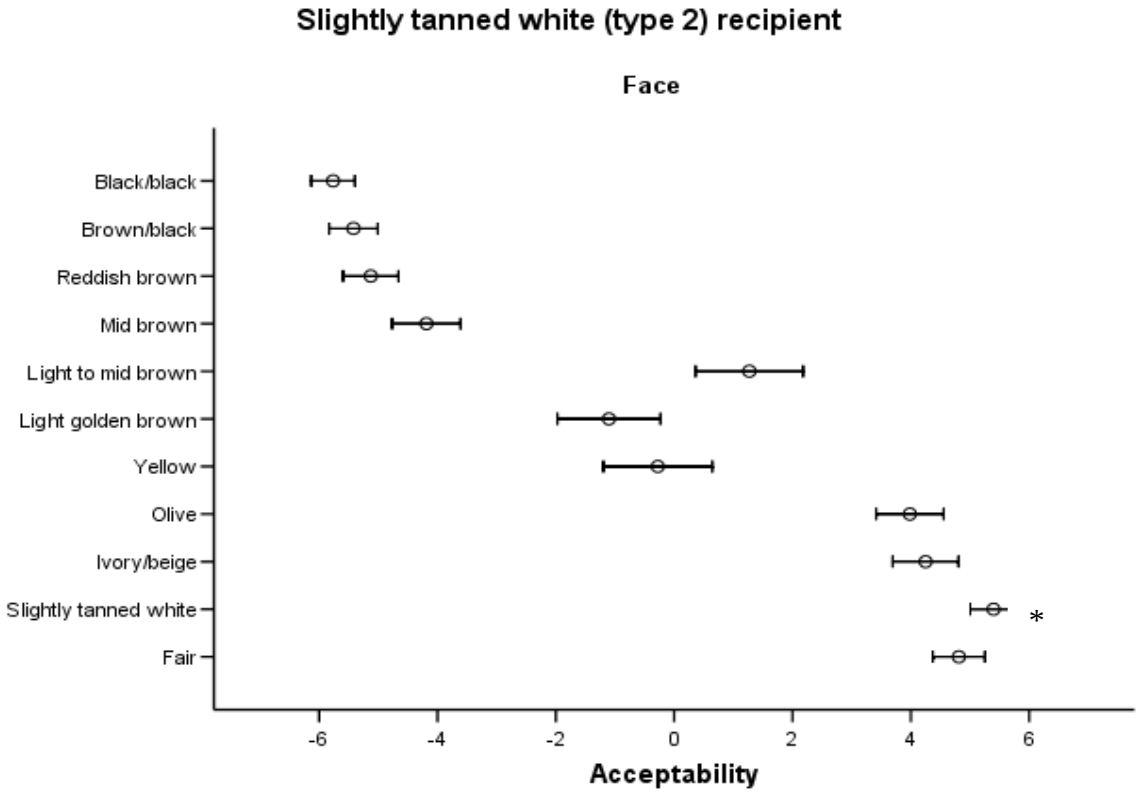


Figure 4.20. More facial transplant skin tonal mismatches are tolerated than hand transplant tonal mismatches. Graph shows acceptability ratings for face transplant simulations in skin tone 2 (slightly tanned white) participants: five groups in total are deemed broadly acceptable. Donor skin tones are listed on the left. Error bars show mean and 95% confidence interval. * Control image.

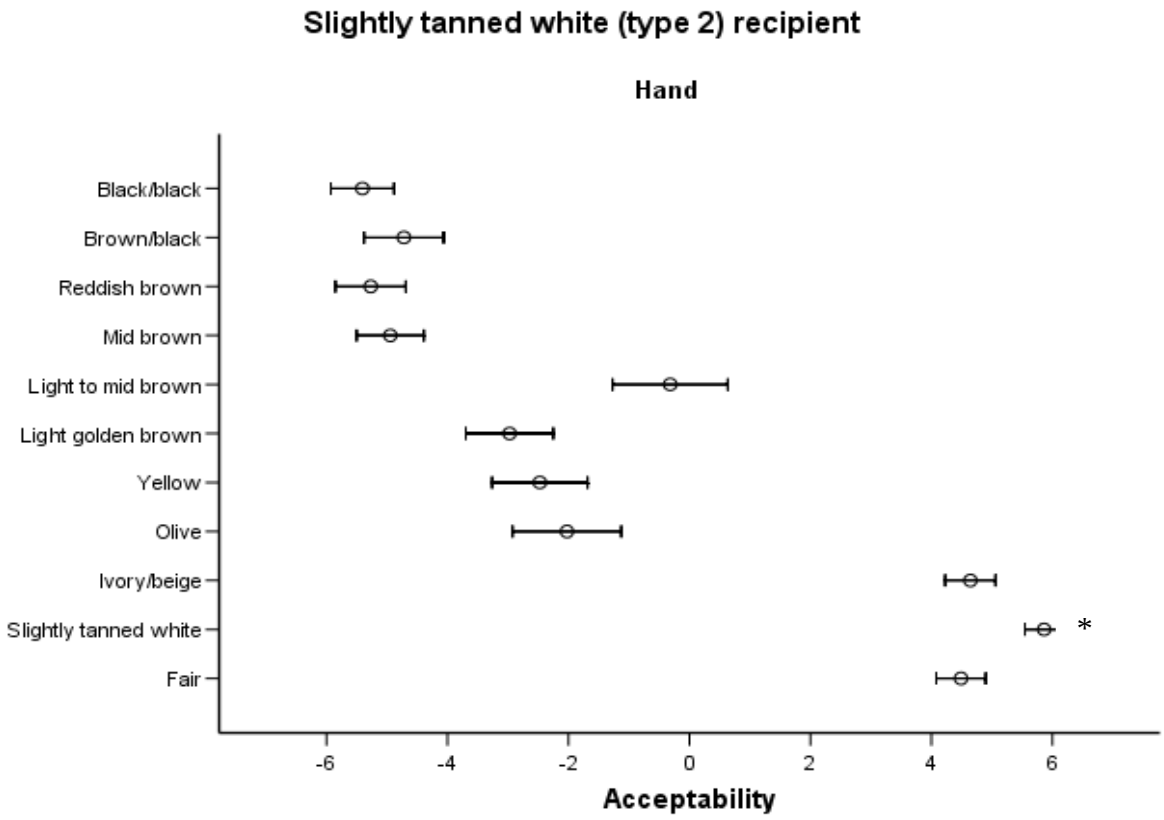


Figure 4.21. More facial transplant skin tonal mismatches are tolerated than hand transplant tonal mismatches. Graph shows acceptability ratings for hand transplant simulations in skin tone 2 (slightly tanned white) participants: three groups are deemed broadly acceptable. Donor skin tones are listed on the left. Error bars show mean and 95% confidence interval. * Control image.

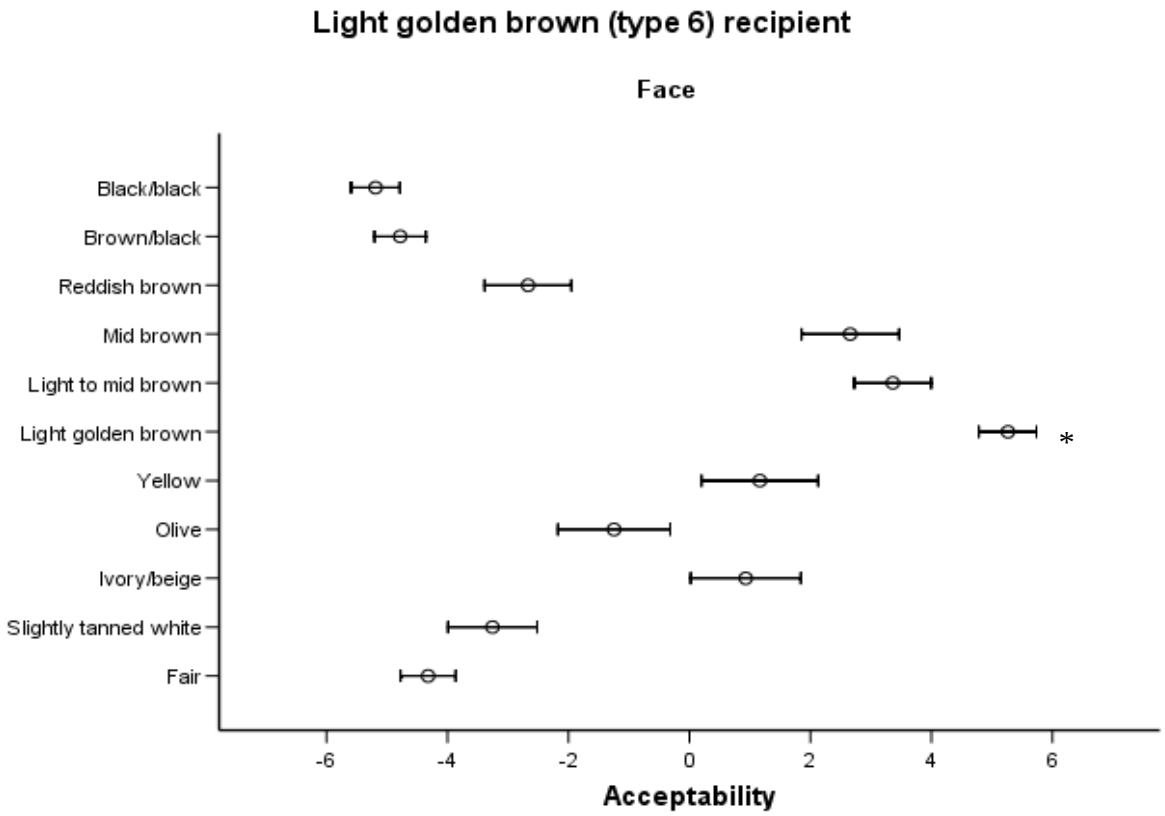


Figure 4.22. More facial transplant skin tonal mismatches are tolerated than hand transplant tonal mismatches. Graph shows acceptability ratings for facial transplant simulations in skin tone 6 (light golden brown) participants: five groups are deemed broadly acceptable. Donor skin tones are listed on the left. Error bars show mean and 95% confidence interval. * Control image.

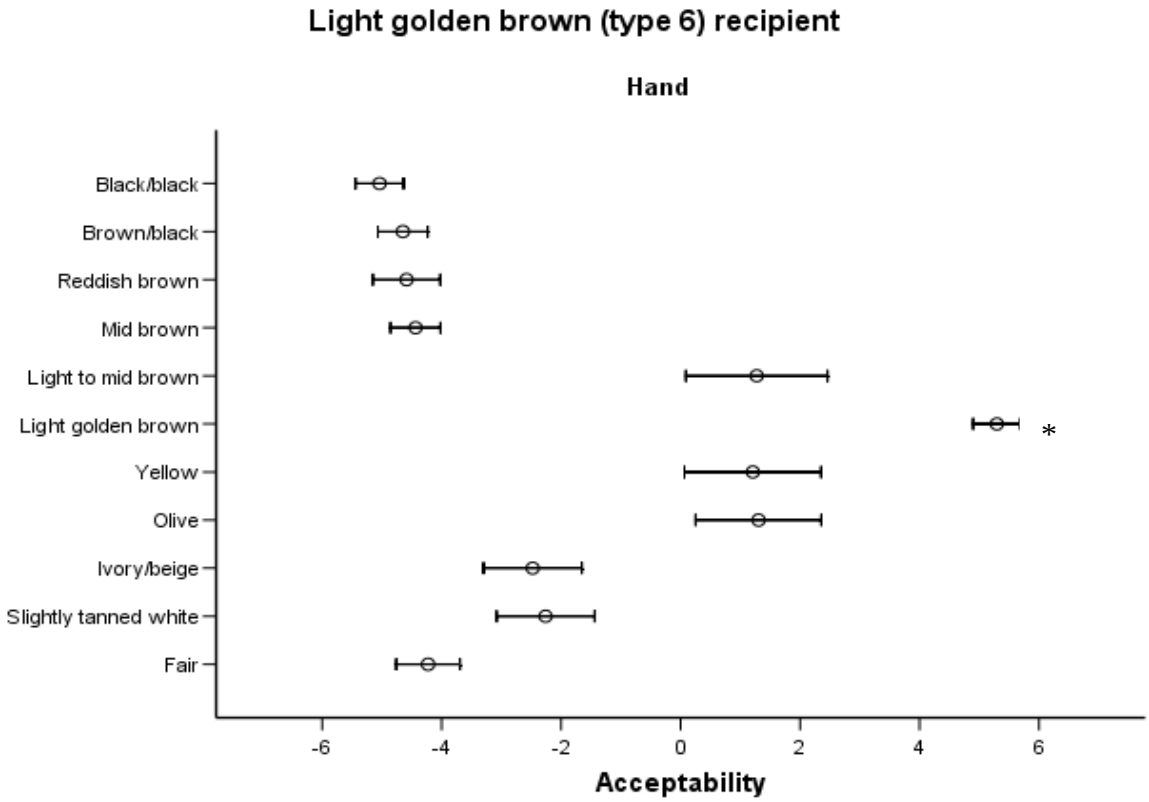


Figure 4.23. More facial transplant skin tonal mismatches are tolerated than hand transplant tonal mismatches. Graph shows acceptability ratings for hand transplant simulations in skin tone 6 (light golden brown) participants: four groups are deemed broadly acceptable. Donor skin tones are listed on the left. Error bars show mean and 95% confidence interval. * Control image.

Table 4.5. Acceptability of facial and hand transplant simulations for participants of slightly tanned white (ST2) and light golden brown (ST6) skin tone. Both viewer and simulated transplant recipient share the same skin tone. * Control image.

	Sample no. *(%)* reporting acceptable donor-recipient match	
Donor skin tone (ST1-11)	*Recipient skin tone (ST1-11)*	
Face	*Slightly tanned white (ST2)*	*Light golden brown (ST6)*
Fair (ST1)	58 *(96.7)*	2 *(3.2)*
Slightly tanned white (ST2)	59 *(98.3)**	7 *(11.3)*
Ivory/beige (ST3)	57 *(95)*	35 *(56.5)*
Olive (ST4)	56 *(93.3)*	23 *(37.1)*
Yellow (ST5)	29 *(48.3)*	22 *(64.5)*
Light golden brown (ST6)	22 *(36.7)*	60 *(96.8)**
Light-to-mid brown (ST7)	39 *(65)*	54 *(85.2)*
Mid-brown (ST8)	3 *(5)*	49 *(79)*
Reddish brown (ST9)	2 *(3.3)*	11 *(17.7)*
Brown/black (ST10)	1 *(1.7)*	1 *(1.6)*
Black/black (ST11)	0 *(0)*	1 *(1.6)*
Hand		
Fair (ST1)	60 *(100)*	4 *(6.5)*
Slightly tanned white (ST2)	60 *(100)**	14 *(22.6)*
Ivory/beige (ST3)	59 *(98.3)*	14 *(22.6)*
Olive (ST4)	14 *(23.3)*	40 *(64.5)*
Yellow (ST5)	12 *(20)*	36 *(58.1)*
Light golden brown (ST6)	10 *(16.7)*	62 *(100)**
Light-to-mid brown (ST7)	28 *(46.7)*	37 *(59.7)*
Mid-brown (ST8)	3 *(5)*	0 *(0)*
Reddish brown (ST9)	3 *(5)*	2 *(3.2)*
Brown/black (ST10)	3 *(5)*	0 *(0)*
Black/black (ST11)	3 *(5)*	0 *(0)*

4.4. Discussion

A number of the findings in this study have practical implications for the facial transplant matching team. First, skin tonal mismatching was tolerated more in the face than in the hand simulated transplants. This could be for a number of reasons. Perhaps individuals feel that they can see their hand themselves, whereas their face is less immediately visible. Results from the facial transplant cohort performed so far would seem to support this, with adaptation seemingly easier to affect in facial graft recipients than in hand transplant recipients (Wysong 2010). Perhaps the quite marked skin tonal difference at the level of the anastomosis in a hand transplant may cause the patient to consider the mismatch more prominent, whilst at the level of the facial anastomosis, there is a natural line where the face meets the neck. It is not unusual for the neck to exhibit different skin tonal characteristics than the face, because of altered ultraviolet light exposure and different structural skin composition. This difference may therefore simply occur because of the site of the anastomosis. This may have clinical repercussions were for example the facial reconstructive surgeon to decide to transplant part of a face, with the line passing through a natural sub-unit. It would be interesting to know if these results would be reproduced in such a case.

Second, there were significant interactions between gender and skin tone on acceptability ($p<0.001$), with males reporting higher mean acceptability ratings than females. More groups were available for matching in males than in females. In skin tone 6 participants, significantly higher acceptability ratings for simulations using skin tone 2 (slightly tanned white) donor were found in females than in males. We therefore suggest that accuracy of skin tonal matching may be even more important in

female transplant candidates. This is supported by work in port wine stain patients, which suggested that females are far more likely than men to use camouflage make-up (Lanigan and Cotterill 1989). Considerably more females than males are dissatisfied with some aspect of their appearance in large scale studies, although appearance is also increasingly important in men (Harris and Carr 2001).

Females exhibit generally lighter pigmentation than males (Jablonski and Chaplin 2000). Some authors have observed that the attraction of human infants and human females is partly due to their lighter pigmentation, that lighter-coloured adult females are perceived as more feminine than are darker females, and therefore are preferred as partners (Frost 1988). Clearly however there exists considerable cultural variability. The skin contains information not just on ethnic origin but also gives an indication of whether a person has been exposed to the sun for a long time, which in some cultures can reflect socio-economic status. The colour of skin has always been a subject of controversy, and still causes discrimination and unfair treatment of (mainly) non-white people, but also of any person whose skin tone is viewed as being markedly different: such as white albinos in Africa where albinism has for centuries been viewed as a stigma (Cruz-Inigo *et al.* 2011).

In this study there was support for the notion that perceptions differ among individuals of differing skin tone. There was more scope available for variability of tonal matching in skin tone 2 (slightly tanned white) than in skin tone 6 (light golden brown) participants. We suggest that this could have occurred for a number of diverse socio-cultural reasons. In the 1960s and 1970s tanning amongst fair individuals was thought of positively in the West, suggesting radiant health, well-

being or wealth – the external sign of being able to afford to travel to sunny destinations. This has encouraged the development of a sun-tanning industry (Randle 1997). Although the 1990s brought the advent of pale-looking models into the cultural milieu, such perceptions do still remain. In contrast, in certain Asian societies - in whose origins sat the majority of the observers assessing the 'light golden brown' simulated facial transplant group - a lighter skin is often thought to indicate a higher social status and sun avoidance is actively pursued. Indeed, in some countries skin bleaching agents containing hydroquinone or steroid preparations are readily available to apply to the skin (Taylor 2002).

All volunteers viewed images of their own gender and skin tone. This was done for two reasons. First, we wished to eliminate perceptions of attractiveness within the opposite sex, which may have biased some of the questionnaire responses. Second, as the primary beneficiary of a composite tissue allotransplant is the recipient, it is the recipient's perception of his own appearance which is of paramount importance. Clearly onlookers' perceptions are significant as well, and the facially disfigured do report experiencing considerable morbidity as a direct consequence. However, it is satisfaction with oneself which ultimately will dictate psychological recovery following surgery to correct facial disfigurement. Participants thus viewed images of their own skin type and gender to assess self perception, specifically because facial transplantation is not primarily proposed to address external 'societal' perceptions. The concepts of proximity to the 'norm' or 'average', coupled with one's perceived physical attractiveness and social acceptability were all chosen as important indicators of satisfaction in one's own body image. Subjective self-assessment of skin tone *per se* clearly differs somewhat among individuals however. In one study of Caucasians,

36.4% overestimated their own skin pigmentation level, with 16.4% underestimating it (Harrison and Buttner 1999). We therefore decided to have only those participants correctly identifying their own skin tone participating in the study.

Two recipient skin tones ('slightly tanned white' and light golden brown') were chosen. This was done in order to provide two of the most likely facial transplant recipient groups which a facial transplant team working in the UK might be expected to encounter (UK Census 2001). All the recipient and donor groups were age-matched in order to prevent the introduction of age-related bias into the observers' ratings.

We chose to use RAW and TIFF files because analysis of other photographic formats such as JPEG formats can lead to compression of colour. This is particularly prominent in burn scars for example where large colour gradients exist. We felt that similar gradients existed in the simulated facial transplant images. The choice of digital photographic imagery was done in order to affect as close to a real transplant simulation as possible. Clearly a real facial transplant recipient may have potentially unusual facial bony architecture compared with the donor, and likely prominent scarring, all of which might act to detract from a skin tonal mismatch. Participants looking at real facial transplant recipients may accept tonal mismatch if this is accompanied by an overall improvement in appearance and facial morphology. Nevertheless this study is important because it highlights a theoretical basis for the matching of potential facial and hand transplant skin tone in commonly encountered skin types found in the UK.

Chapter 5

5. Analysis of Attitudes towards Facial Transplantation

5A. The Transplant Professional's Perspective

5.1. Introduction

Facial reconstruction presents a serious challenge, with current treatment options limited in terms of satisfactory function and cosmesis. Facial transplantation is now emerging as a realistic option for the reconstruction of severe facial disfigurement (Clarke and Butler 2005), with a number of facial transplants now performed worldwide (Devauchelle *et al.* 2006). As with any new procedure, the identification of potential surgical and psychological risk is an important part of the development process and the ethical aspects of this radical reconstructive approach have stimulated a polarised debate (Butler *et al.* 2004; Rumsey 2004; Wiggins *et al.* 2004).

With human facial transplantation no longer an unknown, many of the risks about facial transplantation can be now be quantified, although the longer term outcomes will clearly be important in positioning this procedure as part of the reconstructive options for severe facial injury (Butler *et al.* 2005). The UK facial transplantation team have taken a pragmatic approach to the ethical aspects of facial transplantation, designing a systematic research strategy which encompasses the areas identified as priorities in the Royal College of Surgeons' Working Party Report (Morris *et al.* 2004). We have expanded this framework to include issues identified by the general

public, relevant health professional groups such as transplant coordinators and potential donor families.

Engagement with the general population has produced important information about public attitudes and beliefs towards the procedure. Notions exist of how acceptable the donation of facial material might be. This has allowed us to challenge the suggestion that no-one would be prepared to donate the face of a loved one (Clarke *et al.* 2006). The general public also worry about the potential for identity transfer (Clarke *et al.* 2006). Even in its simplest form (i.e. the use of soft tissue resurfacing) the use of a cadaveric face may result not only in an alteration in the recipient's appearance, but in the acquisition of some superficial facial characteristics of the donor (e.g. eyebrows). This question has been addressed by authors modelling likely identity transfer, using laser scanned images and exchange of their own faces (Clarke and Butler 2005). These studies suggested the creation of a new or third face, rather than the transfer of recognisable features.

The need for lifelong immunosuppression has also been highlighted as a barrier to facial transplantation (Morris *et al.* 2004). Immunosuppressive risks include the predisposition to infection and cancer. However, suggestion that skin might be more allogenic than other tissues has not been supported in the cohort of patients undergoing successful hand and abdominal wall transplantations (Brenner *et al.* 2002; Renshaw *et al.* 2006). Thus the level of immunosuppressive risk for facial transplantation patients is no greater than that accepted by patients undergoing renal transplantation, which is undertaken for similar gains in quality of life. Butler *et al* (Butler *et al.* 2005) have suggested that it is increasingly difficult to justify one

procedure and not another where the risks are essentially the same. Furthermore, Brill and colleagues have suggested that most risks are both predictable and manageable and that this includes psychological risks (Brill *et al.* 2006).

Potential patient groups, potential donor families and relevant health professionals have also been sampled using both qualitative and quantitative methodologies. The latter two groups are of interest due to their focus on the donor family. This may lead to a different set of attitudes and concerns compared with those relating to the recipient. Transplant coordinators and related health professions have unique experience of the practical procedures of transplantation and donor issues. They will be involved in recruitment of facial donors if the procedure becomes a clinical reality. We therefore undertook a review of UK health professionals' attitudes and beliefs about facial transplantation. This group was sampled to provide information about the practical issues concerned with organ retrieval, their concerns for donor families and the perceived impact on the transplant programme as a whole.

5.2. Methods and Materials

5.2.1. Design

A mixed qualitative and quantitative study design was used. A focus group was used to identify the issues highlighted by transplant coordinators. The main themes were then developed into a questionnaire which was administered to a study group attending training days (Appendix D). The study complied with all the ethical requirements for research within a National Health Service institution, and was granted ethical approval by the local research ethics committee.

5.2.2. Sample

The focus group comprised five transplant coordinators who were current members of the North Thames Regional Donor Transplant Coordinators Team. The focus group was surveyed before the reporting of the first partial facial transplantation in France, although all members of the group had read about the procedure as a hypothetical development in professional journals.

The groups sampled by questionnaire comprised 170 health professionals attending separate study days, in Oxford, Cambridge and Bristol in late 2005 – before the first partial facial transplantation but after the procedure had been discussed hypothetically in professional journals.

Nurses (including theatre staff) comprised eighty percent of the sample; 18% were transplant co-coordinators. Fifteen percent had been in post for up to one year, 42% between one and three years, and 43% three years or more. The groups were sampled after a lecture delivered by the consultant surgeon leading the UK facial transplant programme.

5.2.3. Procedure

Each focus group was told that we were interested in their attitudes to facial transplantation, and that we were keen to elucidate any problems they anticipated with respect to their own work. The following one-hour discussion was recorded verbatim. The resulting transcript was assessed and all issues grouped under three main themes: those related to organ retrieval, those affecting the transplant team, and those

impacting on the donor family. A questionnaire was generated to elicit the attitudes of the larger group to these items.

The questionnaire study was completed after an educational session which included video, written and pictorial information about the reconstructive challenges of facial injury including case examples, and technical explanation of the surgical procedures involved in free tissue transfer. Examples were given of 'exchanged' faces between two of the research team members, generated by computer modelling from photographic and laser scanned images (Figure 5.1) (Clarke and Butler 2005).

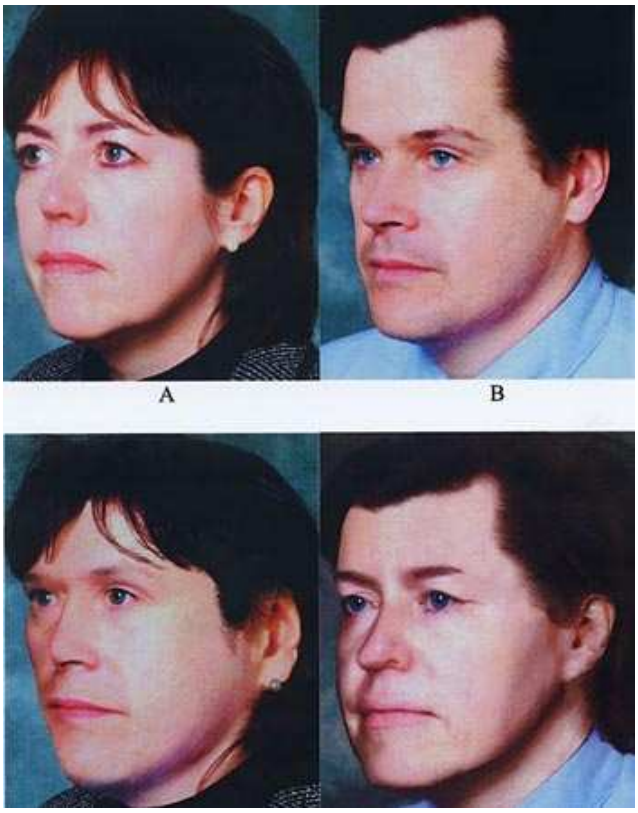


Figure 5.1. Morphing of face B donor onto face A recipient (left); morphing of face A donor onto face B recipient (right). Courtesy of Mr David Bishop, Medical Illustration Department, Royal Free Hospital, London.

Barriers to facial transplantation were also presented to provide a balanced presentation. These included the problems of early graft rejection and the problems of immunosuppression, illustrated by the first hand transplantation in which failure to comply with medication contributed to graft rejection. Suggested figures of acute and chronic rejection as outlined in the Royal College of Surgeons report were made explicit. The aim of the exercise was to present the current issues in face transplantation - including both the advantages and disadvantages of the procedure - in an accessible format. Participants were then asked for consent to complete an anonymised questionnaire. A subset of participants (n=81, those attending the second set of two study days) were asked to rank the importance of the issues identified by the focus group.

5.3. Results

5.3.1. Quantitative Data

A total of 170 people completed the questionnaire; of these participants, 129 (76%) were in favour of facial transplantation now and 39 (23%) felt that further research was needed before the procedure took place. No participant was against facial transplantation in principle. There was no impact of role or length of time in post on this decision.

Sixty-three respondents (36%) reported knowing someone with a facial disfigurement. There was a statistically significant association between being in favour of face transplantation and knowing someone with a facial disfigurement or dysfunction (χ^2_2=8.28, p=0.016).

The Friedman test was conducted for each grouping of items to identify whether the issues had been systematically ranked rather than randomly ordered. Post-hoc pair wise comparisons using the Friedman test and Sign test were used to identify homogeneous subsets of ranked items. Table 5.1 shows the rank order assigned by the questionnaire respondents to the organ retrieval issues (most important issue ranked first and least important ranked last).

Those items ranking highest related to impact on the donor family, in particular appearance after retrieval, whereas factors impacting on the organization as a whole were ranked lower. Application of the Friedman test for the issues in Table 5.1 shows that there is consistency in rank ordering over a random assignment (Friedman χ^2_6=95.7, p<0.001). A post-hoc analysis of the ranks using a pair-wise application of the Sign test indicates that the top 2 items in Table 5.1 (appearance after retrieval and development of donor criteria) form a homogeneous subset (p=0.541), as do development of facial prosthesis and liaison with other retrieval teams (p=0.0151). The final three items (increasing overall time of organ retrieval, amount of tissue retrieved, and delay to operating room time in host hospital) also form a homogeneous subset (p=0.410).

Table 5.2 summarizes the percentage of respondents classifying appearance after retrieval to be more important than the other comparator issues and additionally gives the percentage of times that appearance after retrieval was judged to be equally important. Table 5.3 summarizes the percentage of respondents classifying development of donor criteria to be more important than the other comparator

retrieval issues. The data in Tables 5.2 and 5.3 demonstrate that the top 2 ranked items are consistently identified as most important by the majority of the questionnaire respondents.

Table 5.1. Rank order of organ retrieval issues.

Organ retrieval issues	Mean ranking
Appearance after retrieval	2.62
Development of donor criteria	2.98
Development of facial prosthesis	3.81
Liaison with other retrieval teams	4.18
Increasing overall time of organ retrieval	4.68
Amount of tissue retrieved	4.77
Delay to theatre time in host hospital	4.97

Table 5.2. Percentage of respondents ranking appearance after retrieval to be more important.

Organ retrieval issue	% more important	% of tied rankings
Development of donor criteria	44	17
Development of facial prosthesis	57	33
Liaison with retrieval teams	64	17
Increasing overall time of organ retrieval	75	7
Amount of tissue retrieved	72	14
Delay to theatre time in host hospital	77	9

Table 5.3. Percentage of respondents ranking development of donor criteria to be more important.

Organ retrieval issues	% more important	% of tied rankings
Appearance after retrieval	39	17
Development of facial prosthesis	51	19
Liaison with retrieval teams	71	25
Increasing overall time of organ retrieval	65	14
Amount of tissue retrieved	70	14
Delay to theatre time in host hospital	73	7

Table 5.4 illustrates the rank order assigned by questionnaire respondents (n=81) to the issues affecting the retrieval team. The items ranked of highest importance were those specifically relating to education, team building, and development of links between teams. Negative impact on other transplant programs was ranked lower than team support issues.

Application of the Friedman test for the issues in Table 5.2 shows that there is consistency in rank ordering over a random assignment (Friedman χ^2_6=109.5, $p<0.001$). A significantly higher percentage of respondents (50%) regarded educating professionals about facial transplantation to be more important than development of a specific retrieval team (Sign test, z=2.85, p=0.004, two-sided), with 29% giving tied rankings to these 2 items. Likewise, a significantly higher proportion of respondents (49%) regarded development of specific retrieval team to be of greater importance than development of working links between coordinators and the main facial transplant team (Sign test, z=2.08, p=0.037, two-sided) with 24% of the respondents

giving a tied ranking. Fifty-one percent of respondents ranked development of working links between coordinators and the main facial transplant team to be more important than impact of facial transplantation on operating room and intensive care unit (ICU) staff (Sign test, z=2.02, p=0.044, two-sided), with 19% of respondents giving tied rank values. Application of the Friedman test indicates that there is some evidence that impact of facial transplantation on operating room and ICU staff, debrief and support for health professionals, and negative impact on other transplantation programs form a relatively homogeneous group (Friedman χ^2_2=5.55, p=0.062), as do negative impact on other transplant programs and press intrusion (z=1.47, p=0.143, two-sided). However, a significantly higher percentage of respondents (73%) rated impact of facial transplantation on operating room and ICU staff to be more important than press intrusion (Sign test, z=5.46, p<0.001, two-sided), with 13% giving equal ties. Likewise, a significantly higher percentage of respondents (73%) rated debrief and support for health professionals to be more important than press intrusion (Sign test, z=5.54, p<0.001, two-sided), with 12% giving equal rank importance. Table 5.5 shows the rank order assigned by questionnaire respondents (n=81) to the donor family issues identified by the focus group.

Responses indicate concern for support in the long term. However, responses are less dispersed than on the previous scales with many respondents assigning tied ranks. Interestingly, the question of whether the recipient will resemble the donor is ranked low, as is potential press intrusion for the family. Application of the Friedman test indicates that there is structure in the rank positions in excess of a random assignment (Friedman χ^2_6=21.0, p<0.002). The top 4 ranked issues form one homogeneous

subset (Friedman χ^2_3=0.933, p=0.818) and the other 3 issues form another homogeneous subset (Friedman χ^2_2=1.11, p=0.573).

Table 5.4. Rank order of issues affecting retrieval team.

Team issues	Mean ranking
Educating professionals about facial transplantation	2.58
Development of specific retrieval team	3.36
Development of working links between coordinators and the main facial transplant team	3.58
Impact of facial transplantation on operating room and intensive care unit staff	4.0
Debrief and support for health professionals	4.27
Negative impact on other transplant programs	4.56
Press intrusion for health professionals	5.65

Table 5.5. Rank order of issues affecting the donor family.

Donor family issues	Mean ranking
Likelihood of benefit for the recipient	3.57
Long-term support for donor family	3.58
Discussion of the process involved	3.87
Viewing by relatives after retrieval	3.90
Consent issues and consent form	4.05
Will recipient resemble the donor?	4.28
Donor family press intrusion	4.75

5.3.2. Qualitative Data

The questionnaire also contained an open question inviting respondents to suggest any other issues that they believed to be important and which had not been included on the questionnaire. Seventeen participants (20%) responded to this open-ended question, listing the following:

- Need for increased public awareness of the reasons for facial transplantation (two respondents).
- Plans in the event of graft failure (four respondents)
- Plans in the event of poor psychological adjustment to the new face by the recipient (one respondent)
- Suggestion for improved terminology: ‘donation of facial tissue’ rather than ‘face transplantation,’ and ‘retrieval’ rather than ‘harvest’ of tissue (one respondent)
- Should the donor family meet the recipient? (two respondents)

5.4. Discussion

The first important finding in this study is that the substantial majority of transplant professionals support the development of facial transplantation as a reconstructive option, and that none objected to the concept in principal. A minority were in favour of further research before the procedure is offered. Clearly, since the surgical team will rely on the UK transplant co-coordinators to recruit and consent donor families, it is important to establish broad support for this procedure at the outset, and to identify any concerns which need addressing before the procedure is finally approved.

The relationship between knowing someone with a disfigurement and being in favour of facial transplantation is interesting and has been reported previously in a convenience sample assessed at the Royal Society (Clarke *et al.* 2006), the independent academy of science in the United Kingdom. This result suggests that those who are familiar with the problems that the facially disfigured encounter may find it easier to justify a radical new technique. This is supported by responses to the open-ended question in the questionnaire, namely, that more efforts should be made to educate the general public about the reasons why facial transplantation is being proposed.

However, it is important to note that user groups might interpret this finding in a different way. Rumsey (Rumsey *et al.* 2005) has reported that visible difference (cf. disfigurement) is very readily associated with the need for surgical intervention, even though many people manage an unusual appearance successfully without resort to surgical treatment. Therefore there should be no attempt to justify facial transplantation simply on the basis of the beliefs of observers, as this would overlook the evidence that psychosocial interventions are effective in teaching management skills where the principal problem is one of social interaction. The UK facial transplantation team has stressed the role of these non invasive interventions both in the selection and management processes of facial transplantation, and continue to elicit the input of relevant user groups as part of the continuing public engagement process. We would therefore interpret this relationship as justifying further research into how need is assessed and addressed using a variety of strategies both biomedical and psychosocial.

It is important that we continue to position facial transplantation as a treatment option for severe facial injury and not as an automatic treatment choice for anyone with a facial difference. This also helps people understand that this is not a procedure that has any application in cosmetic treatments.

The questionnaire study supports the focus group findings which suggest that the main concerns of transplant professionals can be divided into the following factors:

- Factors impacting on the donor family, including the appearance of the body after the face has been removed
- Support for the team liaising with the families
- Clear strategies to ensure that the process of retrieval does not disrupt the existing practices of retrieval for other organs

There was thus general support for facial transplantation in principle, provided there is an efficient process with effective support for all involved.

Methodologically, the use of a ranking process was useful despite the number of respondents who assigned equal ranks to all items, thus endorsing all issues as equally important. The clustering of items allows not only a calculation about their relative importance compared with each other, but also further information about how they are categorized by the respondents. For example, the "provision of a facial prosthesis" was originally proposed by the UK facial transplant group as potentially reassuring to the donor family; however, within the focus group, transplant coordinators perceived this to be a means of preserving the dignity of the individual in the operating room

and protection for operating room staff. This finding is supported by the results of the questionnaire in which the "provision of a facial mask" forms a homogeneous subset with "liaison with other retrieval teams" rather than to "appearance after retrieval," which forms a subset with "development of donor criteria."

The importance of education and team building identified by the focus group is supported by questionnaire respondents, as illustrated in Table 5.2. Interestingly, the impact of facial transplantation on the transplant program as a whole, which was an issue flagged by the facial transplant team, is not identified as a primary concern by professionals already working in the transplant setting. It is also clear that press intrusion, again a potential issue with a new procedure, is consistently ranked of lower importance than other factors affecting the team and its links with the facial transplantation team. Finally, responses concerned with factors affecting the donor family are less dispersed than in the previous sections, with a homogeneous subset formed by four items. Of interest is the issue of identity transfer, represented as "will recipient resemble donor?" which is ranked low. This contrasts markedly with early studies by the facial transplantation group in which this item was ranked highest by people most concerned about the concept of facial transplantation. It is likely that the provision of computer-generated images demonstrating the "third face" concept together with the photographs of the first partial facial transplantation have helped to reduce anxiety about this hypothetical problem with the procedure.

Methodologically, the use of a questionnaire study to validate the findings of a focus group has proved useful. The endorsement of items, together with the few respondents who identified issues that were not listed on the questionnaire provides a

justification for the use of focus groups as an appropriate methodology for eliciting the concerns of specific groups in continuing public engagement studies.

We have sampled the concerns of transplant coordinators and other relevant health professionals with regard to facial transplantation. Results demonstrate a substantial majority in favour of the procedure with the needs of the donor family, support for the team, and the development of clear management pathways identified as the main issues of concern. The development of these procedures is now a priority.

5B. The Transplant Donor Family Focus Group

5.5. Introduction

As facial transplantation becomes an option for the reconstruction of severe facial disfigurement, the question of how to maximise potential donation of facial tissue will become more significant. Every individual has their own notion of how best to approach facial graft donation. This may vary from the pre-existing beliefs held by facial transplant teams. Some evidence does exist regarding the opinions of transplant professionals (Clarke *et al.* 2007) and the scientific community (Clarke *et al.* 2006) towards facial transplantation, but the attitudes of donor families toward facial transplant donation have not yet been studied in the literature. For the facial transplant team it is of great interest to assess what opinions regarding facial transplantation exist, whether these might affect the potential for donation, and what modifying factors could alter this potential. Clearly the donor family may have different reference points and priorities than either the recipient family or the transplant team. These attitudes were therefore examined using a specially selected donor focus group.

5.6. Methods and Materials

A research study was designed using a qualitative analysis of themes using a homogenous focus group. Five families with previous experience of donating their relatives' organs were asked in writing to participate in the focus group. All the families had had previous contact with the transplant co-ordinator researcher, lived close to the research facility, and could communicate effectively in English. Families had previously consented to the retrieval of tissues and organs from their loved ones

within the preceding two years. Although all families were willing to participate, only three families were actually able to participate within the time frame available. A total of six participants from these three families attended the focus group. All participants gave informed consent and were free to withdraw at any time. They were fully debriefed about the purpose of the session prior to it commencing.

The group was given instructions that the team was seeking to investigate their attitudes regarding the donation of facial transplant tissue. The researchers took on the role of moderator, commencing the discussion by providing open-ended questions to elucidate the group's opinions on a selection of topics relevant to facial tissue donation. Participants were asked whether it would have been difficult had they been approached to give consent for facial graft retrieval. They were asked to talk about the issues that they thought were important in facial transplantation. Later in the discussion, participants were asked whether they wished to know more information about the risks of the procedure, the likely recipient, and the possible effects on the donor family. This was provided in verbal and audiovisual form by the three members of the facial transplant team: surgeon, psychologist and transplant co-ordinator. Current reconstructive techniques were discussed, along with a short synopsis of the current issues surrounding facial transplant surgery. At all times the researchers attempted to paint a balanced picture of the risks and benefits of facial transplantation.

The transcript from these discussions was analysed and coded into the following themes for the purposes of analysis:

- The timing of body viewing
- Provision of a post-retrieval donor facial prosthesis
- Identity transfer issues associated with facial tissue donation
- The appropriateness of transplant professionals asking families to donate facial tissue
- The need to raise awareness of facial transplantation
- Contact with the donor family after the transplant process
- Information provision to donor families
- The preferred sequence of requesting donation of facial tissue
- Preferred terminology to use in reference to facial tissue donation

5.7. Results

5.7.1. Timing of Body Viewing

Some families needed access to the donor body after death for much longer than others. One participant went in to see her husband three times, and "kept going back into the chapel…" This was done so that her "lasting memory" could be "intact." For another participant this was done to convince her that there were no signs of life. Had she known that facial graft donation was a specific wish of her loved one, this particular participant would not have kept going back to see the body: she stated that she returned on multiple occasions for "purely selfish" reasons.

5.7.2. Provision of Post-Retrieval Donor Facial Prosthesis

Most participants felt that they spent ample time in the intensive care unit, where there was a lot of time to say goodbye. It was felt that the maximally adjusted family is one who says goodbye when the individual is still on life support, rather than when the individual is in the undertakers. The provision of a post-retrieval donor facial prosthesis was therefore not thought to be essential by this focus group, as such a mask did not appear to confer much advantage to the participants. However, it was felt by the group that the provision of a donor prosthesis was "better than nothing."

5.7.3. Identity Transfer

Families needed reassurance in this regard, although they were generally much less concerned once they had seen the computer simulations of the likely appearance of a facial transplant. However there was some variation, with some families much more concerned than others. One participant was "not sure" of their loved one's "face on someone else." One participant commented that the resultant recipient face would not look like the donor, as the dead donor never looked like the recipient. Another participant suggested that "everyone has a double of themselves," and that there are many people in the world who look very similar to each other. The group was however concerned that the donor and recipient should be sufficiently age-matched.

5.7.4. Asking for Consent to Donate Facial Tissue

Participants thought that it was important that the unit proposing facial transplantation were perceived as a specialist unit within the field. Overall there was a strong message that it was acceptable for transplant professionals to ask families whether or not they would agree to donation of facial tissue. The worries about offending people

or worrying them were not supported and there was a strong presumption in favour of asking for facial tissue. Indeed, one participant herself suggested to the hospital that her husband's organs might be donated. Another participant remembered saying at the time that it was "okay to ask the question" when she was asked to consent to retrieval of her loved one's organs. It was however felt by participants that the whole family should be asked, even if some members might be "so traumatised." There should be "family agreement" and families would not want to proceed if there were no consensus.

One participant was at first reluctant to donate her daughter's organs, but then reconsidered and decided that her daughter would have approved of the idea. Families felt that transplant donation was a method of dealing with their loss "in a positive way" at a time "when people are sympathising." Therefore donation was thus seen to be a good way of trying to deal with their loss. It was felt that the whole process would be made easier by including face and hand transplant donation as one of the options on the national donor card. In this way, some responsibility could be taken away from the family. The focus group concluded that transplant professionals "don't have the right not to ask" for donation of facial tissue, and felt that the opportunity to donate organs is a privilege.

5.7.5. Raising Awareness of Facial Transplantation

The families in the focus group were very pro-transplantation. It was a "waste not to do it." Some participants said that they might themselves donate: "it wouldn't matter to me if my face were taken away." The families were very keen on anything that could be done to raise awareness. It was considered that there was not enough

material available regarding transplant donation. One participant felt that "people need to know how much easier this makes the aftermath of a tragedy." Transplant donation acted to bring a kind of positive element to their loss, helping to take attention away from the fact that the individual had died. One participant suggested producing posters with an image of a donor surrounded by scattered images of transplant recipients who had been "helped…to a new life." In this way transplant donation could be seen more of a celebration of their loved one's life. This could be one place where the media could be used in a positive fashion.

5.7.6. Contact Post-Transplant

The sending of letters to the donor family on the anniversary of the donation was discussed. People supported the idea of contact with the facial transplantation team but only after "a considerable time." Meeting the recipient was discussed as an option, but only after a long time frame, when they felt stronger. It was suggested that five years may be an appropriate period of time to wait before meeting the facial transplant recipient.

It was very much felt that "remembering is important." The families "used to be uneasy" about contact – "now there is much more benefit." It was felt that the process needed to be "more about how families feel later on. The real pleasure comes years on….that people genuinely get better lives." Families did feel sorry that friends did not receive contact from the transplant group post-donation, and that consequently their friends did not benefit from this to help them grieve.

It was noted that participants only wanted to hear good news regarding the transplant recipient. They would not want to hear if the recipient had died, nor would they would not want "surprises." However, participants would want to know first about events surrounding the facial transplant recipient before reading about them in the press. Concerns were also raised regarding how the transplant team would manage potential press intrusion post-transplantation, and how one might prevent the recipient from "selling their story."

5.7.7. Information Provision

In order to explore the notion that the most ideal families for facial graft donation were the ones most prepared, the option was given to the group to hear a short presentation on issues surrounding facial transplantation. All participants unanimously agreed to see the presentation. The provision of information was perceived as a good idea by the focus group. In fact, the participants wished that more information were available: "It needs to be on the agenda. We would have donated…if [X] had wanted it."

It was felt that the provision of an educational booklet was beneficial, and that this booklet would not be upsetting for families to read. However, the nature of this information provision was deemed important. Specifically, families felt that they would benefit from knowing about the kind of patient that facial transplantation would be offered to: participants "would want to know what [the recipient] looked like." This was regarded as a helpful aid in the decision-making process. One participant considered that the facial disfigurement exhibited by Simon Weston was "not that severe," and that he was well-adjusted and thus would not merit facial

transplantation. Another participant stated that she was more likely to agree to retrieval of her relative's face were the recipient a child, as such a recipient "had their whole life in front of them." Families stated that information should not however be too graphic as to dissuade families from donating.

Families would want to feel that there was a good reason for taking facial tissue. One person within the group had refused consent to brain tissue for research – this request had been shocking to her because it did not seem like a "good reason" for taking her daughter's tissue. She distinguished between this and giving a new face to a child, which she felt would have been more of a valid reason to donate.

5.7.8. Sequence of Requesting Facial Tissue Donation

The families favoured the phrase 'facial tissue' rather than 'facial transplant' or 'facial graft'. When asked about the sequence in which transplant professionals should ask about tissue or organ donation, the families favoured placing consent to donation of facial tissue last in the sequence. Some participants were hesitant about the donation of corneas: "…don't let them have my eyes, I still need to see…" This is in keeping with previous work suggesting that refusal of corneal donation be set as the cut-off point to facial tissue donation (Clarke *et al.* 2008).

5.8. Discussion

There is little published work about the attitudes of families intimately involved with transplant donation. Overall, this donor family focus group was positive towards facial transplantation. The group thought that the facial transplant team would in time find a donor. The main obstacles were seen to be lack of information ("not enough

publicity") and issues surrounding identity ("looking like loved ones"). The research findings were surprising in parts (such as the relative lack of added value provided by making a facial prosthesis), but confirmed previous pre-conceived ideas we had towards aspects of the facial donor graft procurement process (such as requesting facial tissue at the end of the consent sequence).

Focus groups have recently become popular ways of performing qualitative psychological research. In transplantation, they have been used in a number of different settings to investigate the reasons behind the relative paucity of organ donors (Peters *et al.* 1996), bone marrow donation rates amongst African Americans (Glasgow and Bello 2007) and donor/recipient attitudes toward living renal transplantation (Pradel *et al.* 2003). Our methods were similar to those used in earlier work (Clarke *et al.* 2007) examining attitudes towards facial transplantation in transplant co-ordinators. The number of participants within the focus group was in keeping with recommendations for accurate transcription of focus group discussions (Willig 2001).

Participants were defined as 'concerned' rather than 'naïve' due to their direct interest in the transplant donation process. The nature of our assessments, performed on families who had already experienced donation first-hand, meant that there was no need to extrapolate data from normal volunteers with no prior experience of organ or tissue donation.

The flexible open-ended nature of qualitative research can call into question the validity of its findings. However, this same flexibility also enables participants to

challenge the researcher's own pre-conceived research questions, and can bring with it additional valuable data which would not ordinarily be obtained with quantitative methodology. Group members are able to respond to each other and develop arguments, providing data which would not otherwise be obtained. In addition, the less artificial nature of the focus group acted to increase the validity over standard semi-structured interview techniques. The ability for people to interact with others who have faced similar life experiences can also be of benefit. This contact with other individuals can assist both participant and researcher.

It might be suggested that the invitation to attend a focus group may in itself lead to stress for the individual, if the session were not planned and timed appropriately. However, all participants were under no pressure to attend the focus group and gave of their time freely; the sessions occurred one-to-two years post-bereavement. In this study, participants were made aware that they were free to challenge the researcher's pre-conceived ideas at any time, or to correct any underlying assumptions that may have been made.

Many of the issues explored were unique and hypothetical, lending themselves well to qualitative methodology: the questions we asked were by definition open and provisional, more concerned with 'how' than 'what.' The relatively small numbers in our data set do mean that caution needs to be exercised when generalising about the donor group as a whole. However, through exploring the experience set of the individuals within this focus group, we have obtained a valuable insight into possible future behavioural events. At least some of our participants' responses were products

of societal influences, and so it could be inferred that 'each individual mode of appropriation of the social….. is potentially generalisable' (Willig 2001).

This is first time a group has examined facial transplantation by utilizing the experience base of families with prior exposure to donation of organs and tissues. This provides us with much valuable data regarding how future facial tissue procurement programmes should be organised. It appears that asking for donation of facial tissue should not be seen as problematic, providing that adequate information is provided to families. Programmes should focus on raising awareness, and continue to maintain contact with donor families after facial tissue donation.

Chapter 6

6. An Artificial Prosthesis to Reconstruct Donor Defects Following Facial Transplantation

6.1. Introduction

Facial transplantation is becoming an option for the reconstruction of facial defects following severe facial injury including burns (Butler *et al.* 2005; Butler *et al.* 2006). The reconstruction of the donor face post-operatively is of some importance, due to recommendations that a donor body be restored to a good aesthetic appearance following organ harvesting (Robertson 2004).

The face is the unique identifier, providing both familial characteristics and information about identity. The inability to recognise a face has been likened to a bereavement reaction. Although family members may want to grieve with the donor body immediately post-harvesting, often this grieving process is performed once the diagnosis of brain death has been established within the confines of the intensive care unit. The reconstruction of donor facial features is therefore likely to be of maximal benefit to the transplant recovery team itself; indeed, the appearance of the donor face after retrieval and the development of a suitable facial prosthesis rank highly in surveys of health professionals involved in transplantation (Clarke *et al*, unpublished data). Despite discussion of altered identity, recent public engagement exercises suggest that identity issues are not likely to significantly reduce access to donor faces (Clarke *et al.* 2006).

A number of surgical options to reconstruct the donor face have been suggested, such as autologous skin grafting. This may add time to the harvesting procedure, and may delay other potential transplant harvest teams. In addition, lifelike and cosmetically-acceptable reconstruction using these methods is difficult. This may be due to post-operative bleeding, numerous stitch lines, and technical difficulty in the application of grafts around areas such as the nose or ears. Indeed, the facial graft may include large soft tissue areas such as the nose, which may be difficult to reconstruct using these methods.

Another option is the production of an artificial facial prosthesis (Nandini and Nair 2003). We describe a method of fabricating an artificial prosthesis made from silicone which provides a very satisfactory match for the reconstruction of the facial transplant donor face. It is easily fabricated within the time frame required for facial graft harvesting, a figure likely to approach four hours according to experimental mock human facial transplantation models (Siemionow *et al.* 2006).

6.2. Materials and Methods

The first stage of the process begins with impression-making. An alginate impression material is applied to the donor face. This sets relatively rapidly: a full impression can be taken within 30 minutes. This may be done in the intensive care unit setting whilst awaiting transfer to theatre.

The second stage involves the transportation of the resultant impression moulage to the laboratory where an exact replica of the donor facial morphology is reproduced by

means of a plaster of Paris cast mould (Figure 6.1). This can be produced within 30 minutes.

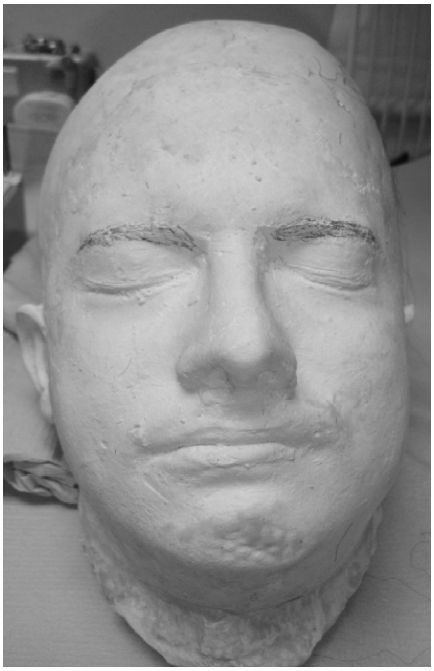


Figure 6.1. A plaster of Paris mould is fabricated from an impression taken of the donor face prior to transplant harvest.

The third stage involves the application of a silicone putty material (Dupiter® silicone putty SP8001/2 and Activator SP8010, Bracon Dental Laboratory Products, Etchingham, UK) over the plaster cast to reproduce the facial plaster of Paris. Once the silicone putty sets, it is removed from the cast and inset into plaster of Paris set within a pre-fabricated steel box (Figure 6.2, right). After setting has taken place, two layers of red soft adhesive dental carding wax (Associated Dental Products Ltd, Parton, UK) are applied. This reproduces the thickness of the skin and subcutaneous tissues required (approximately 5 mm). Plaster of Paris is poured into this wax-coated

moulding box; once filled, a lid is applied to stop the plaster from contracting, and the box left to set for approximately 30 minutes. This produces a second cast, which retains much of the underlying characteristics of the face (Figure 6.2, left).

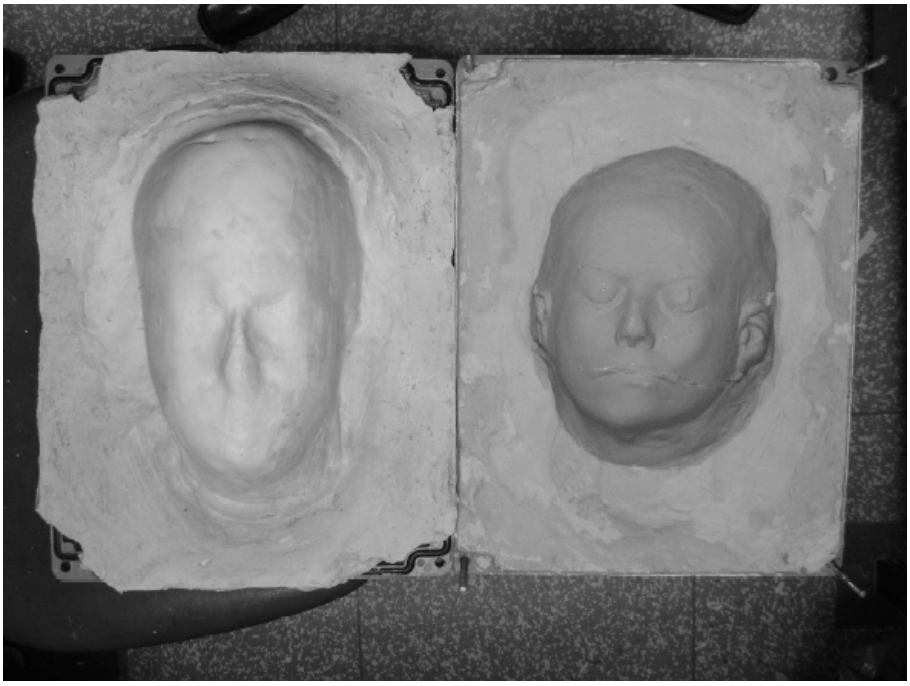


Figure 6.2. Silicone putty is produced of the cast and inset within a pre-fabricated box (right) to which a wax layer is applied. Applying a layer of plaster of Paris over this wax-coated moulding produces a second cast (left) which retains the underlying characteristics of the face.

The final stage involves the mixing of a silicone elastomer (CF3-2186 Part A & B, Polymer System Technology Ltd, High Wycombe, UK) with an appropriate prosthetic colourant to obtain the skin tone required. This silicone elastomer is poured into the moulding box, and the second cast placed on top to create a silicone 'sandwich' which sets in approximately one hour (Figure 6.3). Even in its simplest form (involving soft

tissue resurfacing) a donor facial graft will most likely result in the loss of superficial facial characteristics such as eyebrows. These can be added easily to the prosthesis using artificial hair, or using hair harvested pre-operatively. In addition to this donor-specific method of face transplant donor prosthesis fabrication, we have also produced a panel of generic masks of all facial types and genders. These have been constructed in case unforeseen constraints prevent the immediate fabrication of a donor-specific prosthesis.

Figure 6.3. An artificial silicone prosthesis is created, to which additional facial characteristics may be added.

6.3. Discussion

In order to obtain a satisfactory aesthetic appearance, there must be input from a dedicated bioengineering technician. The benefits of this method however are numerous: it can be performed relatively quickly and cheaply; the prosthesis can be made whilst the surgeon is harvesting the donor face; components such as hair and eyebrows may be incorporated; and the skin tone can be matched as far as possible with the donor. The silicone material is pliable and stretchable and can be trimmed to the required shape of defect. Any underlying bleeding under the prosthesis will not affect it (due to the robust nature of the material) but rather may help in achieving a more life-like result. This contrasts with the often unsightly bruising and haematoma occurring in immediate skin-grafting of the face. Disadvantages include the inherent artificial nature of any facial prosthesis, but this may improve in the future with advances in biomaterials. In addition, the mask needs to be tonally matched to the donor face, although any mismatch can be hidden easily and is thus of minor importance. Nevertheless, the tone chosen for the prosthesis must be lighter in shade in order to take cadaveric pallor into account.

Methods have been described to reconstruct tissues using artificial prostheses (such as those to reconstruct ears or mandibles following neoplasia or trauma) (Nandini and Nair 2003) but the use of artificial prostheses has yet to be described in the reconstruction of the facial transplant donor. We hope the method described above will aid in improving the perceived acceptability of facial transplantation to both transplant teams and potential donors.

Chapter 7

7. Informed Consent for Facial Transplantation

7.1. Introduction

Now that facial transplantation is a reality, attention has been focused on functional, aesthetic and immunological outcomes. However, throughout the process of writing this thesis, the elucidation of a robust informed consent process has been a key goal. Obtaining informed consent is always challenging in new procedures where risk cannot be quantified, as highlighted by The Royal College of Surgeons of England (Morris *et al.* 2004) and others (Agich and Siemionow 2004; Goering 2004; The Lancet 2005). Consent should be a continual process throughout the selection and subsequent planning stages. The purpose of this chapter is to highlight the current issues surrounding informed consent as applicable to face transplantation and to present a strategy for ensuring a robust consent process as the procedure becomes established as part of the reconstructive hierarchy.

Informed consent has traditionally been interpreted as a legal rather than as an ethical obligation of doctors (Gattellari *et al.* 2002). However, there is now greater emphasis on patient choice in the UK (Department of Health 2005) with patients encouraged to ask questions particularly with regard to the risks of the procedure, alternative forms of treatment including the option of no intervention, and clear advice about the likely impact on lifestyle associated with their choice.

The process of informed consent can therefore be seen as a more open exchange of information structured under five main headings: disclosure, decision, understanding, capacity to give consent and voluntarism (del Carmen and Joffe 2005).

7.2. Disclosure

The doctor is obliged to disclose any significant risks to the patient (Pleat *et al.* 2003). The emphasis must be on adequate information, enough to make a reasoned decision about whether or not to proceed. This should involve an exhaustive discussion of all known risks, irrespective of severity and including likelihood and impact, along with discussion of side-effects with potentially severe or fatal consequences.

Finding out how much information patients want to know is clearly important. As a group for example, women with ovarian cancer want as much information as possible at every stage of the disease and prefer to be involved in any decision-making (Tiller *et al.* 2005). Not all patients wish to be informed however. Some try to actively avoid information about their disease, reducing the emotional impact of the disease; this is termed cognitive avoidance. Some commentators warn that providing detailed information to those who do not want it and imposing choice on those who prefer their doctors to assume responsibility for making treatment decisions is harmful and may increase anxiety levels (Tobias and Souhami 1993).

Clinicians frequently underestimate patients' desire for information and discussion and overestimate patients' desire to make decisions (Strull *et al.* 1984). A need for more information does not necessarily equate to a desire to become more involved in decision-making although some evidence supports this (Timmermans *et al.* 2004). A

lack of information giving is associated with heightened levels of anxiety, as is requesting greater patient involvement in decision-making (Gattellari *et al.* 2002).

Integrating all this evidence into a clear strategy for information-giving is therefore difficult. However, for face transplantation, it is proposed that a clear understanding of risk is necessary in order to justify the procedure on ethical grounds. For this reason, only patients who are prepared to engage in a working partnership with clinicians are appropriate for the procedure. This means fill disclosure of information and an active role in decision making. Information should comprise technical details avoiding jargon, screened with a readability formula such as the Flesch-Kincaid (Flesch 1974) or Fry (Fry 1968) formulae. Details of facial anatomy should similarly be appropriate to the individual level of understanding. Information could, in line with government initiatives (Department of Health 2005), include details about the individual clinician or unit, as patients may wish to use this information to base their decisions.

As with any new procedure, disclosure in facial transplantation is limited by the lack of data on outcome. Consent to innovative treatment is an area insufficiently explored in the literature. Conceptually, the component of our understanding of consent which involves the taking of an unknown degree of risk can be separated off from the component which involves the proposed benefits or harms of the procedure. It may be the uncertainty itself which predominates, or the sense of being 'first-to-go,' or the sense of being at the hands of surgeons who are taking a step into the unknown. In most clinical trials, the degree of uncertainty may be relatively small – we may be uncertain how beneficial a new treatment is, or how common or severe the known

side effects are, but the likelihood of entirely novel and unexpected side-effects, or of dramatically overestimating the benefits of the new treatment, is small.

The disclosure of risk in facial transplantation should begin with general risks such as anaesthetic complications, technical problems and graft failure (Morris *et al.* 2004). Specific features of facial transplantation then require special consideration, such as immunological rejection. The Royal College of Surgeons report estimates the risk of graft loss to be around 10% from acute rejection, with chronic rejection accounting for loss of graft function in 30-50% at 2-5 years (Morris *et al.* 2004). These figures are derived from studies of solid-organ transplant recipient populations. A more analogous group would be hand transplantation (Lanzetta *et al.* 2004). Acute rejection episodes occurred in 70% of hand transplants (Banis *et al.* 2004). One graft loss was blamed on ongoing acute rather than chronic rejection, but with pathological features within the skin resembling those of graft-versus-host disease (Kanitakis *et al.* 2003). Acute rejection resulted in one inadvertent intra-arterial steroid injection leading to graft loss, but it is unclear if the graft might have survived had this episode not occurred (Lanzetta *et al.* 2005). Chronic rejection is not a pronounced feature in hand transplantation to date. In addition, comparison of chronic rejection rates to renal transplantation may also not be appropriate, as some long-term renal graft failure is due to drug parenchymal damage and is not immunologically-mediated. Although only speculative at present (as long-term skin and subcutaneous tissue immunological reactivity is not yet known), the expected incidence of chronic rejection may therefore differ significantly between renal and facial transplant groups.

Facial abnormality will rarely lead to death, but graft rejection could do, in serious cases; this has been borne out by the two deaths reported so far post facial transplant. Details must therefore be given of alternative reconstructive options, including those which would be undertaken if the transplant were to be rejected. Special consideration must also be given to altered appearance and its implication, even where there is already experience of extensive disfiguration.

A summary of the information which should be disclosed to face transplant candidates is highlighted in Table 7.1.

7.3. Decision-making

It is important to assess in what way the recipient of a face transplant would arrive at their decision. People have been broadly categorised into three distinct types of decision-maker in health settings: active (where the clinician provides enough information for the patient to make up their own mind), collaborative (where there is a two-way exchange of information), and passive (where the clinician decides which treatment to undertake) (Stiggelbout and Kiebert 1997).

Certain patterns have become apparent when examining decisional preferences in certain patient groups. Approximately 20% of patients choose an active role, with 80% taking a collaborative or passive role (Doherty and Doherty 2005; Mazur and Hickam 1997). Some patients thus prefer to take primary responsibility, the clinician taking no role in the decision making process other than information provision (Tiller *et al.* 2005). A sizeable minority of cancer patients prefer to relinquish decisional control (Gattellari *et al.* 2002). It could be argued that allowing patients greater

control over their medical decisions might actually disempower them. Patients may try to avoid regret and self-blame for the negative consequences resulting from a poor decision.

Married rather than single people (Stiggelbout and Kiebert 1997), older rather than younger people (Mazur and Hickam 1997), men rather than women (Stiggelbout and Kiebert 1997) and those with lower educational attainment (Tiller *et al.* 2005) tend to prefer the doctor to take decisions for them. Patients prefer passive decision making more than do non-patients, suggesting that the 'sick role' (i.e. the act of being a patient per se) may be a significant factor in determining the decisional role taken (Stiggelbout and Kiebert 1997). The sick-role theory supposes that the sick do not hold themselves responsible for normal role behaviour; this may occur because they are in pain, fatigued, on certain medications, or simply 'unwell.' In life-threatening scenarios patients tend to prefer to hand over control to physicians, whereas in cases where morbidity and not mortality are affected they tend to prefer to assume greater control (Doherty and Doherty 2005), although there is some disagreement (Mansell *et al.* 2000).

Table 7.1. Information which should be discussed & understood by the patient

Identity

- The face will adapt to the shape of the underlying bony structure
- There will be some superficial characteristics of the donor
- A 'third' face is likely which will resemble the recipient more than the donor
- The recipient will not take on the identity of the donor postoperatively

Immunosuppression

- The need for immunosuppression will be life-long
- Non-compliance will lead to graft rejection
- There are significant side effects of immunosuppression including cardiovascular, infective, and neoplastic complications
- Regular, thorough monitoring will be necessary for the rest of the patient's life

Rejection

- Rejection may lead to complete graft loss
- Graft loss can occur at any time
- Graft rejection may be treated by altering medication or may require further surgery
- Graft loss may result in an outcome worse than the patient's preoperative condition

Psychosocial issues

- Psychological acceptance of the donor face may take a long time
- Relationships may be challenging, especially in the early stages when family and friends are adjusting to altered appearance
- Psychological challenges are not yet fully understood

Surgical issues

- The risk of technical failure is about 4%
- Peri-operative risks, including mortality, are similar to other free flap surgery

Functional recovery

- Return of facial sensation and function will be variable and difficult to predict
- Time frame for functional recovery is likely to be months/years

Media issues

- Media interest is likely to be high, particularly for the first several patients
- The donor family may become aware of the recipient's identity through the media

Some cultures may indeed prefer to delegate their decision making to family members. In some cultures, the wishes of the elders may override those of a younger member, although this challenges the concept of voluntarism. Other groups often make decisions at a community or family level. Many cultural groups can find negative discussions offensive and some doctors have been supportive of withholding bad news to patients, such as is reported in China (del Carmen and Joffe 2005). Whilst respecting patients own values and beliefs, we would argue that facial transplantation is a situation in which the decision to proceed must be made by the individual themselves. Successful outcome is dependent on post operative behaviour, and in order to comply with strict medical regimen, the individual must make the final decision about consenting to surgery.

7.4. Understanding

A patient can be said to have made an informed choice if they are knowledgeable about the operation, have a positive attitude to the procedure and choose to proceed, or have a negative attitude to the procedure and choose to decline (Clarke and Butler 2004; Marteau *et al.* 2001). Knowledge in itself has not been shown to increase the likelihood of screening; positive attitude on the other hand has a strong association with increased uptake (Michie *et al.* 2005). The patient's own values should be incorporated in the choice made to proceed with surgery; this may indeed be more important than the patient's level of knowledge. Moreover, the patient must appreciate the relevance to their own situation of any information given (Lidz *et al.* 2004).

Increased disease severity has been shown to lessen the retention of information in the consent process (Schaeffer *et al.* 1996). There is evidence that patients undergoing breast reduction have very poor recall of risks and yet are on the whole satisfied with their understanding of the risks involved (Godwin 2000). The literature has yet to reach consensus about what constitutes sufficient understanding and indeed the courts have not tended to agree that failure to understand invalidates consent, preferring to rely on evidence of adequate disclosure (del Carmen and Joffe 2005).

The UK facial transplantation team propose that adequate disclosure is not enough in the case of innovative procedures such as facial transplantation. The Evaluation to Sign Consent Form (DeRenzo *et al.* 1998) has been validated in a variety of populations and can give the surgeon an appreciation of the extent of patients' understanding of a procedure. Additional written or verbal information has been suggested to improve patient understanding, although in femoro-popliteal bypass and carotid surgery this did not improve a patient's perceived and actual understanding of risks and complications (Stanley *et al.* 1998). Use of the cognitive interview technique with independent validation of information retained has been utilised as a means of demonstrating understanding rather than simply disclosure in a service for people with learning difficulties, and this is being developed as a basis for the consent procedure in facial transplantation in the UK (Conboy-Hill 2001). Assessment of pre-transplant compliance can also provide evidence of patient understanding and partnership in care.

7.5. Voluntarism

One of the caveats of informed consent is voluntarism (Macklin 1999). The patient's own wishes should be the only indication for facial transplantation. With every exciting and novel technique, a surgical team is at risk of imparting their own values upon the patient, and through the consent process they might unduly influence the patient's own choice. This would be achieved by either withholding information regarding other options or underplaying the importance of these operative and non-operative alternatives. The ultimate decision about whether or not to go ahead with the procedure must however be left to the patient. There must therefore be non-coercion by the surgical team (Morris *et al.* 2004). Added confounding factors are related to research into new procedures. In providing treatment, a surgeon's primary duty is towards patient care; it might be argued that in evaluating a new surgical procedure, the surgeon must generate valid data and has a commitment to the wider scientific community (Lidz *et al.* 2004). Therefore the caveat of voluntarism must be rigorously pursued in facial transplantation, and can be ensured through the use of patient advocacy.

7.6. Capacity

Patient capacity to consent requires sufficient ability to maintain and communicate stable choices. These choices must be maintained long enough for their implementation (Appelbaum and Grisso 1988). The ability to make one's own decisions is in practice hard to evaluate and we tend to assume that an adult has the capacity unless there is strong conflicting evidence. Guidelines exist examining the ability of patients to evidence a choice and make rational decisions (American

Psychiatric Association 1998); these include the ability to manipulate information rationally and to appreciate the situation and its likely consequences. Certain conditions may preclude this capacity: thought disorder, short-term memory impairment or even extreme ambivalence may lead to a rapid change in the health decision that is made. A patient will require enough memory for words, ideas and sequence of events; intelligence, memory and attention-span may affect this cognitive capacity (Appelbaum and Grisso 1988).

7.7. Attitude to Risk

Attitude to risk is important in making rational choices. This however is difficult to define because an individual's attitude to one type of health risk does not necessarily predict their future behaviour towards a different health risk. A health risk-taker such as a smoker for example is not more likely to undergo life-endangering surgery than a non-smoker, although they may underestimate their own risks from smoking and ignore social conventions which dictate what they do to their health (Weinstein *et al.* 2005). Nevertheless some evidence exists that burns patients (who constitute a considerable proportion of potential face transplant candidates) may have a higher propensity for risk-taking behaviour, as evidenced by increased rates of accidental or violent death in previously burned adults (Onarheim and Vindenes 2005).

There is some evidence showing that people exhibit more risk-taking behaviour when there is a chance of erasing a loss (Thaler and Johnson 1990); framing an event as a gain leads to more risk aversion (Kahneman and Tversky 1982). This is because a loss reduces perceived desirability of a health outcome more than a gain increases it (Edgell *et al.* 2001). It is arguable that in the acute stages of recent injury, patients are

more likely to be focussed on the consequent loss and therefore more likely to accept greater levels of risk involved in reconstructive options. As their post morbid identity develops however, with the gradual evidence that altered appearance does not automatically mean a loss of opportunity or life chances, decisions may be made more in terms of potential gain, with a reluctance to incur unreasonable risks. It can therefore be argued that the stage at which facial transplantation is contemplated, i.e. immediate or delayed, will have an impact on attitude to risk and therefore on informed decision-making.

For the patient a face transplant is a one-off gamble, whereas the surgeon incorporates clinical evidence into their decision-making process. Patients are also more likely than doctors to accept radical treatments even if they have little chance of success. Doctors may feel they have a responsibility for bad outcomes when they have supported a particular treatment regime, especially if this treatment is viewed as more radical. Without accepting risks of radical treatments however, many major advances in medicine could never have been achieved.

Organ transplant recipients perceived risk/benefit ratios of facial transplantation similarly to non-transplanted groups in one preliminary study (Banis *et al.* 2004). Recent evidence suggests that some composite tissue transplant procedures (facial transplants especially) convey benefits which are perceived by individuals (including those living with immunosuppression) to warrant the risks involved (Brouha *et al.* 2006). A number of populations (renal transplant recipients, patients with facial disfigurement, limb amputees and laryngectomy recipients) have been studied using a validated questionnaire-based tool (the Louisville Instrument for Transplantation,

LIFT) to assess attitude to risk (Barker *et al.* 2007b). This was designed to objectively assess the opinions of individuals with real-life experiences in the risks and benefits of transplantation (Soni *et al.* 2010). Specifically the LIFT assesses the amount of risk individuals would be willing to accept to receive non-life-saving, but quality-of-life improving transplants. All patient groups stated that they would risk the most to receive a face transplant.

There is some evidence that the facially disfigured may have different attitudes to immunosuppressive risk (Clarke and Butler 2005), suggesting that familiarity with the concepts and treatment of facial disfigurement impacts on attitude. However, the emphasis on face transplantation as a quality-of-life procedure may inadvertently trivialise the major problems that this group experience in their day-to-day lives. In planning the way ahead we therefore propose a strategy for informed consent in facial transplantation. This is framed under the headings of factors relating to the individual, and factors relating to the process of consent.

7.8. Assessment of the Individual

7.8.1. Cognitive Function

Patients undergoing complex appearance-enhancing surgery must have the ability to retain and comprehend proposed risk/benefit information. In one study of heart transplant candidates 35% were found to have significant cognitive impairment as measured by verbal learning and memory (Putzke *et al.* 1997); lung transplant candidates had essentially normal cognitive function for most tasks but between 25-50% of patients were impaired on verbal and visual memory tasks (Ruchinskas *et al.* 2000). Therefore a face transplant recipient should be of at least average intelligence,

with no evidence of cognitive impairment affecting their decision-making capacity. Although it is not appropriate rule out a patient requiring facial trauma reconstruction because of an accompanying head injury; it must be clear that such injuries do not affect capacity to consent.

7.8.2. Compliance History

The issue of compliance in transplantation has been reported elsewhere (Rosenberger *et al.* 2005). Clearly compliance plays a large role in success of composite tissue grafts, with the first facial transplant graft failing due to his substitution of immunosuppressive medication, and a large group of Chinese hand transplant recipients failing due to non-compliance with medication; whether this was due to patient factors, or general unavailability of immunosuppressants is unclear (Soni *et al.* 2010). Nevertheless, a previous compliance history comprising attendance to clinic, dressing changes, and the taking of prescribed medications gives us documented evidence of the ability to understand, prioritise and execute health behaviours consistently within the patient's own environment.

7.8.3. Cultural Assessment and Attitude to Facial Transplantation

The attitudes of both patient and health professionals towards facial transplantation should be positive and concordant, with clear evidence that motivation for surgery lies within the individual not the family.

7.8.4. Decision-Making Role

Given the large stakes involved in undergoing facial transplantation, we would suggest that the patient should be collaborative rather than active or passive in their

decision-making, which will be evident from their compliance history. The reason for this assertion is that an active decision-maker may be biased in the way they elicit information and therefore may not weigh up fully the risks against the benefits; they may have already made up their mind to have a face transplant prior to full discussion with medical professionals. A passive decision-maker on the other hand may not appreciate the risks of rejection or long-term immunosuppression, and may thus be at risk of coercion; the notion of voluntarism must always be preserved. Decision-making role can be objectively assessed using the compliance history or from the Autonomy Preference Index, a validated set of questions used to establish decision-making role (Doherty and Doherty 2005).

7.8.5. Attitude to Risk

Population studies have assessed attitudes to risk in general. Evidence of high risk-taking behaviour in one area, such as smoking or indulging in illegal activities or high-risk sports for example, does not necessarily predict an individual's attitude to risk in every health decision. Therefore the assessment of attitude to risk is not a particularly helpful construct in face transplantation.

7.8.6. Personality Assessment

Personality disorder is three times more prevalent in populations of cardiothoracic transplant recipients (Stilley *et al.* 2005) and it is postulated that this may predict future non-compliant behaviour. Some hand transplantation literature suggests personality assessment as a screening tool (Carta *et al.* 2001). There is ambivalent evidence however for the value of assessing personality factors, or an emphasis on biological traits, in health settings. It is doubtful if population studies are helpful in

the assessment of individual patients' suitability for face transplant. Although there is a role in assessing psychiatric co-morbidity when obtaining consent, beliefs and behaviours may be more useful in predicting health decisions. Screening programmes need to identify patients who have a negative attitude to the operation or who have an unrealistic optimism about the risks involved (Weinstein 1984).

7.9. Assessment of the Process of Consent

Finally, we feel that the process of obtaining consent should be as important as the content. Therefore an assessment of the efficacy and validity of this process should be made by someone not directly involved with the technical aspects, ideally by an informed health professional such as a psychologist within the face transplant team.

The surgeon performing the procedure should ideally obtain consent, as they are usually the person best placed to answer questions about operative aspects, but this is not exclusive. Indeed it might be argued that the surgeon performing radical new surgery might not be best placed to take consent as they might introduce their own bias.

Screening needs to identify those who have a lack of information or who are using it inappropriately, but it is not enough to be sure that there has been adequate disclosure of information in facial transplantation. There must be both disclosure and confirmation of patient understanding. This can be evaluated as described above.

It is true that in highly innovative procedures such as face transplantation, there is no way of assessing if a patient has made the right decision and will later regret their

autonomous choice, but the psychologist can assess if the decision has been made which is in line with the patient's attitudes. The psychologist should also enquire about the patient's personal goals in having a face transplant. An approach to informed consent that recognises the importance of both perceptual processes and realistic attitude to risk is proposed as a model for informed consent in face transplantation. The assessment framework outlined makes use of the best evidence available in health settings to identify both individual and process factors which must be considered in informing and consenting patients.

Chapter 8

8. Contribution to Knowledge and Suggested Further Work

This work addresses a number of hitherto unanswered questions in the field of facial transplantation. First, we have described a method of assessing facial vasculature in a critical care setting which can be easily performed with relatively minimal training for the transplant team member; training on such selective ultrasound techniques was able to be performed in a matter of 2-3 weeks only. The results obtained correlate well with anatomical studies. We thus feel that this is a rapid and remarkably accurate way of assessing the vasculature at the bedside for operative planning purposes. It would however be interesting to perform these studies on patients in the critical care setting to assess whether these findings can be reproduced on patients with haemodynamic instability. Further study could also include analysis of flow rate, including peak systolic velocity, along with more investigation into reverse flow dynamics of both artery and vein. A number of other parameters could also be measured, such as vessel wall thickness; however this could only practically be done on larger vessels such as facial vein and artery as it is unlikely that meaningful data could be obtained for the transverse facial vessels due to their diameter. It would also be interesting to note if vascular status on the critical care setting affects any of these additional parameters and an extension of this study on a group of twenty or so critical care patients with pre-defined vascular abnormalities could be designed. This could look at both ease of use and comparative data to assess if the technique can indeed be logically extended.

Second, we have produced a skin tonal scale to assist clinicians in accurately assessing facial donor and recipient skin tone using digital imagery. This is important because for the first time an easily accessible method of assessing skin tone is described using widely available and easily accessible digital imagery. This avoids the use of skin phototype nomenclatures used previously, which do not reflect colour tone per se, but rather tanning and burning potential. Instead, the system described attributes discrete tonal values to each of the eleven skin tones described, allowing the clinician more accuracy in attributing skin tone. Again, it would be interesting to examine if the tonal scale is reproducible in the critical care setting. Further photographic assessments could be planned on the intensive care unit, examining the effect of differing ambient lighting levels. There may also be a requirement needed to add allowances to the tonal grading system to account for colour changes associated with altered haemodynamic status in brain-dead patients.

Third, we have ascertained the degree of skin tone matching required between donor and recipient in two of the most commonly encountered skin tones in the UK. This has produced some surprising results; for example, tonal mismatch is more tolerated in facial than in hand transplant simulations. This is significant, as it challenges the notion that a facial graft must (by definition, due to the face's supremacy in attributing attractiveness to an individual) be more matched than an equivalent hand transplant - in tonal appearance at least. That more tonal variation is tolerated by males than females is perhaps not as surprising, but this information does allow the clinician to plan for a more optimised aesthetic end-point. Clearly cultural variations also exist: in the slightly tanned white group, the preference was for a number of darker skin tonal groups; in the light golden brown participants, females preferred

lighter tonal mismatches than darker mismatches. This is perhaps not as remarkable given the literature surrounding cultural differences in attitudes towards skin tonal variation; however, validation of this in a facial transplant setting is extremely important. These findings are significant because they provide facial and hand transplant surgeons with evidence to more rationally assign donor tissue, in a unique field of transplantation where there is relatively less availability of tissue.

It is likely that many of the patterns found in the skin tonal mismatch study will be similar in the other recipient skin types elucidated in the study, especially those that lie within the same spectrum of RGB grade. However, cultural differences dictate that there may be additional factors which facial transplant teams around the world may need to take into consideration, depending on the nature of their native population. This study will thus require repeated validation in each of the nine other skin types in the future; this could be achieved in conjunction with other international teams. It is hoped that we may be able to produce a more total picture of likely acceptable matches in all common facial and hand skin tones.

The development of a system for skin tonal matching using digital photography coupled with suitable professional calibration may allow for the process to be occasioned remotely via telemedicine in the future. It is hoped that a system may be put in place whereby images of potential donors could be sent electronically to a central national or international database, with electronic systems in place to suggest suitable tonal matches. We hope that this study will help clinicians decide where exactly to concentrate their efforts when dealing with aesthetic matching in facial

transplantation, and suggest a more targeted matching of skin tone in composite tissue transplantation in order to optimise this aesthetic end-point.

Fourth, the study of transplant coordinators is important as it provides the facial transplant team with answers to many of the questions posed by both critics and proponents of the procedure. The perceived importance of each component of the process has been examined and, in many cases, challenged. The issue of identity transfer was not a focus of this group, contrary to previous studies (Clarke *et al.* 2006). The impact of facial transplantation on the larger hospital transplant program was not thought to be as important as first thought. This type of population questionnaire study on attitudes toward facial transplantation is of course biased by the fact that presentation of facial transplant information was done prior to the study. It could be argued that only 'interested' parties were taking part, but nevertheless it is an important piece of research given the fact that it is this same group who will be most intimately involved in the facial tissue retrieval process. It is interesting to note that the group examined in this study had a high rate of knowing someone with a facial disfigurement (36%). This is somewhat higher than other population studies on this topic where rates of 14% are quoted (Clarke *et al.* 2006). The reason for this is unclear, as the phrasing of the questions in both studies was the same; perhaps the present study attracted more participants who were acutely aware of facial disfigurement as a concept.

The study on donor family focus groups has revealed a number of important factors which transplant teams should take into account when planning delivery of face transplant services. Importantly, the asking of families to donate their loved ones'

facial tissue is not as much of a challenge as first thought, providing that adequate information is provided and the request is correctly positioned in the context of other organ requests. It might be interesting to repeat the study with more focus groups to ascertain if these observations can be reproduced.

This study has highlighted the rationale why donor face reconstruction is necessarily occasioned in the operating theatre milieu. The prosthetic reconstruction is not done primarily for the donor family, as one might expect: the families surveyed in this study did not report this as a key component of the donation process, as they are not likely to view the body post-harvest. It is the transplant retrieval team who rank donor face prosthesis provision a relatively high priority. The face cannot easily be covered up after facial tissue retrieval as one might suggest, partly because access to the face and neck will likely be required for a number of reasons, such as lymph node retrieval or central venous access.

It is therefore important that we were able to first describe how donor facial prostheses might be produced within a necessarily short time frame on an intensive care setting. The inclusion of a prosthetist on the facial transplant team is of key importance so that a full mask imprint can immediately be made on a potential donor face once one is identified. We first described how fabrication of such a prosthesis can be completed well in advance of the end of the donor graft dissection; global face transplant retrieval teams have since followed similar post-harvest prosthetic facial reconstructions in their case reports (Pomahac *et al.* 2011).

Lastly, the Royal College of Surgeons Working Party Report (Morris *et al.* 2007) highlights fifteen questions which it feels should be answered before facial transplantation can proceed. The fact that five of these centre on the concept of informed consent is significant. Clearly, life-changing surgery with attendant risks of such a wide-reaching nature (from immunosuppressive risk to the risk of media intrusion) necessitates the production of a robust consent process; the formalizing of this process was thus a key goal in the production of this research. Any new procedure can be challenged on the grounds that informed consent is impossible, but this is effectively a barrier to any form of progress. By examining each of the core requirements for informed consent in detail, and reviewing the evidence base, it is possible to propose a standard for facial transplantation which not only meets but extends the current gold standard for consent in new medical procedures. The work contained in this thesis is being used by teams to help frame discussions prior to facial transplantation (Barker 2008). We hope that this will also have relevance to other innovative, novel or potentially high profile medical procedures in the future.

Appendix A

Photographic Imaging Calibration Values

Table A.1. Set up values for calibration of the monitor using the Gretag Macbeth 'Eye-One' monitor calibration system. This involves the initial pre-setting of various computer monitor characteristics to specific standardised values.

Eye-One calibration settings	Selected value
Monitor type	CRT
White Point Colour Temperature (Illuminant Standard D65)	6500°K
Tonal response curve (contrast)	Gamma 2.2
Luminance level	100 / CRT

Table A.2. Before and after adjustment values

Monitor Settings	Pre-set value	Pre-adjustment	Post-adjustment
White Point (°K)	6500	6200	6500
Luminance (cd/m2)	100	97.8	99.9

Appendix B

Randomisation of Simulated Facial and Hand Transplant Images

Table B.1. Simulated facial transplant images.

Image number	Skin tone 2 recipient		Skin tone 6 recipient	
	Donor skin tone (1-11)			
	Female	*Male*	*Female*	*Male*
1	6	10	8	5
2	1	8	6†	2
3	8	2*	7	11
4	5	9	9	10
5	9	4	5	3
6	2*	11	3	9
7	10	1	1	4
8	4	3	10	6†
9	3	6	11	1
10	7	5	2	8
11	11	7	4	7

* = Control image: skin tone 2 donor and recipient

† = Control image: skin tone 6 donor and recipient

Table B.2. Simulated hand transplant images

Image number	Skin tone 2 recipient		Skin tone 6 recipient	
	Donor skin tone (1-11)			
	Female	Male	Female	Male
1	4	8	7	8
2	1	10	2	5
3	10	4	6†	4
4	9	6	9	2
5	8	9	1	7
6	7	1	11	3
7	3	2*	3	11
8	5	5	8	1
9	11	11	4	10
10	2*	7	10	9
11	6	3	5	6†

* = Control image: skin tone 2 donor and recipient

† = Control image: skin tone 6 donor and recipient

Appendix C

Questionnaire for Facial and Hand Transplant Simulation Study

Please tick each box or mark on the line as appropriate.

Q1. Are you:

Male □ **Female** □

Please tick your hair colour:

Red □ **Blonde** □ **Light brown** □ **Brown** □ **Dark brown** □ **Black** □

Please tick your eye colour:

Blue □ **Green** □ **Brown** □

What is your age? ……

What is your ethnic group? ……

What is your nationality? ……

When we graft skin we try to match skin as closely as we can, we don't always obtain a close match. The next few questions are designed to examine this degree of difference.

Q2. A number of the images you will be shown have been altered into a different skin tone. Which **ONE** of the images in **EACH** series is the original?

FACES			**HANDS**		
1.	-	□	1.	-	□
2.	-	□	2.	-	□
3.	-	□	3.	-	□
4.	-	□	4.	-	□
5.	-	□	5.	-	□
6.	-	□	6.	-	□
7.	-	□	7.	-	□
8.	-	□	8.	-	□
9.	-	□	9.	-	□
10.	-	□	10.	-	□
11.	-	□	11.	-	□

Q3. How confident are you about this choice? Please place a **VERTICAL MARK** onto the line below:

FACES

not confident — very confident

HANDS

not confident — very confident

Q4. In the following images of skin grafts of **FACES**, the skin tone may not be a perfect match. Please tell us, by placing a **VERTICAL MARK** onto the line below, to what extent you think the match is:

Image 1

acceptable — unacceptable

---

unattractive — attractive

---

normal — abnormal

Image 2

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 3

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 4

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 5

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 6

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 7

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 8

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 9

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 10

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 11

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Q5. In the following images of skin grafts of **HANDS**, the skin tone may not be a perfect match. Please tell us, by placing a **VERTICAL MARK** onto the line below, to what extent you think the match is:

Image 1

acceptable unacceptable

unattractive attractive

normal abnormal

Image 2

acceptable unacceptable

unattractive attractive

normal abnormal

Image 3

acceptable unacceptable

unattractive attractive

normal abnormal

Image 4

acceptable unacceptable

unattractive attractive

normal abnormal

Image 5

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 6

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 7

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 8

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 9

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 10

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Image 11

acceptable	unacceptable
unattractive	attractive
normal	abnormal

Appendix D

Questionnaire for Transplant Coordinator Study

1. What is your role in transplant coordination? (Please tick appropriate box)

Donor transplant coordinator ☐

Recipient transplant coordinator ☐

Dual transplant coordinator ☐

Donor liaison nurse ☐

Regional transplant coordinators' manager ☐

Other, please specify …….. ☐

2. Please indicate length of time in your current post:

Less than 1 year ☐

Between 1 and 3 years ☐

More than 3 years ☐

3. Do you know anyone with facial disfigurement?

Yes ☐ No ☐

4. Would you feel comfortable discussing face donation with a donor family?

Yes ☐ No ☐

If not, why not? …….

5. Should face transplantation take place?

Now ☐ Not yet ☐ Never ☐

If not yet, why not? ……..

If never, why not? ……..

IN THE FOLLOWING YOU CAN RANK SOME ISSUES THE SAME SCORE

6. Retrieval Issues (Rank in order from 1-7; 1 = most important, 7 = least important)

Development of donor/recipient specific criteria for face transplant ☐

Face transplant increasing overall time of organ retrieval ☐

Delays to theatre lists in host hospital ☐

Liaison between other organs retrieval teams ☐

Amount of tissue retrieved ☐

Appearance of donor after face has been retrieved ☐

Development of a facial prosthesis ☐

7. Retrieval Issues II (Rank in order from 1-7; 1 = most important, 7 = least important)

Developing a specific designated face retrieval team (Surgeons, anaesthetists, scrub nurse, etc.) ☐

Close link of face transplant team with coordinators ☐

Educating professionals about the procedure ☐

Impact of face transplant on theatre and ITU staff ☐

Debriefing and support for healthcare professionals ☐

Exposure of healthcare professionals to press intrusion ☐

Negative impact of face transplant on other transplant programs ☐

8. Donor Issues (Rank in order from 1-7; 1 = most important, 7 = least important)

Consent form and consent form issues	☐
Discussing the process involved in the procedure	☐
Procedure outcome. Likelihood of benefit for the recipient	☐
Whether the recipient will resemble the donor	☐
Viewing by relatives after retrieval	☐
Long term psychological support for the donor family	☐
Exposure of donor family to press intrusion	☐

Of all the issues what do you think is the most important issue?

…….

…….

Are there issues we have not covered? What are they?

……..

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