INVESTIGATING THE ROLE OF THE X-LINKED EFHC2 GENE ON SOCIAL COGNITION IN HEALTHY MALES

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I, Carla Marie Startin, confirm that the work presented within this thesis is my own. Where information has been derived from other sources I confirm that this has been indicated in the thesis.

I recruited all participants, and extracted DNA from all of the cheek swabs. I wrote the scripts for Studies 1, 2, 5 and 6, and designed Studies 3 and 4. I performed all testing of participants, with the exception of two MRI scans which were run by Clare Gibbard. I analysed all of the results within this thesis.

Abstract

Facial emotion recognition and theory of mind abilities are important aspects of social cognition. Genes within the X chromosome may influence these abilities as males show increased vulnerability to impaired social cognition compared to females. An influence of a single nucleotide polymorphism (SNP), rs7055196 (found within the X-linked EFHC2 gene), on facial fear recognition abilities has recently been reported in Turner Syndrome.

This thesis explores the influence of SNP rs7055196 on aspects of social cognition in healthy males. Males possessing the G allele showed poorer facial fear recognition accuracy compared to males possessing the A allele. This group difference in fear recognition accuracy was not due to a difference in gaze fixations made to the eye or mouth regions. Males possessing the G allele also showed smaller N170 amplitudes in response to faces compared to males possessing the A allele. These results suggest males possessing the A allele may use a more holistic / configural face processing mechanism compared to males possessing the G allele, and this difference may account for the difference in fear recognition accuracy between the groups.

Males possessing the G allele were also less accurate at inferring others' mental states during the Reading the Mind in the Eyes task, and showed reduced activity in the right superior temporal gyrus, left inferior parietal lobule and left cingulate gyrus during this task compared to males possessing the A allele. SNP rs7055196 may therefore also influence theory of mind abilities, with males possessing the A allele showing better theory of mind than those possessing the G allele. This result may reflect higher empathising abilities in the males possessing the A allele.

These results suggest an influence of SNP rs7055196 on social cognitive abilities in males. This may help to explain the sex difference in vulnerability to impaired social cognition.

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1 Introduction

1.1 Thesis overview

This thesis will examine the influence of genetic variation within an X-linked gene (specifically a single nucleotide polymorphism (SNP), rs7055196, which is found within the EFHC2 (EF-hand domain containing 2) gene) on social cognition in healthy males. This SNP has previously been associated with fear recognition abilities in women with Turner Syndrome (TS, X-monosomy). As males are also X-monosomic, I have extended this work to investigate an influence of this SNP on different aspects of social cognition in males. Specifically, I investigated an influence of this SNP on facial fear recognition abilities, gaze fixation patterns to facial features, electrophysiological responses to faces, theory of mind abilities and neural activity during a theory of mind task.

Women with TS show poorer social cognition compared to unaffected women. The presence of only one X chromosome in women with TS compared to the two copies found in non-TS women implicates a genetic association between this chromosome and impaired social cognition, suggesting that individuals possessing only one copy of the X chromosome are more vulnerable to impaired social cognition compared to individuals possessing two copies. Males also possess only one copy of the X chromosome, and they are also more vulnerable to impaired social cognition compared to females. Extreme impairments in social cognition are associated with autism spectrum disorders (ASDs), which are more prevalent in males compared to females. This suggests a possible influence of the X chromosome on social cognition in males, and this influence would be greater than its influence in females due to the difference in the number of X chromosomes males and females possess. Any influence of genes on the X chromosome on social cognitive abilities will therefore be greater in males compared to females. Further, traits linked to impaired social cognition found in individuals with an ASD may occur in unaffected individuals within the general population. These traits are more likely to be found in males compared to females, and as any influence of X-linked genes is higher in males compared to females due to females possessing an extra X chromosome, this suggests an influence of genes within the X chromosome on these traits.

Specifically, genes which escape X-inactivation are likely to influence social cognition. Many genes within the X chromosome are inactivated in one copy of this chromosome in females, in order to produce similar expression levels to those in males. However, several genes escape inactivation (including EFHC2). These genes are therefore more highly expressed in individuals possessing two copies of the gene (i.e. healthy women) compared to those possessing one copy (i.e. women with TS and men). This therefore means that those genes

which escape X-inactivation can produce dosage sensitive effects, with a greater influence in individuals possessing only one X chromosome. Influences of genes which escape X-inactivation will therefore be greater in males than females. This may account for the increased vulnerability to impaired social cognition in X-monosomic compared to X-disomic individuals.

Following on from this, it is important to determine specific genetic influences on social cognition within the X chromosome and their influences on social cognitive abilities. SNP rs7055196, which as mentioned above is associated with facial fear recognition abilities in women with TS, is a candidate locus for an influence on social cognition. Influences of this SNP may be revealed by those abilities which are impaired in individuals with an ASD and women with TS.

Within this introduction chapter I will firstly discuss social cognition in neurotypical individuals. Specifically, I will discuss facial emotion recognition abilities, the neural and electrophysiological correlates related to face processing, theory of mind abilities, and neural correlates to theory of mind abilities. This is followed by a discussion of genetic influences on emotion recognition and theory of mind abilities, and I will particularly focus on an influence of the X chromosome. I will then discuss areas of social cognition which are affected in individuals with an ASD and women with TS, as these areas may reveal a possible influence of X-linked genes. I will finally discuss the localisation of SNP rs7055196 and its possible influence on social cognition.

1.2 Social cognition

Social cognition refers to mental processes involved in the encoding, storage and retrieval of social information. This allows us to perceive, understand and empathise with others' behaviours and mental states, giving us the ability to predict how others are feeling, what they are thinking and how they may behave. Understanding others' thoughts is fundamental for normal social interactions and building up communicative skills, and so is important for survival in complex social environments. Social cognition may facilitate survival in many different ways, allowing humans to live and work peacefully in large groups and alerting us about possible dangers in the environment. Our social cognitive abilities comprise a variety of more narrowly defined abilities, including facial emotion recognition and theory of mind abilities. Facial emotion recognition abilities may refer to recognition of basic emotions (specifically happy, sad, fear, anger, surprise and disgust) or recognition of social emotions (including feelings of guilt, embarrassment and amusement) from facial expressions alone. Theory of mind refers to the ability to attribute mental states to yourself and others, including thoughts, intentions, desires and beliefs, and the understanding that others may have different mental states than your own. Although facial emotion recognition abilities may be

considered to be a part of theory of mind abilities, they are typically studied as distinct topics, and so will be referred to separately throughout the introduction and data chapters while links between the two will be made in the general discussion chapter.

1.2.1 The social brain

The existence of the 'social brain', a network of brain regions involved in social cognition, was first proposed by Brothers (1990). Regions within this network include the medial prefrontal cortex, the temporal pole and temporoparietal junction, the anterior cingulate cortex, the inferior frontal gyrus, the superior temporal sulcus, and the amygdala (Figure 1-1) (Frith 2007, Frith and Frith 2007). Interactions between these regions allow us to recognise the mental states of others and predict and understand their behaviour; this is important for theory of mind abilities (discussed in section 1.6). Within the social brain, the medial prefrontal cortex (MPFC) is thought to be important for theory of mind abilities and recognising social emotions (Geraci et al 2010, Shaw et al 2005), with the temporal pole and temporoparietal junction (TPJ) also being important for understanding others' beliefs (Samson et al 2004). A recent meta-analysis has suggested the MPFC and TPJ are particularly important for social cognition, with the TPJ being important for understanding the goals, intentions and beliefs of others, while the MPFC integrates social information over time (Van Overwalle 2009).

The anterior cingulate cortex has been suggested to play a role in social approval, being activated when we view disapproving faces (Burklund et al 2007). The inferior frontal gyrus may aid the cognitive appraisal of other's mental states, allowing us to predict their actions and what actions we should take (Nakamura et al 1999), and this region has further been suggested to contain mirror neurons (Iacoboni 2005). The superior temporal sulcus is important for the perception of facial motion (such as gaze direction, speech related lip movements and facial expressions) (Hoffman and Haxby 2000) and biological motion (Grossman et al 2000a). The amygdala has been suggested to be important for the appraisal of faces, including their facial expression and trustworthiness (Adolphs et al 1998, Fusar-Poli et al 2009a). The superior temporal sulcus and amygdala therefore play important roles in the appraisal of facial stimuli and the recognition of facial expressions. The roles of regions involved in face processing and theory of mind are further discussed in sections 1.4 and 1.6.1 respectively.
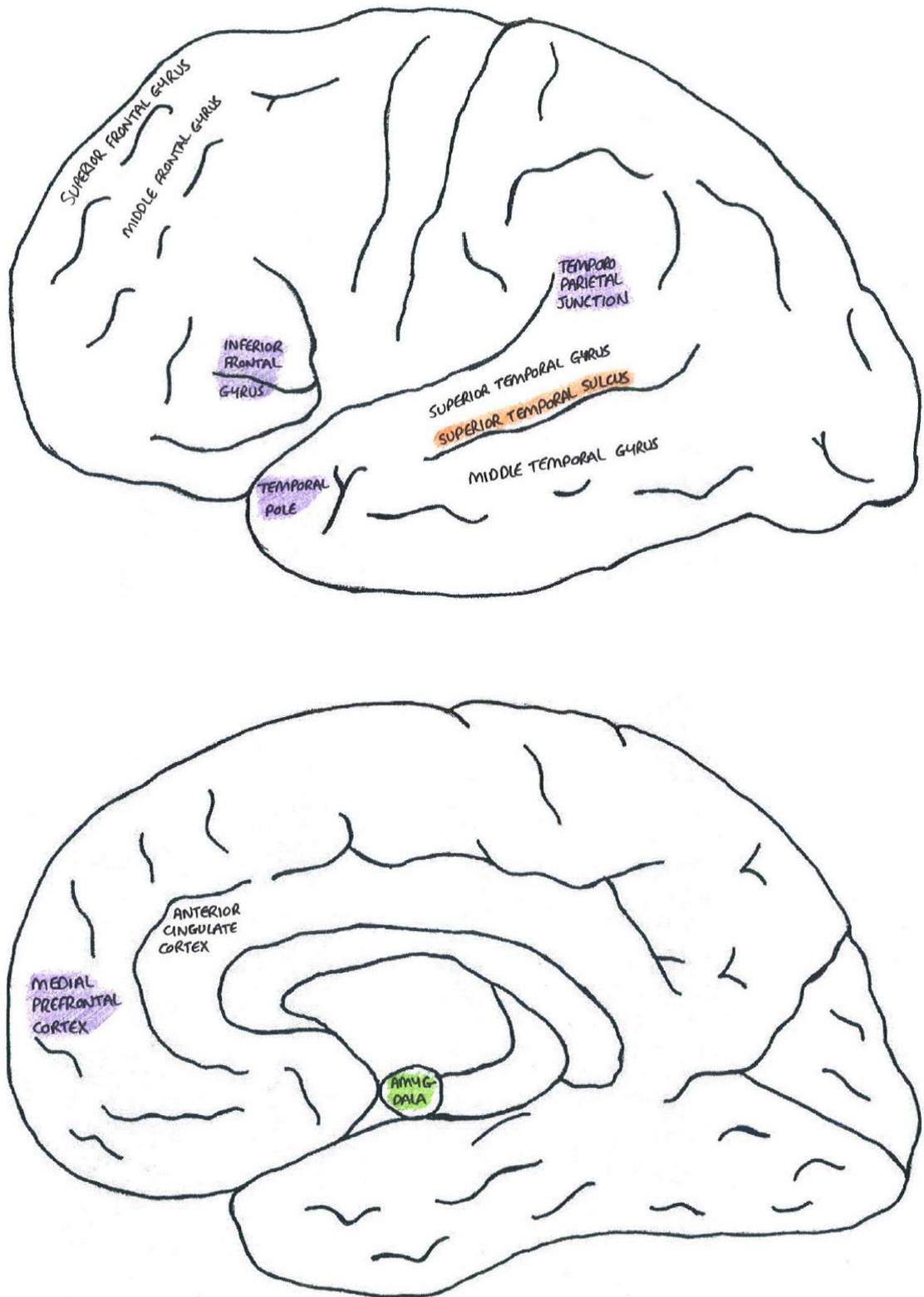
Figure 1-1. Regions of the social brain. Many of these regions are also important for facial emotion recognition (highlighted in green), theory of mind (highlighted in purple), or both facial emotion recognition and theory of mind (highlighted in orange)

1.3 Facial emotion recognition

We are able to recognise how others feel from their facial expressions alone, with these feelings spanning basic emotions and more complex social emotions. To facilitate this, we show a high level of interest in faces, in particular for the eye region. Various theories have been proposed to explain how we process faces, and how we perceive emotions. In the following section I will discuss these issues.

1.3.1 Basic emotions

As previously mentioned, there are generally thought to be six basic emotions: happiness, sadness, fear, anger, surprise and disgust. The recognition and production of these emotions was proposed to be largely innate and similar across cultures by Darwin (1872), and supporting this a recent study has reported no differences in the configuration of expressions between congenitally blind and sighted individuals (Matsumoto and Willingham 2009). Facial expressions for the basic emotions have been suggested to have evolved to accurately portray our internal states to others, and the recognition of fearful and angry expressions in particular is thought to alert us to possible dangers in the surrounding environment. Each emotion is thought to be associated with characteristic facial actions distinct from those of the other emotions, and this low overlap of facial expressions for the six basic emotions has been suggested to have evolved to facilitate their recognition (Schyns et al 2009, Smith et al 2005). These facial actions contribute individually and cumulatively to emotion identification (Kohler et al 2004). Characteristic facial actions produce distinctive facial features, such as the upturned mouth in happy faces, and the saliency of these features has been suggested to enable discrimination decisions (Calvo and Nummenmaa 2011). However, it should be noted that individual differences in the production of facial expressions exist (Fiorentini et al 2012).

Many studies have investigated explicit emotion recognition abilities across the six basic emotions. Happiness is often reported as the most easily recognised emotion, as demonstrated by its accurate and rapid recognition (Calvo and Nummenmaa 2009, Leppanen and Hietanen 2004, Palermo and Coltheart 2004, Rapcsak et al 2000, Williams et al 2009). Although this happy face identification advantage has been suggested to reflect a higher-level asymmetry in the recognition and categorization of positive and negative emotions (Leppanen and Hietanen 2004), a recent study suggested that this advantage instead relies initially on feature processing and later on processing of positive affect as it is observed when happy faces are presented outside our overt visual attention (Calvo et al 2010). In contrast, fear is often found to be the hardest emotion to recognise, and it also has the slowest recognition (Palermo and Coltheart 2004, Rapcsak et al 2000, Williams et al

2009). Rapcsak et al (2000) suggested as fear is the hardest emotion to recognise this helps to explain why brain damage may be associated with impaired fear recognition, but it is not associated with impaired recognition of the other basic emotions.

Fear may be the hardest expression to recognise for several reasons. Firstly, the fearful expressions used in studies may not truly represent fearful faces, as the expressions are usually posed and it may be harder to produce fearful expressions compared to expressions for the other basic emotions. Secondly, fear has been suggested to be expressed more intensely in the left hemiface (Indersmitten and Gur 2003), while we show a bias towards viewing the right hemiface (Guo et al 2012). Expressions in the right hemiface may therefore be better recognised due to the suggested dominance of the right hemisphere in emotion processing (Indersmitten and Gur 2003). Thirdly, fearful expressions are highly similar to surprised expressions; fearful expressions are most likely to be mis-recognised as surprised (Rapcsak et al 2000) and it has been suggested that the facial components important for the recognition of fearful and surprised expressions overlap while components for the other expressions are independent (Huang et al 2009). However, any effect on emotion recognition due to the similarity of fearful and surprised expressions appears to be selective for fear.

In contrast to the pattern of explicit emotion recognition described above, implicit emotion recognition appears to show the opposite pattern, with fear being recognised most accurately and fastest out of the six basic emotions and happiness being recognised least accurately and slowest (Williams et al 2009). Although our conscious recognition of fearful expressions may be poorer compared to that of the other basic emotions, our unconscious brains may still be sensitive to its detection. Supporting this, compared to neutral faces, fearful faces automatically orient our attention (Holmes et al 2005) and we have a tendency to dwell on fearful faces, suggesting they hold our attention (Georgiou et al 2005). Further, infants' attention is captured more by fearful faces than by happy or neutral faces (Peltola et al 2009b). The accurate implicit recognition of fearful expressions is advantageous, helping us to rapidly detect and react to potential dangers in our environment as signalled by others to aid survival, while the accurate explicit recognition of fearful expressions may not offer a survival advantage. This may have resulted in a more specialised development of neural pathways involved in the implicit recognition of fearful expressions compared to those involved in its explicit recognition, resulting in its relatively poor explicit recognition and relatively good implicit recognition. In contrast, being able to accurately recognise happy expressions explicitly promotes positive interactions between individuals while the implicit recognition of happy expressions may not be as advantageous. This may therefore have resulted in a more specialised development of neural pathways involved in the explicit recognition of happy expressions compared to those involved in its implicit recognition, resulting in its relatively good explicit recognition and relatively poor implicit recognition.

1.3.1.1 Rapid detection of fearful and angry faces

Our unconscious rapid recognition of fearful faces may aid our abilities to detect possible dangers in the environment; fearful faces may enhance activity in the primary visual cortex as soon as 90ms after being viewed (Pourtois et al 2004b). In addition, both fearful and angry faces capture our attention more than those displaying other expressions, suggesting an enhanced detection for these expressions (Bannerman et al 2009, Campanella et al 2004, Hodsoll et al 2011, Lundqvist and Ohman 2005, Pourtois et al 2004b). Our enhanced gaze orienting response to fearful faces has been suggested not to be due to low level features, as it does not occur spontaneously when we see the eye region alone, but instead it only occurs after the emotion of the whole face has been appraised (Bayless et al 2011). Our preferential allocation of attention to fearful faces develops early, as 7 month old infants show increased looking times towards fearful compared to happy expressions (Peltola et al 2009a) and longer first fixations to fearful faces compared to happy and neutral faces (Leppanen et al 2007b). This suggests an early functional development of the neural mechanisms involved in processing emotionally significant stimuli, which may occur between 5 and 7 months (Peltola et al 2009a).

1.3.2 Social emotions

In addition to these basic emotions we also use a variety of more complex social emotions to express how we feel or what we are thinking. Examples of social emotions include feeling embarrassed, flirtatious and amused. Social emotions are learnt, unlike basic emotions, and involve interactions with others. In comparison to basic emotions, whose recognition is improved when we are able to view the full face compared to the eyes or mouth alone, for more complex emotions viewing the eyes alone has been suggested to result in similar recognition accuracy as viewing the full face (Baron-Cohen et al 1997).

1.3.3 Humans' innate attraction to faces

Facilitating our ability to recognise facial emotions in complex social scenes is our innate attraction to faces. Humans have been found to produce very fast saccades towards faces (100ms), with these fast saccades occurring automatically and even when participants were instructed to saccade towards non-face objects (Crouzet et al 2010). These involuntary orienting responses are stronger for faces than for other objects, and cannot be accounted for by global low-level visual factors (Morand et al 2010). In particular, we have an interest in the eye region of faces, as confirmed by eye tracking studies, which demonstrate that when we look at face stimuli we direct a large proportion of our gaze fixations to the eyes (Adolphs

et al 2005, Itier et al 2007b), and supported by Schyns et al (2009) who reported we process information about the eyes before any other facial information. This importance of the eye region has been suggested to be due to the role of gaze as a means for signalling (Emery 2000). Our interest in the eyes is likely innate, as neonates preferably direct attention towards open compared to closed eyes (Batki et al 2000) and infants also scan the eye region more than other facial regions (Peltola et al 2009b). Although this attraction towards the eye region was long thought to be due to the saliency of this region, a recent study by Birmingham et al (2009) suggested the eyes have a low saliency and our attraction to them may be due to a default interest in social information, which is often portrayed by the eyes. Supporting this, we concentrate our gaze on the eye region in particular when we are assessing emotional states of others (Buchan et al 2007). However, the eyes are not the only important region for expression recognition, and we also use information from the mouth (Schyns et al 2002). The relative importance of the eyes and mouth has been suggested to depend on the specific expression; an increased number of fixations to the eye region is associated with improved recognition of fearful, angry and sad expressions, whereas an increased number of fixations to the mouth is associated with an improved recognition of happy and disgusted expressions (Sullivan et al 2007).

1.3.3.1 The importance of the eye region in fear recognition

Our interest in the eye region is important for fear recognition, as this region contains the most useful information for the recognition of fearful expressions (Schyns et al 2007) and an increased number of fixations to this region is associated with a better ability to recognise fearful expressions (Sullivan et al 2007) (also see section 1.4.3). The recognition of fearful expressions relies on widened eyes, a feature characteristic of fearful faces (Kohler et al 2004), and this feature may have evolved as widened eyes may enhance perception through producing a larger visual field and allowing faster eye movements during target localisation (Susskind et al 2008). Even when just the eye region is present, our ability to recognise fear is well above chance levels suggesting the eye region alone is sufficient for recognising fear (Leppanen et al 2008).

However, non-eye features of the face are also used to recognise fear, including raised inner eyebrows, a raised upper lip and nostril dilation (Kohler et al 2004). When viewing a full fearful face, fear recognition is more accurate and faster compared to when the eyes alone are shown or when the eyes are covered, suggesting regions other than the eyes are used for fear recognition and the integration of information within the fearful face as a whole facilitates its recognition (Leppanen et al 2008). Further, non-eye regions of fearful faces are also important in attracting our attention, as demonstrated by Peltola et al (2009b) who found that fearful expressions held infants' attention more than neutral faces with fearful eyes.

1.3.4 Emotional face processing: feature based, holistic and configural processing

There are several hypotheses regarding how emotional faces are perceptually processed. Firstly, it has been proposed that feature based processing is used, via a bottom-up mechanism. Using this method we analyse specific facial features (such as the eyes and mouth) for emotion-specific information, and from this make a judgement about the emotion contained within the face. Supporting this hypothesis it has been suggested that single facial features may be assessed separately and they are sufficient for emotion recognition, either when presented in a configurally ambiguous face (Fiorentini and Viviani 2009) or when presented alone (Leppanen et al 2008).

Secondly, it has been proposed that emotional faces are processed holistically (Gestalt processing), with the face being processed as a whole using a top-down mechanism. Our perceptual expertise with faces has been suggested to allow us to use a holistic approach to face processing rather than a feature-based method (Curby and Gauthier 2010), and processing faces holistically may aid a rapid detection of faces in everyday life as holistic processing occurs at an earlier stage than individual discrimination (Taubert et al 2011). Supporting the holistic processing hypothesis, we are less accurate and slower at emotion recognition when faces are inverted compared to when they are upright (Anaki et al 2011, Derntl et al 2009c, Richler et al 2011). Our familiarity with faces aids our processing of upright faces as they all follow the same template, allowing us to process faces as a whole. In contrast, inverted faces contain the same featural information as upright faces but do not fit into the upright face template, and so the individual features are processed independently rather than as a whole. The higher accuracy and faster recognition of emotional expressions for upright compared to inverted faces suggests that we are able to process faces holistically rather than processing the individual features separately.

Thirdly, it has been suggested that emotional faces are processed configurally, another top-down method. In configural processing we assess the relative spatial distances between facial features, and from these make a decision regarding the emotion of the face. It has been suggested that to become facial emotion processing experts we need to process faces using configural cues, and the distance between the eyebrows and the mouth and the height:width ratio offer two particularly important pieces of configural information (Neth and Martinez 2010). Supporting the configural hypothesis is the composite face effect, in which emotion recognition is delayed when the top and bottom halves of a face show different expressions (Calder et al 2000a, Durand et al 2007). This results in a perceptually new expression, with the new face configuration interfering with the processing of the two original expressions and resulting in slower recognition. This effect does not occur when the two halves of the face are misaligned and the processing of their expressions is not influenced by their configuration. Also supporting a configural method for emotional face processing,

configural changes in faces produced by manipulating the distance between facial features can alter our perception of facial expression (Neth and Martinez 2009).

Alternatively, it has also been suggested that we may use a combination of configural and feature-based processing to make a judgement about an emotional face. Fiorentini and Viviani (2009) suggested that although feature based processing is more important than top-down processing, some holistic and configural processing also occurs and the processing of featural and configural information together may improve emotion recognition accuracy compared to the use of one strategy alone. Further supporting the relative importance of feature based processing, priming to the processing of local facial features has recently been reported to produce an advantage in emotion recognition abilities over priming to global processing (Martin et al 2012). Studies investigating non-emotional face processing have also suggested configural and featural information may be integrated and analysed together (Amishav and Kimchi 2010), with different strategies being used for different faces depending on the information available and the discriminability of facial properties (Kimchi and Amishav 2010).

1.3.5 Emotional face processing: dimensional and categorical processing

Two models have been proposed suggesting how we perceive basic emotions. One hypothesis is that emotions may be perceived along dimensions which are continuous and graded, with expressions reflecting underlying variations along these dimensions. Supporting this proposal, there is a large amount of overlap between certain expressions (e.g. anger and disgust, fear and surprise) but not others (e.g. happiness and disgust, sadness and surprise). Expanding this dimensional model has produced the two dimensional system, in which every expression has a level of pleasure and one of arousal (Russell 1980). An alternative hypothesis is that emotions may be perceived as distinct and separate categories, with limited overlap between the different categories. Under this model expressions are produced by facial movements specific to that expression. Supporting this hypothesis is the phenomenon of categorical perception (CP), which is observed when our perceptual system enforces categorical boundaries on continuous stimuli. CP effects can be observed when two facial expressions are morphed together producing a continuous sequence; judgements comparing between category faces are faster than judgements comparing within category faces (Bimler and Kirkland 2001).

It has also been proposed that neither the dimensional nor the categorical model can completely account for our perception of emotional faces, and a mixture of the two models may be used instead (Young et al 1997). We may utilise the two strategies in different situations; categorical processing may be used for recognition of the basic emotions when

their features are consistent with our prototypes for these expressions, whereas dimensional processing may be used for partial expressions which are ambiguous and when a recognisable single feature is present (Mendolia 2007). It has also been suggested that unconscious processing of emotions may occur along a continuous scale whereas conscious processing of emotions may be associated with distinct categories (Herba et al 2007). However, another recent study suggested that the dimensional model is more important for conscious processing, with a weak categorical model predicting effects only under certain conditions as CP effects may occur even if discrete perceptual categories do not exist (Fiorentini and Viviani 2009).

1.3.6 The processing of facial emotion and identity

It is important to remember that during the processing of emotional faces we are also processing information about their identity. Expression and identity were suggested to be processed through separate neural pathways by Bruce and Young (1986), and identity may be processed faster than expression (Martens et al 2010a). Supporting this suggestion of a double dissociation between expression and identity, individuals with bilateral amygdala damage who show impaired emotion recognition abilities do not show impaired identity recognition (Adolphs et al 1994), and conversely individuals with developmental prosopagnosia (a disorder characterised by the inability to recognise the identity of faces) do not show problems with emotion recognition (Duchaine et al 2003, Humphreys et al 2007a). Further, evidence from event-related potential studies suggests that facial emotional expression analysis and identity discrimination are independent and parallel processes (Eimer and Holmes 2002, Eimer et al 2003, Herrmann et al 2002, Streit et al 2000).

However, it has also been suggested that the routes used for expression and identity processing may not be fully independent (Calder and Young 2005). Multiple studies have supported this suggestion, with expression facilitating the recognition of identity and vice versa in neurotypical individuals (Dobel et al 2008, Levy and Bentin 2008, Martens et al 2010b) and expression aiding the recognition of identity in prosopagnosic patients (de Gelder et al 2003). In addition, a correlation between fear recognition and identity recognition abilities has been reported in women, although this effect was not found in men (Campbell et al 2002). Further suggesting some overlap in the neural processing of emotion and identity, individuals with acquired prosopagnosia may also show impairments in emotion recognition (Humphreys et al 2007a), although this may be due to extensive brain damage or an effect later in the face processing stream than that occurring in developmental prosopagnosia. Finally, it has been reported that following adaptation to a particular expression, a higher after-effect was observed to same identity faces compared to different identity faces (Ellamil et al 2008).

1.3.7 The time course of emotional face processing

The processing of emotional faces is thought to occur in stages, started by a rapid categorisation of the face as emotional rather than neutral and identifying its saliency and valence, followed by more detailed processing of the precise emotion conveyed and its intensity (Nakashima et al 2008, Sprengelmeyer and Jentzsch 2006, Utama et al 2009). Luo et al (2010) have further suggested that negative emotions are processed automatically and prior to distinguishing emotional from neutral faces.

Emotional faces are rapidly processed in the brain. A recent study has reported repetition effects to emotional faces in as short as 40-50ms, suggesting an early automatic discrimination of emotional expressions which may be due to low level physical features (Morel et al 2009) with more detailed processing starting around 140ms following stimulus presentation (Schyns et al 2009) and the decoding of emotions being complete after around 240ms (Streit et al 2000). It has been suggested that between 140 and 200ms information regarding common facial features, such as the eyes, is first encoded in both hemispheres regardless of emotion, before the entire face is processed. Emotion specific finer diagnostic features are then processed, such as the widened eyes for fearful faces and the upturned mouth for happy faces (Schyns et al 2009, van Rijsbergen and Schyns 2009). This corresponds to a shift in spatial localisation for processing, moving from the occipito-temporal regions to the centro-parietal region (van Rijsbergen and Schyns 2009).

Our brains are thought to have evolved to allow us to process facial expressions rapidly and accurately, and to help us distinguish and decode emotional expressions. This evolution is thought to have occurred in parallel to the evolution of facial expressions to transmit internal states with little overlap between expressions (Schyns et al 2009, Smith et al 2005). To aid the brain with this rapid processing of facial expressions then a number of structures have specialised functions related to face processing.

1.3.8 Summary

There are thought to be six basic emotions (happy, sad, fear, anger, surprise and disgust), with these emotions producing distinct facial expressions. We are best at recognising happy expressions explicitly, and are poorest at recognising fearful expressions. However, for implicit recognition the opposite pattern is observed, with fearful expressions being recognised most accurately and happy expressions being recognised least accurately. This high accuracy of the implicit recognition of fearful faces is likely to be important for survival, helping us to recognise when there are potential dangers in our environment. Supporting this, fearful along with angry expressions attract our attention more than other emotional expressions.

Our accurate recognition of facial expressions is supported by our attraction to faces, in particular the eye region, as this region conveys a large amount of social information. This interest in the eyes and the characteristic widened eyes of fearful faces is thought to facilitate our ability to recognise fearful expressions. The importance of specific facial features for recognising each of the six basic emotions supports a feature based mechanism for perceptually processing emotional faces, although holistic and configural mechanisms state that we process emotional faces as a whole and other studies support the use of these mechanisms. Other aspects relating to how we process emotional faces include whether the expressions are perceived along dimensional scales or as discrete categories, and the extent to which the processing of the expression and identity of faces overlap. Faces are rapidly processed within our brains, with a number of regions being specialised to facilitate their processing.

1.4 Neural correlates of face processing

A distributed neural system for face processing has been proposed by Haxby et al (2000), with a considerable overlap between this network and regions of the social brain (see section 1.2.1). This network has been suggested to consist of a core system involved in visual analysis (composed of the inferior occipital gyrus, lateral fusiform gyrus and superior temporal sulcus), and an extended system involved with further neural processing (composed of the intraparietal sulcus, auditory cortex, amygdala, insula, limbic system, and anterior temporal lobe) (Figure 1-2). Information may reach areas important for face processing via a cortical route, resulting in the conscious processing of faces and involving the lateral occipital cortex and inferior ventral temporal cortex, or via a subcortical route, resulting in the unconscious processing of faces and involving the superior colliculus, pulvinar and amygdala (Johnson 2005). This subcortical pathway may facilitate the rapid detection of fearful faces to alert us to possible dangers within the environment. Supporting the existence of a subcortical pathway to the amygdala, the unconscious presentation of fearful faces has been reported to produce amygdala activity (Morris et al 1999) and individuals with damage to the visual cortex have been reported to accurately detect faces and some expressions, in addition to showing neural activation in the amygdala in response to emotional faces (Morris et al 2001, Pegna et al 2005).

Within the proposed neural system for face processing the different regions are important for different aspects of face processing. The inferior occipital gyrus is important for the early perception of facial features. The fusiform gyrus plays a major role in the general processing of facial stimuli, and along with the inferior occipital gyrus helps us to recognise and identify faces. The superior temporal sulcus processes facial motion, and along with the intraparietal
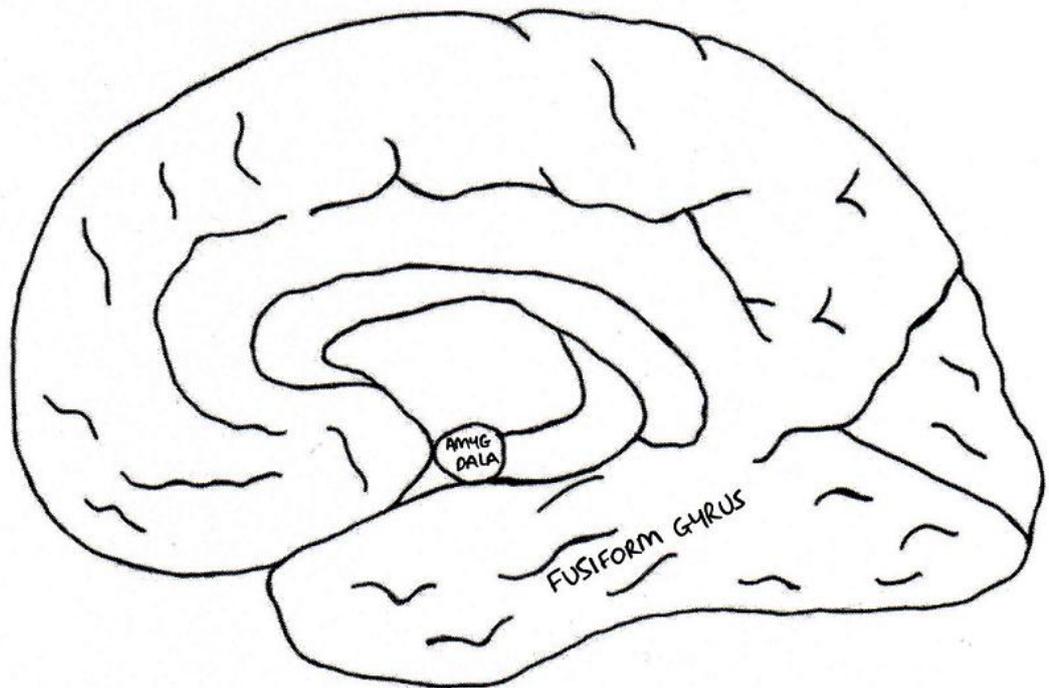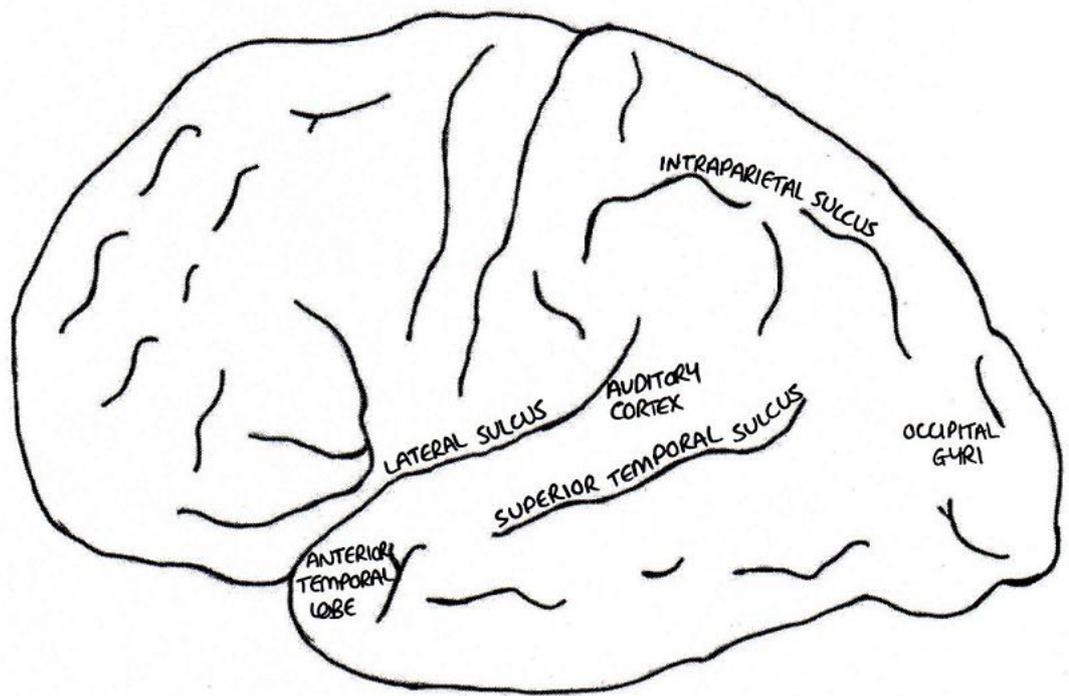
Figure 1-2. Regions of the brain which are involved in face processing. The insula is located deep in the fold of the lateral sulcus, between the frontal and temporal lobes

sulcus processes gaze direction and head position, while the auditory system aids in speech perception. The limbic system, amygdala and insula are important for the perception of emotional facial expressions, and the anterior temporal lobe assists with retrieving information associated with faces. Although these neural substrates involved in the different aspects of face processing are thought to be dissociable, they are also thought to interact (for example the fusiform gyrus has a supporting role in expression processing), suggesting the processing of facial aspects is interdependent (Haxby et al 2000).

Regions within the face processing neural system are activated when we view neutral faces (Benuzzi et al 2007, Fusar-Poli et al 2009a, Puce et al 1995). Emotional faces also activate these regions, along with others within visual areas (middle occipital gyrus, lingual gyrus), temporoparietal areas (parietal lobule, superior and middle temporal gyri, precuneus), prefrontal areas (superior, medial and inferior frontal gyri), limbic areas (parahippocampal gyrus, posterior cingulate cortex) and subcortical areas (putamen) (Fusar-Poli et al 2009a, Fusar-Poli et al 2009b, N'Diaye et al 2009, Nomi et al 2008, Winston et al 2003). In addition, damage to the somatosensory cortex (Adolphs et al 2000) or inhibiting its activity using transcranial magnetic stimulation (Pourtois et al 2004a) impairs emotion recognition abilities, suggesting a role for this region in emotion processing. It has been suggested that specialised systems involving different brain networks are involved in the processing of the different basic emotions (Hsu and Young 2004), and this may aid us with directing our visual attention to possible dangers in the environment (Surguladze et al 2003). The amygdala and insula have been suggested to be important for fear and disgust recognition respectively (see sections 1.4.3 and 1.4.4), with other emotion-specific activations having been reported in the anterior cingulate cortex, orbitofrontal cortex and ventral striatum for angry faces (Blair et al 1999, Calder et al 2004, Jehna et al 2011), the parahippocampal region for surprised faces (Schroeder et al 2004), and the temporal pole and thalamus for sad faces (Blair et al 1999, Cheung et al 2006).

1.4.1 Fusiform gyrus

The lateral region of the fusiform gyrus (FG) is thought to be specialised for face perception, with this region being named the fusiform face area (FFA). Allison et al (1994) reported that a face specific N200 is produced during intracranial recordings using electrodes in the FG, and the stimulation of this area inhibited the ability to name familiar faces. Activity in the FG is higher for intact faces compared to houses, hands, and scrambled faces (Kanwisher et al 1997), and is selective for human faces (Kanwisher et al 1999). Gauthier (1999, 2000) later suggested that this increased activity is due to our expertise and familiarity with faces, rather than being due to faces per se. Supporting the role of the FG in face processing, individuals with developmental prosopagnosia show reduced FFA activity in response to face stimuli compared to neurotypical individuals (Furl et al 2011).

The FFA is activated during both facial expression and identity processing (Critchley et al 2000a, Fitzgerald et al 2006, Ganel et al 2005), showing a release from adaptation following a change in either expression or identity (Fox et al 2009a, Xu and Biederman 2010). Fusiform activity is also positively correlated with the intensity of emotional expressions, and is greater for fearful and disgusted expressions compared to happy and sad expressions (Surguladze et al 2003). Intracranial recordings within the fusiform cortex have found an early activation (within 150ms of stimulus onset) which likely reflects perceptual encoding of facial information, with later activity occurring in this region between 200 and 1000ms reflecting activity related to expression, identity and gaze processing (Pourtois et al 2010).

1.4.2 Superior temporal sulcus

The superior temporal sulcus (STS) is thought to play an important role in many tasks, including face and speech processing, audio-visual integration, processing of biological motion, and theory of mind (Allison et al 2000, Hein and Knight 2008). A recent review suggested that the STS is not split into distinct functional sub-regions for each of these abilities, but instead its activity depends on the specific demands of tasks (Hein and Knight 2008).

The role of the STS in face perception is supported by early studies which recorded intracranial neuronal responses of monkey STS to faces. Perrett et al (1982) found face specific responses within the monkey STS, with different neurons responding to different parts of faces. It has further been reported that STS neurons also show expression and identity specific responses (Hasselmo et al 1989). A recent case study of an individual with damage to the posterior STS has suggested a role for the STS in facial expression processing due to this individual showing impaired expression recognition (Fox et al 2011). However, the STS is not thought to be necessary for identity processing, as in the same case study identity recognition was unaffected (Fox et al 2011), and the removal of the STS in monkeys is not associated with altered face recognition (Heywood and Cowey 1992).

The STS has also been proposed to have an important role in the detection of biological motion (Grossman et al 2000a, Puce and Perrett 2003, Saygin 2007) and gaze (Allison et al 2000). Face specific neurons within the monkey STS have further been reported to show sensitivity to head orientation and gaze direction (Perrett et al 1985), and following removal of the STS monkeys were not able to accurately perceive gaze (Campbell et al 1990). Both eye gaze and mouth movements activate the STS in humans (Hoffman and Haxby 2000, Puce et al 1998), with this activity being greatest for dynamic gaze shifts towards the observer (Ethofer et al 2011). Inhibition of activity in the superior lateral temporal cortex using transcranial magnetic stimulation slows down judgements regarding gaze shifts, further suggesting a role for this region in gaze processing (Pourtois et al 2004a).

1.4.3 Amygdala

The amygdala is thought to be the main structure involved with the processing of emotional stimuli, including emotional faces. Leonard et al (1985) reported activation of a population of monkey amygdala neurons in response to faces, with these responses having longer latencies than those of neurons in the STS and a proportion of neurons being activated more by emotional compared to neutral faces. Face specific activity to faces has also been reported in humans using intracranial recordings of medial temporal lobe neurons, with responses in these neurons being specific to expression and identity (Fried et al 1997). It has recently been reported that amygdala neurons show selectivity to the parts of faces that they respond to (Rutishauser et al 2011), with greater amygdala activity being produced to images of the eye region alone of fearful and happy faces compared to images of the full faces or the mouth region, suggesting an overall selectivity to the eyes (Meletti et al 2012).

The amygdala was first suggested to be activated in particular for fearful facial expressions by Morris et al (1996), with greater activity being seen for fearful compared to happy expressions and activity increasing as the intensity of the fearful expression increases. A rapid habituation of this activity has been suggested to occur (Breiter et al 1996) which is stronger than that for neutral faces (Ishai et al 2004). This activation of the amygdala in response to fearful expressions has been reported in many later imaging studies (Asghar et al 2008, Breiter et al 1996, Derntl et al 2009b, Goossens et al 2009, Hung et al 2012, Morris et al 1998, Phillips et al 1997, Surguladze et al 2003, Winston et al 2003), and studies recording intracranial amygdala neuron responses have reported activity to fearful faces after 200ms (Krolak-Salmon et al 2004, Meletti et al 2012). It has also been reported that the amygdala is activated in response to the other basic emotions and neutral expressions (Blair et al 1999, Breiter et al 1996, Derntl et al 2009b, Fitzgerald et al 2006, Goossens et al 2009, Kim et al 2003, Surguladze et al 2003, Winston et al 2003), and a recent meta-analysis concluded that happy, sad and fearful facial expressions, but not angry or disgusted expressions, activate the amygdala more than neutral faces, and this effect was greatest for fearful faces (Fusar-Poli et al 2009a). Further supporting a role of the amygdala in the processing of fearful expressions, positive correlations between amygdala activity and facial fear recognition in males (Derntl et al 2009b) and perceived intensity of fearful faces (Sato et al 2010) have been reported. In addition to the amygdala activation produced by fearful expressions, it has been suggested that fearful eyes alone (Asghar et al 2008, Morris et al 2002) and fearful eye whites (Whalen et al 2004) may be sufficient to evoke amygdala activity. However, amygdala activity is higher for fearful faces with the eye region covered compared to neutral faces with the eyes covered, suggesting that its fear-selective activity is not dependent on the presence of the eyes (Asghar et al 2008).

The role of the amygdala in the processing of fearful faces can be further studied using individuals with amygdala damage, with SM being the most extensively studied subject. SM

is a sufferer of Urbach-Wiethe disease, and she has extensive well characterised amygdala damage. This damage is unique as it has caused almost complete destruction of the bilateral amygdala and it is selective, not affecting surrounding brain regions (Adolphs et al 1994). SM has repeatedly been shown to have a severe impairment in the recognition of fear from facial expressions, with slight impairments for the recognition of anger and surprise and a largely normal recognition of the other basic emotions and intact identity recognition (Adolphs et al 1994, Adolphs et al 2005). Impaired facial fear recognition has been reported in other individuals following bilateral amygdala damage, with some individuals also exhibiting impaired recognition of other emotions (Adolphs et al 1999, Becker et al 2012, Broks et al 1998, Calder et al 1996, Sato et al 2002, Young et al 1995, Young et al 1996). Although it was originally suggested that unilateral amygdala damage is not associated with impaired emotion recognition abilities (Adolphs et al 1995), a recent case study of an individual with right amygdala damage has reported impaired fear recognition (Heutink et al 2011). It has further been suggested a sex related functional asymmetry of the amygdala may exist, with right side damage being associated with impaired social cognition in males only and left side damage being associated with impaired social cognition in females only (Tranel and Bechara 2009).

1.4.3.1 Role of the amygdala in the rapid subcortical processing of faces

Amygdala activity in response to fearful expressions is rapid, occurring within 100ms, suggesting early subcortical processing (Hung et al 2010, Streit et al 2003). This activity is faster than responses in visual areas in the occipital cortex (occurring after approximately 165ms) (Furl et al 2010), supporting the suggestion of a fast, direct route to the amygdala from the thalamus which bypasses the visual cortex (Morris et al 1999). Further, Luo et al (2007) reported amygdala activity occurs before visual cortical activity specifically for fearful faces and not for angry faces, suggesting the proposed subcortical route may be specialised for the processing of fearful expressions.

However, despite SM's impairment in consciously recognising fear, she has recently been reported to show a typical rapid detection and unconscious processing of fearful faces, suggesting that the amygdala may not be essential for the early stages of fear processing but may instead be important in evaluating and modulating its recognition and social judgement (Tsuchiya et al 2009). Further supporting a role for the amygdala in the conscious detection of fearful expressions, an individual with right amygdala damage has been reported to show intact implicit recognition of fearful expressions in the absence of explicit recognition (Heutink et al 2011), and patients with unilateral amygdala removals have also been reported to be able to detect fearful expressions for briefly presented faces but not

faces presented for longer durations (Palermo et al 2010). These results suggest the amygdala is not necessary for the rapid detection of fearful faces, and instead other structures in the suggested subcortical pathway for face processing may be important.

1.4.3.2 Role of the amygdala in directing gaze

The amygdala has been suggested to play a role in orienting attention towards facial features, in particular the eyes. Adolphs et al (2005) reported that SM exhibits a lack of spontaneous fixations to the eye region while freely viewing emotional faces, suggesting she does not utilise the information in this region in a typical way, and her reduced fixation to the eyes is particularly prominent for her first fixation (Kennedy and Adolphs 2010). SM also shows a similar pattern of reduced fixations to the eye region, coupled with an increased number of fixations to the mouth, during real-life conversations with either familiar or unfamiliar people which results in her eliminating almost all direct eye contact (Spezio et al 2007b), and when viewing social scenes containing peoples' faces (Birmingham et al 2011).

Although Adolphs et al (2005) reported that SM demonstrates a lack of eye fixations when viewing each of the basic emotions, her selective impairment in fear recognition was suggested to be due to the eyes being the most important feature for recognising fear. This is supported by her ability to recognise fearful expressions being similar whether the eyes are present or absent. Crucially, SM's impairment in fear recognition was reversed following explicit instructions to look at the eye region of the face, causing her to be able to recognise fear at a level similar to that of individuals with no amygdala damage. This provides strong evidence for her impaired fear recognition being due to a failure to fixate on the eye region, supporting a role for the amygdala in directing attention and gaze towards the eye region for the detection of potentially relevant social stimuli.

SM's lack of fixations to the eye region represents a lack of attraction to the eyes and is not due to an active avoidance of this region (Birmingham et al 2011). Although it was originally suggested this may be due to a lack of top-down modulation from the amygdala, resulting in her attention not being directed correctly to this region (Adolphs et al 2005), it has more recently been suggested that she may show atypical bottom up attention effects due to non-eye facial features and a reduced saliency of the eyes, as her reduced gaze to the eyes only occurs when she sees a whole face, and when other regions of the face are covered she fixates on the eyes first (Kennedy and Adolphs 2010).

Further linking the amygdala to the directing of attention, amygdala activity has been reported to be higher when viewing whole neutral faces compared to either the upper or lower half of the faces (Benuzzi et al 2007). For the processing of fearful faces directing attention towards the eyes may be critical, with amygdala activity having been suggested to be enhanced when attention is shifted from the mouth to the eye region for fearful faces but

not for angry, happy, or neutral faces (Gamer and Buchel 2009). The amygdala has also been associated with the detection of salient face stimuli (Santos et al 2011), particularly the detection of potential threats (Nomura et al 2004, Suslow et al 2006). Supporting this, higher amygdala activity has been reported for angry expressions with a direct gaze and fearful expressions with an averted gaze compared to that for direct gaze fearful and averted gaze angry expressions (Boll et al 2011, N'Diaye et al 2009). However, these results may also suggest the sensitivity of the amygdala to viewing salient stimuli (such as the eye region), resulting in increased amygdala activity, rather than a role of the amygdala in directing gaze.

1.4.4 Insula

The role of the insula in emotional face processing is thought to be mainly related to the processing of disgusted expressions. The insula is activated in response to disgusted faces (Jehna et al 2011, Phillips et al 1997, Schroeder et al 2004, Sprengelmeyer et al 1998), and its activity increases as the intensity of disgusted expressions increases (Surguladze et al 2003). A recent meta-analysis reported that both disgusted and angry faces activate the insula, with a greater sensitivity to disgusted faces (Fusar-Poli et al 2009a). Disgust specific activity as recorded by intracranial electrodes in the ventral interior insula have also been described, which occur after 300ms (Krolak-Salmon et al 2003). Further supporting a role for the insula in disgust processing, impaired disgust recognition has been reported both in individuals with damage to the insula (Calder et al 2000b) and in individuals diagnosed with Huntington's disease, which is associated with degeneration of the insula (Hayes et al 2009, Sprengelmeyer et al 1996).

1.4.5 Hemispheric localisation of emotional face processing

Although both hemispheres have been reported to be activated during the processing of emotional faces (Fusar-Poli et al 2009b), many studies have suggested different contributions of the two hemispheres towards the processing of emotional expressions. Differences in the results of these studies are likely to be due to differences in the tasks used (e.g. whether it is purely a perceptual task or whether it involves evoking an emotion within the participant). While several studies have suggested there is a bias for right hemisphere dominance for expression processing (Bourne 2005, Sato and Aoki 2006, Tamietto et al 2006), others have suggested the right hemisphere primarily processes negative expressions only and the left hemisphere primarily processes positive expressions (Shamay-Tsoory et al 2008, Shamay-Tsoory et al 2010). Supporting this, it has been suggested we are better at correctly identifying positive emotions presented to the right visual field (i.e. processed by the left hemisphere) and negative emotions presented to the

left visual field (i.e. processed by the right hemisphere) (Jansari et al 2011). It has also been suggested the right hemisphere may process the basic emotions, whereas the left hemisphere processes social emotions (Prodan et al 2001, Shamay-Tsoory et al 2008). Alternatively, the right hemisphere may be specialised for processing holistic and configural information while the left hemisphere is specialised for processing featural information (Bourne 2011). However, even if the left and right hemispheres play different roles in the processing of emotional faces, interhemispheric co-operation occurs to facilitate emotion recognition (Tamietto et al 2007).

1.4.6 Summary

A specialised face processing network has developed within our brains, with regions within this network being involved in the processing of faces. This network has been proposed to include a core system involved in the visual analysis of faces (composed of the inferior occipital gyrus, lateral fusiform gyrus and superior temporal sulcus) and an extended system involved in extracting meaning from faces (composed of the intraparietal sulcus, auditory cortex, amygdala, insula, limbic system, and anterior temporal lobe). The fusiform gyrus is thought to show specialisation in the processing of faces. This may be due a role of the fusiform gyrus in processing of familiar objects and our familiarity with faces rather than specialisation of this region for face processing per se. The superior temporal sulcus is important for the processing of biological motion, including movements of the eye region and mouth, and this region is particularly important for processing eye gaze. The amygdala plays a role in processing emotional stimuli, and this region is thought to be particularly important for the processing of fearful expressions. This may be due to a role of the amygdala in directing attention towards the eye region. Finally, the insula is thought to be important for the processing of disgusted faces. Although neuroimaging studies and those involving individuals with brain damage help us to determine the role of different parts of the brain in face processing, these studies do not provide us with information regarding the time course of face processing and so it is important to use other methods to fully investigate how we process faces.

1.5 Electrophysiological correlates of face processing

Event related potentials (ERPs) may be used to accurately determine the time course of face processing. While we view faces distinct waveform patterns can be observed in the ERPs produced, and in the following section I will focus on the P1 and N170 components

(Figure 1-3). The P1 component is a positive deflection which occurs approximately 100ms following stimulus presentation, and is thought to reflect the holistic processing of faces and general visual processing. The N170 component is a negative deflection which occurs approximately 170ms following stimulus presentation, and it has been suggested to be a face selective component which may reflect the structural encoding of faces and configural processing.

Later stages of face processing may also show sensitivity to faces. These later stages play a role in the processing of detailed information within faces and elaborate perceptual analysis (van Rijsbergen and Schyns 2009), contributing towards the decoding and cognitive analysis of emotional expressions (Wong et al 2009), and also the recognition of faces (Eimer 2000a).
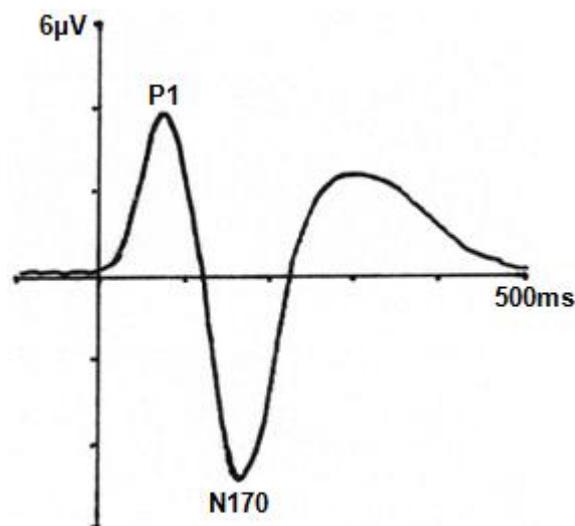
Figure 1-3. Example of the waveform produced when we view faces. The P1 component, occurring approximately 100ms following stimulus onset, has been associated with general visual processing and the holistic processing of faces. The N170 component, which occurs approximately 170ms following stimulus onset, is face selective and has been associated with the structural encoding of faces

1.5.1 Early stages of face processing: the P1 component

The P1 component, which has a peak occurring between 90 and 120ms post-stimulus, represents a general visual perceptual component, and is associated with the processing of low level features of stimuli. This component is largest over posterior temporal parietal occipital regions (Batty and Taylor 2003, Feng et al 2009, Luo et al 2010, Pourtois et al 2005, Utama et al 2009), and has been suggested to be larger over the right compared to

the left hemisphere (Batty and Taylor 2003, Utama et al 2009). Source localisation has suggested that the P1 originates from activity in the bilateral fusiform gyri (Herrmann et al 2005) and the visual cortex (Pourtois et al 2005, Wong et al 2009).

1.5.1.1 The P1 component and face processing

The P1 component is sensitive to faces, with faces producing larger P1 amplitudes and longer P1 latencies than buildings (Herrmann et al 2005). This component has been suggested to represent face categorisation and holistic processing (Luo et al 2010, Wong et al 2009), and it is thought to be important for detecting emotional faces (Utama et al 2009). It has been suggested that there is no effect of attentional load on P1 amplitude (Holmes et al 2009).

1.5.1.2 The effect of emotion on P1 amplitude

Results of studies investigating the effect of emotion on P1 amplitude are inconsistent. Some studies have suggested an effect of emotion on P1 amplitude, with emotional faces producing a larger P1 compared to neutral faces (Batty and Taylor 2003). Other studies have suggested that this effect is specific to fearful faces (Holmes et al 2003, Holmes et al 2008, Luo et al 2010, Pourtois et al 2005), and a greater P1 amplitude for fearful faces (but not happy) compared to neutral faces may be enhanced in individuals with high trait anxiety (Holmes et al 2008). Feng et al (2009) reported an increased P1 amplitude to increased intensities of fearful eye whites, suggesting the eyes alone can express the intensity of fearful expressions and influence P1 amplitude. It has also been reported that there is no effect of emotion (Fruhholz et al 2011, Leppanen et al 2008, Streit et al 2000) or expression intensity (Leppanen et al 2007a, Sprengelmeyer and Jentzsch 2006) on P1 amplitude.

1.5.1.3 The effect of emotion on P1 latency

Studies have suggested there is no effect of emotional expression or expression intensity on P1 latency (Batty and Taylor 2003, Leppanen et al 2007a). However, increased intensities of fearful eye whites have been reported to produce shorter P1 latencies (Feng et al 2009), suggesting P1 latency may be sensitive to the intensity of fearful expressions.

1.5.2 The face selective N170 component

The N170 component, which has a peak occurring 170-200ms post-stimulus, represents a face-selective activation. This component is largest over the posterior temporo-occipital region (Balconi and Lucchiari 2005, Bentin et al 1996, Blau et al 2007, Leppanen et al 2007b, Leppanen et al 2008), and has been reported to be larger with a shorter latency over the right hemisphere both for full faces (Balconi and Lucchiari 2005, Bentin et al 1996, Blau et al 2007, Eimer et al 2010, Leppanen et al 2008, Sprengelmeyer and Jentzsch 2006) and for the eye region alone (Beaton et al 2012) compared to activity over the left hemisphere. Source localisation has associated the N170 with activity originating from the fusiform gyri, with further activity in the parieto-temporal-occipital network (Campanella et al 2002, Herrmann et al 2005, Luo et al 2010, Petroni et al 2011, Sprengelmeyer and Jentzsch 2006, Utama et al 2009, Wong et al 2009). Supporting a role for the fusiform gyri in producing the N170, Iidaka et al (2006) reported a strong relationship between lateral fusiform gyrus activity and the N170 using a combined fMRI-ERP study design. N170 activity has also been suggested to originate from the posterior superior temporal sulcus (Itier and Taylor 2004).

1.5.2.1 The N170 component and face processing

The face-selective N170 component was first described by Bentin et al (1996). This component was reported to be evoked by human faces, but not animate or inanimate non-face stimuli. The N170 is thought to show selectivity for human faces, being larger for human faces compared to that evoked by faces of other species (de Haan et al 2002, Gajewski and Stoerig 2011, Itier et al 2011), and is also able to distinguish dummy from real faces, having a shorter latency to real faces (Ponkanen et al 2008). Adaptation of the N170 occurs when faces and even expressions are shown repeatedly, resulting in its reduced amplitude (Campanella et al 2002, Eimer et al 2010, Mercure et al 2011). Further supporting an association between the N170 and face processing, this component has been reported to be absent in a patient with prosopagnosia after the presentation of faces (Eimer and McCarthy 1999). The N170 is not thought to represent face recognition, being unaffected by face familiarity (Anaki et al 2007, Eimer 2000a, Gosling and Eimer 2011). It may be sensitive to facial identity as viewing sequential faces with different identities has been reported to produce larger N170 amplitudes compared to viewing sequential faces with the same identity (Campanella et al 2000), although another study reported no difference in N170 amplitude due to repetition of same or different identity faces (Amihai et al 2011).

The N170 is thought to reflect the late stages of the structural encoding of faces, specifically global face configuration (Ashley et al 2004, Balconi and Lucchiari 2005, Bentin et al 1996, Eimer 2000b, Holmes et al 2003, Luo et al 2010, McPartland et al 2010, van Rijsbergen and Schyns 2009, Wong et al 2009). During the structural encoding of faces, representations of

global face configurations are produced which are then utilised by later processes (Bentin et al 1996, Eimer 1998, Eimer 2000b). The N170 has been suggested to represent the analysis of first-order relational face configuration and holistic processing (Eimer et al 2011); supporting this disrupting face configuration and holistic processing increases both the amplitude and latency of the N170 component (Jacques and Rossion 2010). The N170 also represents the second order relational encoding of faces, as it is affected by face inversion. Inverted faces produce a delayed N170 with a larger amplitude compared to upright faces (Ashley et al 2004, Bentin et al 1996, de Haan et al 2002, Eimer et al 2010, Eimer et al 2011, Gajewski and Stoerig 2011, Itier et al 2007a). This effect occurs in both the left and right hemispheres, with a smaller amplitude in the left compared to the right hemisphere and no difference in latency (Honda et al 2007). It has been suggested this inversion effect may be due to the processing of inverted faces being more cognitively demanding compared to the processing of upright faces, involving both face and object processing areas (de Haan et al 2002). Supporting a role for the activity of the N170 component in the structural encoding of faces rather than head detection or the presence of a specific facial feature, the N170 is attenuated to views of the cheeks and backs of heads and to faces missing internal or external features (Eimer 2000b). During the structural encoding of emotional faces, the N170 has been suggested to represent the integration of visual information specific to each expression, starting with the eyes and moving down the face to the nose and mouth (Schyns et al 2007).

Viewing the eye region alone, but not the nose and lip region alone, is sufficient to produce the N170, and the N170 evoked by the eye region alone has a larger amplitude compared to the N170 evoked by full faces (Bentin et al 1996, Eimer et al 2010, Eimer et al 2011). A recent study has suggested that viewing salient face features may influence the N170, with a greater amplitude and longer latency when gaze is directed towards either the upper of lower parts of faces compared to the central region (McPartland et al 2010). However, it is possible that the directing of gaze may produce additional activity in the superior temporal sulcus which results in these effects on N170 amplitude and latency.

The larger N170 amplitude evoked by the eye region alone compared to full faces led Bentin et al (1996) to suggest the N170 may reflect the activation of an eye-sensitive region of the cortex. However, there is no effect on N170 amplitude when faces without eyes are viewed compared to faces with eyes, although N170 latency is longer for faces without eyes (Eimer 1998). This suggests that the N170 is not directly related to the activity of regions sensitive to the presence of the eyes, and although the N170 is sensitive to the presence of the eyes, this region is not necessary to produce the N170. It has recently been proposed that the N170 has two distinct contributions, one from face selective neurons, and the other from eye selective neurons (Eimer et al 2010, Itier et al 2007a, Jacques and Rossion 2010). The activation of these sources is dependent on the context of the face; when full upright faces are viewed only the face sensitive neurons are activated and the eye sensitive neurons are

inhibited, and when the eyes alone or inverted faces are shown (i.e. normal face configuration is disrupted) both the face sensitive and eye sensitive neurons are activated. This results in larger N170 amplitudes for the eyes alone and inverted faces compared to that for upright full faces, and the delayed N170 latency in response to these stimuli may be due to delayed activity in the face specific neurons.

1.5.2.2 The effect of emotion on N170 amplitude

The N170 has been reported to be larger for fearful, happy, angry and disgusted faces compared to neutral faces (Caharel et al 2005, Luo et al 2010, Morel et al 2009, Rellecke et al 2011, Wronka and Walentowska 2011). Further, Leppanen et al (2008) found a negative shift after 160-210ms at lateral temporal sites for fearful compared to neutral faces only when the eye region was present. Several studies have also reported fearful faces evoke larger N170 amplitudes compared to faces expressing other emotions (Batty and Taylor 2003, Blau et al 2007, Fruhholz et al 2011, Leppanen et al 2007b, Leppanen et al 2008, Morel et al 2009, Pegna et al 2008, Stekelenburg and de Gelder 2004). However, many other studies have reported emotion in faces has no effect on N170 amplitude (Ashley et al 2004, Balconi and Lucchiari 2005, Eimer and Holmes 2002, Eimer et al 2003, Herrmann et al 2002, Holmes et al 2003, Holmes et al 2005, Kiss and Eimer 2008, Leppanen et al 2008, Sprengelmeyer and Jentzsch 2006, Streit et al 2000). This difference may reflect task and attentional differences; tasks which produced an enhanced N170 to fearful faces generally required less attention than those tasks which did not produce differences in N170 amplitude for emotional and neutral faces. Emotion intensity has also been suggested to influence N170 amplitude, with increased intensity producing a larger N170 amplitude (Sprengelmeyer and Jentzsch 2006, Utama et al 2009), although another study did not find an effect of emotion intensity on N170 amplitude (Leppanen et al 2007a). Similarly, the intensity of fearful eye whites did not have an effect on N170 amplitude (Feng et al 2009).

1.5.2.3 The effect of emotion on N170 latency

Again, studies investigating the differences in N170 latency between emotional and neutral faces have had mixed results. Batty and Taylor (2003) suggested that both positive and neutral expressions evoked the N170 component earlier than negative emotions, while Luo et al (2010) suggested both fearful and happy expressions evoke the N170 component earlier than neutral expressions. Schyns et al (2007) have suggested that the latency of the N170 depends upon the expression within the face, as information relating to the expression is integrated starting with the eyes and moving down the face. They suggested the peak of the N170 occurs around 50ms after the information for a particular expression has been

integrated, which results in a short latency in response to fearful expressions (as the eyes contain the most important information), a longer latency for disgusted expressions (for which the nose contains the most important information) and the longest latency for happy expressions (as the mouth contain the most important information). Other studies have reported emotion has no effect on N170 latency (Blau et al 2007, Herrmann et al 2002, Holmes et al 2003, Holmes et al 2005). N170 latency has been reported to increase as the intensity of fearful expressions increases (Leppanen et al 2007a), with no effect of intensity of fearful eye whites alone (Feng et al 2009) or the intensity of happy expressions (Leppanen et al 2007a).

1.5.3 Summary

When we view faces distinct ERP waveforms are produced, with both the P1 and N170 components being sensitive to faces and showing larger amplitudes in response to face compared to non-face stimuli. The P1 component is thought to reflect general visual processing and the holistic processing of faces, and its activity has been suggested to originate from the visual cortex and the fusiform gyri. Studies investigating the effect of emotion within faces on P1 amplitude have mixed results, with some studies suggesting that larger amplitudes are produced for emotional compared to neutral faces, others suggesting this effect is limited to fearful faces and additional studies finding no effect of emotion. It has more consistently been reported that there is no effect of emotion on P1 latency. The N170 is a face selective component, and shows selectivity towards human compared to non-human faces. This component is thought to reflect the structural encoding of faces, being important for processing face configuration and the integration of facial information. N170 activity is thought to originate from the fusiform gyri. Similar to studies investigating the effect of emotion on P1 amplitude, reports of the effect of emotion on N170 amplitude are inconsistent. Larger N170 amplitudes in response to emotional compared to neutral faces have been reported in some studies, while others have suggested this effect may be limited to fearful faces. It has also been suggested that N170 latency may be affected by the emotion within the face. However, other studies have found no effect of emotion on either N170 amplitude or latency.

1.6 Theory of mind abilities

Theory of mind is the ability to interpret and understand the mental states of yourself and others, including feelings, thoughts, intentions, beliefs and desires (Premack and Woodruff 1978). This ability allows us to predict the actions of others, and empathise with them. Joint attention and following eye gaze are essential precursors to the development of theory of

mind abilities, and it has been reported that by the age of three years old anticipatory looking behaviours of many children suggests the presence of a theory of mind (Southgate et al 2007). This indicates an early development of this ability.

The original tasks designed to test theory of mind abilities required participants to understand false beliefs of others and to predict their behaviour based on these beliefs, with the 'Sally-Ann' task being one of the best known examples (Baron-Cohen et al 1985). In this task participants are told that one character (e.g. Sally) hides a marble in a box then leaves the room. Another character (e.g. Ann) then moves the marble to a covered basket, and Sally returns to the room. Participants are then asked where will Sally look for the marble, with the correct answer being in the box. In order to answer correctly participants must therefore understand that Sally holds a false belief about where the marble is, and she behaves accordingly. Control questions are also asked, for example to ensure that the participant can remember that Sally placed the marble in the box. Typically developing children are able to pass this task by the age of 4. This task tests first order false beliefs, as it requires participants to understand a false belief held by another individual and to predict behaviour based on this false belief rather than that based on reality.

Other theory of mind tasks have since been developed, all of which require participants to understand others' mental states. These tasks may test cognitive theory of mind abilities, which require participants to make inferences based on the knowledge and beliefs of others, or affective theory of mind abilities, which require participants to make inferences based on the emotional states of others. Examples of theory of mind tasks include the Faux Pas task (Baron-Cohen et al 1999a), which requires participants to recognise faux pas, and Happé's strange stories (Happe 1994), in which participants are required to interpret non-literal utterances. Theory of mind tasks which are more sensitive to detecting differences in task performance between groups of typically developing individuals include the Reading the Mind in the Eyes task (Baron-Cohen et al 1997, Baron-Cohen et al 2001c) and the Frith-Happé Animated Triangles task (Abell et al 2000), which are both discussed in detail below. It is important to remember that performance on theory of mind tasks may be influenced by executive functioning (a set of abilities which facilitate goal directed behaviours, including working memory, mental flexibility and inhibition), and verbal abilities. Interpreting performance in theory of mind tasks should therefore take into account more general cognitive functioning.

1.6.1 Neural correlates of theory of mind abilities

Multiple regions within the social brain have been associated with activity during theory of mind tasks (see section 1.2.1), suggesting the involvement of multiple diverse regions. A recent meta-analysis reported that all tasks rely on the involvement of core regions,

specifically the prefrontal cortex and superior temporal sulcus, and the involvement of other regions depends upon the task (Carrington and Bailey 2009). In particular, the temporal poles and temporoparietal junction have been suggested to play a role in understanding others beliefs (Samson et al 2004).

It has further been suggested that cognitive and affective tasks may involve different regions (Kalbe et al 2010, Shamay-Tsoory et al 2009). Cognitive theory of mind tasks have been proposed to engage the dorsomedial and dorsolateral prefrontal cortices, the dorsal anterior cingulate cortex, the dorsal temporal poles and the dorsal striatum, while affective theory of mind tasks have been proposed to engage the ventromedial prefrontal cortex, the orbitofrontal cortex, the inferior lateral frontal cortex, the ventral anterior cingulate cortex, the ventral temporal poles, the ventral striatum and the amygdala (Abu-Akel and Shamay-Tsoory 2011).

1.6.2 Reading the Mind in the Eyes task

The Reading the Mind in the Eyes task (Eyes task) was developed by Baron-Cohen et al (1997) as an advanced theory of mind task. In this task, individuals are shown images of the eye regions of faces, and are asked to choose from two options which word they think best represents the individual's mental state (Baron-Cohen et al 1997). This task is considered a theory of mind task rather than an emotion recognition task as participants are required to attribute complex cognitive mental states (such as beliefs or intentions) to the images rather than simple emotions. A revised version of this task was published several years later, with the main revisions being the addition of more pictures and each image being associated with four words to choose from rather than two (Baron-Cohen et al 2001c). This task was first developed to overcome problems with using previous theory of mind tasks in adults. These tasks often produce ceiling effects in adults, suggesting a need for more advanced tasks to detect subtle differences in theory of mind abilities in individuals who are able to pass simpler tasks such as the false belief tasks. This is not an issue with the Eyes task, with variation being observed in the scores of adults (Baron-Cohen et al 2001c). A further advantage of the Eyes task compared to other theory of mind tasks is that the Eyes task is less dependent on cognitive processes relating to executive functioning, suggesting it is a more 'pure' test of theory of mind abilities (Baron-Cohen et al 1997, Baron-Cohen et al 2001c).

Neural activity produced during the Eyes task is contrasted with a control task, in which participants are asked to judge the gender and / or age of individuals in the image. This allows us to take account of activity due to low level visual factors, so that we can investigate activity due to the mentalising component of the task. Activity during the Eyes task has been reported in many parts of the social brain, being found most consistently for frontal regions

including the medial prefrontal cortex, superior and frontal middle gyri and inferior frontal gyrus, and temporal regions including the superior temporal sulcus, superior temporal gyrus, middle temporal gyrus, temporal pole and the temporoparietal junction (Adams et al 2009, Baron-Cohen et al 1999b, Baron-Cohen et al 2006, Castelli et al 2010, Focquaert et al 2010, Moor et al 2012, Platek et al 2004, Russell et al 2000) (Table 1-1). Electrophysiological activity produced during the Eyes task has implicated firstly a N270-400 component produced over the inferior frontal and anterior temporal regions of the right hemisphere which may originate from orbitofrontal and medial temporal regions, and secondly a P300-500 component over posterior central and parietal sites (Sabbagh et al 2004).

Impaired performance on the Eyes task following brain damage has also suggested the involvement of the amygdala (Adolphs et al 2002, Shaw et al 2005, Stone et al 2003) and frontal regions, in particular the prefrontal cortex (Farrant et al 2005, Geraci et al 2010, Shaw et al 2005). However, the application of transcranial magnetic stimulation to inhibit neural activity over either the left inferior frontal gyrus (Keuken et al 2011) or medial prefrontal cortex (Krause et al 2012) did not affect accuracy on the task, suggesting these regions are not necessary during the task.

1.6.3 The Frith-Happé Animated Triangles task

The Frith-Happé Animated Triangles task (Triangles task) consists of a series of videos of two triangles interacting with each other within a box (Abell et al 2000). This task was based on the work of Heider and Simmel (1944), who created a set of videos consisting of animated triangles and circles, and found that adults perceived the shapes to have intentional actions. Within the Triangles task there are three different types of interaction; random, goal directed (GD) and theory of mind (ToM). During the random animations the triangles do not move with any specific intention and they do not appear to interact with each other (e.g. the triangles are simply drifting or bouncing off the walls of the box). During the GD animations the triangles appear to move with an intention of accomplishing a goal, and they appear to interact physically (e.g. following or fighting). During the ToM animations the triangles appear to move with mental state intentions, and they therefore appear to have mental interactions (e.g. surprising or mocking). During the task participants are asked to describe the movements of the triangles, and responses are marked in terms of appropriateness, intentionality and length. Alternatively, participants may be asked to classify the type of interaction (i.e. none, physical or mental) after watching the clip and to choose from a list of responses about the mental states of the triangles for the ToM clips (White et al 2011). Typically developing individuals are highly accurate at inferring mental states from the animations (Abell et al 2000, Castelli et al 2000, Castelli et al 2002). It has

	Participants	Tasks[a]	Task accuracy	Neural activity
Adams et al (2009)	14 white native American (5 male) 14 native Japanese (5 male)	Modified Eyes task plus Asian Eyes task (72 images, 2 choice), control gender task	Accuracy higher for same vs other culture	Across groups: activity in bilateral portions of the pSTS extending into the TPJ, bilateral TP, left posterior and anterior rostral MPFC, bilateral IFG American vs Japanese: higher activity in bilateral pSTS for same vs other culture
Baron-Cohen et al (1999b)	6 ASD (4 male) 12 control (6 male)	Original Eyes task (30 images, 2 choice), control gender task	Accuracy higher in control group	Across groups: activity in left DLPFC, left MPFC, supplementary motor area, bilateral MTG, bilateral STG, bilateral angular gyri, bilateral supramarginal gyri, left amygdala, left hippocampal gyrus, bilateral insulae, left striatum ASD vs controls: higher activity in left amygdala, right insula and left IFG in controls, higher activity in bilateral STG in ASD

	Participants	Tasks[a]	Task accuracy	Neural activity
Baron-Cohen et al (2006)	12 ASD parents (6 male) 12 controls (6 male)	Modified Eyes task (30 images, 2 choice), control gender task	No group differences in accuracy	ASD parents vs controls: higher activity in left MTG and bilateral IFG in controls All males vs all females: higher activity in left angular gyrus and left DLPFC in males, higher activity in bilateral IFG in females Control males vs control females: higher activity in bilateral IFG in females, higher activity in left STG and left superior IFG in males Control females > control males > ASD parents: left MTG, left DLPFC IFG activity bilateral in control females and left lateralised for control males and ASD parents
Castelli et al (2010)	12 young adults (age 21-30, 2 male) 12 older adults (age 60-78, 4 male)	Eyes task (24 images, 2 choice), control gender task	No group differences in accuracy	Across groups: activity in pSTS, TP, left middle frontal gyrus, right medial frontal gyrus, bilateral IFG, left MTG, parietal and temporo-occipital visual areas, bilateral basal ganglia, bilateral cerebellum Young adults vs older adults: higher activity in bilateral precentral gyrus, left IFG, left STG and bilateral claustrum in older adults, higher activity in left ACC, right superior frontal gyrus and bilateral lingual gyrus in young adults

	Participants	Tasks[a]	Task accuracy	Neural activity
Focquaert et al (2010)	12 high EQ[b] / low SQ[b] (empathising group, all male) 12 low EQ / high SQ (systemising group, all male)	Modified Eyes task (36 images, 2 choice), control gender task	Accuracy higher in empathising group	Empathising: activity in left MTG, left IFG, left medial frontal gyrus, left superior frontal gyrus, left cingulate gyrus Systemising: activity in left MTG, left STG, left IFG Empathising vs systemising: higher activity in left IFG, bilateral STG, bilateral MTG, bilateral angular gyrus, left inferior parietal lobule, left supramarginal gyrus, bilateral TPJ, bilateral FG in empathising group, higher activity in left MTG, left STG, left TP, right superior frontal gyrus, left middle frontal gyrus, left IFG and left parahippocampal gyrus in systemising group
Moor et al (2012)	19 early adolescents (10-12 years, 8 male) 16 mid adolescents (14-16 years, 8 male) 20 young adults (19-23 years, 9 male)	Child Eyes task (28 images, 4 choice), control gender/age task (young male, young female, old male, old female)	Accuracy poorer for mid adolescent group vs early adolescents and young adults	Across groups: activity in bilateral pSTS, bilateral MTG, bilateral STG, left IFG, bilateral insula, right middle cingulate cortex, supplementary motor area, left precentral gyrus As age increased activity in VMPFC, right ACC, right TP, bilateral IFG and right posterior insula decreased

	Participants	Tasks[a]	Task accuracy	Neural activity
Platek et al (2004)	5 controls[c]	Modified Eyes task (36 images, subjects asked to think about mental state), control rest condition	-	Activity in bilateral middle frontal gyrus, left medial superior frontal gyrus, left STG, left TP
Russell et al (2000)	5 schizophrenia (all male) 7 controls[c]	Original Eyes task (30 images), control gender task	Accuracy higher in control group	Controls: activity in left IFG, left MTG, left STG Schizophrenia vs controls: higher activity in left IFG in controls

Table 1-1. Studies investigating neural activation during the Eyes task

[a] **original Eyes task refers to Baron-Cohen et al (1997), modified Eyes task refers to Baron-Cohen et al (2001c), child Eyes task refers to Baron-Cohen et al (2001a),** [b] **EQ (empathising quotient, see Baron-Cohen and Wheelwright (2004)), SQ (systemising quotient, see Baron-Cohen et al (2003)),** [c] **gender of participants not given**

Abbreviations: ACC (anterior cingulate cortex), ASD (autism spectrum disorder), DLPFC (dorsolateral prefrontal cortex), FG (fusiform gyrus), IFG (inferior frontal gyrus), MPFC (medial prefrontal cortex), MTG (middle temporal gyrus), pSTS (posterior superior temporal sulcus), STG (superior temporal gyrus), TP (temporal pole), TPJ (temporoparietal junction), VMPFC (ventromedial prefrontal cortex)

been suggested that the ToM animations may show greater depth of processing compared to the GD and random animations, as longer gaze fixations are made to the ToM animations (Klein et al 2009).

Mental state attribution while viewing the ToM interactions produces more activity in the medial prefrontal cortex, temporoparietal junction (at the superior temporal sulcus), basal temporal regions (at the fusiform gyrus, inferior temporal gyrus and temporal poles adjacent to the amygdala), and in extrastriate regions (at the inferior occipital gyrus) compared to viewing the random and GD interactions (Castelli et al 2000, Castelli et al 2002).

1.6.4 Summary

Theory of mind refers to our ability to attribute mental states, including feelings, thoughts, intentions, beliefs and desires. This ability develops early, with 3 year olds showing evidence of possessing theory of mind. Many regions of the social brain are important for theory of mind, in particular the prefrontal cortex and superior temporal sulcus. Tasks designed to test theory of mind abilities may test cognitive theory of mind (i.e. the ability to make inferences about someone's knowledge and beliefs), or affective theory of mind (i.e. the ability to make inferences about someone's emotional state). The original theory of mind tasks tested participants' abilities to understand false beliefs held by others, and to predict their behaviours based on these false beliefs. These tasks are not suitable for use in adults, and more recently tasks have been developed which may be used to test the theory of mind abilities of adults, such as the Eye task and the Triangles task. The Eyes task consists of a set of images of the eye region, and participants are required to interpret the mental states of the individuals in the images. During this task then neural activity occurs in frontal regions and temporal regions. The Triangles task consists of a series of videos of two triangles which appear to move randomly, interact physically or interact mentally. Participants are required to describe and / or classify the interactions. Viewing the mental interactions has been associated with neural activity in the medial prefrontal cortex, in temporal regions and in extrastriate regions.

1.7 Genetic influences on facial emotion recognition and theory of mind abilities

The development of facial emotion recognition and theory of mind abilities is thought to be influenced by genetics, although as with many other cognitive processes, these genetic influences are likely to be complex with many genes involved. Few studies to date have investigated specific genetic influences on theory of mind abilities, and so the majority of

work discussed in this section will relate to genetic influences on emotion recognition abilities.

A recent study by Lau et al (2009) investigated the influences of genetics and environment on emotion recognition abilities using a twin study, with 10 year old monozygotic and dizygotic twins. The results suggested genetic influences accounted for approximately 17-20% of the variance in recognition abilities across the six basic emotions, and genetic influences were strongest for the recognition of fear. Genetic factors have also been suggested to have an important contribution to ERP responses to emotional faces in a twin study using 12 year olds, specifically influencing the N240 (thought to have a similar role to the N170 in adults) which was suggested to have a genetic contribution which accounted for 36-64% of individual variability, and the P300 (thought to correspond to processes involved in knowledge of emotions) which had a genetic contribution of 42-62% which accounted for individual variability (Anokhin et al 2010).

Twin studies investigating genetic influences on theory of mind abilities have suggested that in 3 year olds there is a strong genetic influence on theory of mind abilities as assessed using a false belief task, with genetics accounting for 67% of the observed variance in task performance (Hughes and Cutting 1999). Further, both prosocial and antisocial theory of mind abilities have been reported to show strong genetic influences in 2-4 year olds, with a genetic contribution of 25-57% accounting for variability (Ronald et al 2005). However, twin studies investigating genetic influences on theory of mind abilities in older children have suggested lower genetic influences, with genetics accounting for 15% of the variance in a false belief task in 5 year olds (Hughes et al 2005) and 12% of the variance in performance on Happé's strange stories task in 9 year olds (Ronald et al 2006).

1.7.1 Specific genetic influences on emotion recognition and theory of mind abilities

Several genes have been identified to date as potentially influencing emotion recognition and theory of mind abilities, including the serotonin transporter gene and genes involved in the dopamine system (see below). The MET and AKT genes have also been suggested to influence facial emotion perception (Lin et al 2012), and an association between the oxytocin receptor and performance on the Eyes task has been reported (Rodrigues et al 2009). The BDNF gene has been associated with fear processing, influencing fear recognition abilities and neural activity in the anterior cingulate cortex, brainstem and insula and functional connectivity between the anterior cingulate cortex and left hippocampus while viewing fearful faces (Mukherjee et al 2011). The AVPR1A gene has also been associated with influencing amygdala activity in response to emotional faces (Meyer-Lindenberg et al 2009), and the CNR1 gene has been associated with influencing striatal responses to happy faces

(Chakrabarti et al 2006). Finally, the ZNF804A gene (which has been associated with the development of psychosis) has been associated with influencing prefrontal functional connectivity during an emotion recognition task (Esslinger et al 2011), and influencing neural activity within the medial prefrontal cortex, left temporo-parietal cortex, left inferior parietal cortex and left inferior frontal cortex, and functional connectivity between frontal and temporo-parietal regions during a theory of mind task which required participants to detect changes in mental states in cartoon characters (Walter et al 2011). However, this gene has been reported not to influence performance on the Eyes task (Hargreaves et al 2012).

1.7.1.1 Serotonin transporter gene

The serotonin transporter gene is the most widely researched gene in terms of a genetic influence on neural responses to emotional faces (Canli and Lesch 2007). This gene plays an important regulatory role in serotonergic neurotransmission (Heils et al 1996, Lesch et al 1994), and a polymorphism within its promoter region (5HTTLPR) results in two different variants, the short and long alleles. The short allele is dominant over the long allele, and short allele carriers show reduced transcription of the serotonin transporter, leading to less efficient serotonin reuptake in synapses compared to individuals homozygous for the long allele (Heils et al 1996). A single nucleotide polymorphism within the long allele has also been reported which decreases expression of the serotonin transporter (Hu et al 2006).

It was first suggested by Hariri et al (2002) that individuals possessing at least one short allele at 5HTTLPR showed increased amygdala responses to fearful faces compared to individuals possessing two long alleles. A meta-analysis confirmed a significant influence of 5HTTLPR on amygdala activation, estimating this gene to account for up to 10% of phenotypic variation (Munafo et al 2008). Increased amygdala activation in individuals carrying at least one short allele compared to those homozygous for the long allele has also been suggested for masked sad faces, but not for masked happy faces (Dannlowski et al 2010). Short allele homozygous individuals have also been suggested to show greater right fusiform gyrus activity in response to fearful faces and greater functional connectivity between the right fusiform gyrus and both the right amygdala and the right ventrolateral prefrontal cortex compared to individuals homozygous for the long allele (Surguladze et al 2008).

In addition to the influence of 5HTTLPR genotype on neural activation, differences between individual possessing the different alleles have also been reported for other aspects of emotional face processing. Adults possessing at least one short allele have been reported to show better fear recognition and poorer happy recognition from facial expressions compared to adults homozygous for the long allele (Defrancesco et al 2011), while those possessing two copies of the short allele have been reported to show an increased sensitivity to the

recognition of angry expressions compared to those possessing at least one long allele (Antypa et al 2011). Further, under acute tryptophan deletion (which reduces the synthesis of serotonin in the brain) the fear recognition abilities of individuals carrying at least one short allele were reduced, while there was no effect on those homozygous for the long allele (Marsh et al 2006). Individuals homozygous for the short allele may show a greater difficulty in disengaging attention from happy, sad and fearful expressions compared to long allele homozygotes (Beevers et al 2009), and it has also been reported that individuals homozygous for the short allele may show a greater bias towards angry faces and a smaller bias towards happy faces compared to those possessing at least one long allele (Perez-Edgar et al 2010). Adults possessing at least one short allele may show a gaze bias towards positive compared to sad, fearful and neutral faces which was absent in those homozygous for the long allele (Beevers et al 2011), although another study has reported selective attention towards positive over negative pictures in individuals homozygous for the long allele, with this pattern being absent in individuals possessing at least one short allele (Fox et al 2009b).

Results of these studies suggest that the short allele may be associated with an enhanced reactivity to negative stimuli, although other studies do not support this conclusion. Children carrying at least one short allele show a smaller N400 amplitude to angry faces compared to children homozygous for the long allele (Battaglia et al 2005), and compared to individuals possessing at least one long allele, possessing two copies of the short allele has been reported to be associated with impaired matching of fearful faces in children (Szekely et al 2011). The difference between these results and those which suggest an increased sensitivity to emotional faces in individuals possessing at least one copy of the short allele may be due to the age of participants used; studies which suggested an association between the short allele and an enhanced reactivity to negative stimuli used adult participants, while studies which suggested a decreased reactivity used children participants.

1.7.1.2 Genes in the dopamine system

Genetic variations within the dopamine system have been suggested to influence emotion recognition abilities for sad, fearful, angry, surprised and disgusted faces, with the largest effects on disgust and surprise recognition (accounting for 18% and 10% of the variance respectively) (Zhu et al 2012). The influence of variation at codon 158 within the COMT gene has been most widely studied, with a substitution of valine for methionine at this codon resulting in the reduced degradation of dopamine, noradrenaline and adrenaline. Individuals homozygous for the Val allele have been reported to show better and faster recognition of negative emotions (especially sad and anger) compared to individuals homozygous for the Met allele (Weiss et al 2007a), although another study reported better recognition of

disgusted and angry expressions in individuals possessing at least one Met allele (Soeiro-de-Souza et al 2012) and another study found no influence of COMT variant on emotion recognition abilities (Defrancesco et al 2011). These differences in results may be due to task differences in the studies.

The COMT gene has also been suggested to influence neural activity in response to emotional faces, with children homozygous for the Met allele showing shorter N170 latencies than children possessing at least one Val allele, with no effect on N170 amplitude (Battaglia et al 2007). In addition, while viewing sad faces, individuals homozygous for the Val allele showed increased amygdala activation while individuals homozygous for the Met allele showed greater ventromedial and ventrolateral prefrontal cortex activity (Lelli-Chiesa et al 2011), and another study reported higher right parahippocampal gyral activity to fearful expressions as the number of Met alleles increased in children (Mechelli et al 2009).

In addition to influences of the COMT gene, the DRD2 gene has been associated with influencing amygdala and dorsolateral prefrontal cortex activity and functional connectivity between these regions while viewing emotional faces (Blasi et al 2009). Further, variation within the DRD4 gene (but not within the COMT or DAT1 genes) has been associated with influencing theory of mind abilities in 3-4 year olds, as assessed using false belief tasks (Lackner et al 2012).

1.7.2 Influence of genes within the X chromosome

An influence of genes within the X chromosome on social cognition has also been suggested (Skuse 2006). A general role of the X chromosome on the development of cognitive abilities has been proposed due to the association of X-linked genes to mental retardation (Ropers and Hamel 2005, Zechner et al 2001), and the finding that genes on the X chromosome are highly expressed in the brain (Nguyen and Disteche 2006). A specific influence of genes on the X chromosome on social cognitive abilities has been suggested due to the sexual dimorphism for impairments in these abilities, with boys showing increased vulnerability to impaired social cognition compared to girls (Skuse et al 2009). Extreme impairments are characteristic of the autism spectrum disorders (ASDs) (APA 1994), a set of disorders which are more prevalent in males compared to females (3:1) (Levy et al 2009). Women affected by Turner Syndrome (TS, X-monosomy) also show impaired social cognition compared to unaffected women (see section 1.8.3). As neurotypical females possess two X chromosomes while males and women with TS possess only one, any influence of genes within the X chromosome on social cognition will therefore be greater in males and women with TS than in neurotypical women. This influence may account for the increased vulnerability to impaired social cognition in males, the gender bias in ASD

prevalence and the poorer social cognition in women with TS compared to neurotypical females.

1.7.3 Summary

Twin studies have confirmed that genetic influences on emotion recognition and theory of mind abilities exist. Several candidate genes have been identified, including the serotonin transporter gene and genes involved in the dopamine system. The serotonin transporter gene has been studied the most, with a polymorphism in its promoter region influencing neural responses to fearful faces, facial emotion recognition abilities, and attention to facial stimuli. In general, results from studies investigating influences of this gene have suggested that the short allele may be associated with an enhanced reactivity to negative expressions. For genes involved in the dopamine system, the COMT gene has been suggested to influence emotion recognition and neural activity in response to emotional faces, and other genes within this system may influence emotional face processing and theory of mind abilities. It has also been suggested that genes within the X chromosome may influence emotion recognition and theory of mind abilities, as males are more vulnerable to impairments in these abilities compared to females, and the ASDs which are associated with extreme impairments are more prevalent in males compared to females. Further, women with TS show poorer social cognition compared to unaffected women. It is therefore important to further investigate specific influences of genes within the X chromosome on emotion recognition and theory of mind abilities.

1.8 Increased vulnerability to poor social cognition in X-monosomy compared to X-disomy

As discussed in section 1.7.2, genes within the X chromosome may influence emotion recognition and theory of mind abilities. This influence may help to explain the poorer emotion recognition and theory of mind abilities in males compared to females, the gender bias in the prevalence of the autism spectrum disorders, and the poorer social cognition of women with Turner Syndrome compared to unaffected women. In the following sections I will review emotion recognition and theory of mind abilities in these populations, as this may indicate influences of genes within the X chromosome. I will then discuss work which has used women with Turner Syndrome as a model to localise a possible genetic influence to the EFHC2 gene.

1.8.1 Healthy males

Within the neurotypical population boys have been suggested to be more vulnerable to poor social cognition compared to girls, with boys showing poorer social and communicative abilities (Skuse et al 2009). Several other studies have also provided evidence for differences in social cognitive abilities between the sexes.

1.8.1.1 Facial emotion recognition abilities

Several studies have suggested that females perform more accurately on facial emotion recognition tasks compared to males (Hall et al 2010, Sasson et al 2010, Startin et al unpublished observations), although other studies have failed to replicate this finding, reporting no difference in the performance of males and females (Derntl et al 2010, Palermo and Coltheart 2004). Further, the variation in fear recognition abilities has been suggested to be larger in 10 year old boys compared to girls (Lau et al 2009).

Corden et al (2006) investigated facial emotion recognition abilities in the general population, and found impairments in fear recognition in a subset of males which were similar to those reported in individuals with amygdala damage. This study used an online questionnaire to test facial emotion recognition abilities, and out of 341 male respondents then 8.8% showed a serious impairment in fear recognition (correctly identifying 5 or fewer fearful faces out of 10), along with mild impairments in the recognition of anger and sadness. These low fear scorers (LFS) formed a distinct population from normal fear scorers (NFS, 68.9% of men), who correctly identified at least 8 fearful faces out of 10. These results suggest large individual differences exist in fear recognition abilities in the male population. This poorer facial fear recognition in a subset of the male population is similar to that found in individuals with an autism spectrum disorder (ASD) (see section 1.8.2.1), suggesting that the poorer emotion recognition abilities in individuals with an ASD also occur in a subset of neurotypical individuals within the general population. This suggests the differences between individuals with an ASD and neurotypical individuals may also be found within the general population, and poor fear recognition abilities are not limited to individuals with an ASD.

1.8.1.2 Neural correlates of face processing

After identifying differences in fear recognition abilities within the male population, Corden et al (2006) compared neural activity in populations of LFS and NFS males in response to neutral faces showing varying head and eye gaze orientations. Participants were asked to judge the gender of the face, with no differences in accuracy being found between the groups.

Higher activity to faces with a direct gaze compared to faces with an averted gaze was found in the left lateral fusiform gyrus, left and right amygdalae, left anterior superior temporal gyrus, right temporal pole and right medial prefrontal cortex in NFS males but not in LFS males. Further, when comparing this difference in activity for direct and averted gazes between groups, NFS males showed higher activity compared to the LFS males in the left lateral posterior fusiform gyrus, left amygdala and left superior temporal gyrus, with trends towards higher activity in corresponding areas in the right hemisphere.

1.8.1.3 Theory of mind abilities

The number of mental states correctly identified in the Eyes task has been reported to be higher for females compared to males (Baron-Cohen et al 1997, Dorris et al 2004, Wakabayashi et al 2012). In addition, using the Triangles task, the LFS males identified by Corden et al (2006) gave fewer and less accurate mental state attributions to the theory of mind animations compared to the NFS males.

1.8.1.4 Summary

Males have been suggested to be more vulnerable to poor social cognition compared to females. This may account for the suggested poorer accuracy of males compared to females during both emotion recognition tasks and the Eyes task. A subset of males have been reported to show extreme impairments in facial fear recognition compared to the majority of males, with this group also showing reduced neural activity in the fusiform gyrus, amygdala and superior temporal gyrus while viewing faces and a poorer performance in attributing mental states during the Triangles task. The results of these studies support a potential influence of the X chromosome on emotion recognition and theory of mind abilities.

1.8.2 Autism spectrum disorders

The autism spectrum disorders (ASDs) are a group of pervasive neurodevelopmental behavioural disorders including autism, Asperger's Syndrome and pervasive developmental disorder - not otherwise specified (PDD-NOS). They have a suggested prevalence of 60 cases per 10,000 children, and they affect boys three times as often as girls (Levy et al 2009). This sex difference in prevalence may be even higher (10:1) when considering high functioning individuals such as those diagnosed with Asperger's Syndrome alone (Skuse et al 2009). The first reported cases of the ASDs were in the 1940s, when groups of children showing severe social and language impairments and repetitive and restrictive behaviours

were described (Asperger 1944, Kanner 1943). The current diagnosis of ASDs relies on similar traits to those first described, with DSM-IV characterising the ASDs with severe verbal and non-verbal impairments in social and communicative functioning, and restricted and repetitive stereotyped behaviours and interests (APA 1994). In the case of autism, delayed language development is also found. These behavioural impairments in social and communicative functioning cause problems in everyday social interactions for affected individuals, producing difficulties in social reciprocity and relationships. There is thought to be a strong genetic influence on the development of these disorders, with multiple candidate genes having been identified although many more genes are yet to be found (Geschwind 2011). The existence of the broad autism phenotype in the family members of individuals with an ASD supports an influence of genetics on the impaired social cognition of affected individuals (see section 1.8.2.7). Although genetic influences on the development of the ASDs are not limited to the X chromosome, the influence of X-linked genes may help to explain the higher prevalence of the ASDs in males compared to females.

1.8.2.1 Facial emotion recognition abilities

Many studies have reported that individuals with an ASD are poorer at accurately recognising basic emotional expressions from faces compared to neurotypical individuals. These impairments are found particularly for fear recognition, but may also be seen for the recognition of other negative emotions (i.e. sadness, anger and disgust) (Ashwin et al 2006, Boraston et al 2007, Corden et al 2008, Critchley et al 2000b, Falkmer et al 2011, Gross 2008, Humphreys et al 2007b, Pelphrey et al 2002, Rump et al 2009, Sawyer et al 2012, Wallace et al 2008). It has further been suggested that these abilities may develop differently in individuals with an ASD compared to neurotypical individuals, with emotion recognition accuracy increasing with age in neurotypical individuals but not in those with an ASD (Rump et al 2009). Further, individuals with an ASD have been suggested to show poorer emotion recognition for images of the upper halves of faces (Gross 2004), and they have been reported to show impaired fear recognition from the eye region alone and impaired disgust recognition from the mouth region alone (Wallace et al 2008).

Although some studies have reported no differences in the facial emotion recognition abilities of ASD and neurotypical individuals (Baron-Cohen et al 1997, Castelli 2005, Gepner et al 2001, Grossman et al 2000b, Jones et al 2011, Katsyri et al 2008, Tracy et al 2011, Wang et al 2004), this does not rule out emotion recognition impairments during social interactions for those with an ASD. These individuals may be able to accurately recognise emotions when explicitly instructed to and therefore consciously assessing facial expressions during experimental tasks, but this ability may be lost during everyday social interactions for which no explicit instructions are given (Wang et al 2004). Supporting this, Begeer et al (2006) suggested that children with an ASD may spontaneously show less

attention to the emotion in faces compared to neurotypical children, but this difference disappears when they are explicitly asked to attend to this information. Further, a general increased attention to faces during tasks may act as a compensatory mechanism to mask possible underlying impaired emotion recognition abilities in the ASDs. Other differences between emotion recognition tasks and everyday social interactions may reduce the impact of emotion recognition impairments in individuals with an ASD during tasks. The expressions used in many emotion recognition studies are exaggerated and static, and individuals with an ASD may show similar recognition levels for these expressions to neurotypical individuals but not for the more subtle and dynamic expressions seen in everyday life. In addition, everyday interactions rely on processes other than simple emotion recognition, such as executive function, and the integration of these processes may affect social interactions of ASD and neurotypical individuals in different ways.

1.8.2.1.1 Reasons for varying results in individuals with an ASD

There are a variety of possible reasons why the results of studies investigating the emotion recognition abilities of individuals with an ASD differ. The populations used in each study vary greatly, with differences between studies being found in terms of the age (in particular whether a study includes adults or children), gender and specific diagnosis of individuals included in the study. Some studies include only those diagnosed with Asperger Syndrome or high functioning autism, while others include individuals diagnosed with low functioning autism. Relating to the diagnosis of individuals, this also affects IQ, and IQ differences between studies may affect the results. The severity of ASD symptoms may also affect these abilities. Another source of variation between studies which may influence the results comes from the specific task and stimuli used. Finally, if differences between ASD and neurotypical individuals are subtle, the sample sizes used may not be powerful enough to detect group differences. It is important to bear these points in mind when comparing studies investigating social cognition in individuals with an ASD.

1.8.2.1.2 Mechanisms resulting in impaired emotion recognition abilities

Several theories have been proposed to explain the suggested impaired emotion recognition abilities in individuals with an ASD, which are not thought to be due to low level perceptual difficulties (Humphreys et al 2007b). Individuals with an ASD have been suggested to show a lack of interest in faces, which results in a lack of experience with them and an inability to utilise the information within them efficiently (Schultz 2005). Alternatively, this lack of experience with faces may be produced due to an active avoidance of face stimuli. This lack of interest in faces may result in a less specialised system for processing faces in individuals with an ASD. Other theories accounting for the poorer emotion recognition abilities in

individuals with an ASD include atypical gaze fixation patterns to faces, the use of an atypical face processing style, atypical amygdala functioning, and impaired theory of mind abilities. A combination of these theories may also help to explain the impairments in emotion recognition abilities in individuals with an ASD. These different mechanisms are discussed further in the following sections.

1.8.2.2 Attention to faces and facial features

Individuals with an ASD have been suggested to show a reduced interest to faces in social scenes compared to neurotypical individuals (Freeth et al 2010, Freeth et al 2011, Kikuchi et al 2009, Sasson et al 2007), and this may be due to either a reduced attraction to or an active avoidance of them. Supporting this lack of interest in faces, individuals with an ASD are less sensitive to detecting subconsciously presented faces (Hall et al 2007) and disengage their attention from faces faster (Chawarska et al 2010, Nakano et al 2010) compared to neurotypical individuals.

Individuals with an ASD have been reported to make fewer gaze fixations to the eye region compared to neurotypical individuals, with a reduced total fixation time to the eyes (Bal et al 2010, Boraston et al 2008, Corden et al 2008, Falkmer et al 2011, Hernandez et al 2009, Jones et al 2008, Klin et al 2002, Pelphrey et al 2002, Spezio et al 2007a, Spezio et al 2007c). This may be due to a reduced saliency of or a lack of interest in the eyes in individuals with an ASD. This lack of fixations to the eye region is not absolute; similar to neurotypical individuals, those with an ASD are often reported to look at the eye region more than any other facial region, but individuals with an ASD show a lower number of total fixations to the eyes (Hernandez et al 2009). However, it has been suggested that the underlying reasons for fixating on the eyes may differ between ASD and neurotypical individuals, with those with an ASD being attracted to the high contrast of the eye region and neurotypical individuals being attracted to the emotional information contained within this region (Chawarska and Shic 2009). In addition, although Bar-Haim et al (2006) reported that both ASD and neurotypical children attend to the eye region more than the mouth region during early processing, they suggested that children with an ASD may lose interest in the eye region or avoid this region at a later stage of processing. The total length of time used to measure fixations is therefore important to consider for results of eye tracking studies.

Further investigating gaze fixations to the eye region, both young children (Chawarska and Shic 2009) and adults (Kliemann et al 2010, Kliemann et al 2012, Spezio et al 2007c) with an ASD have been reported to divert their gaze away from the eyes more than neurotypical individuals. This reduced preference to the eyes in individuals with an ASD may be due to a combination of a reduced orientation to the eyes and an active avoidance of this region (Kliemann et al 2010, Kliemann et al 2012), although Kylliainen et al (2012) suggested that it

is due to a lack of a typical approach related motivational response to direct eye contact only and not due to an active avoidance of this region.

Although some studies have also reported individuals with an ASD fixate less on the mouth than neurotypical individuals (de Wit et al 2008, Spezio et al 2007c), others have reported individuals with an ASD make a higher number of fixations to the mouth region compared to neurotypical individuals (Falkmer et al 2011, Jones et al 2008, Klin et al 2002, Neumann et al 2006, Spezio et al 2007a). This atypical bias for mouth fixations in individuals with an ASD has been suggested to be due to an atypical top-down strategy for allocation of visual attention, and not an exaggerated sensitivity to the bottom-up saliency of the features (Neumann et al 2006). Supporting a decreased reliance on the eyes and an increased significance of the mouth for those with an ASD, children with an ASD show an advantage for recognising face parts when the mouth was present compared to when the eyes were present, while the opposite was found for neurotypical children (Joseph and Tanaka 2003).

1.8.2.3 Emotional face processing style

Individuals with an ASD have been suggested to use a reduced top-down configural / holistic processing style when viewing faces compared to neurotypical individuals, instead using an increased bottom-up feature based processing style (Loth et al 2010, Rosset et al 2008, Rutherford and McIntosh 2007, Wallace et al 2008). Gross (2005) reported that children with an ASD are less sensitive to the global configurations of faces compared to neurotypical children, suggesting those with an ASD utilise local information more and global information less than neurotypical individuals. Further supporting a general reduction in the integration of facial information in those with an ASD, these individuals may show a reduced interaction of processing emotion and identity compared to neurotypical individuals (Krebs et al 2011). A reduced inversion effect has also been reported in children with an ASD compared to neurotypical children, suggesting they are less affected by the disrupted holistic processing of inverted faces (Annaz et al 2009, Bookheimer et al 2008, Gross 2008, Rosset et al 2010, van der Geest et al 2002). This may be due to a disruption of the specialised system for processing upright faces which is present in neurotypical children (Annaz et al 2009).

This suggested reduced holistic / configural face processing style in individuals with an ASD may result from atypical early visual perceptual processes, affecting feedback to visual areas and subsequent holistic processing (Batty et al 2011). Results from ERP studies have further supported the proposed impaired holistic / configural processing style in children with an ASD, possibly resulting in a reduced N170 amplitude and longer latency to faces compared to that found for neurotypical children (see section 1.8.2.5.2). However, it is still possible that a mixture of configural and feature based processing occurs in individuals with an ASD, even if the overall style is different from that observed in neurotypical individuals

(Annaz et al 2009). Joseph and Tanaka (2003) reported that similar to neurotypical children, those with an ASD are better at recognising face parts in whole faces than in parts of faces, suggesting the use of holistic processing and indicating that impaired holistic processing cannot completely account for problems with face processing associated with the ASDs.

1.8.2.4 Neural correlates of face processing

1.8.2.4.1 Fusiform gyrus

Individuals with an ASD have been reported to show reduced activity in the fusiform gyrus (FG) for both neutral (Pierce et al 2001, Schultz et al 2000) and emotional faces (Corbett et al 2009, Critchley et al 2000b, Hubl et al 2003, Kleinhans et al 2011, Perlman et al 2011, Piggot et al 2004, Wang et al 2004) compared to neurotypical individuals. This difference may be due at least in part to a difference in fixation patterns to the faces; when individuals with an ASD were instructed to fixate on the eye region while viewing fearful faces this increased their FG activity so that it no longer differed from that of controls (Perlman et al 2011). Similarly, Dalton et al (2005, 2007) reported decreased FG activation in those with an ASD compared to neurotypical individuals in response to faces, and they further suggested that FG activity positively correlated with eye fixations in the ASD group.

1.8.2.4.2 Superior temporal sulcus

Activity in the superior temporal sulcus (STS) has also been reported to be reduced for individuals with an ASD compared to neurotypical individuals in response to neutral faces (Hadjikhani et al 2007, Pierce et al 2001), although a recent meta-analysis has suggested STS activity is higher for those with an ASD compared to neurotypical individuals while viewing emotional faces (Sugranyes et al 2011). It has also been suggested that STS activity shows reduced sensitivity in individuals with an ASD compared to neurotypical individuals to congruent compared to incongruent gazes (Pelphrey et al 2005) and to facial motion (Pelphrey et al 2007).

1.8.2.4.3 Amygdala

Amygdala activity has been suggested to be lower for individuals with an ASD compared to neurotypical individuals while viewing neutral (Dalton et al 2007, Hadjikhani et al 2007, Pierce et al 2001) and emotional faces (Ashwin et al 2007, Corbett et al 2009, Critchley et al

2000b, Ishitobi et al 2011, Kleinhans et al 2011, Pelphrey et al 2007, Perlman et al 2011), with a reduced habituation in the individuals with an ASD (Kleinhans et al 2009). In contrast, it has also been reported that individuals with an ASD produce higher amygdala activity in response to faces compared to neurotypical individuals (Dalton et al 2005, Monk et al 2010, Weng et al 2011), and this activity may be positively correlated with fixations to the eye region in individuals with an ASD (Dalton et al 2005). However, it is unknown whether this increased activity was due to the possible increased directing of gaze from the amygdala towards the eyes or due to increased arousal as a result of increased fixations on the eyes. Results from Kliemann et al (2012) support an increased activity of the amygdala when directing gaze towards the eyes in individuals with an ASD compared to neurotypical individuals, while directing gaze towards the mouth was associated with lower amygdala activity for the individuals with an ASD compared to the neurotypical individuals.

1.8.2.5 Electrophysiological correlates of face processing

As mentioned in section 1.8.2.3, differences in ERPs for faces between individuals with an ASD and neurotypical individuals may support a difference in face processing styles. Further supporting processing differences, dipole source analysis of ERP data has suggested that while viewing neutral and emotional faces, children with an ASD may show delayed activity in the visual cortex (suggesting slower face detection) and reduced activity in the fusiform gyrus and the medial prefrontal lobe (suggesting reduced configural face processing and mental state decoding respectively) compared to neurotypical children (Wong et al 2008).

1.8.2.5.1 Effect on P1

For both neutral and emotional faces, P1 amplitude has been reported to be smaller for individuals with an ASD compared to neurotypical individuals (Batty et al 2011) with a longer latency (Batty et al 2011, O'Connor et al 2005), although other studies have found no group differences in either amplitude or latency (Akechi et al 2010, Wong et al 2008). It has also been reported that there are no differences in either P1 amplitude or latency to neutral full faces, eyes or mouths between ASD and neurotypical individuals, with both groups showing larger amplitudes to the eyes alone and shorter latencies to the full faces (O'Connor et al 2007). In addition, whereas the P1 of neurotypical individuals is sensitive to the orientation of faces, producing a higher amplitude for inverted compared to upright emotional faces, there may be no effect of face orientation in children with an ASD (Hileman et al 2011).

1.8.2.5.2 Effect on N170

One study has reported a smaller N170 amplitude for neutral and emotional faces in individuals with an ASD compared to neurotypical individuals (O'Connor et al 2005), while another has suggested a trend towards smaller N170 amplitudes in children with an ASD compared to neurotypical children when viewing faces (Kylliainen et al 2006). However, the majority of studies have found no differences in amplitudes between those with an ASD and neurotypical individuals for both neutral and emotional upright and inverted faces (Batty et al 2011, Hileman et al 2011, McPartland et al 2004, O'Connor et al 2007, Webb et al 2006, Wong et al 2008). Similar N170 amplitudes between individuals with an ASD and neurotypical individuals have also been reported for the eye and mouth regions alone, although both groups produced a larger N170 to the eyes alone compared to the mouth alone and full faces (O'Connor et al 2007).

While viewing both neutral and emotional faces, individuals with an ASD have been reported to show longer N170 latencies compared to neurotypical individuals, with no effect on N170 latency to objects and no effect of emotion (Batty et al 2011, Hileman et al 2011, McPartland et al 2004, O'Connor et al 2005, O'Connor et al 2007). Delayed N170 latencies to both the eye and the mouth regions have also been reported in those with an ASD compared to neurotypical individuals, although both groups show faster N170 latencies to full faces compared to the eyes and mouth regions and to the eyes compared to the mouth (O'Connor et al 2007). In addition, neurotypical children show faster N170 responses to faces compared to objects, whereas the reverse occurs for children with an ASD (Webb et al 2006). The longer latencies for individuals with an ASD compared to neurotypical individuals have been reported to occur for both upright and inverted faces (Hileman et al 2011), with neurotypical children showing longer latencies to inverted compared to upright faces and no difference between the two for children with an ASD (McPartland et al 2004). In contrast, other studies have reported no differences in N170 latencies between those with an ASD and neurotypical individuals for neutral and emotional faces (Akechi et al 2010, Churches et al 2010, Wong et al 2008).

1.8.2.6 Theory of mind abilities and related neural activity

Individuals with an ASD are often reported as showing an impaired theory of mind; a majority of autistic children aged 10 fail false belief tasks, whereas typically developing 4 year olds are able to pass these tasks (Baron-Cohen et al 1985). Impaired performance is also observed in other theory of mind tasks in individuals with an ASD compared to neurotypical individuals.

1.8.2.6.1 Reading the Mind in the Eyes Task

Both adults (Baron-Cohen et al 1997, Baron-Cohen et al 1999b, Baron-Cohen et al 2001c, Craig et al 2004, Kirchner et al 2011, Losh et al 2009) and children (Brent et al 2004, Kaland et al 2008) with an ASD have been reported to show an impaired performance on the Eyes task compared to neurotypical individuals, correctly identifying fewer mental states. Performance on this task has been positively correlated with eye fixations for negatively valenced complex expressions in individuals with an ASD (Kirchner et al 2011). However, other studies have reported no differences in the performance of adults with an ASD and neurotypical adults on this task (Couture et al 2010, Spek et al 2010). Baron-Cohen et al (1999b) reported that during the Eyes task, adults with an ASD show decreased activity in the amygdala, insula and inferior frontal gyrus compared to neurotypical individuals, and higher activity in the superior temporal gyrus.

1.8.2.6.2 The Frith-Happé Animated Triangles task

During the Triangles task both children and adults with an ASD give fewer and less accurate mental state descriptions for the theory of mind (ToM) animations compared to neurotypical individuals, scoring poorer on both appropriateness and intention, with no differences in the descriptions given for the random and goal directed animations (Abell et al 2000, Campbell et al 2006, Castelli et al 2002, Jones et al 2010, Salter et al 2008, Schwenck et al 2012, White et al 2011). Adults with an ASD are also poorer at categorising the interactions, and identifying the mental states of the triangles in the ToM animations (White et al 2011). While viewing the ToM animations, higher brain activity has been reported in neurotypical individuals compared to individuals with an ASD in the medial prefrontal cortex, superior temporal sulcus and basal temporal area (Castelli et al 2002).

1.8.2.7 Broad autism phenotype

Studies investigating the social cognitive abilities of relatives of individuals with an ASD support the existence of the broad autism phenotype (BAP). The BAP suggests that traits which contribute towards impaired social cognition in individuals with an ASD are also found in the family members of these individuals. These endophenotypic traits are therefore likely to be heritable and are influenced by genetic variation, and so the endophenotypic approach supports a role for genetics in the development of autistic-like traits.

1.8.2.7.1 Emotion recognition abilities

The parents and siblings of children with an ASD have been reported to show impaired recognition of fearful, sad and disgusted facial expressions compared to individuals who have no first degree relatives with an ASD (Palermo et al 2006, Wallace et al 2010). These impairments may occur in only a subset of family members and may be subtle; supporting this parents on the BAP may show impaired fear recognition at low intensities only (Losh et al 2009). Further, Fiorentini et al (in preparation) found that although relatives of children with an ASD were not impaired on their emotion recognition abilities compared to control relatives, the ASD relatives showed faster RTs. The authors suggested this difference may be due to the ASD relatives utilising a more feature based style.

1.8.2.7.2 Attention to facial features

The siblings of individuals with an ASD have been reported to show decreased eye fixations compared to individuals with no first degree relative with an ASD during a face recognition task (Dalton et al 2007). Similarly, the infant siblings of children with an ASD may show reduced fixations to their mothers eyes compared to control siblings (Merin et al 2007). However, another study found no differences in gaze fixation patterns to faces between fathers of children with an ASD compared to control fathers (Greimel et al 2010). This suggests that an influence on gaze fixations to the eye region may be greater in ASD siblings compared to ASD fathers. An effect in ASD parents may be limited to those who are considered to be 'aloof', with these individuals showing a reduced use of information from the eye region and an increased use of information from the mouth region during an emotion recognition task compared to control parents (Adolphs et al 2008).

1.8.2.7.3 Neural and electrophysiological correlates of face processing

The siblings of individuals with an ASD may show a similar decrease in fusiform gyrus activity during a face recognition task to their relatives with an ASD compared to control individuals (Dalton et al 2007), while the fathers of children with an ASD may show reduced fusiform gyrus and amygdala activity during a facial emotion recognition task compared to control fathers (Greimel et al 2010). Using electrophysiological recordings to investigate neural activations, it has been reported that while control parents show a faster N170 latency for faces compared to objects this difference may not be present in parents of children with an ASD (Dawson et al 2005).

1.8.2.7.4 Theory of mind abilities and related neural activity

Family members of individuals with an ASD may also show subtle impairments in accuracy on the Eyes task, with siblings of children with an ASD performing poorer than control children (Dorris et al 2004). Although it has been reported that parents of children with an ASD do not show impaired performance on this task (Baron-Cohen et al 2006, Gokcen et al 2009), Losh and colleagues (2007, 2009) have suggested that a subset of parents of children with an ASD, specifically those who may be considered more 'aloof' or who lie on the BAP, show an impaired performance on this task compared to control parents. If an effect on performance during this task is found only in those more 'aloof' parents or those who lie on the BAP this may explain the lack of an effect in previous studies (Baron-Cohen et al 2006, Gokcen et al 2009).

During the Eyes task parents of children with an ASD may also show altered neural activity, with decreased activation in the inferior frontal gyrus (IFG) and middle temporal gyrus compared to controls. Further, while control females showed bilateral IFG activity compared to the left lateralised IFG activity of control males, there was no difference between the mothers and females of those with an ASD, with both groups showing left lateralised IFG activity (Baron-Cohen et al 2006). This suggests a male-pattern activation of the IFG in the mothers of children with an ASD, which may be due to genetic factors which are associated with ASD traits.

1.8.2.8 Summary

The ASDs are characterised by impaired social and communicative functioning, along with restricted and repetitive interests. The prevalence of the ASDs is higher for boys compared to girls (3:1), and a larger sex difference may exist when considering high functioning individuals only (10:1). This gender bias may suggest an influence of genes within the X chromosome on those social cognitive abilities which are impaired in individuals with an ASD. It has frequently been reported that individuals with an ASD are less accurate at recognising facial expressions, in particular for fear. This may be due to those with an ASD showing a lack of interest in faces, and reduced fixations to the eye region of faces, or due to those with an ASD using a more local feature based and less global configural face processing style compared to neurotypical individuals. Individuals with an ASD have also been suggested to show decreased fusiform gyrus and amygdala activity for faces compared to neurotypical individuals. These individuals also show decreased N170 latencies to faces, suggesting a decreased configural processing style. Individuals with an ASD have been suggested to possess an impaired theory of mind, performing less accurately on both the Eyes task and the Triangles task compared to neurotypical individuals, and showing atypical neural activity during these tasks. Subtle differences in the

above behaviours and activation patterns have also been suggested in the relatives of those with an ASD compared to individuals who have no first degree relatives with an ASD, supporting a role for genetic factors in the development of these abilities and related neural activities.

1.8.3 Turner Syndrome

Similar to individuals with an ASD, women with Turner Syndrome (TS) also often suffer from impaired social cognition. The prevalence of TS has been estimated at 1 in 2500 women (Good et al 2003), and TS is characterised by the presence of only one complete X chromosome compared to the two X chromosomes found in unaffected women. The second sex chromosome (either X or Y) is often missing completely, although in some cases part of it may be present. The complete X chromosome may either be of maternal or paternal origin; around two thirds of women with TS possess a maternal X chromosome (Xm) while the remaining third possess a paternal X chromosome (Xp).

Supporting reports of impaired social cognition in women with TS compared to unaffected women, it has been suggested that the ASDs occur relatively commonly in women with TS compared to unaffected women; in unaffected women the prevalence of ASDs is approximately 1 in 10,000, while the prevalence has been suggested to be approximately 300 times higher in women with TS (with 5 out of the 150 women involved in one study having been diagnosed with an ASD) (Creswell and Skuse 1999). Differences in social cognition have further been found between Xm and Xp women, with Xp women showing higher social and communication skills compared to Xm women, as demonstrated by fewer social difficulties and higher behaviour inhibition (Skuse et al 1997). Similarly, unaffected women (who possess a paternal X) show higher social and communication skills than males (who possess only a maternal X) (also see section 1.8.1). These results suggest the existence of an imprinted X-linked genetic locus which has an important role in the development of social cognition, and which is expressed only on paternal X chromosomes and is inactive in maternal X chromosomes. The presence of a paternal X chromosome may therefore offer protection against social cognitive disorders (such as the ASDs) in X-disomic females, contributing towards the explanation as to why males (who do not possess the paternal imprinted locus) are more vulnerable to disorders of social cognition than females. Supporting this, in the population of women with TS studied by Creswell and Skuse (1999) all five of the women with an ASD possessed only a maternal X chromosome.

1.8.3.1 Facial emotion recognition abilities

Women with TS have been suggested to show poorer accuracy during tasks investigating facial emotion recognition abilities compared to unaffected women, with these impairments being found specifically for fear and anger recognition. This impaired recognition has been found both with images of the whole face (Good et al 2003, Lawrence et al 2003a, Mazzola et al 2006, Skuse et al 2005) and images of just the eye region (Lawrence et al 2003b). No differences between the Xm and Xp TS groups have been found (Good et al 2003, Mazzola et al 2006, Weiss et al 2007b).

1.8.3.2 Attention to facial features

It has further been investigated whether poorer facial emotion recognition accuracy in women with TS may be accounted for by a difference in fixation patterns to faces. Women with TS have been suggested to show reduced eye contact compared to unaffected women (Lawrence et al 2003b), and while viewing images of emotional faces, women with TS have been reported to fixate on the mouth region more than unaffected women (Mazzola et al 2006). This difference in mouth fixations was observed in particular for fearful faces, and in addition, a subset of the women with TS (around a third) also showed a very low number of fixations to the eye region compared to the unaffected women. Similar to the emotion recognition results, no differences were found within the TS group based on the parental origin of the X chromosome.

1.8.3.3 Emotional face processing style

Configural face processing has been suggested to be unaffected by TS, with women with TS showing a similar sensitivity to face orientation and a similar preference to whole faces compared to partial faces to that shown by unaffected women. However, fear recognition and face identity recognition abilities show correlation in unaffected women but not in Xm women with TS, and Xm women with TS show impaired face identity recognition skills. Differences in face processing between TS and unaffected women may therefore exist (Lawrence et al 2003a).

1.8.3.4 Neural correlates of face processing

Skuse et al (2005) compared neural activations in response to fearful faces between TS and unaffected women. They found similar fusiform gyrus activity between the groups, with both

groups showing a positive correlation between left, but not right, fusiform gyrus activity and fear recognition abilities. Both groups also showed bilateral amygdala activity in response to fearful faces, despite impaired fear recognition abilities in the women with TS. However, left amygdala activity was lower and right amygdala activity was higher for the TS compared to the unaffected women, and for both amygdalae activity was more persistent in the women with TS suggesting lower habituation than in the unaffected women. Further, the unaffected women showed a positive correlation between fear recognition abilities and bilateral amygdala activation, while the fear recognition abilities of the women with TS showed no correlation with left amygdala activity and a negative correlation with right amygdala activity. These results suggest women with TS show a functional dissociation between the cognitive appraisal and autonomic arousal for fearful faces; despite their impaired cognitive abilities in recognising fearful facial expressions they show typical or enhanced autonomic responses as measured using amygdala activation. This may further suggest a possible functional dissociation between the left and right amygdalae in women with TS, with the two amygdalae playing different roles in the processing of fearful faces. In support of this, the left and right amygdalae have been suggested to show functional differences in emotion processing, with the left amygdala involved in cognitive processing and the right amygdala linked to autonomic arousal (Dyck et al 2011).

1.8.3.5 Theory of mind abilities

Poorer theory of mind abilities have also been suggested in women with TS compared to unaffected women, with women with TS correctly identifying fewer mental states on the Eyes task (Lawrence et al 2003b) and Xm women with TS scoring lower on intentionality when describing the theory of mind animations in the Triangles task (Lawrence et al 2007).

1.8.3.6 Summary

TS is characterised by the presence of only one complete X chromosome in women. The prevalence of ASDs is higher in women with TS compared to unaffected women, suggesting that possessing a second X chromosome in women may be protective against disorders of social cognition. Women with TS have been suggested to show poorer social cognitive abilities compared to unaffected women, with women with TS showing poorer facial fear and anger recognition. These women may also show altered gaze fixation patterns to faces, with an increased number of fixations to the mouth. It has also been suggested that face processing mechanisms may differ between TS and unaffected women, although this difference may not be due to a difference in the use of configural processing. Neural activity in response to fearful faces has also been suggested to differ between TS and unaffected

women; while both groups show similar fusiform gyrus activity the women with TS may show a functional disconnectivity between the left and right amygdalae. This may result in a dissociation between their cognitive processing and autonomic arousal in response to fearful faces, with impaired accuracy in recognising fearful expressions and typical or enhanced amygdala activity. Finally, women with TS have been suggested to show poorer theory of mind abilities compared to unaffected women, as women with TS have been reported to correctly identify fewer mental states in the Eyes task and to describe the mental interactions during the Triangles task with a lower accuracy.

1.9 Localising a potential locus associated with fear recognition abilities to the EFHC2 gene

As discussed in section 1.8.3, women with TS show impaired facial fear recognition abilities compared to unaffected women (Good et al 2003, Lawrence et al 2003a, Lawrence et al 2003b, Mazzola et al 2006, Skuse et al 2005). This suggests a possible role of the X chromosome in fear recognition abilities, involving one or more X-linked genes irrespective of any involvement of the Y chromosome (Good et al 2003). Further, Xm women show poorer social and communication skills compared to Xp women, suggesting the existence of an imprinted locus on the X chromosome which contributes towards social cognition (Skuse et al 1997).

To map this imprinted locus, Skuse et al (1997) studied a further group of females with partial deletions of the short arm of the paternal X chromosome using neuropsychological and molecular techniques. Based on the social and communicative skills of these women and the locations of their deletions on the paternal X chromosome, it was suggested the locus probably lies on Xq or close to the centromere on Xp and it escapes X-inactivation. Extending this work, Good et al (2003) used a deletion mapping strategy to localise the genes responsible for impaired fear recognition in TS females with structural X-anomalies of the short arm (Figure 1-4). They found an apparent dosage-sensitive genetic locus at Xp11.3 (no greater than 4.96Mb) influenced fear recognition abilities; females who had this critical locus deleted in their second X chromosome, irrespective of the parental origin of their deletion, showed impaired fear recognition abilities despite normal intelligence, and further, they showed enlarged amygdala and orbitofrontal cortex volumes. These alterations in brain structure may contribute towards the observed impaired fear recognition. Further investigating this apparent dosage-sensitive genetic locus at Xp11.3, Weiss et al (2007b) used dense mapping to identify the genes influencing fear recognition in this region; the variability in fear recognition accuracy seen in women with TS suggests the existence of a quantitative trait locus (QTL) revealed by X-monosomy. In total, 294 single nucleotide polymorphisms (SNPs) in this region were initially genotyped across 93 women with TS, with

77 of these SNPs showing a possible association to fear recognition abilities. These 77 SNPs were then genotyped in a further 77 women with TS. Both populations of women with TS showed an association between fear recognition abilities and four SNPs in a particular region of interest. These four SNPs were in strong linkage disequilibrium (LD), spanning 40kb within a novel transcript, EF-hand domain containing 2 (EFHC2). The association with fear recognition was maximal at two of these SNPs, rs7055196 and rs7887763, with these two SNPs being in perfect LD.
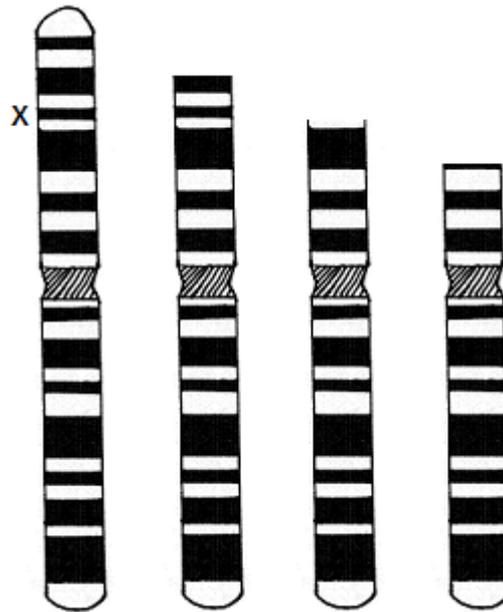
Figure 1-4. The deletion mapping strategy can be used to identify genetic loci which are important for a particular trait. If individuals who possess a particular locus (e.g. X) show a particular trait and individuals who do not possess that locus do not show that trait, it can be inferred that locus X is important for that trait

In this study by Weiss et al (2007b), which found a maximal association to impaired fear recognition at SNPs rs7055196 and rs7887763 within the EFHC2 gene, women possessing the G allele at SNP rs7055196 showed poorer fear recognition accuracy compared to women possessing the A allele at this SNP (P = 0.00007, Figure 1-5). The G allele occurred at a frequency of 8.8%, and this SNP had an estimated effect size accounting for over 13% of the variance in fear recognition. When the sample of women with TS was further divided into normal fear scorers (NFS) and low fear scorers (LFS), the G allele was found at a frequency of 1% in the NFS and 20% in the LFS. Although a later study did not find an association between SNP rs7055196 and facial fear recognition abilities in women with TS, this study used a much smaller sample (97 women, 11 of whom possessed the G allele) (Zinn et al 2008).
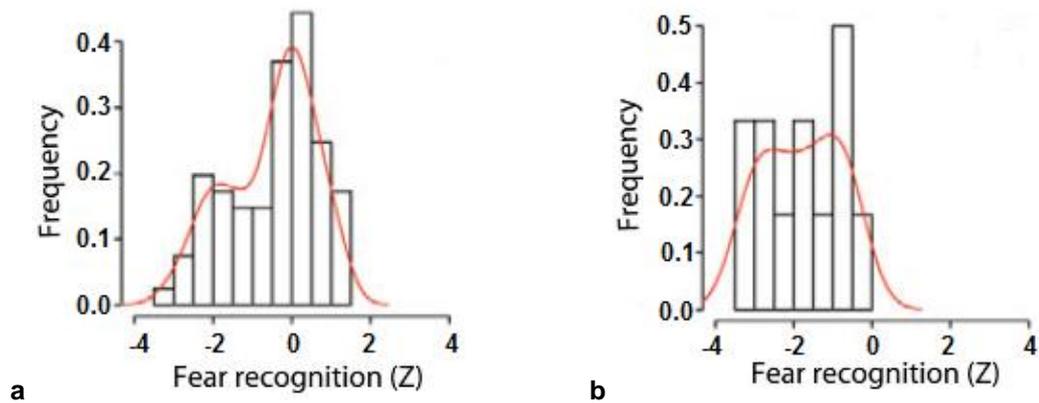
Figure 1-5. Frequency distributions for the facial fear recognition abilities (Z-scores) of women with TS possessing different alleles at SNP rs7055196; women possessing the A allele (a, mean Z-score = -0.54) showed higher accuracy than women possessing the G allele (b, mean Z-score = -1.80) (figure adapted from Weiss et al (2007b))

1.9.1 The EFHC2 gene

As mentioned, the EFHC2 gene is located on the X chromosome at Xp11.3. This gene is a human paralog to the EFHC1 gene, which is found on chromosome 6 (Suzuki et al 2004). Paralog genes are those with shared ancestry, and the presence of paralogs occurs due to a duplication event within the genome. The EFHC2 gene was first studied by Gu and colleagues (2005), who reported that this gene spans approximately 195kb of genomic DNA, and contains 15 exons. The EFHC2 protein contains 749 amino acids within six domains: three DM10 domains and three EF-hand motifs. The function of the DM10 domain is unknown, but the EF hand domains are thought to be involved in calcium binding. Due to this, the EFHC2 protein has been suggested to have a role in calcium binding. This protein may therefore influence processes involved in neuronal and intracellular signalling, which may in turn affect the development of neural circuits involved in social cognition. The EFHC2 gene has recently been reported to escape inactivation (Castagne et al 2011), which may contribute towards the dosage sensitive effects of Xp11.3 on fear recognition abilities and amygdala and orbitofrontal cortex volume reported by Good et al (2003). This would also suggest that any effects due to variation within this gene are dosage sensitive, and therefore are greater in males compared to females.

1.9.1.1 SNP rs7055196

As discussed above, SNP rs7055196 consists of either an A or a G allele, and this SNP has been implicated in influencing fear recognition abilities in women with TS (Weiss et al

2007b). The A allele is much more common than the G allele, although prevalence of the two alleles varies across ethnic groups. Within populations of Caucasian and Asian descent the A allele has been suggested to show a prevalence of approximately 91%, while in populations of African descent the prevalence of the A allele has been suggested to be lower, around 65%.

SNP rs7055196 is located within the non-coding (i.e. intronic) region of the EFHC2 gene, and it has been suggested to have a functional role in regulating transcription (http://compbio.cs.queensu.ca/F-SNP/). As a part of its role it may influence the transcription of the EFHC2 gene, other genes, or a combination of the two.

1.9.1.2 Other roles of the EFHC2 gene

In addition to the suggested role of the EFHC2 gene in fear recognition abilities, a SNP within this gene (rs1562875) has been associated with harm avoidance (accounting for over 3% of the variance), a trait related to anxiety, with a weak association between this SNP and both behavioural inhibition and panic disorder (Blaya et al 2009). The EFHC2 gene has also been associated with the presence of juvenile myoclonic epilepsy in males, both through a SNP linkage (Gu et al 2005) and in a case study of an individual who had a partial deletion within the X chromosome (Rodriguez-Revenga et al 2007).

1.9.1.3 Evolutionary history of EFHC2 and SNP rs7055196

Weiss et al (2007b) reported that the G allele at SNP rs7055196 is the ancestral allele, despite being the rarer allele in humans, and supporting this the G allele has been found within all other species genotyped at this position to date. It was also reported that the haplotype block containing the alleles linked to poor fear recognition at SNPs rs7055196 and rs7887763 was most similar to the ancestral haplotype, and 12 mutational steps from the common haplotype in the population. These results suggest SNP rs7055196 has undergone strong positive selection towards the A allele in humans.

Evolution across the EFHC2 gene can be further investigated using extended haplotype homozygosity (EHH). EHH was developed by Sabeti and colleagues (2002) as a method for detecting recent natural selection in humans, through analysing long-range haplotypes. EHH measures the LD at a distance *x* from the core haplotype region, and is the probability that two randomly chosen chromosomes from the samples carrying a tested core haplotype of interest are homozygous for all SNPs for the entire interval from the core region to distance *x* (Figure 1-6). In this way, EHH therefore detects the transmission of an extended haplotype without recombination, and estimates the level of haplotype splitting due to recombination

and mutation at each distance to the core haplotype. Under neutral selection LD would be predicted to be short range for common haplotypes due to recombination and mutation, resulting in a low EHH score. In comparison, a high EHH score for common haplotypes indicates long range LD, suggesting positive selection towards that haplotype.

AGCCGTAATAGAGCCTATCGGGTCAACGATTAGCG

A   B   C
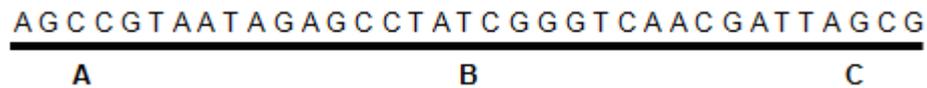
Figure 1-6. Extended haplotype homozygosity (EHH) is a measure of homozygosity between two points within chromosomes. Chromosomes which show homozygosity between points A and C show a longer range of linkage disequilibrium and higher EHH scores than chromosomes which show homozygosity only between points A and B

Weiss et al (2007b) investigated EHH across the EFHC2 gene using dense genotype data in multiple populations. Four out of nine haplotype blocks within the EFHC2 gene showed relative EHH above the 95th percentile of all haplotypes on the X chromosome, with a haplotype at the 3' end of EFHC2 showing a relative EHH score within the top 0.5% of all haplotypes. As the X chromosome is known to be subject to strong selective forces this suggests strong positive selection across the EFHC2 gene. When EHH at SNPs rs7055196 and rs7887763 was compared against markers within the above mentioned haplotype block at the 3' end of EFHC2, LD and a significantly high relative EHH score were found, suggesting strong positive selection at these SNPs. This may suggest an important influence of these SNPs on cognitive functioning in humans.

1.9.2 Genes located close to EFHC2

In addition to the Xp11.3 region containing the EFHC2 gene, this region also contains the genes for monoamine oxidases A and B (MAO-A and MAO-B respectively). Both MAO-A and MAO-B are involved in the oxidative deamination of several neurotransmitters, including serotonin, noradrenaline and dopamine, all of which may play a role in neurodevelopmental social cognitive disorders. Levels of MAO-A and MAO-B therefore reflect neurotransmitter activity and may represent functioning of the social brain. As discussed above, the function of SNP rs7055196 is as yet unknown although it may modulate the expression of other genes, with variation at this SNP producing differences in gene expression. The close proximity of the MAO-A and MAO-B genes to SNP rs7055196 makes them strong candidate genes for modulation of expression by this SNP.

Investigating platelet MAO-B, which is related to expression of the MAO-B gene, it has been suggested that women with TS and men show lower levels compared to unaffected women, suggesting platelet levels are dose sensitive and a haploinsufficiency of this enzyme may contribute towards lower social cognitive abilities (Good et al 2003). However, no association between MAO-B enzymatic activity and mentalising ability as measured by the Triangles task was found in either TS or unaffected women by Lawrence et al (2007). Further work is therefore needed to fully determine the influence of the MAO-A and MAO-B genes on social cognition, and a possible influence of SNP rs7055196 on their expression.

1.9.3 Summary

The poorer social cognitive abilities of women with TS compared to unaffected women suggests a possible influence of genes within the X chromosome on these abilities. Using a deletion mapping strategy it has been suggested a dosage-sensitive genetic locus at Xp11.3 influences fear recognition abilities and amygdala and orbitofrontal cortical volumes in women with TS, as women who have this region deleted on their second X chromosome show poorer fear recognition accuracy and larger amygdala and orbitofrontal cortical volumes compared to women who do not. Dense mapping of this region in women with TS possessing only one X chromosome localised an influence on fear recognition abilities to SNPs rs7055196 and rs7887763 within the EFHC2 gene. At SNP rs7055196, women possessing the G allele (prevalence approximately 9%) showed poorer fear recognition accuracy compared to women possessing the A allele. The EFHC2 gene has been suggested to have a role in calcium binding, and it has been suggested to escape X-inactivation meaning that effects due to variation within this gene will be dosage sensitive and will be greater in males compared to females. SNP rs7055196 is located within the intronic region of this gene, and it has been suggested to influence gene transcription and therefore expression, possibly of the EFHC2 gene or other nearby genes (including MAO-A and MAO-B). It has been reported that there has been a strong positive selection towards the A allele at SNP rs7055196 in humans, which may suggest an important influence of this allele in cognitive functioning. It is important that further work investigating the influence of SNP rs7055196 on social cognition is performed, to fully determine its effects.

1.10 Aims of the thesis

This thesis will extend the work which has suggested an influence of SNP rs7055196 within the EFHC2 gene on facial fear recognition abilities in women with TS to investigate an influence of this SNP on social cognition in healthy males by comparing males possessing the A and G alleles at this SNP. Firstly, I determined whether this SNP had a similar

influence on fear recognition accuracy in males as its influence in women with TS. I next investigated whether an influence of this SNP on fear recognition accuracy was due to a difference in gaze fixation patterns to facial features between the groups. I also used electrophysiological measures to explore whether a difference in face processing style may account for the group difference in fear recognition. I also investigated whether an influence of this SNP was limited to fear recognition accuracy or whether it extended to theory of mind abilities in males, and whether its influence on theory of mind abilities may be due to an influence on neural activation patterns between the groups.

The results within this thesis aim to determine whether SNP rs7055196 influences social cognition in healthy males. An influence of this SNP and its location within the X chromosome may help to explain why males are more vulnerable to impaired social cognition compared to females.

2 General methods

In this chapter I will discuss participant recruitment and selection. I will give a brief overview of the testing schedules used, and will discuss the different experimental techniques used within this thesis. Detailed methods for each study can be found in chapters 3-6.

2.1 Participant recruitment

Participants were recruited via emails circulated to staff and students at University College London and Imperial College London. Males aged 18-40 who were interested in participating in the study were sent an information sheet and asked to complete a consent form and provide a buccal cell sample, which was obtained using either a cheek swab or buccal brush. To collect the cell sample participants were asked to rub the swab or brush against the inside of their cheek for approximately one minute. Although participants were not asked how long they did so, or how much time passed between the swab being taken and being returned to us, all samples produced enough DNA for the genotyping procedure and the majority were successfully genotyped, suggesting the majority of swabs contained good quality DNA. A consent form and a form requesting information regarding date of birth, ethnicity, handedness, and any previous history of neurological or psychiatric disorders along with the cheek swabs / buccal brushes were posted to participants. After forms were completed and the cell sample taken participants returned the forms and cheek swab / buccal brush to the Institute of Child Health (ICH). Informed written consent was obtained from all participants before their inclusion in each subsequent part of the study. Ethical approval was obtained for the project; the collection of DNA samples, Studies 1, 2, 3, 4 and 7 were approved by the West London REC 2 (10/H0711/38), while Studies 5, 6, 8, and 9 were approved by the UCL REC (3045/001).

2.2 Genetic analysis

In total, 567 buccal cell samples were obtained. After receiving the samples, DNA extraction and genotyping at SNP rs7055196 were performed.

2.2.1 DNA extraction

DNA was extracted from all swabs and brushes using a method based on that provided by Isohelix (Cell Projects Ltd, Kent UK). All solutions used were those supplied by Isohelix. When samples were received 500µl of LS solution (lysis buffer) was added to the tube containing the swab or brush. Swabs and brushes were then stored at 4°C until needed. 20µl of PK solution (proteinase K) was next added to the tube, which was incubated at 60°C using either a water bath for one hour or using an oven overnight. The swab or brush was then removed from the tube, and 400µl of the sample was mixed with 400µl of CT solution (capture buffer). The sample was spun in a microfuge at 13Krpm for 7 minutes to pellet the DNA, and the supernatant was carefully removed. This was repeated to ensure all the liquid was removed. 100µl of TE solution (re-hydration buffer) was next added to the tube, and the solution left at room temperature for 5 minutes. Finally, the tube was incubated at 80°C in an oven for five minutes. All samples of DNA were then stored at -20°C before genotyping.

The yield of DNA was greater than 1µg for over 97% of samples (minimum yield 0.38µg) which greatly exceeded the quantity necessary for genotyping; a minimum of 20ng of DNA is required for genotyping at one SNP.

2.2.2 Genotyping

Genotyping at SNP rs7055196 was performed by a commercial genotyping company, KBioSciences (Hertfordshire, UK, http://www.kbioscience.co.uk/), using KASP assays. Of the 567 DNA samples obtained, genotyping was successful for 557 samples with the remaining 10 being of poor quality. From the 557 samples genotyped at SNP rs7055196, 54 possessed a G allele (10.7%), and the remaining 503 possessed an A allele. This population difference is in line with the prevalence of the G allele found in other studies which have compared prevalence of the two alleles in the general population (http://www.ensembl.org/Homo_sapiens/Variation/Population?r=X:44104038-44105038;source=dbSNP;v=rs7055196;vdb=variation;vf=4901149).

2.3 Schedule of testing sessions

A summary of the tasks used, the order the tasks were administered in, and the number of participants who were tested during each task can be seen in Figure 2-1.

Study 1: basic emotion recognition using the Ekman-Friesen
test of facial affect recognition

Study 2: fear recognition using partial and full faces

Study 3: fear recognition using fear-neutral morph faces with

Study 4: eye tracking using fear-neutral morph faces

Autism Spectrum Quotient

Study 7: the Reading the Mind in the Eyes task

Wechsler Abbreviated Scales of Intelligence

G allele n = 46, A allele n = 45

Study 6: electrophysiological responses to varying intensities of
fearful and angry expressions

Study 5: electrophysiological responses to partial and full
fearful, angry and neutral expressions

Study 9: the Frith-Happé Animated Triangles task

G allele n = 17, A allele n = 12

Study 8: neural activations during the Reading the Mind in the
Eyes task

G allele n = 9, A allele n = 7

**Figure 2-1. The studies within this thesis and the number of participants who took
part in each stage of testing**

2.3.1 First testing session

Following genotyping at SNP rs7055196, all 54 participants possessing the G allele were invited to the ICH for testing in the first test battery. Participants from the A allele group were individually age and ethnicity matched to those in the G allele group, and one A allele male from all possible matches was randomly selected and invited to the ICH for testing. This gave an equal number of participants with the G and the A alleles, with participants in the two groups being individually matched for age and ethnicity. In total, 46 individuals possessing the G allele agreed to participate in testing, and a further 46 individuals possessing the A allele also agreed to participate in testing. One participant possessing the A allele had a previous diagnosis of depression and was excluded from analyses. No other participants had a history of any psychiatric or neurological disorder which is associated with impaired social cognition; this was assessed via participant report. Further, no participants had any first degree relatives with an autism spectrum disorder. All participants had normal or corrected-to-normal vision. Neither the participant nor the experimenter was aware which variant of SNP rs7055196 participants possessed during testing. All individuals who participated were reimbursed with £25 to compensate them for their time.

The first battery of tests administered to selected participants consisted of several emotion recognition tasks (Studies 1-3), an eye tracking study (Study 4), a theory of mind task (Study 7), an IQ test (the Wechsler Abbreviated Scales of Intelligence, WASI), and a personality questionnaire (the Autism Spectrum Quotient, AQ). Tasks were administered to all participants in the same order (Study 1, Study 2, Studies 3 and 4 together, AQ, Study 7, WASI). Before testing, to ensure participants understood the concepts of each basic emotion, they were asked to give examples of when someone may feel each of the six emotions (happy, sad, fear, anger, surprise, disgust) and how someone may react or behave when feeling each emotion. All participants provided appropriate answers as judged by the experimenter.

During the first battery of tests, testing was performed in a quiet room at ICH. Tasks during Studies 1-3 were administered on a computer, and participants were seated in a comfortable chair approximately 60cm from the screen. During Studies 3 and 4 participants rested their chin on a padded chin rest; this minimised head movements and maintained a constant distance between the participant and the computer screen. The room was well lit for all tasks with the exception of Studies 3 and 4; for this task the room was dimly lit as eye tracking technology was used which requires low light levels to ensure the optimum capture of eye movements. In total, testing lasted for approximately 3 hours, and regular breaks were given to participants between tasks.

2.3.1.1 Wechsler Abbreviated Scales of Intelligence

To measure IQ, participants were administered the Wechsler Abbreviated Scales of Intelligence (WASI, The Psychological Corporation, San Antonio, TX). The WASI consists of 4 subtests; vocabulary, similarities, block design, and matrix reasoning. During the vocabulary task participants are asked to define words, and during the similarities task participants are asked to describe how two things are similar to each other; scores from these two tasks were used to determine verbal IQ. During the block design task participants are asked to create images using a set of blocks and they are timed while doing so, and during the matrix reasoning task participants are asked to identify a missing piece of an image; scores from these two tasks were used to determine performance IQ. Scores for all four subtests were used to determine full scale IQ. All raw subtest scores were adjusted for participant age before calculating IQ scores. Using the WASI to measure IQ, mean scores for verbal, performance and full scale IQs are equal to 100 (SD 15), and a score below 70 is consistent with mental retardation. The WASI was administered by the experimenter and participant's responses recorded using the standard response form.

2.3.1.2 Autism Spectrum Quotient

Participants were also administered the Autism Spectrum Quotient (AQ) (Baron-Cohen et al 2001b) to investigate autistic-like traits. The AQ consists of 50 statements, and participants are asked how much they agree or disagree with each statement. Depending on their answer they are awarded a mark of either 0 or 1 for each statement, and then a final score is calculated (maximum score 50, higher scores indicate more autistic-like traits). Baron-Cohen et al (2001b) reported that the mean score for individuals with an ASD was 35.8 (SD 6.5), while for unaffected individuals the mean score was 16.4 (SD 6.3) with males scoring slightly higher than females (males M 17.8 SD 6.8, females M 15.4 SD 5.7). The AQ was computer administered and scored using Matlab (The Mathworks, Inc., Natick, MA), with text presented using the Psychophysics Toolbox extension (Brainard 1997, Pelli 1997).

2.3.2 Second testing session

Participants who were tested in the second test battery were selected from those who took part in the first test battery. For Studies 5, 6 and 9 all males aged 18-26 were invited to take part; narrowing the inclusion age reduced possible confounding effects due to age. In total, 17 individuals possessing the G allele and 12 individuals possessing the A allele agreed to participate in testing. All individuals who participated were reimbursed with £15 to compensate them for their time. For Study 8 all Caucasian, right handed males aged 18-26

were invited to take part; narrowing the inclusion criteria reduced possible confounding effects due to ethnicity, handedness or age. In total, 9 individuals possessing the G allele and 7 individuals possessing the A allele agreed to participate in testing. All individuals who participated were reimbursed with £10 to compensate them for their time.

The studies within the second battery of tests consist of two event related potential studies (Studies 5 and 6), a theory of mind test (Study 9), and a functional magnetic resonance imaging study (Study 8). All participants were administered Study 6 before Study 5; in Study 6 participants were passively viewing the faces and were not actively analysing their expression while in Study 5 participants were explicitly recognising the expression within the faces. Administration of Study 5 first may therefore have resulted in active analysis of the emotion in the faces in Study 6, and so to avoid this all participants took part in Study 6 before Study 5. All participants then took part in Study 9. For those individuals who took part in Study 8, this was administered before Study 6, after Study 9, or on a different day.

Studies 5, 6 and 9 took place in a quiet well lit room in ICH. Participants were seated approximately 90cm from the stimulus display monitor. During Studies 5 and 6 the experimenter watched the participants using a video camera set up above the monitor to ensure their attention was on the screen. In total, this testing lasted for approximately 2 hours, and regular breaks were given to participants between tasks. Study 8 took place in a quiet dimly lit room in Great Ormond Street Hospital, and in total this study lasted approximately 75 minutes.

2.4 Techniques used within this thesis

2.4.1 Behavioural tests of social cognition

Many behavioural tasks have been developed to investigate social cognitive abilities, including tasks to test emotion recognition and theory of mind abilities using images of faces. These tasks are thought to relate to real world behaviour, and so are useful for comparing the social cognitive abilities of different populations. However, such tasks are limited in terms of the stimuli used; these are posed by actors, and may often be exaggerated. Although images used in these tasks are validated, for example to confirm that the posed emotion is accurately recognised, there may still be differences between the posed expression and that which occurs in real life. In addition, many tasks use static images as stimuli, whereas in real life expressions are dynamic. Finally, results from these tasks do not inform us about why groups differ, for example whether different neural processes are used.

2.4.2 Eye tracking

Eye tracking cameras use an infrared light directed at the eye to produce a corneal reflection, and using the location of this reflection along with that of the pupil centre it is possible to determine the point of gaze (i.e. fixations) on images. Eye tracking provides us with information regarding the relative importance of different features of images for each participant, and also allows us to compare attention levels towards stimuli. Using eye tracking provided us with a quantitative and objective measure of participants' attention to stimuli features, although it does not provide us with information as to why participants look at particular features. A major problem with the use of eye tracking is that there can be problems with the calibration, resulted in a high proportion of missing data.

2.4.3 Event related potentials

Event related potentials (ERPs) allow us to measure electrophysiological correlates to stimuli by recording electrical currents across the scalp using electrodes. ERPs represent changes in voltage of electroencephalogram (EEG) recordings, which can be related to presentation of a stimulus. The temporal resolution of ERPs is extremely high (several ms), and spatial resolution is poor (several cm). Although analysis techniques exist which allow us to predict sources of activity this is much less accurate than using fMRI. Measuring ERPs can help us to investigate different stages of processing of a stimulus, and they may be more sensitive to population differences compared to behavioural measures. ERPs are a non-invasive method to measure neural activity, and this method does not use ionising radiation or strong magnetic fields. However, the functional significance of ERP components is unknown, and background noise is high when recording neural activity using EEG meaning that a large number of trials are needed to average out this noise to zero. Further, EEG recordings are limited to detecting activity from cortical structures, and they are unable to record subcortical activity.

2.4.4 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) uses blood oxygenation level dependant (BOLD) measures to infer which parts of the brain are active during tasks, by detecting changes in blood flow. Blood flow is higher in active compared to inactive regions, and there is therefore a higher level of blood deoxygenation in the active regions. The level of deoxygenation in the blood influences the magnetic field within the MR scanner, and from this information we can determine which areas of the brain are active during tasks. In contrast to ERPs, fMRI offers excellent spatial resolution (several mm), although its temporal

resolution is poor (several seconds). fMRI also allows us to measure activity in subcortical structures, unlike ERPs. Further, fMRI is a relatively safe method for recording neural activity, as it is non-invasive and does not use ionising radiation. However, although fMRI provides information on which brain regions are active during tasks it does not give us any information regarding what that activity means. Further, fMRI is sensitive to participant movement, and undergoing MRI scans is unadvisable in individuals who have metal implants, suffer from claustrophobia or are sensitive to loud noises.

2.5 Statistical analysis

All statistical analysis, with the exception of the fMRI results in Study 8, was performed using SPSS version 19 (IBM Corp., Armonk, NY). Assumptions of normality were checked for each data set and validated with the exception of data in Study 9. For all analysis covariance of both age and full scale IQ was checked. For all repeated measures analysis, where the assumption of sphericity was not met then a Greenhouse-Geisser correction was applied. A Bonferroni correction was also applied where appropriate to correct for multiple comparisons. The analysis of simple main effects was performed to investigate significant interactions in all repeated measures ANOVAs.

3 Investigating facial emotion recognition abilities

3.1 Introduction

Our ability to recognise emotional expressions from faces is important for social cognition, allowing us to predict how others are feeling, what they are thinking and how they may behave. These abilities facilitate social interactions and communication between individuals, and have an important role in survival, for example in alerting us to potential dangers in the environment. We show an innate attraction to faces, in particular the eye region, suggesting faces and the eyes are an important source of social information for emotion recognition (Adolphs et al 2005, Morand et al 2010, Peltola et al 2009b).

There have been proposed to be six different basic emotions: happy, sad, fear, anger, surprise and disgust, and the recognition of these expressions was suggested to be innate by Darwin (1872). In studies investigating the explicit recognition of these emotions from facial expressions, happy has been reported to be the most accurately and quickest recognised expression and fear has been reported to be the least accurately and slowest recognised expression (Palermo and Coltheart 2004, Rapcsak et al 2000, Williams et al 2009). Each emotional expression is thought to have a unique and specific facial configuration, such as the upturned mouth for happy faces and the widened eyes for fearful expressions (Kohler et al 2004). Supporting the importance of the characteristic widened eyes in fearful expressions, the eye region contains the most useful information for the recognition of fearful expressions (Adolphs et al 2005, Schyns et al 2007), and we are able to recognise fearful expressions when the eye region alone is shown (Leppanen et al 2008).

It has been suggested that our ability to recognise emotional expressions is influenced by genetic factors. A recent twin study reported that additive genetic factors account for approximately 17-20% of the variance across the recognition of the basic emotions, and this genetic influence was strongest for the recognition of fear (Lau et al 2009). The X chromosome may be one source of genetic influence on facial emotion recognition abilities; genes on the X chromosome are thought to play a major role in influencing brain development, as X-linked genes are highly expressed in the brain (Nguyen and Disteche 2006) and X-linked genes have a much stronger influence on the development of mental retardation than would be expected based on the number of genes (Ropers and Hamel 2005, Zechner et al 2001). Supporting a potential influence of genes on the X chromosome on social cognition, males are more vulnerable to impaired social cognition compared to

females (Skuse et al 2009), with extreme impairments being characteristic of the autism spectrum disorders (ASDs). These disorders are more prevalent in males (X-monosomic) compared to females (X-disomic) (3:1) (Levy et al 2009), and as males possess only one X chromosome while females possess two any influence of X-linked genes will therefore be greater in males. In addition, women affected by Turner Syndrome (TS, X-monosomy) also show impaired social cognition compared to unaffected women, further supporting an influence of X-linked genes on social cognition. One aspect of social cognition which is associated with impairments in both individuals with an ASD and women with TS is facial emotion recognition abilities, and so this ability may be influenced by genes within the X chromosome. In particular, this impairment has been suggested to be strongest for the recognition of fearful expressions, with impaired fear recognition being observed for both full faces and the eye region alone (Corden et al 2008, Lawrence et al 2003a, Lawrence et al 2003b, Pelphrey et al 2002, Wallace et al 2008). A subset of neurotypical males (approximately 8.8%) have also been reported to show strong impairments in facial fear recognition (Corden et al 2006), and boys have been suggested to show a larger variation in fear recognition abilities compared to girls (Lau et al 2009). It has been suggested that impairments in fear recognition abilities are stronger than impairments for the recognition of other emotions as fearful faces are more difficult to recognise than the other emotions (Rapcsak et al 2000) rather than fear being the only expression affected.

The presence of only one complete X chromosome with the other sex chromosome missing completely or being partially present in women with TS means that these women are ideal candidates to investigate possible specific genetic influences of the X chromosome on emotion recognition abilities. Using a deletion mapping strategy, Good et al (2003) suggested a dosage-sensitive genetic locus for fear recognition abilities is found at Xp11.3, with women lacking this locus on their second partial X chromosome showing impaired fear recognition abilities compared to women possessing this locus despite no differences in intelligence between the groups. Further work using a dense mapping strategy in this region in women with TS possessing one complete X chromosome and no partial sex chromosome by Weiss et al (2007b) suggested a quantitative trait locus important for fear recognition at SNP rs7055196, found within the EFHC2 gene. Women possessing a G allele at this SNP showed impaired fear recognition abilities compared to women possessing an A allele. The G allele occurred at a frequency of 8.8%, and this SNP had an estimated effect size accounting for over 13% of the variance in fear recognition abilities. These results suggest an association between the EFHC2 gene, specifically SNP rs7055196, and fear recognition abilities in women with TS. As males also possess only one X chromosome, these impairments in fear recognition associated with the G allele at SNP rs7055196 may also be found in neurotypical males possessing this allele. Supporting this, the prevalence of the G allele shows a striking similarity to the percentage of neurotypical males in the subset which Corden et al (2006) reported to show impairments in facial fear recognition abilities, and it is possible that variance within SNP rs7055196 may explain this impairment.

3.1.1 Aim and hypotheses

The purpose of this study was to investigate differences in the facial emotion recognition abilities, specifically fear recognition abilities, in males possessing different alleles at SNP rs7055196 within the EFHC2 gene.

Firstly, I hypothesised that males possessing the G allele would show poorer accuracy of fear recognition in faces compared to males possessing the A allele. In addition, due to the importance of the eye region in fear recognition, I also hypothesised that poorer fear recognition in the G allele group may be due to an inability to utilise the information in the eye region in the correct way. I therefore predicted that the G allele group would show poorer fear recognition abilities when the eyes alone or eyes and eyebrows alone were shown compared to the A allele group, whereas when the eyes or eyes and eyebrows were covered in a face there would be no differences in fear recognition between the two groups.

3.2 Participant information

In total 91 participants were tested; 45 who possessed the A allele at SNP rs7055196 and 46 who possessed the G allele.

3.2.1 Age, handedness and ethnicity

Information regarding the age and ethnicity of participants can be seen below in Table 3-1. Participant age did not significantly differ between the two groups when compared using an independent samples t-test (t (89) = -0.451, P = 0.653, 95% CI (-2.27, 1.43)). The majority of participants were right handed; 3 males in the A allele group and 2 males in the G allele group were left handed. The ethnicity of participants also did not differ between the two groups.

	A allele	G allele
Number	45	46
Age	22.71 ± 4.22 (18-39)	23.13 ± 4.63 (19-41)
Ethnicity	23 Caucasian, 3 Hispanic, 16 Asian, 1 African, 2 mixed race	22 Caucasian, 4 Hispanic, 16 Asian, 2 African, 2 mixed race

Table 3-1. Information regarding the age (mean ± SD (range)) and ethnicity of participants tested in each group

3.2.2 IQ

Participant IQ was measured using the Wechsler Abbreviated Scales of Intelligence (WASI) and compared across groups using independent samples t-tests. Full scale IQ did not significantly differ between the two groups (t (89) = 0.072, P = 0.943, 95% CI (-3.56, 3.83)). Similarly, neither verbal IQ nor performance IQ significantly differed between the two groups (t (89) = -0.433, P = 0.666, 95% CI (-5.67, 3.64) and t (89) = 0.726, P = 0.470, 95% CI (-2.47, 5.31) respectively) (Table 3-2).

The mean scores for participant IQ are high due to the majority of participants being university students. Comments on possible effects of these high IQ scores on the results obtained can be found in the discussion (section 3.6.2.1).

	A allele	G allele
Full scale IQ	121.18 ± 8.15	121.04 ± 9.50
Verbal IQ	119.38 ± 11.06	120.39 ± 11.29
Performance IQ	118.36 ± 9.30	116.93 ± 9.37

Table 3-2. Full scale, verbal and performance IQs of each group (mean ± SD)

3.2.3 Autism Spectrum Quotient

Participants were also administered the Autism Spectrum Quotient (AQ) (Baron-Cohen et al 2001b). Scores did not differ between groups when compared using an independent samples t-test (t (89) = -0.622, P = 0.536, 95% CI (-3.07, 1.61)) (Table 3-3).

Participants' AQ scores are similar to those reported in other neurotypical adult male populations (Baron-Cohen et al 2001b), suggesting neither group shows an excess of autistic-like traits.

	A allele	G allele
AQ	16.38 ± 5.42	17.11 ± 5.78

Table 3-3. AQ scores for each group (mean ± SD)

3.3 Study 1: basic emotion recognition using the Ekman-Friesen test of facial affect recognition

3.3.1 Method

For this task participants were administered the Ekman-Friesen test of facial affect recognition (Ekman and Friesen 1976). This test consists of a series of halftone photographic images of faces of actors posing the six basic emotions (happy, sad, fear, anger, surprise, disgust) (Figure 3-1), and participants were asked to identify the emotion displayed in each face from a list of the six basic emotions. Participants first practised the task using 6 faces shown in a random order (6 emotions × 1 actor) and then performed the task using 60 faces shown in a random order (6 emotions × 10 actors (5 male, 5 female)). Each face was shown once, giving a total number of 60 trials in the test block. None of the images used in the practice block were used in the test block and none of the responses given in the practice block were analysed. No feedback was given for any images. The task was computer administered and written in Matlab (The Mathworks, Inc., Natick, MA), with images presented using the Psychophysics Toolbox extension (Brainard 1997, Pelli 1997).

Images were shown one at a time in the centre of the screen, and each image subtended a visual angle of 13.78° (width) × 20.78° (height). When participants thought they were able to
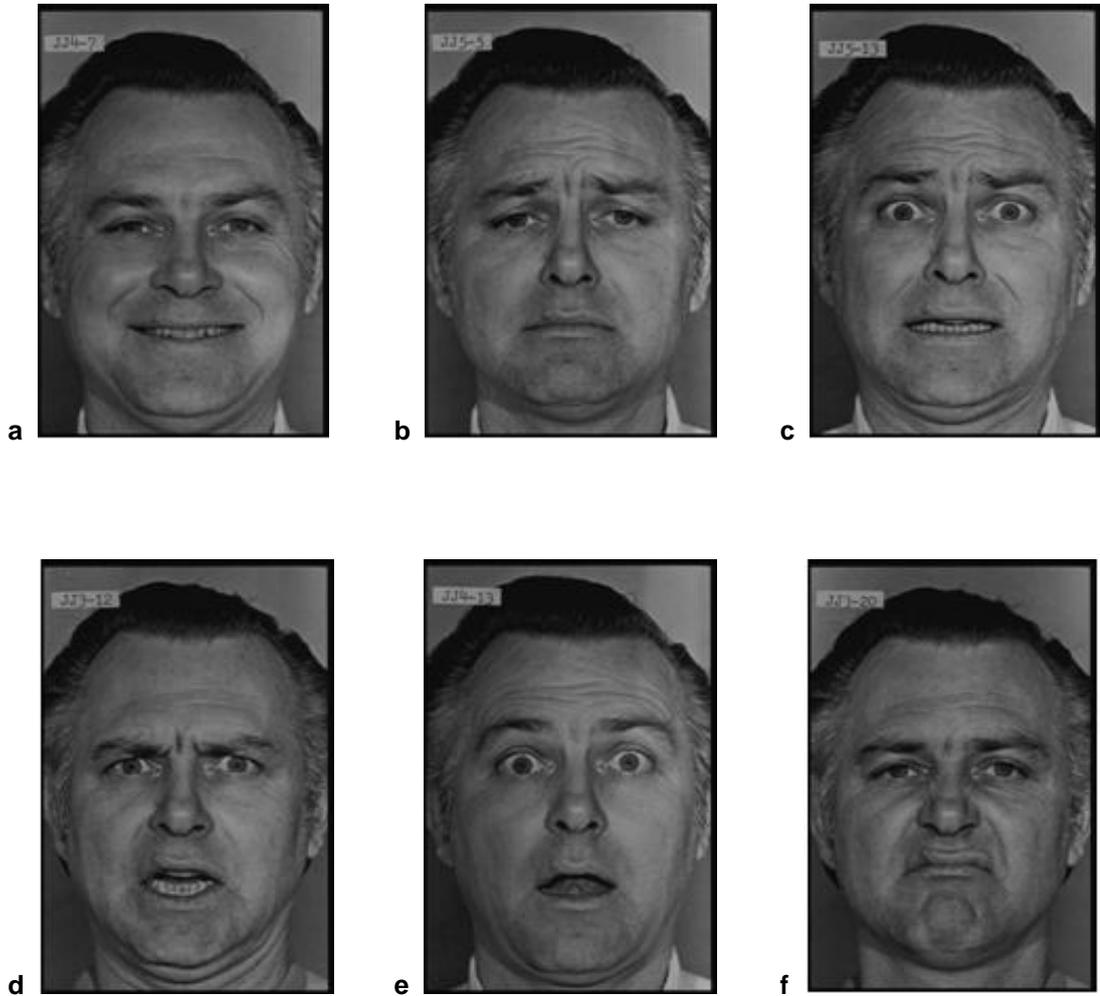
Figure 3-1. Examples of images used in Study 1 displaying facial expressions of the six basic emotions (a) happy, (b) sad, (c) fear, (d) anger, (e) surprise, (f) disgust (images from the Ekman series (Ekman and Friesen 1976))

recognise the emotion the face was portraying they pressed the spacebar. A new screen with a list of the 6 possible emotions then appeared asking participants to select the appropriate emotion; this was done by pressing the corresponding key on the keyboard. Participants were asked to respond as accurately and as quickly as possible, although they had an unlimited time to respond, and they were not instructed which hand to use while responding. Following a response the next trial started. At the start of each trial, prior to the image being presented, a blank screen was shown for 500ms followed by a fixation cross in the centre of the screen for 500ms, giving a total inter stimulus interval (ISI) of 1 second. The task lasted approximately 3.5 minutes (60 trials × 3.5 seconds = 210 seconds = 3.5 minutes). The response key pressed for each face was recorded, along with the response time (RT, in ms) to press the spacebar.

3.3.1.1 Analysis

For each emotion the number of correctly identified images was calculated (score out of 10) along with the mean RT for each participant. Any RTs with values outside the range mean ± 3 standard deviations (<2% all trials) were replaced with the value equal to mean ± 3 standard deviations. The numbers of correctly identified expressions and mean RTs were then compared across the G and A allele groups using 2 (group) × 6 (emotion) repeated measures ANOVAs with the Greenhouse-Geisser and Bonferroni corrections applied.

3.3.2 Results

3.3.2.1 Emotion recognition accuracy

The mean number of expressions correctly identified by each group can be seen in Table 3-4 and Figure 3-2. These values were compared in a 2 (group) × 6 (emotion) repeated measures ANOVA with the Greenhouse-Geisser and Bonferroni corrections applied. There were no differences in the emotion recognition abilities of males possessing the different variants of SNP rs7055196 ($F_{(1,89)}$ = 1.331, P = 0.252, 95% CI (-0.15, 0.56)), although differences for the recognition levels of the different emotions occurred ($F_{(3.85,342.90)}$ = 51.741, P < 0.0005). Happy (M 9.92 SD 0.27) was the best recognised emotion followed by surprise (M 9.13 SD 1.14), sadness (M 8.17 SD 1.61), disgust (M 7.82 SD 1.83) and anger (M 7.08 SD 1.79), with fear (M 6.99 SD 2.37) being the poorest recognised emotion. All emotion pairs significantly differed from each other (all P < 0.0005 apart from anger / disgust P = 0.015), with the exception of sadness / disgust (P = 1.000), fear / anger (P = 1.000), and fear / disgust (P = 0.083). There was no significant interaction effect between EFHC2 variant

and emotion (F (3.85,342.90) = 0.544, P = 0.697). Neither age (F (1,88) = 0.091, P = 0.764) nor full scale IQ (F (1,88) = 0.423, P = 0.517) were significant when included as covariates.

As a specific hypothesis had been made regarding fear recognition abilities, the mean number of fearful expressions correctly identified by the two groups was compared in an independent samples t-test. No significant effect of SNP rs7055196 was found for the number of fearful expressions correctly recognised (t (89) = 0.932, P = 0.354, 95% CI (-0.52, 1.45)).

	A allele	G allele
Happy	9.93 ± 0.25	9.91 ± 0.28
Sad	8.42 ± 1.56	7.91 ± 1.66
Fear	7.22 ± 2.41	6.76 ± 2.31
Anger	7.20 ± 1.71	6.96 ± 1.86
Surprise	9.11 ± 1.05	9.15 ± 1.23
Disgust	7.84 ± 1.49	7.80 ± 2.11

Table 3-4. Mean numbers of correctly identified expressions for each of the six basic emotions for participants possessing either the A or G allele at SNP rs7055196 (mean ± SD)
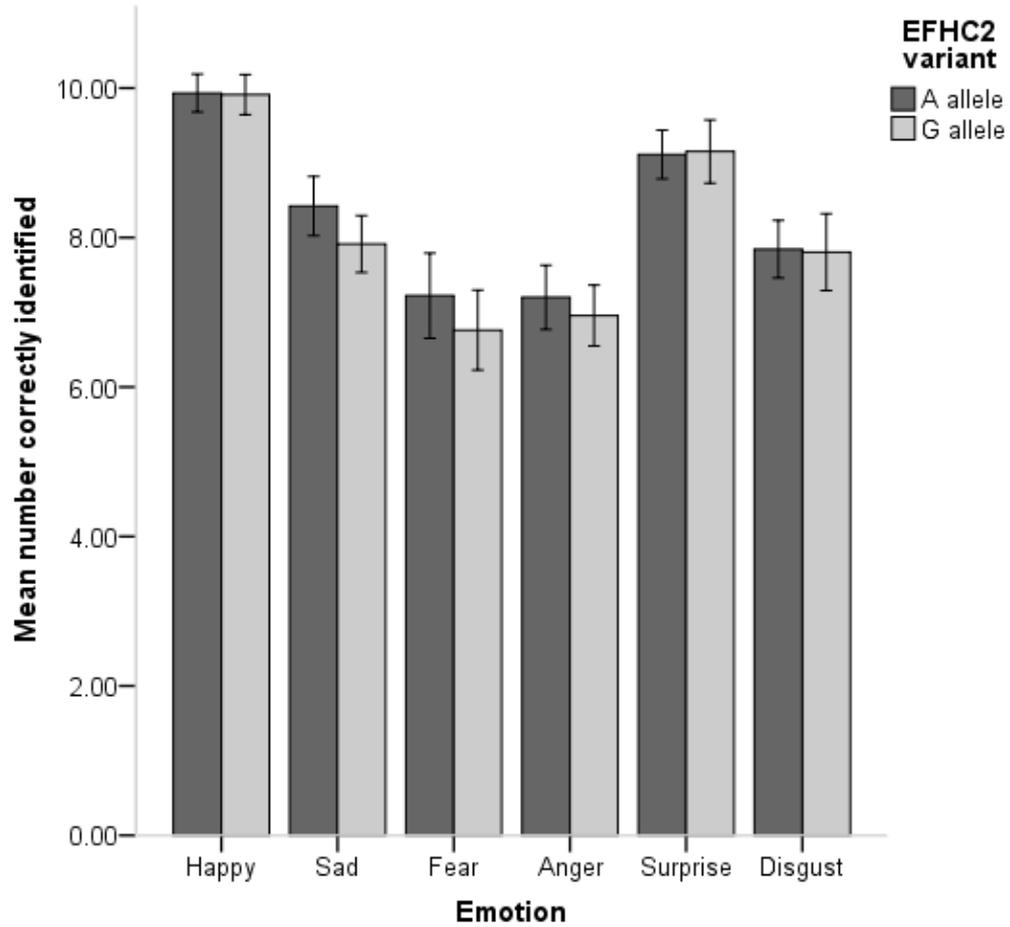
Figure 3-2. Mean numbers of correctly identified expressions for each of the six basic emotions for participants possessing either the A or G allele at SNP rs7055196 (error bars represent 95% CI)

3.3.2.2 Response time

Mean RTs for each group for each emotion can be seen in Table 3-5 and Figure 3-3. These values were compared in a 2 (group) × 6 (emotion) repeated measures ANOVA with the Greenhouse-Geisser and Bonferroni corrections applied. There were no overall differences in RTs between males possessing the different variants of SNP rs7055196 (F (1,89) = 0.045, P = 0.832, 95% CI (-489, 395)), although the emotional expression of the face significantly affected the RT (F (4.19,372.52) = 50.923, P < 0.0005). RTs were much faster for happy faces (M 1397 SD 678) compared to those for any of the other expressions, with RTs for surprised faces (M 2224 SD 1166) being second fastest followed by disgusted (M 2564 SD 1317), fearful (M 2665 SD 1387), and sad faces (M 2781 SD 1507), with angry faces (M 3172 SD 1520) being recognised slowest. All emotion pairs significantly differed from each other (all P < 0.0005 apart from sad / anger P = 0.049, fear / anger P = 0.001, and surprise / disgust P = 0.009), with the exceptions of sad / fear (P = 1.000), sad / disgust (P = 0.701), and fear / disgust (P = 1.000). There was no significant interaction effect between emotion and EFHC2 variant (F (4.19,372.52) = 1.412, P = 0.227). Neither age (F (1,88) = 0.745, P = 0.390) nor full scale IQ (F (1,88) = 0.961, P = 0.330) were significant when included as covariates.

	A allele	G allele
Happy	1339 ± 647	1455 ± 707
Sad	2645 ± 1123	2917 ± 1805
Fear	2742 ± 1194	2589 ± 1553
Anger	3200 ± 1631	3143 ± 1403
Surprise	2309 ± 1281	2140 ± 1041
Disgust	2426 ± 1126	2702 ± 1481

Table 3-5. Mean RTs (ms) for each of the six basic emotions for participants possessing either the A or G allele at SNP rs7055196 (mean ± SD)

Figure 3-3. Mean RTs (ms) for each of the six basic emotions for participants possessing either the A or G allele at SNP rs7055196 (error bars represent 95% CI)

3.4 Study 2: fear recognition using partial and full faces

3.4.1 Method

During this task participants were shown a mixture of partial and full fearful and neutral faces and asked to determine which emotional state the face was showing in a two-alternative forced choice task (i.e. whether it was fearful or neutral). Images were obtained from the Ekman series (Ekman and Friesen 1976) (4 faces, 2 male, 2 female) and using faces produced by actors from Fiorentini and Viviani (2009) (4 faces, 2 male, 2 female).

In total there were five different facial compositions for each face; the full face, the eyes alone, the eyes and eyebrows alone, faces with the eyes covered, and faces with the eyes and eyebrows covered (Figure 3-4). Facial compositions with only the eyes or eyes and eyebrows showing were created using 'letterbox' images of the eye region. Facial compositions with the eyes or eyes and eyebrows covered were created by drawing 'sunglasses' on the original faces using Paint; in this way the faces looked relatively natural compared to covering the eyes or eyes and eyebrows with a rectangle. The facial compositions used were based on those used by Leppanen et al (2008). There were therefore 10 different emotion-facial composition pairs for each actor's face (2 emotions × 5 facial compositions). Each image was shown 5 times, giving a total of 400 trials (8 actors × 10 emotion-facial composition pairs × 5 repetitions). Trials were presented in two blocks with a break in the middle of each block; one block contained all the faces from the Ekman series, and the other contained all the faces from Fiorentini and Viviani's series (200 trials per block). The order the blocks were presented in was counterbalanced across participants. Within each block images were presented in a random order. No feedback was given for any images. The task was computer administered and written in Matlab (The Mathworks, Inc., Natick, MA), with images presented using the Psychophysics Toolbox extension (Brainard 1997, Pelli 1997).

For each block, images were shown one at a time in the centre of the screen. Full faces and those with sunglasses subtended a visual angle of 13.78° (width) × 20.78° (height), while letterbox images of the eye regions subtended a visual angle between 8.58° - 9.53° (width) × 1.43° - 3.34° (height). When participants thought they could identify whether the face was fearful or neutral they pressed the corresponding key on the keyboard; the left hand was used to respond for fearful expressions while the right hand was used to respond for neutral expressions. Participants were asked to respond as accurately and as quickly as possible, although there was no time limit. After responding, the next trial started. At the start of each
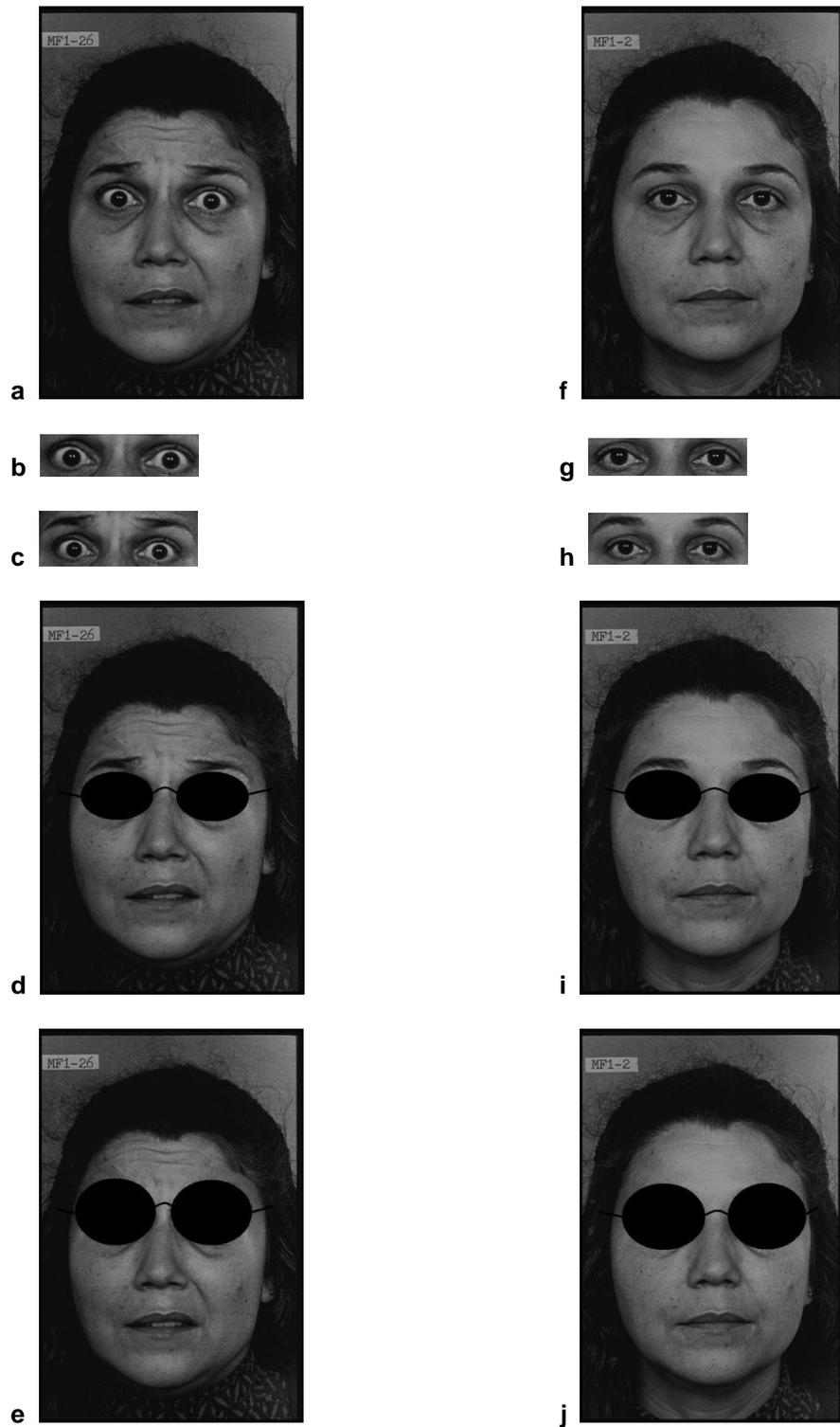
Figure 3-4. Examples of images used in Study 2 (a) fearful full face, (b) fearful eyes, (c) fearful eyes and eyebrows, (d) fearful faces with the eyes covered, (e) fearful eyes and eyebrows covered, (f) neutral full face, (g) neutral eyes, (h) neutral eyes and eyebrows, (i) neutral faces with the eyes covered, (j) neutral eyes and eyebrows covered (images adapted from Ekman and Friesen (1976))

trial, prior to the image being presented, a blank screen was shown for 500ms followed by a fixation cross in the centre of the screen for 500ms; this gave an ISI of 1 second. Each block lasted approximately 7 minutes (200 trials × 2 seconds = 400 seconds = 6.67 minutes). The response key pressed for each face was recorded, along with the RT (in ms).

3.4.1.1 Analysis

For all analysis the results using the faces from the Ekman series (Ekman and Friesen 1976) and those from Fiorentini and Viviani (2009) have been combined. For each of the 10 emotion-facial composition pairs the percentage of correctly identified emotional states was calculated (score out of 40 (8 actors × 5 repetitions)) along with the mean RT for each participant. Any RTs with values outside the range mean ± 3 standard deviations (<2% all trials) were replaced with the value equal to mean ± 3 standard deviations. The percentages of correctly identified expressions and mean RTs were compared between males possessing the G and A alleles at SNP rs7055196 using 2 (group) × 2 (emotion) × 5 (face composition) repeated measures ANOVAs with the Greenhouse-Geisser and Bonferroni corrections applied.

3.4.2 Results

3.4.2.1 Emotion recognition accuracy

Mean percentages of correctly identified expressions for the two groups can be seen in Table 3-6 and Figure 3-5. These values were compared in a 2 (group) × 2 (emotion) × 5 (face composition) repeated measures ANOVA using the Greenhouse-Geisser and Bonferroni corrections. There was a trend towards males possessing the G allele at SNP rs7055196 showing poorer emotion recognition abilities compared to males possessing the A allele (F (1,89) = 3.204, P = 0.077, 95% CI (-0.20, 3.73), A allele M 94.26 SD 4.71, G allele M 92.49 SD 4.71). There were no differences in emotion recognition for the fearful and neutral expressions (F (1,89) = 1.664, P = 0.200, 95% CI (-3.25, 0.69)). Facial composition significantly affected emotion recognition accuracy (F (2.412,214.682) = 108.494, P < 0.0005); all composition pairs significantly differed from one another apart from the eyes covered condition and the eyes and eyebrows covered condition (P = 1.000) (all other P < 0.0005 with the exceptions of full face / eyes covered P = 0.001 and full face / eyes and eyebrows covered P = 0.003) (full faces M 96.96 SD 3.96, eyes alone M 88.00 SD 7.52, eyes and eyebrows alone M 91.04 SD 6.52, faces with the eyes covered M 95.32 SD 4.77, faces with the eyes and eyebrows covered M 95.55 SD 4.47). Generally, expression

recognition was highest for full faces and faces with the eyes or eyes and eyebrows covered, and lowest for the eyes alone or eyes and eyebrows alone.

There were no significant interactions between EFHC2 variant and either emotion or facial composition ($F_{(1,89)} = 2.571$, $P = 0.112$ and $F_{(2.412,214.682)} = 0.734$, $P = 0.505$ respectively), although there was a significant interaction between facial composition and emotion ($F_{(1.975,175.785)} = 21.029$, $P < 0.0005$). Recognition accuracy was higher for fearful compared to neutral expressions when the eyes and eyebrows were seen alone ($P = 0.011$), and for neutral compared to fearful expressions for faces with the eyes covered ($P < 0.0005$) or the eyes and eyebrows covered ($P < 0.0005$). There were no differences in the recognition accuracy of the two expressions for full faces ($P = 0.101$) or for the eyes alone ($P = 0.500$). There was no significant interaction effect between EFHC2 variant, emotion and face composition ($F_{(1.975,175.785)} = 0.333$, $P = 0.715$). Neither age ($F_{(1,88)} = 1.419$, $P = 0.237$) nor full scale IQ ($F_{(1,88)} = 0.942$, $P = 0.334$) were significant when included as covariates.

I had also made an a priori hypothesis that males possessing the G allele would show poorer fear recognition when the eyes alone or eyes and eyebrows alone were shown compared to the A allele group, whereas when the eyes or eyes and eyebrows were covered in a face there would be no differences in fear recognition between the two groups. I tested this hypothesis in a 2 (group) × 2 (stimulus type) repeated measures ANOVA, with accuracy for the two stimulus types being calculated by averaging firstly over fearful eyes alone and fearful eyes and eyebrows alone, and secondly over fearful faces with the eyes covered and fearful faces with the eyes and eyebrows covered. Males possessing the G allele showed poorer fear recognition compared to males possessing the A allele ($F_{(1,89)} = 4.716$, $P = 0.033$, 95% CI (0.32, 7.17), A allele M 93.38 SD 8.22, G allele M 89.63 SD 8.22). Fear recognition accuracy was again higher when the eye region was covered compared to when the eye region alone was shown ($F_{(1,89)} = 11.266$, $P = 0.001$, 95% CI (-4.29, -1.10), eyes present M 90.16 SD 10.27, eyes absent M 92.85 SD 7.68). Contrary to my prediction, there was no interaction between EFHC2 variant and stimulus type ($F_{(1,89)} = 0.232$, $P = 0.631$).

	A allele		G allele	
	Fear	Neutral	Fear	Neutral
Full face	98.56 ± 2.58	96.33 ± 5.93	96.74 ± 6.64	96.20 ± 6.32
Eyes alone	89.11 ± 9.97	88.22 ± 11.96	85.76 ± 13.63	88.91 ± 10.05
Eyes / eyebrows alone	94.56 ± 5.89	89.39 ± 10.34	91.20 ± 11.93	89.02 ± 8.83
Faces with the eyes covered	94.83 ± 6.56*	98.28 ± 4.16	90.82 ± 9.66*	97.34 ± 4.26
Faces with the eyes / eyebrows covered	95.00 ± 5.38*	98.28 ± 4.42	90.76 ± 9.54*	98.15 ± 3.59

Table 3-6. Percentages of correctly identified expressions for each of the different emotion-facial composition pairs for participants possessing either the A or G allele at SNP rs7055196 (mean ± SD), * $P < 0.05$ when comparing males possessing the A or G allele
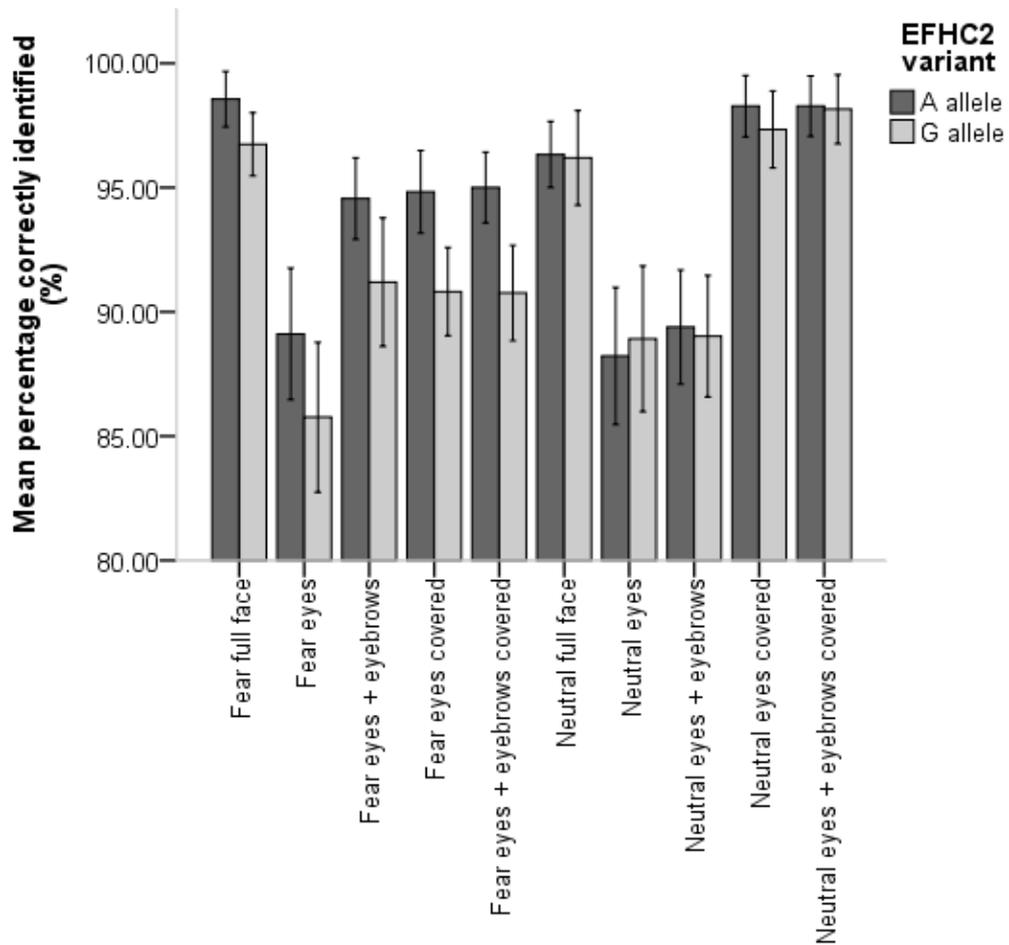
Figure 3-5. Percentages of correctly identified expressions for each of the different emotion-facial composition pairs for participants possessing either the A or G allele at SNP rs7055196 (error bars represent 95% CI)

3.4.2.2 Response time

Mean RTs for each group for each emotion-facial composition pair can be seen in Table 3-7 and Figure 3-6. These values were compared in a 2 (group) × 2 (emotion) × 5 (facial composition) repeated measures ANOVA with the Greenhouse-Geisser and Bonferroni corrections applied. RTs of males possessing the different variants of SNP rs7055196 did not significantly differ ($F_{(1,89)}$ = 0.238, P = 0.627, 95% CI (-179, 108)). There was a trend towards responses to fearful faces being faster than those to neutral faces ($F_{(1,89)}$ = 3.881, P = 0.052, 95% CI (-76, 0), fear M 1072 SD 340, neutral M 1110 SD 373). Facial composition significantly affected RT ($F_{(3.455,307.475)}$ = 39.052, P < 0.0005); RTs for full faces, faces with the eyes covered and faces with the eyes and eyebrows covered were all significantly faster than RTs for the eyes alone and eyes and eyebrows alone conditions (all P < 0.0005), while RTs between full faces, faces with the eyes covered and faces with the eyes and eyebrows covered did not differ, and neither did those between the eyes alone and eyes and eyebrows alone conditions (all P = 1.000) (full faces M 1050 SD 350, eyes alone M 1169 SD 365, eyes and eyebrows alone M 1169 SD 401, faces with the eyes covered M 1034 SD 337, faces with the eyes and eyebrows covered M 1032 SD 334).

There was no significant interaction effect between EFHC2 variant and either emotion or facial composition ($F_{(1,89)}$ = 1.986, P = 0.162 and $F_{(3.455,307.475)}$ = 1.100, P = 0.353 respectively). There was a significant interaction between emotion and facial composition ($F_{(2.953,262.844)}$ = 24.366, P < 0.0005), which was driven by faster responses to fearful compared to neutral faces when full faces, the eyes alone or the eyes and eyebrows alone were shown (i.e. when the eyes were present), and faster responses to neutral compared to fearful faces when faces with the eyes covered or faces with the eyes and eyebrows covered were shown (i.e. when the eyes were absent) (all P < 0.05). There was no significant interaction between EFHC2 variant, emotion and face composition ($F_{(2.953,262.844)}$ = 1.167, P = 0.323).

Age ($F_{(1,88)}$ = 0.111, P = 0.739) was not significant when included as a covariate. However, full scale IQ significantly affected RTs when it was included as a covariate ($F_{(1,88)}$ = 4.077, P = 0.047), with a higher IQ being associated with shorter RTs. Including full scale IQ as a covariate did not affect the influence of SNP rs7055196 or any interactions involving this SNP on RT.

	A allele		G allele	
	Fear	**Neutral**	**Fear**	**Neutral**
Full face	999 ± 312	1082 ± 308	994 ± 337	1126 ± 542
Eyes alone	1150 ± 326	1174 ± 313	1103 ± 362	1249 ± 499
Eyes / eyebrows alone	1089 ± 375	1228 ± 349	1085 ± 389	1276 ± 565
Faces with the eyes covered	1049 ± 352	949 ± 225	1084 ± 411	1053 ± 413
Faces with the eyes / eyebrows covered	1053 ± 287	960 ± 251	1115 ± 465	1001 ± 366

Table 3-7. Mean RTs (ms) for each of the different emotion-facial composition pairs for participants possessing either the A or G allele at SNP rs7055196 (mean ± SD)
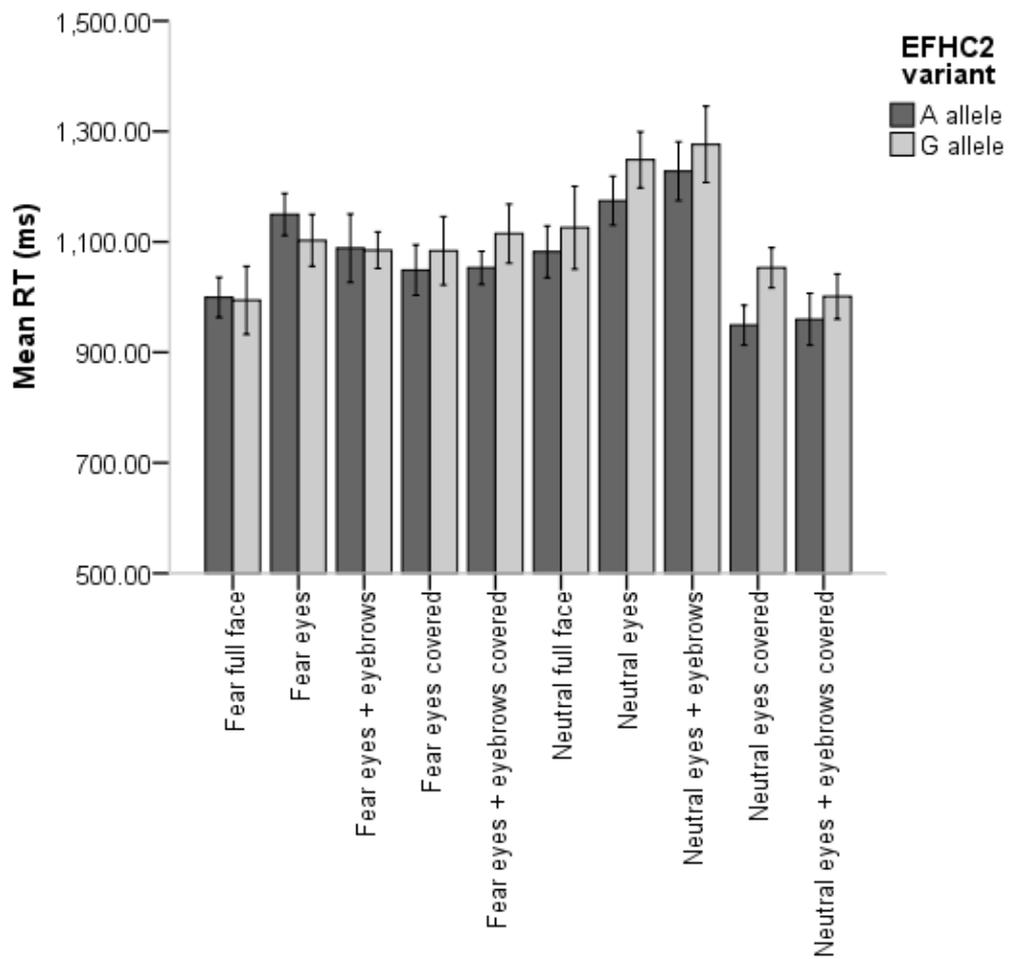
Figure 3-6. Mean RTs (ms) for each of the different emotion-facial composition pairs for participants possessing either the A or G allele at SNP rs7055196 (error bars represent 95% CI)

3.5 Study 3: fear recognition using fear-neutral morph faces

3.5.1 Method

For this task, participants were shown a series of faces which were created by blending together a fearful and neutral face. The resultant faces contained different proportions of fearful and neutral expressions, and participants were asked to decide whether they thought each face looked more like a fearful or a neutral face in a two-alternative forced choice task. Faces were produced by morphing together fearful and neutral prototypical faces posed by actors, obtained from Fiorentini and Viviani (2009), with two fearful faces and their corresponding neutral faces being used (1 male, 1 female). Nine equally spaced morphs were created between the two faces from the same actor using LOKI software (Viviani et al 2007), producing ranked faces containing differing amounts of the fearful expression from 0% fear to 100% fear, with incremental steps of 10% fear (Figure 3-7). In total, this gave 11 ranked faces per actor; nine composite faces plus the fearful and neutral prototype faces (for further details see Fiorentini and Viviani (2009)). Each face was shown 10 times, giving a total of 110 trials per actor. Trials were presented in two blocks; one using images of the male face and the other using images of the female face. The order the blocks were presented in was counterbalanced across participants. Within each block images were presented in a random order, with the constraint that the same face was not shown twice in a row. No feedback was given for any images. The task was computer administered and run using purpose written software which simultaneously controlled an eye-tracking device; gaze fixations recorded using the eye-tracking device and details of this device are discussed in section 4.3.1.

Within each block, participants were first shown the fearful and neutral prototypical faces sequentially on the screen and were informed which expression each face was showing. Participants were asked to study the faces carefully so that they felt comfortable in differentiating between them. When participants indicated they could recognise the two expressions the task started. During the task, images were shown one at a time in the centre of the screen for three seconds before disappearing; images subtended a visual angle of 21.7° (width) × 21.7° (height). A text screen then appeared, prompting the participant to press the key on the keyboard corresponding to whether they thought the face was more like the fearful prototypical face or more like the neutral prototypical face. Participants were asked to respond as accurately and as quickly as possible, although they had unlimited time to respond, and they were not given instructions as to which hand to use. After responding,

Figure 3-7. Examples of images used in Study 3 displaying the faces morphed between a fearful and a neutral expression. Both series show faces containing 0%, 20%, 40%, 60%, 80%, and 100% fear (a) female face, (b) male face (images adapted from Fiorentini and Viviani (2009))

the next trial started. At the start of each trial, prior to the image being presented, a blank screen was shown for 500ms followed by a fixation cross in the centre of the screen for 500ms, producing an ISI of 1 second. Each block lasted approximately 9 minutes (110 trials × 5 seconds = 550 seconds = 9.17 minutes). The response key pressed for each image was recorded, along with the RT (in ms).

3.5.1.1 Analysis

Results were processed separately for each actor due to individual differences in the expressions produced. First, the number of times each of the 11 faces presented for each actor was judged to look more like the prototypical fearful face than the prototypical neutral face was calculated (score out of 10). From this a psychometric function for each participant was plotted using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA). Each psychometric function was produced from a cumulative Gaussian function comparing the percentage of fearful expression in the face to the frequency that the face was considered to be fearful (Figure 3-8). From this function two values were calculated; the mean and the standard deviation. The mean value of the function represents the point of subjective equality (PSE), and is equal to the proportion of fear in the face when the participant could not differentiate whether the face was more like the fearful or the neutral face (i.e. percentage fear when recognition is at chance level). The standard deviation of the function represents the just noticeable difference (JND). This value signifies the certainty of recognition, and therefore the sensitivity of recognition between the two expressions. Higher JND values signify a poorer sensitivity of fear recognition. The values of PSE and JND were calculated for each participant, and then compared across the G and A allele groups firstly using a 2 (group) × 2 (actor) repeated measured ANOVA and secondly using independent samples t-tests for each actor to further investigate group differences for the two actors.

In addition, mean RTs for each participant were calculated for each image. Any RTs with values outside the range mean ± 3 standard deviations (<2% all trials) were replaced with the value equal to mean ± 3 standard deviations. Mean RTs were then compared across the two groups using a 2 (group) × 2 (actor) × 11 (rank) repeated measures ANOVA with the Greenhouse-Geisser and Bonferroni corrections applied.
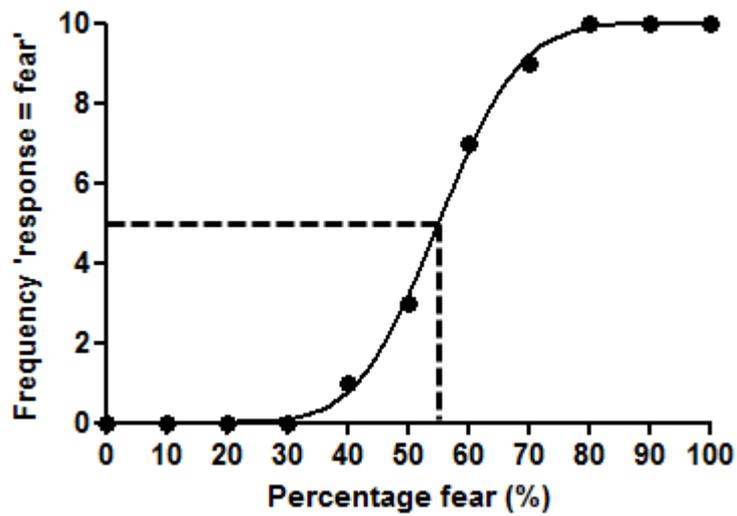
Figure 3-8. Example of the psychometric profile obtained when investigating accuracy of fear recognition using faces morphed between fearful and neutral expressions. The PSE represents the percentage of fear needed in the face for fear to be undistinguishable from neutral (i.e. % fear when frequency = 5, represented by dotted line), and the JND represents the sensitivity of fear recognition (calculated from the inverse gradient of the slope; a less steep slope is associated with a higher JND)

3.5.2 Results

All individual psychometric functions fit well to data points, with values of R^2 all lying above 0.8 (minimum R^2 female face = 0.84, minimum R^2 male face = 0.88). Examples of the psychometric functions produced from participants can be seen in Figure 3-9.
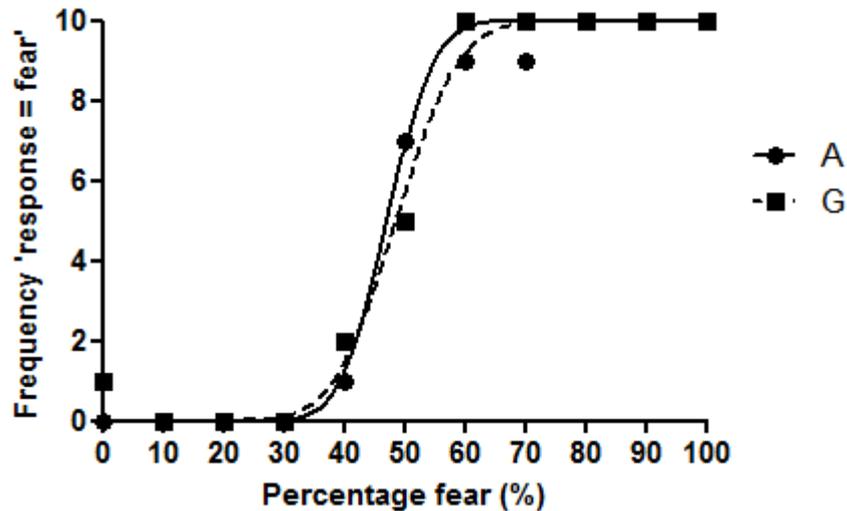
Figure 3-9. Examples of the psychometric functions produced from males possessing the A or G allele at SNP rs7055196 for the female face

3.5.2.1 Point of subjective equality (PSE)

Mean PSE values for males possessing the A or G allele at SNP rs7055196 for each actor can be seen in Table 3-8 and Figure 3-10. PSE values were compared using a 2 (group) × 2 (actor) repeated measures ANOVA. There were no differences in the PSEs of males possessing the different alleles at SNP rs7055196 ($F_{(1,89)}$ = 1.147, P = 0.287, 95% CI (-4.70, 1.41)), indicating there were no group differences in terms of the proportion of fearful expression in the faces when fear recognition was at chance levels. The actor significantly affected PSE values ($F_{(1,89)}$ = 36.636, P < 0.0005, 95% CI (3.14, 6.21)), with the female having a higher PSE than the male (female M 44.28 SD 8.75, male M 48.95 SD 7.63). The female face therefore needed to contain a higher proportion of fearful expression for recognition to be at chance levels compared to the male face. There was no significant interaction between EFHC2 variant and actor ($F_{(1,89)}$ = 0.624, P = 0.432). Neither age ($F_{(1,88)}$ = 0.389, P = 0.534) nor full scale IQ ($F_{(1,88)}$ = 0.005, P = 0.943) were significant when included as covariates.

	A allele	G allele
Female actor	47.82 ± 7.38	50.08 ± 7.86
Male actor	43.76 ± 8.28	44.79 ± 9.18

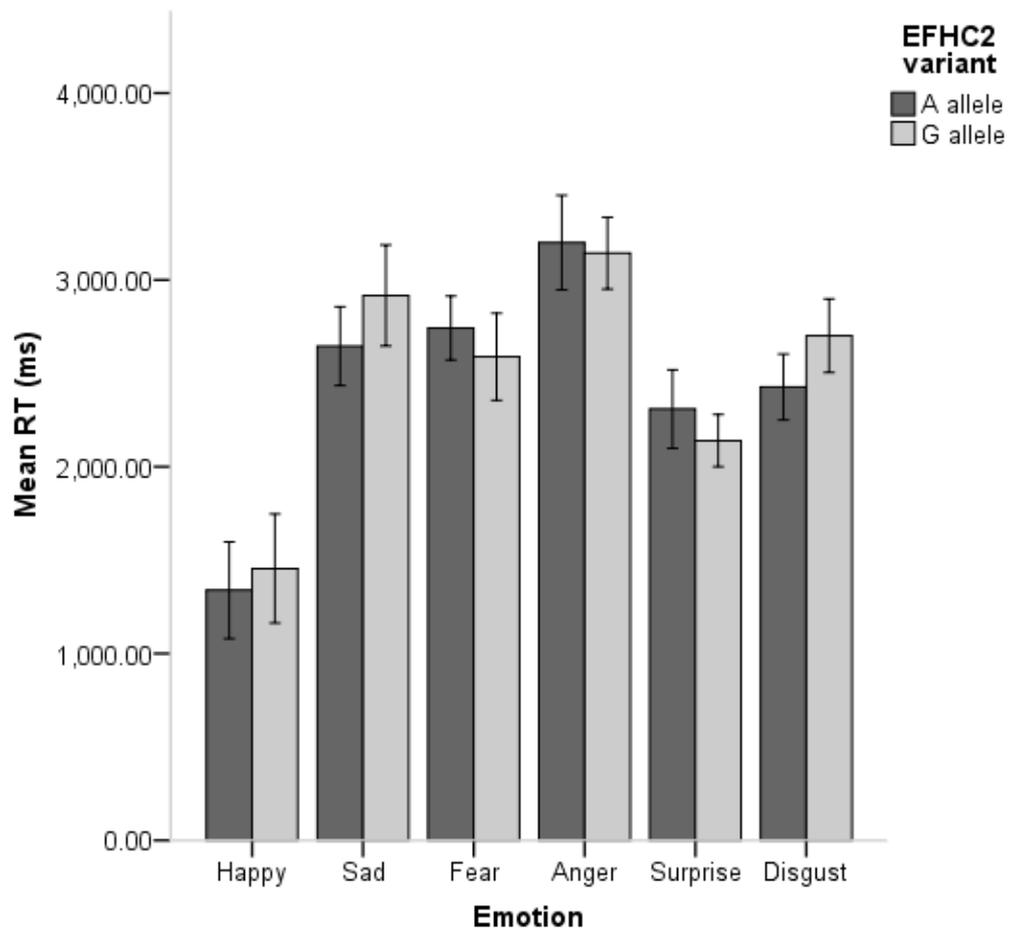**Table 3-8. Mean PSE values (%) for each actor for participants possessing either the A or G allele at SNP rs7055196 (mean ± SD)**
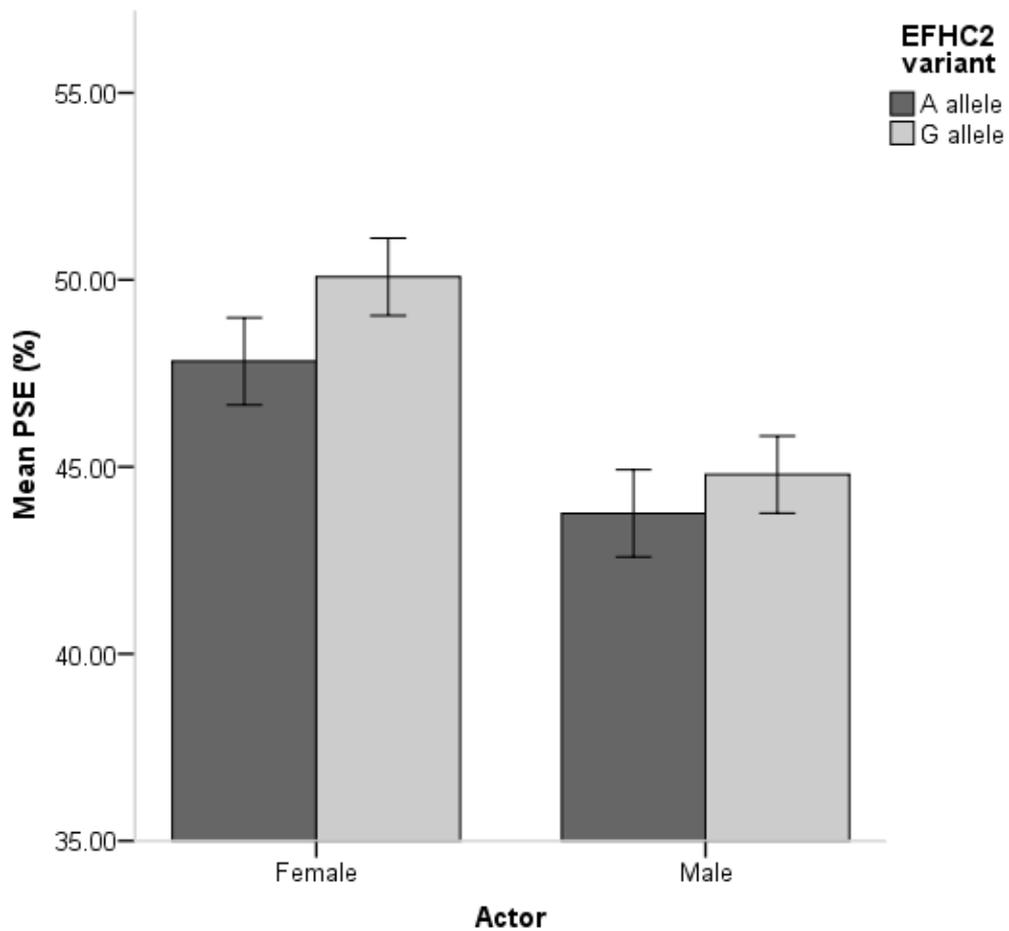
Figure 3-10. Mean PSE values (%) for each actor for participants possessing either the A or G allele at SNP rs7055196 (error bars represent 95% CI)

3.5.2.2 Just noticeable difference (JND)

Mean JND values for males possessing the A or G allele at SNP rs7055196 can be found in Table 3-9 and Figure 3-11. JND values were compared in a 2 (group) × 2 (actor) repeated measures ANOVA. There was a trend towards males possessing the G allele having higher JNDs compared to males possessing the A allele (F (1,89) = 3.091, P = 0.082, 95% CI (-3.21, 0.20), A allele M = 6.09 SD = 5.81, G allele M = 7.59 SD = 5.74), with an effect size of 0.311[1]. This suggests males possessing the G allele may be less sensitive at fear recognition than males possessing the A allele. There was no significant effect of the actor on JND value (F (1,89) = 0.131, P = 0.719, 95% CI (-0.79, 1.14), and no significant interaction between EFHC2 variant and actor (F (1,89) = 1.463, P = 0.230). Neither age (F (1,88) = 3.276, P = 0.074) nor full scale IQ (F (1,88) = 0.088, P = 0.767) were significant when included as covariates.

I next further investigated the above mentioned effect of SNP rs7055196 on JND values. From the results in Table 3-9 and Figure 3-11 it appears that the difference in JND values between males possessing the different alleles at SNP rs7055196 may be greater for the female face compared to the male face, and this possible smaller effect for the male face may reduce the overall significant effect. Further, the higher PSE value for the female face suggests a reduced intensity of her expression compared to that of the male face, which may influence the JND.

I therefore compared the JND values between males possessing the different alleles of SNP rs7055196 for the two actors separately using independent sample t-tests. For the female face, the JND value was significantly higher for males possessing the G allele compared to that of males possessing the A allele (t (89) = -2.067, P = 0.042, 95% CI (-4.11, -0.08)), with an associated effect size equal to 0.214[2]. This suggests that males possessing the G allele were less sensitive at fear recognition than males possessing the A allele for the female face. This effect of EFHC2 variant on JND value can also be seen in Figure 3-9, with the male possessing the G allele showing a reduced slope gradient compared to that of the male possessing the A allele. For the male face, although the JND value for males possessing the G allele was again larger than that of males possessing the A allele, this difference was not significant (t (89) = -0.959, P = 0.340, 95% CI (-2.82, 0.98)). Neither age nor full scale IQ were significant covariates for JND values for either actor (female face age

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[1] Effect size = $\sqrt{\dfrac{F^2}{F^2 + df}}$

[2] Effect size = $\sqrt{\dfrac{t^2}{t^2 + df}}$

F (1,88) = 3.300, P = 0.073, female face full scale IQ F (1,88) = 0.004, P = 0.948, male face age F (1,88) = 1.705, P = 0.195, male face full scale IQ F (1,88) = 0.215, P = 0.644).

	A allele	G allele
Female actor	5.88 ± 4.00*	7.98 ± 5.53*
Male actor	6.29 ± 3.67	7.21 ± 5.29

Table 3-9. Mean JND values for each actor for participants possessing either the A or G allele at SNP rs7055196 (mean ± SD) * P < 0.05 when comparing males possessing the A or G allele
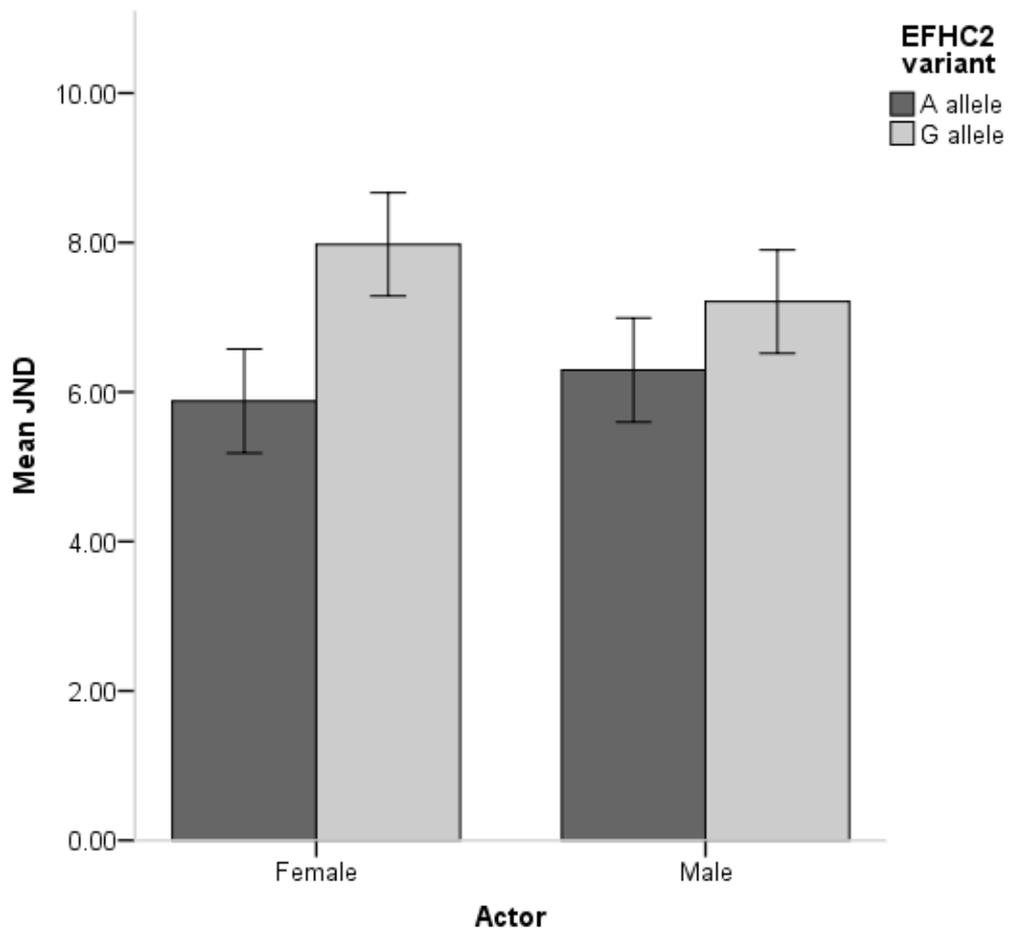
Figure 3-11. Mean JND values for each actor for participants possessing either the A or G allele at SNP rs7055196 (error bars represent 95% CI), * P < 0.05 when comparing males possessing the A or G allele

3.5.2.3 Response time

Mean RTs for each group can be found in Table 3-10 and Figure 3-12. These values were compared in a 2 (group) × 2 (actor) × 11 (rank) repeated measures ANOVA with Greenhouse-Geisser and Bonferroni corrections applied. The RTs of males possessing the different alleles at SNP rs7055196 did not differ between the groups ($F_{(1,89)} = 0.315$, $P = 0.576$, 95% CI (-115, 64)), and RTs for the two actors did not differ ($F_{(1,89)} = 0.566$, $P = 0.454$, 95% CI (-24, 53)). RTs differed depending upon the rank of the face ($F_{(6.213,552.942)} = 14.191$, $P < 0.0005$); longer RTs were found for mid-rank faces compared to those with a low or high rank. This means RTs were longer for faces containing an approximately equal blend of the two expressions compared to those containing a high proportion of either expression (see Table 3-11). There were no significant interactions between EFHC2 variant and actor ($F_{(1,89)} = 1.469$, $P = 0.229$), EFHC2 variant and rank ($F_{(6.213,552.942)} = 0.618$, $P = 0.722$) or actor and rank ($F_{(5.813,517.376)} = 1.694$, $P = 0.123$). In addition, there was no three-way interaction between EFHC2 variant, actor and rank ($F_{(5.813,517.376)} = 0.679$, $P = 0.662$). Age was not significant when included as a covariate ($F_{(1,88)} = 1.115$, $P = 0.294$). Full scale IQ however did significantly affect RT when included as a covariate ($F_{(1,88)} = 4.720$, $P = 0.032$), with a higher IQ being associated with a shorter RT. Including full scale IQ as a covariate did not influence the main effect of SNP rs7055196 on RT or any of its interactions.

	Female actor		Male actor	
	A allele	**G allele**	**A allele**	**G allele**
0% fear	528 ± 173	598 ± 290	556 ± 251	502 ± 174
10% fear	546 ± 166	576 ± 238	547 ± 271	526 ± 217
20% fear	561 ± 196	594 ± 285	553 ± 250	571 ± 274
30% fear	555 ± 213	619 ± 300	571 ± 269	588 ± 320
40% fear	594 ± 253	703 ± 441	604 ± 284	620 ± 326
50% fear	674 ± 262	705 ± 351	663 ± 326	635 ± 291
60% fear	655 ± 261	687 ± 392	661 ± 258	703 ± 432
70% fear	563 ± 181	585 ± 217	624 ± 262	642 ± 367
80% fear	567 ± 233	633 ± 302	570 ± 228	584 ± 270
90% fear	555 ± 205	582 ± 238	571 ± 261	567 ± 307
100% fear	574 ± 194	624 ± 357	549 ± 227	555 ± 287

Table 3-10. Mean RTs (ms) for each ranked face for participants possessing either the A or G allele at SNP rs7055196 (mean ± SD)
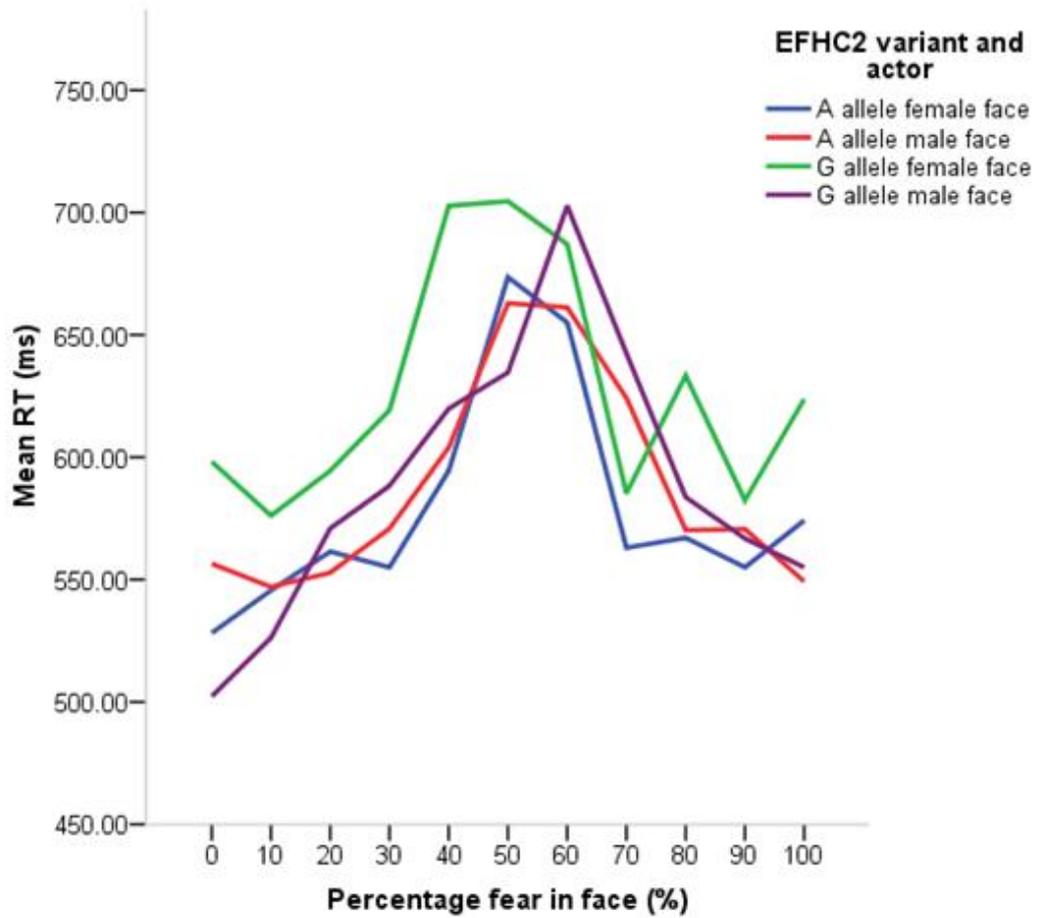
Figure 3-12. Mean RTs (ms) for each ranked female and male face for participants possessing either the A or G allele at SNP rs7055196

	0% fear	10% fear	20% fear	30% fear	40% fear
10% fear	P = 1.000	-	-	-	-
20% fear	P = 1.000	P = 1.000	-	-	-
30% fear	P = 0.732	P = 0.964	P = 1.000	-	-
40% fear	P = 0.004	P = 0.001	P = 0.099	P = 0.716	-
50% fear	P < 0.0005	P < 0.0005	P < 0.0005	P < 0.0005	P = 0.322
60% fear	P < 0.0005	P < 0.0005	P < 0.0005	P < 0.0005	P = 0.619
70% fear	P = 0.044	P = 0.045	P = 1.000	P = 1.000	P = 1.000
80% fear	P = 0.159	P = 0.879	P = 1.000	P = 1.000	P = 1.000
90% fear	P = 1.000	P = 1.000	P = 1.000	P = 1.000	P = 0.072
100% fear	P = 1.000	P = 1.000	P = 1.000	P = 1.000	P = 0.218

	50% fear	60% fear	70% fear	80% fear	90% fear
60% fear	P = 1.000	-	-	-	-
70% fear	P = 0.001	P = 0.001	-	-	-
80% fear	P = 0.001	P < 0.0005	P = 1.000	-	-
90% fear	P < 0.0005	P < 0.0005	P = 0.524	P = 1.000	-
100% fear	P < 0.0005	P < 0.0005	P = 1.000	P = 1.000	P = 1.000

Table 3-11. Pairwise comparisons for RTs (ms) for the different ranked faces

3.6 Discussion

These studies investigated facial emotion recognition abilities, with an emphasis on facial fear recognition abilities, between neurotypical males possessing different variants of SNP rs7055196 within the EFHC2 gene.

3.6.1 The influence of SNP rs7055196 on fear recognition abilities

Although no differences in recognition accuracy were found between males possessing the A or G allele when using the Ekman-Friesen test of facial affect recognition, males possessing the G allele showed a trend towards poorer recognition accuracy for fearful and neutral expressions compared to males possessing the A allele when viewing full and partial faces. Further, males possessing the G allele showed poorer recognition for partial fearful faces compared to males possessing the A allele. This effect occurred whether the eye region was shown alone or whether the eye region was covered in a face. These results do not support my hypothesis that males possessing the G allele would show poorer fear recognition than males possessing the A allele when viewing images of the eye region, with no difference between the groups when viewing faces with the eyes covered. Instead, the poorer fear recognition of males possessing the G allele is not dependent on the presence of any particular facial features.

In addition, when faces containing varying proportions of fearful and neutral expressions were used then a difference in sensitivity to fear recognition was observed between males possessing the different alleles. Specifically, males possessing the G allele at SNP rs7055196 showed poorer fear recognition sensitivity, suggesting a lower sensitivity to fearful expressions, than males possessing the A allele, which supported my hypothesis of lower fear recognition accuracy in males possessing the G allele. Although this result was found for one of the test faces used but not the other (the effect was present for the female face but not the male face), this difference may be due to the female face having a higher PSE than the male face. The female face may therefore show a less intense fearful expression than the male face, and so the female face may be more sensitive to detecting a difference in fear recognition accuracy between males possessing the different alleles at SNP rs7055196. Alternatively, this difference may be due to differences in the facial features which expressed fear between the two faces (further discussed in section 3.6.3). Finally, using these morphed faces no differences were found between males possessing the different alleles in terms of the proportion of fear in the faces when its recognition was at chance levels.

The finding that males possessing the different alleles at SNP rs7055196 showed differences in their fear recognition sensitivity using the fear-neutral morphed faces but not

for the Ekman-Friesen test is likely due to the sensitivity of the tasks in detecting fear recognition accuracy. The Ekman-Friesen test uses just 10 images of faces for each emotion, resulting in maximum accuracy scores of 10 for each emotion. This therefore limits variation in scores. In addition, the expressions in this task may be considered to be exaggerated, which may aid emotion recognition. These two factors may therefore mask subtle group differences. In contrast, the morphed faces used contained differing proportions of fearful and neutral expressions, and due to the more subtle differences between the resulting expressions this task is likely to be more sensitive to detecting differences in fear recognition abilities. This suggests that the difference in fear recognition accuracy between males possessing the different alleles at SNP rs7055196 is relatively subtle.

Although these studies mainly investigated influences of SNP rs7055196 on fear recognition abilities, it is possible that subtle differences in recognition of the other basic emotions occur in males possessing the different variants of this SNP. The effects of this SNP are therefore not necessarily fear specific, and further studies are needed to clarify this issue. It will be important for these studies to compare the relative influences of variance at SNP rs7055196 on recognition accuracy for different emotions; as fear has been suggested to be the hardest emotion to recognise (Palermo and Coltheart 2004, Rapcsak et al 2000, Williams et al 2009) then it is possible variance at this SNP will have a greater effect on fear recognition accuracy compared to accuracy of the other basic emotions.

3.6.2 Fear recognition abilities in other populations

3.6.2.1 Women with Turner Syndrome

Weiss et al (2007b) previously reported that SNP rs7055196 within the EFHC2 gene is associated with facial fear recognition abilities in women with TS, with women possessing the G allele being less accurate at fear recognition compared to those possessing the A allele. While the current study also found an influence of this SNP on fear recognition accuracy in neurotypical males, with poorer fear recognition in males possessing the G allele compared to those possessing the A allele, this effect was less pronounced than the one found in the women with TS. Weiss and colleagues reported a significant influence of this SNP using the Ekman-Friesen test, with women possessing the A allele showing a mean Z score of -0.54 and women possessing the G allele showing a mean Z score of -1.80. In comparison, the current study did not find a significant effect of this SNP using the Ekman-Friesen test. Instead the current study found a significant effect of this SNP when investigating fear recognition accuracy using faces containing varying proportions of fearful

and neutral expressions. This suggests a more subtle influence of SNP rs7055196 on facial fear recognition abilities in neurotypical males compared to women with TS.

There are several possible reasons for this difference. Firstly, the populations differed in terms of their age and IQ. Although the mean ages were similar across the two groups, the standard deviation in the current study was lower (current study M 22.9 SD 4.4, Weiss study M 26.8 SD 10.9). The majority of participants in the current study were aged 18-24, producing a positive skew, and likely resulting in the lower standard deviation than that in the Weiss study. This suggests there are a larger number of older participants in the Weiss study, and emotion recognition abilities have been suggested to decrease with age (Calder et al 2003). In addition, there was a large difference in the mean IQ of the two groups, with participants in the current study scoring much higher than those in the Weiss study (current study M 121.1 SD 8.8, Weiss study M 97.2 SD 16.6). A higher IQ may offer protection against impaired emotion recognition abilities, possibly through improved receptiveness to social signals or more varied life experiences. Differences in age and IQ across the two groups may therefore contribute to the smaller influence of SNP rs7055196 on fear recognition abilities in the current study compared to that of Weiss and colleagues.

Secondly, there are likely to be more widespread impairments in facial emotion recognition abilities in women with TS compared to neurotypical men, regardless of the variant of SNP rs7055196 individuals possess. This may then result in a greater impairment in fear recognition in women with TS possessing the G allele at this SNP compared to neurotypical males. Supporting this, women with TS have been reported to show an overall impairment in facial fear recognition abilities compared to unaffected women (Lawrence et al 2003a) whereas the difference between neurotypical males and females is much smaller (Startin et al unpublished observations, Wade et al 2006). Extreme impairments in social cognitive abilities resulting in the diagnosis of an ASD are more common in women with TS compared to males suggesting more widespread impairments in social cognition in women with TS compared to males; there is a 300 fold increase in the prevalence of ASDs in women with TS compared to non-TS women (Creswell and Skuse 1999), in comparison to a 3 fold increase in boys compared to girls (Levy et al 2009). In addition, amygdala volume is larger in women with TS compared to both neurotypical males and females (Good et al 2003), and as the amygdala is thought to have a role in fear recognition (Adolphs et al 1994, Fusar-Poli et al 2009a, Morris et al 1996) its abnormal development in women with TS may contribute to the poorer facial fear recognition and the higher prevalence of ASDs in this population. These factors may all contribute to SNP rs7055196 having a larger effect on fear recognition abilities in women with TS compared to neurotypical males.

Finally, although both the males in the current study and the women with TS in the Weiss study possessed only one X chromosome, the males in the current study also possessed a Y chromosome whereas the women in the TS study did not. Whilst the EFHC2 gene is not in the pseudoautosomal region of the X chromosome suggesting there is no direct homolog on

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the Y chromosome, other genes on the Y chromosome may contribute towards the development of emotion recognition abilities. This may decrease the influence of SNP rs7055196 on fear recognition accuracy in neurotypical males compared to TS females.

3.6.2.2 Neurotypical males

The differences in facial fear recognition accuracy between the groups were also not as pronounced as those reported by Corden et al (2006) in a subset of neurotypical males, with that subset of males scoring poorly for fear recognition on the Ekman-Friesen test (fewer than 5 out of 10 correct). This suggests that the variant of SNP rs7055196 the males possessed in the Corden study is unlikely to solely account for their poorer fear recognition, and instead other factors, genetic or otherwise, contributed towards this.

3.6.2.3 Individuals with an ASD

Many studies investigating facial emotion recognition abilities in individuals with an ASD have reported impairments compared to unaffected individuals, in particular for fear recognition (Corden et al 2008, Pelphrey et al 2002, Wallace et al 2008). These impairments are more prominent than those found in the current study; however as impaired social cognition is a characteristic feature of the ASDs it should be expected that the impairments in the current study would not be as pronounced as those in individuals with an ASD.

3.6.3 Mechanisms resulting in the influence of SNP rs7055196 on facial fear recognition abilities

Although the results of Studies 2 and 3 indicate an influence of SNP rs7055196 on facial fear recognition abilities in neurotypical males, the cause of this difference between males possessing the different variants is unknown. Various suggestions have been put forward to explain the facial emotion recognition impairment observed in individuals with an ASD or women with TS compared to neurotypical individuals. These include a difference in face processing styles, a difference in expertise in processing faces, a difference in gaze fixation patterns to faces, a difference in amygdala functioning, and a difference in theory of mind abilities. It is possible that one or a combination of these factors may also account for the differences in fear recognition in males possessing the different variants of SNP rs7055196 in the current study. However, it is also important to note that group differences in attention levels or in memory for the prototypical expressions in Study 3 cannot be ruled out (see section 4.4.1 for further discussion on the possible effect of attention).

Results from the current studies may support a difference in face processing style between the groups of males possessing the different variants of SNP rs7055196. The results of Study 2 may suggest that males possessing the G allele are less able to integrate available information from faces compared to males possessing the A allele, and this results in the poorer fear recognition observed in the males possessing the G allele for the partial faces.

It will be important for future studies to investigate holistic and configural processing in groups of males possessing the different alleles at SNP rs7055196. Holistic and configural processing allow us to process information within faces as a whole, whereas feature based processing relies on emotion-specific information from facial features, such as the eye region in fearful faces. Holistic processing may be investigated using upright and inverted faces, while configural processing may be investigated using the composite face effect (see section 1.3.4). Further, electrophysiological responses to faces are thought to reflect different stages of face processing and the different mechanisms used, so comparing ERP waveforms between males possessing the different alleles at SNP rs7055196 in response to faces may also aid understanding of the influence of this SNP on face processing.

Supporting a possible difference in face processing style between males possessing the different alleles at SNP rs7055196, it can be seen from the images of the stimuli used in Study 3 (see Figure 3-7) that the majority of changes between the ranked images occur in the eye region for the male face, whereas both the eye and mouth regions appear to show changes in the female face. Poorer integration of information from different facial features (i.e. as occurs in holistic / configural processing) may therefore show a greater effect on fear recognition accuracy for the female face compared to that for the male face. This may help to explain why poorer fear recognition accuracy was found for males possessing the G allele compared to those possessing the A allele for the female face but not the male face. Males possessing the G allele may therefore possess a reduced ability to process faces holistically / configurally and to integrate facial information compared to males possessing the A allele, with this difference resulting in the poorer fear recognition accuracy in males possessing the G allele. Similarly, it has been suggested that individuals with an ASD show a greater reliance on feature based processing of emotional faces compared to holistic processing compared to neurotypical individuals (Rosset et al 2008, Rutherford and McIntosh 2007, Wallace et al 2008). However, it is possible that other explanations may also contribute towards the effects of SNP rs7055196 on fear recognition abilities.

3.6.4 Additional findings

3.6.4.1 Study 1: influence of emotion on recognition

Results from the Ekman-Friesen test of facial affect recognition suggested that happy was the best and fastest recognised emotion, while fearful and angry expressions were the poorest recognised and angry expressions took longer to recognise than the other expressions. These results are in accordance with those of previous studies (Palermo and Coltheart 2004, Rapcsak et al 2000, Williams et al 2009).

3.6.4.2 Study 2: influence of facial composition on emotion recognition

Results using the partial fearful and neutral faces suggested the two expressions can be accurately recognised from the eye region alone, although this region is not necessary to distinguish fearful and neutral expressions as both were well recognised when the eye region was covered. Recognition levels were highest for full faces and lowest when the eyes were shown alone, while RTs were slowest when the eye region alone (with or without eyebrows) was shown and fastest for the other conditions. There were significant interactions between emotion and facial composition, with higher recognition accuracy for fearful compared to neutral expressions when the eyes and eyebrows were seen alone and for neutral compared to fearful expressions for faces with the eyes or eyes and eyebrows covered. In addition, RTs were faster for fearful expressions when the eyes were present and for neutral expressions when the eyes were covered. These findings support the previously suggested importance of the eye region in the recognition of fearful faces (Adolphs et al 2005, Leppanen et al 2008, Schyns et al 2007). The presence or absence of the eyebrows did not appear to influence recognition accuracy or RT, as these were similar for the eyes alone / eyes and eyebrows alone conditions and for the faces with eyes covered / faces with eyes and eyebrows covered conditions. In addition, the fearful expressions trended towards a faster recognition compared to the neutral expressions.

Results are comparable to those found by Leppanen et al (2008), who also found that the eye region is sufficient for fear recognition, although recognition levels are best when the whole face is viewed. Leppanen et al (2008) reported for fearful expressions recognition was best for full faces, followed by images of the eye region alone, with faces with the eye region covered being recognised poorest. They found no differences between facial compositions for the recognition of neutral expressions. These differences in findings with the current study may be due to a difference in the stimuli used, or a difference in the procedure. In the

Leppanen study participants viewed the face for a limited time (500ms), whereas participants had an unlimited time to view the image in the current study (mean RT 1091ms). In the present study viewing the eye region alone produced the poorest accuracy and longest RTs. Longer viewing times (i.e. in the current study) may be associated with high level cortical processing compared to low level subcortical processing which may be more dominant for shorter viewing times (i.e. in the Leppanen study). We may be more sensitive to the recognition of fearful expressions from the eye region when they are processed using subcortical pathways compared to cortical pathways; supporting this when identifying facial emotions implicitly (which is dependent on subcortical processing) then fear is recognised most accurately and fastest out of the six basic emotions (Williams et al 2009), whereas for explicit recognition (which is dependent on cortical processing) fear is recognised poorest and slowest (Palermo and Coltheart 2004, Rapcsak et al 2000, Williams et al 2009). This difference may help to explain the difference between the results in the present study and those of Leppanen et al. This difference may alternatively be due to an effect of memory; fewer actors were used in each block in the current study, suggesting a greater influence of memory. This effect is likely to be more pronounced for images of faces with the eyes region covered compared to images of the eye region alone due to the amount of information available in the images, and so may help to explain the difference in results.

3.6.4.3 Study 3: influence of rank on response time

Results using the faces morphed between fearful and neutral prototypes suggest a difference in RTs for faces containing differing proportions of the two expressions. Specifically, images containing approximately equal proportions of the fearful and neutral expressions (i.e. towards the PSE) produced longer RTs compared to images containing a high proportion of either the fearful or neutral expressions (i.e. towards the prototypical images). This effect of rank is related to the perceived difficulty of the task; it is easier to identify the emotion of a face with a high proportion of either a fearful or a neutral expression compared to faces where the proportions of the two emotions are more similar. A similar result has been reported previously (Fiorentini and Viviani 2009).

3.6.4.4 Studies 2 and 3: influence of IQ on response time

In both Studies 2 and 3 significant negative associations were found between RT and full scale IQ. This may be due to higher processing speeds in individuals with a higher IQ, resulting in shorter RTs.

3.7 Summary

Our ability to recognise emotions from facial expressions allows us to understand how others feel and how they may behave. There are six basic emotions (happy, sad, fear, anger, surprise, and disgust), and it has been reported that happy is the easiest recognised emotion and fear the poorest recognised. Facial configurations differ across these six emotions, with the widened eyes being important for fear recognition. The recognition of facial expressions has been suggested to be influenced by genetic factors, and an influence of genes on the X chromosome has been proposed. In women with TS, work over the last decade has identified a locus at Xp11.3, specifically SNP rs7055196 within the EFHC2 gene, which influences facial fear recognition abilities; women possessing the G allele at this SNP show poorer fear recognition accuracy compared to women possessing the A allele. The present studies investigated whether this same SNP also influences the facial fear recognition abilities of neurotypical males. I found an influence of this SNP on fear recognition abilities in neurotypical males, with males possessing the G allele showing poorer fear recognition compared to those possessing the A allele. Males possessing the G allele showed poorer fear recognition when viewing partial faces, and this did not depend on the presence of the eye region. These males also showed a lower sensitivity to changes in fearful expression intensity. This influence of SNP rs7055196 on fear recognition was more subtle than that seen in the women with TS. These results may suggest a difference in face processing styles between males possessing the different alleles at SNP rs7055196, with increased holistic / configural processing in males possessing the A allele compared to those possessing the G allele.

4 Investigating gaze fixations while viewing fearful-neutral morph faces

4.1 Introduction

In the previous chapter I found an influence of SNP rs7055196 within the EFHC2 gene on facial fear recognition in males; males possessing the G allele at this SNP showed poorer fear recognition than males possessing the A allele. To determine whether this difference may be due to differences in gaze fixation patterns to facial features between the groups I compared fixations to the eye and mouth regions when viewing faces.

Humans show an innate interest in faces, and our attention is rapidly and involuntarily directed towards face stimuli (Crouzet et al 2010). When we view faces both passively and during facial emotion recognition tasks we spend the majority of our time directing our gaze towards the eye region (Adolphs et al 2005, Buchan et al 2007, Itier et al 2007b). This information from the eye region has been reported to be processed before information from any other region (Schyns et al 2009), suggesting the importance of this region during facial emotion recognition. Our interest in the eyes is thought to be innate, as infants direct more attention to the eyes compared to any other facial region (Peltola et al 2009b), and our attraction to this region has been suggested to be due to a default interest in social information which is often portrayed by the eyes, rather than a saliency of this region per se (Birmingham et al 2009). In addition, information from the mouth is used during facial expression recognition (Schyns et al 2002). The eye region is thought to be particularly important for the recognition of fearful facial expressions (Schyns et al 2007), with widened eyes being a characteristic feature of fearful faces (Kohler et al 2004). Further, the eyes alone are sufficient for recognising fearful expressions, although information from other regions is also used (Leppanen et al 2008).

Impairments in fear recognition are commonly found in individuals with an autism spectrum disorder (ASD) compared to neurotypical individuals (Corden et al 2008, Pelphrey et al 2002, Wallace et al 2008), and the atypical scan paths of individuals with an ASD while viewing faces has been suggested to account for this difficulty with fear recognition. It has been reported that individuals with an ASD show a lack of fixations to the eye region (Corden et al 2008, Jones et al 2008, Klin et al 2002, Pelphrey et al 2002) and they divert

their gaze away from the eyes (Chawarska and Shic 2009, Kliemann et al 2010, Spezio et al 2007c). This has been suggested to be due to a lack of a typical approach related motivational response to direct eye contact rather than an active avoidance of this region (Kylliainen et al 2012). This reduced number of fixations made to the eye region has been suggested to account for the impairments in emotion recognition abilities in individuals with an ASD as increased eye fixations have been associated with higher emotion recognition abilities and less severe symptoms (Corden et al 2008, Jones et al 2008, Kliemann et al 2010). Several studies have also reported that individuals with an ASD show a higher number of fixations to the mouth region compared to unaffected individuals (Jones et al 2008, Klin et al 2002).

Women with Turner Syndrome (TS, X-monosomy) also often show impaired facial emotion recognition for fearful expressions (Good et al 2003, Lawrence et al 2003a, Mazzola et al 2006, Skuse et al 2005). These women also show abnormal scan paths compared to unaffected women while viewing emotional faces, with an increased number of fixations made to the mouth. A subgroup of women with TS also show very few fixations to the eyes (Mazzola et al 2006). These atypical scan paths have been suggested to contribute towards the poorer emotion recognition abilities of women with TS. However, these atypicalities are less pronounced than those for individuals with an ASD.

4.1.1 Aim and hypotheses

In Study 3 I found that variation at SNP rs7055196, found within the EFHC2 gene, influences facial fear recognition accuracy in males. Males possessing the G allele showed poorer sensitivity to recognising fearful facial expressions compared to males possessing the A allele. I investigated whether this difference may be due to differences in gaze fixation patterns between the two groups.

Specifically, I investigated a possible influence of SNP rs7055196 on the number of fixations made to the eye and mouth regions of faces, and the length of time spent fixating these regions. I hypothesised that a reduced accuracy of fear recognition in males possessing the G allele of this SNP compared to the A allele as found in Study 3 may be due to a reduced number of fixations to or a reduced length of time spent fixating the eye region.

4.2 Participant information

Eye tracking was performed for all participants during Study 3. Unfortunately, due to problems with calibration and maintaining a constant image of the eye, data was only available from 73 participants for analysis (A allele n = 36, G allele n = 37). In total, eye

tracking data was analysed for 66 individuals for the female face (A allele n = 34, G allele n = 32) and for 68 individuals for the male face (A allele n = 32, G allele n = 36). Data for both faces was analysed for 61 participants (A allele n = 30, G allele n = 31).

For individuals whose data was not available for analysis, this was due to calibration problems for a total of 13 participants for the female face and 15 participants for the male face. In addition, some participants possessed poor quality data; this was defined as more than 10% of trials containing no fixations or more than 20% of all fixations being made off screen. For the female face, 12 individuals produced poor quality data, while 8 individuals produced poor quality data for the male face.

4.2.1 Age, handedness and ethnicity

Information regarding the age and ethnicity of participants used in the analysis can be seen below in Table 4-1. There was no significant difference in age between the two groups when compared using an independent samples t-test (t (71) = -1.169, P = 0.246, 95% CI (-3.20, 0.84). The majority of participants were right handed; 2 males possessing the G allele and 1 male possessing the A allele were left handed. Ethnicities between the two groups were also similar.

	A allele	G allele
Number	36	37
Age	22.17 ± 3.63 (18-33)	23.35 ± 4.91 (19-41)
Ethnicity	21 Caucasian, 3 Hispanic, 10 Asian, 1 African, 1 mixed race	22 Caucasian, 3 Hispanic, 9 Asian, 2 African, 1 mixed race

Table 4-1. Information regarding the age (mean ± SD (range)) and ethnicity of participants tested in each group

4.2.2 IQ

There were no differences between groups for full scale IQ (t (71) = 0.653, P = 0.516, 95% CI (-2.84, 5.61)), verbal IQ (t (71) = 0.266, P = 0.791, 95% CI (-4.62, 6.04) or performance IQ (t (71) = 0.877, P = 0.384, 95% CI (-2.42, 6.21)) as compared using independent samples t-tests (Table 4-2).

	A allele	G allele
Full scale IQ	122.17 ± 8.20	120.78 ± 9.81
Verbal IQ	121.33 ± 11.34	120.62 ± 11.48
Performance IQ	118.17 ± 9.08	116.27 ± 9.39

Table 4-2. Full scale, verbal and performance IQs of each group (mean ± SD)

4.3 Study 4: eye tracking using fear-neutral morph faces

4.3.1 Method

During Study 3 (section 3.5) eye tracking was also performed to measure gaze fixations made to the eye and mouth regions of the faces. While each image was shown to participants, eye gaze and pupil size was recorded at 60Hz using an ASL Model 504 remote infrared pupil-corneal reflection eye-tracker and EyeTrac 6 system (Applied Science Laboratories, Bedford, MA). At the start of the task a brief calibration was performed; in this participants were asked to look at nine points on the screen with recorded positions. This corrected for any individual differences in head positions between participants.

4.3.1.1 Analysis

Any trials which showed a loss in tracking integrity were excluded from subsequent analysis, as were off-screen gazes. Regions of interest (ROIs, namely the eye and mouth regions) were defined prior to analysis for each actor (Figure 4-1). Although these areas differed in appearance and shape across the series of images for each actor they maintained a constant position and size for each actor, and so regions were the same across images from each actor. The ROIs used included the area surrounding the eyes and mouth; this provided more flexibility as to what was included as a fixation on either of the ROIs to compensate for slight problems with calibration. Analysis was also performed using smaller ROIs which provided stricter definitions of the eye and mouth regions to investigate differences in gaze fixations using just the eyes and mouth and not the surrounding areas. Whether the larger or smaller ROIs were used did not affect differences between the two participant groups, however it should be noted that for the larger ROIs but not the smaller ROIs there was a

larger number and duration of fixations to the male eyes compared to the female eyes. As there were no group-wise differences whether the larger or smaller ROIs were used, all data presented are for the larger ROIs to account for slight calibration issues.

Gaze fixations were analysed using ASL results (Applied Science Laboratories, Bedford, MA). Fixations were defined as a set of consecutive gaze coordinates confined within a diameter of 1° of visual angle for a minimum duration of 100ms (Noton and Stark 1971). The mean numbers of fixations and total duration of fixations on each ROI were calculated for each participant across trials (trial duration 3000ms). In addition, the percentage of all fixations made to each ROI and the percentage of time spent fixating on each ROI were calculated. Results within this thesis reflect only comparisons between the percentage of fixations made to and the percentage of time spent fixating each ROI. Using the absolute values may mask group differences in the total number of fixations or total duration of fixations to the face, and so it was decided to report the percentage values. However, it should be noted that analysis was also performed using the absolute values, and there were no quantitative or qualitative differences using the absolute number of fixations and percentage of fixations, or using the absolute duration of time and percentage of time.

Each measure of gaze fixations for the two ROIs was compared in independent sample t-tests between the two groups possessing the different alleles at SNP rs7055196. In addition, to investigate differences in gaze fixations between the female and male faces, for the 31 individuals for whom data was available for both faces then each measure of gaze fixations was compared for the two ROIs separately in 2 (group) × 2 (actor) repeated measures ANOVAs.
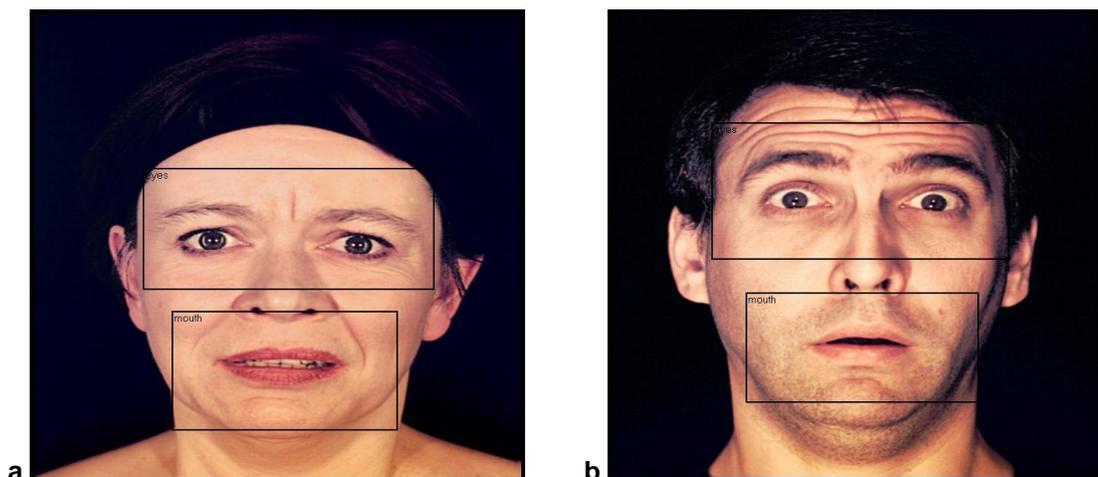
Figure 4-1. The regions of interest used for analysis of gaze fixations for (a) the female face and (b) the male face

4.3.2 Results

4.3.2.1 Percentage of fixations

Results for the mean percentages of fixations to the eye and mouth regions for the two groups can be seen in Table 4-3 and Figure 4-2. Both groups made a larger percentage of fixations to the eye region compared to the percentage of fixations to the mouth region for both series of faces, with the percentage of eye fixations being almost three times the percentage of mouth fixations.

4.3.2.1.1 Percentage of fixations to the eye region

When comparing the percentages of fixations made to the eyes of the two series of faces using independent samples t-tests, there were no differences between the groups possessing the different variants of SNP rs7055196 for either the female face (t (64) = 0.009, P = 0.993, 95% CI (-8.56, 8.64)) or the male face (t (66) = 0.491, P = 0.625, 95% CI (-6.55, 10.82)).

Using a 2 (group) × 2 (actor) repeated measures ANOVA to compare fixations between the two series of faces for those individuals who had data for both series of faces, there was no difference in the percentage of fixations made to the eye region for males possessing the A or G allele at SNP rs7055196 (F (1,59) = 0.002, P = 0.968, 95% CI (-8.35, 8.02)). There was however a significant difference between the percentage of fixations made to the eyes for the two actors (F (1,59) = 15.424, P < 0.0005, 95% CI (-11.98, -3.89)), with a higher percentage of fixations being made to the eyes of the male face compared to the eyes of the female face (female face M 62.98 SD 17.91, male face M 70.91 SD 17.73). There was no interaction effect between EFHC2 variant and actor (F (1,59) = 0.435, P = 0.512). Neither age (F (1,58) = 3.091, P = 0.084) nor full scale IQ (F (1,58) = 2.071, P = 0.156) had a significant effect on the percentage of fixations made to the eyes when included as covariates.

4.3.2.1.2 Percentage of fixations to the mouth region

When comparing the percentages of fixations made to the mouth region of the two series of faces using independent samples t-tests, there were no differences in the percentage of fixations made to the mouth between the groups possessing the different variants of SNP rs7055196 for either the female face (t (64) = -0.305, P = 0.761, 95% CI (-7.60, 5.59)) or the male face (t (66) = -0.354, P = 0.725, 95% CI (-5.94, 4.15)).

Using a 2 (group) × 2 (actor) repeated measures ANOVA to compare fixations between the two series of faces for those individuals who had data for both series of faces, there was no difference in the percentage of fixations made to the mouth region between males possessing the A and G alleles at SNP rs7055196 ($F_{(1,59)} = 0.045$, P = 0.832, 95% CI (-6.21, 5.02)). The number of fixations made to the mouth region differed between the male and female faces ($F_{(1,59)} = 51.48$, P < 0.0005, 95% CI (7.11, 12.60)), with significantly more fixations being made to the mouth of the female face than to that of the male face (female face M 23.56 SD 13.68, male face M 13.70 SD 10.52). There was no interaction effect between EFHC2 variant and actor ($F_{(1,59)} = 0.015$, P = 0.904). When included as a covariate, age significantly affected the percentage of fixations made to the mouth region ($F_{(1,58)} = 9.499$, P = 0.003), with increasing age being associated with a higher percentage of fixations made to the mouth. Including age as a covariate did not influence the effect of SNP rs7055196 on the percentage of fixations made to the mouth, or the interaction between SNP rs7055196 and actor. Full scale IQ was not significant when included as a covariate in the analysis ($F_{(1,58)} = 3.544$, P = 0.065).

	Female face		Male face	
	A allele	**G allele**	**A allele**	**G allele**
Eyes	63.56 ± 17.72	63.52 ± 17.23	71.65 ± 18.59	69.52 ± 17.28
Mouth	22.52 ± 12.05	23.53 ± 14.71	13.19 ± 10.51	14.08 ± 10.29

Table 4-3. Mean percentage of fixations (%) made to the eye and mouth regions of each series of faces
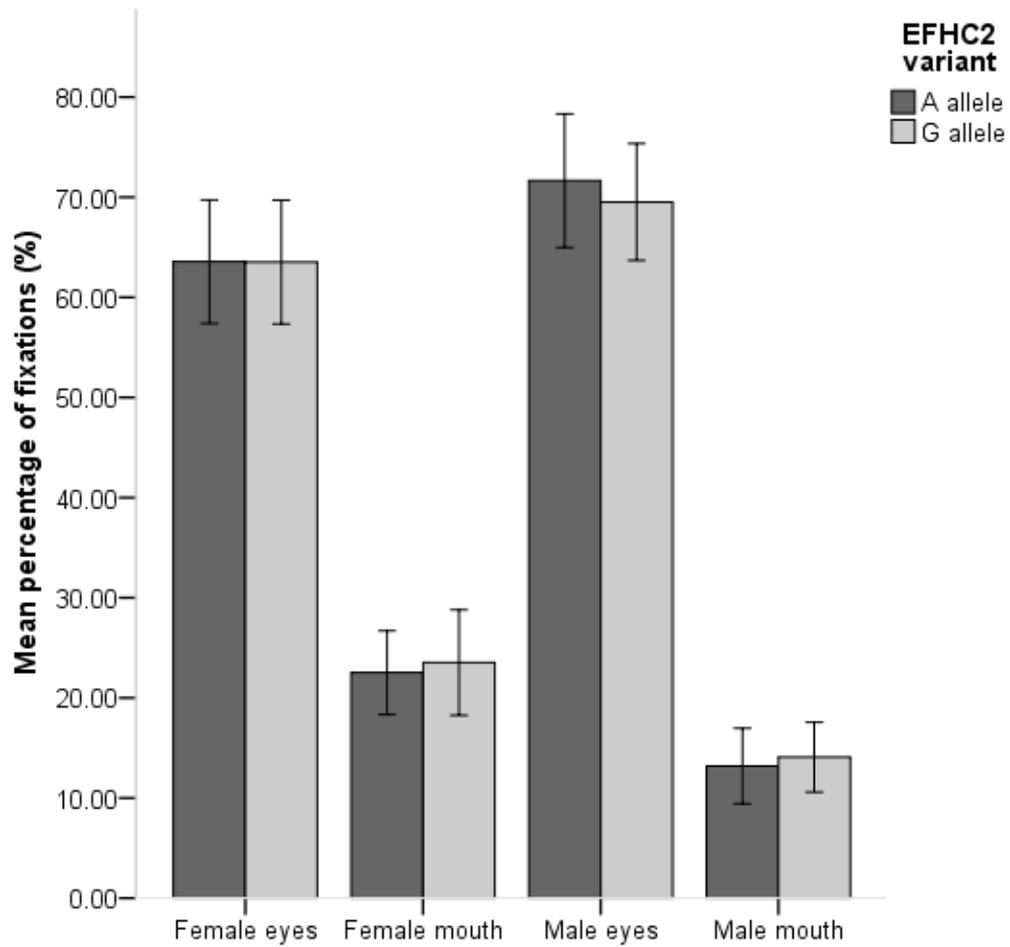
Figure 4-2. Mean percentage of fixations (%) made to the eye and mouth regions of each series of faces (error bars represent 95% CI)

4.3.2.2 Percentage of total duration of fixations

Results for the mean percentages of time spent fixating the eye and mouth regions for the two groups can be seen in Table 4-4 and Figure 4-3. The total percentage of time spent fixating the eye region was longer than the total percentage of time spent fixating the mouth region for both faces for both groups, with the percentage of time spent fixating the eye region being nearly three times the percentage of time spent fixating the mouth region.

4.3.2.2.1 Percentage of total duration of fixations to the eye region

Comparing the percentage of time spent fixating the eye region of the two series of faces between the two groups of males possessing the different alleles at SNP rs7055196 using independent samples t-tests, there were no differences for either the female face (t (64) = 0.214, P = 0.831, 95% CI (-8.27, 10.25)) or the male face (t (66) = 0.254, P = 0.800, 95% CI (-7.83, 10.12)).

Using a 2 (group) × 2 (actor) repeated measures ANOVA to compare fixations between the two series of faces for those individuals who had data for both series of faces, there were no differences in the percentages of time spent fixating the eye region between males possessing the different alleles at SNP rs7055196 (F (1,59) < 0.0005, P = 0.984, 95% CI (-8.92, 8.73)). There were differences in the percentage of time spent fixating the eyes for the two faces (F (1,59) = 17.839, P < 0.0005, 95% CI (-12.44, -4.44)), with a higher percentage of fixations being made to the eyes of the male face than to those of the female face (female M 63.99 SD 19.33, male M 72.43 SD 18.47). There was no significant interaction effect between EFHC2 variant and actor (F (1,59) = 0.060, P = 0.807). When included as a covariate, age significantly affected the percentage of time spent fixating the eyes (F (1,58) = 4.218, P = 0.045), with increasing age being associated with a lower percentage of time spent fixating the eyes. Including age as a covariate did not affect the influence of SNP rs7055196 on the percentage of total duration of fixations to the eyes or the interaction between SNP rs7055196 and actor. Full scale IQ (F (1,58) = 2.335, P = 0.132) was not significant when included as a covariate.

4.3.2.2.2 Percentage of total duration of fixations to the mouth region

When comparing the percentages of time spent fixating the mouth of the two series of faces using independent samples t-tests, there were no differences between the groups possessing the different variants of SNP rs7055196 for the female face (t (64) = -0.600, P = 0.551, 95% CI (-9.76, 5.25)) or the male face (t (66) = -0.280, P = 0.781, 95% CI (-6.00, 4.53)).

Using a 2 (group) × 2 (actor) repeated measures ANOVA to compare fixations between the two series of faces for those individuals who had data for both series of faces, there were no differences in the percentages of the total length of time spent fixating the mouth region between males possessing the A and G alleles at SNP rs7055196 ($F_{(1,59)} = 0.138$, $P = 0.711$, 95% CI (-7.50, 5.15)). There was a significant difference between the two actors for the percentage of the total time spent fixating the mouth ($F_{(1,59)} = 55.308$, $P < 0.0005$, 95% CI (7.76, 13.48)), with a higher percentage of the total length of fixations being spent looking at the mouth of the female face compared to the male face (female face M 23.65 SD 15.63, male face M 13.03 SD 11.06). There was no significant interaction effect between EFHC2 variant and actor ($F_{(1,59)} = 0.132$, $P = 0.718$). When included as a covariate then age significantly affected the percentage of time spent fixating the mouth ($F_{(1,58)} = 11.710$, $P = 0.001$), with increasing age being associated with a higher percentage of time spent fixating the mouth. Including age as a covariate did not affect the influence of SNP rs7055196 on the percentage of fixations made to the mouth, or the interaction between SNP rs7055196 and actor. Full scale IQ was not significant when included as a covariate ($F_{(1,58)} = 3.926$, $P = 0.052$).

	Female face		Male face	
	A allele	**G allele**	**A allele**	**G allele**
Eyes	65.13 ± 18.41	64.14 ± 19.25	72.76 ± 19.15	71.62 ± 17.91
Mouth	21.90 ± 13.05	24.15 ± 17.29	12.55 ± 10.89	13.28 ± 10.83

Table 4-4. Mean percentages of duration of time (%) spent fixating the eye and mouth regions of each series of faces
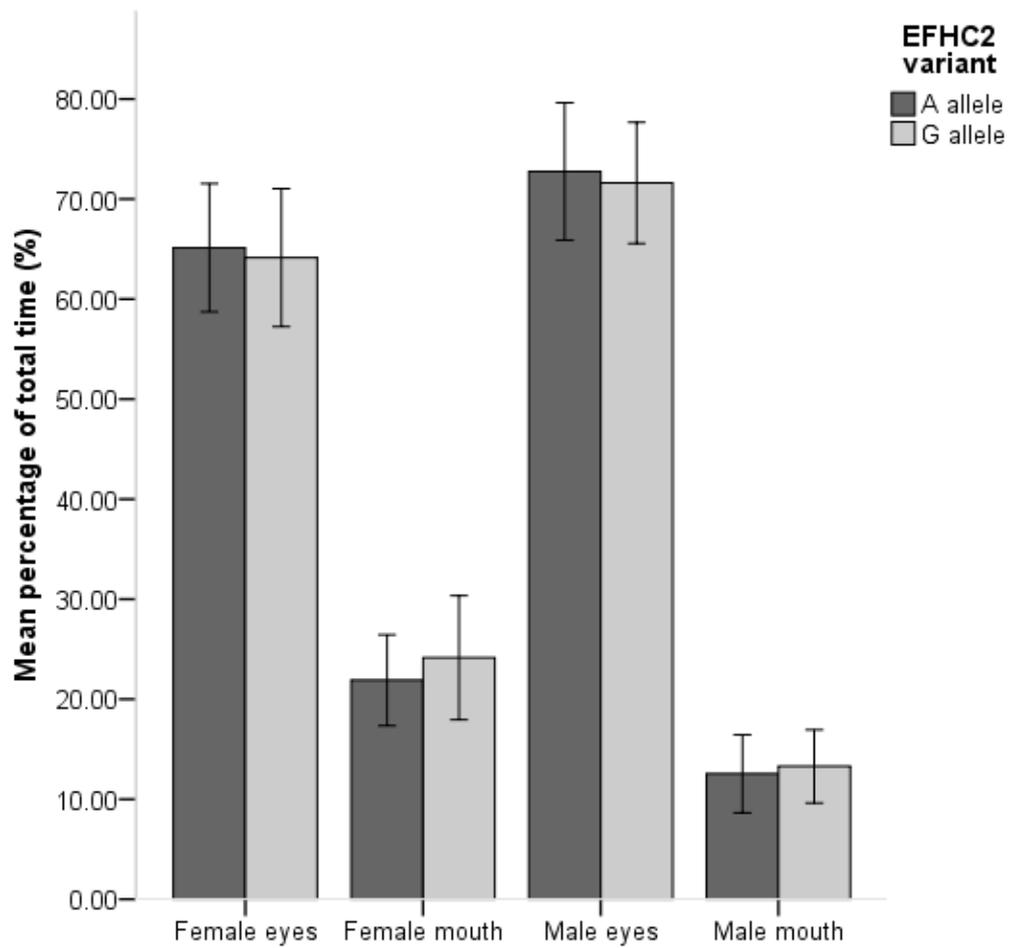
Figure 4-3. Mean percentages of duration of time (%) spent fixating the eye and mouth regions of each series of faces (error bars represent 95% CI)

4.3.2.3 Percentage of fixations made to the eye region of all fixations made to the eye or mouth regions

To investigate the distributions of fixations made to the eye and mouth regions I compared the numbers of fixations made to the eyes relative to the total number of fixations made to either the eye or mouth regions. Results for the mean percentages of fixations made to the eye region for each group can be seen in Table 4-5 and Figure 4-4.

Comparing the percentages of fixations to the eye region for the two series of faces between the two groups of males possessing the different alleles at SNP rs7055196 using independent samples t-tests, there were no differences for either the female face (t (64) = 0.178, P = 0.859, 95% CI (-7.06, 8.45)) or the male face (t (66) = 0.488, P = 0.627, 95% CI (-5.08, 8.37)).

Using a 2 (group) × 2 (actor) repeated measures ANOVA to compare fixations between the two series of faces for those individuals who had data for both series of faces, there were no differences in the percentages of fixations to the eye region between males possessing the different alleles at SNP rs7055196 (F (1,59) = 0.003, P = 0.956, 95% CI (-6.69, 7.08)). There were differences in the percentages of fixations to the eye region for the two faces (F (1,59) = 43.177, P < 0.0005, 95% CI (-14.32, -7.63)), with a higher percentage of fixations being made to the eye region of the male face than to that of the female face (female M 71.33 SD 16.10, male M 82.30 SD 13.67). There was no significant interaction effect between EFHC2 variant and actor (F (1,59) = 0.150, P = 0.700). When included as a covariate, age significantly affected the percentage of fixations to the eye region (F (1,58) = 6.835, P = 0.011), with increasing age being associated with a lower percentage of time spent fixating the eye region. Including age as a covariate did not affect the influence of SNP rs7055196 on the percentage of fixations to the eye region or the interaction between SNP rs7055196 and actor. Full scale IQ was not significant when included as a covariate (F (1,58) = 2.790, P = 0.100).

	Female face		Male face	
	A allele	**G allele**	**A allele**	**G allele**
Eyes	72.34 ± 15.50	71.64 ± 16.03	82.95 ± 14.28	81.31 ± 13.48
Mouth	27.66 ± 15.50	28.36 ± 16.03	17.05 ± 14.28	18.69 ± 13.48

Table 4-5. Mean percentages of fixations (%) spent fixating the eye and mouth regions of all fixations made to either the eye or mouth regions for each series of faces
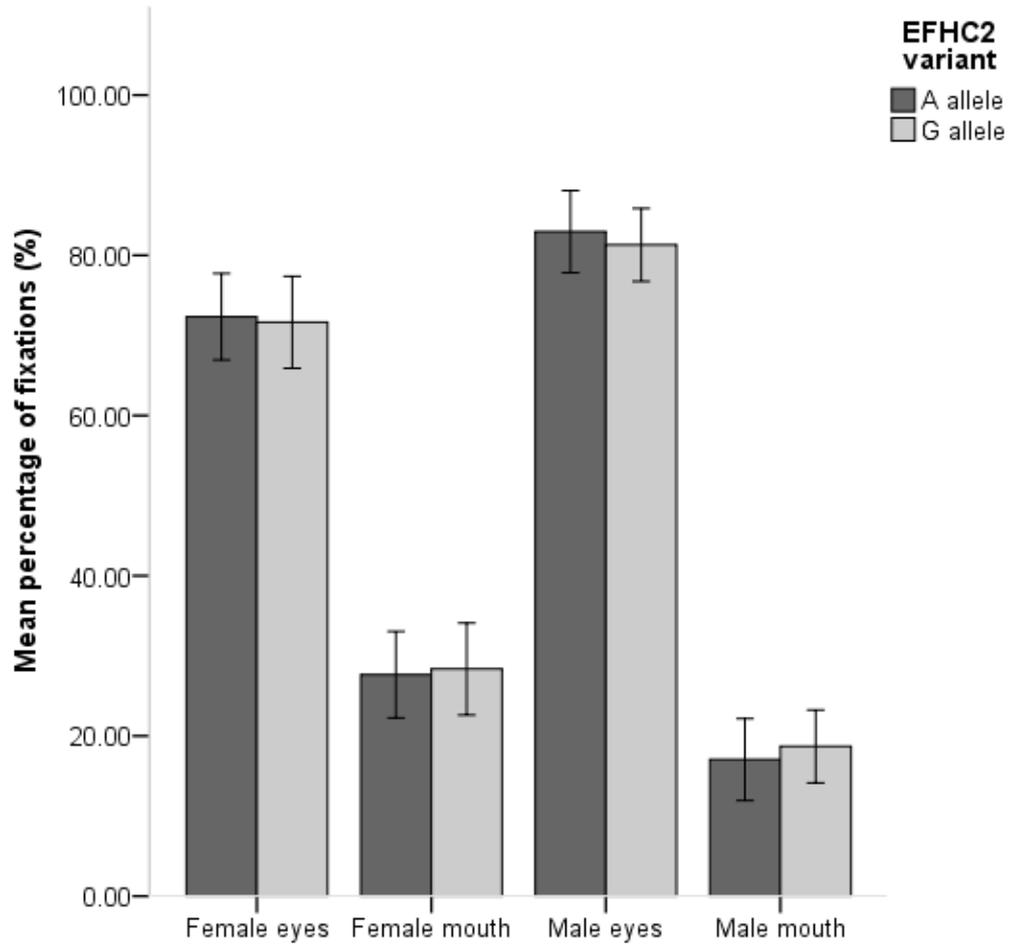
Figure 4-4. Mean percentages of fixations (%) spent fixating the eye and mouth regions of all fixations made to either the eye or mouth regions for each series of faces (error bars represent 95% CI)

4.4 Discussion

This study investigated gaze fixations to faces morphed between neutral and fearful expressions in males possessing different alleles at SNP rs7055196 within the EFHC2 gene.

4.4.1 The influence of SNP rs7055196 on fixation patterns to faces

There were no differences between males possessing the A or G allele for the percentage of fixations to either the eye region or mouth region while judging the expression within the face, for the percentage of time spent fixating either region, or for the distribution of fixations made to the two regions.

Differences in scan paths are therefore not likely to contribute towards the impaired fear recognition accuracy in males possessing the G allele relative to those possessing the A allele. This difference is also unlikely to be due to a difference in attention levels during the task between the two groups, as a difference in attention levels would be likely to produce a difference in scan paths. Further, these results suggest there is no difference between the two groups in terms of attraction or avoidance to either the eye or mouth region, and there is no difference in the perceived importance of information from the eyes and mouth between males possessing the different alleles at SNP rs7055196. There is also likely to be no difference in the facial information received by the brains of males possessing the different variants. The difference in facial fear recognition accuracy between the two groups may therefore be due to a difference in the way that information from faces is processed, such as a different processing style.

4.4.2 Face processing styles

Both groups made a larger number of fixations to the eye region compared to the mouth region and spent longer viewing the eyes. This finding is similar to that which has been previously reported, with individuals fixating primarily on the eye region and fixations also being made to the mouth region (Adolphs et al 2005, Buchan et al 2007, Itier et al 2007b, Schyns et al 2002). This finding supports the suggestion that the eye region is the most important region for identifying facial expressions, in particular for fear (Adolphs et al 2005, Schyns et al 2007).

However, when comparing the fixation patterns to the eye and mouth regions of the female and male faces, differences were observed. Fewer fixations were made with a shorter total duration to the female eyes compared to the male eyes, and to the male mouth compared to the female mouth. This difference likely reflects differences in the relative importance of the

eyes and mouth in determining whether the expression is fearful or neutral across the two series of faces. The female face series shows more variation in mouth shape than the male face series, suggesting that the mouth is relatively more important in determining the expression within the female face. This may then lead to a higher number of fixations and a longer duration of fixations being made to the female mouth compared to the male mouth. This would then result in fewer fixations and a shorter duration of fixations being made to the female eyes compared to the male eyes. This difference may also result in slight differences in processing styles being used for the two faces, with the female face relying on a more holistic / configural style, with the face being processed as a whole and information integrated from the eye and mouth regions, and the male face being less dependent on holistic / configural processing and instead relying on a more feature based style, with an emphasis on processing information from the eye region alone.

This potential difference in processing style being used for the two faces may have resulted in the differences in fear recognition accuracy between the two groups possessing the different variants of SNP rs7055196 in Study 3. If males possessing the G allele were less able to process faces holistically / configurally than males possessing the A allele this may result in poorer fear recognition accuracy for males possessing the G allele, with a greater effect being seen for the female face compared to the male face. This is what was found in Study 3, as males possessing the G allele showed poorer fear recognition accuracy than males possessing the A allele for the female face with no difference between the groups for the male face.

4.4.3 The role of the amygdala in orienting gaze to the eye region

A difference in fear recognition accuracy between the two groups may also suggest a potential difference in amygdala function. The amygdala is thought to play an important role in directing our attention towards the eye region while viewing faces (Adolphs et al 2005). SM, a sufferer of Urbach-Wiethe disease, has almost complete and selective bilateral amygdala destruction and shows impaired facial fear recognition (Adolphs et al 1994). While freely viewing emotional faces SM shows a lack of spontaneous fixations to the eye region, with this lack of directed eye contact thought to be due to a lack of attraction to this region rather than an active avoidance of the eyes (Adolphs et al 2005, Birmingham et al 2011). Her reduced fixations to the eye region is particularly prominent for her first fixation (Kennedy and Adolphs 2010), and she also shows a lack of eye contact during real-life conversations (Spezio et al 2007b). Adolphs et al (2005) further suggested that SM's abnormal fixation pattern to the eye region suggests she does not utilise information from the eyes correctly, and this may help explain her impairment in facial fear recognition. However, when instructed to look at the eye region of faces her fear recognition abilities became similar to those of unaffected individuals, strongly suggesting that her impairment

was due to a failure to fixate on the eye region. This also suggests the amygdala plays an important role in directing attention and gaze towards the eye region. Further supporting this role, amygdala activity is enhanced when we orient our attention towards the eyes in both fearful (Gamer and Buchel 2009) and neutral (Benuzzi et al 2007) faces.

As there is no difference in the percentage of fixations or percentage of duration of time spent fixating the eye region between the two groups of males possessing the different alleles at SNP rs7055196, these results may support similar amygdala functioning between the two groups. However, a difference in amygdala functioning cannot be ruled out on the basis of the present study, and future studies, such as imaging studies to investigate amygdala activity in response to viewing fearful faces, will shed further light on this issue.

4.4.4 Scan paths in other populations

Individuals with an ASD have been reported to show atypical scan paths compared to neurotypical individuals while viewing faces, with a reduced number of fixations to the eye region (Corden et al 2008, Jones et al 2008, Klin et al 2002, Pelphrey et al 2002) and an increased number of fixations made to the mouth (Jones et al 2008, Klin et al 2002). Women with TS may also show atypical scan paths while viewing faces compared to unaffected women, with an increased number of fixations to the mouth, and a subgroup of women with TS may also show very few fixations to the eyes (Mazzola et al 2006). For both individuals with an ASD and women with TS these atypical fixation patterns have been suggested to contribute towards their difficulties in facial emotion recognition abilities. It is possible that the absence of differences in the scan paths of males possessing the different variants of SNP rs7055196 may result in the more subtle difference in facial fear recognition accuracy in males possessing the G or A allele at SNP rs7055196, compared to that observed in individuals with an ASD and women with TS compared to unaffected individuals.

4.4.5 Additional findings: influence of age on fixation patterns

The results suggest an association between age and fixation patterns to the eye and mouth regions. Increasing age was associated with an increased number and duration of fixations to the mouth region, and a decreased duration of fixations to the eye region. A similar pattern has been reported by Sullivan et al (2007), who found that older adults look proportionately more at the mouth than the eyes compared to younger adults. Although the older adults used in Sullivan et al's study were older than the adults in the present study (present study maximum age 41 years, Sullivan et al age range for older participants 61-95 years), the results from the present study suggest these age-related differences in fixation patterns may occur across adulthood. Sullivan et al suggested this age-related effect may be

due to a decrease in processing speed as age increases, and as a result older adults need to look at the facial features for longer periods of time compared to younger adults to achieve similar levels of emotion recognition. In the present study, to obtain enough information from the mouth for expression recognition this may therefore have resulted in more fixations to this region in the older individuals compared to the younger adults. As the majority of fixations are made to the eyes the older adults may therefore have reduced their fixations to this region to compensate for the higher number of fixations to the mouth, with the number of fixations made to the eyes being sufficient to obtain information from this region for recognition. Supporting this, no effect of age on fear recognition accuracy was found in Study 3. Alternatively, age-related cultural differences or age-related differences in brain structure or function may account for this difference in fixation patterns. Further studies are needed to investigate these possible explanations.

4.5 Summary

When we view both neutral and emotional faces we spend the majority of our time fixating on the eye region, suggesting this region is important for emotion recognition. The eyes have been suggested to be important in particular for the recognition of fearful expressions. Information from the mouth region is also important. Atypical scan paths, consisting of fewer fixations made to the eye region and an increased number of fixations made to the mouth region, may contribute towards the impairments in facial emotion recognition abilities found in individuals with an ASD or women with TS. This study investigated whether differences in fixation patterns while viewing faces containing varying proportions of fearful and neutral expressions could account for differences in facial fear recognition accuracy in males possessing the A and G alleles at SNP rs7055196 within the EFHC2 gene. No differences in the percentage of fixations to or the percentage of time spent fixating either the eye or mouth regions were found between males possessing the different alleles at this SNP, suggesting no between group differences in terms of attraction or avoidance to either region. Differences in scan paths therefore do not contribute towards the differences in fear recognition accuracy between the two groups. Instead, it is possible that a difference in face processing strategy may account for this difference, with a greater ability to process faces holistically / configurally in the A allele group.

5 Investigating electrophysiological responses to faces

5.1 Introduction

Previous results within this thesis suggest that males possessing the G allele at SNP rs7055196 within the EFHC2 gene show poorer fear recognition accuracy compared to males possessing the A allele. Specifically, this effect has been found for images of the eye region alone and for faces with the eye region covered (Study 2, section 3.4). Males possessing the A allele are also more sensitive to differences in the intensity of fearful faces than males possessing the G allele (Study 3, section 3.5).

To explore these effects in more detail, I used event related potentials (ERPs) to compare electrophysiological responses to fearful faces in males possessing the different variants of SNP rs7055196. I compared ERPs in response firstly to fearful faces with and without the eye region showing and images of the eye region alone, and secondly to fearful faces displaying different intensities of expression between the groups. This allowed me to investigate possible electrophysiological correlates to the behavioural differences between the groups. To further investigate whether any influences of SNP rs7055196 were limited to fearful expressions, I also compared ERPs to faces with and without the eye region showing and the eye region alone of angry and neutral expressions, to different intensities of angry faces, and to neutral faces and butterflies between the two groups to determine if any differences found were due to an influence of emotion or specific to fear, or were due to viewing faces in general. Specifically, I compared the P1 and N170 components in the ERP waveforms produced between the two groups. The N170 component is a face selective component and may therefore be influenced by this SNP. Comparing group differences in the P1 component allowed me to investigate whether any group differences in N170 may be due to earlier electrophysiological differences.

The studies within this chapter were based on work by Leppanen et al (2008) and Utama et al (2009). Leppanen et al (2008) used ERPs to compare electrophysiological responses to fearful and neutral expressions for full faces, images of the eye region alone and faces with the eyes covered. They found that fearful faces produced greater N170 amplitudes than neutral faces only when the eye region was visible. Utama et al (2009) et al compared

electrophysiological responses to emotional faces showing different intensities of a happy or disgusted expression, and they found a positive correlation between intensity level and N170 amplitude. It is possible that based on the behavioural differences in fear recognition accuracy between males possessing the different variants at SNP rs7055196 that they may show different electrophysiological responses in tasks similar to those by Leppanen et al (2008) and Utama et al (2009), and so the tasks used were based on these studies.

In addition, the results of the studies within this chapter will help to determine the effects of emotional expressions within faces, facial composition, and intensity of emotional expressions on the P1 and N170 components. Previous studies investigating these effects have often found conflicting results, and so the current studies will help to determine the effects of different facial manipulations on the P1 and N170 components.

5.1.1 P1 component

The P1 component is thought to reflect general visual processing and the processing of low level features. Its peak occurs between 90 and 120ms post-stimulus, and P1 amplitude has been reported to be larger in the right compared to the left hemisphere (Batty and Taylor 2003, Utama et al 2009). The P1 component may represent face categorisation and holistic processing during face processing (Luo et al 2010, Wong et al 2009) along with the processing of emotion within faces (Utama et al 2009). However, studies investigating the effect of emotion in faces on P1 are inconsistent. Although one study has reported emotional faces produce larger P1 amplitudes than neutral faces (Batty and Taylor 2003), some have suggested this effect is limited to fearful faces (Holmes et al 2003, Holmes et al 2008, Luo et al 2010, Pourtois et al 2005) while others have found no influence of emotion (Fruhholz et al 2011, Leppanen et al 2008, Streit et al 2000). This suggested greater P1 amplitude for fearful (but not happy) compared to neutral faces may be enhanced in individuals with high trait anxiety (Holmes et al 2008). Further, it has been reported that there is no effect of attentional load on P1 amplitude (Holmes et al 2009).

It has been suggested there is no effect of emotion on P1 latency (Batty and Taylor 2003). The intensity of emotional expressions has also been reported to have no influence on either P1 amplitude or latency (Leppanen et al 2007a, Sprengelmeyer and Jentzsch 2006), although Utama et al (2009) reported P1 amplitudes increased as the intensity of expressions increased. Finally, larger amplitudes and longer latencies of the P1 component have been reported when viewing the eye region alone compared to viewing full faces (O'Connor et al 2007).

Studies comparing P1 waveforms between individuals with an ASD and neurotypical individuals have suggested its amplitude may be smaller in the individuals with an ASD (Batty et al 2011) and its latency may be longer (Batty et al 2011, O'Connor et al 2005).

However, other studies have found no differences in P1 amplitude or latency between the two groups (Akechi et al 2010, O'Connor et al 2007, Wong et al 2008). Further, it has been reported that there are no differences in either P1 amplitude or latency to the eyes or mouths alone between ASD and neurotypical individuals, although similar to neurotypical individuals, the ASD group showed larger amplitudes to the eyes alone and shorter latencies to full faces (O'Connor et al 2007). These results suggest that poorer emotion recognition abilities in individuals with an ASD may not be due to a difference in the use of holistic face processing compared to neurotypical individuals.

5.1.2 N170 component

The N170 component is thought to be face selective. It was first described by Bentin et al (1996), who reported larger N170 amplitudes for human faces compared to other visual stimuli. The peak of the N170 occurs approximately 170-200ms following stimulus presentation, and it has been suggested to be larger with a shorter latency over the right hemisphere (Beaton et al 2012, Bentin et al 1996, Blau et al 2007, Leppanen et al 2008, Sprengelmeyer and Jentzsch 2006). This component has been suggested to reflect a late stage of the structural encoding of faces, specifically global face configuration and configural face processing (Bentin et al 1996, Eimer 2000b, Luo et al 2010) and it may also reflect the analysis of first-order relational face configuration and holistic processing (Eimer et al 2011). Viewing the eye region alone, but not the nose and lip region alone, is sufficient to produce the N170, and the N170 elicited by the eye region alone has been reported to have a larger amplitude compared to that elicited by full faces (Bentin et al 1996, Eimer et al 2010, Eimer et al 2011).

Multiple studies have suggested that emotional faces produce larger N170 amplitudes than neutral faces (Luo et al 2010, Morel et al 2009, Wronka and Walentowska 2011), and for fearful expressions at least this may be dependent on the presence of the eyes (Leppanen et al 2008). It has further been reported that N170 amplitudes to fearful faces are larger than those to faces displaying another emotion (Batty and Taylor 2003, Blau et al 2007, Fruhholz et al 2011, Morel et al 2009). However, many other studies have reported emotion in faces has no effect on N170 amplitude (Ashley et al 2004, Eimer and Holmes 2002, Herrmann et al 2002, Sprengelmeyer and Jentzsch 2006, Streit et al 2000). It has also been suggested that there is no effect of the emotion within a face on N170 latency (Blau et al 2007, Herrmann et al 2002), although other studies have reported longer latencies for negative compared to neutral and positive expressions (Batty and Taylor 2003), or for neutral compared to fearful and happy expressions (Luo et al 2010). In addition, Schyns et al (2007) suggested that N170 latency depends upon the expression within the face and which facial features are important for its recognition. They suggested the shortest latencies occur for expressions for which the most important feature is the eyes (e.g. fear) followed by those for

which the nose (e.g. disgust) and finally mouth (e.g. happy) are important. It has also been suggested that increasing the intensity of expressions may increase N170 amplitudes (Sprengelmeyer and Jentzsch 2006, Utama et al 2009), and although Leppanen et al (2007a) did not replicate this finding they found N170 latencies increased as expression intensity increased.

The majority of studies comparing the N170 between individuals with an ASD and neurotypical individuals have reported no difference in amplitudes between the groups (Batty et al 2011, Hileman et al 2011, McPartland et al 2004, O'Connor et al 2007, Webb et al 2006, Wong et al 2008), although O'Connor et al (2005) reported smaller N170 amplitudes in individuals with an ASD compared to neurotypical individuals for both neutral and emotional faces. Many studies have however found a difference between the groups for N170 latency, with longer latencies for individuals with an ASD for both neutral and emotional faces (Batty et al 2011, Hileman et al 2011, McPartland et al 2004, O'Connor et al 2005, O'Connor et al 2007), although other studies have not found a difference between the groups (Akechi et al 2010, Churches et al 2010, Wong et al 2008). It has further been suggested that are no differences in N170 amplitudes in response to the eyes or mouth alone between individuals with an ASD and neurotypical individuals, although latencies were longer for the individuals with an ASD (O'Connor et al 2007). Similar to the neurotypical individuals, individuals with an ASD showed larger N170 amplitudes for the eyes alone compared to the mouth alone and full faces, along with faster latencies to full faces compared to the eyes and mouth regions and to the eyes compared to the mouth (O'Connor et al 2007). These results suggest that configural processing in individuals with an ASD may be slower than that in neurotypical individuals, and this difference may help to explain the poorer emotion recognition abilities of individuals with an ASD.

5.1.3 Aim and hypotheses

The aim of these studies was to compare electrophysiological responses to angry, fearful and neutral faces, specifically for the P1 and N170 components, between males possessing the A and G alleles at SNP rs7055196. As mentioned above, the use of these different expressions allowed me to investigate whether any influences of this SNP were limited to fearful expressions or not, and investigating the P1 component allowed me to determine whether any effects on the N170 may be due to earlier processing.

In Study 5 I compared electrophysiological responses to angry, fearful and neutral faces which displayed different facial compositions, specifically full faces, the eye region alone, and faces with the eye region covered. I had previously found that males possessing the G allele showed poorer fear recognition accuracy for images of the eyes alone and for faces with the eyes covered compared to males possessing the A allele. I therefore predicted that

males possessing the G allele would show smaller N170 amplitudes for fearful eyes and fearful faces with the eyes covered compared to males possessing the A allele.

In Study 6 I compared electrophysiological responses to angry and fearful faces displaying different intensities of expression. I had previously found that males possessing the A allele showed greater sensitivity to changes in the intensity of fearful expressions compared to males possessing the G allele. I therefore predicted that the N170 amplitude of males possessing the A allele would show a greater sensitivity to different intensities of fearful expressions than that of males possessing the G allele.

5.2 Participant information

In total 29 participants were tested; 12 who possessed the A allele at SNP rs7055196 and 17 who possessed the G allele. Due to computer errors, intensity ratings from one male possessing the G allele were not obtained for either Study 5 or 6, and EEG recordings were not made for one male possessing the G allele during Study 5.

5.2.1 Age, handedness and ethnicity

Information regarding the age and ethnicity of participants can be seen below in Table 5-1. All participants were right handed. There was no difference in age between the two groups when compared using an independent samples t-test ($t (27) < 0.0005$, $P = 1.000$, 95% CI (-1.49, 1.49)). In addition, the ethnicities of the two groups were similar.

	A allele	G allele
Number	12	17
Mean age	22.00 ± 1.95 (20-26)	22.00 ± 1.90 (20-26)
Ethnicity	7 Caucasian, 5 Asian	12 Caucasian, 4 Asian, 1 mixed race

Table 5-1. Information regarding the age (mean ± SD (range)) and ethnicity of participants tested in each group

5.2.2 IQ

Using independent samples t-tests to compare groups, there were no differences between the two groups regarding full scale IQ ($t_{(27)}$ = 1.353, P = 0.187, 95% CI (-2.00, 9.73)), verbal IQ ($t_{(27)}$ = 0.359, P = 0.722, 95% CI (-6.36, 9.06)) or performance IQ ($t_{(27)}$ = 1.735, P = 0.094, 95% CI (-1.04, 12.37)) (Table 5-2).

	A allele	G allele
Full scale IQ	123.75 ± 5.15	119.88 ± 8.87
Verbal IQ	121.58 ± 10.17	120.24 ± 9.82
Performance IQ	120.67 ± 6.92	115.00 ± 9.68

Table 5-2. Full scale, verbal and performance IQs of each group (mean ± SD)

5.3 Study 5: electrophysiological responses to partial and full fearful, angry and neutral expressions

5.3.1 Method

5.3.1.1 Task

During Study 5 participants were shown a mixture of partial and full fearful, angry and neutral faces and asked to determine which emotional state the face was showing in a three-alternative forced choice task. Faces used were adapted from the NimStim set of faces, and actors with well recognised fearful, angry and neutral open mouthed expressions were selected (Tottenham et al 2009). In total three facial compositions were used for each face; the full face, the eye region alone (including the eyebrows) and faces with the eye region (including the eyebrows) covered (Leppanen et al 2008) (Figure 5-1). Similar to Study 2 (section 3.4), facial compositions with only the eye region showing were created using 'letterbox' images of the eye region and facial compositions with the eye region covered were created by drawing 'sunglasses' on the original faces.
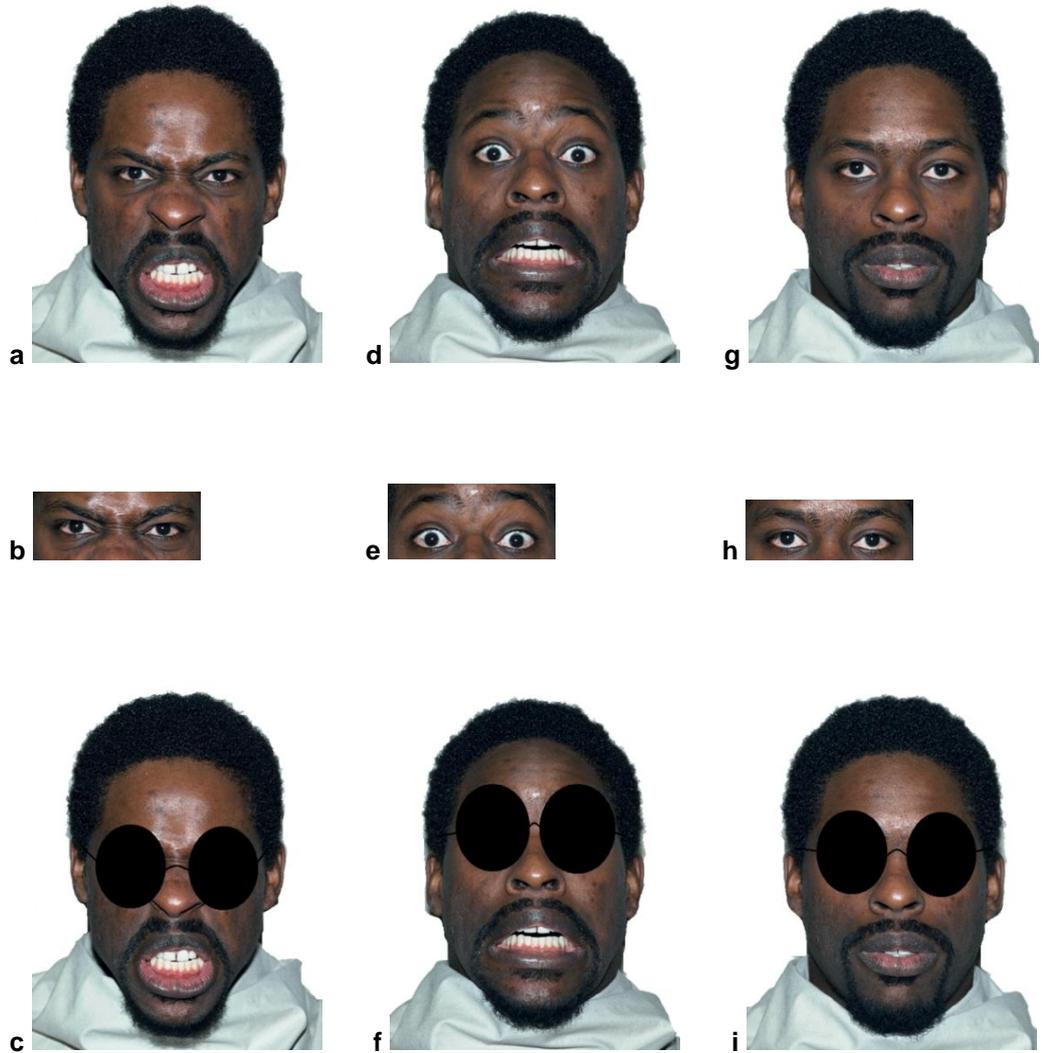
Figure 5-1. Examples of the images used in Study 5 (a) angry full face, (b) angry eyes, (c) angry faces with the eyes covered, (d) fearful full face, (e) fearful eyes, (f) fearful faces with the eyes covered, (g) neutral full face, (h) neutral eyes, (i) neutral faces with the eyes covered (images adapted from Tottenham et al (2009))

In total there were therefore 9 different emotion-facial composition pairs for each actor's face (3 emotions × 3 facial compositions). A total of 10 actors were used (5 male, 5 female), resulting in a total number of 90 stimuli. Each stimulus was shown 6 times, producing 60 trials per emotion-facial composition pair, and over the 9 emotion-facial composition pairs this therefore gave a total of 540 trials (9 emotion-facial composition pairs × 10 actors × 6 repetitions). Trials were presented in two equal blocks, each containing 3 repetitions of each stimulus, and within each block images were presented in a random order. A practice block was administered prior to the first block; this consisted of 2 actors × 9 emotion-facial composition pairs (giving a total of 18 stimuli), with each image being shown once. This produced 2 trials per emotion-facial composition pair and a total number of 18 trials. None of the images used in the practice block were used in the test block and none of the responses given in the practice block were analysed. No feedback was given for any images. The task was computer administered, and was written in E-Prime (Psychology Software Tools, Pittsburgh, PA).

The practice block was administered first, followed by the two test blocks. For each trial, images were shown one at a time in the centre of the screen for 500ms followed by a fixation cross presented for 1000ms. At the start of each trial a fixation cross was presented in the centre of the screen for a variable length of time between 1000 and 1200ms. Images of the full face or faces with the eyes covered subtended a visual angle of 23.08° (width) × 23.08° (height), while images of the eye region alone subtended a visual angle of 13.31° (width) × 4.77° (height). Participants were asked to respond whether they thought the face was fearful, angry or neutral by pressing the corresponding key on the keyboard; participants were not instructed as to which hand to use. Participants were asked to respond as accurately and as quickly as possible. Participants had a maximum time of 1500ms to respond to each image (i.e. during 500ms of image presentation followed by 1000ms of fixation cross presentation), and any responses entered after this time were not recorded. Each test block lasted approximately 12 minutes (270 trials × 2.6 seconds = 702 seconds = 11.7 minutes). The response key pressed for each face was recorded, along with the RT (in ms). The method used was based on that reported in Leppanen et al (2008).

5.3.1.1.1 Analysis

Results from the two blocks were combined for analysis. For each of the 9 emotion-facial composition pairs the percentage of correctly identified emotional states was calculated (score out of 60 (10 actors × 6 repetitions)) along with the mean RT for each participant. Any responses with RTs less than 300ms were not included as this was determined to be the minimum time required for a valid response to be made, as were any responses not made within the 1500ms time limit (in total <8% all responses were excluded). The number of correctly identified images and mean RTs were then compared across the G and A allele

groups using 2 (group) × 3 (emotion) × 3 (facial composition) repeated measures ANOVAs with the Greenhouse-Geisser and Bonferroni corrections.

5.3.1.2 Intensity ratings

To ensure there were no differences in the perceived intensities of the expressions between the two groups each participant also gave an intensity rating for each of the emotional full faces following the ERP task. For each of the 30 full faces, a fixation cross was first shown in the centre of the screen for 1 second followed by the face. Participants were instructed to rate the intensity of the emotion on the face using a scale of 0 (low intensity) to 9 (high intensity), and the emotional face was displayed until a rating was made. Participants had unlimited time to respond. Emotional faces were presented in a random order. Ratings for each face were recorded and analysed using a 2 (group) × 3 (emotion) repeated measures ANOVA with the Bonferroni correction applied.

5.3.1.3 Acquisition and processing of ERPs

5.3.1.3.1 Acquisition
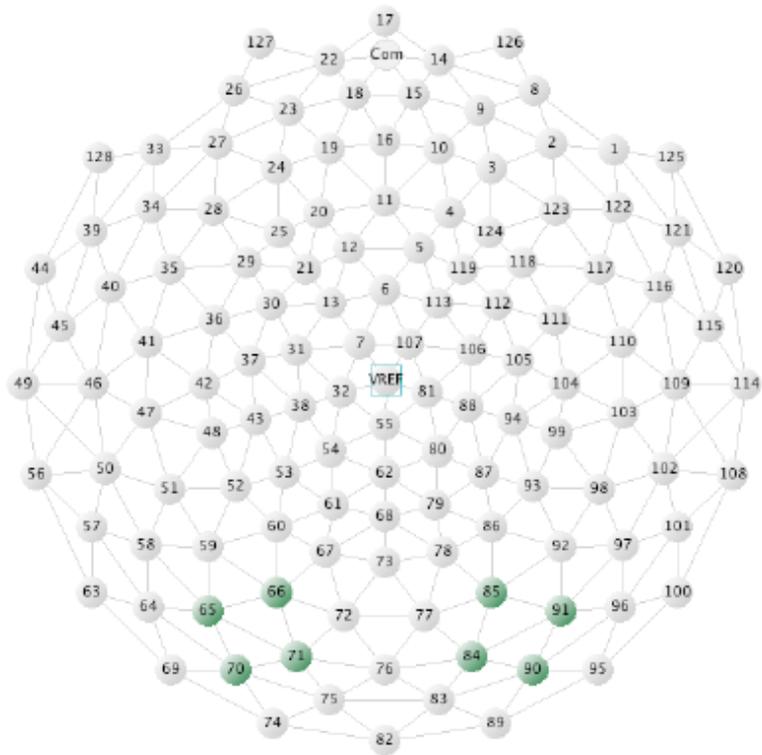
Continuous electroencephalogram (EEG) was recorded from participants using appropriately sized EGI geodesic high density sensor nets, which contain 128 channel silver-silver chloride electrodes. Electrodes were evenly distributed across the scalp, from nasion to inion and from left to right mastoids, although due to individual scalp differences electrode positions may vary 1-2cm between participants. Electrodes above and below each eye and beside the outer canthus of each eye recorded vertical (VEOG) and horizontal (HEOG) electrooculogram respectively. Electrode impedances were maintained below 50kΩ during recording; prior to recording each sensor was hydrated and its contact with the scalp was checked. At the start of each recording gain and zero calibration were performed. The EEG signal was referenced to the vertex during recording, and signals were recorded using a bandpass filter of 0.1-100 Hz, amplified using a gain of 10,000 and sampled at a rate of 250Hz. Recordings were made using NetStation (Electrical Geodesics, Inc., Eugene, OR), and information regarding stimulus onset and participant response was sent via a parallel port from E-Prime.

5.3.1.3.2 Processing
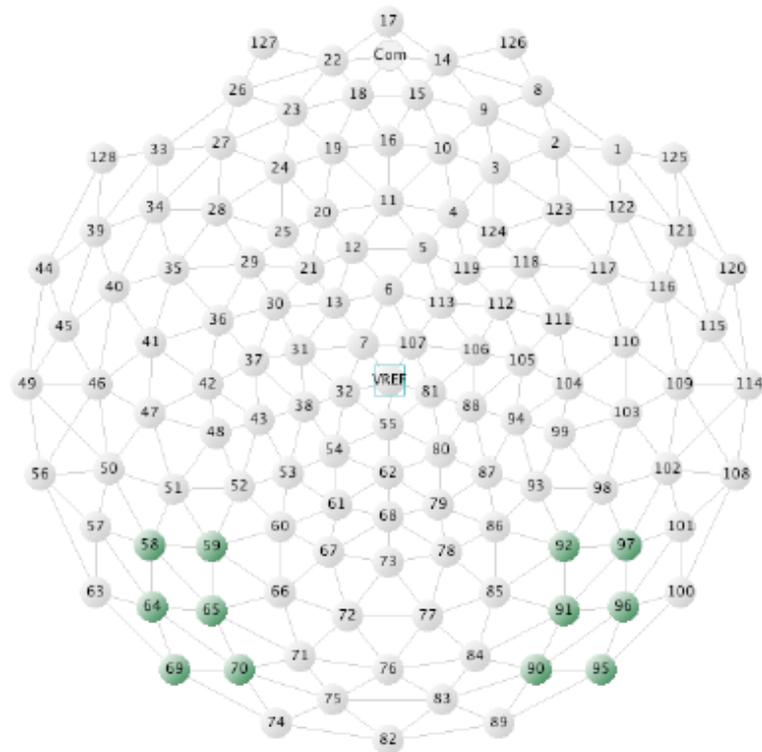
All processing of EEG signals was performed using NetStation (Electrical Geodesics, Inc., Eugene, OR). The continuous EEG signal was digitally filtered offline using a lowpass filter of 30Hz, and segmented into 600ms epochs (time locked to the onset of stimulus presentation, 100ms pre-stimulus and 500ms post-stimulus). Only segments associated with a correct behavioural response were included, and segments were grouped depending on condition (i.e. emotion-facial composition pair). An automatic artefact detection procedure was applied to detect artefacts and remove trials containing artefacts from further analysis. Eye artefacts (i.e. eye blinks and movements) were defined using thresholds of ±70μV for the EOG channels. All other channel artefacts were defined as containing a fast average amplitude above ±80μV, a difference in average amplitude above ±80μV or zero variance. Further, any channels which were marked as bad in more than 20% of segments were marked as bad across all other segments, and any segments containing more than 12 bad channels were marked as bad and excluded from further analysis. Bad channels were replaced using spherical spline interpolation, and an average waveform for each participant for each of the 9 conditions created. Waveforms were re-referenced to the average electrode across all channels, with the exception of the eye electrode channels (numbers 125, 126, 127 and 128), and were then baseline corrected against the mean voltage during the 100ms preceding stimulus onset. In total, 74.83% of all trials from the A allele group and 77.95% of all trials from the G allele group were included in the average waveforms produced.

5.3.1.3.3 Analysis

All statistical extraction of amplitudes and latencies for ERP components was performed using NetStation (Electrical Geodesics, Inc., Eugene, OR). Two components were analysed: the P1 and the N170. Channels used to determine the P1 were located at occipital sites and consisted of numbers 65, 66, 70 and 71 (O1) on the left and 84 (O2), 85, 90 and 91 on the right, while those used to determine the N170 were located over occipital-temporal regions and consisted of numbers 58 (T5), 59, 64, 65, 69 and 70 on the left and 90, 91, 92, 95, 96 and 97 (T6) on the right (Figure 5-2); these channels are similar to those used in other studies which have measured the P1 and N170 using high density electrode arrays (McPartland et al 2004, O'Connor et al 2007). The time windows for component definition were 80-180ms post-stimulus for P1, and 120-220ms for N170; these were selected based on visual inspection of the data. For both the P1 and N170, for each condition for each participant peak amplitudes and the latencies to the peaks were determined for each electrode in the selected channel groups during the specified time windows. For both the P1 and N170 components these values were then averaged across electrode groups in the left

a

b

Figure 5-2. Electrode groups used for (a) the P1 component and (b) the N170 component

and right hemispheres for each condition for each participant. Amplitudes and latencies were compared between participants possessing the A and G alleles at SNP rs7055196 using 2 (group) × 3 (emotion) × 3 (facial composition) × 2 (hemisphere) repeated measures ANOVAs, with Greenhouse-Geisser and Bonferroni corrections applied where appropriate, performed in SPSS (IBM Corp., Armonk, NY).

5.3.2 Results

5.3.2.1 Task performance

The percentage of expressions correctly identified in Study 5 by the two groups of males possessing the different variants of SNP rs7055196 can be found in Table 5-3 and Figure 5-3. Accuracy was compared using a 2 (group) × 3 (emotion) × 3 (facial composition) repeated measures ANOVA with Greenhouse-Geisser and Bonferroni corrections applied. There was no significant difference in expression recognition accuracy between the groups of males possessing the different variants at SNP rs7055196 ($F_{(1,27)} = 0.131$, $P = 0.720$, 95% CI (-10.19, 7.13)). The emotion of the face significantly affected recognition accuracy ($F_{(2,54)} = 22.156$, $P < 0.0005$), with neutral expressions being recognised most accurately followed by fearful expressions, and the least accurate recognition for angry expressions (anger M 77.56 SD 14.25, fear M 83.15 SD 12.01, neutral M 88.21 SD 10.67, anger vs fear $P = 0.009$, 95% CI (-9.98, -1.20), anger vs neutral $P < 0.0005$, 95% CI (-15.16, -6.14), fear vs neutral $P = 0.001$, 95% CI (-8.29, -1.83)). Facial composition also significantly affected recognition accuracy ($F_{(1.585,42.803)} = 28.222$, $P < 0.0005$), with lower recognition accuracy for the eyes alone compared to full faces and faces with the eyes covered (full face M 85.52 SD 10.61, eyes alone M 78.73 SD 13.27, faces with the eyes covered M 84.67 SD 11.24, full face vs eyes alone $P < 0.0005$, 95% CI (3.82, 9.75), full face vs faces with the eyes covered $P = 0.728$, 95% CI (-0.96, 2.66), eyes alone vs faces with the eyes covered $P < 0.0005$, 95% CI (-8.55, -3.32)).

There was a significant interaction between emotion and facial composition ($F_{(2.379,64.243)} = 3.044$, $P = 0.046$). For angry expressions, recognition accuracy was higher for full faces compared to the eyes alone ($P < 0.0005$, 95% CI (6.69, 16.07)) and for faces with the eyes covered compared to the eyes alone ($P < 0.0005$, 95% CI (-13.81, -5.05)). For fearful expressions, recognition accuracy was higher for faces with the eyes covered compared to viewing the eyes alone ($P = 0.028$, 95% CI (-10.43, -0.49)), and for neutral expressions recognition accuracy was higher for full faces compared to the eyes alone ($P = 0.041$, 95% CI (0.17, 9.83)). There were no significant interactions between EFHC2 variant

	Full face		Eyes only		Faces with the eyes covered	
	A allele	**G allele**	**A allele**	**G allele**	**A allele**	**G allele**
Anger	80.83 ± 14.42	82.84 ± 14.75	71.94 ± 16.85	69.71 ± 15.86	79.72 ± 15.32	80.29 ± 12.28
Fear	84.03 ± 10.31	84.31 ± 12.36	77.22 ± 19.93	82.25 ± 12.03	85.00 ± 13.76	86.08 ± 10.09
Neutral	89.31 ± 11.69	91.76 ± 7.85	85.00 ± 12.25	86.27 ± 14.83	86.81 ± 13.09	90.10 ± 9.83

Table 5-3. Mean percentages of the number of expressions correctly recognised for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 (mean ± SD)

Figure 5-3. Mean percentages of expressions correctly recognised for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 (error bars represent 95% CI)

and emotion (F (2,54) = 0.295, P = 0.746), EFHC2 variant and facial composition (F (1.585,42.803) = 0.012, P = 0.973), or EFHC2 variant, emotion and facial composition (F (2.379,64.243) = 1.010, P = 0.381). Neither age (F (1,26) = 1.038, P = 0.318) nor full scale IQ (F (1,26) = 0.424, P = 0.521) were significant when included as covariates.

5.3.2.1.1 Response time

Mean group RTs for the task during Study 5 can be seen in Table 5-4 and Figure 5-4. RTs were compared using a 2 (group) × 3 (emotion) × 3 (facial composition) repeated measures ANOVA with the Bonferroni correction applied.

There was no difference in RTs between males possessing the different variants at SNP rs7055196, although males possessing the G allele responded slower than males possessing the A allele for all conditions (F (1,27) = 1.031, P = 0.319, 95% CI (-127, 43)). The expression of the face significantly affected RT (F (2,54) = 8.148, P = 0.001), with faster RTs for neutral compared to both angry and fearful expressions (anger M 886 SD 106, fear M 890 SD 123, neutral M 845 SD 124, anger vs fear P = 1.000, 95% CI (-30, 23), anger vs neutral P = 0.012, 95% CI (8, 74), fear vs neutral P = 0.007, 95% CI (11, 79)). There was also a significant effect of facial composition on RT (F (2,54) = 33.018, P < 0.0005), with fastest RTs for full faces followed by faces with the eyes covered, and the slowest RTs for the eyes alone (full face M 857 SD 117, eyes alone M 893 SD 110, faces with the eyes covered M 872 SD 110, full faces vs eyes alone P < 0.0005, 95% CI (-48, -24), full faces vs faces with the eyes covered P = 0.002, 95% CI (-26, -5), eyes alone vs faces with the eyes covered P < 0.0005, 95% CI (9, 31)).

There was a significant interaction between emotion and facial composition (F (4,108) = 4.146, P = 0.004). For angry expressions, RTs were faster for full faces compared to viewing the eye region alone (P = 0.024, 95% CI (-50, -3)). For fearful faces, RTs were faster for full faces compared to both the eyes alone (P = 0.002, 95% CI (-41, -8)) and faces with the eyes covered (P = 0.044, 95% CI (-38, 0)). For neutral faces, RTs were faster for full faces compared to the eyes alone (P <0.0005, 95% CI (-75, -39)) and to faces with the eyes covered (P = 0.002, 95% CI (-32, -6)), and they were also faster for faces with the eyes covered compared to the eyes alone (P < 0.0005, 95% CI (19, 56)). There were no significant interactions between EFHC2 variant and emotion (F (2,54) = 0.568, P = 0.570), EFHC2 variant and facial composition (F (2,54) = 1.066, P = 0.352) or EFHC2 variant, emotion and facial composition (F (4,108) = 0.532, P = 0.712). Full scale IQ was significant when included as a covariate in the analysis (F (1,26) = 6.488, P = 0.017), with shorter RTs as IQ increases. The inclusion of full scale IQ as a covariate had no effect on the influence of SNP rs7055196 on RT or any interactions involving SNP rs7055196. Age was not significant when included as a covariate (F (1,26) = 2.987, P = 0.096).

	Full face		Eyes only		Faces with the eyes covered	
	A allele	G allele	A allele	G allele	A allele	G allele
Anger	845 ± 146	905 ± 90	871 ± 126	932 ± 86	858 ± 122	907 ± 86
Fear	852 ± 142	898 ± 112	876 ± 127	922 ± 115	885 ± 124	907 ± 123
Neutral	805 ± 149	835 ± 105	862 ± 151	892 ± 105	822 ± 142	856 ± 104

Table 5-4. Mean RTs (ms) for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 (mean ± SD)

Figure 5-4. Mean RTs (ms) for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 (error bars represent 95% CI)

5.3.2.2 Intensity ratings
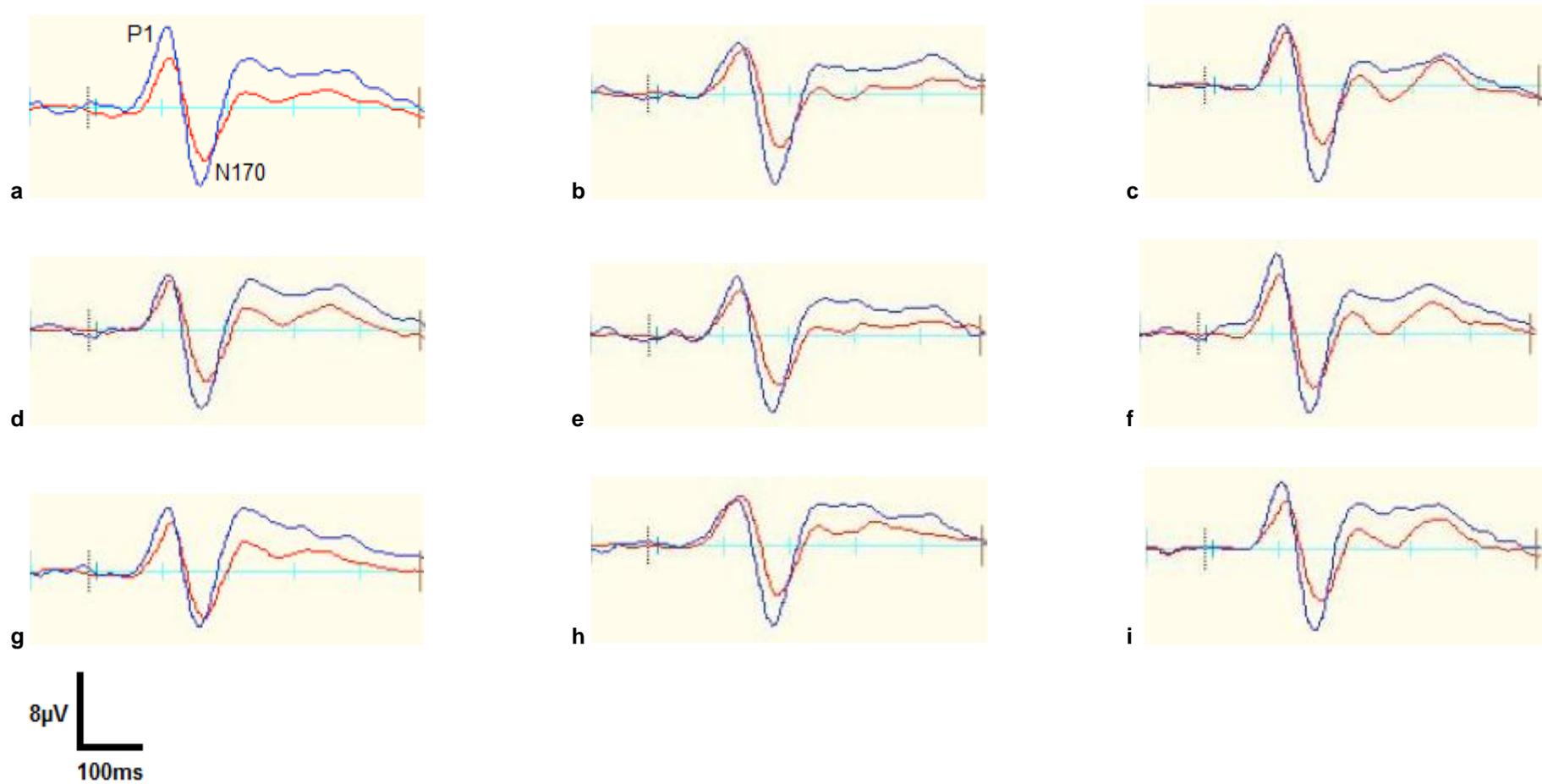
The mean intensity ratings for the full faces given by males possessing the different variants of SNP rs7055196 can be seen in Table 5-5. These ratings were compared using a 2 (group) × 3 (emotion) repeated measures ANOVA, with a Bonferroni correction applied. There were no differences in ratings between males possessing the different variants of SNP rs7055196 ($F_{(1,26)}$ = 0.306, P = 0.585, 95% CI (-0.36, 0.62)). Ratings significantly differed for the three expressions ($F_{(2,52)}$ = 682.110, P < 0.0005), with angry expressions rated as most intense, followed by fearful expressions and neutral expressions being rated as least intense (anger M 7.36 SD 0.98, fear M 6.84 SD 0.95, neutral M 0.62 SD 0.69, anger vs fear P = 0.009, 95% CI (0.12, 0.92), anger vs neutral P < 0.0005, 95% CI (6.16, 7.31), fear vs neutral P < 0.0005, 95% CI (5.65, 6.78)). There was no significant interaction between EFHC2 variant and emotion ($F_{(2,52)}$ = 1.659, P = 0.200).

	A allele	G allele
Anger	7.49 ± 0.94	7.22 ± 1.00
Fear	7.04 ± 0.99	6.63 ± 0.90
Neutral	0.48 ± 0.56	0.76 ± 0.76

Table 5-5. Mean intensity ratings for full faces of the three expressions for the groups of males possessing the different variants of SNP rs7055196 (mean ± SD)

5.3.2.3 ERP results

Average waveforms produced for each of the different stimulus types in Study 5 are shown in Figure 5-5, Figure 5-6 and Figure 5-7. All waveform amplitude and latency results were compared using 2 (group) × 3 (emotion) × 3 (facial composition) × 2 (hemisphere) repeated measures ANOVAs, with Greenhouse-Geisser and Bonferroni corrections applied where appropriate.

Figure 5-5. Average ERP waveforms produced by males possessing the different variants of SNP rs7055196 for a) angry full faces, b) angry eyes alone, c) angry faces with the eyes covered, d) fearful full faces, e) fearful eyes alone, f) fearful faces with the eyes covered, g) neutral full faces, h) neutral eyes alone, i) neutral faces with the eyes covered (all recordings measured at electrode 92, blue A allele, red G allele)
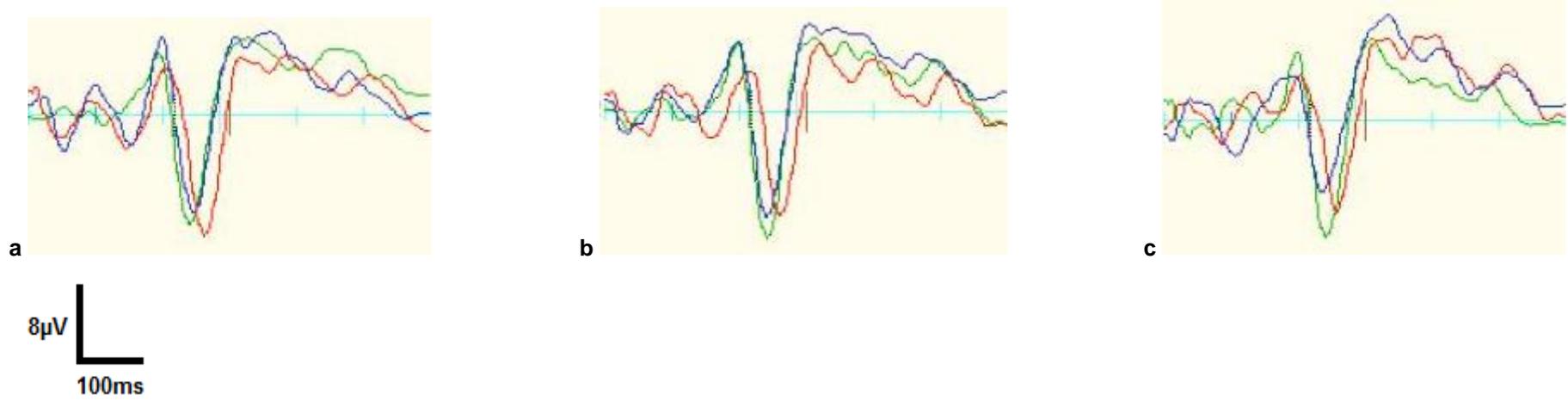
Figure 5-6. Average waveforms produced for each facial composition for a) angry, b) fearful, c) neutral expressions (all recordings measured at electrode 92, blue full faces, red eyes alone, green faces with the eyes covered)
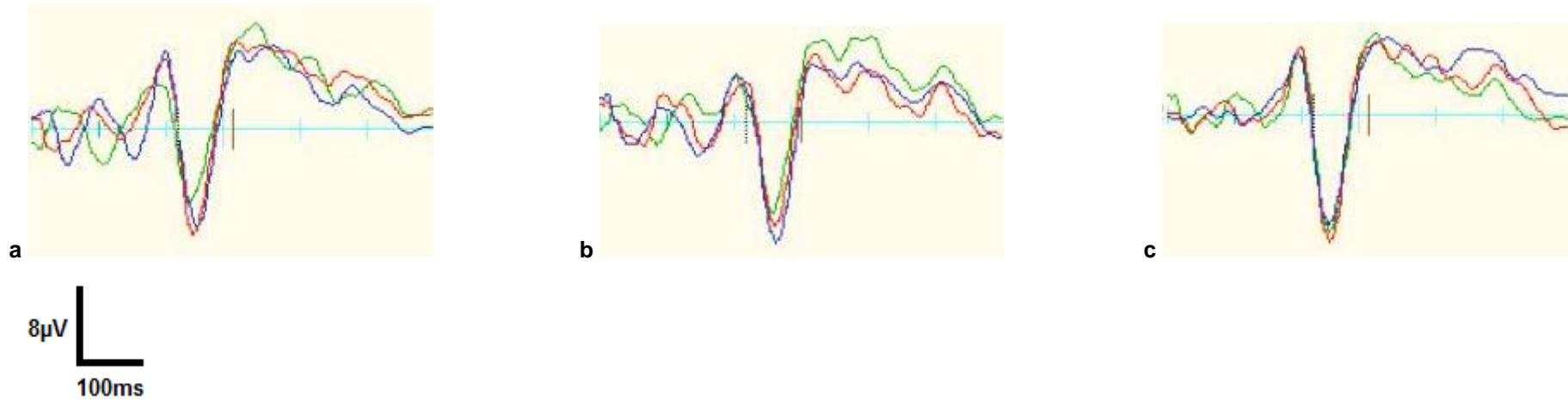
Figure 5-7. Average waveforms produced for each emotion for a) full faces, b) the eyes alone, c) faces with the eyes covered (all recordings measured at electrode 92, blue angry expressions, red fearful expressions, green neutral expressions)

5.3.2.3.1 P1 amplitude

Results for the mean P1 amplitude for each group for each emotion-facial composition pair in each hemisphere can be seen in Table 5-6. Values in the right hemisphere can also be seen in Figure 5-8. There was no difference in P1 amplitude between males possessing different alleles at SNP rs7055196 ($F_{(1,26)}$ = 1.528, P = 0.227, 95% CI (-0.73, 2.94)), and no difference between the three expressions ($F_{(1.613,41.938)}$ = 1.512, P = 0.233)). Facial composition significantly affected P1 amplitude ($F_{(1.534,39.894)}$ = 11.870, P < 0.0005; faces with the eyes covered showed larger P1 amplitudes compared to both full faces (P = 0.001, 95% CI (-1.13, -0.26)) and the eye region alone (P = 0.002, 95% CI (-1.84, -0.39)) with no difference between full faces and the eye region alone (P = 0.224, 95% CI (-0.16, 1.00)) (full face M 4.97 SD 2.52, eyes alone M 4.55 SD 2.03, faces with the eyes covered M 5.67 SD 2.79). There was no significant difference between P1 amplitudes across the left and right hemispheres ($F_{(1,26)}$ = 0.653, P = 0.426, 95% CI (-0.63, 0.28)).

There was a significant interaction between emotion and facial composition ($F_{(4,104)}$ = 3.520, P = 0.010). Angry expressions showed larger P1 amplitudes for faces with the eyes covered compared to the eye region alone (P = 0.007, 95% CI (0.25, 1.80)). Fearful expressions showed larger P1 amplitudes for faces with the eyes covered compared to full faces (P = 0.001, 95% CI (-1.91, -0.45)) and images of the eye region alone (P = 0.012, 95% CI (0.24, 2.27)). Neutral faces showed larger P1 amplitudes for faces with the eyes covered compared to full faces (P = 0.029, 95% CI (-1.38, -0.06)). There was a further significant interaction between EFHC2 variant, emotion and facial composition ($F_{(4,104)}$ = 4.070, P = 0.004), which was driven by trends towards larger amplitudes in males possessing the A allele compared to those for males possessing the G allele for angry full faces (P = 0.060, 95% CI (-0.10, 4.37)) and for fearful faces with the eyes covered (P = 0.066, 95% CI (-0.14, 4.16)). There were no further significant interactions (EFHC2 variant and emotion $F_{(1.613,41.938)}$ = 1.062, P = 0.342, EFHC2 variant and facial composition $F_{(1.534,39.894)}$ = 2.051, P = 0.152, EFHC2 variant and hemisphere $F_{(1,26)}$ = 1.280, P = 0.268, emotion and hemisphere $F_{(1.538,39.982)}$ = 0.671, P = 0.479, facial composition and hemisphere $F_{(2,52)}$ = 1.299, P = 0.281, EFHC2 variant, emotion and hemisphere $F_{(1.538,39.982)}$ = 1.536, P = 0.228, EFHC2 variant, facial composition and hemisphere $F_{(2,52)}$ = 1.763, P = 0.182, emotion, facial composition and hemisphere $F_{(4,104)}$ = 0.858, P = 0.492, EFHC2 variant, emotion, facial composition and hemisphere $F_{(4,104)}$ = 1.852, P = 0.125). Age was significantly associated with P1 amplitude when included as a covariate ($F_{(1,25)}$ = 8.966, P = 0.006), with increasing age being associated with a smaller P1 amplitude. When age was included as a covariate this had no effect on the influence of SNP rs7055196 on P1 amplitude or any of its interactions. There was no association between full scale IQ and P1 amplitude ($F_{(1,25)}$ = 1.497, P = 0.232) when included as a covariate.

		Left hemisphere		Right hemisphere	
		A allele	G allele	A allele	G allele
Anger	Full face	5.98 ± 2.84	4.05 ± 2.86	6.68 ± 3.54	4.34 ± 2.68
	Eyes only	4.83 ± 2.57	3.62 ± 2.66	4.65 ± 2.85	4.06 ± 2.02
	Faces with the eyes covered	5.84 ± 3.15	4.66 ± 2.45	5.59 ± 4.13	5.16 ± 2.63
Fear	Full face	5.06 ± 2.88	4.25 ± 2.14	5.08 ± 3.00	4.60 ± 2.10
	Eyes only	4.97 ± 2.05	4.27 ± 2.34	5.01 ± 2.35	4.44 ± 2.28
	Faces with the eyes covered	7.23 ± 2.63	4.80 ± 2.81	6.83 ± 3.16	5.25 ± 2.74
Neutral	Full face	5.22 ± 2.72	4.11 ± 2.41	5.65 ± 2.94	4.65 ± 2.33
	Eyes only	4.98 ± 2.60	4.24 ± 1.70	4.58 ± 2.50	4.94 ± 1.70
	Faces with the eyes covered	6.76 ± 2.97	4.68 ± 2.78	6.15 ± 3.15	5.08 ± 2.63

Table 5-6. Mean P1 amplitudes (µV) for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 (mean ± SD)

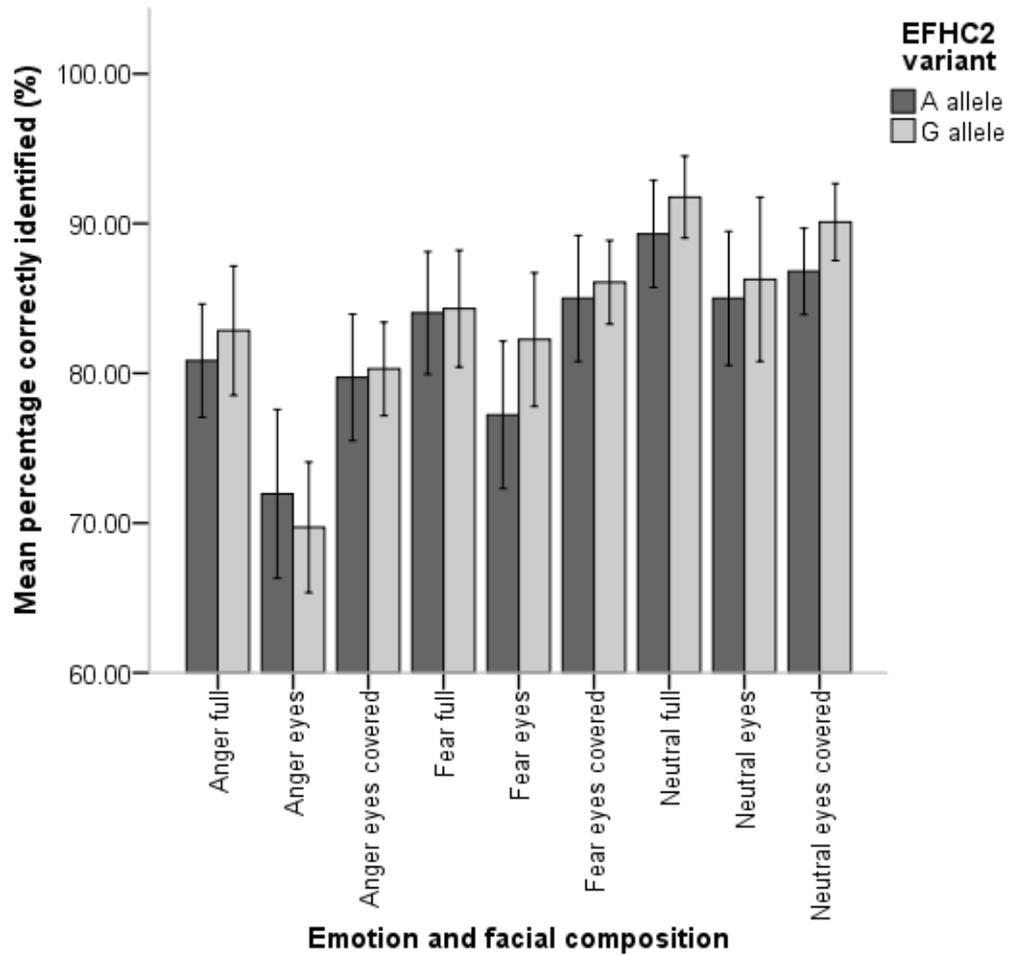**Figure 5-8. Mean P1 amplitudes (µV) for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 in the right hemisphere (error bars represent 95% CI)**

5.3.2.3.2 P1 latency

Mean P1 latencies for the two groups for each emotion-facial composition pair in each hemisphere can be seen in Table 5-7, with mean latencies for the right hemisphere being shown in Figure 5-9. There was no significant difference between P1 latencies for the groups of males possessing the different variants at SNP rs7055196 (F (1,26) = 1.690, P = 0.205, 95% CI (-12, 3)), and no difference in latencies for the different expressions (F (1.640,42.652) = 0.363, P = 0.656). Facial composition significantly affected P1 latency (F (1.366,35.527) = 108.664, P < 0.0005), with longest latencies for the eyes alone, followed by the full faces, with faces with the eyes covered having the shortest latencies (full faces M 104 SD 10, eyes alone M 117 SD 11, faces with the eyes covered M 101 SD 9, full faces vs eyes alone P < 0.0005, 95% CI (-17, -11), full faces vs faces with the eyes covered P = 0.004, 95% CI (1, 5), eyes alone vs faces with the eyes covered P < 0.0005, 95% CI (12, 20)). There was no difference in the latencies in the two hemispheres (F (1,26) = 0.576, P = 0.455, 95% CI (-3, 2)).

There was a significant interaction between emotion and facial composition (F (2.943,76.527) = 4.626, P = 0.005). For angry faces, smaller P1 latencies were found for faces with the eyes covered compared to both full faces (P = 0.001, 95% CI (1, 5)) and the eyes alone (P < 0.0005, 95% CI (16, 25)), and for full faces compared to the eyes alone (P < 0.0005, 95% CI (-21, -13)). For fearful faces, smaller P1 latencies were found for faces with the eyes covered compared to both full faces (P = 0.015, 95% CI (0, 4)) and the eyes alone (P < 0.0005, 95% CI (11, 18)), and for full faces compared to the eyes alone (P < 0.0005, 95% CI (-15, -9)). For neutral faces smaller P1 latencies were found for both full faces (P < 0.0005, 95% CI (-18, -7)) and faces with the eyes covered (P < 0.0005, 95% CI (9, 20)) compared to the eyes alone. There was also a significant interaction between emotion and hemisphere (F (2,52) = 4.893, P = 0.011), which was driven by a trend towards longer latencies in the left hemisphere for angry compared to fearful expressions (P = 0.078, 95% CI (0, 3)). There were no further significant interactions (EFHC2 variant and emotion F (1.640,42.652) = 0.754, P = 0.452, EFHC2 variant and facial composition F (1.366,35.527) = 1.775, P = 0.191, EFHC2 variant and hemisphere F (1,26) = 0.762, P = 0.391, facial composition and hemisphere F (1.587,41.267) = 0.772, P = 0.441, EFHC2 variant, emotion and facial composition F (2.943,76.527) = 1.419, P = 0.244, EFHC2 variant, emotion and hemisphere F (2,52) = 0.388, P = 0.681, EFHC2 variant, facial composition and hemisphere F (1.587,41.267) = 1.486, P = 0.238, emotion, facial composition and hemisphere F (2.806,72.950) = 1.270, P = 0.291, EFHC2 variant, emotion, facial composition and hemisphere F (2.806,72.950) = 1.032, P = 0.380). Neither age (F (1,25) = 2.132, P = 0.157) nor full scale IQ (F (1,25) = 0.203, P = 0.656) were significantly associated with P1 latencies when included as covariates.

		Left hemisphere		Right hemisphere	
		A allele	G allele	A allele	G allele
Anger	**Full face**	101 ± 10	105 ± 13	102 ± 9	105 ± 11
	Eyes only	115 ± 14	124 ± 15	118 ± 10	124 ± 14
	Faces with the eyes covered	97 ± 6	102 ± 10	98 ± 7	103 ± 12
Fear	**Full face**	102 ± 9	104 ± 11	103 ± 8	106 ± 10
	Eyes only	110 ± 13	116 ± 18	118 ± 7	119 ± 14
	Faces with the eyes covered	98 ± 4	104 ± 11	101 ± 7	103 ± 11
Neutral	**Full face**	105 ± 18	104 ± 12	103 ± 9	105 ± 11
	Eyes only	110 ± 14	123 ± 15	114 ± 11	118 ± 12
	Faces with the eyes covered	99 ± 7	107 ± 16	98 ± 6	103 ± 12

Table 5-7. Mean P1 latencies (ms) for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 (mean ± SD)
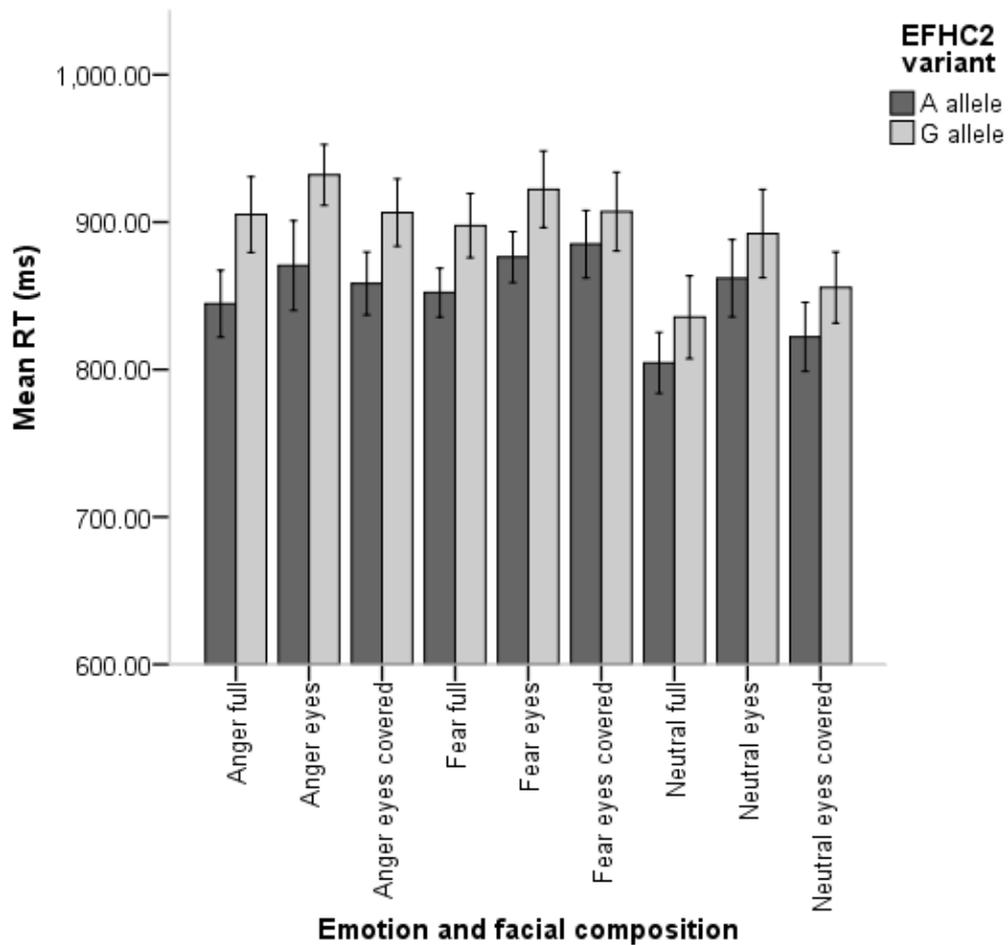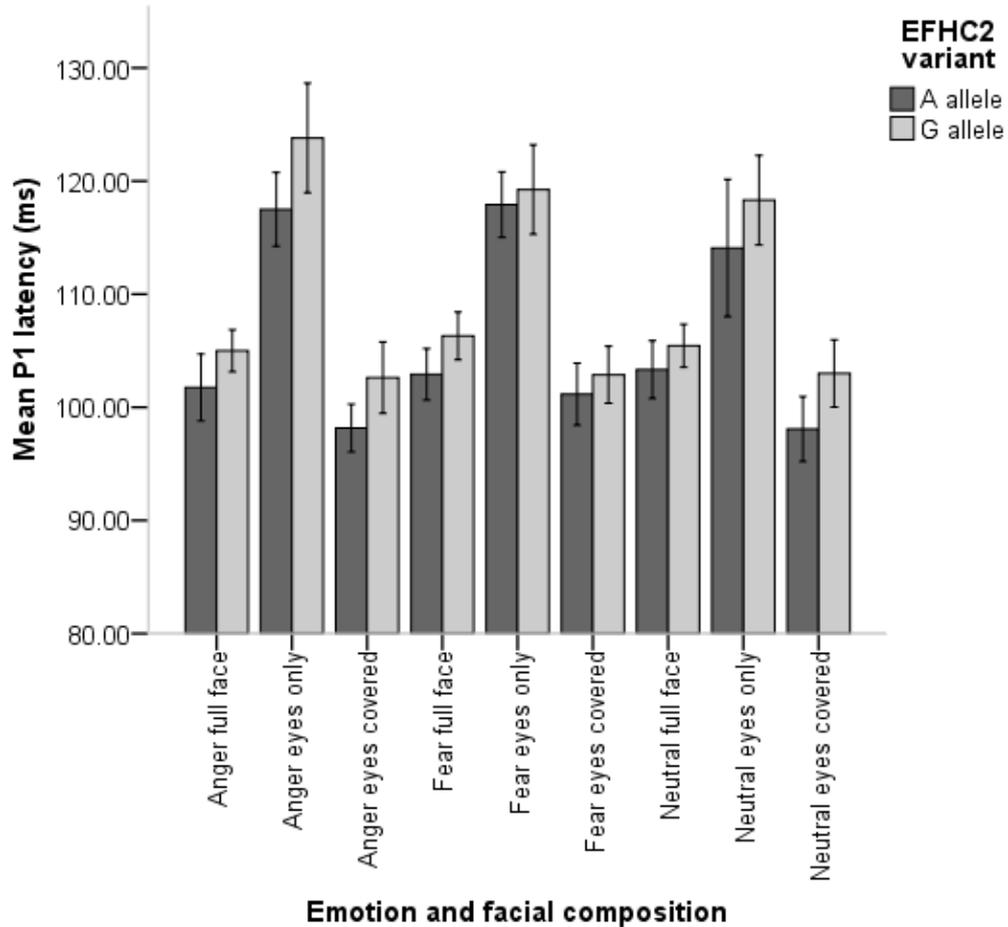
Figure 5-9. Mean P1 latencies (ms) for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 in the right hemisphere (error bars represent 95% CI)

5.3.2.3.3 N170 amplitude

Mean N170 amplitudes for each group for each emotion-facial composition pair and each hemisphere can be found in Table 5-8. Mean N170 amplitudes for the right hemisphere can also be seen in Figure 5-10. N170 amplitudes were significantly larger for males possessing the A allele at SNP rs7055196 compared to those for males possessing the G allele (F (1,26) = 5.000, P = 0.034, 95% CI (-4.12, -0.17), A allele M -7.35 SD 3.84, G allele M -5.21 SD 3.32), with an effect size equal to 0.700[3]. There was also a significant effect of emotion on N170 amplitude (F (1.463,38.045) = 4.508, P = 0.027), with angry expressions producing larger amplitudes compared to neutral expressions (P = 0.021, 95% CI (-0.88, -0.06)) and no significant difference between fearful and either angry (P = 0.405, 95% CI (-0.79, 0.20)) or neutral expressions (P = 0.384, 95% CI (-0.44, 0.11)) (angry M -6.53 SD 2.76, fear M -6.24 SD 2.52, neutral M -6.07 SD 2.47). Facial composition also significantly affected N170 amplitude (F (1.428,37.118) = 5.489, P = 0.015); faces with the eyes covered produced larger amplitudes compared to the eyes alone (P = 0.011, 95% CI (0.14, 1.31)), and there was a trend towards faces with the eyes covered producing larger amplitudes compared to full faces (P = 0.062, 95% CI (-0.01, 0.71)). There was no significant difference between full faces and the eyes alone (P = 0.517, 95% CI (-1.06, 0.31)) (full faces M -6.29 SD 2.71, eyes alone M -5.91 SD 2.31, faces with the eyes covered M -6.64 SD 2.83). N170 amplitudes were larger in the right hemisphere compared to the left hemisphere (F (1,26) = 4.357, P = 0.047, 95% CI (0.02, 2.04), left M -5.77 SD 2.75, right M -6.79 SD 2.95).

There was a significant interaction between emotion and facial composition (F (2.819,73.305) = 4.367, P = 0.008), with larger N170 amplitudes for fearful compared to neutral expressions for the full faces (P = 0.004, 95% CI (-1.28, -0.22)). There was also a significant interaction between emotion and hemisphere (F (2,52) = 5.840, P = 0.005), with angry expressions producing larger amplitudes over the right hemisphere compared to the left hemisphere (P = 0.032, 95% CI (0.11, 2.26)), and a trend towards fearful expressions producing larger amplitudes over the right hemisphere compared to the left hemisphere (P = 0.053, 95% CI (-0.02, 1.98). There was also a significant interaction between EFHC2 variant, emotion and hemisphere (F (2,52) = 3.345, P = 0.043), which was driven by males possessing the A allele showing a trend towards larger N170 amplitudes for angry faces in the right compared to the left hemisphere (P = 0.098, 95% CI (-0.39, 3.93)). There were no more additional significant interactions between any of the variables (EFHC2 variant and emotion F (1.463,38.045) = 0.478, P = 0.565, EFHC2 variant and facial composition F (1.428,37.118) = 0.790, P = 0.422, EFHC2 variant and hemisphere F (1,26) = 0.492, P = 0.489, facial composition and hemisphere F (1.610,41.866) = 1.438, P = 0.248, EFHC2 variant, emotion and facial composition F (2.819,73.305) = 1.239, P = 0.301, EFHC2 variant,

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[3] Effect size = $\sqrt{\dfrac{F^2}{F^2 + df}}$

facial composition and hemisphere F (1.610,41.866) = 1.762, P = 0.189, emotion, facial composition and hemisphere F (4,104) = 0.359, P = 0.837, EFHC2 variant, emotion, facial composition and hemisphere F (4,104) = 1.055, P = 0.382). Neither age (F (1,25) = 0.008, P = 0.928) nor full scale IQ (F (1,25) = 3.917, P = 0.059) were significantly associated with N170 amplitudes when included as covariates.

Based on my previous behavioural results from Study 2, I also predicted that males possessing the G allele would show smaller N170 amplitudes than males possessing the A allele for fearful eyes and for fearful faces with the eyes covered. To test this a priori hypothesis I therefore compared N170 amplitudes for the two groups for the different stimuli types averaged across the two hemispheres in a 2 (group) × 2 (facial composition) repeated measures ANOVA. Again, males possessing the A allele at SNP rs7055196 showed larger N170 amplitudes than males possessing the G allele (F (1,26) = 4.529, P = 0.043, 95% CI (-3.96, -0.07), A allele M -7.00 SD 3.78, G allele M -4.99 SD 3.28). N170 amplitudes were smaller for the eyes alone compared to faces with the eyes covered (F (1,26) = 7.903, P = 0.009, 95% CI (0.26, 1.66), eyes alone M -5.52 SD 2.45, faces with the eyes covered M -6.48, SD 2.86). Finally, there was no significant interaction between EFHC2 variant and facial composition (F (1,26) = 0.544, P = 0.467). This result therefore supports my original prediction.

		Left hemisphere		Right hemisphere	
		A allele	G allele	A allele	G allele
Anger	Full face	-6.59 ± 2.79	-4.79 ± 3.07	-7.86 ± 3.62	-5.82 ± 3.09
	Eyes only	-6.41 ± 2.95	-5.16 ± 2.87	-8.25 ± 3.16	-5.49 ± 2.71
	Faces with the eyes covered	-7.20 ± 3.08	-5.28 ± 3.48	-9.40 ± 4.44	-6.13 ± 3.20
Fear	Full face	-7.61 ± 2.90	-4.92 ± 3.20	-8.64 ± 4.15	-5.68 ± 2.81
	Eyes only	-5.92 ± 2.75	-4.24 ± 3.11	-6.88 ± 2.63	-5.04 ± 2.41
	Faces with the eyes covered	-6.82 ± 2.44	-4.89 ± 3.23	-8.40 ± 3.55	-5.80 ± 3.16
Neutral	Full face	-6.50 ± 2.40	-4.74 ± 2.82	-7.02 ± 3.74	-5.28 ± 2.69
	Eyes only	-6.18 ± 2.36	-4.72 ± 3.16	-7.42 ± 2.75	-5.23 ± 2.72
	Faces with the eyes covered	-6.77 ± 2.67	-5.04 ± 2.96	-8.45 ± 2.93	-5.44 ± 3.01

Table 5-8. Mean N170 amplitudes (µV) for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 (mean ± SD)
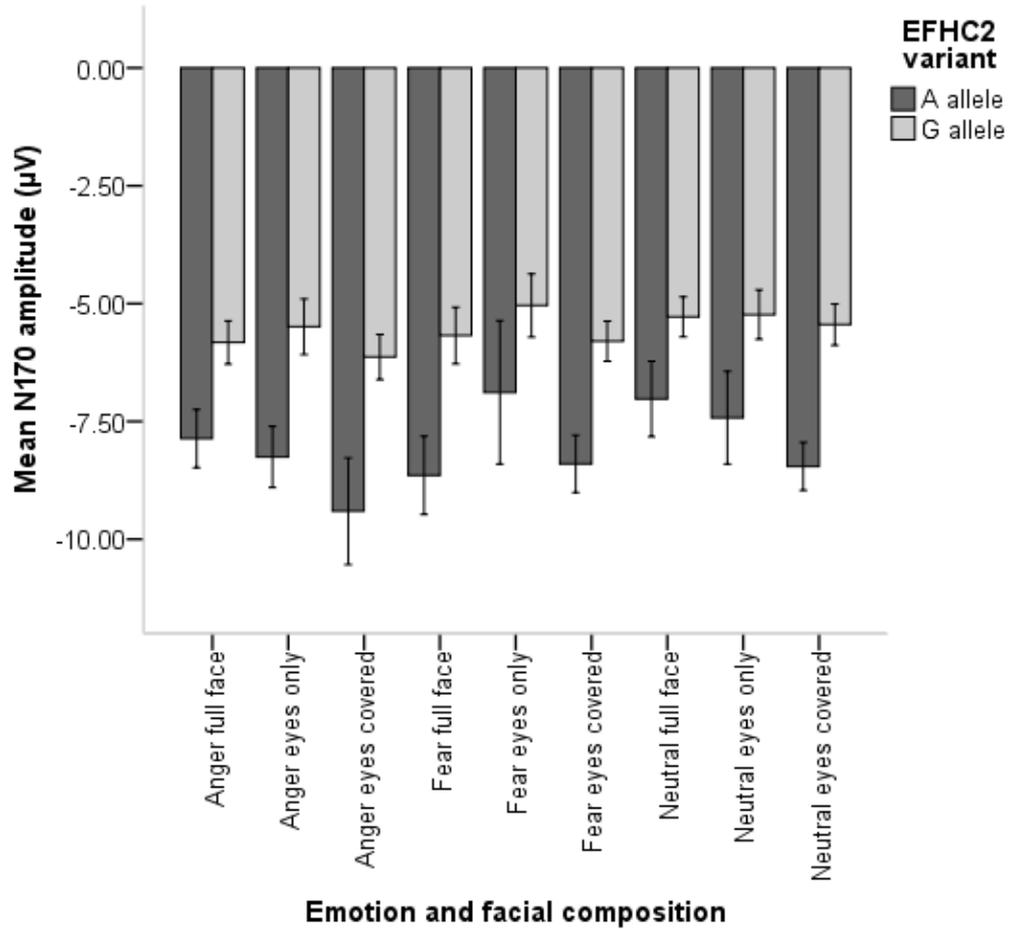
Figure 5-10. Mean N170 amplitudes (µV) for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 in the right hemisphere (error bars represent 95% CI)

5.3.2.3.4 N170 latency

Results for the mean N170 latency for each group for each emotion-facial composition pair in each hemisphere can be found in Table 5-9, and for the right hemisphere these results are shown in Figure 5-11. Males possessing the G allele at SNP rs7055196 showed longer latencies than those possessing the A allele (F (1,26) = 5.130, P = 0.032, 95% CI (-18, -1), A allele M 157 SD 16, G allele 167 SD 14), with an effect size equal to 0.709[4]. There was also a significant effect of emotion on N170 latency (F (2,52) = 12.377, P < 0.0005), with shorter latencies for neutral compared to both angry (P < 0.0005, 95% CI (2, 5)) and fearful expressions (P = 0.049, 95% CI (0, 4)) and no difference in latencies for angry and fearful expressions (P = 0.130, 95% CI (0, 3)) (anger M 164 SD 11, fear M 162 SD 11, neutral M 160 SD 11). Facial composition significantly affected N170 latency (F (1.624,42.233) = 196.839, P < 0.0005), with the eyes alone producing longer latencies compared to both full faces (P < 0.0005, 95% CI (-21, -16)) and faces with the eyes covered (P < 0.0005, 95% CI (14, 21)), while there was no difference in latencies between full faces and faces with the eyes covered (P = 1.000, 95% CI (-3, 2)) (full faces M 156 SD 10, eyes alone M 174 SD 12, faces with the eyes covered M 156 SD 11). There was no significant difference in N170 latencies between the left and right hemispheres (F (1,26) = 0.653, P = 0.426, 95% CI (-4, 2)).

There was a significant interaction between emotion and facial composition (F (2.570,66.826) = 3.263, P = 0.033). For the full faces, N170 latencies were shorter for neutral expressions compared to both angry (P = 0.024, 95% CI (-7, 0)) and fearful expressions (P = 0.010, 95% CI (-10, -1)), and for the eyes alone latencies were longer for angry expressions compared to both fearful (P = 0.001, 95% CI (2, 7)) and neutral expressions (P = 0.002, 95% CI (1, 7)). There was also a significant interaction between EFHC2 variant, facial composition and hemisphere (F (2,52) = 4.081, P = 0.023), with males possessing the G allele showing longer N170 latencies than males possessing the A allele for full faces in the right hemisphere (P = 0.035, 95% CI (-17, -1)), for the eyes alone in the left hemisphere (P = 0.042, 95% CI (-21, 0)), and for faces with the eyes covered in both the left (P = 0.029, 95% CI (-18, -1)) and right (P = 0.011, 95% CI (-21, -3)) hemispheres. There were no other significant interactions (EFHC2 variant and emotion F (2,52) = 0.880, P = 0.421, EFHC2 variant and facial composition F (1.624,42.233) = 1.076, P = 0.338, EFHC2 variant and hemisphere F (1,26) < 0.0005, P = 0.990, emotion and hemisphere F (2,52) = 0.752, P = 0.477, facial composition and hemisphere F (2,52) = 0.087, P = 0.917, EFHC2 variant, emotion and facial composition F (2.570,66.826) = 0.185, P = 0.880, EFHC2 variant, emotion and hemisphere F (2,52) = 1.174, P = 0.317, emotion, facial composition and hemisphere F (2.816,73.204) = 1.211, P = 0.311, EFHC2 variant, emotion, facial

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[4] Effect size = $\sqrt{\dfrac{F^2}{F^2 + df}}$

composition and hemisphere F (2.816,73.204) = 0.676, P = 0.560). Neither age (F (1,25) = 0.162, P = 0.691) nor full scale IQ (F (1,25) = 0.002, P = 0.964) were significantly associated with N170 latency when included as covariates.

		Left hemisphere		Right hemisphere	
		A allele	G allele	A allele	G allele
Anger	**Full face**	152 ± 12	160 ± 10	153 ± 11	160 ± 11
	Eyes only	171 ± 13	183 ± 14	175 ± 14	180 ± 11
	Faces with the eyes covered	154 ± 13	161 ± 14	152 ± 11	163 ± 15
Fear	**Full face**	154 ± 15	162 ± 16	152 ± 10	163 ± 12
	Eyes only	166 ± 12	176 ± 14	170 ± 11	177 ± 16
	Faces with the eyes covered	150 ± 11	162 ± 12	150 ± 11	164 ± 14
Neutral	**Full face**	149 ± 11	154 ± 14	149 ± 11	159 ± 14
	Eyes only	167 ± 13	177 ± 14	170 ± 13	176 ± 13
	Faces with the eyes covered	149 ± 10	160 ± 11	150 ± 11	161 ± 12

Table 5-9. Mean N170 latencies (ms) for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 (mean ± SD)

5.3.2.3.5 Results summary

A summary of the main effects for the ERP results found in Study 5 can be seen in Table 5-10.
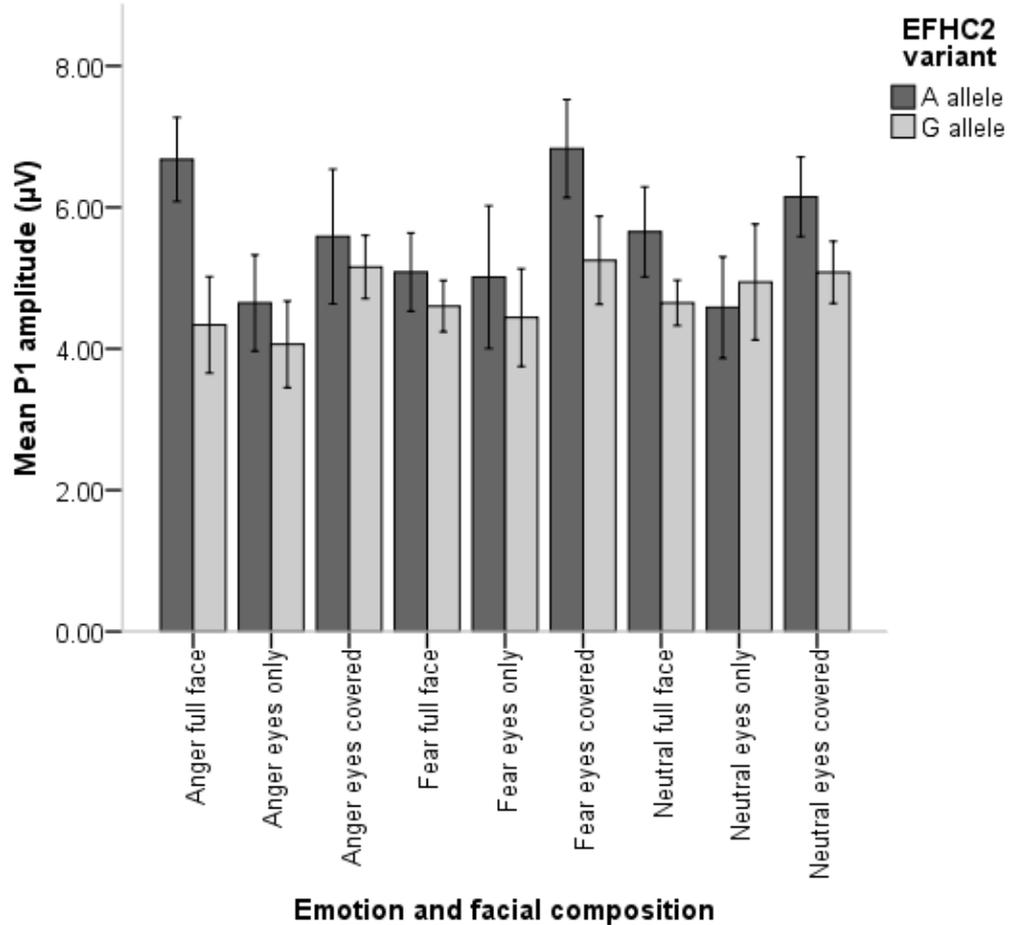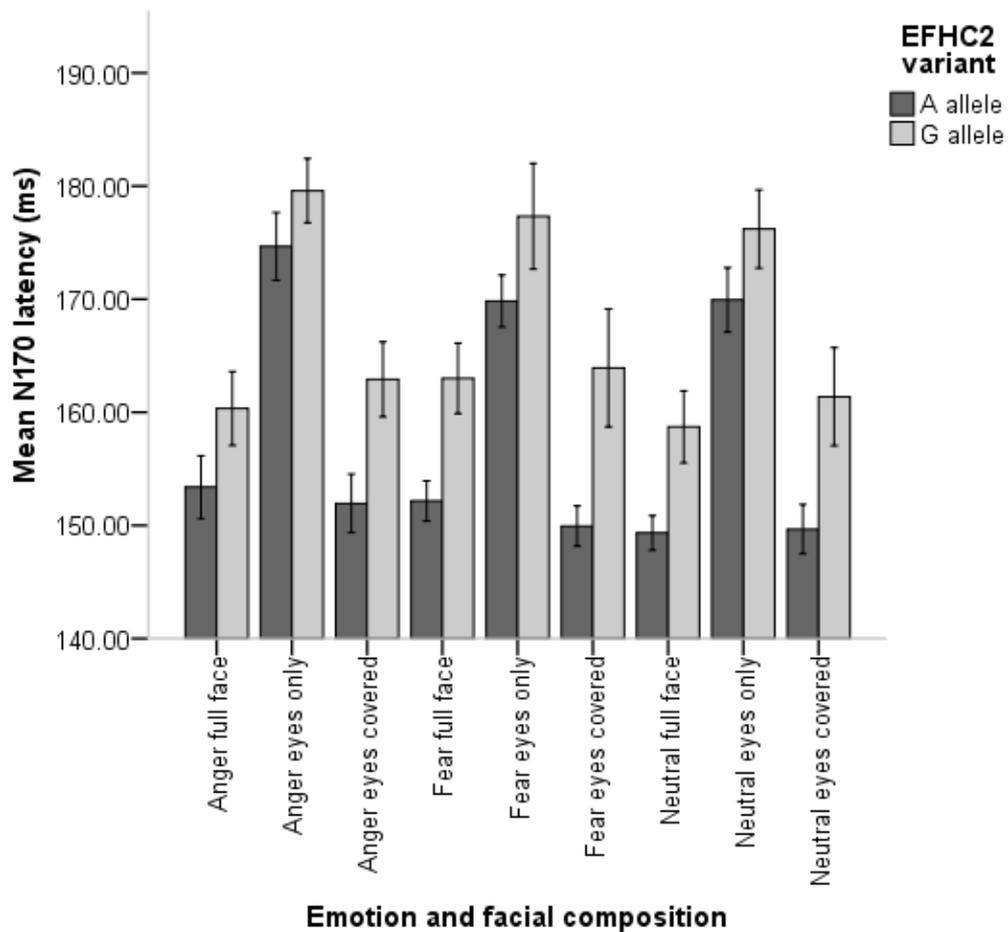
Figure 5-11. Mean N170 latencies (ms) for each emotion-facial composition pair for males possessing the different variants of SNP rs7055196 in the right hemisphere (error bars represent 95% CI)

	Main effect SNP rs7055196	Main effect emotion	Main effect facial composition	Main effect hemisphere
P1 amplitude	A allele = G allele	Angry = fearful = neutral	Faces with the eyes covered > full faces = eyes alone	Left = right
P1 latency	A allele = G allele	Angry = fearful = neutral	Eyes alone > full faces > faces with the eyes covered	Left = right
N170 amplitude	A allele > G allele	Angry > neutral	Faces with the eyes covered > eyes alone	Right > left
N170 latency	G allele > A allele	Angry = fearful > neutral	Eyes alone > full faces = faces with the eyes covered	Left = right

Table 5-10. Summary of the main effects of the influences on the P1 and N170 in Study 5

5.4 Study 6: electrophysiological responses to varying intensities of fearful and angry expressions

5.4.1 Method

5.4.1.1 Pilot study

The stimuli in Study 6 consisted of angry and fearful expressions of different intensity levels (low, medium and high). To ensure that the intensities of the two expressions were perceived as similar for each intensity level, an online questionnaire was first used to determine the intensity of expressions to use as stimuli. The stimuli used in the questionnaire were created by morphing a neutral expression with either a fearful or angry expression. The prototypical faces used were from the same two actors used in Study 3 (1 male, 1 female, faces from Fiorentini and Viviani (2009)). For each of the two angry and two fearful faces a sequence of faces containing different proportions of its emotion were created by producing nine equally spaced morphs between the face and its corresponding prototypical neutral face using LOKI software (Viviani et al 2007). This produced four sets of ranked faces (anger female, anger male, fear female, fear male) containing differing amounts of expression from 10% to 100%, with incremental steps of 10%. In total, each set contained 10 ranked faces, nine composite faces plus the fearful or angry prototypical face (for further details see Fiorentini and Viviani (2009)).

The online questionnaire was used to determine the perceived intensity of each of the ranked faces. A link was emailed to all students at UCL, and participation was entirely voluntary. Within the questionnaire each of the 40 faces (4 emotional sets × 10 ranked emotional faces containing between 10% and 100% of fear or anger) was presented underneath its corresponding neutral face. Participants were informed that the first face was neutral, and they were asked to rate the intensity of the emotional face compared to the neutral face (ratings from 1 (low intensity) to 10 (high intensity). Participants were also asked for their age and sex. Results from this pilot study for males aged 18-25 can be seen below in Table 5-11 and Figure 5-12 (n = 45, age M 20.96 SD 1.86).

	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Anger female	1.49	2.62	4.47	5.93	6.36	7.38	8.67	9.11	9.24	9.38
Anger male	1.67	2.87	4.11	5.47	5.49	5.96	6.60	6.53	6.71	7.40
Fear female	1.53	1.43	2.18	2.98	4.07	4.98	5.89	5.84	5.71	6.60
Fear male	2.20	2.93	3.80	4.69	5.67	5.76	5.93	6.82	6.80	7.11

Table 5-11. Mean intensity ratings for each of the ranked faces containing varying percentages of emotion (from 10% to 100%) in the four emotion sets
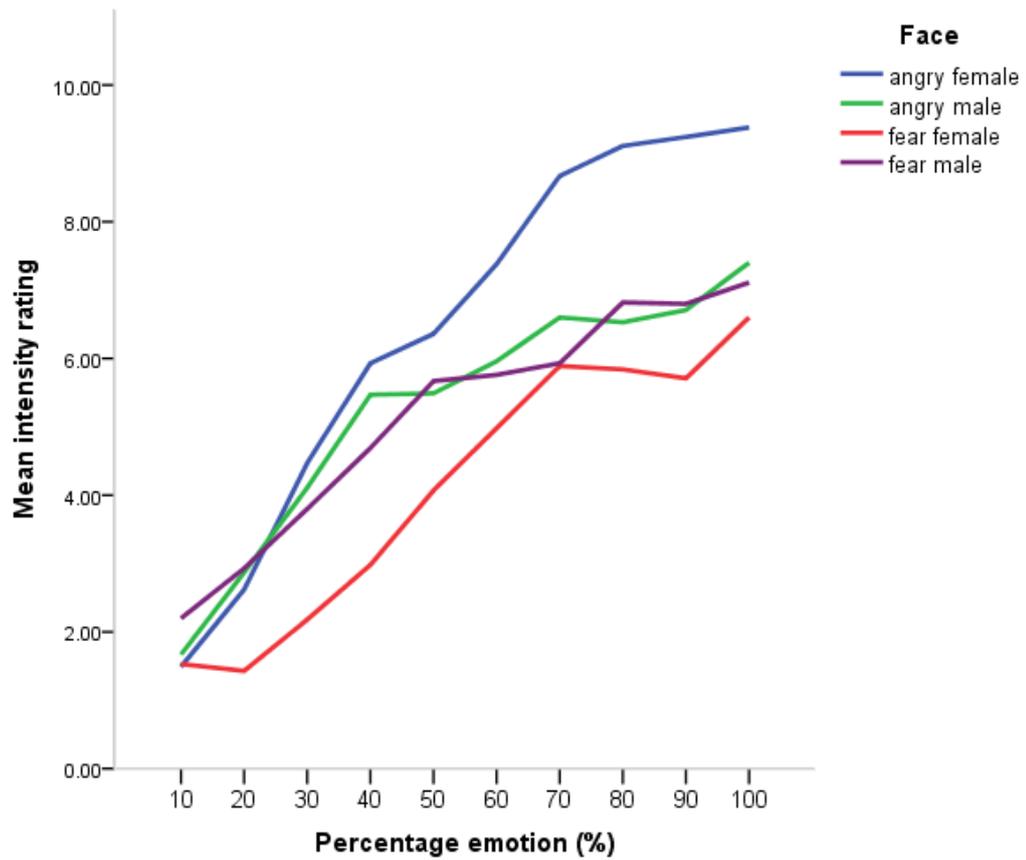
Figure 5-12. Mean intensity ratings for each of the ranked faces containing varying percentages of emotion (from 10% to 100%) in the four emotion sets

5.4.1.2 Task

During this task participants were shown a mixture of fearful and angry faces which differed in the intensity of their expression (Figure 5-13). Three different intensity levels were used (low, medium and high), with the perceived emotional intensity of the face being similar across all 4 faces for each level. The proportion of expression used in each face for each intensity level was selected based on the results from the pilot study, and can be seen below in Table 5-12. In total this gave 12 test faces to be used (2 emotions × 3 intensity levels × 2 actors).

Each test face was shown 40 times, resulting in a total of 480 face trials. An image of a butterfly was also shown for 40 trials (7.7% of trials); this image was downloaded from the internet and cropped into a face shape. Trials were presented in two blocks, each consisting of 20 repetitions of each face stimulus and the butterfly, and within each block images were presented in a random order. Participants were instructed to watch the screen and to press a button when a butterfly (target) was shown; participants were not instructed as to which hand to use to respond. No feedback was given for any images. The task was computer administered, and was written in E-Prime (Psychology Software Tools, Pittsburgh, PA).

During each face trial a neutral face was first shown for 650ms followed by one of the test faces for 500ms. The neutral face shown was of the same identity as the test face, and reduced any ERP responses due to the brightness, colour, lines and texture of the image, or due to the identity of the actor. During the butterfly trials the image of the butterfly was shown for 1150ms. Images subtended a visual angle of 22.62° (width) × 22.62° (height), and were shown one at a time in the centre of the screen. At the start of each trial a fixation cross was displayed in the centre of the screen for a variable length of time between 1000 and 1200ms. In total each block lasted for approximately 10 minutes (260 trials × 2.25 seconds = 589.5 seconds = 9.825 minutes). The number of targets identified and the corresponding RT (in ms) was recorded for each participant; only responses made while the butterfly was on the screen were recorded. The method used was based on that of Utama et al (2009).

5.4.1.2.1 Analysis

The number of butterflies correctly detected was calculated for each participant, and the mean RT for butterfly detection. These values were compared across the two groups using independent samples t-tests.
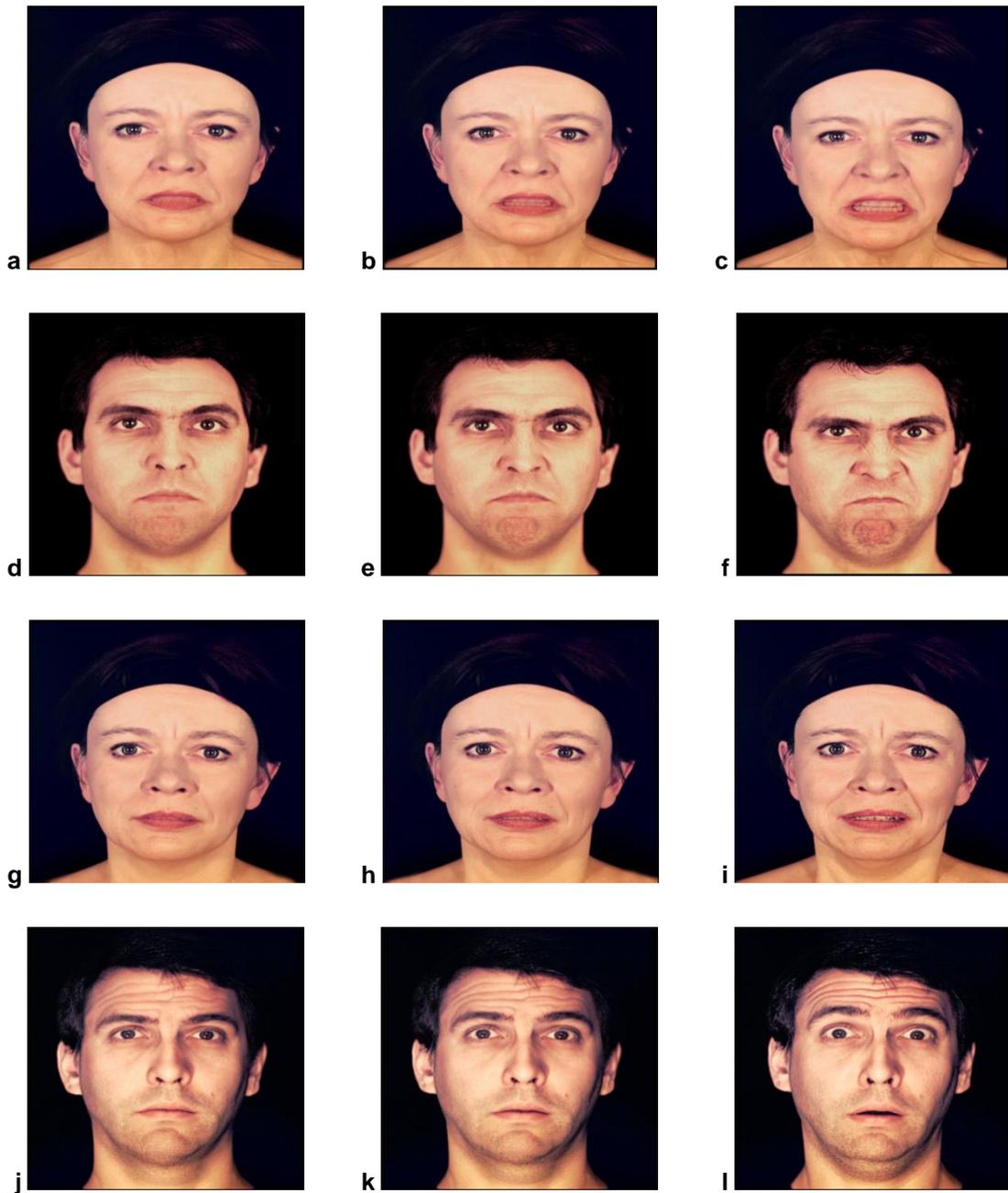
Figure 5-13. Images used in Study 6 (a) female low intensity anger, (b) female medium intensity anger, (c) female high intensity anger, (d) male low intensity anger, (e) male medium intensity anger, (f) male high intensity anger, (g) female low intensity fear, (h) female medium intensity fear, (i) female high intensity fear, (j) male low intensity fear, (k) male medium intensity fear, (l) male high intensity fear

	Low intensity		Medium intensity		High intensity	
	% emotion	Rating	% emotion	Rating	% emotion	Rating
Anger female	25	3.55	40	5.93	60	7.38
Anger male	25	3.49	50	5.49	100	7.40
Fear female	40	2.98	60	4.98	100	6.60
Fear male	25	3.37	50	5.67	100	7.11

Table 5-12. The percentage of emotion in the test faces used in Study 6 and their corresponding intensity ratings

5.4.1.3 Intensity ratings

To ensure there were no differences in the perceived intensities of the expressions between the two groups each participant also gave intensity ratings for each of the emotional faces following the ERP task. For each of the 12 emotional faces, a fixation cross was first shown in the centre of the screen for 1 second, then the corresponding neutral face was shown for 2 seconds followed by the emotional face. Participants were instructed to rate the intensity of the emotion on the emotional face compared to the neutral face using a scale of 0 (low intensity) to 9 (high intensity), and the emotional face was displayed until a rating was made. Participants had unlimited time to respond. Emotional faces were presented in a random order. Ratings for each face were recorded and analysed using a 2 (group) × 3 (intensity level) × 2 (emotion) repeated measures ANOVA with the Bonferroni correction applied.

5.4.1.4 Acquisition and processing of ERPs

The acquisition, processing and analysis of ERPs were identical to the procedure used in Study 5 (see section 5.3.1.3) with exceptions as listed below.

5.4.1.4.1 Processing

Segments of 600ms epochs were produced which were time-locked to the onset of the angry or fearful face (100ms pre-stimulus and 500ms post-stimulus). In addition, segments of 600ms epochs were also produced which were time-locked to the onset of the neutral face or the butterfly (again 100ms pre-stimulus and 500ms post-stimulus). For each participant, average waveforms for each of the 6 emotion-intensity level pairs were produced

for the male and female faces combined (2 emotions × 3 intensity levels). In total, 79.31% of all trials from the A allele group and 79.01% of all trials from the G allele group were included in the average waveforms produced. Further, average waveforms for the neutral faces (male and female combined) along with the butterfly were produced for each participant. In total, 80.79% of all trials from the A allele group and 82.29% of all trials from the G allele group were included in the average waveforms produced.

5.4.1.4.2 Analysis

Amplitudes and latencies for the P1 and N170 components were compared for the angry and fearful faces between participants possessing the A and G alleles using 2 (group) × 2 (emotion) × 3 (intensity level) × 2 (hemisphere) repeated measures ANOVAs with Greenhouse-Geisser and Bonferroni corrections applied where appropriate. Amplitudes and latencies for the P1 and N170 components were compared for the neutral faces and butterflies between participants possessing the A and G alleles using 2 (group) × 2 (stimulus) × 2 (hemisphere) repeated measures ANOVAs. All analysis was performed in SPSS (IBM Corp., Armonk, NY).

5.4.2 Results

5.4.2.1 Task performance

The mean numbers of butterflies correctly identified and RTs for males possessing the different variants of SNP rs7055196 during Study 6 can be seen in Table 5-13. Using independent samples t-tests, there were no differences in the mean number of butterflies detected (t (27) = 0.394, P = 0.697, 95% CI (-2.56, 3.77)) or the mean RT (t (27) = 0.191, P = 0.850, 95% CI (-65, 78)) between the two groups. All participants detected more than 80% of butterflies, suggesting a high level of attention during the task.

	A allele	G allele
Number butterflies detected	38.67 ± 2.06	38.06 ± 5.03
Mean RT	536 ± 76	529 ± 102

Table 5-13. The mean numbers of butterflies detected and mean RTs (ms) for participants possessing the different variants of SNP rs7055196 (mean ± SD)

5.4.2.2 Intensity ratings

The mean intensity ratings for the emotional faces used in Study 6 can be seen in Table 5-14. Intensity ratings were compared using a 2 (group) × 2 (emotion) × 3 (intensity level) repeated measures ANOVA with a Bonferroni correction.

There were no differences in the intensity ratings given to the faces between males possessing the A and G alleles at SNP rs7055196 ($F_{(1,26)} = 0.074$, $P = 0.788$, 95% CI (-0.86, 0.66)). Angry expressions were rated to be more intense compared to the fearful expressions ($F_{(1,26)} = 63.719$, $P < 0.0005$, 95% CI (0.81, 1.38), angry M 4.92 SD 1.17, fear M 3.83 SD 0.94), and the intensity level of the expression also affected its intensity rating ($F_{(2,52)} = 118.537$, $P < 0.0005$). Low intensity faces were rated as least intense and high intensity faces were rated as most intense (low intensity M 2.83 SD 0.91, medium intensity M 4.06 SD 1.27, high intensity M 6.24 SD 1.42, low vs medium $P < 0.0005$, 95% CI (-1.69, -0.77), low vs high $P < 0.0005$, 95% CI (-4.09, -2.72), medium vs high $P < 0.0005$, 95% CI (-2.72, -1.63)). There were no significant interactions between EFHC2 variant and emotion ($F_{(1,26)} = 0.052$, $P = 0.821$), EFHC2 variant and intensity level ($F_{(2,52)} = 0.659$, $P = 0.522$), emotion and intensity level ($F_{(2,52)} = 0.821$, $P = 0.446$) or EFHC2 variant, emotion and intensity level ($F_{(2,52)} = 0.977$, $P = 0.383$).

	Low intensity		Medium intensity		High intensity	
	A allele	G allele	A allele	G allele	A allele	G allele
Anger	3.29 ± 1.39	3.25 ± 0.98	4.46 ± 1.36	4.94 ± 1.64	6.92 ± 1.40	6.69 ± 1.52
Fear	2.17 ± 0.98	2.63 ± 0.90	3.38 ± 1.30	3.47 ± 0.99	5.75 ± 1.76	5.59 ± 1.46

Table 5-14. Mean intensity ratings for each expression and intensity level for the groups of males possessing the different variants of SNP rs7055196 (mean ± SD)

5.4.2.3 ERP results for fearful and angry expressions

Average waveforms produced for each of the different stimulus types in Study 5 are shown in Figure 5-14 and Figure 5-15. Wave amplitudes and latencies were compared using 2 (group) × 2 (emotion) × 3 (intensity level) × 2 (hemisphere) repeated measures ANOVAs with Greenhouse-Geisser and Bonferroni corrections applied where appropriate.
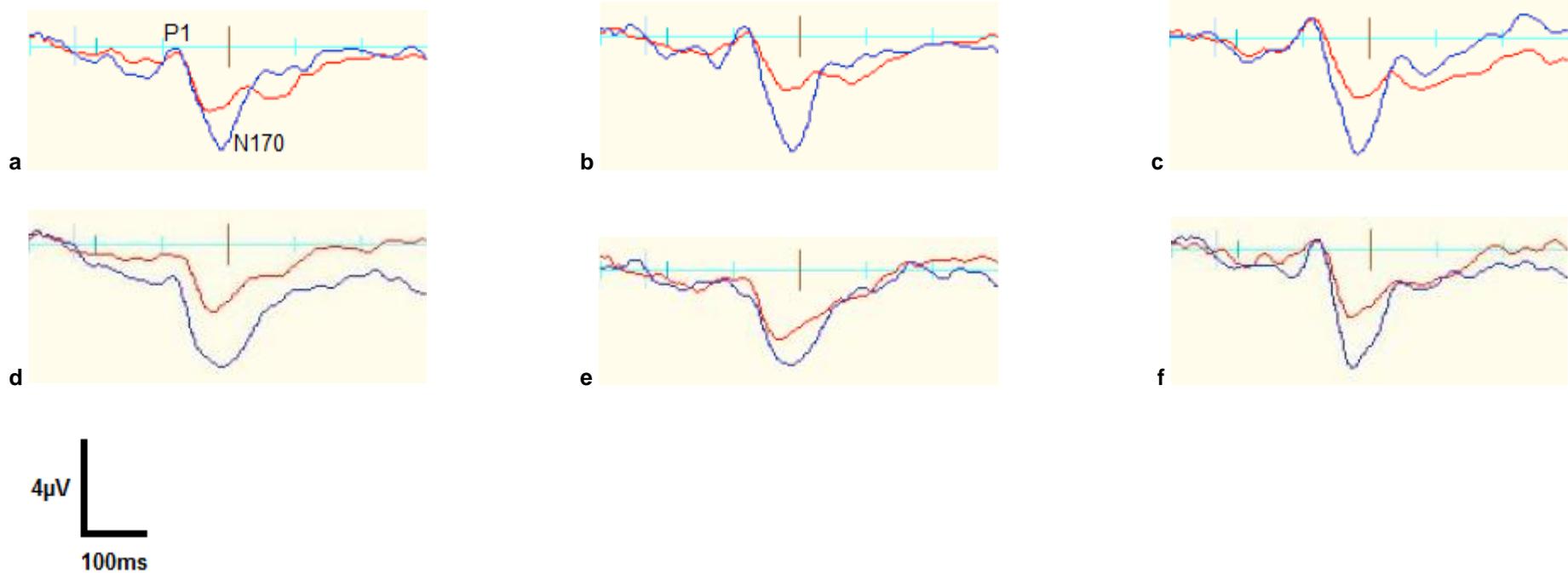
Figure 5-14. Average ERP waveforms produced by males possessing the different variants of SNP rs7055196 for a) anger low intensity faces, b) anger medium intensity faces, c) anger high intensity faces, d) fear low intensity faces, e) fear medium intensity faces, f) fear high intensity faces (all recordings measured at electrode 92, blue A allele, red G allele)
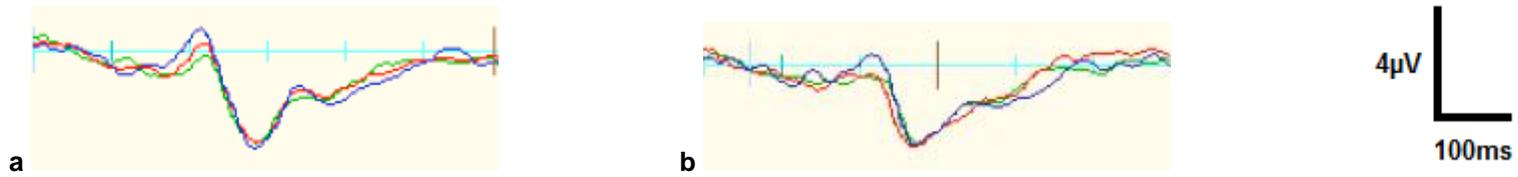
Figure 5-15. Average ERP waveforms produced by the different intensity levels for a) angry expressions, b) fearful expressions (all recordings measured at electrode 92, blue high intensity, red medium intensity, green low intensity)

5.4.2.3.1 P1 amplitude

As can be seen from the waveforms in Figure 5-14 and Figure 5-15 and the values in Table 5-15, the amplitudes for P1 are much smaller than would usually be expected and from those found in Study 5 (section 5.3.2.3.1). This is likely due to the task design used, as the angry and fearful faces were displayed following a neutral face. The processing which occurred due to viewing the neutral face likely influenced the subsequent processing for the angry and fearful faces, resulting in the small P1 amplitudes.

Mean P1 amplitudes for the two groups can be seen in Table 5-15, and amplitudes in the right hemisphere can be seen in Figure 5-16. Males possessing the G allele at SNP rs7055196 produced larger P1 amplitudes than males possessing the A allele ($F (1,27) = 6.167$, $P = 0.020$, 95% CI (-1.11, -0.11), A allele M 0.13 SD 0.65, G allele M 0.73 SD 0.65), with an effect size equal to 0.765[5]. Angry expressions produced greater P1 amplitudes than fearful expressions ($F (1,27) = 9.812$, $P = 0.004$, 95% CI (0.16, 0.76), angry M 0.66 SD 0.76, fearful M 0.20 SD 0.76). There was also a significant effect of intensity level of the expression on P1 amplitudes ($F (2,54) = 13.755$, $P < 0.0005$), with low intensity expressions producing smaller amplitudes than both medium and high intensity expressions and no difference between the amplitudes for medium and high intensity expressions (low intensity M -0.05 SD 0.92, medium intensity M 0.53 SD 0.65, high intensity M 0.81 SD 0.92, low vs medium $P = 0.008$, 95% CI (-1.03, -0.13), low vs high $P < 0.0005$, 95% CI (-1.26, -0.48), medium vs high $P = 0.334$, 95% CI (-0.73, 0.16)). There were no differences in P1 amplitudes between the left and right hemispheres ($F (1,27) = 0.893$, $P = 0.353$, 95% CI (-0.12, 0.33)).

There was a significant interaction effect between emotion and hemisphere ($F (1,27) = 4.630$, $P = 0.041$), with smaller P1 amplitudes for fearful expressions compared to angry expressions in the right hemisphere only ($P = 0.018$, 95% CI (0.10, 1.02)). There were no other significant interactions between any of the variables (EFHC2 variant and emotion $F (1,27) = 1.780$, $P = 0.193$, EFHC2 variant and intensity level $F (2,54) = 1.493$, $P = 0.234$, EFHC2 variant and hemisphere $F (1,27) = 0.771$, $P = 0.388$, emotion and intensity level $F (2,54) = 2.167$, $P = 0.124$, intensity level and hemisphere $F (2,54) = 0.062$, $P = 0.940$, EFHC2 variant, emotion and intensity level $F (2,54) = 2.652$, $P = 0.080$, EFHC2 variant, emotion and hemisphere $F (1,27) = 0.055$, $P = 0.817$, EFHC2 variant, intensity level and hemisphere $F (2,54) = 0.635$, $P = 0.534$, emotion, intensity level and hemisphere $F (1.418,38.280) = 0.443$, $P = 0.578$, EFHC2 variant, emotion, intensity level and hemisphere $F (1.418,38.280) = 0.207$, $P = 0.737$). Neither age ($F (1,26) = 0.022$, $P = 0.884$) nor full scale

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[5] Effect size = $\sqrt{\dfrac{F^2}{F^2 + df}}$

IQ (F (1,26) = 1.582, P = 0.220) were significantly associated with P1 amplitude when included as covariates.

		Left hemisphere		Right hemisphere	
		A allele	G allele	A allele	G allele
Anger	**Low intensity**	-0.23 ± 1.09	0.29 ± 1.00	-0.20 ± 1.24	0.50 ± 1.01
	Medium intensity	0.48 ± 0.94	0.92 ± 0.76	0.53 ± 0.93	0.95 ± 0.70
	High intensity	1.17 ± 1.35	1.20 ± 1.08	0.95 ± 1.34	1.31 ± 1.11
Fear	**Low intensity**	-0.67 ± 0.71	0.55 ± 1.18	-0.98 ± 1.41	0.30 ± 1.09
	Medium intensity	0.36 ± 1.09	0.55 ± 1.14	0.00 ± 0.68	0.41 ± 0.78
	High intensity	0.23 ± 1.16	0.90 ± 1.26	-0.15 ± 1.01	0.90 ± 1.05

Table 5-15. Mean P1 amplitudes (μV) for each expression and intensity level for males possessing the different variants of SNP rs7055196 (mean ± SD)

Figure 5-16. Mean P1 amplitudes (µV) for each expression and intensity level for males possessing the different variants of SNP rs7055196 in the right hemisphere (error bars represent 95% CI)

5.4.2.3.2 P1 latency

Mean P1 latencies for each group and each stimulus type for each hemisphere can be found in Table 5-16. Mean P1 latencies for the right hemisphere can be seen in Figure 5-17. There were no differences in P1 latencies between males possessing the different alleles at SNP rs7055196 (F (1,27) = 1.202, P = 0.283, 95% CI (-14, 4)). P1 latencies were shorter for fearful compared to angry expressions (F (1,27) = 5.276, P = 0.030, angry M 111 SD 16, fearful M 104 SD 13, 95% CI (1, 13)). There were no differences in P1 latencies for the different intensity levels of the expressions (F (2,54) = 0.115, P = 0.892), and no difference in latencies between the left and right hemispheres (F (1,27) = 2.378, P = 0.135, 95% CI (-1, 6)).

None of the interaction terms between any of the variables reached significance (EFHC2 variant and emotion F (1,27) < 0.0005, P = 0.989, EFHC2 variant and intensity level F (2,54) = 0.086, P = 0.918, EFHC2 variant and hemisphere F (1,27) = 0.130, P = 0.721, emotion and intensity level F (2,54) = 2.191, P = 0.122, emotion and hemisphere F (1,27) = 0.310, P = 0.582, intensity level and hemisphere F (2,54) = 0.143, P = 0.867, EFHC2 variant, emotion and intensity level F (2,54) = 0.389, P = 0.680, EFHC2 variant, emotion and hemisphere F (1,27) = 0.074, P = 0.787, EFHC2 variant, intensity level and hemisphere F (2,54) = 0.755, P = 0.475, emotion, intensity level and hemisphere F (2,54) = 0.659, P = 0.521, EFHC2 variant, emotion, intensity level and hemisphere F (2,54) = 0.866, P = 0.426). Age was significantly associated with P1 latency when included as a covariate (F (1,26) = 4.912, P = 0.036), with increasing age being associated with a decreasing P1 latency. Including age as a covariate did not influence the effect of SNP rs7055196 on P1 latency or any interactions involving this SNP. Full scale IQ (F (1,26) = 2.577, P = 0.120) was not significantly associated with latency when included as a covariate.

		Left hemisphere		Right hemisphere	
		A allele	**G allele**	**A allele**	**G allele**
Anger	**Low intensity**	109 ± 14	110 ± 21	107 ± 14	110 ± 26
	Medium intensity	109 ± 16	118 ± 25	111 ± 16	115 ± 23
	High intensity	111 ± 10	115 ± 23	104 ± 13	114 ± 23
Fear	**Low intensity**	108 ± 17	110 ± 20	98 ± 18	109 ± 24
	Medium intensity	100 ± 14	105 ± 17	97 ± 21	102 ± 16
	High intensity	102 ± 19	109 ± 22	104 ± 15	106 ± 17

Table 5-16. Mean P1 latencies (ms) for each expression and intensity level for males possessing the different variants of SNP rs7055196 (mean ± SD)

Figure 5-17. Mean P1 latencies (ms) for each expression and intensity level for males possessing the different variants of SNP rs7055196 in the right hemisphere (error bars represent 95% CI)

5.4.2.3.3 N170 amplitude

Mean N170 amplitudes for the two groups of males possessing the different alleles at SNP rs7055196 for each expression and intensity level in each hemisphere can be seen in Table 5-17, and mean amplitudes for the right hemisphere can be found in Figure 5-18. Males possessing the G allele at SNP rs7055196 showed smaller N170 amplitudes than males possessing the A allele (F (1,27) = 6.729, P = 0.015, 95% CI (-1.92, -0.22), A allele M -3.65 SD 1.09, G allele M -2.58 SD 1.09), with an effect size equal to 0.792[6]. Amplitudes for the N170 component were greater for fearful compared to angry expressions (F (1,27) = 9.419, P = 0.005, 95% CI (0.14, 0.68), angry M -2.91 SD 1.13, fearful M -3.32 SD 1.20). There was also a significant effect of intensity level on N170 amplitude (F (2,54) = 4.021, P = 0.024), with larger amplitudes for high intensity faces compared to medium intensity faces (P = 0.017, 95% CI (0.06, 0.68)), a trend towards larger amplitudes for high intensity faces compared to low intensity faces (P = 0.079, 95% CI (-0.03, 0.83)), and no difference between low and medium intensity faces (P = 1.000, 95% CI (-0.41, 0.47)) (low intensity M -2.97 SD 1.31, medium intensity M -3.01 SD 0.95, high intensity M -3.37 SD 1.33). Finally, N170 amplitudes showed a trend towards being greater in the right hemisphere compared to the left hemisphere (F (1,27) = 3.784, P = 0.062, 95% CI (-0.02, 0.65), left M -2.96 SD 1.12, right M -3.28 SD 1.26).

There was a significant interaction between EFHC2 variant, emotion and intensity level (F (1.648,44.502) = 3.638, P = 0.042), with males possessing the A allele showing larger N170 amplitudes compared to males possessing the G allele for angry medium intensity expressions (P = 0.004, 95% CI (-2.22, -0.45)) and fearful high intensity expressions (P = 0.022, 95% CI (-2.83, -0.24)). There were no further significant interactions (EFHC2 variant and emotion F (1,27) = 1.101, P = 0.303, EFHC2 variant and intensity level F (2,54) = 0.287, P = 0.751, EFHC2 variant and hemisphere F (1,27) = 0.956, P = 0.337, emotion and intensity level F (1.648,44.502) = 2.870, P = 0.077, emotion and hemisphere F (1,27) = 0.112, P = 0.741, intensity level and hemisphere F (2,54) = 0.332, P = 0.719, EFHC2 variant, emotion and hemisphere F (1,27) = 0.012, P = 0.915, EFHC2 variant, intensity level and hemisphere F (2,54) = 2.549, P = 0.088, emotion, intensity level and hemisphere F (1.390,37.525) = 1.482, P = 0.238, EFHC2 variant, emotion, intensity level and hemisphere F (1.390,37.525) = 1.029, P = 0.342). Neither age (F (1,26) = 0.507, P = 0.483) nor full scale IQ (F (1,26) = 0.178, P = 0.677) were significantly associated with N170 amplitudes when included as covariates.

Based on my results from Study 3, I also predicted that males possessing the A allele would show a greater sensitivity to different intensities of fearful expressions than that of males

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[6] Effect size = $\sqrt{\dfrac{F^2}{F^2 + df}}$

possessing the G allele. To test this a priori hypothesis I compared N170 amplitudes for the two groups for fearful expressions across the three intensity levels averaged across the two hemispheres in a 2 (group) × 3 (intensity) repeated measures ANOVA. Again, males possessing the A allele at SNP rs7055196 showed greater N170 amplitudes than males possessing the G allele (F (1,27) = 7.348, P = 0.012, 95% CI (-2.13, -0.29), A allele M -3.93 SD 1.18, G allele M -2.72 SD 1.18). There was also a significant effect of intensity level on N170 amplitude (F (1,27) = 6.248, P = 0.004), with high intensity fearful expressions producing greater amplitudes than either low or medium intensity expressions (low intensity vs medium intensity P = 1.000, 95% CI (-0.53, 0.72), low intensity vs high intensity P = 0.002, 95% CI (0.26, 1.27), medium intensity vs high intensity P = 0.047, 95% CI (0.01, 1.33), low intensity M -3.03 SD 1.42, medium intensity M -3.13 SD 1.02, high intensity M -3.80 SD 1.70). There was no significant interaction effect between EFHC2 variant and intensity level (F (1,27) = 2.141, P = 0.127), in contrast to my prediction.

Topographical plots to illustrate the difference in activation for the N170 component between males possessing the different variants of SNP rs7055196 can be found in Figure 5-19. It can be seen that there is a greater negativity over temporo-occipital regions in males possessing the A allele compared to those possessing the G allele, which supports the difference in amplitudes found between the groups.

		Left hemisphere		Right hemisphere	
		A allele	G allele	A allele	G allele
	Low intensity	-3.40 ± 2.00	-2.39 ± 1.03	-3.39 ± 1.89	-2.47 ± 1.03
Anger	Medium intensity	-3.33 ± 1.98	-1.97 ± 1.13	-3.76 ± 1.26	-2.46 ± 0.97
	High intensity	-2.64 ± 1.31	-2.68 ± 1.26	-3.73 ± 1.54	-2.72 ± 1.74
	Low intensity	-3.37 ± 1.18	-2.24 ± 1.14	-4.15 ± 2.53	-2.38 ± 1.26
Fear	Medium intensity	-3.30 ± 1.65	-2.70 ± 1.25	-3.61 ± 1.48	-2.91 ± 0.90
	High intensity	-4.43 ± 2.62	-3.04 ± 1.36	-4.70 ± 2.26	-3.02 ± 1.15

Table 5-17. Mean N170 amplitudes (μV) for each expression and intensity level for males possessing the different variants of SNP rs7055196 (mean ± SD)
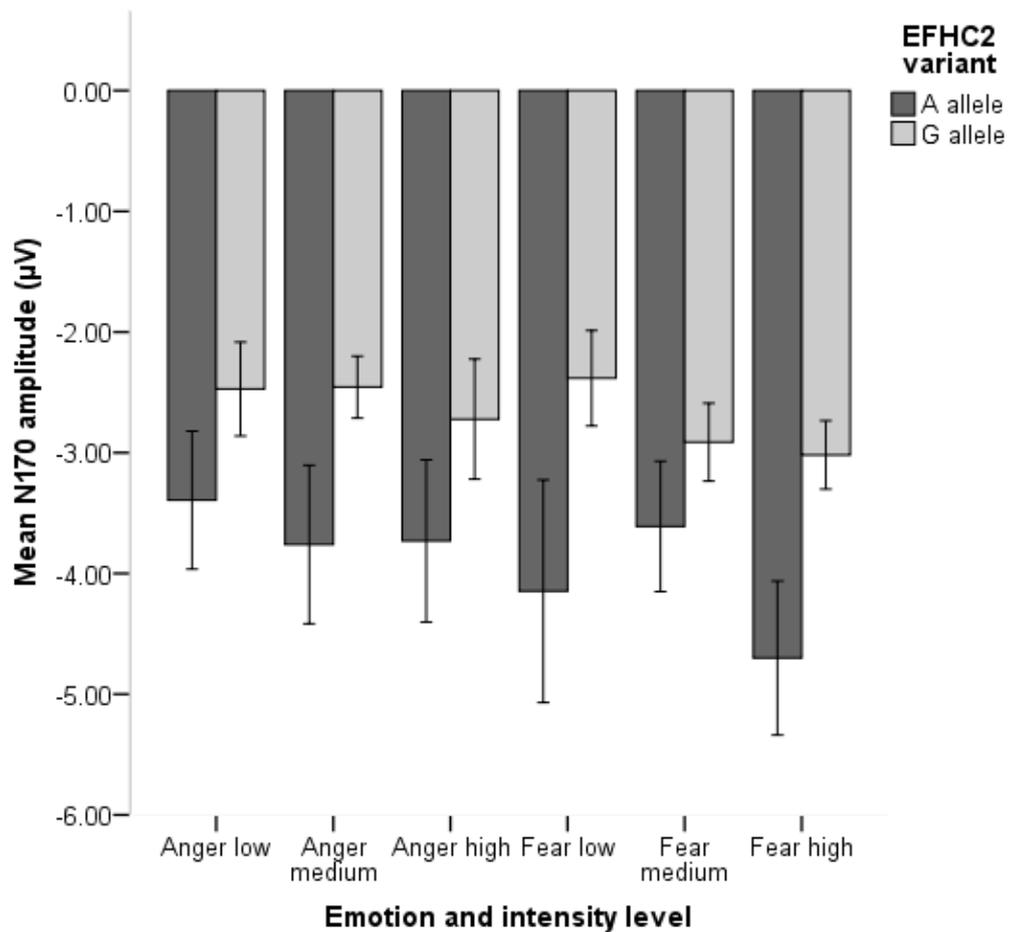
Figure 5-18. Mean N170 amplitudes (µV) for each expression and intensity level for males possessing the different variants of SNP rs7055196 in the right hemisphere (error bars represent 95% CI)
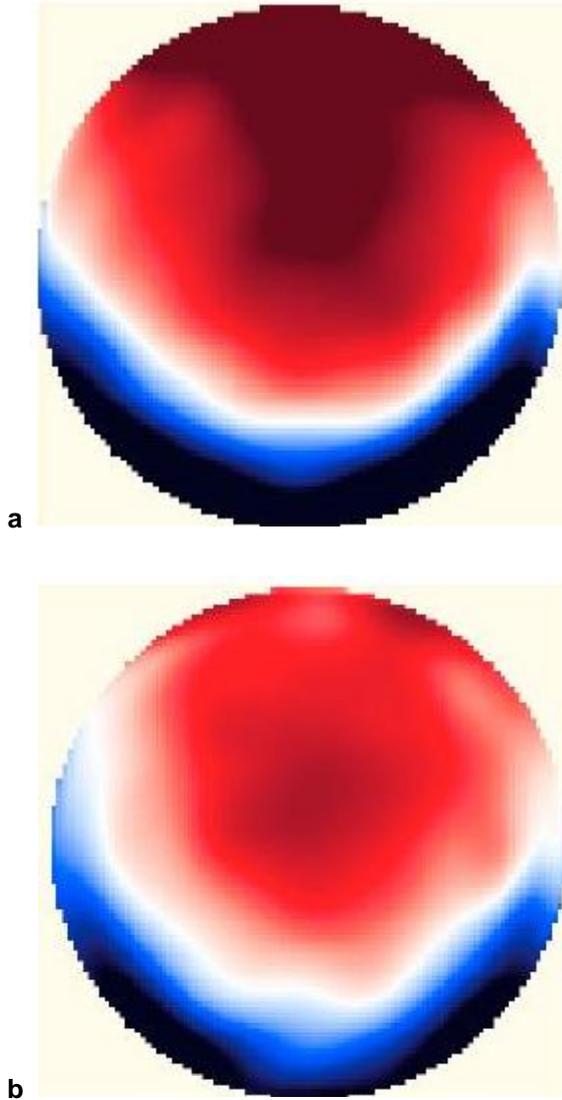
Figure 5-19. Topographical plots of activation for males possessing the different variants of SNP rs7055196 for high intensity fearful expressions a) males possessing an A allele, b) males possessing a G allele (activation map taken at 185ms following stimulus onset)

5.4.2.3.4 N170 latency

Mean N170 latencies for each group of males possessing the different alleles at SNP rs7055196 for each stimulus type in each hemisphere can be seen in Table 5-18, and mean latencies for the right hemisphere can be seen in Figure 5-20. There were no differences in the mean latencies for the groups of males possessing the different variants of SNP rs7055196 ($F_{(1,27)} = 0.047$, $P = 0.831$, 95% CI (-9, 11)). There were further no significant differences in N170 latencies for angry and fearful expressions ($F_{(1,27)} = 2.517$, $P = 0.124$, 95% CI (-1, 8)), or for faces displaying different intensities of expressions ($F_{(1.517,40.960)} = 1.185$, $P = 0.305$). There was however a significant difference between latencies in the two hemispheres, with shorter latencies in the left compared to the right hemisphere ($F_{(1,27)} = 8.325$, $P = 0.008$, 95% CI (-11, -2), left M 184 SD 14, right M 190 SD 14).

There was a significant four-way interaction between EFHC2 variant, emotion, intensity level and hemisphere ($F_{(2,54)} = 3.754$, $P = 0.030$), with longer latencies for males possessing the G allele for high intensity angry faces in the left hemisphere only ($P = 0.044$, 95% CI (-26, 0)). There were no further significant interactions between any of the variables (EFHC2 variant and emotion $F_{(1,27)} = 0.003$, $P = 0.957$, EFHC2 variant and intensity level $F_{(1.517,40.960)} = 1.424$, $P = 0.250$, EFHC2 variant and hemisphere $F_{(1,27)} = 2.379$, $P = 0.135$, emotion and intensity level $F_{(1.480,39.960)} = 0.201$, $P = 0.751$, emotion and hemisphere $F_{(1,27)} = 0.801$, $P = 0.379$, intensity level and hemisphere $F_{(2,54)} = 0.190$, $P = 0.828$, EFHC2 variant, emotion and intensity level $F_{(1.480,39.960)} = 1.593$, $P = 0.218$, EFHC2 variant, emotion and hemisphere $F_{(1,27)} < 0.0005$, $P = 0.994$, EFHC2 variant, intensity level and hemisphere $F_{(2,54)} = 0.647$, $P = 0.528$, emotion, intensity level and hemisphere $F_{(2,54)} = 2.103$, $P = 0.132$). Full scale IQ was significantly associated with N170 latency when included as a covariate ($F_{(1,26)} = 6.178$, $P = 0.020$), with latency increasing as IQ increased. Including full scale IQ as a covariate did not influence the effect of SNP rs7055196 on N170 latency or any interactions involving this SNP. Age was not significantly associated with latency when included as a covariate ($F_{(1,26)} = 2.123$, $P = 0.157$).

5.4.2.3.5 Results summary

A summary of the main effects for the ERP results found in Study 6 can be seen in Table 5-19

		Left hemisphere		Right hemisphere	
		A allele	G allele	A allele	G allele
	Low intensity	187 ± 19	184 ± 20	192 ± 9	190 ± 18
Anger	Medium intensity	188 ± 10	185 ± 23	200 ± 6	190 ± 21
	High intensity	176 ± 14	189 ± 18	192 ± 13	191 ± 21
	Low intensity	179 ± 18	182 ± 23	192 ± 16	186 ± 18
Fear	Medium intensity	181 ± 18	186 ± 20	193 ± 17	186 ± 21
	High intensity	184 ± 16	183 ± 16	187 ± 21	185 ± 18

Table 5-18. Mean N170 latencies (ms) for each expression and intensity level for males possessing the different variants of SNP rs7055196 (mean ± SD)
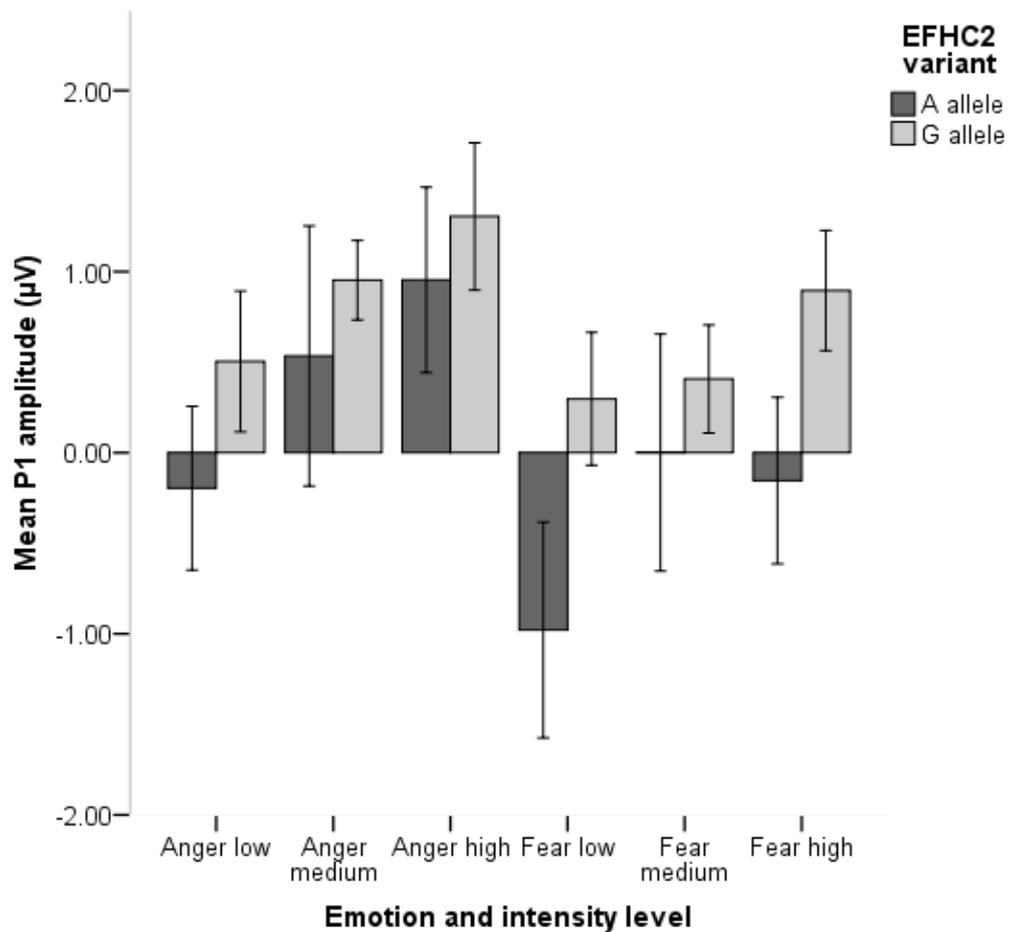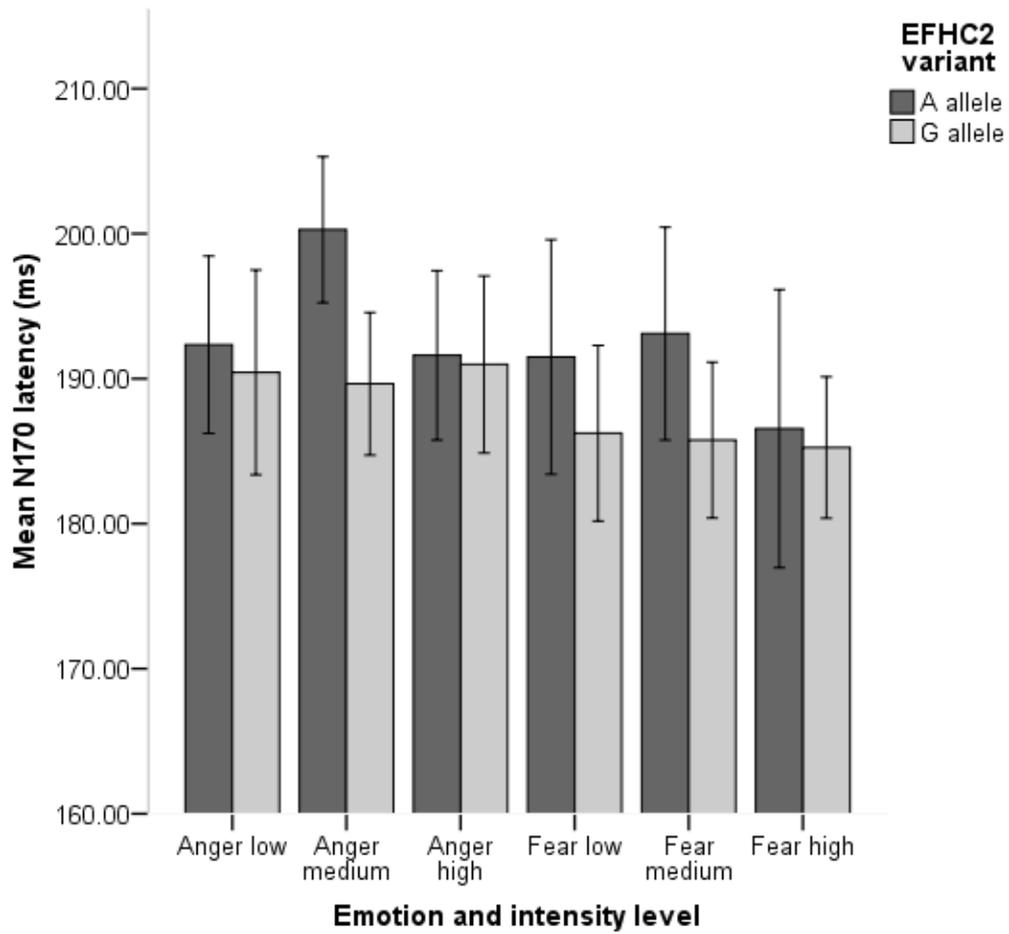
Figure 5-20. Mean N170 latencies (µV) for each expression and intensity level for males possessing the different variants of SNP rs7055196 in the right hemisphere (error bars represent 95% CI)

	Main effect SNP rs7055196	Main effect emotion	Main effect intensity	Main effect hemisphere
P1 amplitude	G allele > A allele	Angry > fearful	High = medium > low	Left = right
P1 latency	A allele = G allele	Angry > fearful	High = medium = low	Left = right
N170 amplitude	A allele > G allele	Fearful > angry	High > medium	Left = right
N170 latency	A allele = G allele	Angry = fearful	High = medium = low	Right > left

Table 5-19. Summary of the main effects of the influences on the P1 and N170 in Study 6

5.4.2.4 ERP results for neutral faces and butterflies

To further investigate influences of SNP rs7055196 on electrophysiological responses to faces I also compared the P1 and N170 amplitudes and latencies for the neutral faces and the butterflies during Study 6 using 2 (group) × 2 (stimulus type) × 2 (hemisphere) repeated measures ANOVAs. Average waveforms for the two groups for each stimulus type can be found in Figure 5-21.

5.4.2.4.1 P1 amplitude

Mean P1 amplitudes for the two groups can be found in Table 5-20. There were no differences in amplitudes between males possessing the different variants of SNP rs7055196 (F (1,27) = 0.171, P = 0.682, 95% CI (-1.40, 2.11)) or for the neutral faces compared to the butterflies (F (1,27) = 0.181, P = 0.674, 95% CI (-0.64, 0.42)). There was also no difference in amplitudes between the two hemispheres (F (1,27) = 3.223, P = 0.084, 95% CI (-1.01, 0.07)). There was a significant interaction between the stimulus type and hemisphere (F (1,27) = 5.090, P = 0.032), with larger amplitudes in the right hemisphere compared to the left hemisphere for the butterflies but not for the neutral faces. No further interactions were significant (EFHC2 variant and stimulus type F (1,27) = 3.340, P = 0.079, EFHC2 variant and hemisphere F (1,27) = 2.955, P = 0.097, EFHC2 variant, stimulus type and hemisphere F (1,27) = 0.674, P = 0.419).

	Left hemisphere		Right hemisphere	
	A allele	G allele	A allele	G allele
Neutral face	5.81 ± 2.77	5.62 ± 1.81	5.60 ± 2.89	6.03 ± 1.67
Butterfly	6.16 ± 3.06	4.75 ± 2.59	6.42 ± 3.48	6.18 ± 1.94

Table 5-20. Mean P1 amplitudes (μV) for the neutral faces and butterflies for males possessing the different variants of SNP rs7055196 (mean ± SD)
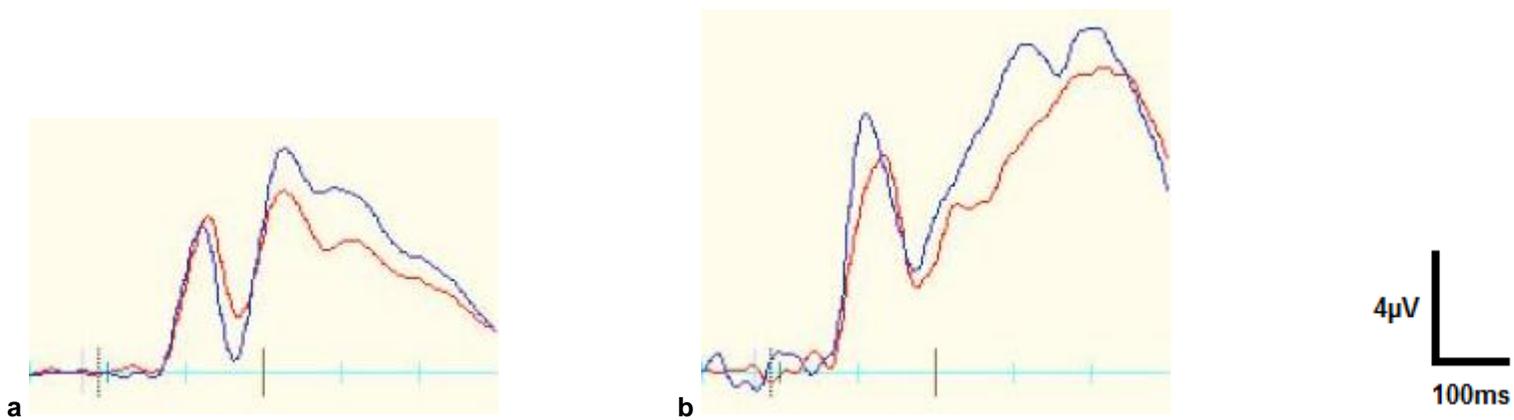
Figure 5-21. Average waveforms for males possessing the different alleles at SNP rs7055196 for a) the neutral faces and b) the butterflies (all recordings measured at electrode 92, blue A allele, red G allele)

5.4.2.4.2 P1 latency

Mean P1 latencies for each group can be seen in Table 5-21. Latencies did not differ between males possessing the different alleles at SNP rs7055196 ($F_{(1,27)} = 2.333$, $P = 0.138$, 95% CI (-20, 3)). Latencies were longer for butterflies compared to the neutral faces ($F_{(1,27)} = 13.027$, $P = 0.001$, neutral face M 125 SD 14, butterfly M 140 SD 21, 95% CI (-22, -6)), and they were also longer in the left hemisphere compared to the right hemisphere ($F_{(1,27)} = 5.434$, $P = 0.027$, left M 135 SD 18, right M 130 SD 14, 95% CI (1, 11)). There was a significant interaction between the stimulus type and hemisphere ($F_{(1,27)} = 9.277$, $P = 0.005$), with longer latencies for butterflies but not neutral faces in the left compared to the right hemisphere. There were no further significant interactions (EFHC2 variant and stimulus type $F_{(1,27)} = 1.699$, $P = 0.203$, EFHC2 variant and hemisphere $F_{(1,27)} = 0.004$, $P = 0.952$, EFHC2 variant, stimulus type and hemisphere $F_{(1,27)} = 0.449$, $P = 0.509$).

	Left hemisphere		Right hemisphere	
	A allele	G allele	A allele	G allele
Neutral face	123 ± 16	127 ± 16	125 ± 14	127 ± 13
Butterfly	140 ± 31	152 ± 20	126 ± 27	141 ± 19

Table 5-21. Mean P1 latencies (ms) for the neutral faces and butterflies for males possessing the different variants of SNP rs7055196 (mean ± SD)
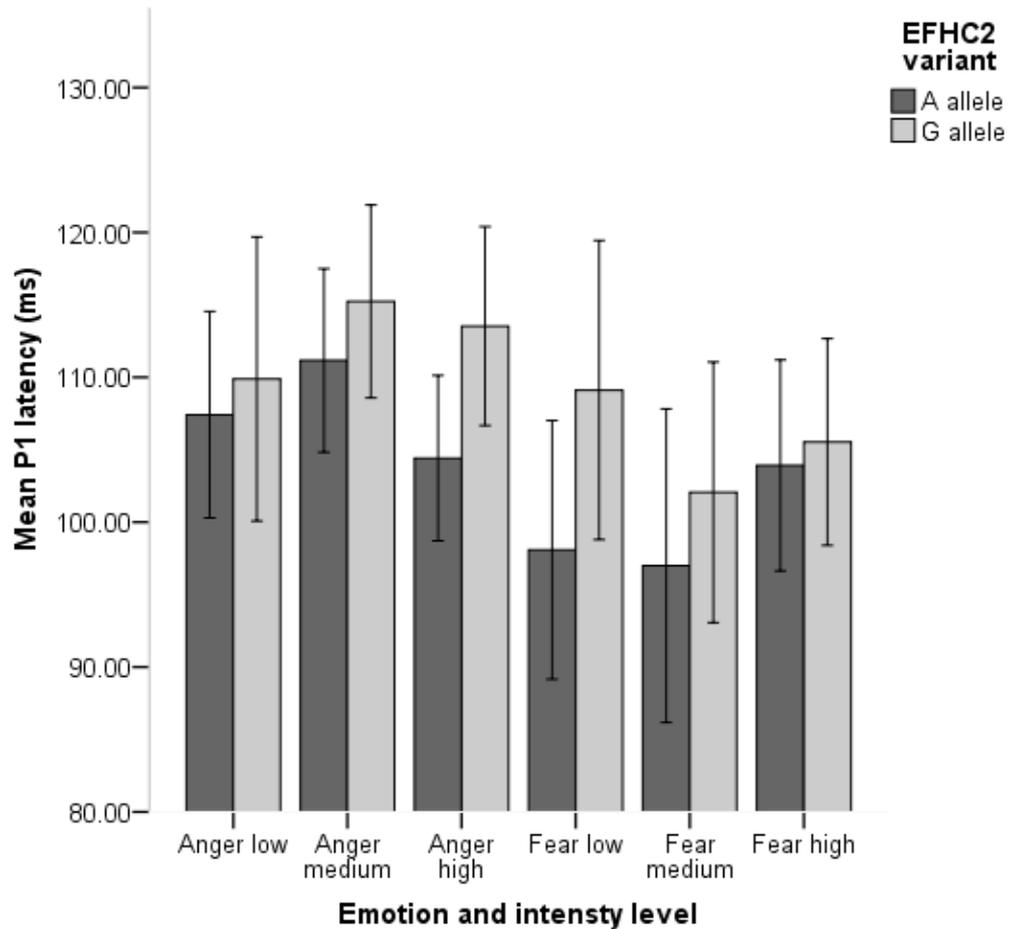
5.4.2.4.3 N170 amplitude

For N170 amplitudes, there were no differences between males possessing the different variants of SNP rs7055196 ($F_{(1,27)} = 0.486$, $P = 0.492$, 95% CI (-1.99, 0.98)). There was a trend towards larger amplitudes for the neutral faces compared to the butterflies ($F_{(1,27)} = 4.182$, $P = 0.051$, neutral faces M -0.39 SD 2.00, butterflies M 0.39 SD 2.37, 95% CI (-1.56, 0.00)). There were no differences in N170 amplitudes between the left and right hemispheres ($F_{(1,27)} = 0.171$, $P = 0.682$, 95% CI (-0.70, 0.47)), and no significant interactions between any of the variables (EFHC2 variant and stimulus type $F_{(1,27)} = 2.745$, $P = 0.109$, EFHC2 variant and hemisphere $F_{(1,27)} = 2.008$, $P = 0.168$, stimulus type and hemisphere $F_{(1,27)} = 2.131$, $P = 0.156$, EFHC2 variant, stimulus type and hemisphere $F_{(1,27)} = 0.003$, $P = 0.959$). Mean N170 amplitudes for the two groups can be found in Table 5-22.

	Left hemisphere		Right hemisphere	
	A allele	G allele	A allele	G allele
Neutral face	-0.65 ± 2.08	0.07 ± 1.78	-1.27 ± 3.05	0.28 ± 1.85
Butterfly	0.42 ± 2.66	-0.10 ± 1.95	0.47 ± 3.50	0.74 ± 2.21

Table 5-22. Mean N170 amplitudes (μV) for the neutral faces and butterflies for males possessing the different variants of SNP rs7055196 (mean ± SD)

5.4.2.4.4 N170 latency

Mean N170 latencies for each group can be found in Table 5-23. There were no differences between males possessing the different alleles at SNP rs7055196 ($F_{(1,27)}$ = 0.406, P = 0.530, 95% CI (-18, 10)). There were also no differences for the neutral faces and the butterflies ($F_{(1,27)}$ = 0.639, P = 0.431, 95% CI (-15, 7)), or between the two hemispheres ($F_{(1,27)}$ = 0.013, P = 0.910, 95% CI (-5, 6)). There were no significant interactions between any of the variables (EFHC2 variant and stimulus type $F_{(1,27)}$ = 0.007, P = 0.935, EFHC2 variant and hemisphere $F_{(1,27)}$ = 0.767, P = 0.389, stimulus type and hemisphere $F_{(1,27)}$ = 1.080, P = 0.308, EFHC2 variant, stimulus type and hemisphere $F_{(1,27)}$ = 0.597, P = 0.447).

	Left hemisphere		Right hemisphere	
	A allele	G allele	A allele	G allele
Neutral face	166 ± 16	170 ± 20	162 ± 16	168 ± 22
Butterfly	170 ± 27	169 ± 32	167 ± 27	175 ± 30

Table 5-23. Mean N170 latencies (ms) for the neutral faces and butterflies for males possessing the different variants of SNP rs7055196 (mean ± SD)

5.5 Discussion

This study investigated electrophysiological responses to emotional and neutral faces in neurotypical males possessing different alleles at SNP rs7055196 within the EFHC2 gene. The amplitudes and latencies of the P1 and N170 components were analysed; both components were easily recognised and occurred at similar latencies to those reported in previous studies.

In Study 5 I compared electrophysiological responses between two groups of males possessing different variants at SNP rs7055196 to angry, fearful and neutral expressions, with either the full face, the eye region alone or faces with the eyes covered being viewed. In Study 6 I compared electrophysiological responses between the groups of males possessing the different variants at SNP rs7055196 to angry and fearful expressions of different intensity levels. Summaries of the results for both studies can be found in Table 5-10 and Table 5-19.

5.5.1 The influence of SNP rs7055196 on electrophysiological responses to faces

In Study 5 there was no main effect of EFHC2 variant on P1 amplitude, although there were trends towards males possessing the A allele showing larger P1 amplitudes than males possessing the G allele for angry full faces and for fearful faces with the eyes covered. In Study 6 males possessing the G allele at SNP rs7055196 showed larger P1 amplitudes than males possessing the A allele. In this study participants viewed a neutral face followed by an emotional face and I investigated electrophysiological changes in response to this change in facial expression. Males possessing the G allele may be more sensitive to changes in visual stimuli than males possessing the A allele, resulting in the larger P1 amplitudes for males possessing the G allele. This difference in effect of SNP rs7055196 on P1 amplitude between the two studies may be due to a difference in the tasks used. However, P1 amplitudes in Study 6 were extremely small, and so caution must be taken when interpreting this group difference in P1 amplitude. There were no differences in P1 latencies between the two groups for either study.

For both Studies 5 and 6 I found males possessing a G allele at SNP rs7055196 showed smaller N170 amplitudes compared to males possessing an A allele. In Study 5 I also found a significant interaction with males possessing the A allele showing a trend towards larger N170 amplitudes for angry faces in the right compared to the left hemisphere. This effect may be due to the higher perceived intensity of the angry expressions compared to the fearful expressions.

I had made specific predictions regarding interaction effects influencing N170 amplitudes in both studies. In Study 5 I predicted that males possessing the G allele would show smaller N170 amplitudes than males possessing the A allele for fearful eyes and for fearful faces with the eyes covered. This prediction was supported by my results. In Study 6 I predicted that the N170 amplitude of males possessing the A allele would be more sensitive to the intensity of the fearful expression than that of males possessing the G allele. This prediction was not supported by my results, and this may be due to the small sample size used.

Males possessing the G allele were also found to show longer N170 latencies than males possessing the A allele in Study 5. Although no main effect for EFHC2 variant was found in Study 6, males possessing the G allele showed longer N170 latencies for high intensity angry expressions in the left hemisphere compared to the N170 latencies of males possessing the A allele. Although no differences in recognition accuracy between the two groups were found in Study 5, my previous results suggest males possessing the G allele show a subtle impairment in fear recognition compared to males possessing the A allele, and this effect may influence emotion processing speed and result in slower processing (and therefore longer N170 latencies) in males possessing the G allele. This effect may have been a general effect in Study 5 due to the explicit recognition of the expressions, whereas it may have been limited to the high intensity angry expressions in Study 6 as there was no explicit emotion recognition in this task and the high intensity angry expressions may have been affected more by emotion processing speed than the other expressions as they were perceived to be more intense than any of the other expressions used.

Several explanations may account for these differences in males possessing the different variants of SNP rs7055196. Firstly, attention levels to the faces may have differed between the groups. However, the lack of a difference in the number of butterflies detected in Study 6 for the two groups suggests similar attention levels between the two groups during this task, and similar fixation patterns to faces in Study 4 would suggest there are unlikely to be differences in the present studies. Secondly, the way that the expressions were perceived between the two groups may differ. However, there were no differences in the perceived intensities of the expressions between the two groups, as there were no differences in intensity ratings between the groups for the expressions used in either study. In addition, although my previous results suggest a possible subtle difference in fear recognition abilities between the two groups, there was no difference between the two groups in recognition accuracy or RT for the different expressions in Study 5 which suggests that differences in ERP waveforms are not due to a difference in the way that the expressions were perceived. A significant difference in the fear recognition abilities of the two groups may have been found in Study 3 but not Study 5 as the results of Study 3 suggest this difference is subtle, and so Study 5 may not have been sensitive enough to detect this difference. Thirdly, there may have been group differences in the mechanism of face processing used. The lack of a behavioural difference between males possessing the different variants of SNP rs7055196 in

Study 5 despite a strong influence of this SNP on N170 amplitude suggests that different neural mechanisms for face processing can result in similar abilities to recognise expressions. Further, the effect size of the influence of this SNP on N170 amplitude is much larger than that found for its influence on fear recognition abilities in Study 3 (section 3.5.2.2). This suggests that a large difference in activation does not necessarily result in a large behavioural effect.

5.5.2 The influence of SNP rs7055196 on face processing style

The N170 has been suggested to reflect a late stage of the structural encoding of faces, specifically global face configuration (Bentin et al 1996, Eimer 2000b, Eimer et al 2011, Luo et al 2010). This suggested association between the N170 and the configural processing of faces is supported by its increased amplitude and latency when face configuration is disrupted (Jacques and Rossion 2010) or when viewing inverted faces compared to upright faces (Ashley et al 2004, Bentin et al 1996, de Haan et al 2002, Eimer et al 2010, Eimer et al 2011, Itier et al 2007a). During this stage of face processing it has been suggested that representations of global face configurations are produced which are then utilised by later processes (Bentin et al 1996, Eimer 1998, Eimer 2000b).

The larger N170 amplitude of males possessing the A allele at SNP rs7055196 found in the current studies may suggest a more configural face processing style in these males compared to those possessing the G allele, supporting a role for SNP rs7055196 in face processing. Further, as this effect was found when participants explicitly identified facial expressions (Study 5) and passively viewed emotional faces (Study 6) this suggests that the effect of this SNP occurs regardless of the attention level to the expression within the face, and it is a general effect when viewing emotional faces. The poorer fear recognition accuracy of males possessing the G allele compared to those possessing the A allele as found in Studies 2 and 3, along with similar gaze fixation patterns between the groups as found in Study 4 also suggest a difference in face processing mechanism between the groups with males possessing the A allele utilising a more holistic / configural mechanism. Itier and Taylor (2002) suggested that the P1 component may reflect holistic processing, while the N170 component reflects configural processing. The greater effect of SNP rs7055196 on N170 amplitude compared to P1 amplitude therefore suggests a greater influence of this SNP on configural face processing than on holistic face processing.

Although these results support an influence of SNP rs7055196 on face processing style they cannot rule out a general influence of this SNP on visual processing. In order to explore this effect further I compared the waveforms produced by males possessing different variants of this SNP in response to the neutral faces and the butterflies in Study 6. I did not find any differences in P1 or N170 amplitudes or latencies between males possessing the different

variants of this SNP, suggesting an influence of this SNP may be limited to emotional faces. This suggests a specific association between this SNP and the processing of emotional faces, and this effect is not due to a general influence of this SNP on visual processing. However, caution should be taken when comparing the ERPs for the neutral faces and butterflies, as participants pressed a button when they saw a butterfly but not when they saw a neutral face. This motor response may influence electrophysiological activity. Further, many more faces were seen than butterflies, resulting in butterflies being an oddball target. Both of these factors may influence the results.

The activity of the N170 has been suggested to originate from the fusiform gyri (Campanella et al 2002, Herrmann et al 2005, Iidaka et al 2006, Luo et al 2010, Petroni et al 2011, Utama et al 2009, Wong et al 2009). This region is activated by faces (Kanwisher et al 1997), and in particular fusiform gyrus activity has been associated with the holistic / configural processing of faces (Liu et al 2010, Maurer et al 2007, Zhang et al 2012). The influence of SNP rs7055196 on N170 amplitude may therefore be due to an influence of this SNP on fusiform gyral activity during emotional face processing, with males possessing the G allele showing lower fusiform gyrus activity compared to males possessing the A allele. As the fusiform gyrus is connected to other regions involved in face processing, including the amygdala and superior temporal sulcus, it is possible that an influence of SNP rs7055196 on fusiform gyral activity may also affect activity in other regions involved in face processing, and the functional connectivity between the fusiform gyrus and these regions. This may also contribute towards the difference in facial fear recognition accuracy between males possessing different variants of SNP rs7055196. Although the present study did not assess activity in the fusiform gyri and other regions involved in face processing during the tasks, this will be important to investigate during further studies.

5.5.3 Additional findings

5.5.3.1 Expression recognition accuracy

During the task in Study 5 participants were most accurate and fastest at recognising neutral expressions compared to fearful or angry expressions. When identifying the expressions within the stimuli participants may have been assessing firstly whether the face was neutral or not, and then for non-neutral faces they may have assessed whether the face was angry or fearful. This would result in faster RTs for neutral faces. In addition, it is plausible that it is easier to determine whether a face is neutral or not than determining the emotion within the face, and this strategy may also account for the faster recognition and higher accuracy for identifying neutral compared to angry or fearful expressions.

In terms of the facial information available, recognition was best and fastest for full faces, and slowest and worst for the eyes alone. These results are similar for those found in Study 2 and those reported by Leppanen et al (2008). The full faces contain the most visual information, followed by the faces with the eyes covered, with the eyes alone showing the least visual information. This difference is likely to account for the recognition pattern observed.

5.5.3.2 The influence of emotion on electrophysiological responses to faces

Results from Study 5 suggest that the expression within the faces did not influence P1 amplitude. However, in Study 6 P1 amplitudes were found to be larger for the angry expressions compared to those for the fearful expressions, although P1 amplitudes in this study were small meaning this difference may not be reliable. This apparent effect may be due to the perceived intensity of the expression; the angry expressions were perceived to be more intense compared to the fearful expressions. This influence may not have been found in Study 5 as the difference in intensity ratings between angry and fearful expressions was larger for Study 6. Alternatively, this effect may be due to the difference in the tasks in the studies; in Study 5 participants were explicitly identifying the expression in the face while in Study 6 participants were passively viewing neutral faces followed by an angry or fearful face. This change in expression may have captured participants attention more for the angry expressions compared to the fearful expressions based on their perceived intensity, therefore resulting in a difference in P1 amplitude for the angry compared to the fearful expressions. In contrast, in Study 5 as participants were attending to the faces in order to identify their expressions this effect may not have occurred. It is also possible that a combination of these explanations may account for these findings; if the angry expressions are perceived to be more intense than the fearful expressions in Study 6 they are likely to be perceived as more different to the neutral expressions than the fearful expressions are. As the P1 component is important during general visual processing its amplitude would be likely to be greater when viewing larger changes in visual stimuli. This greater change from the neutral expressions to the angry expressions compared to that to the fearful expressions may therefore result in a larger P1 amplitude for the angry expressions. Previous studies investigating the influence of expression on P1 amplitude have found mixed results; the results from Study 5 support those studies which did not find a difference in amplitudes between neutral and emotional faces (Fruhholz et al 2011, Leppanen et al 2008, Streit et al 2000), although others have found larger P1 amplitudes for emotional (Batty and Taylor 2003), in particular fearful (Holmes et al 2003, Luo et al 2010, Pourtois et al 2005) faces compared to neutral faces.

In Study 5 no main effect of emotion was found for P1 latency. In Study 6 P1 latencies were found to be longer for the angry expressions compared to the fearful expressions. This effect may be due to the larger amplitudes for the angry expressions compared to the fearful expressions in Study 6, which results in a longer length of time for the amplitude to reach its maximum. Supporting this, larger P1 amplitudes were significantly correlated with longer latencies (Pearson = 0.433, P = 0.001). Previous studies have reported no effect of expression on P1 latency (Batty and Taylor 2003, Leppanen et al 2007a).

Results from Study 5 suggest N170 amplitudes are larger for angry compared to neutral expressions, and amplitudes for both angry and fearful expressions were larger over the right hemisphere compared to the left hemisphere. The angry expressions were rated to be more intense than the fearful expressions, and so an effect of emotion within the face may therefore have been larger for angry expressions than for fearful expressions. If more intense fearful expressions were used then N170 amplitudes for these faces may also be larger than for the neutral faces. In addition, there was a significant interaction between emotion and facial composition, which revealed that when considering full faces alone then larger N170 amplitudes were found for fearful compared to neutral expressions. For Study 6 N170 amplitudes were greater for fearful expressions compared to angry expressions, similar to the results of Study 5 involving only full faces and again despite the lower intensity of the fearful expressions. In both studies the fearful faces may have captured attention more than the angry faces, resulting in the larger amplitudes for the fearful faces. Previous studies have also found greater N170 amplitudes for fearful compared to neutral faces (Leppanen et al 2008, Luo et al 2010, Morel et al 2009) and for angry compared to neutral faces (Rellecke et al 2011, Wronka and Walentowska 2011). However, many other studies have found no influence of emotion in faces on N170 amplitude (Ashley et al 2004, Balconi and Lucchiari 2005, Eimer and Holmes 2002, Eimer et al 2003, Herrmann et al 2002, Holmes et al 2003, Holmes et al 2005, Kiss and Eimer 2008, Leppanen et al 2008, Sprengelmeyer and Jentzsch 2006, Streit et al 2000).

In Study 5 N170 latencies were shorter for neutral expressions compared to either the fearful or angry expressions. This may be in part due to the perceived intensity of the expression, with longer latencies for higher intensities. No differences in N170 latencies were found for the angry and fearful expressions in Study 6; this study used full faces and similarly there was no difference between angry and fearful expressions for the full faces in Study 5. Previous studies reporting on N170 latencies to emotional and neutral faces have been mixed; Batty and Taylor (2003) found both positive and neutral expressions elicited the N170 component earlier than negative expressions which supports the results of Study 5, although Luo et al (2010) suggested both fearful and happy expressions evoke the N170 component earlier than neutral expressions. Many other studies have found no effect of expression on N170 latency (Blau et al 2007, Herrmann et al 2002, Holmes et al 2003, Holmes et al 2005).

5.5.3.3 The influence of facial composition on electrophysiological responses to faces

In Study 5 P1 amplitudes were larger for faces with the eyes covered compared to full faces and the eyes alone. This may be due to faces with the eyes covered needing more processing to classify them as faces. In contrast, O'Connor et al (2007) found that viewing the eye region alone produced larger P1 amplitudes compared to viewing full faces.

In Study 5 P1 latencies were longest for faces with the eyes covered and shortest for the eyes alone. The longer latencies for faces with the eyes covered may be due to it taking a longer length of time to classify faces with the eyes covered as facial stimuli. In contrast, the stimuli in the eyes alone condition contain less visual information than the stimuli in the full faces and faces with the eyes covered conditions, which may mean less processing is necessary, explaining the shorter latencies for the eyes alone condition. Although this result is in contrast to a previous report that P1 latencies are longer when viewing the eye region alone compared to viewing full faces (O'Connor et al 2007), I found longer latencies in response to the eye region alone in angry faces. Again, this may be due to the higher perceived intensity of the angry expressions.

For Study 5 N170 amplitudes were largest for the faces with the eyes covered condition, which may suggest that it is more cognitively demanding to process faces with the eyes covered compared to full faces or the eye region alone, for example if they were not so easily classified as faces. However, this result does not support that which has previously been reported. Leppanen et al (2008) reported that N170 amplitudes were greater when the eyes were present in faces compared to when they were covered, while Eimer (1998) found no difference in amplitudes for viewing faces with the eyes covered and full faces. Others have reported larger N170 amplitudes when viewing the eye region alone compared to viewing full faces (Bentin et al 1996, Eimer et al 2010, Eimer et al 2011).

In Study 5 N170 latency was longer for the eyes alone compared to full faces either with the eyes present or covered. This effect may be related to the recent proposal that the N170 is produced due to the activation of face sensitive and eye sensitive neurons (Eimer et al 2010, Itier et al 2007a, Jacques and Rossion 2010). Viewing the eye region alone activates both of these populations, whereas the eye sensitive neurons are inhibited when viewing full faces and would not be activated when viewing faces with the eyes covered. This therefore means that a greater number of neurons would be activated for the eyes alone, which may increase the latency to the peak of the N170 in this condition. Alternatively, activity in the eye sensitive neurons may be delayed compared to that in the face sensitive neurons, which may result in a longer latency for viewing the eyes alone. I did not find any differences in latencies for full faces and faces with the eyes covered which is in contrast to the results reported by Eimer (1998), who found longer latencies for faces without eyes. This difference

in results may be due to a difference in the images used; in the current study the eyes were covered in sunglasses, whereas in the Eimer study the eyes were blanked out. The faces in the current study may therefore have looked more natural than the faces in the Eimer study, explaining the difference in results.

5.5.3.4 The influence of expression intensity on electrophysiological responses to faces

In Study 6 P1 amplitudes were smallest for the low intensity faces. Although P1 amplitudes in Study 6 were small and so must be interpreted with caution, this apparent effect is likely to be due to an effect of the perceived intensity as low intensity faces were perceived to be less intense than the other intensities. Utama et al (2009) also found that P1 amplitude increases as the intensity of expressions increases, although others have found no influence of expression intensity on P1 amplitude (Leppanen et al 2007a, Sprengelmeyer and Jentzsch 2006). This difference may be due to a difference in the tasks used. Both Study 6 and Utama et al's study involved viewing neutral faces which were followed by an emotional face. The change in appearance of the stimulus would be greater for high intensity faces compared to low intensity faces, and due to the importance of P1 in visual processing it would be likely to have a greater amplitude for stimuli with a greater change. In contrast the studies of Leppanen et al and Sprengelmeyer and Jentzsch did not involve a change in stimuli, which may explain the lack of an influence of intensity of expressions. This effect found in the current study therefore may not be due to the intensity of the expression per se, which may be processed during a later stage of face processing, but instead may be due to the change in stimulus appearance.

In Study 6 results suggested there was no effect of expression intensity on P1 latency. A similar result has been reported previously (Leppanen et al 2007a).

For Study 6 then N170 amplitudes increased as the intensity of the expressions increased. This effect has been reported previously (Sprengelmeyer and Jentzsch 2006, Utama et al 2009), although another study found no effect of intensity (Leppanen et al 2007a).

In Study 6 there was no effect of intensity on N170 latency. Although a previous study has reported latencies to increase as the intensity of fearful expressions increases (Leppanen et al 2007a), this study compared caricatured (150% intensity) compared to prototypical expressions (100%) whereas the current study used expressions containing less than 100% fear. This difference may explain the discrepancy in results.

5.5.3.5 The influence of hemisphere on electrophysiological responses to faces

The results suggest there were no differences in P1 amplitude or latency between the two hemispheres in either Study 5 or 6, although in Study 6 P1 amplitudes were smaller in the right hemisphere for fearful faces but not angry faces. This is in contrast to previous reports of larger P1 amplitudes in the right hemisphere in response to emotional faces (Batty and Taylor 2003, Utama et al 2009). As the P1 amplitudes in Study 6 were small and so any differences between amplitudes in the left and right hemispheres were small, this may help to explain this discrepancy in findings. In Study 5 N170 amplitude was larger in the right compared to the left hemisphere, and this same effect almost reached significance in Study 6. Many previous studies have also found N170 amplitudes to be larger in the right compared to the left hemisphere (Balconi and Lucchiari 2005, Bentin et al 1996, Blau et al 2007, Eimer et al 2010, Leppanen et al 2008, Sprengelmeyer and Jentzsch 2006). In Study 5 there were no differences in N170 latency between the hemispheres, although in Study 6 latencies were shorter in the left compared to the right hemisphere. These results are in contrast to those previously reported, as the majority of studies have reported shorter latencies over the right hemisphere (Balconi and Lucchiari 2005, Bentin et al 1996, Blau et al 2007, Eimer et al 2010, Leppanen et al 2008, Sprengelmeyer and Jentzsch 2006).

5.5.4 ERPs for faces in individuals with an ASD

The results of studies investigating P1 amplitude and latency in individuals with an ASD and neurotypical individuals are varied; while several studies have found no differences between the groups (Akechi et al 2010, O'Connor et al 2007, Wong et al 2008) others have reported smaller amplitudes (Batty et al 2011) and longer latencies (Batty et al 2011, O'Connor et al 2005) in individuals with an ASD. This variation in results means it is difficult to compare these results with those found in the present study.

Although one study has reported smaller N170 amplitudes in individuals with an ASD compared to neurotypical individuals for both neutral and emotional faces (O'Connor et al 2005), most studies have found no difference in N170 amplitudes between the groups (Batty et al 2011, Hileman et al 2011, McPartland et al 2004, O'Connor et al 2007, Webb et al 2006, Wong et al 2008). Instead, many studies have reported longer N170 latencies for individuals with an ASD compared to neurotypical individuals (Batty et al 2011, Hileman et al 2011, McPartland et al 2004, O'Connor et al 2005, O'Connor et al 2007), although others have found no difference between the groups (Akechi et al 2010, Churches et al 2010, Wong et al 2008). My results suggest that SNP rs7055196 influences N170 amplitude and possibly latency, with males possessing the G allele showing smaller N170 amplitudes and

possible longer latencies compared to males possessing the A allele. This suggests that the influence of SNP rs7055196 on N170 is different to and may be much larger than the difference found when comparing ASD and neurotypical individuals.

5.6 Summary

When we view faces distinct ERP waveforms are produced, with the different components representing different stages in the processing of faces. The P1 component reflects general visual processing and the holistic processing of faces, while the N170 component, which may be thought to be face selective, reflects the structural encoding of faces and their holistic / configural processing. Differences in the amplitudes and latencies of these components between different populations may suggest possible differences in face processing styles. Previous results within this thesis suggest that variation at SNP rs7055196 within the EFHC2 gene may influence face processing in neurotypical males, and to further investigate this I investigated a possible influence of this SNP on electrophysiological responses to faces in males possessing the different variants of this SNP. I found that males possessing the A allele showed larger N170 amplitudes to faces than males possessing the G allele, which may suggest a more holistic / configural based face processing style in the males possessing the A allele. This more holistic / configural face processing mechanism may help to explain my previous finding that males possessing the A allele show better fear recognition accuracy than males possessing the G allele. My results suggest this difference in processing style is limited to the processing of emotional faces, and it is not likely to be due to a more general influence of SNP rs7055196 on visual processing, a difference in attention levels or a difference in the perceived intensity of the emotion within the faces. The effect size for the influence of SNP rs7055196 on N170 amplitude is much larger than that found for fear recognition.

6 Investigating theory of mind abilities and its neural correlates

6.1 Introduction

Previous results in this thesis have suggested an influence of SNP rs7055196 within the EFHC2 gene on facial fear recognition and electrophysiological responses to emotional faces in males. These abilities and responses are important for social cognition. I next explored additional influences of this SNP on another aspect of social cognition, specifically theory of mind abilities and their related neural activity. This allowed me to determine whether an influenced of this SNP was limited to emotional face processing or if it had a wider influence on social cognition. I compared the performance of males possessing the different alleles at SNP rs7055196 on two different theory of mind tasks, the Eyes task and the Triangles task, and also compared activity between the two groups during the Eyes task.

Theory of mind refers to our ability to understand the feelings, thoughts, intentions, desires and beliefs of others, allowing us to predict how they may act (Premack and Woodruff 1978). This ability may be thought of as one of the fundamental impairments in individuals with an autism spectrum disorder (ASD), with children with an ASD failing simple false belief tasks which younger neurotypical children pass (Baron-Cohen et al 1985). A number of more advanced theory of mind tasks have since been developed, which are not thought to be limited by ceiling effects when neurotypical adults are tested, allowing these tasks to be used in the general population. Two such tasks are the Reading the Mind in the Eyes task and the Frith-Happé Animated Triangles task.

6.1.1 Reading the Mind in the Eyes task

The Reading the Mind in the Eyes task (Eyes task) was developed by Baron-Cohen et al (1997), and a revised version of the task was produced several years later (Baron-Cohen et al 2001c). This task requires participants to infer mental states of others based on photographs of the eye region, with participants having a choice of 4 possible mental states to select from in the revised version. Both individuals with an ASD (Baron-Cohen et al 2001c, Kaland et al 2008, Kirchner et al 2011, Losh et al 2009) and women with Turner Syndrome (TS, X-monosomy) (Lawrence et al 2003b) show a less accurate performance on this task compared to neurotypical individuals, correctly identifying fewer mental states. A

subtle impairment in performance during the Eyes task has also been reported in a subset of ASD parents, specifically those who lie along the broad autism phenotype (BAP) (Losh et al 2009), compared to controls. This supports the suggestion that the Eyes task may be used to investigate theory of mind abilities in neurotypical adults (Baron-Cohen et al 2001c).

Identifying the mental states portrayed by the images of the eyes has been associated with neural activity in regions of the social brain including the medial prefrontal cortex, superior, middle and inferior frontal gyri in the frontal lobe, and the superior temporal sulcus and gyrus, middle temporal gyrus, temporal poles and temporoparietal junction in the temporal lobe (Adams et al 2009, Baron-Cohen et al 1999b, Baron-Cohen et al 2006, Castelli et al 2010, Focquaert et al 2010, Moor et al 2012, Platek et al 2004, Russell et al 2000). ASD adults have been reported to show increased activity in the bilateral superior temporal gyrus and reduced activity in the left inferior frontal gyrus, left amygdala and right insula during this task compared to neurotypical adults (Baron-Cohen et al 1999b). In addition, the parents of children with an ASD have been suggested to show decreased activation in the bilateral inferior frontal gyrus and left middle temporal gyrus compared to controls (Baron-Cohen et al 2006).

6.1.2 The Frith-Happé Animated Triangles task

The Frith-Happé Animated Triangles task consists of a series of videos which show two triangles interacting with each other (Abell et al 2000). There are three types of interaction within the task: random interactions (during which the triangles do not appear to be interacting with each other, e.g. bouncing off the walls), physical interactions (consisting of the triangles appearing to move in order to achieve a goal, e.g. following), and mental interactions (in which the triangles may be thought to possess mental states, e.g. mocking). Participants may be asked to describe the triangles' movements, classify the type of interaction (i.e. none, physical or mental), or identify the mental states of the triangles during the mental state interactions. While neurotypical individuals are highly accurate at inferring mental states from the animations (Abell et al 2000, Castelli et al 2000, Castelli et al 2002), individuals with an ASD (Abell et al 2000, Castelli et al 2002, Salter et al 2008, White et al 2011) and women with TS (Lawrence et al 2007) are less accurate at describing the mental interactions, categorising the interactions and identifying the mental states. Further, a subset of males identified by Corden et al (2006) who showed poor facial fear recognition abilities were also less accurate at attributing mental states to the interactions compared to males who did not show impaired fear recognition.

6.1.3 Aim and hypotheses

The aim of these studies was to investigate theory of mind abilities and associated neural activation between males possessing the G and A alleles at SNP rs7055196. As facial emotion recognition abilities may be related to theory of mind abilities and this SNP was associated with fear recognition accuracy, I also investigated a possible influence of this SNP on theory of mind abilities.

I first predicted that males possessing the G allele would show poorer theory of mind abilities compared to males possessing the A allele, as demonstrated by males possessing the G allele correctly identifying fewer mental states during the Eyes task (Study 7). Following this, I predicted that during the Eyes task males possessing the G allele would show reduced neural activity compared to males possessing the A allele in some of the regions previously reported to be activated during this task (including the medial prefrontal cortex, superior, middle and inferior frontal gyri, superior temporal sulcus and gyrus, middle temporal gyrus, temporal poles and temporoparietal junction) (Study 8). I predicted males possessing the G allele would show reduced activity during this task as previous studies investigating neural activity in the Eyes task have found lower activity in groups who score lower on this task. I also predicted that males possessing the G allele would perform less accurately in the Triangles task, correctly classifying fewer interactions and identifying fewer mental states (Study 9).

6.2 Participant information

Participants for Study 7 were the same as those tested in Studies 1-3 (A allele n = 45, G allele n = 46, see section 3.2 for further information). Participants for Study 9 were the same as those tested in Studies 5 and 6 (A allele n = 12, G allele n = 17, see section 5.2 for further information).

For Study 8 a total of 16 participants were tested; 7 who possessed the A allele at SNP rs7055196 and 9 who possessed the G allele.

6.2.1 Age, handedness and ethnicity

Information regarding the age and ethnicity of participants in Study 8 can be seen below in Table 6-1. All participants were right handed. There was no difference in age between the two groups when compared using an independent samples t-test (t (14) = -0.389, P = 0.703, 95% CI (-1.96, 1.36)). In addition, there were no differences in ethnicity between the two groups.

	A allele	G allele
Number	7	9
Mean age	21.14 ± 1.77 (20-25)	21.44 ± 1.33 (20-23)
Ethnicity	7 Caucasian	9 Caucasian

Table 6-1. Information regarding the age (mean ± SD (range)) and ethnicity of participants tested in each group during Study 8

6.2.2 IQ

Information regarding the IQ of participants in Study 8 can be seen below in Table 6-2. There were no differences in full scale IQ between the groups ($t_{(14)} = 0.406$, $P = 0.691$, 95% CI (-5.85, 8.58)). Further, neither verbal IQ nor performance IQ differed between the two groups ($t_{(14)} = 0.067$, $P = 0.948$, 95% CI (-9.36, 9.97) and $t_{(14)} = 0.467$, $P = 0.648$, 95% CI (-6.96, 10.84) respectively).

	A allele	G allele
Full scale IQ	125.14 ± 5.98	123.78 ± 7.16
Verbal IQ	125.86 ± 9.92	125.56 ± 8.13
Performance IQ	118.71 ± 8.14	116.78 ± 8.30

Table 6-2. Full scale, verbal and performance IQs of each group during Study 8 (mean ± SD)

6.3 Study 7: the Reading the Mind in the Eyes task

6.3.1 Method

During this study participants were administered the Reading the Mind in the Eyes task (Eyes task) (Baron-Cohen et al 2001c). In this task participants are shown a series of 36 halftone photographic images of the eye region, and asked to select which label from four they think best represents how the person was feeling (Figure 6-1).

Participants were given a list of the words used in the task along with their definitions, and they were instructed to look up the meanings of any words they were unfamiliar with. This task was administered on paper, with participants indicating their choice for the mental state of each image on the response sheet by circling it, underlining it or indicating it in some other way. In total this task consists of 36 images, with an additional image being used as a practice image at the start of the task. Responses to this practice image were not analysed, and no feedback was given for any images.

Figure 6-1. Example of an image from the Eyes task; possible answers are contemplative, flustered, encouraging, amused (correct answer contemplative) (image from Baron-Cohen et al (2001c))

6.3.1.1 Analysis

The number of correctly identified mental states was calculated (score out of 36) for each participant. These values were then compared across the G and A allele groups using an independent samples t-test.

6.3.2 Results

The mean numbers of correctly identified mental states during the Eyes task for each group can be seen in Table 6-3 and Figure 6-2. These values were compared across groups using an independent samples t-test. Males possessing the A allele at SNP rs7055196 correctly identified more mental states than males possessing the G allele (t (89) = 2.036, P = 0.045, 95% CI (0.03, 2.40)), with an effect size equal to 0.211[7]. Neither age (F (1,88) = 0.063, P =

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[7] Effect size = $\sqrt{\dfrac{t^2}{t^2 + df}}$

0.803) nor full scale IQ (F (1,88) = 0.647, P = 0.423) significantly affected the results when included as covariates.

	A allele	G allele
Eyes task score	28.80 ± 2.63	27.59 ± 3.03

Table 6-3. Mean numbers of mental states correctly identified during the Eyes task for males possessing the A and G alleles at SNP rs7055196 (mean ± SD, maximum score 36)
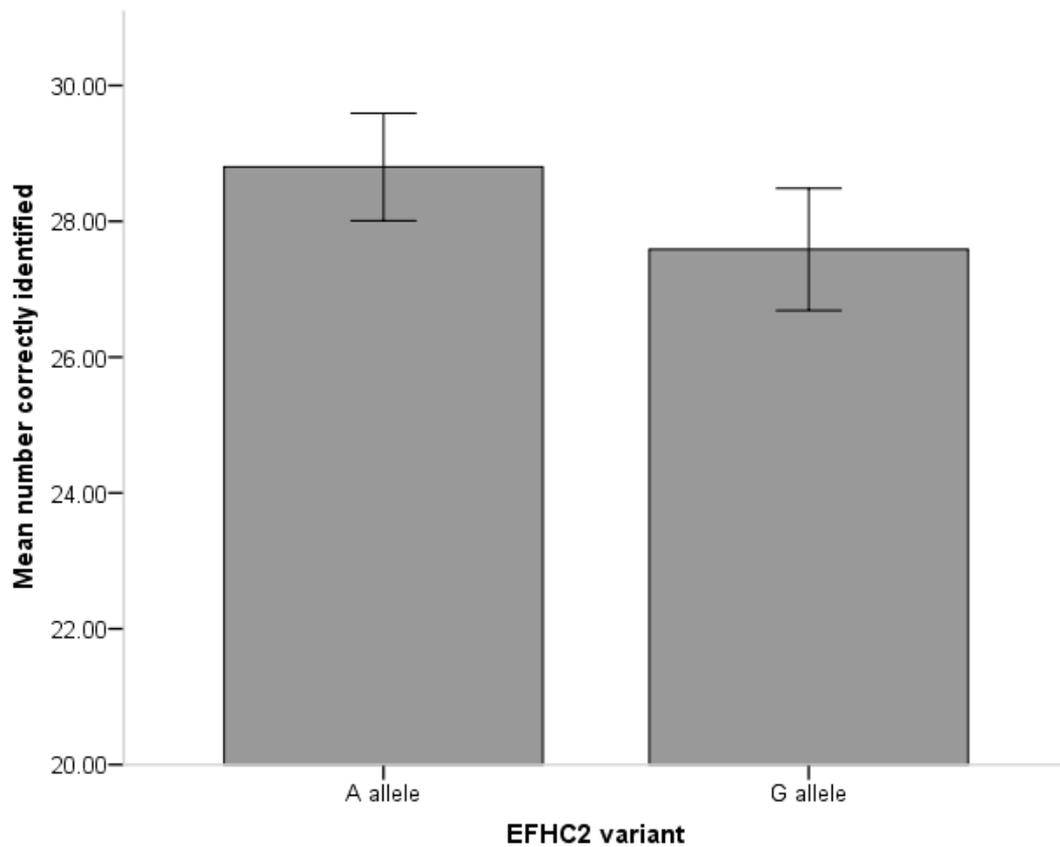
Figure 6-2. Mean numbers of correctly identified mental states during the Eyes task for males possessing the A and G alleles at SNP rs7055196 (error bars represent 95% CI)

6.4 Study 8: neural activations during the Reading the Mind in the Eyes task

6.4.1 Method

6.4.1.1 Task

The task used was a modified version of the Eyes task (Baron-Cohen et al 2001c). During this modified version, which is computer administered, participants are asked to identify either what the person in the image is thinking or feeling ('mind task'), or their age range ('age task'). The age ranges used were based on a pilot study in which participants guessed the age of the individuals in the photographs, with the age range most commonly selected by participants in the pilot study being assigned to the correct answer. Similar to the original version, this modified version also uses a forced choice paradigm, with four possible answers for both the mind and age tasks. The list of possible answers was shown on the screen along with each image during each task. Participants were asked to select either how the person feels or their age range by pressing the corresponding key. The task was written using the Cogent 2000 toolbox for Matlab (The Mathworks, Inc., Natick, MA). Cogent 2000 was developed by the Cogent 2000 team at the FIL and the ICN, and Cogent Graphics was developed by John Romaya at the LON at the Wellcome Department of Imaging Neuroscience.

At the start of the study, participants were asked to look through the list of possible mental states used in the task to ensure they understood all the words; for any unfamiliar words the participant was asked to read the word definition. Before entering the scanner participants practised the task. This practice session consisted of a block of 3 images in the mind task followed by a block of 3 images in the age task. Participants were instructed to press the corresponding key for what they thought was the correct answer for each image. None of the images used in the practice block were used in the test block, and none of the responses given in the practice block were analysed. No feedback was given for any images.

While in the scanner participants saw 60 images one at a time, 30 for the mind task and 30 for the age task. These images were further split into two levels of difficulty, easy and hard. This gave 4 categories, each containing 15 images (i.e. easy mind, hard mind, easy age and hard age). The incorrect possible answers for images in the easy mind group were the same as those in the original Eyes task, whereas the incorrect possible answers for images in the hard mind group were chosen to have more similar meanings to that of the correct answer.

Similarly, for the age task, the incorrect age ranges for the hard age group were more similar to that of the correct answer than those for the easy age group. Images in the easy mind group were also shown in the hard age group, while images in the hard mind group were also shown in the easy age group. In this way each of the 30 images was seen twice, once in the mind task and once in the age task. The set of images shown in the easy mind and hard age groups or the hard mind and easy age groups was counterbalanced between participants. Images were shown in blocks of three, with images in each block being of the same category, and blocks alternated between the mind task and the age task. Images within each category were displayed in a random order. The order of block presentation was weighted so that blocks for the easy mind and age tasks were presented more at the start of the task, and blocks for the hard mind and age tasks were presented more at the end of the task.

Prior to each block of 3 stimuli then an instruction screen was shown for 3 seconds to inform participants whether the next block would be for the mind task or the age task. Prior to the presentation of each image or the instruction screen, a fixation cross in the centre of the screen was displayed for a random length of time between 0.5 and 4.5 seconds. Images were shown in the centre of the screen for 7 seconds, and only responses made within the first 6 seconds were recorded. The response key pressed for each image was recorded, along with the RT (in ms); responses were entered through the use of a box containing four buttons using the participants' right hand. In total, this task lasted for approximately 12 minutes.

6.4.1.1.1 Analysis

Results from the easy and hard tasks were grouped together for analysis. The total number of mental states and age ranges correctly identified by each participant were calculated, along with their mean RTs. Only responses and RTs made within the 7 seconds the images were displayed on the screen were included in the analysis. Results were compared between participants possessing the A and G alleles using 2 (group) × 2 (task) repeated measures ANOVAs.

6.4.1.2 Acquisition and processing of neural activity using fMRI

6.4.1.2.1 Acquisition

Echo-planar images (EPIs) were acquired using a Siemens Avanto 1.5T MRI machine (Erlangen, Germany) with a 32 channel head coil. Head movements were reduced through

the use of cushions within the head coil. A T1 weighted anatomical sagittal image was first obtained (176 slices, slice thickness = 1.0mm, TR = 20ms, TE = 4.76ms, flip angle = 20°, field of view = 260mm, voxel size = 1.0×1.0×1.0mm, in-plane resolution = 256).

For the functional scan during the modified Eyes Task, we acquired continuous T2 weighted blood oxygenation level dependant (BOLD) EPIs, consisting of 300 volumes (TR = 2376ms, TE = 30ms, flip angle = 90°, field of view = 210mm, voxel size = 3.3×3.3×3.0mm, in-plane resolution = 64, rotation = 0°), with each volume comprised of 33 consecutive transversal slices (slice thickness = 3.0 mm, gap = 1.0mm). Slices were acquired across the whole brain. The task started on the acquisition of the third volume; this allowed us to discard the first two volumes to ensure that the magnet had reached equilibrium.

6.4.1.2.2 Pre-processing

Pre-processing of functional scans was performed using the statistical parametric mapping package SPM8 (Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (The Mathworks, Inc., Natick, MA).

Scans were first realigned to the first volume to minimise artefacts due to head movement, and motion correction for each participant checked to ensure it was less than 2mm in each direction. The T1 weighted anatomical image was then co-registered to the mean realigned functional image. Functional images were next spatially normalised to the participants' co-registered anatomical scan using a voxel size of 3×3×3mm, and then spatially smoothed using an 8mm full width at half maximum isotopic Gaussian kernel to compensate for anatomical variability between subjects.

6.4.1.2.3 Analysis

Analysis of functional scans was performed using SPM8 (Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (The Mathworks, Inc., Natick, MA).

For the first level model, for each participant statistical parametric maps were created and estimated using a general linear model (Friston et al 1995). Twelve boxcar regressors were modelled, representing the four categories of stimuli (i.e. easy mind, hard mind, easy age, hard age), along with hits and misses for each category. Regressors for the four categories were modelled during the blocks of three stimuli for each type, while those for the hits and misses were modelled during stimuli presentation (i.e. over 7 seconds). Errors were not modelled out. Realignment parameters were included in the models to reduce motion effects. A high pass filter with a cut-off of 150s was used, with a canonical haemodynamic

response function with time and dispersion derivatives. A high pass filter with a cut-off of 150s was used rather than the standard 128s as the four block types rotated on average every 126s, meaning that the standard filter of 128s was too low.

Specific effects were then modelled using linear contrasts to compare parameter estimates for each participant between the mind and age tasks; as with the behavioural responses, results for the easy and hard tasks were combined to improve power to find group differences. Contrast images from each participant were entered in to second level random effects analyses to compare models for the mind task and the age task. This was done firstly across all participants, using pairwise contrasts between the mind and age tasks to investigate a main effect of task ($P = 0.001$ uncorrected). No clusters survived family wise-error (FWE) whole brain correction ($P = 0.05$). Secondly, contrasts for each participant were compared between males possessing the different variants of SNP rs7055196; pairwise contrasts between the two tasks were performed for each participant, and these were then entered into a subsequent contrast to compare males possessing the A allele and those possessing the G allele to investigate an effect of genotype ($P = 0.001$ uncorrected). No clusters survived FWE whole brain correction ($P = 0.05$).

6.4.2 Results

6.4.2.1 Task performance

The mean numbers of mental states and age ranges correctly identified for the two groups possessing the different alleles at SNP rs7055196 during the modified Eyes task can be seen in Table 6-4 and Figure 6-3. These results were analysed using a 2 (group) × 2 (task) repeated measures ANOVA. Although males possessing the A allele had higher mean scores for both the mind and age tasks compared to males possessing the G allele, this difference was not significant ($F_{(1,14)} = 0.222$, $P = 0.645$, 95% CI (-3.24, 5.07)). Across both groups participants performed better on the mind task compared to the age task ($F_{(1,14)} = 32.872$, $P < 0.0005$, 95% CI (3.59, 7.89), mind task M 16.77 SD 4.72, age task M 11.03 SD 3.97). Finally, although the between group difference was greater for the mind task compared to the age task, there was no significant interaction between EFHC2 variant and task ($F_{(1,14)} = 0.164$, $P = 0.692$). Neither age ($F_{(1,13)} = 0.007$, $P = 0.936$) nor full scale IQ ($F_{(1,13)} = 1.976$, $P = 0.183$) were significant covariates when included in the analysis.

	A allele	G allele
Mind task	17.43 ± 4.04	16.11 ± 5.11
Age task	11.29 ± 2.98	10.78 ± 4.52

Table 6-4. Mean scores for the numbers of mental states correctly identified in the mind task and the numbers of age ranges correctly identified in the age task during the modified Eyes task for males possessing the A and G alleles at SNP rs7055196 (mean ± SD, maximum score for each task 30)
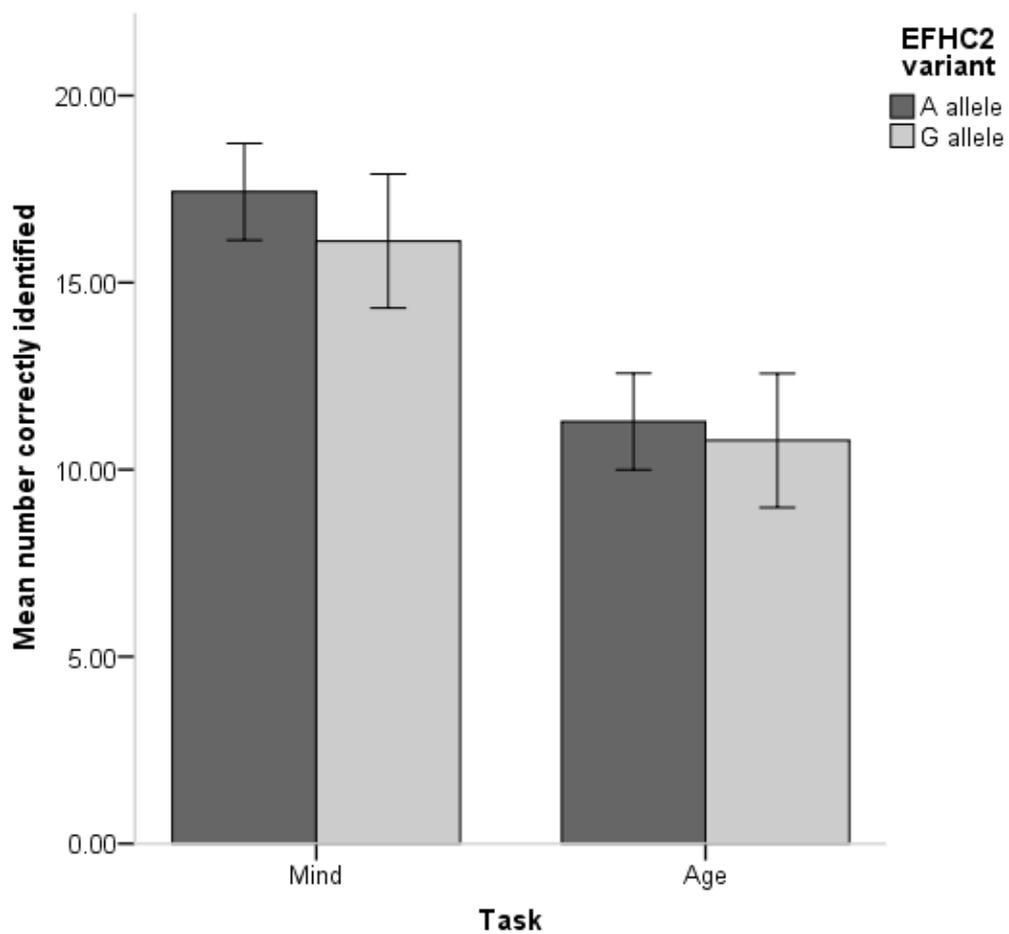
Figure 6-3. Mean numbers of correctly identified mental states and age ranges during the modified Eyes task for males possessing the A and G alleles at SNP rs7055196 (error bars represent 95% CI)

6.4.2.2 Response time

The mean RTs for participants possessing the different variants of SNP rs7055196 during the modified Eyes task can be seen in Table 6-5 and Figure 6-4. RTs were compared using a 2 (group) × 2 (task) repeated measures ANOVA. There were no differences in RTs between males possessing the different variants at SNP rs7055196 ($F_{(1,14)} = 1.635$, $P = 0.222$, 95% CI (-905, 229)), although faster responses were made for the age task compared to the mind task ($F_{(1,14)} = 22.821$, $P < 0.0005$, 95% CI (176, 464), mind task M 4414 SD 550, age task M 4094 SD 541). There was no significant interaction between EFHC2 variant and task ($F_{(1,14)} = 0.420$, $P = 0.527$). Neither age ($F_{(1,13)} = 1.519$, $P = 0.240$) nor full scale IQ ($F_{(1,13)} = 0.135$, $P = 0.719$) were significant when included as covariates in the analysis.

	A allele	G allele
Mind task	4267 ± 614	4561 ± 488
Age task	3903 ± 594	4285 ± 490

Table 6-5. Mean RTs (ms) for the mind and age tasks during the modified Eyes task for males possessing the A and G alleles at SNP rs7055196 (mean ± SD)

6.4.2.3 Neural activations

Comparisons of neural activity across the mind and age tasks can be seen in Table 6-6 and Figure 6-5. Greater activity was produced in the left inferior frontal gyrus, the left precentral gyrus, the left middle temporal gyrus, the right lentiform nucleus, and the left culmen during the mind task compared to the age task.

Males possessing the A allele at SNP rs7055196 activated three regions more than males possessing the G allele during the mind task compared to age task contrast (i.e. activity due to identifying the mental state of the person in the image and not due to low level visual features): the right superior temporal gyrus, the left inferior parietal lobule and the left cingulate gyrus. These results are shown in Table 6-6 and Figure 6-6.
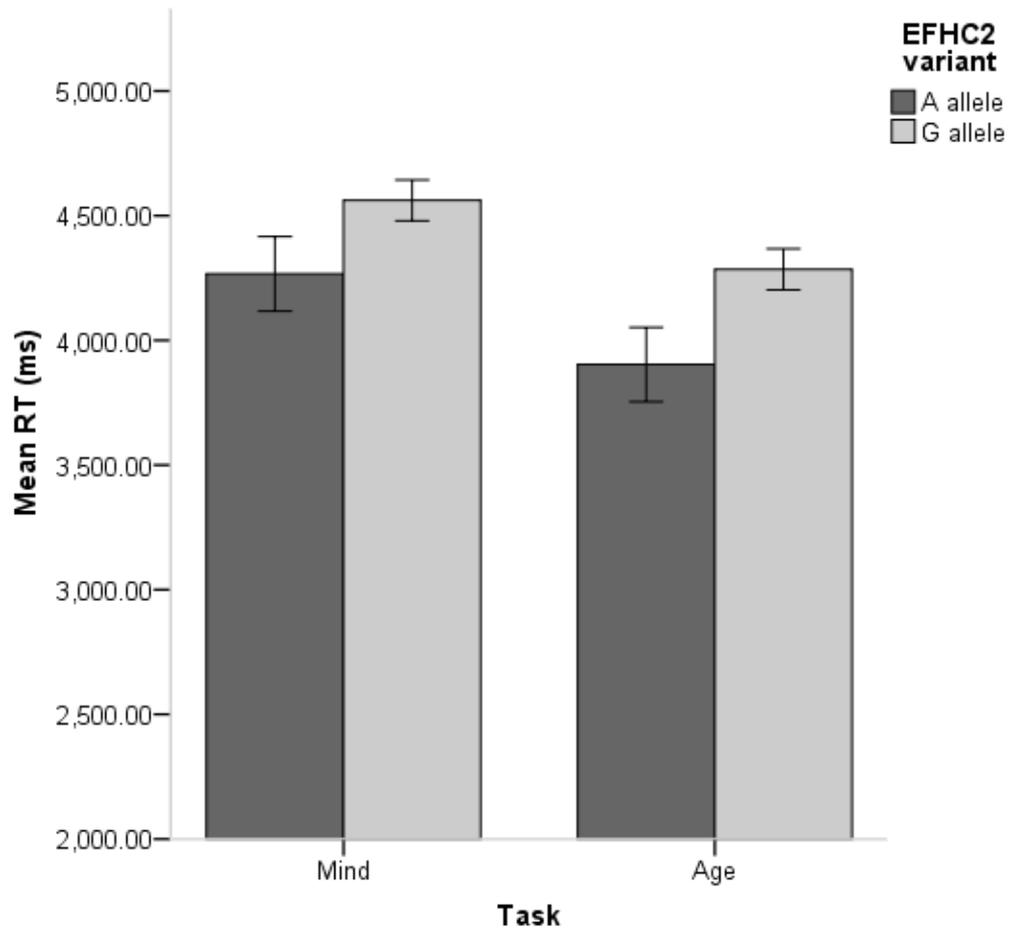
Figure 6-4. Mean RTs (ms) during the mind and age tasks of the modified Eyes task for males possessing the A and G alleles at SNP rs7055196 (error bars represent 95% CI)

Region	Side	BA	Cluster size	MNI coordinates			Z score	P value
				x	y	z		
Mind vs age task								
Inferior frontal gyrus	L	47	14	-51	17	-5	3.34	< 0.0005
Precentral gyrus	L	6	6	-33	-13	37	3.52	< 0.0005
Middle temporal gyrus	L	21	1	-60	-37	-5	3.12	0.001
Lentiform nucleus	R	N/A	2	30	2	-2	3.28	0.001
Culmen (cerebellum)	L	N/A	2	-42	-46	-26	3.30	< 0.0005
A allele vs G allele								
Superior temporal gyrus	R	22	1	39	-49	19	3.22	0.001
Inferior parietal lobule	L	40	1	-36	-25	28	3.16	0.001
Cingulate gyrus	L	31	1	-9	-34	31	3.21	0.001
Cingulate gyrus	L	31	1	-12	-31	34	3.13	0.001

Table 6-6. Brain regions showing differences in neural activity for the mind compared to the age task across groups and between groups of males possessing the different variants at SNP rs7055196 (P < 0.001 uncorrected)
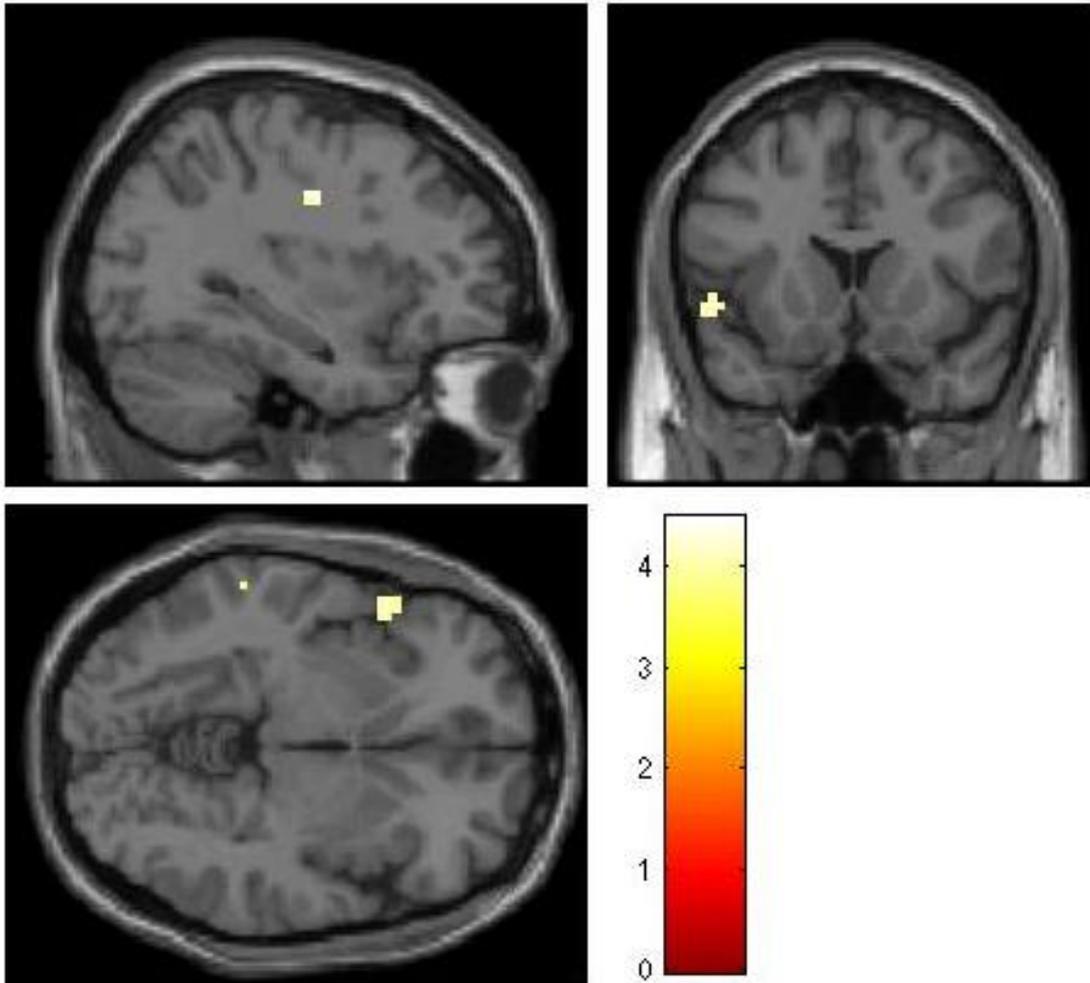
Figure 6-5. Activation map showing regions producing higher neural activity during the mind compared to the age task across both groups (P < 0.001 uncorrected)
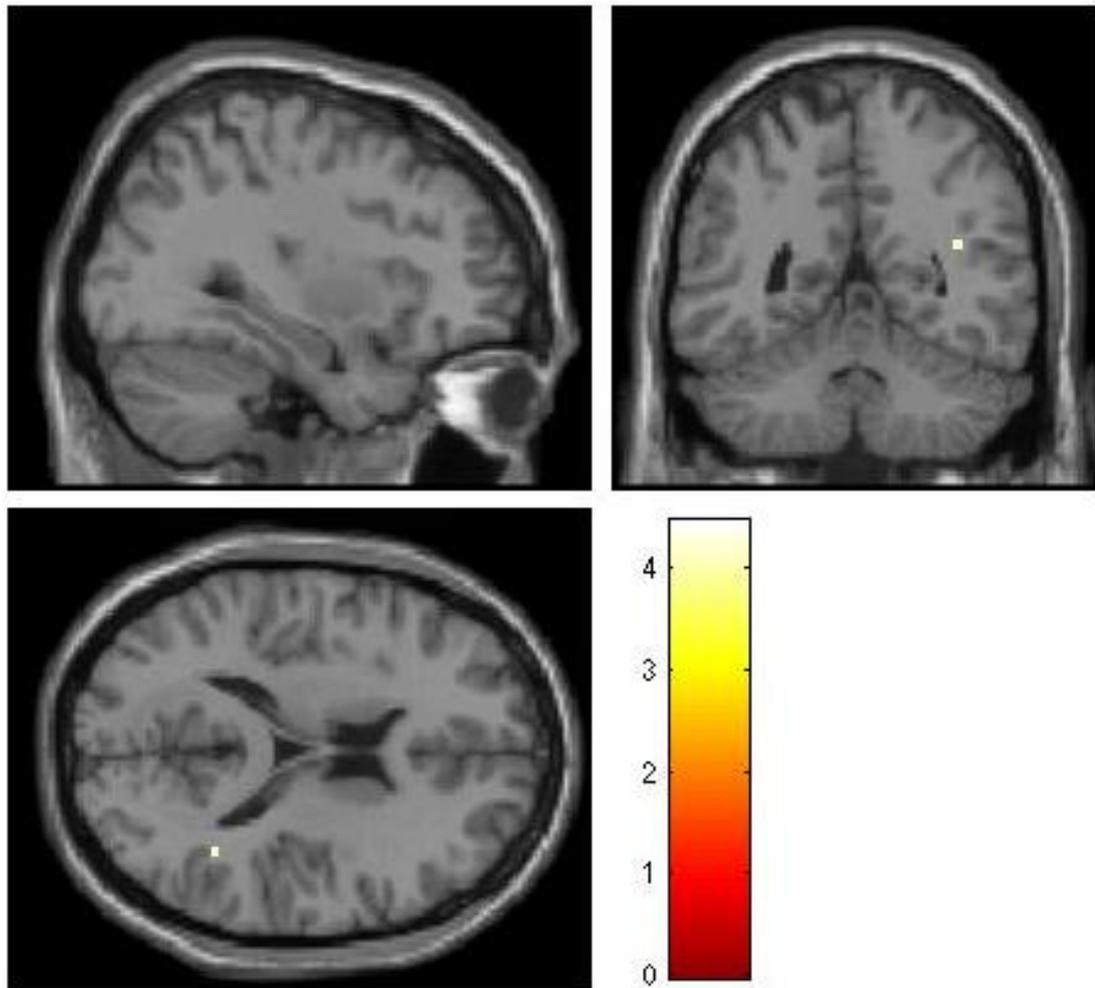
Figure 6-6. Activation map showing higher activity in the superior temporal gyrus in males possessing the A allele compared to males possessing the G allele for the mind task compared to the age task (P < 0.001 uncorrected)

6.5 Study 9: the Frith-Happé Animated Triangles task

6.5.1 Method

Participants were administered the Frith-Happé Animated Triangles task (Abell et al 2000, Castelli et al 2000, Castelli et al 2002). This task consists of a series of 12 silent short film clips and an additional 3 practice clips (around 40 seconds each) which were shown on a computer screen. Each clip consists of a large red triangle and a small blue triangle moving around on a framed white background. Animations are divided into three groups: random movements (i.e. no interaction), goal directed movements (i.e. physical interaction), and theory of mind movements (i.e. mental interaction). In clips displaying no interaction the movements of the two triangles are not related to each other (e.g. they are drifting or bouncing off the frame). In clips displaying physical interactions then the actions of the triangles respond to the actions of the other triangle (e.g. following, fighting). In clips displaying mental interactions then the actions of the two triangles respond to the mental state of the other triangle (e.g. mocking, coaxing). The task consists of 4 animations per group (3 categories × 4 animations per category, giving a total of 12 clips), with an additional animation in each group used for the practice block. The sequences of animations in both the practice and task blocks were randomised, and animations were shown one at a time. Animations were presented on a screen at a distance of 90cm from the participant.

Participants first read the task instructions (Castelli et al 2000, White et al 2011). Following each animation participants were asked to categorise the interaction between the triangles as no interaction, a physical interaction or a mental interaction. Participants were given written definitions of the three types of interaction before the start of the practice, and were free to refer to the definitions during the task. For correctly identified mental interactions participants were asked a further two questions regarding the mental states of the triangles at the end of the clip; for this participants were asked to select how each triangle felt from a list of five options (4 animations × 2 triangles, giving a total of 8 mental states) (see White et al (2011) for details and interaction definitions). Feedback regarding the type of interaction was given for the practice animations, with incorrect answers being corrected. No feedback was given during the task although verbal encouragement was given.

6.5.1.1 Analysis

The total numbers of animations correctly classified and mental states correctly identified were calculated for each participant. In total, participants could score a maximum of 12 (4 per category) for correctly categorising the type of interaction within the clip. Participants

could also score up to a maximum of 8 for correctly identifying the mental states of the triangles. Scores for the two groups were compared using Mann-Whitney U tests; non-parametric tests were used due to the small range of scores on the measures (White et al 2011).

6.5.2 Results

Results from the Triangles task can be found in Table 6-7. Group results were compared using Mann-Whitney U tests. There were no between group differences regarding the number of animations correctly categorised (P = 0.194), or the number of mental states correctly identified (P = 0.604). Further, there were no between group differences for the number of random (P = 0.302), physical (P = 0.209), or mental (P = 0.363) animations correctly categorised.

	A allele	G allele
Random (max 4)	4.00 (0.75)	4.00 (1.00)
Physical (max 4)	4.00 (1.75)	3.00 (0.50)
Mental (max 4)	4.00 (0.00)	4.00 (1.00)
Categorisation total (max 12)	11.00 (2.00)	10.00 (1.50)
Mental states (max 8)	5.50 (2.50)	6.00 (2.00)

Table 6-7. Median scores during the Triangles task for the numbers of animations and mental states correctly classified for males possessing the A and G alleles at SNP rs7055196 (median (interquartile range))

6.6 Discussion

This study investigated theory of mind abilities and associated neural activity in neurotypical males possessing different alleles at SNP rs7055196 within the EFHC2 gene.

6.6.1 The influence of SNP rs7055196 on theory of mind abilities

During the Eyes task in Study 7, males possessing the A allele at SNP rs7055196 correctly identified more mental states than males possessing the G allele, as predicted. Although no difference in task performance was found in Study 8 this was likely due to the small sample size used; supporting this then the effect sizes for Study 7 and the mind task in Study 8 were similar (Study 7 effect size = 0.211, Study 8 effect size = 0.148). There were no group differences for the number of interactions correctly classified or the number of mental states correctly identified during the Triangles task in Study 9, in contrast to my prediction.

The results of these Studies may therefore suggest an influence of SNP rs7055196 on theory of mind abilities is limited to the Eyes task. However, the Eyes task may be more difficult than the Triangles task and therefore more sensitive to detect subtle differences in group performance; supporting this then the scores for the Triangles task were much closer to the ceiling level than those in the Eyes task. In addition, the sample size for the Triangles task was much smaller than that for the Eyes task, and this may also have influenced the results. If an effect of SNP rs7055196 on theory of mind abilities is limited to the Eyes task, then differences between this task and the Triangles task may help to explain this effect. The Eyes task utilises images of the eye region of faces whereas the Triangles task does not use facial stimuli, and it is possible based on my previous results that the difference between males possessing the A and G alleles at SNP rs7055196 on the Eyes task may be due to a difference in processing information from faces and determining mental states based on this information. This may explain the group difference in accuracy during the Eyes task but not the Triangles task. To further investigate whether a general difference in theory of mind abilities exists between males possessing different variants of SNP rs7055196 or whether this difference is due to the use of face stimuli then more difficult theory of mind tasks will need to be employed to compare group performance, such as the Director task (Dumontheil et al 2010a, Dumontheil et al 2010b).

6.6.2 The influence of SNP rs7055196 on neural activity during the Eyes task

Supporting my prediction of greater neural activation during the Eyes task for males possessing the A allele at SNP rs7055196 compared to those possessing the G allele, during Study 8 I found that males possessing the A allele showed greater activity in the right superior temporal gyrus, the left inferior parietal lobule and the left cingulate gyrus, despite the lack of a group difference at the behavioural level. This difference in neural activity between the groups is related to the activity for decoding another's mental state and is not due to low level visual features of the stimuli, as this group difference was found when comparing activity for the mind task compared to that for the age task. This difference may contribute towards the poorer accuracy of males possessing the G allele in the Eyes task found in Study 7, and based on the small sample size in Study 8 and the lack of a behavioural difference between the groups in Study 8 then the influence of SNP rs7055196 on mental state decoding is much greater at the level of neural activation compared to the behavioural level. These results should be considered preliminary due to the small sample size used, and it is important to replicate this result using a larger sample in the future.

The right superior temporal gyrus has previously been reported to be activated during the Eyes task (Baron-Cohen et al 1999b, Focquaert et al 2010, Moor et al 2012), suggesting a role for this region in decoding others' mental states from images of the eye region. This region has also previously been reported to be activated in other theory of mind tasks (Vollm et al 2006) and when viewing neutral (Vaina et al 2001, Wicker et al 1998) and emotional faces (Fusar-Poli et al 2009a, Nomi et al 2008), supporting a role in processing faces and theory of mind. The superior temporal gyrus has also been suggested to be activated by biological motion (Vaina et al 2001) and imitation (Decety et al 2002, Leslie et al 2004). This region is also sensitive to mouth movements and is activated when lip-reading (Calvert et al 1997), and this may be associated with its role in language and auditory processing (Gernsbacher and Kaschak 2003, Martin 2003). Although the bilateral superior temporal gyrus is activated during language tasks, the left superior temporal gyrus contains Wernicke's area and so may be considered to be more important for language processing. As the difference in activity in the superior temporal gyrus found between males possessing the G and A alleles was found only in the right hemisphere this difference is therefore not likely to be due to a difference in processing the words between the two groups, and is instead due to processing the mental state information within the eyes.

The left inferior parietal lobule has also previously been reported to be activated during the Eyes task (Focquaert et al 2010) and when viewing emotional faces (Fusar-Poli et al 2009a, Nomi et al 2008), suggesting a role for this structure in decoding others' mental states. This region has also been activated when imitating others' actions (Decety et al 2002). This suggests similar roles in social cognition for the superior temporal gyrus and inferior parietal

lobule. The cingulate gyrus has roles in emotional and pain processing (Vogt 2005) and in reward based decision making (Bush et al 2002), both of which may contribute towards a role in social cognition.

Activity in the bilateral superior temporal gyrus, the left inferior parietal lobule and the left cingulate gyrus has been suggested to be higher during the Eyes task for males who show high empathising abilities compared to males who show low empathising abilities (Focquaert et al 2010). Further, activation of the superior temporal gyrus and the inferior parietal lobule has been associated with empathising and sharing others emotions when viewing emotional faces (Nomi et al 2008). This suggests a role for these regions in empathy, and the higher activation in these regions in males possessing the A allele at SNP rs7055196 may be due to higher empathising abilities in these males compared to males possessing the G allele. This may also account for the higher accuracy of males possessing the A allele in the Eyes task; supporting this then the high empathising males in the study by Focquaert et al (2010) were also more accurate on this task compared to the low empathising males. These results suggest that SNP rs7055196 may influence empathising abilities in neurotypical males. Unfortunately, no measures of empathising abilities were obtained from participants in these studies, and so it will be important for future studies to investigate differences in empathising abilities between males possessing the different variants of SNP rs7055196 and to take account of these abilities.

However, other explanations may account for the differences in neural activity during the Eyes task between the two groups. As the neural activity in the mind task compared to that in the age task was compared between the groups, this analysis cannot determine whether males possessing the G allele activate the right superior temporal gyrus, the left inferior parietal lobule and the left cingulate gyrus during both tasks whereas these regions were only activated in the males possessing the A allele during the mind task. This would then result in a difference in activity for the two tasks in these regions in males possessing the A allele but not in those possessing the G allele, and when comparing activity between the two groups this difference would be higher for males possessing the A allele. This may occur if the males possessing the G allele processed social information regarding how the person felt during both tasks. Alternatively, a different interaction effect may have occurred, for example males possessing the G allele may show lower activity during both tasks compared to males possessing the A allele, with a greater difference in the activity between the two tasks in males possessing the G allele compared to in those possessing the A allele. Again, this scenario would result in the pattern of results obtained. It is important that future studies with larger samples investigate these possibilities, and if either were the case then it would be important to determine why males possessing the G allele are less accurate at decoding mental states than those possessing the A allele.

Alternatively, this result may occur if the males possessing the G allele had less experience with the mental states or the words used. To reduce this possibility all participants were

given a list of the words used in the task prior to its start and asked to read the description for any they were unfamiliar with to ensure they were familiar with the words used. Finally, this group difference in activation patterns may occur if there were group differences in terms of attention to the stimuli or effort during the task.

It is interesting to note that those regions which show a difference in activity between males possessing the different variants of SNP rs7055196 do not show a difference in activity between the mind and the age tasks when considering all participants together. This suggests that regions other than those activated during the mind-age contrast are important for mental state decoding.

6.6.3 Comparing the mind and age tasks in the modified Eyes task

In addition to the between group differences found in Study 8, I also found significant across group differences for the two tasks. Firstly, participants correctly identified a greater number of mental states compared to age ranges. This suggests the age task is more difficult than the mind task. However, the RTs were longer for the mind task compared to the age task, which may suggest the mind task is more difficult than the age task. Attention levels during the age task may be lower than during the mind task as we may be primed to look for information about others mental states. In addition, while someone's mental state can be accurately determined from the eyes alone it is much harder to determine someone's age. These two factors may result in the lower accuracy for the age task compared to the mind task, and may also produce the faster RTs. If the age task is more difficult than the mind task then it is possible that the age task utilises greater neural resources than the mind task in some regions, which may influence activity levels and result in an underestimation of the difference in neural activation between the two tasks.

Comparing neural activity during the mind and age tasks, I found greater activity in the left inferior frontal gyrus, the left middle temporal gyrus, the left precentral gyrus, the right lentiform nucleus, and the left culmen during the mind task. This activation pattern is similar to that previously reported during the Eyes task; the inferior frontal gyrus has been reported to be activated both in the left hemisphere (Baron-Cohen et al 1999b, Focquaert et al 2010, Moor et al 2012, Russell et al 2000) and bilaterally (Adams et al 2009, Baron-Cohen et al 2006, Castelli et al 2010), the middle temporal gyrus has been reported to be activated in the left hemisphere (Castelli et al 2010, Focquaert et al 2010, Russell et al 2000) and bilaterally (Baron-Cohen et al 1999b, Baron-Cohen et al 2006, Moor et al 2012), and the precentral gyrus has been reported to be activated in the left hemisphere (Moor et al 2012) and bilaterally (Castelli et al 2010). Bilateral cerebellar activity has also been reported by Castelli et al (2010).

The inferior frontal gyrus has been suggested to be a part of the social brain, being important for assessing others' mental states (Nakamura et al 1999), as has the middle temporal gyrus which has been associated with face processing (Fusar-Poli et al 2009a, Fusar-Poli et al 2009b, Nomi et al 2008). The presence of mirror neurons has been suggested in both the inferior frontal gyrus (Grezes et al 2003, Iacoboni 2005) and the precentral gyrus (Leslie et al 2004), suggesting a role for both regions during imitation. Based on these functions, the left inferior frontal gyrus, the left middle temporal gyrus and the left precentral gyrus are therefore likely to be involved in identifying how others feel, explaining their higher activity during the mind task compared to the age task. The precentral gyrus, the lentiform nucleus and the culmen are involved in voluntary muscle movements, and their higher activity during the mind task compared to the age task may be associated with higher levels of movement during the mind task. This may have occurred if participants were imitating the expressions of the eyes in the images in the mind task to assist them with identifying the mental states of the individuals.

We did not find differences in neural activity between the mind and age tasks in other regions which have previously been reported to be activated during the Eyes task, including the superior temporal sulcus (Adams et al 2009, Castelli et al 2010, Moor et al 2012), superior temporal gyrus (Baron-Cohen et al 1999b, Baron-Cohen et al 2006, Focquaert et al 2010, Moor et al 2012, Platek et al 2004, Russell et al 2000) and regions of the prefrontal cortex (Adams et al 2009, Baron-Cohen et al 1999b, Baron-Cohen et al 2006). These differences may have arisen due to differences in the non-mind contrast task used; while I used a task which required participants to select an age range for the person in the image the majority of other contrast tasks required participants to select the gender of the person. Identifying the gender of the person is likely to be easier than identifying their age range, and so may not utilise as many neural resources. This may result in a greater difference in neural activity between the mind and gender tasks compared to the mind and age tasks, explaining why I did not find significant differences in activation for the two tasks in a larger number of regions.

6.6.4 Theory of mind abilities in other populations

Both individuals with an ASD (Baron-Cohen et al 2001c, Kaland et al 2008, Kirchner et al 2011, Losh et al 2009) and women with TS (Lawrence et al 2003b) have been reported to correctly identify fewer mental states during the Eyes task compared to neurotypical individuals, although similar to fear recognition abilities, these impairments are much larger than those found for males possessing the G allele at SNP rs7055196 compared to males possessing the A allele. The poorer performance of siblings of individuals with an ASD (Dorris et al 2004) and ASD parents who lie along the BAP (Losh et al 2009) on this task is also greater than the impairment found in the current study.

Individuals with an ASD have been reported to show increased bilateral superior temporal gyral activity and decreased activity in the left inferior frontal gyrus, left amygdala and right insula during the Eyes task compared to neurotypical adults (Baron-Cohen et al 1999b), while the parents of children with an ASD have been reported to show decreased activation in the bilateral inferior frontal gyrus and left middle temporal gyrus compared to controls (Baron-Cohen et al 2006). These results are not similar to mine; I found decreased activity in males possessing the G allele at SNP rs7055196 in the right superior temporal gyrus, the left inferior parietal lobule and the left cingulate gyrus. This suggests that the poorer performance in males possessing the G allele is not due to a similar neural mechanism as that which results in a poorer performance in individuals with an ASD and their relatives.

Finally, individuals with an ASD (Abell et al 2000, Castelli et al 2002, Salter et al 2008, White et al 2011), women with TS (Lawrence et al 2007) and males who show poor fear recognition abilities (Corden et al 2006) show impaired performance on the Triangles task whereas no differences in task performance were found in the current study for males possessing the different variants at SNP rs7055196. It is important to note however accuracy for these previous studies was largely determined by scoring descriptions of the animations whereas accuracy for the current study was determined by classifying the interactions between the triangles. This difference may contribute towards the lack of a group difference in the current study. In addition, Salter et al (2008) found this task relatively poor at discriminating between children with an ASD and controls, suggesting this task may not detect subtle group differences. This may help to explain the lack of a difference in the current study.

6.7 Summary

Theory of mind abilities allow us to understand how others are feeling, and predict how they may act. These abilities may be tested using the Eyes task and the Triangles task; performance on both of these tasks is impaired in individuals with an ASD and women with TS. Theory of mind abilities are related to our ability to accurately recognise emotions from facial expressions, and so I investigated a possible influence of SNP rs7055196 within the EFHC2 gene on performance during the Eyes and Triangles tasks in neurotypical males. Further, I compared neural activity between males possessing different variants of this SNP during a modified version of the Eyes task. The variant of SNP rs7055196 males possessed influenced the number of mental states they correctly identified on the Eyes task, with males possessing the A allele correctly identifying more mental states than males possessing the G allele. No group differences in task performance were found for the Triangles task. Further studies are therefore needed to investigate whether the influence of SNP rs7055196 on performance during the Eyes task is due to a general influence on theory of mind abilities or

whether it is limited to the Eyes task, possibly due to the facial information within this task. Males possessing the A allele also showed higher neural activity than males possessing the G allele in the right superior temporal gyrus, the left inferior parietal lobule and the left cingulate gyrus during the Eyes task when identifying the mental state of the person in the images compared to identifying their age range. These regions have also been reported to be activated more in high empathising males compared to low empathising males, and so SNP rs7055196 may influence empathising abilities in males.

7 General discussion

7.1 Main findings

The work in this thesis has explored the influence of SNP rs7055196 within the EFHC2 gene on social cognition in neurotypical males. Specifically, I have investigated facial emotion recognition abilities, gaze fixations to facial features, electrophysiological responses to faces, theory of mind abilities and neural activations during a theory of mind task in males possessing either the A or G allele at this SNP. Results suggest a subtle influence of this SNP on facial fear recognition abilities, with males possessing the A allele showing higher sensitivity to recognising fearful expressions compared to males possessing the G allele. A higher recognition accuracy for fearful expressions for males possessing the A allele compared to those possessing the G allele was also found for partial faces. This difference in fear recognition accuracy is not due to a difference in fixation patterns to facial features (i.e. the eye and mouth regions) between the groups. Males possessing the A allele were also found to show larger amplitudes for the N170 component in response to emotional faces compared to that of males possessing the G allele. I also found an influence of this SNP on performance during the Eyes task, with males possessing the A allele correctly identifying more mental states than males possessing the G allele. No group differences in performance were found for the Triangles task, and so this influence of SNP rs7055196 on theory of mind abilities may be limited to the Eyes task. Neural activations during a version of the Eyes task also differed between the groups, with males possessing the A allele showing greater activity in the right superior temporal gyrus, the left inferior parietal lobule and the left cingulate gyrus when identifying the mental states of others.

The differences between males possessing the different variants of SNP rs7055196 for N170 amplitudes in response to emotional faces and neural activity during the Eyes task are much larger than the differences between the groups for fear recognition accuracy and performance accuracy during the Eyes task. This suggests a much greater influence of this SNP at the level of neural activation compared to that at the behavioural level. In addition, these differences were found despite a lack of a difference between the groups for their scores using the Autism Spectrum Quotient (AQ), suggesting that these differences do not have a great effect on daily social interactions and communication.

7.2 Influence of SNP rs7055196 on social cognition

The finding that males possessing the G allele at SNP rs7055196 are less accurate at facial fear recognition compared to males possessing the A allele along with the finding that males possessing the G allele show smaller N170 amplitudes in response to emotional faces compared to males possessing the A allele suggests an influence of SNP rs7055196 on face processing. The poorer accuracy of males possessing the G allele during a fear recognition task which used images of faces containing different proportions of fearful and neutral expressions may be due to these males being less able to integrate information from the different facial features (e.g. the eyes and the mouth), with no difference in the fixation patterns to these features between the two groups. The N170 component is thought to reflect a late stage of the structural encoding of faces, specifically global face configuration and holistic processing (Bentin et al 1996, Eimer 2000b, Eimer et al 2011, Luo et al 2010), and this component has also been suggested to represent the integration of visual information from facial features (Schyns et al 2007). The smaller N170 amplitudes of males possessing the G allele may therefore represent reduced holistic / configural processing in these males, supporting a reduced integration of facial information from different facial features. These results suggest males possessing the A allele may use a more holistic / configural face processing mechanism than males possessing the G allele. Future studies should therefore compare face processing mechanisms between groups of males possessing the different alleles at this SNP.

In addition, I found that males possessing the G allele were less accurate at identifying mental states during the Eyes task compared to males possessing the A allele, and males possessing the G allele also showed reduced activity in the right superior temporal gyrus, the left inferior parietal lobule and the left cingulate gyrus during this task. Similarly, high empathising males correctly identify more mental states during the Eyes task and show higher activity in the above listed regions during the task compared to low empathising males (Focquaert et al 2010). It is therefore possible that SNP rs7055196 may influence empathising abilities in neurotypical males, with males possessing the G allele showing poorer empathising abilities compared to those possessing the A allele. A difference in empathising abilities between the groups may also contribute towards the poorer fear recognition accuracy of males possessing the G allele. It is therefore important for future studies to compare empathising abilities between males possessing the different alleles. However, it is unknown whether a possible association between SNP rs7055196 and empathising abilities would be causative or correlational.

It is unknown whether the suggested differences between males possessing the different variants of SNP rs7055196 in terms of face processing strategy and performance on the Eyes task are due to a common influence of this SNP or not. Males possessing the G allele showed poorer fear recognition from partial faces and were less accurate at determining

mental states of individuals from images of the eye region during the Eyes task compared to males possessing the A allele. This supports a common influence of SNP rs7055196, and suggests that males possessing the G allele may be less able to process information from incomplete facial stimuli compared to those possessing the A allele. Further supporting a common influence of this SNP, a negative correlation between the JND scores for the female face and the number of mental states identified on the Eyes task was found (Pearson = -0.228, P = 0.030), meaning a greater sensitivity to fearful expressions was related to a higher accuracy on the Eyes task. Finally, it has previously been suggested that accuracy on the Eyes task is correlated with the extent to which N170 amplitude distinguishes between positively and negatively valenced faces (Petroni et al 2011), suggesting an overlap between performance on this task and face processing.

The results within this thesis suggest that SNP rs7055196 does not influence performance on the Triangles task, and does not influence AQ scores. This may suggest that this SNP does not have a general influence on social cognitive abilities. Supporting a dissociation between general social cognition and face processing abilities, it has been reported that individuals with congenital prosopagnosia show impaired facial emotion and identity recognition abilities (suggesting impaired face processing) compared to unaffected individuals, with no group differences in performance on the Triangles task or AQ scores (Duchaine et al 2009). These results may suggest a dissociation between facial emotion recognition abilities and general theory of mind abilities, although performance on some theory of mind tasks may be related to emotion recognition abilities. Supporting this, reduced accuracy for both fear recognition and mental state identification on the Eyes task were found in males possessing a G allele at SNP rs7055196, suggesting an association between performance levels on these two tasks. Further, a recent study investigating three individuals with congenital prosopagnosia found all three showed similar scores on the Eyes task to those originally reported by Baron-Cohen et al (2001c), and these individuals did not show impaired facial emotion matching abilities, suggesting an association between emotional face processing and performance on the Eyes task (Lee et al 2010).

Despite the findings within this thesis and the suggested influences of SNP rs7055196 on social cognition it is unknown how these effects occur. This SNP is located within the intronic region of the EFHC2 gene, and although its precise functional significance is unknown it has been suggested to have a functional role in regulating transcription (http://compbio.cs.queensu.ca/F-SNP/). This suggested role may influence the transcription and expression for the EFHC2 gene itself, or other nearby genes such as the monoamine oxidase A and B genes (MAO-A and MAO-B respectively). Little is known about the function of the EFHC2 protein, although based on its structure it has been proposed to have a role in calcium binding (Gu et al 2005), and so it may influence neurotransmission or intracellular signalling processes. This may then influence the development of neural networks involved in face processing and / or social cognition. Both the MAO-A and MAO-B proteins influence

the neurotransmission of serotonin, noradrenaline and dopamine, and so these proteins may also influence the development of regions involved in face processing and / or the social brain.

7.2.1 Possible influence of SNP rs7055196 on brain development

As mentioned above, it is possible that the influence of SNP rs7055196 on face processing and the Eyes task may occur through influencing the development of regions involved in face processing and / or within the social brain. Electrophysiological responses to faces develop throughout childhood, suggesting that cortical face processing systems show a gradual specialisation with a maturation of configural processing (de Haan et al 2002, Taylor et al 2001). In addition, the social brain (Blakemore 2012) and mentalising abilities (Dumontheil et al 2010a, Dumontheil et al 2012) continue to develop throughout adolescence.

The EFHC2 gene is expressed in brain regions including those in the temporal, frontal and parietal lobes, the cingulate gyrus, the striatum, and the hypothalamus (http://human.brain-map.org/mri_viewer?donor=14380&location=112,134,109&mriRange=0,700&exprRange=-2.5,2.5&selectedProbe=0&probes=1038556). Many of these regions are important for social cognition and face processing, supporting a possible influence of this SNP on the development of the social brain and face processing network.

It has previously been reported that the Xp11.3 locus (which contains SNP rs7055196) influences amygdala development in a dose dependent manner in women with Turner Syndrome; women possessing two copies of this locus possessed similar amygdala and orbitofrontal cortical volumes to neurotypical women along with similar fear recognition abilities, while women possessing just one copy of this locus possessed larger amygdala and orbitofrontal volumes compared to neurotypical women, along with poorer fear recognition abilities (Good et al 2003). The EFHC2 gene has recently been reported to escape inactivation (Castagne et al 2011), which may contribute towards these dosage sensitive effects of Xp11.3. Specifically, women with TS possessing only one copy of the EFHC2 gene show larger amygdala and orbitofrontal cortical volumes and poorer facial fear recognition abilities compared to women possessing two copies. This suggests a possible influence of SNP rs7055196 on development of the amygdala and orbitofrontal cortex, regions important for social interactions. Further, as the fusiform gyri have been suggested to play a role in the holistic / configural processing of faces (Liu et al 2010, Maurer et al 2007, Zhang et al 2012) and the N170 component has been reported to originate from activity in this region (Campanella et al 2002, Herrmann et al 2005, Iidaka et al 2006, Luo et al 2010, Petroni et al 2011, Utama et al 2009, Wong et al 2009) it is possible that SNP rs7055196 may influence the development of this region.

Work in our group has started to investigate an influence of SNP rs7055196 on structural volumes within the brain and white matter tractography. Preliminary results using the participants from Study 8 have found a difference for left caudate volume between males possessing the different variants of this SNP, with males possessing the G allele showing larger volumes than males possessing the A allele (P = 0.02). This effect did not survive multiple comparisons, although it is a promising result for future work with larger sample sizes (Clare Gibbard, personal communication).

7.2.2 Possible influence of SNP rs7055196 on poorer social cognition in males compared to females

Genes within the X chromosome have previously been suggested to influence social cognition (Skuse 2006), and it has been suggested that boys show poorer social and communicative skills than girls (Skuse et al 2009). Extreme impairments in social and communicative abilities are characteristic of the autism spectrum disorders (ASDs) (APA 1994), a set of disorders which are more prevalent in males compared to females (3:1) (Levy et al 2009). As males possess only one copy of the X chromosome while females possess two copies it is therefore possible males are more vulnerable to impaired social cognition than females due to genetic influences found within the X chromosome, as due to the imbalance in the number of X chromosomes these influences would affect males more than females.

The results within this thesis suggest an influence of the X-linked SNP rs7055196 on aspects of social cognitive abilities in neurotypical males, and so influences of this SNP may help to explain why males are more vulnerable to impaired social cognitive abilities than females. It is important to investigate a possible influence of this SNP on disorders of social cognition further. Recent work in our group investigating the prevalence of the different alleles at SNP rs7055196 in males with high functioning autism compared to controls has found no difference between the two groups (Irene Lee, personal communication). However, despite this lack of a difference in SNP prevalence it is possible that this SNP may interact differently with other genetic factors in the two groups to influence social cognitive abilities, with a greater influence of the G allele in males with an ASD compared to neurotypical males. Further, there may not be a large difference in SNP prevalence if this gene is one of many which are involved in a pathway which is disrupted in some way in individuals with an ASD.

An association between the EFHC2 gene and females with an ASD has recently been reported, further supporting an association between this gene and impaired social cognition (Tsang et al 2012). Although SNP rs7055196 was not associated with ASD diagnosis, this SNP showed moderate to high linkage disequilibrium with several of the SNPs which were

associated with ASD diagnosis. Further work is needed to fully determine associations between this gene and disorders of social cognition, in both males and females.

7.3 Limitations of the studies

7.3.1 Participants

Although the sample sizes in Studies 1-4 and 7 are reasonable sizes, the sample sizes in Studies 5, 6, 8 and 9 are much smaller. Participants for this second set of studies were selected from participants from the first set of studies, and unfortunately not all of the participants initially tested were available for further testing. Although I found significant group differences in the results of Studies 5, 6 and 8 suggesting these small sample sizes may not be an issue, it is important to repeat these studies with a larger sample size to replicate the findings of an association between SNP rs7055196 and both electrophysiological responses to faces and neural activation during the Eyes task. This is particularly important for Study 8, as the clusters of activation differences between males possessing the different variants of SNP rs7055196 were very small.

In addition, it must be noted that the samples used are not representative of the general population; the majority of participants were university students, and the mean IQs obtained were much higher than those in the general population (around 120 in the current studies, around 100 in the general population). A higher IQ may compensate for poor fear recognition accuracy and performance on the Eyes task, resulting in the subtle influence of SNP rs7055196 on behaviour in this thesis, and a larger behavioural difference may be observed with individuals with lower IQs. In addition, the majority of participants in the current studies were aged 18-26. The findings from the current studies cannot therefore be extrapolated to the general population, and further studies using participants with a larger IQ and age range are needed in order to fully investigate influences of SNP rs7055196 on face processing and performance during the Eyes task.

A final potential issue relating to the participants included in the studies is that all participants who took part in Study 6 had taken part in Study 3, and similarly, all participants who took part in Study 8 had taken part in Study 7. The fearful stimuli used in Studies 3 and 6 were the same, as were the images used in Studies 7 and 8. Further, the participants in Study 8 had previously done the eyes task in Study 7. There may therefore be an effect of memory for the stimuli seen in Studies 6 and 8, which may have affected the electrophysiological and neural responses to the stimuli. Although Studies 3 and 7 were performed approximately a

year before Studies 6 and 8, a possible effect of memory in the latter studies cannot be discounted.

7.3.2 Tasks and stimuli

7.3.2.1 Emotional face stimuli used in the studies

For the partial faces used in Studies 2 and 5, it is possible that confounding effects relating to the position of the sunglasses in faces with the eyes or eyes and eyebrows covered may have influenced the results. In particular, cues relating to the position of the sunglasses may have had an effect, with the sunglasses being higher for fearful compared to neutral and angry faces (see Figure 3-4 and Figure 5-1). These cues may have affected emotion recognition and processing of the faces in these studies.

In addition, only two identities were used in Studies 3 and 6 which may limit the generalisability of the findings. This is particularly true for study 3, which found a significant effect of SNP rs7055196 genotype on sensitivity to fear recognition for only one of the faces. The use of additional facial identities will help to define whether the effects observed in these studies are also seen for other facial identities.

7.3.2.2 The use of static emotional faces compared to dynamic expressions

One of the major issues with using static emotional faces for testing emotion recognition is that in real life facial expressions are dynamic, and everyday expressions may not be as intense as those seen in standard facial expression stimuli. Although the stimuli used in Study 3 showed a range of intensities of fearful expressions allowing us to investigate more subtle group differences in fear recognition accuracy, these stimuli were all static. Dynamic expressions may be recognised more accurately than static expressions, especially for low intensity expressions, with dynamic information in the eyes and mouth attracting attention and being most important for emotion recognition (Ambadar et al 2005, Back et al 2009, Bould and Morris 2008). This advantage has been suggested to be due to the use of information that is only available over time (Cunningham and Wallraven 2009). Both electrophysiological responses and neural activation patterns have also been suggested to differ for dynamic compared to static stimuli, with greater temporal activity as measured using ERPs (Mayes et al 2009) and increased activity in the inferior occipital gyri, middle temporal gyri, amygdala and superior temporal sulci as measured using fMRI (Arsalidou et

al 2011, Foley et al 2012) for dynamic compared to static expressions. However, not all studies have supported this advantage for emotion recognition in dynamic faces compared to static faces (Fiorentini and Viviani 2011), and the beneficial effect of the dynamic information may depend upon the emotion (Fujimura and Suzuki 2010).

7.3.2.3 The influence of gaze on emotion recognition abilities

The direction of gaze of faces influences the perceived emotion of the face, and no measures of gaze perception were taken in the studies within this thesis. A direct gaze facilitates the processing of both happy and angry expressions, whereas an averted gaze facilitates the processing of fearful and sad expressions (Adams and Kleck 2003, Sander et al 2007). Recent studies have suggested that it is in fact head orientation that influences emotion processing, rather than gaze direction (Ganel 2011, Hess et al 2007). The gaze direction of expressions has also been reported to influence neural activity, with larger P2 amplitudes in response to fearful faces with an averted gaze and happy faces with a direct gaze compared to fearful faces with a direct gaze and happy faces with an averted gaze (Rigato et al 2010) and increased amygdala activity for angry faces with a direct gaze and fearful faces with an averted gaze compared to angry faces with an averted gaze and fearful faces with a direct gaze (N'Diaye et al 2009).

7.3.2.4 Emotion recognition from non-facial cues

Various non-facial stimuli also provide information regarding how individuals feel, such as body postures (Bannerman et al 2009), body language (Meeren et al 2005), body movements (Clarke et al 2005) and gait (Ikeda and Watanabe 2009). Non-visual stimuli also facilitate facial emotion recognition, in particular vocalisations including both prosody (Paulmann and Pell 2010) and non-verbal expressions (Sauter et al 2010). Olfactory cues may also facilitate fear recognition (Zhou and Chen 2009). Finally, the context in which emotional faces are observed can facilitate expression recognition (Righart and de Gelder 2008).

7.3.2.5 The Eyes task

The Eyes task only tests one aspect of theory of mind abilities, as participants are required only to identify the mental states of others and not to determine why they are feeling that way or predict their actions or intentions (Baron-Cohen et al 2001c). Further limitations with the task are discussed in Johnston et al (2008); the 'correct' answers for the mental states in

each image were determined by the authors of the task rather than the actors, and this task does not distinguish between genuine and posed expressions. In addition, no contextual information is given for the images which may influence the perceived mental state.

7.3.2.6 The Triangles task

The scores for the Triangles task approached ceiling levels, which may suggest the task was not sensitive enough to possible performance differences between males possessing the different variants of SNP rs7055196. The scoring sheet used may not have been as sensitive to group differences as scoring participants' descriptions of the triangles movements, although this analysis method is also not ideal as it is subjective with a crude scoring system.

7.3.3 Other factors influencing social cognition

Participants in the two groups were similar in terms of age, ethnicity and IQ, suggesting these factors did not influence the results within this thesis. However, many other group differences may have influenced the results. Factors such as hormonal levels and personality traits have previously been associated with emotion recognition abilities and performance on the Eyes task and related neural activities, and so it is possible that these factors may have differed between the groups of participants used in the studies within this thesis. This may then have affected the results. Although there is no reason to believe this would be the case these factors cannot be discounted.

7.3.3.1 Emotion recognition abilities

Testosterone levels have been reported to show a positive correlation with amygdala activity in males in response to fearful faces, although there was no association between testosterone levels and emotion recognition abilities (Derntl et al 2009a). Oxytocin administration has been suggested to improve fear recognition abilities (Fischer-Shofty et al 2010), increase fixations to the eye region of faces (Guastella et al 2008) and reduce amygdala activity in response to fearful faces (Domes et al 2007a, Gamer et al 2010). Emotion recognition abilities may also be influenced by personality traits, with higher levels of social shyness in children being associated with poorer emotion recognition abilities (Battaglia et al 2004), and similarly, increasing prosocial behaviour in adults being associated with higher fear recognition abilities (Marsh et al 2007). Mood may also influence how expressions are perceived (Coupland et al 2004), and supporting this it has been

reported that inducing a happy mood in individuals produces a positivity bias in emotion recognition while inducing a sad mood produces a negativity bias (Schmid and Schmid Mast 2010). Individuals showing high levels of social intelligence have been reported to be better at emotion recognition compared to individuals showing low levels of social intelligence (Petrides et al 2011), and an increased level of psychiatric symptoms has been suggested to be associated with poorer emotion recognition abilities (Csukly et al 2008). Personality traits have also been suggested to influence neural responses to emotional faces, with higher anxiety levels being associated with increased amygdala activity in response to fearful faces (Ewbank et al 2009).

7.3.3.2 The Eyes task

Performance on the Eyes task may be negatively correlated with levels of foetal testosterone (Chapman et al 2006). Administration of oxytocin has been reported to increase performance on this task (Domes et al 2007b), while performance may be decreased following administration of vasopressin (Uzefovsky et al 2012). Task performance and activation patterns during the task may also be related to personality traits. As discussed, males who possess high empathising traits and low systemising traits have been reported to correctly identify more mental states and show greater neural activity compared to males possessing low empathising traits and high systemising traits (Focquaert et al 2010). This effect may be due to SNP rs7055196, or empathising abilities may influence performance on the Eyes task independently of SNP rs7055196 genotype. AQ score has also been reported as being inversely correlated with task accuracy (Baron-Cohen et al 2001c) although another study found no correlation between AQ score and accuracy on the Eyes task (Miu et al 2012). Increased dysphoria has also been associated with an improved task performance (Harkness et al 2005), and increased schizotypal personality traits has been associated with impaired performance (Platek et al 2005). Task performance has not been associated with emotional intelligence (Ferguson and Austin 2010) or any of the five main personality traits (Nettle and Liddle 2008). Further, it has been suggested that there is a maternal influence on performance in the Eyes task, with this influence being stronger in males compared to females. This influence may be due to genetic or environmental factors, and may act through influencing aspects of executive functioning such as inhibiting behaviours (Ragsdale and Foley 2011).

It has previously been suggested that performance in many theory of mind tasks is dependent on executive functioning (Aboulafia-Brakha et al 2011), with cognitive processes relating to executive functions such as working memory and reasoning being important for these tasks. This therefore suggests that performance on theory of mind tasks may be influenced by executive functioning, and the difference in performance on the Eyes task between males possessing the different SNPs at rs7055196 may be due to a difference in

executive functioning between the groups. In particular, it has been suggested that inhibitory processes may be important during the Eyes task, as participants may be required to inhibit thoughts about the person's age and gender in order to judge their mental state (Bull et al 2008). However, Baron-Cohen et al (1997, 2001c) suggested that the Eyes task is less dependent on executive functioning compared to other theory of mind tasks, and it is a more 'pure' test of theory of mind abilities. Supporting this it has been reported that there is no relationship between performance on the Eyes task and executive functioning abilities (Ahmed and Stephen Miller 2011).

7.4 Future work

The results in this thesis offer a large scope for future work to further investigate influences of SNP rs7055196 on social cognition. Firstly, it is important to replicate the studies within this thesis using new samples of participants. As has already been discussed these studies should investigate the influence of this SNP using samples more representative of the general population (for example using a larger IQ and age range). In addition, larger sample sizes are needed to fully investigate influences of this SNP on electrophysiological responses to faces and on neural activations during the Eyes task. It would also be of interest to investigate the influence of this SNP on social cognition in neurotypical females by comparing females possessing zero, one or two copies of the G allele. Comparing results between males and females would help to determine a possible dose dependent influence of this SNP on social cognitive abilities.

It is also important to extend the findings within this thesis to further investigate a more general influence of this SNP in neurotypical males on emotion recognition abilities, face processing style, theory of mind abilities and empathising abilities. Differences between males possessing the different variants of this SNP for emotion recognition accuracy using other expressions should be explored, for example investigating anger recognition accuracy using faces containing differing percentages of angry and neutral expressions. This will help to determine whether the influence of SNP rs7055196 on emotion recognition abilities is specific to fearful expressions or whether it extends to the recognition of other expressions. The influence of this SNP on face processing styles should also be investigated, to determine more thoroughly whether an influence of this SNP on emotion recognition accuracy may be due to a difference in face processing mechanisms, for example by investigating the composite face effect and electrophysiological responses to upright and inverted faces. Differences between males possessing the different alleles at this SNP on different advanced theory of mind tasks should also be investigated, for example using the Director task (Dumontheil et al 2010a, Dumontheil et al 2010b), to determine whether the influence of this SNP on performance in the Eyes task is due to the importance of theory of

mind abilities during this task or whether the effect is due to the stimuli being from faces. Finally, an influence of this SNP on empathising abilities should be investigated to determine whether this effect accounts for the differences in performance and neural activation during the Eyes task between the groups, and whether this can also account for differences in fear recognition accuracy between the groups.

As discussed above, work investigating structural differences in the brains of males possessing the different variants of SNP rs7055196 is on-going within our group, and this will help us to understand how variance at this SNP influences social cognitive abilities. The location of this SNP within the X chromosome may help to explain why males are more vulnerable to impaired social cognition than females, and so a potential association between this SNP and disorders of social cognition such as the ASDs should be further explored.

7.5 Summary

Within this thesis I have investigated differences in social cognitive abilities between males possessing the A and G alleles at SNP rs7055196 within the X-linked EFHC2 gene. I have found that males possessing the G allele show a subtle impairment in facial fear recognition accuracy, in particular for partial faces, and are less sensitive at detecting differences in expression intensity compared to males possessing the A allele. There were no differences in the gaze fixation patterns to facial features between the groups. Males possessing the G allele also show smaller N170 amplitudes in response to emotional faces compared to males possessing the A allele. These results suggest that males possessing the G allele may use a less holistic / configural face processing mechanism, therefore being less able to integrate information from different facial features to make a judgement regarding the expression of faces compared to males possessing the A allele. In addition, during the Eyes task males possessing the G allele are less accurate at identifying mental states and show reduced neural activity compared to males possessing the A allele. This influence of SNP rs7055196 may be due to an influence on empathising abilities. No differences regarding performance on the Triangles task or AQ scores were found between males possessing different variants of this SNP, suggesting it may not have a general influence on social cognition. The influences of SNP rs7055196 on social cognitive abilities found within this thesis and its location within the X chromosome may help to explain why males are more vulnerable to impaired social cognition compared to females.

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