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Synaesthesia: Discordant *male* monozygotic twins

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Grapheme-color synaesthesia, a condition in which achromatic graphemes elicit vivid experiences of color is believed to be a genetically determined trait. We describe a study of 10-year-old twin brothers who are physically identical in appearance but who have considerably different conscious experiences. A phenotypic analysis that measured the consistency of grapheme-color pairings over test-retest confirmed that one twin has grapheme-color synaesthesia and the other twin does not. A genotypic analysis using sixteen microsatellite loci confirmed that the twins are monozygotic. These findings are problematic for previous suggestions that synaesthesia is an X-linked dominant trait. At the very least, the findings show that the penetrance of the genotype for synaesthesia is incomplete and that any view suggesting that synaesthesia is simply an X-linked dominant trait is therefore also incomplete and possibly even incorrect. The findings also negate a previous suggestion, based on a study of female monozygotic twins, that discordance of synaesthesia in identical twins is due to X-inactivation. In general, the findings raise serious questions regarding whether it is possible at this time to establish the genetic contribution to synaesthesia.

Introduction

Synaesthesia is a condition in which certain stimuli elicit conscious experiences that are not normally elicited by the stimuli. For instance, for some synaesthetes, tastes elicit tactile experiences (Cytowic, 1989; 1993) and for other synaesthetes, sound elicits vivid perceptions of color (Wheeler, 1920). In these cases, the inducing stimulus and the concurrent experience occur in different modalities. However, the inducer and the synaesthetic concurrent can also occur within the same modality. For example, in grapheme-color synaesthesia, perhaps the most common and most researched form of synaesthesia, visually presented achromatic letters or digits elicit additional perceptions of color (Dixon *et al.*, 2000; Mattingley *et al.*, 2001). Finally, abstract concepts can also elicit synaesthetic experiences. For example, units of time such as months of the year or days of the week can elicit colorful percepts that are experienced as being both external to the individual and localized in specific areas of space (Duffy, 2001).

One issue that has received considerable attention in studies and theories of synaesthesia is the role that genetics might play in the development of synaesthesia. From at least the time of Galton (1883), there has been continued speculation that there is a strong genetic basis for synaesthesia (Cytowic, 1989; Bailey & Johnson, 1997; Baron-Cohen *et al.*, 1993; 1996; Harrison & Baron-Cohen, 1997). There are good reasons for such speculations. First, it appears that synaesthesia may run in families (Bailey & Johnson, 1997). Second, the ratio of female to male synaesthetes is generally skewed, whereby considerably more females than males report having synaesthetic experiences. For example, Baron-Cohen and his colleagues (1996) estimated that there are seven females with synaesthesia for every male with synaesthesia. Based on these two lines of evidence, Baron-Cohen and his colleagues suggested that synaesthesia is likely an X-linked dominant trait. To account for the skewed female to male ratio, they speculated that there might be 50% *in utero* lethality for affected males. Despite these interesting speculations regarding the role of genetics in synaesthesia, there have actually been few formal studies on the topic.

In a recent report, we (Smilek *et al.*, 2002) presented findings that, on the surface, appear to be inconsistent with a strong genetic basis for synaesthesia. We reported a case study of twin sisters (EB and JB) who, according to their subjective reports, appeared to be discordant for synaesthesia. A genotypic analysis using eight microsatellite loci plus a gender-specific locus (amelogenin) revealed that the sisters were identical (monozygotic) twins. A behavioural assessment of synaesthesia using a variant of the Stroop task (Dixon *et al.*, 2000; Mattingley *et al.*, 2001; Odgaard *et al.*, 1999; Wollen and Rugiero, 1983) confirmed that EB had grapheme-color synaesthesia for digits and that her twin sister, JB, did not have synaesthesia. These findings were interesting in the context of previous speculations that synaesthesia is an X-linked dominant trait because discordance of synaesthesia in monozygotic twins is not readily consistent with such a speculation.

To reconcile this discordance of synaesthesia in monozygotic twins with speculations that synaesthesia is an X-linked

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trait, we (Smilek *et al.*, 2002) hypothesized a more nuanced genetic explanation of the discordance in monozygotic female twins. Specifically, we hypothesized that the phenotypic discordance between the twins was due to different patterns of *X chromosome inactivation* across the twin sisters. It is well known that in females there is X-inactivation or lyonization (Lyon, 1961; 1999) of one of the two X chromosomes during development. Patterns of X-inactivation can be different in monozygotic twins even though they have an identical genetic makeup if X-inactivation occurs after the twinning process (Chitnis *et al.*, 1999; Monteiro *et al.*, 1998). In such a case, the twins may have different active X chromosomes and consequently may be discordant for phenotypes determined by the X chromosome. X-inactivation has been used to explain discordance of numerous phenotypes in monozygotic female twins including red-green color blindness (Jorgensen *et al.*, 1992), haemophilia B (Revesz *et al.*, 1972) and muscular dystrophy (Richards *et al.*, 1990). In light of the research on X-inactivation, we hypothesized that if the synaesthesia gene is carried by one of the two X chromosomes and X-inactivation occurs after the twinning process, then it is possible to have discordance in synaesthesia between monozygotic female twins even though synaesthesia is a genetic trait.

Our X-inactivation hypothesis leads to a clear and testable prediction. Specifically, according to the X-inactivation hypothesis, there should be no male monozygotic twins who are discordant for synaesthesia. This prediction is based on the fact that X-inactivation occurs only in females; males have only one X chromosome which is never inactivated. Thus, if a case of male monozygotic twins discordant for synaesthesia were found, such a case would clearly be inconsistent with the hypothesis that discordance of synaesthesia in monozygotic twins reflects differential X-inactivation. More generally, such a finding would be problematic for the notion that synaesthesia is solely determined by an X-linked dominant gene (Baron-Cohen *et al.*, 1996).

In this paper, we report a case study of *male* monozygotic twins (JWB and ZJB) who are discordant for synaesthesia. One of the brothers (JWB) reports that he experiences colors for letters and numbers, whereas the other brother (ZJB) reports having no such experiences. In the study, we first conducted a genotypic analysis to confirm that the twins were in fact monozygotic. We then conducted a phenotypic analysis to confirm that JWB did indeed have synaesthetic experiences and that his identical twin brother, ZJB, did not have such experiences

Case Description

JWB and ZJB are twin brothers. ZJB was born first followed by JWB twelve minutes later. The brothers were ten years old at the time of testing. Based on physical appearance, the brothers appear to be identical. This observation was partly supported by reports from their mother indicating that at the time of birth the doctors told her that the boys were identical twins. However, we did not have access to the records of any genetic tests that may have been done at that time. The boys have lived all of their lives in southern Ontario, Canada and at the time of testing, both brothers were in the fifth grade at school. JWB's synaesthesia first became apparent to his mother in a discussion she had with him about his problems learning to read at school. When asked by his mother why he thought he was reading slowly, JWB mentioned that the colors of some letters, especially the letters "N" and "O", elicited bright colors that distracted him. In contrast, JWB's brother, ZJB, did not appear to have any trouble learning to read and told his mother that for him, letters were not associated with any specific colors.

Our initial interview with JWB strongly suggested that JWB had grapheme-color synaesthesia. JWB reported that each printed letter and digit elicited a highly specific experience of color. For example, the digit 7 elicited a yellow color experience and the letter D elicited a green color experience. He also reported that in general, the colors of letters and digits did not change over time. There were, however, a few graphemes that did change colors depending on situational context. These included the digits 1, 8, 9 and 10 and the letters U, Z, J, S, Q and X. Whether the changes in the colors for these graphemes followed any systematic rules was not readily apparent. JWB reported that the synaesthetic colors elicited by letters and digits are not under his intentional control, which suggests that these experiences are more or less automatic. Though JWB is very articulate for his age, it was difficult to ascertain from his responses to our questions whether his synaesthetic colors were experienced "in the mind's eye" or whether they were projected onto the visually presented graphemes (Dixon, Smilek, and Merikle, 2004); at times he would indicate that they were "in his mind's eye" and at other times that they were "out there on the page". Interestingly, even though JWB has strong synaesthetic colors for printed letters, he does not have any synaesthetic colors for cursive writing. On numerous occasions JWB mentioned that he found the lack of synaesthetic colors for cursive writing frustrating. JWB is now learning to write in cursive script, and it will be interesting to see whether letters written in cursive script begin to elicit synaesthetic colors as he becomes more proficient at writing and reading cursive script.

JWB also has other forms of synaesthesia. For instance, he reports that each month of the year has a specific color and is experienced in a specific spatial location. The months of the year are organized into an oval perceived in front of his body with January, February and March being on the left and August, September, October being on the right. The months are arranged in order in a clockwise direction, but they are unevenly spaced, with December and November taking up more space on the oval than the other months. The colors associated with each month are as follows: January = blue, February = pink, March = light green, April = red, May = green, June = blue, July = blue, August = red, September = orange, October = orange, November = pink, December = green. We refer to this type of synaesthesia as *time-space synaesthesia*.

JWB also perceives what he calls "auras" or "colored halos" surrounding people. For example, he perceives a purple aura surrounding his mother (See Ward, 2004 for a report on this form of synaesthesia).

In contrast to JWB, his brother, ZJB, reports having none of the experiences described by JWB. In fact, during our interview, ZJB expressed amazement at his brother's experiences because they were so different from his own subjective experiences. Taken together, the subjective reports of JWB and ZJB during our initial interviews strongly suggested that JWB is a synaesthete and that his brother ZJB is not.

Genotypic Analysis

DNA for the genotypic analysis was extracted from saliva samples taken from JWB and ZJB. The DNA analyses were conducted by Genetrack Biolabs, Vancouver, British Columbia, Canada. The DNA samples were amplified at 16 microsatellite loci. These 16 microsatellite loci and the corresponding amplification scores for JWB and ZJB are shown in Table 1. The table clearly shows that JWB and ZJB have identical genetic profiles. The probability that this match occurred from two independent fertilization events is 1 in 9.33 X 10^{18}. Thus, the genotypic analysis verified our initial conclusion based on physical appearance that JWB and ZJB are monozygotic twins.

Phenotypic Analysis

At the present time, the accepted criterion for categorizing an individual as a grapheme-color synaesthete is the consistency with which that individual pairs colors with graphemes over successive testing sessions (Baron-Cohen *et al.*, 1987; 1993; Dixon *et al.*, 2000; Mattingley *et al.*, 2001; Odgaard *et al.*, 1999; Svartdal and Iversen, 1989). When grapheme-color synaesthetes are asked to match colors with letters and digits, they typically choose a unique color for each letter and digit. Strikingly, when tested weeks, months, and even years later, synaesthetes tend to match the same colors to graphemes as they did in the initial testing session. Previous studies have shown that when synaesthetes match color labels (e.g., red, green etc.) to graphemes, over 85% of the grapheme-color pairings are identical across testing sessions (Dixon *et al.*, 2000; Mattingley *et al.*, 2001). In contrast, for non-synaesthetes, grapheme-color pairings vary substantially over time with typically less than 30% of the grapheme-color pairings remaining invariant over successive testing sessions (Mattingley et al., 2001). While no existing behavioral measure is a perfect indicator of synaesthesia, a high degree of consistency in grapheme-color pairings across successive testing sessions is currently the best way to corroborate the subjective reports of synaesthetes regarding their synaesthetic experiences.

We used three different measures of consistency to corroborate the radically different subjective experiences elicited when JWB and ZJB perceived graphemes. The first measure of consistency involved having JWB and ZJB apply color labels to graphemes over two testing sessions separated by a one-month interval (*categorical consistency assessment*). For the second measure of consistency, JWB and ZJB were asked to choose a precise color for each grapheme from a color palette displayed on a computer screen in two testing sessions (*continuous consistency assessment*). For the third measure of consistency, the consistency of JWB's and ZJB's grapheme-color matches was compared to the consistency of the color matches made by a normative group of 100 non-synaesthetes (*normative consistency assessment*). As will become apparent, each measure of consistency confirmed that JWB does in fact have grapheme-color synaesthesia and that his brother, ZJB, does not have grapheme-color synaesthesia.

Table 1. The 16 microsatellite loci used in the genotypic analysis and the corresponding amplification scores for JWB and ZJB

DNA Locus	Amplification Scores		Matching Probability (n^{-1})
	JWB	ZJB	
D8S1179	13:14	13:14	10.03
D21S11	30:30	30:30	16.97
D7S820	10:12	10:12	11.76
CSF1P0	11:12	11:12	5.86
D3S1358	16:16	16:16	11.47
TH01	6:08	6:08	22.72
D13S317	10:11	10:11	25.46
D16S539	11:12	11:12	7.05
D2S1338	16:25	16:25	150.51
D19S433	13.2:15	13.2:15	82.16
vWA	17:17	17:17	17.84
TPOX	8:11	8:11	3.95
D18S51	15:18	15:18	48.7
D5S818	11:13	11:13	9.02
FGA	19:23	19:23	44.46
AMELOGENIN	XY	XY	

Categorical consistency assessment

JWB and ZJB were presented with a list of 36 achromatic (i.e., black) graphemes which included the upper-case letters A to Z (26 graphemes) and the digits 0 to 9 in random order (10 graphemes). Both twins were required to write the color label that they associated with each grapheme. JWB wrote the labels of the synaesthetic colors induced by the graphemes, whereas, ZJB (the twin putatively without synaesthesia) was asked to write down a different color label for each grapheme. Approximately one month later (28 days), this procedure was repeated. In the later testing session, the graphemes were presented in a different random order than in the first testing session. To determine the level of consistency for each twin, we counted the number of grapheme-color pairings that were identical across the two testing sessions.

The results showed that JWB reported the same grapheme-color matches for 32 of the 36 graphemes (88.9%) across the two testing sessions. Because JWB reports that 9 of the graphemes (i.e., 1, 8, 9, U, Z, J, S, Q and X) change color from time to time, we also calculated his consistency with these graphemes removed. When only the remaining 27 graphemes were considered, JWB had consistent grapheme-color pairings for 25 (92.6%) of the graphemes. Such a high level of consistency is similar to that shown by other synaesthetes (Dixon *et al.*, 2000; Mattingley *et al.*, 2001). In contrast to JWB's high consistency, ZJB showed low consistency. He generated the same color labels across the two testing sessions for only one of the 36 graphemes (2.8%). ZJB's low level of consistency clearly supports his claim that he does not have grapheme-color synaesthesia. Thus, the results of this first consistency assessment support the conclusion that the twins are discordant for grapheme-color synaesthesia.

Continuous consistency assessment

For the second measure of consistency, JWB and ZJB were presented with a color palette on a computer screen and asked to choose the precise colors for the upper-case letters A to Z and the digits 0 to 9. JWB was asked to choose the color that matched the synaesthetic color induced by the grapheme, whereas ZJB was asked to select any color he wanted in response to each grapheme, but to choose different colors for different graphemes. An example of the stimulus display is shown in Figure 1. For each grapheme, the twins were required to move the mouse pointer over the color that best matched the experienced color of the grapheme on the screen. As the mouse moved over the palette, the color which the mouse pointed to was displayed in the square below the palette beside the grapheme. Once a color was matched to each grapheme, the procedure was repeated a second time with a different randomized ordering of the graphemes. The two testing sessions were completed in immediate succession. The Red, Green and Blue (RGB) values associated with the color selection for each grapheme were recorded. These values allowed the consistency of the grapheme-color pairings to be measured on a continuous scale.

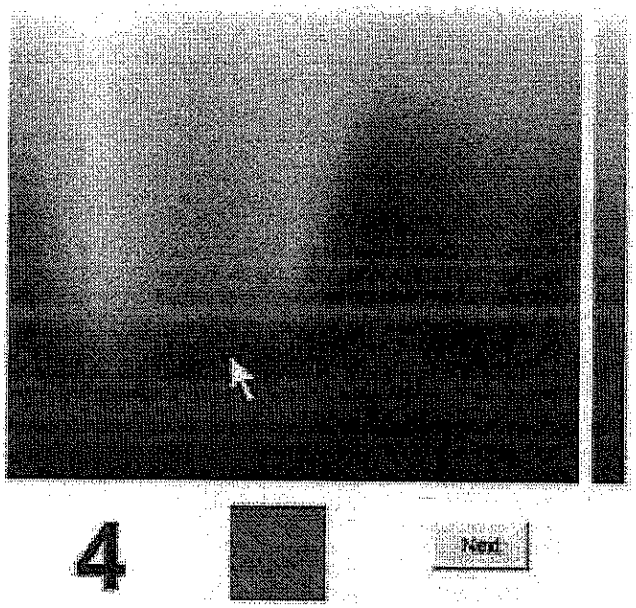

Fig. 1. The stimulus display used in the continuous consistency assessment and the normative continuous consistency assessment.

To estimate how consistently a particular color was paired with a given grapheme, we calculated the Euclidian distance (*delta*-E) in color space between the colors chosen for a grapheme in the first and second matching sessions. The distance between the two successive color selections for each grapheme required that the RGB values for each selected video color be transformed into CIE Lab values[1]. In CIE Lab space, the L value indicates the amount of lightness, the a value indicates the relative amount of red or green and the b value indicates the relative amount of yellow or blue. A delta-E score for the two successive color selections for each grapheme was calculated using the following formula:

$$delta-E=\sqrt{(L_2-L_1)^2+(a_2-a_1)^2+(b_2-b_1)^2}$$

In this formula, L_1, a_1 and b_1 are the CIE Lab values for the first color selection for a given grapheme and L_2, $a2$ and b_2

[1] The RGB values were first converted to values ranging from 0 to 1 using the following formulas:

$r = 0.0039215 \times R$

$g = 0.0039215 \times G$

$b = 0.0039215 \times B$

The r, g and b values were then used to calculate CIE XYZ scores as follows:

$X = (0.431 \times r) + (0.342 \times g) + (0.178 \times b)$

$Y = (0.222 \times r) + (0.707 \times g) + (0.071 \times b)$

$Z = (0.020 \times r) + (0.130 \times g) + (0.939 \times b)$

The CIE XYZ scores were then converted to CIE Lab scores in the following manner:

$$L = \left(116 \times Y^{\frac{1}{3}}\right) - 16 \quad [\text{if } Y > 0.008856]$$

$$L = 903.3 \times Y \quad [\text{if } Y <= 0.008856]$$

$$a = 500 \times \left(X^{\frac{1}{3}} - Y^{\frac{1}{3}}\right)$$

$$b = 200 \times \left(Y^{\frac{1}{3}} - Z^{\frac{1}{3}}\right)$$

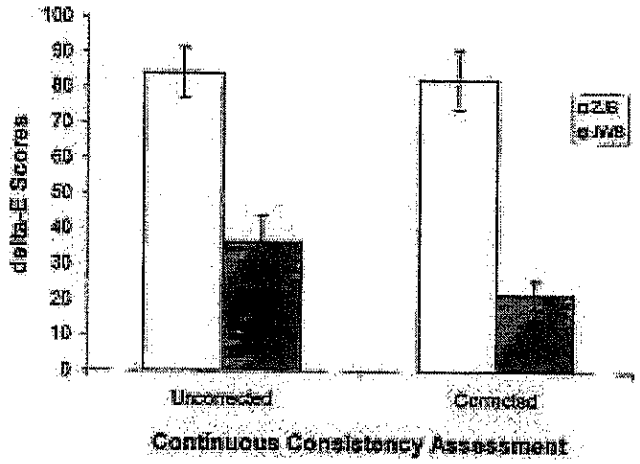

Fig. 2. Mean uncorrected and corrected delta-E scores for ZJB and JWB. High delta-E scores indicate low consistency and low delta-E scores indicate high consistency. Error bars indicate one standard error of the mean.

are the CIE Lab values for the second color selection for that grapheme. Low delta-E scores indicate a short distance in color space between the successive color selections and thus reflect high consistency, whereas high delta-E scores indicate a greater distance in color space between the successive color selections and reflect lower consistency.

By comparing the delta-E scores for each grapheme in the twins, it was possible to arrive at a fine-grained comparison of the consistency of their grapheme-color matches. We calculated an average delta-E score for all of the graphemes (0-9 and A-Z) as well as a corrected average delta-E score, which excluded the graphemes that for JWB changed from time to time (i.e., 1, 8, 9, U, Z, J, S, Q and X). The uncorrected and corrected delta-E scores for JWB and ZJB are shown in Figure 2. Independent sample t-tests conducted on both uncorrected and corrected average delta-E scores showed that the average delta-E scores for JWB were much smaller than those for ZJB, $t(70) = 4.621$, $p < 0.0001$, and $t(52) = 6.538$, $p < 0.0001$, respectively. These comparisons clearly indicate that JWB's grapheme-color matches were much more consistent than ZJB's. These results further support the conclusion that JWB has grapheme-color synaesthesia whereas his twin brother ZJB does not.

Normative continuous consistency assessment

For the final measure of the consistency of grapheme-color matches, we compared the performance of the twins on the continuous consistency assessment to the performance of a normative group of 100 undergraduate students at the University of Waterloo who reported having no synaesthetic experiences[2].

To create the normative scores, we calculated a delta-E score for each grapheme for each non-synaesthetic participant in the normative group. The delta-E scores for each grapheme were averaged across these non-synaesthetes. These average delta-E scores provide the basis for evaluating whether or not someone is a synaesthete. This is done in the following manner. A delta-E score is calculated for each grapheme. For each grapheme, the delta-E score is subtracted from the average delta-E score for the normative group and these differences are summed. An average consistency score is then calculated by dividing the summed differences of the delta-E scores by the number of graphemes being considered.

Using this general formula, three different consistency scores can be calculated: a consistency score for all 36 graphemes, a consistency score for letters only (26 graphemes) or for digits only (10 graphemes). The consistency scores for non-synaesthetes are normally distributed around a mean of zero. Some non-synaesthetes are more consistent than average, yielding positive consistency scores, whereas other non-synaesthetes are less consistent than average, yielding negative consistency scores. Most non-synaesthetes have consistency scores near zero. For synaesthetes, graphemes typically induce the same synaesthetic colors each time they are presented. For this reason, synaesthetes tend to be more consistent in their grapheme-color pairings than non-synaesthetes. Thus, the difference between a synaesthete's delta-E score for each grapheme and the average Delta-E score of the normative sample for the same grapheme tends to be a positive value, which elevates the synaesthete's overall consistency score. Any given participant can be classified as a synaesthete or a non-synaesthete based on where their consistency score falls on the distribution of consistency scores from the normative group. Participants are categorized as synaesthetes if their consistency scores lie greater than 1.96 standard deviation units away from the mean of the normative group (i.e., in the upper 2.5% of the normative consistency score distribution). All other participants are categorized as non-synaesthetes.

Table 2 shows JWB and ZJB's consistency scores expressed in terms of standard deviation units (i.e., z scores) for all graphemes, for letters only and for digits only. The

[2] The average age of the control sample was greater than the age of the twin brothers. While typically it is better to compare groups of equivalent age, in this case the comparison between the twins and the university aged control group is useful because it constitutes a more conservative test of the twins' synaesthesia than if the twins were compared with individuals their own age. Non-synaesthetic university students are likely more consistent in their grapheme-color matches than 10-year old non-synaesthetes. In other words, the university age non-synaesthetes set a higher standard of consistency than would controls matched in age to the twins. As such, if one of the twins shows a substantially higher consistency than the university age control group, we can be confident that the twin has synaesthesia.

Table 2. The standard deviations of JWB and ZJB's consistency scores for all graphemes, letters and digits, when compared to the distributions of the consistency scores of the control group of non-synaesthetes.

	All Graphemes	Letters	Digits
JWB			
Unadjusted Consistency	2.18	2.23	1.36
Adjusted Consistency	2.91	2.78	2.21
ZJB			
Unadjusted Consistency	−1.25	−1.08	−1.17

table also shows JWB's *adjusted* consistency scores. These adjusted consistency scores were based on only those graphemes which for him do not change over time. As can be seen from the table, with the exception of his uncorrected consistency scores for digits, JWB's consistency scores in all other cases are more than 2.18 standard deviations ($p < .05$) above the mean of the consistency scores of the normative group of non-synaesthetes. Thus, when compared to non-synaesthetes, JWB's consistency scores are clearly outliers. In contrast, ZJB's consistency scores have small negative values which are well within the normative distribution of non-synaesthetes. In sum, JWB's unusually high normative continuous consistency scores confirm that he is a synaesthete. By contrast his twin brother is if anything less consistent than the average non-synaesthete in our normative sample. These findings further corroborate both the subjective reports of the twins and the conclusions from the other measures of consistency. Taken together, the findings indicate that although they are monozygotic twins, JWB and ZJB are discordant for grapheme-color synaesthesia.

Discussion

The present findings have important implications both for our previous suggestion that the discordance of synaesthesia in monozygotic twins is due to X-chromosome inactivation (Smilek *et al.*, 2002) and for the generally held assumption that synaesthesia is determined by an X-linked dominant gene (Baron-Cohen *et al.*, 1996). With regard to our previous suggestion that X inactivation is responsible for the observed discordance of synaesthesia in monozygotic twins, the present findings show that this suggestion is simply incorrect. The suggestion was plausible given the results of our previous study, because the study was based on an assessment of *female* monozygotic twins. However, the present study is based on an assessment of *male* monozygotic twins and given that males have just one X chromosome, X-chromosome inactivation simply does not occur. Therefore, the fact that the male monozygotic twins in the present study are discordant for synaesthesia shows that X inactivation is not a viable explanation of the discordance in synaesthesia between monozygotic twins.

The present findings are also problematic for the idea that synaesthesia is an X-linked dominant trait. If synaesthesia is determined solely by an X-linked dominant gene (Baron-Cohen *et al.*, 1996), then male monozygotic twins would never be discordant for synaesthesia. The general assumption has been that the putative X-linked dominant gene would show complete penetrance, meaning that anyone with the critical X-linked dominant gene should be a synaesthete. Given that the male twins assessed in the present study are discordant for synaesthesia, it is clear that the penetrance of the genotype for synaesthesia is incomplete. A similar conclusion follows from our previous study of female monozygotic twins who were discordant for synaesthesia. Taken together, these findings clearly show that any view suggesting simply that synaesthesia is an X-linked dominant trait is incomplete and possibly incorrect.

There are other reasons to believe that synaesthesia is not an X-linked dominant trait. The idea that synaesthesia is an X-linked dominant trait was initially based on reports of a skewed female to male ratio. Until recently, it was generally assumed that the ratio of female to male synaesthetes was 6 or 7 female synaesthetes to every male synaesthete (Baron-Cohen *et al.*, 1996). However, these skewed ratios were based on data obtained in situations where each participant's identity was known and the participants volunteered to report their synaesthetic experiences. Given the way in which the data were collected, it is possible that the observed skewed ratios reflect the fact that females are more likely than males to freely report and talk about their synaesthetic experiences. Two recent large-scale studies support this speculation. In one study, 179 children ranging in age from 7 to 14 were screened using the normative continuous consistency assessment (as described above) of their grapheme-color associations (Stephan, 2004). These children were assessed in a school situation where all children enrolled in the school were expected to participate, assuming parental approval. In a second study which was conducted at the London Science Museum, 1690 anonymous participants were questioned regarding their synaesthetic experiences and evaluated regarding the consistency of their grapheme-color associations (Simner *et al.*, 2005). In both studies, it was found that synaesthetic experiences were equally divided between the sexes. Thus, these recent studies provide no evidence whatsoever for a skewed female to male ratio of synaesthetes, which was one of the primary reasons why it was originally suspected that synaesthesia may be an X-linked dominant trait.

Another widely held assumption underlying genetic theories of synaesthesia is that synaesthesia tends to run in families. There is no question that some synaesthetes have close relatives who also have some form of synaesthesia. But there are probably more synaesthetes who do not have any close relatives with synaesthesia than there are synaesthetes who do. It is difficult to know how to interpret familiar patterns of synaesthesia in the absence of accurate data as to the prevalence of synaesthesia in the population. Estimates of the prevalence of synaesthesia range from 1 in 4 (Calkins, 1895)

to 1 in 25,000 (Cytowic, 1993), with the most widely cited figure being 1 in 2000 (Baron-Cohen *et al.*, 1996). If one in every four people has synaesthesia, then it is certainly not surprising to find that many synaesthetes have close relatives who are also synaesthetes. This could occur simply on the basis of chance and wouldn't necessarily imply a genetic basic for synaesthesia. In contrast, if one in every 25,000 people has synaesthesia, then the fact that many synaesthetes have close relatives who are also synaesthetes would imply that synaesthesia can run in families.

The more recent large-scale studies point to a relatively high prevalence of synaesthesia in the population. In the study conducted by Stephan (2004), it was found that 8 out of the 179 children, or approximately 4.5%, had grapheme-color synaesthesia, as established by a standardized test of the consistency of grapheme-color associations. Simner *et al.* (2005), on the other hand, found that 1.0% of the 1690 people who were assessed at the London Science Museum had grapheme-color synaesthesia and that another 3.6% of the people had other variants of synaesthesia. Although the findings regarding the prevalence of synaesthesia reported by Stephan and Simner *et al.* are not completely consistent, the findings in both studies clearly indicate that synaesthesia is much more prevalent than has been generally assumed in recent years. The findings indicate that at least 1 in 20 people has some form of synaesthesia, which interestingly is the same figure proposed by Galton in 1883. If as many as 1 in 20 people does in fact have some form of synaesthesia, then it is certainly not surprising that many synaesthetes have close relatives who also have synaesthesia. Family relations would be expected to occur simply on the basis of chance and would not necessary suggest that there was a genetic basis for synaesthesia.

Taken together, therefore, the available evidence suggests that the genetic contribution to synaesthesia is not as simple as was previously thought. Given that the penetrance of the genotype for synaesthesia is incomplete, one can only speculate as to what other factors may play a critical role in the development of synaesthesia.

Environmental factors are an obvious possibility and modifier genes and gene mutation may play important roles. Another possibility is that random changes in brain morphology during brain development determine whether or not an individual becomes synaesthetic. This latter possibility is consistent with the fact that monozygotic twins can exhibit different brain morphologies (Casanova *et al.*, 1990a; 1990b), which would explain why monozygotic twins can be discordant for synaesthesia.

Previously, we (Smilek *et al.*, 2002) have suggested that molecular genetic analyses of synaesthetes and their relatives were appropriate to identify both the "synaesthesia" gene and the exact location of this gene. We now believe that it is premature to pursue molecular genetic analyses of synaesthesia. A valid molecular genetic analysis of synaesthesia is predicated on an appropriate classification of individuals with synaesthesia and a clear understanding of how different forms of synaesthesia relate to one another. However, at the present time, there is no agreed upon way in which to categorize individuals with synaesthesia and it is unclear whether the numerous forms or variants of synaesthesia (e.g., grapheme-color, touch-taste, sound-color) reflect the variable expressivity of a single "synaesthesia" gene or reflect the expression of different "synaesthesia" genes. Until this question is answered, it may be difficult, if not impossible, to ever establish the genetic basis for synaesthesia. In light of these considerations, it may be more appropriate at this time to develop a more complete taxonomy of synaesthesia than to conduct molecular genetic studies of a condition that has yet to be adequately described.

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