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Research report

The genetics of colored sequence synesthesia: Suggestive evidence of linkage to 16q and genetic heterogeneity for the condition

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ABSTRACT

Synesthesia is a perceptual condition in which sensory stimulation triggers anomalous sensory experiences. In colored sequence synesthesia (CSS), color experiences are triggered by sequences such as letters or numbers. We performed a family based linkage analysis to identify genetic loci responsible for the increased neural crosstalk underlying CSS. Our results implicate a 23 MB region at 16q12.2-23.1, providing the first step in understanding the molecular basis of CSS.

1. Introduction

In synesthesia, ordinary stimuli elicit anomalous perceptual experiences [1–3]. For example, in a form we term colored sequence synesthesia (CSS), the visual experience of a specific color is triggered by the viewing of a letter, digit, weekday or month (Fig. 1A) [1,4]. These associations are thought to result from amplified crosstalk between brain areas, such that activity in one area kindles activity in another (Fig. 1B). Although there are several forms of synesthesia, this work will focus exclusively on understanding CSS due to its clustering within families and its straightforward phenotyping, as described below.

Altered levels of crosstalk between brain regions have been found in various disease states, including autism [5,6], Alzheimer's disease [7], and schizophrenia [8,9]. Unfortunately, these studies are merely descriptive, not prescriptive, and give no information about the etiology or modifiability of abnormal patterns. Synesthesia is an ideal model for studying hyperconnectivity at the simplest level because synesthetes are healthy, the condition is easy to phenotype reliably, and it runs in families. The aim of this work is to use genetics to understand how neural crosstalk arises in a healthy brain, in the hopes of ultimately understanding how this mechanism might be modified in a disease state.

One hypothesis of the origin of synesthetic crosstalk suggests that excess connections in the newborn brain are insufficiently pruned during development [10–12], while a second hypothesis posits that synesthesia results from reduced functioning of inhibitory neural networks, either within or across brain regions [1,13,14]. These two hypotheses are indistinguishable by behavior [12,15] and neuroimaging [16,17], both of which demonstrate functional cross-activation but cannot explain the mechanism for the hyperconnectivity. The aim of our genetic study is to find the gene(s) underlying the functional crosstalk. A genetic finding hopes to reveal which of the above hypotheses is correct, and will represent the first genetic mechanism directly linked to increased neural crosstalk.

It has long been noted that synesthesia appears to run in families [18]. Analyses of pedigrees are consistent with the hypothesis of heritability and suggest that the genetic component(s) may be inherited in a dominant fashion with incomplete penetrance [19,20]. Unfortunately, those studies involved no DNA collection.

Asher et al. [29] published the first attempt to link the perceptual traits of a type of synesthesia with a genetic basis by completing a whole-genome scan of synesthetic families. Asher et al. reported linkage to several chromosomal regions, suggesting genetic heterogeneity and several patterns of inheritance; however, it is important to clarify that their study examined a different

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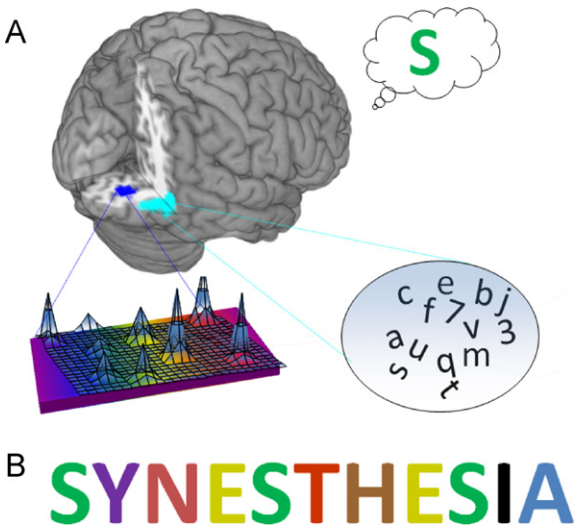

Fig. 1. (A) In this model of synesthesia, neural populations coding for graphemes (right inferior temporal gyrus, light blue) ramify on those coding for colors (area V4, dark blue). As a result of these connections, activity triggered by a grapheme kindles V4 activity, and (B) synesthetes experience an automatic color association, an example of which is shown here.

form of synesthesia (auditory–visual synesthesia) than we examine here (colored weekdays, months, letters, and numbers). Data from our lab indicate that different subtypes of synesthesia fall into clusters, suggesting the possibility that different genetic mechanisms underlie different forms of synesthesia (Novich, Cheng, Eagleman, in press). Thus, previous studies have opened an encouraging line of inquiry but offer no specific genetic conclusions. Our study combines DNA linkage analysis with rigorous phenotyping methods to set the foundation for understanding the genetic mechanism of colored sequence synesthesia.

2. Materials and methods

In an attempt to identify the gene for colored sequence synesthesia, we have performed a family linkage analysis. Although synesthesia has been reported in many forms (e.g., tasting shapes, seeing sounds, etc.) [1], for our analysis we concentrated on the triggering of color perception by letters, numbers, weekdays, or months (colored sequences). This decision was motivated by our analysis of 3194 verified colored sequence synesthetes, which indicated that color synesthesia for one type of sequence (e.g., letters) gives a ~79% likelihood of having color synesthesia for other types of sequences (e.g., weekdays, months or numbers), but gives only chance likelihood of possessing another type of synesthesia (Novich, Cheng, Eagleman, in press). This finding suggests that colored sequences may share a common genetic mechanism, while other forms of synesthesia may have different bases (including possibly non-genetic sources). Therefore, we only pursue the genetic etiology of colored sequence synesthesia here.

For the purposes of rigorous phenotyping, we have previously developed the Synesthesia Battery (www.synesthete.org), an online battery of tests that sensitively discriminates synesthetes from non-synesthetes [21]. Participants are serially presented with a full set of graphemes (A–Z, 0–9), three times each in a random order. For each grapheme, they are asked to choose the best associated color from an online palette of 16.7 million colors. The palette orientation and the slider bar are randomly rotated with each new grapheme presentation to prevent memorization of a color's location (Fig. 2A). The color choices are then analyzed for consistency within the session (e.g., determining whether the participant chose a similar shade of green upon seeing the letter J). The color variation for each letter (v_j) is measured by

$$v_j = \sum_{c=\{R,G,B\}} \left|x_1^c - x_2^c\right| + \left|x_2^c - x_3^c\right| + \left|x_3^c - x_1^c\right| \quad (1)$$

which represents the geometric distance in RGB (red, green, and blue) color space. The total variation score for each participant is

$$V = \frac{\sum_{j=\{A-Z,0-9\}} v_j}{N} \quad (2)$$

where N is the total number of graphemes for which the participant experiences synesthetic colors. Control subjects display low consistency when associating colors

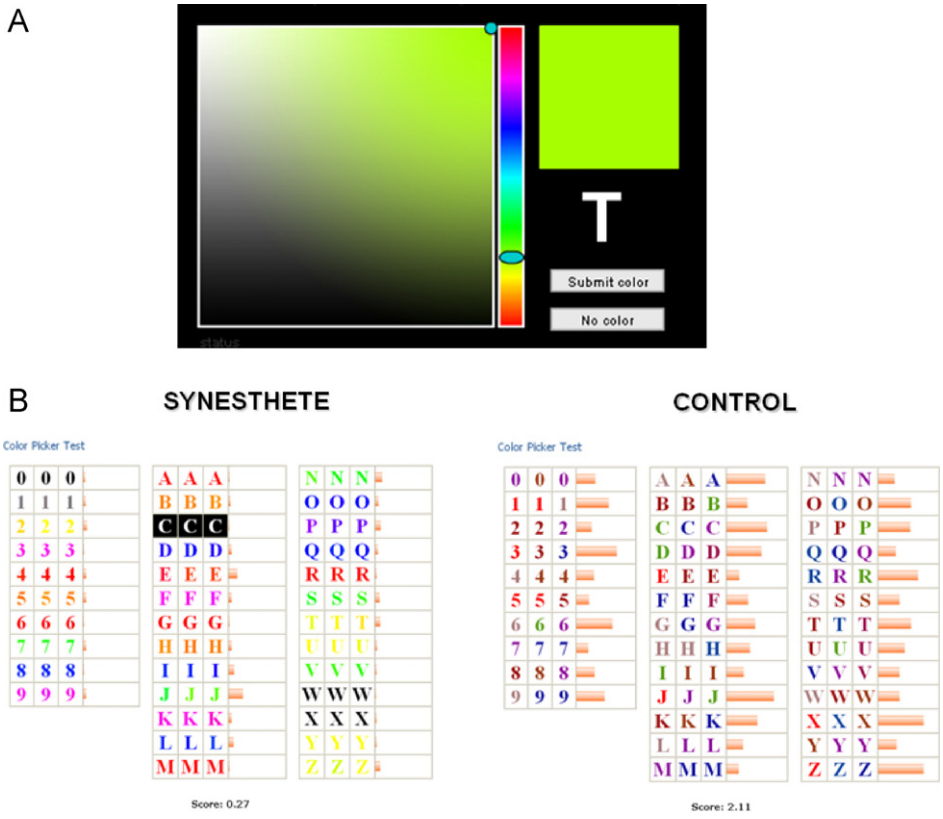

Fig. 2. (A) Participants are presented with randomly-ordered graphemes a total of three times each (108 trials). Using a palette with 16 million colors, participants choose the precise color that best matches their synesthetic percept for that grapheme. (B) Representative alphabets and variability scores from one synesthete and one control.