Behavioural Brain Research 286 (2015) 93–96

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Synesthesia in twins: Incomplete concordance in monozygotes suggests extragenic factors

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HIGHLIGHTS

- We conducted the first comparative twin study of colored-sequence synesthesia (CSS).
- We found 73.9% pairwise concordance in monozygotic and 36.4% in dizygotic twins.
- Same-sex dizygotic pairs had 75% concordance; opposite-sex pairs had 14.3%.
- It seems that environmental or epigenetic factors influence expression of CSS.
- Findings suggest a mechanism of CSS development that differs from previous models.

ARTICLE INFO

Article history:
Received 1 October 2014
Received in revised form 27 January 2015
Accepted 12 February 2015
Available online 19 February 2015

Keywords:
Synesthesia
Behavioral genetics
Perception
Twin
CSS

ABSTRACT

Colored-sequence synesthesia (CSS) is a neurological condition in which sequential stimuli such as letters, numbers, or days of the week trigger simultaneous, involuntary color perception. Although the condition appears to run in families and several studies have sought a genetic link, the genetic contribution to synesthesia remains unclear. We conducted the first comparative twin study of CSS and found that CSS has a pairwise concordance of 73.9% in monozygotic twins, and a pairwise concordance of 36.4% in dizygotic twins. In line with previous studies, our results suggest a heritable element of synesthesia. However, consonant with the findings of previous single-pair case studies, our large sample size verifies that synesthesia is not completely conferred by genetics; if it were, monozygotic twins should have 100% concordance. These findings implicate a genetic mechanism of CSS that may work differently than previously thought: collectively, our data suggest that synesthesia is a heritable condition with incomplete penetrance that is substantially influenced by epigenetic and environmental factors.

1. Introduction

Synesthesia is a neurological condition in which stimuli such as letters or musical notes trigger a simultaneous, involuntary perception in another sensory modality. A prevailing hypothesis is that synesthesia arises from neural "cross-talk" – in other words, activation in one area of the brain elicits activation in another area [1–3].

Anecdotal evidence suggests that synesthesia may be heritable [4], and family linkage studies have supported this possibility [5–7], although none has yet identified a specific genetic mechanism by which synesthesia is transmitted. One genetic linkage analysis of five synesthetic families found evidence of linkage to chromosome 16q in two of the families [7]. Specifically, results from this study pointed to the 16q12.2-23.1 region which contains 343 genes, many of which are expressed in the brain. The authors highlighted six of these as candidate genes that may fit the profile of synesthesia; however, no variants or polymorphisms of these genes emerged in their analysis of affected individuals. Another study determined significant linkage to chromosome 2q24 (HLOD = 3.025, $p = .047$), and also identified suggestive linkage to several other chromosomal loci [5]. These results suggest the possibility that multiple genes independently influence the development of synesthesia.

Although it has been suggested that synesthesia has a single-gene X-linked dominant mode of inheritance [8,9], studies and pedigree analyses have shown this to be unlikely. For example, Asher et al. [5] confirmed male-to-male transmission of synesthesia in two families [5], and Smilek et al. [10] identified a pair of male monozygotic twins in which only one twin experienced synesthesia [10].

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http://dx.doi.org/10.1016/j.bbr.2015.02.024
0166-4328/

Genetics may not be the only factor at play in the development of synesthesia. Smilek et al. [11] reported a pair of discordant female monozygotic twins; one experienced synesthesia and one did not [11]. The authors hypothesized that the discordance was due to either X chromosome inactivation or an epigenetic event. These findings indicate that genetic inheritance alone may not offer a full explanation of synesthesia.

Our study seeks to understand the genetic contribution to synesthesia by examining both monozygotic and dizygotic twins, recruiting a large cohort of twin pairs for the analysis, and using rigorous phenotyping. We compare the concordance rates of synesthesia in monozygotic and dizygotic twin pairs to estimate the extent to which epigenetic or environmental factors may play a role in the development of synesthesia.

2. Methods

Many varieties of synesthesia have been reported; for this study we focus specifically on colored-sequence synesthesia (CSS) in which sequences such as letters, numbers, days of the week, and months trigger color perception. Our previous analysis of 3194 colored-sequence synesthetes revealed that having synesthetic color associations for one type of sequence (e.g., letters) gives a ~79% likelihood of having color associations for another type of sequence (e.g. numbers), but only chance likelihood of having another form of synesthesia [12], indicating that CSS is a distinct subtype of synesthesia that may result from a distinct mechanism. Motivated by this finding, our prior genetics research has also focused on CSS [7].

For phenotyping, we used the Synesthesia Battery, a standardized online test that distinguishes synesthetes from non-synesthetes [13]. The Synesthesia Battery presents participants with graphemes (A–Z, 0–9), months (January–December) or weekdays (Monday–Sunday). All stimuli are presented in random order three times each. Participants are asked to select the synesthetically associated color for each stimulus from a color palette of 16.7 million colors. The color choices for each grapheme are analyzed for consistency across the three trials within the session (for example, choosing the same color of red each time a participant saw the letter A; for full details, see [13]). Non-synesthetic controls have low consistency in associating the colors to the stimuli, while synesthetes display high consistency in their repeated choices.

From the pool of Synesthesia Battery participants, we contacted 151 individuals who completed the grapheme-color portion of the test and reported having a twin in an optional text field. 38 twin pairs (76 individuals) gave consent to participate in the study. We conducted interviews with interested twin pairs online and over the phone to determine zygosity (via self-report), concordance, and demographic information (including whether the pair was reared together – which was true for all pairs in the sample). All twins reporting synesthesia or uncertainty about having synesthesia were instructed to take the Synesthesia Battery to verify their phenotype.

Recent research [25] indicated that a Synesthesia Battery consistency score of 1.43 is an optimal cutoff score to discriminate synesthetes from non-synesthetes. Thus, participants scoring below a threshold of 1.43 on any of the colored-sequence Battery tests (numbers, letters, weekdays, or months) were categorized as probands. Those who either reported having no experience of CSS or scored above 1.43 on all of the colored-sequence Battery tests were categorized as unaffected. Eagleman et al. [13] originally suggested a more conservative Battery score of 1.0 as the optimal cutoff score; however, only four participants (representing three twin pairs) scored above 1.0 and would have been excluded at the more conservative classification threshold (see Supplementary Tables 1a and 1b for details). Analyses were repeated with and without these three twin pairs to obtain results at both classification thresholds.

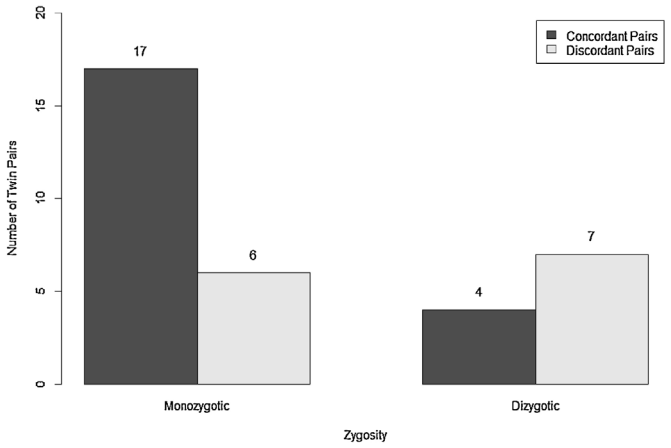

Fig. 1. Monozygotic twins have a greater pairwise concordance for CSS than dizygotic twins. Seventeen of 23 monozygotic twin pairs (73.9%) were concordant for colored sequence synesthesia, while only 4 of 11 (36.4%) dizygotic pairs were concordant.

Supplementary Tables 1a and 1b related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2015.02.024.

After interviews and testing, one twin pair was excluded from the study because neither twin scored below 1.43 on a colored-sequence battery test, classifying both twins as unaffected. Two pairs were excluded due to lost contact, and one pair was excluded because of indeterminate zygosity. Although zygosity was determined through self-report, all pairs included in the analysis either reported reasonable confidence in their zygosity or provided medical evidence (e.g. blood tests, physicians' reports at birth). The final analysis includes 34 twin pairs (68 individuals; based on [25]) and is repeated at the more conservative classification threshold with 31 twin pairs (62 individuals; based on [13]).

3. Results

The study had complete ascertainment as all probands met testing criteria for having CSS. Of the participant twins, 23 pairs were monozygotic (21 female, 2 male) and 11 pairs were dizygotic (3 female, 1 male, 7 sex-discordant). Participant information and test results are detailed in Supplementary Tables 1a and 1b.

The monozygotic group contained 17 concordant twin pairs (pairwise concordance 73.9%) and the dizygotic group had 4 concordant pairs (pairwise concordance 36.4%), as shown in Fig. 1.

Fisher's Exact Test was used to assess the significance of the difference in concordance between the two groups ($p = 0.059$, odds ratio = 4.69). This result approaches but does not reach the .05 threshold of statistical significance; however, we can interpret this finding as suggestive of possible group differences. Repeating the analysis without the three twin pairs who scored above 1.0 on the synesthesia battery, we see a decrease in the trend toward statistical significance ($p = 0.218$, odds ratio = 3.19).

Potential sex differences also emerged. Of the 68 individuals in the study, 56 were probands. The probands in this study had a male:female ratio of 1:6 (8 males, 48 females), while the 12 unaffected individuals had a male:female ratio of 5:7. Fisher's Exact Test indicates this difference is not statistically significant ($p = 0.109$, odds ratio = 0.279). However, when we exclude the three twin pairs who met criteria for inclusion at the 1.43 threshold but not the more conservative 1.0 threshold (see Supplementary Tables 1a