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Is synaesthesia an X-linked dominant trait with lethality in males?

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Abstract. In previous research the inheritance patterns of synaesthesia (eg experiencing colours from graphemes) has been studied and it was concluded that synaesthesia is most likely to be the outcome of a single gene passed on the X chromosome in a dominant fashion. In addition, it has been reported that the female – male ratio of synaesthetes is as high as 6 : 1 and the families of synaesthetes contain more female than male members. This raises the possibility that the gene may be associated with lethality in males. In this study we replicate and extend previous research by investigating the female – male ratio and inheritance patterns in a large sample of synaesthetic families ($N = 85$). We were able to verify the authenticity of grapheme – colour associates in at least one proband from each family using internal consistency. As before, our results show a female – male bias and are broadly consistent with an X-linked dominant mode of inheritance. However, there was no evidence of male lethality (eg synaesthetes are just as likely to give birth to sons as to daughters). Moreover, our female – male ratio of synaesthetes within families was 2 : 1—considerably lower than previous estimates. We speculate that men may be more reluctant to disclose synaesthesia than women (indeed, our female – male ratio based on self-referral was 3.7 : 1). Finally, we discuss how the genotype may give rise to the phenotype in terms of changes in synaptogenesis or plasticity extending into childhood, to be subsequently shaped by the environment.

1 Introduction

Research into the genetic basis of perception, cognition, and behaviour has lagged behind the significant recent advances made in the core biological sciences (as typified by the mapping of the human genome). Human behaviour is likely to be governed by multiple constraints, arising from the concerted action of many different genes and through interactions with the environment (eg Karmiloff-Smith et al 2002). In addition, many genetic disorders affecting cognition are also accompanied by physical and/or mental handicap (eg Williams, Downs, and fragile-X syndrome). This makes simple genotype – phenotype mapping difficult. In this paper we ask whether synaesthesia could provide researchers with a relatively simple model of how genes can affect brain development to produce atypical perception.

People with synaesthesia have anomalous perceptual experiences that are elicited in the presence of other cognitive or perceptual stimuli (for reviews see Cytowic 2002; Rich and Mattingley 2002). For example, people may experience colours in response to music (eg Ward et al, in press) or tastes in response to words (Ward and Simner 2003). Here, we examine the most prevalent form, grapheme – colour synaesthesia[(1)] (eg Baron-Cohen et al 1993), in which letters, numbers, and words trigger sensations

[(1)] Different terminology has been used in the literature to describe synaesthetic manifestations, and this has raised questions whether these might reflect more substantive differences in kind. We have adopted the nomenclature of placing the inducing stimulus before the synaesthetic experience, separated by a dash (eg grapheme – colour). We use the term grapheme to denote the minimal functional distinctive unit of a writing system (Henderson 1985). This implies abstract entities corresponding to single letters and digits.

of colour. The colour of each grapheme is apparent in the word overall, but one particular grapheme (usually the initial letter or initial vowel) dominates. The synaesthetes in our sample experience colour both when hearing speech (also called 'coloured hearing') and when reading words, and so resemble other cases reported in the literature (eg Baron-Cohen et al 1996). While some synaesthetes state that the colours may be more vivid or automatic when elicited in a particular way (reading versus hearing), the colours themselves tend not to depend on the mode of input (see Simner et al, in press, for an in-depth description of this variant).

Synaesthesia is normally defined in phenomenological terms, although a number of different methods provide converging objective evidence for these phenomenological reports. People with synaesthesia show greater internal consistency than nonsynaesthetes given memory/imagery instruction (eg Baron-Cohen et al 1993); they may show facilitation on tasks of perception (Palmeri et al 2002; Ramachandran and Hubbard 2001) or memory (Smilek et al 2002a); and they show Stroop-like interference when the elicited synaesthetic colour differs from the veridical colour of a stimulus (Mills et al 1999). Moreover, functional imaging has suggested that some of the neural resources that, in other individuals, support normal colour perception, are used in synaesthesia (Nunn et al 2002).

That synaesthesia may advance our understanding of genetic influences on perception was first recognised by polymath Sir Francis Galton (Galton 1990; Galton 1883/1997). Galton noted that synaesthesia tends to cluster in families and is more common in women. However, it was not until the seminal work of Baron-Cohen and colleagues, 100 years later, that this suggestion appeared in a well-developed model (Baron-Cohen 1996; Baron-Cohen et al 1987, 1993, 1996). Synaesthesia may be an ideal system for neurogenetics in a number of respects. First, a relatively simple pattern of inheritance has been put forward. Baron-Cohen et al (1996) postulate that synaesthesia could result from a single dominant gene inherited via the X chromosome. Second, a neurodevelopmental mechanism has also been advanced. Synaesthesia may reflect aberrant connections between two unimodal perceptual regions, or between polymodal and unimodal regions. Baron-Cohen (1996) suggests that synaesthesia is something that we all possess in the first few months of life, but which is lost through programmed cell death (apoptosis). Synaesthetes, because of a genetic modification, may retain these pathways (see also Maurer 1997). Third, the phenotype appears to be relatively restricted and is unlikely to have been subjected to direct external intervention (eg remediation). Synaesthesia is not harmful or disruptive either in terms of physical health or cognitive ability (eg Cytowic 2002), and many synaesthetes remain unaware that their experiences are unusual until quite late in life (ie they may be unaware that other people do not experience, say, coloured numbers). Finally, the phenotype itself is intrinsically interesting. It may, for example, shed light on the neural substrate of conscious perceptual experiences, and colour in particular (Gray 2003; Gray et al 2002). In synaesthesia, people report conscious perceptual experiences in the absence of stimulation of the normal sensory pathways (eg from the eye to the visual cortex) as is evidenced by the fact that colour-selective regions can be activated from spoken input (eg Nunn et al 2002).

The aim of the present study is to replicate and extend the findings of Baron-Cohen et al (1996) and, as such, their study will be considered in some detail. Their first aim was to establish the prevalence and female – male ratio of synaesthesia within the general population. An advert was placed in two local newspapers in the city of Cambridge (UK), aimed at tapping the separate student and town populations. The advert described the phenomenon of synaesthesia and asked potential synaesthetes to contact the researchers. There were 26 confirmed cases: 22 had coloured words (related to graphemes within the words), and 4 had coloured music. The female – male ratio was 5.5 : 1 (22 women, 4 men). Baron-Cohen et al estimated the prevalence of synaesthesia to be a minimum of 1 in 2000, based on newspaper circulation figures of 55 000.

In an additional study, they considered 6 families in detail (see also Bailey and Johnson 1997). These were selected on the basis of having several affected family members. The female – male ratio of affected members was 7.7 : 1. There was no evidence for father – son transmission, but all other possible parent – offspring patterns of transmission were observed. In order to account for this, Baron-Cohen et al (1996) speculated that synaesthesia may be the outcome of a single gene on the X chromosome. To account for the heavily skewed female – male ratio, they suggested that the trait may be lethal in males, causing death in utero. In support of this, it was found that the families of synaesthetes tend to contain far more women than men.

None of the 6 families reported by Baron-Cohen et al (1996) showed the skipping of generations. However, 6 out of 11 of the pedigrees reported by Cytowic (2002) exhibited this pattern, as did the family reported by Hubbard and Ramachandran (2003). Although tests of consistency were not always reported, taken at face value these results suggest that the genotype can be transmitted without apparent expression of the phenotype (ie reduced penetrance of the trait). A study of a single pair of monozygotic female twins is also consistent with these data and suggests a possible genetic mechanism (Smilek et al 2002b). Smilek et al (2002b) found (using consistency and Stroop measures) that synaesthesia can be present in one twin but not the other. They interpreted the data in terms of X inactivation (for a summary see Lyon 1999). To prevent a double dosage of the gene products of the X chromosome, women inactivate one of their X chromosomes. This occurs early in development and is retained by subsequent cell divisions, such that women are a mosaic of the two cell types. If the X chromosome containing the hypothetical 'synaesthesia gene' is inactivated, then the phenotype would not be expressed and the trait could skip a generation. There is some evidence to suggest that the process of twinning in women can produce skewed X inactivation (Goodship et al 1996; but see Machin 1996). The only other reported case of synaesthetic twins was noted by Alford (1918). These were both male and both displayed synaesthesia (it was not clear whether they were monozygotic, however). An alternative account to X inactivation would be that different chromosomes are expressed in different parts of the brain (Rehen et al 2001).

The most problematic finding for this model of inheritance would be any evidence of father – son transmission. Jordan (1917) does indeed report the presence of synaesthesia in his own son, Eric (as well as his niece), and the colours were noted to be consistent over time. Laignel-Lavastine (1901) reported another apparent example of father – son transmission (ML to CL) in a family with 9 synaesthetic members (out of 11). However, to establish father – son transmission, one would also need to show that it was not coincidentally present in the maternal line. This may not be a trivial task if synaesthesia can skip generations.

The aim of this study is to replicate and extend the previous findings considering a much larger sample of families ($N = 85$). Baron-Cohen et al (1996) selected families on the basis that each contained more than one synaesthete. However, in order to have a more reliable estimate of the penetrance of a trait, it is important to also include those synaesthetes who do not report other affected family members. It will be shown that our results offer support for an X-linked dominant model of inheritance but offer no evidence for male lethality, and suggest that the female – male ratio may be considerably lower than previously assumed.

2 Method

2.1 *Participants*

Our research group (see http://www.syn.ucl.ac.uk) had been contacted by 85 potential grapheme–colour synaesthetes, for whom we have had the opportunity to assess their consistency over time and obtain a family tree. These consisted of 67 females and 18 males.

Thus, the female–male ratio in this self-referred sample was 3.72 : 1. There were 72 people who were right-handed when holding a pen, 11 who were left-handed, and 2 who claimed to be ambidextrous. The proportion of left-handers in the group (13%) is similar to that reported for the UK population in general (eg McManus 2002), and matches that found for the Australian sample of synaesthetes reported by Rich and Mattingley (2002). The mean age of the sample was 40.2 years. The oldest person was aged 81 and the youngest 19 years. We have chosen to concentrate on grapheme–colour synaesthesia because (i) it is the most common type, (ii) the methods for establishing the authenticity of this type of synaesthesia have been replicated many times, and (iii) we wish to make a direct comparison with the study of Baron-Cohen et al (1996). We note that many of the sample additionally reported colours for stimuli other than graphemes. The other types of stimuli that elicit synaesthetic colours were distributed amongst our sample as follows: days–colour (95%), months–colour (91%), other English words–colour (81%), music–colour (29%), smell–colour (15%), taste–colour (14%), and pain/touch–colour (14%). Synaesthetic experiences in other sensory modalities are far less common, and were distributed as follows: x–taste (18%), x–pain/touch (11%), x–smell (9%), and x–sound (5%) (where x denotes the inducing stimuli which were too numerous to document individually). The fact that different types of synaesthesia tend to co-occur has important implications for linking genotype to phenotype, and we return to this in section 4.

2.2 *Test of consistency*

Synaesthetes were asked to describe their colour experience in response to the 26 letters of the alphabet and 10 single-digit numerals on two separate occasions. The retest interval was between 5 weeks and 14 months (median 5 months). On the first occasion, the stimuli were presented in alphanumeric order and on the second occasion they were randomised. Performance was compared to a set of 48 control subjects who were all retested after a 1–3 week interval. Thus, we 'stacked the deck' against our synaesthetes by giving them a longer period over which to be tested. Controls were asked to free associate the first colour that came to mind and were required to give a colour for every item.

2.3 *Analysis of pedigrees*

First of all, each synaesthete indicated the structure of his/her family in terms of number of sons, daughters, brothers, sisters, aunts and uncles (maternal and paternal), and male and female cousins (maternal and paternal). This enables us to assess the hypothesis that there is male lethality in the families of synaesthetes. In order to evaluate patterns of inheritance, each proband in our sample was asked about the presence of other known synaesthetes within the family. Synaesthetes were strongly discouraged from guessing whether a family member has synaesthesia (eg because they are artistic) and to consider only those cases that had been *directly* asked (following Baron-Cohen et al 1996). As such, each family member was classified in one of three ways: having synaesthesia, not having synaesthesia, or unknown.

3 Results

3.1 *Validation of the grapheme–colour phenotype*

The mean consistency of the synaesthetes was 92% (SD = 10.8%), compared to 33% (SD = 14.2%) from controls ($t_{131} = 26.82$, $p < 0.001$). Figure 1 shows the distribution of consistency scores for both of our samples. As can be seen, the distribution is essentially bimodal, with very little overlap between the groups. In terms of their internal consistency, people with synaesthesia do not seem to lie on a continuum with other members of the population. This adds weight to the suggestion that the synaesthetic phenotype is either present or absent in a given individual. We will return to the issue in section 4.

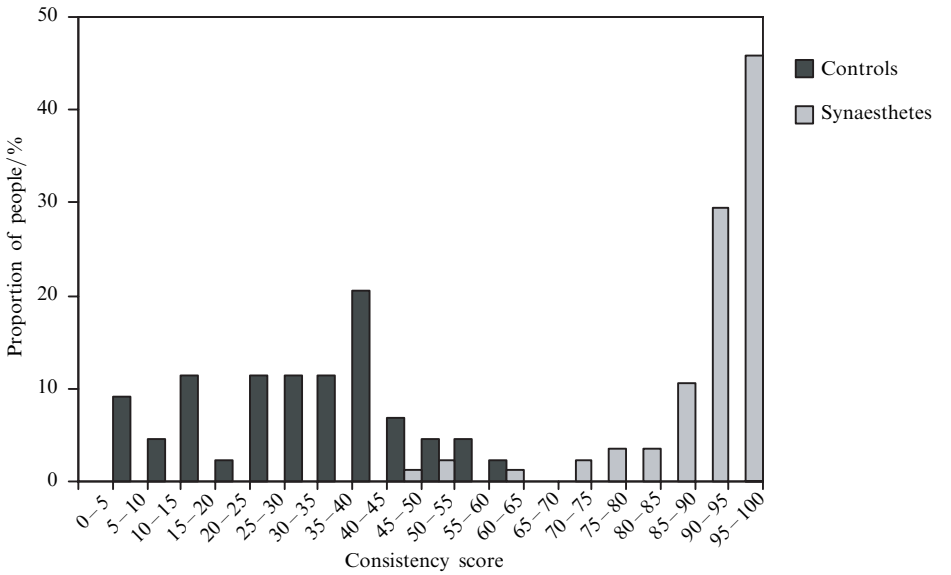

Figure 1. The distribution of grapheme–colour consistency scores is bimodal.

3.2 *Male lethality? No*

A preliminary analysis yielded no differences between male and female synaesthetic probands and so the data are collapsed across this dimension. Table 1 shows that there was no evidence of male lethality. The observed distribution was compared to the expected 50 : 50 distribution (based on the null hypothesis of no sex-linked lethality) by means of the χ^2 test. Synaesthetes are just as likely to give birth to a son as to a daughter, and are just as likely to have a brother as a sister. There was no difference in the number of maternal aunts to maternal uncles, the number of maternal female to maternal male cousins, the number of paternal aunts to paternal uncles, or the number of paternal male to paternal female cousins. We note that measuring the female–male ratio of relatives is an indirect measure of lethality, compared to measuring rates of miscarriage (although even the latter method is prone to difficulty without inspection of menses). However, the present method to demonstrate lethality has been used in other studies (Green and Keverne 2000; Turner 1995). We believe that the previous report of female-to-male bias in the family composition of synaesthetes (Baron-Cohen et al 1996) is an artifact of the small number of pedigrees ($N = 6$) that were analysed.

Table 1. The female : male ratio of various relative groups of synaesthetes and comparison of results to a 50 : 50 ratio. The 85 families of the verified synaesthetes contain equal numbers of males and females.

	Female : male ratio	χ^2, p	N
Daughters : sons	1.23 : 1	0.82, ns	78
Sisters : brothers	1.13 : 1	0.50, ns	128
Maternal aunt : uncle	0.99 : 1	0.01, ns	163
Maternal cousins	0.88 : 1	1.02, ns	252
Paternal aunt : uncle	0.89 : 1	0.52, ns	155
Paternal cousins	0.92 : 1	0.47, ns	257

3.3 *Female – male ratio of synaesthesia revisited*

We can recalculate the female – male ratio in synaesthesia, taking into consideration the other affected family members. The synaesthetes directly asked 351 other family members about the presence of synaesthesia (159 males, 192 females; 266 first-degree relatives, 85 second-degree relatives). Of these, 19 males and 39 females reported the presence of synaesthesia, resulting in a female – male ratio of 1.7 : 1, ie (39/192) : (19/159). If one includes the initial 85 synaesthetes themselves, then the female – male ratio is 2 : 1. Both of these estimates are considerably lower than the 3.7 : 1 estimate based upon the self-referred sample of 85 synaesthetes, and lower still than the 5.5 : 1 ratio of Baron-Cohen et al (1996). There are two possible reasons why this might be. First, it could be the case that some family members said that they have synaesthesia when in fact they do not. As we did not test all of the other family members, we cannot exclude this possibility. However, in order to account for the change in female – male ratio we would need to make the further assumption that men are more likely to falsely report the presence of synaesthesia than women. Whilst we cannot refute this, it strikes us as unlikely. The second possibility could relate to the sampling method. Female synaesthetes may be more likely to come forward and volunteer for research, leading to an inflated female – male ratio. It is perhaps only when one tries to look inside the families that the male synaesthetes are found in their true numbers. Indeed, for the only other estimate of the female – male ratio a survey was used rather than self-referral; this yielded a female – male ratio very similar to our recalculated ratio. Uhlich (1957) reported 2.2 : 1. It is well established that men are less likely to engage in self-disclosure with strangers than are women (Dindia and Allen 1992). Further empirical studies are needed to unequivocally establish whether synaesthesia research has fallen foul of this bias.

3.4 *Familial aggregation and transmission characteristics*

Of the 85 families, 44% contain at least 1 other known synaesthete (according to questioning by a researcher or other family member). There was 1 family containing 6 reported synaesthetes, 4 families containing 4 known synaesthetes, 9 containing 3 known synaesthetes, 23 containing 2 known synaesthetes, and 48 containing only 1 known synaesthete. However, it is to be noted that the number of family members directly asked about the presence of synaesthesia varied greatly (mean = 4.1 family members asked, range = 0 – 27), as did the size of the families themselves (mean = 14.1, range = 2 – 51; counting sons, daughters, parents, aunts, uncles, and cousins). Whilst we cannot make any claims about the family members that were not asked about synaesthesia, our study provides evidence that synaesthesia has a tendency to cluster in families.

The transmission characteristics of synaesthesia are shown in figure 2. Male synaesthetes are significantly more likely to have synaesthetic daughters than sons ($\chi^2_1 = 6.12$, $p < 0.05$) and are significantly more likely to have a synaesthetic mother than father ($\chi^2_1 = 8.08$, $p < 0.005$). In fact, there was a complete absence of father – son transmission. This is consistent with an X-linked dominant mode of inheritance. Male synaesthetes are just as likely to have a synaesthetic sister as brother ($\chi^2_1 = 1.84$, ns).

Female synaesthetes are just as likely to have synaesthetic daughters as sons (although there is a nonsignificant trend to have more synaesthetic daughters ($\chi^2_1 = 2.88$, $p = 0.09$), and are just as likely to have synaesthetic sisters as brothers ($\chi^2_1 = 0.92$, ns). However, female synaesthetes are more likely to have a synaesthetic mother than father ($\chi^2_1 = 4.06$, $p < 0.05$).

It is to be noted that we found one family (whom we shall call 'R') that could potentially contradict an X-linked mode of inheritance. Their family tree is shown

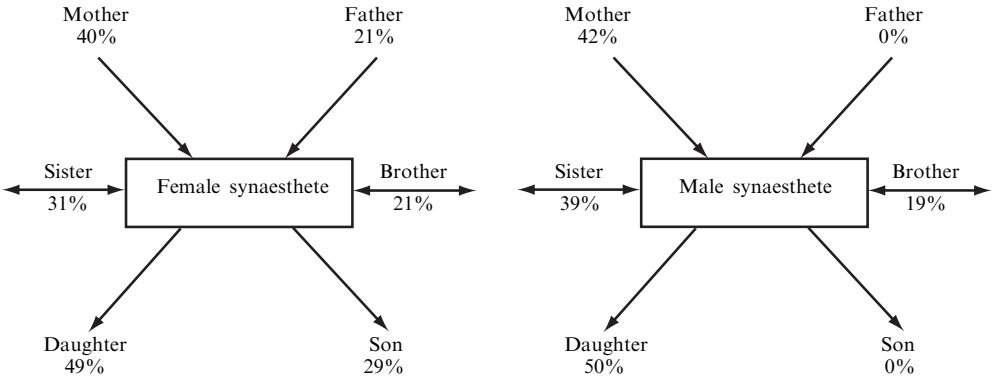

Figure 2. The 'risk factor' for the relatives of male and female synaesthetes. The percentages indicate the proportion of family members who claimed to have synaesthesia.

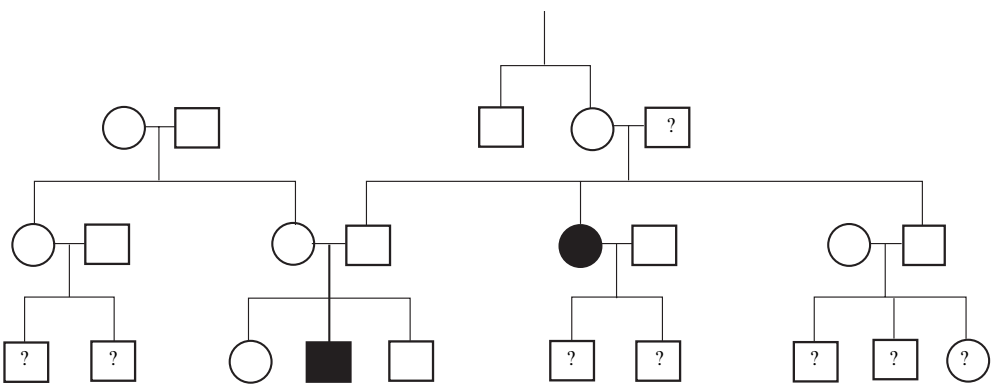

Figure 3. The 'R' family has synaesthesia in the paternal line and a synaesthetic son. Squares represent males, and circles females. Black shapes are synaesthetes, white ones are nonsynaesthetes, and question marks are family members that we cannot be certain about (ie they are either too young to be asked, deceased, or not in contact with other family members).

in figure 3. The 'R' family consisted of a boy and his *paternal* aunt who both reported synaesthesia. Both the boy and his aunt were consistent at a 5-month retest (95% and 100%, respectively). The father of the boy did not, however, report synaesthesia and obtained a grapheme–colour consistency score within the control range (33% at a 2-week retest), as did his mother (50%), older sister (33%), and younger brother (25%). There was no evidence of synaesthesia in the maternal line (neither the mother's sister nor her parents report the trait). While skewed X inactivation can account for skipping generations down the maternal line, this explanation cannot apply to the paternal line and would appear to implicate some other mechanism of reduced penetrance, bilineality of the trait, or an alternative mode of inheritance. We return to this later.

4 General discussion

The aim of this study was to extend the analysis of 6 synaesthetic families conducted by Baron-Cohen et al (1996) to a larger sample, with a view to establishing a possible mode of inheritance. In some respects, our results are similar. We find synaesthesia to be more common in women than men, and find broadly similar transmission characteristics to other studies. A meta-analysis of three studies is summarised in table 2. The results offer general support for a single-gene X-linked dominant mode of inheritance as postulated before (eg Bailey and Johnson 1997) and discussed in more

Table 2. The 'risk factor' for transmission of synaesthesia from affected mothers or fathers to their offspring from three different studies, and a meta-analysis of the three studies.

	Baron-Cohen et al (1996)	Cytowic (2002)	Ward and Simner (present study)	Meta-analysis
Mother → daughter	78% (14/18)	56% (5/9)	49% (21/43)	57% (40/70)[a]
Mother → son	11% (1/9)	40% (6/15)	29% (8/28)	28% (15/52)
Father → daughter	100% (5/5)	50% (4/8)	50% (9/18)	58% (18/31)[b]
Father → son	0% (0/0)	0% (0/2)	0% (0/8)	0% (0/10)

[a] Synaesthetic mothers are more likely to pass the trait to daughters than sons: $\chi^2_1 = 9.65$, $p < 0.005$.
[b] Synaesthetic fathers are more likely to pass the trait to daughters than sons: $\chi^2_1 = 5.29$, $p < 0.05$.

detail below.(2) However, our results are not in full agreement with previous research. We estimate the female – male ratio in synaesthesia to be approximately 2 : 1, and can find no evidence of male lethality. The families of synaesthetes do not contain more female members, as would be predicted by this hypothesis. The absence of male lethality is good news for synaesthetes, and suggests that synaesthesia has no negative implications, at least in terms of early survival. It is possible that in previous research different results have been obtained because male synaesthetes may be less likely to disclose their synaesthesia and, hence, less likely to volunteer for research. Indeed, our own female – male ratio for self-referred synaesthetes (3.7 : 1) is higher than the 2 : 1 found within the families. Nonetheless, this debate is unlikely to be resolved until a prevalence study is conducted that relies on large-scale survey (together with an objective measure of authenticity) rather than self-referral.(3) Uhlich (1957) reported a 2.2 : 1 female – male ratio in his survey of men and women, but no objective test of synaesthesia was used. As for male lethality, we can only assume that this was an artifact of the small number of families previously sampled. A high female – male ratio (>2) is problematic for the hypothesis that synaesthesia is an X-linked dominant trait but a 2 : 1 ratio is not.(4)

It is important to acknowledge the limitations of a study of this nature, and to be circumspect in our claims. First of all, it was not possible for us to verify the presence or absence of synaesthesia in each of the family members. Whilst this may well introduce noise into our data, it does not necessarily invalidate them. The sample of synaesthetic probands that we were able to test all appeared to be genuine (ie the rate of false positives was low). Furthermore, this source of noise cannot have affected our estimates of whether verified synaesthetes are more likely to give birth to sons or

(2) One may wonder why there appears to be differences in sample sizes across these four categories. This is explicable by the fact that in our initial sample there is a 3.7 : 1 bias in favour of women. Thus, there are numerically more mother – child pairings to consider than father – child pairings, even though (proportionally speaking) the chance of a synaesthete giving birth to a son or daughter is the same. For this analysis, we also counted transmission from the parents of the proband to the proband, as well as from probands to their own children. As there are more female probands, there are numerically more father-to-female proband observations than father-to-male proband observations. This distorts the sample sizes further. Future research focused on male synaesthetes would redress this.

(3) Indeed, a large-scale prevalence study ($N = 1700$) conducted by our research groups reveals a female – male ratio that is more in line with the present estimate than previous ones, and a prevalence of around 1% for grapheme – colour synaesthesia.

(4) The mathematics of this limit are as follows. If p males will carry the gene for synaesthesia and be synaesthetic, then $p^2 + [2 \times (1 - p)]$ of females will be synaesthetic (allowing for the fact that they can be homozygous or heterozygous for the allele). The female – male ratio thus simplifies to $(p + 2) : 1$. Since p must fall between 0 and 1, the ratio must be between 1 and 2 for this mode of inheritance, assuming no complicating factors.

daughters, nor can it affect estimates of the overall female–male ratio (unless we assume that males are more likely to falsely report synaesthesia). Another limitation to our approach is that we concentrated on the most common type of synaesthesia (grapheme–colour) for our initial selection of synaesthetes. Synaesthesia is a heterogeneous phenomenon in which individuals may exhibit several variant manifestations, and in which colour is not always the affected modality (eg Ward et al 2005). This oversimplification was done on pragmatic grounds, rather than from a belief that each type of synaesthesia has an independent cause. We shall return to this later.

4.1 *Modes of inheritance*

First, we consider whether the apparent aggregation of synaesthesia within families could have arisen in an artifactual way. We might imagine a number of ways in which such an artifact could have occurred, and these are discussed below (although we do not consider any of these reasons entirely plausible). It could be the case that synaesthesia affects (for whatever reason) a proportion of the population at random. In this case, a family with 2 synaesthetic members would be explained as a coincidence of 2 independent events. The key to dismissing this hypothesis lies in the low prevalence of synaesthesia (at least 1 in 2000—Baron-Cohen et al 1996) in contrast to the high proportion of families (44%) containing 2 or more synaesthetes, and the fact that 16% of family members asked reported synaesthesia. To reach this figure purely on the basis of sampling coincidence, one would need to assume a prevalence rate of 13.5%,[(5)] even then, it would not explain the sex ratio.

Another artifactual explanation is in terms of shared environment, although this explanation is lacking in a number of respects. First, one would need an ad hoc explanation for the female–male ratio and the pattern of sex-biased transmission. More direct evidence against cultural transmission is that related synaesthetes typically do not agree upon what colour letters should be (Baron-Cohen et al 1996; Jordan 1917), which we might have expected if, say, a mother had instructed her daughter what colour the letter 'A' should be. The manifestation of the phenotype can vary more grossly within families, which also speaks against cultural transmission. Out of the 6 families reported by Baron-Cohen et al (1996), 2 contained a mix of grapheme–colour and music–colour synaesthesia, and Ward et al (2005) found that people with synaesthetic tastes typically report relatives having synaesthetic colour (this being the statistically most probable outcome).

An autosomal recessive mode of inheritance is unlikely because of the high number of families containing 2 or more known family members in different generations. Recessive traits require allele to be present in both parents of the offspring, but the parents themselves would not express the phenotype unless they had two copies of the allele.

An autosomal dominant model of inheritance is also considered unlikely, but cannot be ruled out. The fact that synaesthesia can skip generations would not be predicted by this mode of inheritance and nor would the observed sex ratio, unless one also postulated sex limitation (reduced expression in males). Even with sex limitation, however, it is not obvious why the mother–son risk rate would be higher than that of father–son, if the trait were indeed inherited autosomally. The sex of the parent seems to be as important as the sex of the offspring. This could potentially point to epigenetic factors

[(5)] The calculation is as follows. We assume that 4 family members are asked about the presence of synaesthesia (based on our own figures). What prevalence rate x is needed to generate a probability of 0.44 of finding at least 1 other synaesthete if one assumes that the presence of synaesthesia is independent of shared genes or shared environment? The probability of finding no family members who are synaesthetes is 0.56 ($= 1 - 0.44$), and this figure is equivalent to $(1 - x)^4$; thus x is $(1 - 0.56^{1/4}) = 0.135$.

(eg an imprinted locus). If father–son transmission turns out to be possible (eg Jordan 1917; Laignel-Lavastine 1901), then this mode of inheritance would be the favoured one.

As with previous research, we consider an X-linked dominant mode of inheritance to be the most likely method of transmission. This mode can account for our female–male ratio of 2 : 1, and the absence of father–son transmission. It could also account for skipping generations on the maternal line if there is an uneven pattern of X inactivation (Smilek et al 2002b) or some other mechanism of differential chromosome expression (Rehen et al 2001). However, other factors are also likely to come into play. The expected risk rates for this mode of inheritance are: father → daughter = 100%, father → son = 0%, mother → daughter = 50%, mother → son = 50% (assuming the mother is heterozygous for the trait allele). A comparison with our meta-analysis suggests reduced penetrance when the offspring is male or the affected parent is male. Under this account, we would explain the 'R' family showing apparent paternal line inheritance as coincidental bilineality of an infrequent but not exceptionally rare trait.

4.2 *Is synaesthesia continuous or dichotomous?*

There has been virtually no debate in the synaesthesia literature whether one person might be 'more synaesthetic' than another. However, a discussion along these lines is essential for making claims about the relationship between phenotype and genotype, and also for ascertaining whether synaesthesia is continuous with the 'normal' population. It is undoubtedly the case that some individuals manifest with more types of synaesthesia than do others. The famous case study by Luria (1968) had synaesthesia involving elements of taste, sound, colour, shape, and touch. Other individuals may have colours only with, say, days of the week (eg Cytowic 2002). However, it is not at all obvious that variations in the number of types of synaesthesia exhibited necessitates the view that synaesthesia is a continuous dimension in any behavioural sense or in terms of underlying gene expression.

In many X-linked conditions (eg red–green colour blindness, Duchenne muscular dystrophy) males exhibit stronger symptoms than women because women have a second X chromosome which they can fall back on. In fact, many women effectively act as 'carriers' in the sense that the effects of possessing the gene are negligible. At present, there are no obvious signs that synaesthetic men are 'more synaesthetic' than women, and indeed, there is some evidence to the contrary (ie greater mother–daughter than mother–son transmission). It would be interesting to know the transmission rates and phenotypic traits of women who have both a synaesthetic mother and a synaesthetic father. In summary, although there is heterogeneity in the synaesthetic phenotype, there is no convincing evidence that synaesthetes can be ranked in any meaningful way.

We might similarly ask whether our synaesthetes appear to be different from others because they are sampled from the tail end of a single normal distribution. In terms of their internal-consistency scores, this appears not to be the case. The scores of synaesthetes appear to have a distribution of their own (centred around a mean of $\sim$95%). A similar, virtually nonoverlapping, distribution of consistency scores has been reported for sound–colour synaesthesia (Ward et al, in press). This suggests to us that synaesthesia may be a trait that is either present or absent in an individual, although this may still be related to continuous variation in gene expression (eg, if the level of expression is above or below a certain threshold, then different developmental trajectories may be triggered). It is hoped that this discussion will stimulate further empirical research and debate on this key topic.

4.3 *From genotype to phenotype*

At present, very little is known about the sequence of events that translate the genotype into the observed phenotype. The neonatal synaesthesia hypothesis (NSH) states that synaesthesia is found in all human neonates but is only retained into adulthood by a

small number of people (Baron-Cohen 1996; Maurer 1997). Neurobiological studies carried out with hamsters (Frost 1984) and kittens (Dehay et al 1984; Innocenti and Clarke 1984) show connections between unimodal auditory and visual regions in early development. It has been suggested that, because of a genetic modification, these connections may not be eliminated in adult human synaesthetes.

Whilst the NSH theory is attractive in its simplicity, the situation is likely to be more complex. In humans, the time scale of synaptogenesis and synapse elimination is different from other species. In visual areas, synaptogenesis and synapse elimination occur concurrently with a peak in synapse density at around 4 months postnatal, but not approaching adult levels until 4 years of age (Huttenlocher and de Courten 1987). Glucose metabolism in the occipital lobe (an index of synaptic use rather than density) is greatest in early childhood at the age of 3 to 8 years (Chugani et al 1987). Furthermore, visual ERPs (event related potentials) to auditory stimuli decrease after 6 months but are still present at between 20 and 30 months of age (Neville 1995). This suggests that synaesthesia-like responses may exist in everyone well beyond the neonatal period.

In terms of neuronal development, we can consider at least three candidate mechanisms: synaptogenesis, synapse elimination, and programmed cell death (apoptosis). Whilst synaptogenesis (Bourgeois et al 1989) and programmed cell death (Margolis et al 1994) are under intrinsic control, synapse elimination is environmentally regulated (eg Blakemore et al 1978; Neville et al 1983). This makes synapse formation or programmed cell death more likely candidates for genetic influences on synaesthesia than synapse elimination. NSH supporters have advocated programmed cell death, although there may be an unusual density of synapses formed in some areas. Perhaps the timing of synapse formation versus elimination is delayed in synaesthesia such that atypical connections may form at later periods (eg during literacy acquisition). The fact that synaesthesia tends to be evoked by graphemes is not an obvious outcome of any theory grounded in the neonatal period. At present, this is no more than speculation, although we may turn to other genetic conditions for clues.

Fragile-X syndrome is a single-gene X-linked condition with a prevalence of 1 in 5000 and a female–male ratio of 1.5 : 1 (De Vries et al 1997). Unlike synaesthesia, the genotype is reasonably well understood (excessive repetition of a trinucleotide sequence). The behavioural phenotype is harder to characterise in specific terms. All aspects of cognition are affected, resulting in mental retardation, although adults show an uneven cognitive profile with particular weaknesses in attention and visuospatial cognition (for review see Karmiloff-Smith et al 2002). Despite a simple genotype, the genotype–phenotype relationship is unlikely to be simple because the available neurobiological evidence points to *experience-dependent* synaptic plasticity determining the phenotypic outcome (Churchill et al 2002). For example, Bayley et al (2001) report that the level of expression of the affected gene accounts for a small but significant variance in the level of development, but not the rate of development. The lesson from fragile-X syndrome is that a full understanding will only come about by considering how a single gene may interact with other genes and the environment within a developmental (ie nonstatic) context (eg Churchill et al 2002).

In conclusion, we suggest that a dynamic interaction between gene expression (possibly relating to synaptogenesis and plasticity) and early environmental experience would offer the best account of synaesthesia. The distribution of gene expression is unlikely to be localised to one specific region, given the fact that it is possible for multiple sensory modalities to be affected by synaesthesia both within individuals and within families. It may, however, be disproportionately concentrated within certain regions (eg left occipitotemporal regions) given the fact that certain phenotypes predominate. The gene may affect the amount, timing, or nature of synaptogenesis,

but with environmental influences shaping the nature of the associations. For example, our own research has shown that experiences of synaesthetic taste more closely resemble a childhood diet than the adult one (Ward and Simner 2003), and that the lexical–gustatory associations themselves are shaped by learned-vocabulary knowledge of food (Ward et al 2005). Given our review of the development and plasticity of sensory areas presented above, it seems unlikely to us that the sensitive period would be restricted to the neonatal period of development, but may extend until later into childhood. We hope that future studies will investigate synaesthesia in developing populations.

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References

Alford L B, 1918 "A report of two cases of synesthesia" *Journal of Abnormal Psychology* **13** 1–11

Bailey M E S, Johnson K J, 1997 "Synaesthesia: Is a genetic analysis feasible?", in *Synaesthesia: Classic and Contemporary Readings* Eds S Baron-Cohen, J E Harrison (Oxford: Blackwell)

Baron-Cohen S, 1996 "Is there a normal phase of synaesthesia in development?" *Psyche* [on-line serial] **2**(27) available: http://psyche.cs.monash.edu.au/v2/psyche-2-27-baron_cohen.html

Baron-Cohen S, Burt L, Smith-Laittan F, Harrison J, Bolton P, 1996 "Synaesthesia: Prevalence and familiarity" *Perception* **25** 1073–1079

Baron-Cohen S, Harrison J, Goldstein L H, Wyke M, 1993 "Coloured speech perception: Is synaesthesia what happens when modularity breaks down?" *Perception* **22** 419–426

Baron-Cohen S, Wyke M A, Binnie C, 1987 "Hearing words and seeing colours: an experimental investigation of a case of synaesthesia" *Perception* **16** 761–767

Bayley D B, Hatton D D, Tassone F, Skinner M, Taylor A K, 2001 "Variability in FMRP and early development in males with fragile X syndrome" *American Journal of Mental Retardation* **106** 16–27

Blakemore C, Garey L J, Vital-Durand F, 1978 "The physiological effects of monocular deprivation and their reversal in the monkey's visual cortex" *Physiology* **283** 223–262

Bourgeois J-P, Jastreboff P, Rakic P, 1989 "Synaptogenesis in the visual cortex of normal and preterm monkeys: evidence for intrinsic regulation of synaptic overproduction" *Proceedings of the National Academy of Sciences of the USA* **86** 4297–4301

Chugani H T, Phelps M E, Mazziotta J C, 1987 "Positron emission tomography study of human brain functional development" *Annals of Neurology* **22** 487–497

Churchill J D, Grossman A W, Irwin S A, Galvez R, Klintsova A Y, Weiler I J, Greenough W T, 2002 "A converging methods approach to Fragile X Syndrome" *Developmental Psychobiology* **40** 323–338

Cytowic R E, 2002 *Synaesthesia: A Union of the Senses* 2nd edition (Cambridge, MA: MIT Press)

Dehay C, Bullier J, Kennedy H, 1984 "Transient projections from the fronto-parietal and temporal cortex to areas 17, 18, 19 in the kitten" *Experimental Brain Research* **57** 208–212

Dindia K, Allen M, 1992 "Sex differences in self-disclosure: A meta-analysis" *Psychological Bulletin* **112** 106–124

Frost D O, 1984 "Axonal growth and target selection during development: Retinal projections to the ventrobasal complex and other 'nonvisual' structures in neonatal Syrian hamsters" *Journal of Comparative Neurology* **230** 576–592

Galton F, 1880 "Visualised numerals" *Nature* **21** 252–256

Galton F, 1883/1997 "Colour associations", in *Synaesthesia: Classic and Contemporary Readings* Eds S Baron-Cohen, J E Harrison (Oxford: Blackwell, 1997) pp 43–48; originally published in *Inquiries into Human Faculty and Its Development* (London: Macmillan, 1883) pp 105–112

Goodship J, Carter J, Burn J, 1996 "X-inactivation patterns in monozygotic and dizygotic female twins" *American Journal of Medical Genetics* **61** 205–208

Gray J, 2003 "How are qualia coupled to functions?" *Trends in Cognitive Sciences* **7** 192–194

Gray J A, Chopping S, Nunn J, Parslow D, Gregory L, Williams S, Brammer M J, Baron-Cohen S, 2002 "Implications of synaesthesia for functionalism" *Journal of Consciousness Studies* **9** 5–31

Green R, Keverne E B, 2000 "The disparate maternal aunt–uncle ratio in male transsexuals: An explanation invoking genomic imprinting" *Journal of Theoretical Biology* **202** 55–63

Henderson L, 1985 "On the use of the term 'grapheme'" *Language and Cognitive Processes* **1** 135–148

Hubbard E M, Ramachandran V S, 2003 "Refining the experimental lever: A reply to Shanon and Pribram" *Journal of Consciousness Studies* **10** 77 – 84
Huttenlocher P R, Courten C de, 1987 "The development of synapses in striate cortex of man" *Human Neurobiology* **6** 1 – 9
Innocenti G, Clarke S, 1984 "Bilateral transitory projection to visual areas from auditory cortex in kittens" *Brain Research* **14** 143 – 148
Jordan D S, 1917 "The colors of letters" *Science* **46** 311 – 312
Karmiloff-Smith A, Scerif G, Thomas M, 2002 "Different approaches to relating genotype to phenotype in developmental disorders" *Developmental Psychobiology* **40** 311 – 322
Laignel-Lavastine .., 1901 "Audition colorée familiale" *Revue Neurologique* **9** 1152 – 1162
Luria A, 1968 *The Mind of a Mnemonist* (New York: Basic Books)
Lyon M F, 1999 "X-chromosome inactivation" *Current Biology* **9** R235 – R237
Machin G A, 1996 "Some causes of genotypic and phenotypic discordance in monozygotic twin pairs" *American Journal of Medical Genetics* **61** 216 – 228
McManus I C, 2002 *Right Hand, Left Hand* (London: Weidenfeld and Nicolson)
Margolis R L, Chuang D M, Post R M, 1994 "Programmed cell death: Implications for neuropsychiatric disorders" *Biological Psychiatry* **35** 946 – 956
Maurer D, 1997 "Neonatal synaesthesia: Implications for the processing of speech and faces", in *Synaesthesia: Classic and Contemporary Readings* Eds S Baron-Cohen, J E Harrison (Oxford: Blackwell) pp 224 – 242
Mills C B, Boteler E H, Oliver G K, 1999 "Digit synaesthesia: A case study using a Stroop-type test" *Cognitive Neuropsychology* **16** 181 – 191
Neville H J, 1995 "Developmental specificity in neurocognitive development in humans", in *The Cognitive Neurosciences* Ed. M Gazzaniga (Cambridge, MA: MIT Press) pp 219 – 231
Neville H J, Schmidt A, Kutas M, 1983 "Altered visual evoked potentials in congenitally deaf adults" *Brain Research* **266** 127 – 132
Nunn J A, Gregory L J, Brammer M, Williams S C R, Parslow D M, Morgan M J, Morris R G, Bullmore E T, Baron-Cohen S, Gray J A, 2002 "Functional magnetic resonance imaging of synesthesia: Activation of V4/V8 by spoken words" *Nature Neuroscience* **5** 371 – 375
Palmeri T J, Blake R, Marois R, Flanery M A, Whetsell W, 2002 "The perceptual reality of synesthetic colors" *Proceedings of the National Academy of Sciences of the USA* **99** 4127 – 4131
Ramachandran V S, Hubbard E M, 2001 "Psychophysical investigations into the neural basis of synaesthesia" *Proceedings of the Royal Society of London B* **268** 979 – 983
Rehen S K, McConnell M J, Kaushal D, Kingsbury M A, Yang A H, Chun J, 2001 "Chromosomal variation in neurons of the developing and adult mammalian nervous system" *Proceedings of the National Academy of Sciences of the USA* **98** 13361 – 13366
Rich A N, Mattingley J B, 2002 "Anomalous perception in synaesthesia: A cognitive neuroscience perspective" *Nature Reviews Neuroscience* **3** 43 – 52
Simner J, Glover L, Mowat A, in press "Linguistic determinants of word colouring in grapheme – colour synaesthesia" *Cortex*
Smilek D, Dixon M J, Cudahy C, Merikle P M, 2002a "Synaesthetic colour experiences influence memory" *Psychological Science* **13** 548 – 552
Smilek D, Moffatt B A, Pasternak J, White B N, Dixon M J, Merikle P M, 2002b "Synaesthesia: A case study of discordant monozygotic twins" *Neurocase* **8** 338 – 342
Turner W J, 1995 "Homosexuality, type 1: An Xq28 phenomenon" *Archives of Sexual Behavior* **24** 109 – 134
Uhlich E, 1957 "Synesthesia in the two sexes" *Zeitschrift für Experimentelle und Angewandte Psychologie* **4** 31 – 57
Vries B B A De, Oweland A M W van den, Mohkamsing S, Duivenvoorden H J, Mol E, Gelsema K, Rijn M van, Halley D J J, Sandkuijl L A, Oostra B A, Tibben A, Niermeijer M F, 1997 "Screening and diagnosis for the fragile X syndrome among the mentally retarded: An epidemiological and psychological survey" *American Journal of Human Genetics* **61** 660 – 667
Ward J, Huckstep B, Tsakanikos E, in press "Sound – colour synaesthesia: To what extent does it use cross-modal mechanisms common to us all?" *Cortex*
Ward J, Simner J, 2003 "Lexical – gustatory synaesthesia: linguistic and conceptual factors" *Cognition* **89** 237 – 261
Ward J, Simner J, Auyeung V, 2005 "A comparison of lexical – gustatory and grapheme – colour synaesthesia" *Cognitive Neuropsychology* **22** 28 – 41

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