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When and how does 2 turn blue? The neural timing and mechanisms underlying synesthesia

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Psychology

by

David Joseph Brang

Committee in charge:

Professor Vilayanur S Ramachandran, Chair
Professor Seana Coulson
Professor Karen Dobkins
Professor Mingxiong Huang
Professor Don MacLeod

2012

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Chair

University of California, San Diego

2012

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ABSTRACT OF THE DISSERTATION

When and how does 2 turn blue? The neural timing and mechanisms underlying synesthesia

by

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Doctor of Philosophy in Psychology

University of California, San Diego, 2012

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Synesthesia is a perceptual experience in which stimuli presented through one perceptual stream will spontaneously evoke unrelated sensory experiences. While synesthesia can occur in response to drugs, sensory deprivation, or brain damage, research has largely focused on heritable variant comprising roughly 4% of the general population. This condition is by definition involuntary, automatic, and stable over time, and evidence suggests that the condition occurs from increased connectivity between the senses. However, the precise

mechanisms that give rise to these sensations remain a matter of active debate. Across five studies using electroencephalography, magnetoencephalography, and behavioral measures, we present evidence that early and quick communication between low-level perceptual centers mediates the initial processing stage in synesthesia. Furthermore, this research also suggests early synesthetic mechanisms partially overlap with those that support multisensory processes in the general population. This work clarifies the mechanisms that underlie this interesting condition, and provides a roadmap to using synesthesia as a tool to better understand perceptual and conceptual processes present in all individuals.

INTRODUCTION

Synesthesia is a condition present in roughly 4% of the population (Simner et al., 2006) in which a sensory stimulus presented to one modality triggers concurrent sensations in an additional modality. Synesthesia can theoretically link any pair of senses, but research has largely focused on two of the most common variants in which graphemes (numbers and letters) and sounds elicit the experience of colors (grapheme-color and auditory-color synesthesias, respectively; Baron-Cohen, Burt, Smith-Laittan, Harrison, & Bolton, 1996; Cytowic & Wood, 1982). For example, to a particular synesthete the number 2 may appear a greyish blue and the letter m a bright red, even when written in black ink. Indeed synesthetes report a dual percept, simultaneously experiencing synesthetic and ink-based colors. Synesthesia typically begins in early childhood and displays a remarkable degree of consistency over time (Cytowic & Wood, 1982). Further, synesthesia runs in families (Asher et al., 2009; Baron-Cohen et al., 1996; Ward & Simner, 2005), and familial linkage analyses suggest it is a highly heritable trait (for a review see Brang et al., 2011). Although researchers have studied this phenomenon for nearly two hundred years (Galton, 1883; Sachs, 1812), the mechanisms and processes underlying synesthesia remain a matter of continued debate.

One leading theory of synesthesia, known as the cross-activation hypothesis, suggests that the condition arises from increased connectivity between neighboring regions in the brain due to a deficient pruning process early in development (Ramachandran & Hubbard, 2001). In grapheme-color synesthesia, for example, it has been suggested that connections between visual color areas (e.g. V4) and grapheme regions in the temporal lobe present in typically developing infants are maintained into adulthood in grapheme-color synesthetes (Ramachandran & Hubbard, 2003; Ramachandran & Hubbard, 2001). Consequently, when numbers activate number regions of the temporal lobe, they also excite neurons in V4 giving

rise to the concurrent sensation of color. Consistent with this theory, several studies have identified anatomical differences near regions related to grapheme and color processing in synesthetes, including increased fractional anisotropy areas assessed by diffusion tensor imaging (Rouw and Scholte, 2007; Jancke, Beeli, Eulig, Hanggi, 2009), and increased gray matter volume as assessed by voxel-based morphometry (Jancke, Beeli, Eulig, Hanggi, 2009; Weiss and Fink, 2009).

As an alternative account, the disinhibited feedback proposal provides that synesthetic concurrents arise due to disinhibited feedback from higher-level visual areas in pathways common to synesthetes and non-synesthetes alike (Grossenbacher & Lovelace, 2001). A hybrid, the reentrant processing model posits hyperconnectivity between form and color processing areas in the fusiform (as in the cross-activation model), but, as in the disinhibited feedback model, it also suggests that synesthetic colors require neural activity from higher-level areas in the temporal lobe (e.g., anterior inferior temporal) to feed back to V4 (Smilek, Dixon, Cudahy, & Merikle, 2001).

Thus, each model makes a distinct prediction about the amount of time it should take for the activation of grapheme areas to elicit activity in concurrent synesthetic regions (e.g. color area V4). Specifically, the cross-activation theory predicts the activation of V4 during the initial sweep of activity in the posterior temporal lobe, while the disinhibited feedback theory predicts V4 activation later in the processing stream as a consequence of feedback from anterior temporal and parietal areas. These two theories cannot be distinguished on the basis of extant fMRI and behavioral studies, as these methods lack the temporal resolution needed to identify the relative sequence of cortical activations in synesthesia; that is whether activations in V4 occur nearly simultaneously with activity in grapheme regions, as predicted by the cross-activation theory, or whether such activations occur only after substantial processing as

predicted by the disinhibited feedback theory. Furthermore, if synesthesia indeed relies on the activity of early grapheme regions in the temporal lobe, there should be present effects of grapheme similarity on synesthesia, as basic form features are represented in topographically similar regions of the posterior temporal lobe.

Lastly, synesthesia is an extreme variant of possible interactions between the senses. However, the existence of connections between the senses is indeed not unique to synesthetes, and has been empirically studied in non-synesthetic participants within the field of multisensory processing (e.g., Calvert, Spence, Stein, 2004). The relationship between these typical multisensory processes and synesthesia remain unknown, particularly with respect to whether the processes share common mechanisms. Indeed synesthesia is thought to occur particularly from direct anatomical connections between grapheme and color regions, and auditory-color synesthesia through connections from auditory cortex to color areas. The presence of these myelinated connections have been demonstrated in non-synesthetic individuals using diffusion tensor imaging, and through anatomical tracing studies in non-human primates (e.g. Falchier, et al., 2002), begging the question of whether synesthetic experiences are mediated by the same network of connections as those of typical multisensory processes.

In line with past research and these present questions, across five studies we examine the neural timing of synesthesia to better under the mechanisms underlying the phenomenon, the effect of shape similarity on synesthetic colors to examine the development of the condition, and the relationship of synesthesia to multisensory processes present in the general population to further elucidate the mechanisms that support this interesting condition.

Research Report

Is the Sky 2?

Contextual Priming in Grapheme-Color Synaesthesia

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University of California, San Diego

ABSTRACT—*Grapheme-color synaesthesia is a neurological phenomenon in which particular graphemes, such as the numeral 9, automatically induce the simultaneous perception of a particular color, such as the color red. To test whether the concurrent color sensations in grapheme-color synaesthesia are treated as meaningful stimuli, we recorded event-related brain potentials as 8 synaesthetes and 8 matched control subjects read sentences such as "Looking very clear, the lake was the most beautiful hue of 7." In synaesthetes, but not control subjects, congruous graphemes, compared with incongruous graphemes, elicited a more negative N1 component, a less positive P2 component, and a less negative N400 component. Thus, contextual congruity of synaesthetically induced colors altered the brain response to achromatic graphemes beginning 100 ms postonset, affecting pattern-recognition, perceptual, and meaning-integration processes. The results suggest that grapheme-color synaesthesia is automatic and perceptual in nature and also suggest that the connections between colors and numbers are bidirectional.*

Although somewhat bizarre to most people, statements such as "The southern California sky is almost always a beautiful shade of 2" are quite meaningful to people with grapheme-color synaesthesia. In these individuals, achromatic graphemes, such as the numeral *2* or the letter *P*, automatically elicit the concurrent perception of a particular color, such as bright blue or a metallic shade of green. Grapheme-color synaesthesia typically begins in early childhood and displays a remarkable degree of consistency over time (Cytowic & Wood, 1982). Although researchers have studied synaesthesia for well over a century (Galton, 1880), key aspects of this phenomenon remain unclear. One basic question is whether synaesthesia is simply a set of overlearned associations that have persisted since childhood (Cytowic & Wood, 1982), or whether it has a perceptual basis grounded in altered cortical connectivity (Ramachandran & Hubbard, 2001). Further, although the phenomenology of synaesthesia is unidirectional—that is, graphemes induce color sensations, but colors do not induce the sensation of their corresponding graphemes—some researchers have suggested that connections between color- and form-processing areas in synaesthetes might be bidirectional (Cohen Kadosh, Cohen Kadosh, & Henik, 2007; Knoch, Gianotti, Mohr, & Brugger, 2005).

Although the neural substrate of grapheme-color synaesthesia has been elegantly studied with functional magnetic resonance imaging (Hubbard, Arman, Ramachandran, & Boynton, 2005; Nunn et al., 2002) and diffusion tensor imaging (Rouw & Scholte, 2007), few studies have addressed the real-time processing of graphemes in this population (though see Sagiv & Ward, 2006; Schiltz et al., 1999). In order to explore the extent to which grapheme-color synaesthesia invokes perceptual versus conceptual processes, we employed electrophysiological techniques to examine grapheme-color synaesthetes' brain response to graphemes embedded in sentence contexts. Whereas previous researchers used mental arithmetic to invoke the concept of an inducer (e.g., "7") and showed that it affected the processing of its corresponding color (e.g., yellow) in a color-naming task (Dixon, Smilek, Cudahy, & Merikle, 2000), in the present study we utilized linguistic context (e.g., "The sky is") to invoke the concept of a color ("blue") in order to examine its impact on event-related potential (ERP) responses to an inducer grapheme.

In particular, we focused on the N400 contextual-priming effects observed for meaningful linguistic stimuli (color terms), nonlinguistic stimuli (color patches), and color-inducing graphemes presented in the same sentence contexts. A negative-going wave that peaks approximately 400 ms after the onset of a contextually relevant stimulus, the N400 is sensitive to the degree to which a meaningful stimulus is primed by the preceding context (Hagoort, Hald, Bastiaansen, & Petersson, 2004; Kutas & Hillyard, 1984). The N400 is elicited by all words, whether spoken, written, or signed, though different stimulus modalities alter its scalp topography in a way that suggests the contribution of different neural generators. The size of the N400

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elicited by words is reduced by the presence of congruous context. Consequently, the N400 to a word such as *cat* is smaller when the word is preceded by a related word (*dog*) than when it is preceded by an unrelated word (*sugar*), and is also reduced in a congruous sentence context (*Growing up, every kid should have either a dog or a cat*) relative to an incongruous sentence context (*I take my coffee with cream and cat*; Kutas & Hillyard, 1980). Meaningful nonlinguistic stimuli, such as line drawings, photographs, cospeech gestures, and even environmental sounds, also elicit N400 components whose amplitude is similarly affected by contextual priming (i.e., reduced by the presence of a congruous context; Wu & Coulson, 2005).

In contrast, musically incongruous stimuli typically elicit a positive-going response in the ERP (Besson & Macar, 1987). This response has been linked to both the P300 (Donchin & Coles, 1998), a general response to unexpected events, and the P600 (Patel, Gibson, Ratner, Besson, & Holcomb, 1998), which is often elicited by ungrammatical language. These positive-going ERP responses to incongruities are thought to reflect arbitrary or overlearned rules, and differ from semantic-integration processes indexed by the N400 (Besson & Macar, 1987).

To test whether grapheme-color synaesthetes' concurrent sensations of color when perceiving graphemes are subject to contextual integration effects, we recorded ERPs as participants read sentence frames that suggested a particular color term as the sentence-final item (e.g., "Looking very clear, the lake was the most beautiful hue of . . ."). These sentences were completed with congruous or incongruous color words ("blue" or "yellow"), congruous or incongruous color patches (blue rectangle or yellow rectangle), or graphemes known to elicit congruous or incongruous colors for a given synaesthete (e.g., in the case of 1 of our synaesthetes, "2," which appears blue, or "7," which appears yellow). If synaesthetic experiences are meaningful stimuli, then the congruity manipulation in the grapheme condition would be expected to give rise to N400 effects. Alternatively, if synaesthetic percepts are overlearned associations, then incongruous graphemes would be expected to elicit a positive-going wave.

METHOD

Participants

Eight grapheme-color synaesthetes and 8 age- and handedness-matched control subjects participated either for cash or in fulfillment of a course requirement. All were healthy fluent English speakers, all had normal or corrected-to-normal color vision, and none had any history of psychiatric or neurological disorder. Participants' age ranged between 18 and 31 ($M = 22.3$ years for synaesthetes and 21.0 years for control subjects). Handedness was assessed via the Edinburgh Inventory (Oldfield, 1971), which yields a laterality quotient ranging from +1 (strongly right-handed) to −1 (strongly left-handed). The majority of our participants were right-handed (6 right-handed and 2 left-handed in both groups), as suggested by the average laterality quotient of +.34 for synaesthetes and +.31 for control subjects. Synaesthesia was confirmed by means of consistency matching (on-line testing with the Synesthesia Battery; Eagleman, Kagan, Sagaram, & Sarma, 2007), including reaction time testing for color consistency.

Materials and Procedure

Stimuli consisted of 240 sentences ending in one of three ways. In *text* blocks, sentence frames (e.g., "Looking very clear, the lake was the most beautiful hue of . . .") were completed either with the predictable, contextually congruous color term ("blue") or with an incongruous color term ("yellow"). In *color* blocks, sentences ended with a rectangular color patch that was either congruous (blue) or incongruous (yellow). In *grapheme* blocks, sentences ended with an achromatic grapheme known to induce a particular concurrent color in a given synaesthete. For example, in 1 of our synaesthetes, "2" induces the color blue and "7" induces the color yellow, so for this synaesthete, "2" was considered to be a congruous completion of the sentence about the lake, whereas "7" was considered to be an incongruous completion. Half of the sentences in each block ended as expected (congruous completions), and half ended with an unexpected color word, an unexpected color patch, or (for the synaesthetes) a grapheme that induced an unexpected color (see Fig. 1). (Congruity of sentence-final words was established in a separate normative study.) Sentences were presented one word at a time at the rate of 2 words per second. Each sentence-final word, color patch, or grapheme was presented for 200 ms and followed by a blank screen for 1,300 ms.

To control for effects of surprise due to nonlinguistic stimuli being introduced into sentence contexts, we presented the three types of sentence endings in separate blocks (two blocks of each condition, for a total of six blocks). Block order was pseudorandomized for each subject such that blocks of the same type were not presented sequentially. Block order was approximately counterbalanced across subjects (3 synaesthetes viewed a text block first, 3 viewed a color block first, and 2 viewed a grapheme block first). Each synaesthete was matched with a control subject who viewed exactly the same stimulus list (in the same order).

The experiment took place in a sound-attenuated room. Participants were seated in a comfortable chair and viewed the computer monitor from a distance of 37 in. During the initial instructions, participants were told that they would be reading sentences presented one word at a time in the center of the screen, and they were instructed to fixate the centrally presented words, whose location would be indicated by the initial appearance of a fixation cross.

Electroencephalographic and Electro-Oculographic Recording

Participants' electroencephalogram (EEG) was monitored with a commercial electrode cap with 29 scalp sites arranged according

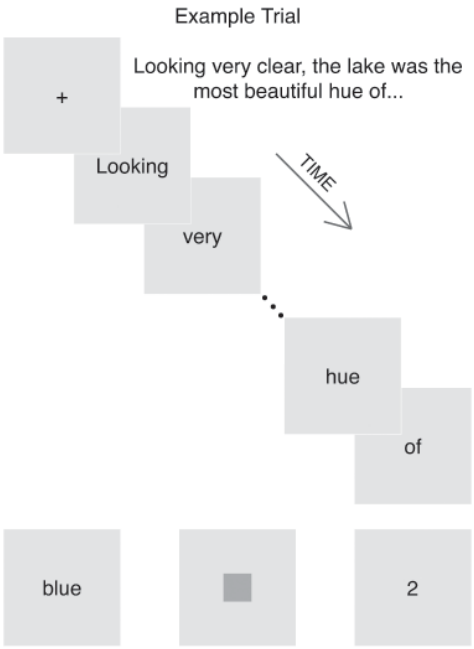


Fig. 1. Illustration of the display sequence in a trial. Depending on the condition, the final display showed a color word, color patch, or grapheme.

to the International 10–20 system. Horizontal eye movements were measured with a bipolar derivation of electrodes placed at the outer canthi. Vertical eye movements and blinks were monitored with an electrode under the right eye. All electrodes were referenced on-line to the left mastoid, and all impedances were maintained below 5 kΩ. The EEG at a band pass from 0.01 to 100 Hz was amplified with SA Instruments (Stony Brook, NY) 32-channel bioamplifiers, digitized at 250 Hz, and stored on a computer hard disk for later averaging.

Analysis of ERPs

ERPs were time-locked to the onset of the sentence-final stimulus. Analyses focused on a time window from 100 ms before through 920 ms after that onset. The 100-ms period preceding the onset of the sentence-final stimulus served as the baseline. Epochs containing blinks, eye movements, amplifier drift, or blocking were rejected prior to averaging, resulting in the exclusion of 18.85% of trials, on average, for synaesthetes and 12.63% of trials, on average, for control subjects, $F(1, 14) = 2.89$, n.s.

Unless noted otherwise, analysis involved mean amplitude measurements of each participant's ERPs elicited in three time windows: 100 to 150 ms after onset of the sentence-final stimulus (intended to capture the N1 component), 150 to 250 ms after onset of the sentence-final stimulus (intended to capture the P2 component), and 300 to 450 ms after onset of the sentence-final stimulus (intended to capture the N400 component). Measurements were subjected to repeated measures analyses of variance with the between-subjects factor of group (synaesthetes vs. control subjects) and within-subjects factors of congruity (congruous vs. incongruous), probe type (text vs. color vs. grapheme), and scalp distribution. In the analysis of midline sites (FPz, Fz, FCz, Cz, CPz, Pz, Oz), the distribution factor was electrode (seven levels, from anterior to posterior); in the analysis of medial sites (FP1/FP2, F3/F4, FC3/FC4, C3/C4, CP3/CP4, P3/P4, O1/O2), the distribution factors were hemisphere (left vs. right) and electrode (seven levels, from anterior to posterior); and in the analysis of lateral sites (F7/F8, FT7/FT8, TP7/TP8, T5/T6), the distribution factors were hemisphere (left vs. right) and electrode (four levels, from anterior to posterior). Although the original degrees of freedom are reported here for clarity, p values were subjected to Greenhouse-Geisser correction (Greenhouse & Geisser, 1959), when appropriate. Results of analysis are presented in the tables, which list theoretically meaningful effects. The hemisphere factor had no significant main effects and was not involved in any significant interactions, so is not discussed further.

RESULTS AND DISCUSSION

Tables 1 through 3 present results of analyses of mean amplitude in three time windows, corresponding to the N400, N1, and P2 ERP components, respectively.

Results for the text blocks were in keeping with previous ERP language research. In both groups of participants, congruous completions elicited a less negative N400 than did incongruous completions (see Fig. 2), as revealed by overall effects of the congruity factor, as well as by a reliable interaction between the congruity and electrode factors in the analysis of midline electrode sites (see Table 1).[1] In both groups, the N400 was broadly distributed across the scalp, began 200 ms after the onset of the sentence-final word, and returned to baseline by 600 ms postonset. These findings suggest that the altered perceptual experience that can accompany reading in grapheme-color synaesthesia, namely, the perception of colored letters, has little detectable impact on the contextual integration processes indexed by the N400 component in the ERP.

The two groups of participants also displayed a similar N400 response to the critical items in the color blocks (see Fig. 2). Congruous color patches elicited a less negative N400 than did incongruous ones (see Table 1). The time course of the color-congruity effect was similar between the two groups, beginning

[1]Because the N400 component is larger over some electrode sites than others, differences in N400 amplitude are often revealed by interactions between experimental conditions and electrode factors. In the present study, congruity effects on the N400 were revealed by congruity-by-electrode interactions in the statistical analyses.

TABLE 1

Analysis of Mean Amplitude 300 to 450 Ms After Onset of the Sentence-Ending Stimulus (N400)

	Midline sites		Medial sites		Lateral sites	
Analysis and effect	*F*	*p*	*F*	*p*	*F*	*p*
Text condition: between groups						
Group	$F(1, 14) = 5.76$	$< .05$	$F(1, 14) = 5.40$	$< .05$	$F(1, 14) = 2.73$	n.s.
Congruity	$F(1, 14) = 31.03$	$< .001$	$F(1, 14) = 28.76$	$< .001$	$F(1, 14) = 23.53$	$< .001$
Group × Congruity	$F(1, 14) = 0.91$	n.s.	$F(1, 14) = 0.45$	n.s.	$F(1, 14) = 0.02$	n.s.
Congruity × Electrode	$F(6, 84) = 4.85$	$< .05$	$F(6, 84) = 1.14$	n.s.	$F(3, 42) = 0.07$	n.s.
Group × Congruity × Electrode	$F(6, 84) = 1.77$	n.s.	$F(6, 84) = 3.16$	n.s.	$F(3, 42) = 0.37$	n.s.
Color condition: between groups						
Group	$F(1, 14) = 1.36$	n.s.	$F(1, 14) = 0.73$	n.s.	$F(1, 14) = 0.01$	n.s.
Congruity	$F(1, 14) = 8.24$	$< .05$	$F(1, 14) = 8.69$	$< .05$	$F(1, 14) = 9.92$	$< .01$
Group × Congruity	$F(1, 14) = 0.30$	n.s.	$F(1, 14) = 0.28$	n.s.	$F(1, 14) = 0.03$	n.s.
Congruity × Electrode	$F(6, 84) = 5.37$	$< .05$	$F(6, 84) = 6.08$	$< .05$	$F(3, 42) = 0.48$	n.s.
Group × Congruity × Electrode	$F(6, 84) = 0.18$	n.s.	$F(6, 84) = 0.01$	n.s.	$F(3, 42) = 0.09$	n.s.
Grapheme condition: between groups						
Group	$F(1, 14) = 5.06$	$< .05$	$F(1, 14) = 5.39$	$< .05$	$F(1, 14) = 2.00$	n.s.
Congruity	$F(1, 14) = 5.79$	$< .05$	$F(1, 14) = 4.46$	n.s.	$F(1, 14) = 2.11$	n.s.
Group × Congruity	$F(1, 14) = 0.22$	n.s.	$F(1, 14) = 0.24$	n.s.	$F(1, 14) < 1$	n.s.
Congruity × Electrode	$F(6, 84) = 8.62$	$< .01$	$F(6, 84) = 6.73$	$< .05$	$F(3, 42) = 6.21$	$< .05$
Group × Congruity × Electrode	$F(6, 84) = 3.95$	$< .05$	$F(6, 84) = 4.17$	n.s.	$F(3, 42) = 5.85$	$< .05$
Grapheme condition: synaesthetes						
Congruity × Electrode	$F(6, 42) = 7.33$	$< .01$	$F(6, 42) = 6.47$	$< .05$	$F(3, 21) = 8.91$	$< .05$
Grapheme condition: control subjects						
Congruity × Electrode	$F(6, 42) = 2.62$	n.s.	$F(6, 42) = 1.21$	n.s.	$F(3, 21) = 0.07$	n.s.

Note. The electrode factor refers to the anterior-posterior location of the electrode.

250 ms postonset and ending 450 ms postonset, as was the scalp topography.

In contrast to the similarities observed in the two groups for the text and color blocks, responses of synaesthetes and control subjects differed in the grapheme blocks (see Fig. 2). In control subjects, N400 amplitude did not vary as a function of sentence congruity (see Table 1). Given that recognition of sentence congruity was specifically designed to require that the grapheme induce an experience of color, our failure to observe an N400 effect in control subjects in the grapheme block is unsurprising. In synaesthetes, however, congruous graphemes elicited a less negative N400 than incongruous graphemes, as shown in a follow-up analysis of data recorded from the synaesthetes (see Table 1).

Although the congruous and incongruous inducer graphemes were equally incompatible with the sentence context (i.e., it makes as much sense to say that the lake is "2" as it does to say that the lake is "7"), the contextual congruity of the color sensation synaesthetes experienced modulated the size of the N400 elicited by the graphemes. This finding supports the idea that the color-induction process in grapheme-color synaesthesia is automatic and suggests that the concurrent color sensation is treated by the brain as a meaningful stimulus subject to contextual integration processes.

Further, the synaesthetes' N400 effect in the grapheme blocks was preceded by congruity effects on two earlier ERP components: the N1 and the P2. The N1 is an occipitotemporal negativity that typically peaks between 140 and 180 ms after onset of the stimulus (Vogel & Luck, 2000). Between 100 and 150 ms after onset of the sentence-final stimulus, ERPs to congruous graphemes were more negative than ERPs to incongruous graphemes in the group of synaesthetes (see Table 2). This effect was not present in the text or color blocks or in control subjects (see Table 2). This negativity peaked at approximately 153 ms in grapheme blocks. An additional analysis of the peak amplitude observed between 140 and 180 ms at lateral sites revealed a reliable congruity effect in grapheme blocks among synaesthetes only, $F(1, 7) = 19.27$, $p < .01$ (see Fig. 3), but not in text blocks, $F(1, 7) = 0.06$, n.s., or color blocks, $F(1, 7) = 0.23$, n.s.

TABLE 2

Effect of Congruity at Lateral Sites 100 to 150 Ms After Onset of the Sentence-Ending Stimulus (N1)

Group and condition	*F*(1, 7)	*p*
Synaesthetes		
Text condition	4.98	n.s.
Color condition	1.67	n.s.
Grapheme condition	5.78	$< .05$
Control subjects		
Text condition	0.04	n.s.
Color condition	3.52	n.s.
Grapheme condition	0.96	n.s.

TABLE 3

Analysis of Mean Amplitude in the Grapheme Condition 150 to 250 Ms After Onset of the Sentence-Ending Stimulus (P2)

	Midline sites		Medial sites		Lateral sites	
Analysis and effect	*F*	*p*	*F*	*p*	*F*	*p*
Between groups						
Group	$F(1, 14) = 4.94$	$< .05$	$F(1, 14) = 2.87$	n.s.	$F(1, 14) = 0.17$	n.s.
Congruity	$F(1, 14) = 4.11$	n.s.	$F(1, 14) = 4.69$	$< .05$	$F(1, 14) = 6.89$	$< .05$
Group × Congruity	$F(1, 14) = 10.08$	$< .01$	$F(1, 14) = 12.38$	$< .005$	$F(1, 14) = 11.8$	$< .005$
Congruity × Electrode	$F(6, 84) = 1.63$	n.s.	$F(6, 84) = 1.22$	n.s.	$F(3, 42) = 0.44$	n.s.
Group × Congruity × Electrode	$F(6, 84) = 3.85$	$< .05$	$F(6, 84) = 1.93$	n.s.	$F(3, 42) = 0.34$	n.s.
Synaesthetes						
Congruity	$F(1, 7) = 12.35$	$< .01$	$F(1, 7) = 15.21$	$< .01$	$F(1, 7) = 27.85$	$< .01$
Congruity × Electrode	$F(6, 42) = 5.50$	$< .05$	$F(6, 42) = 3.36$	n.s.	$F(3, 21) = 0.93$	n.s.
Control subjects						
Congruity	$F(1, 7) = 0.73$	n.s.	$F(1, 7) = 0.73$	n.s.	$F(1, 7) = 0.23$	n.s.
Congruity × Electrode	$F(6, 42) = 0.19$	n.s.	$F(6, 42) = 0.26$	n.s.	$F(3, 21) = 0.16$	n.s.

Note. The electrode factor refers to the anterior-posterior location of the electrode.

Remarkably, the onset of reliable grapheme-congruity effects in synaesthetes emerged 150 ms before the onset of color-congruity effects, as the N400 diverged from the baseline between 250 and 300 ms after the onset of the color patch in the color blocks.

Thus, as in prior N1 research, the N1 response to target stimuli (in this case, contextually congruous graphemes) was more negative than the N1 response to nontarget stimuli (contextually incongruous graphemes). The amplitude of the occipitotemporal N1 has been shown to be modulated by tasks involving form or color discrimination, has been implicated in the perceptual categorization of visual stimuli (Curran, Tanaka, & Weiskopf, 2002), and is also modulated by attention (for a

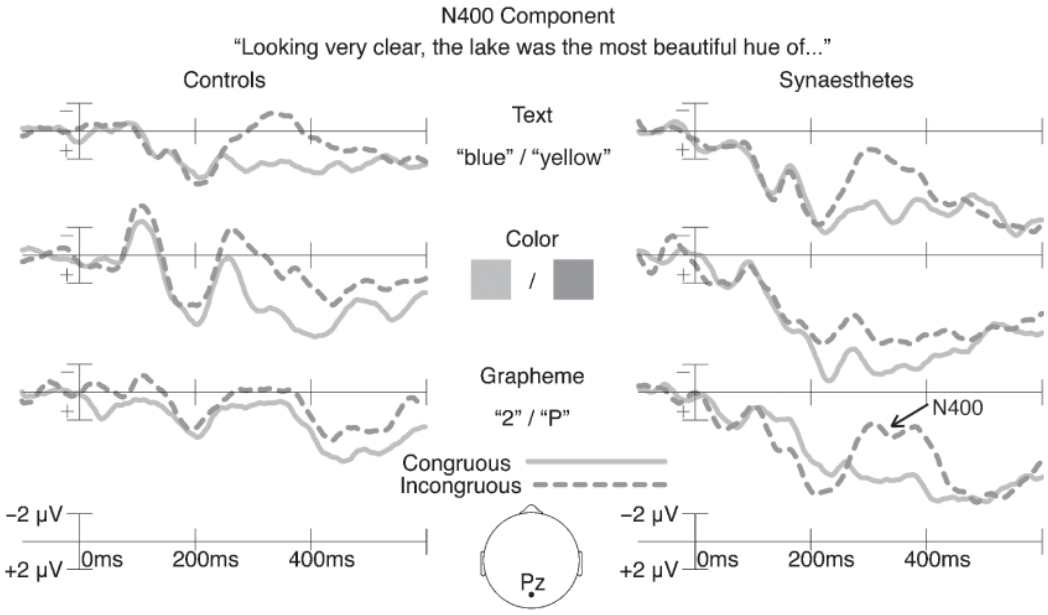


Fig. 2. Grand-average event-related potentials at posterior electrode Pz for congruous and incongruous sentences. Results are shown separately for the three probe types (text, color, grapheme), for both synaesthetes ($n = 8$) and control subjects ($n = 8$). The N400 for synaesthetes in the grapheme condition is labeled. For purposes of display (but not analysis), these data were digitally low-pass-filtered at 20 Hz. Negative voltage is plotted upward.

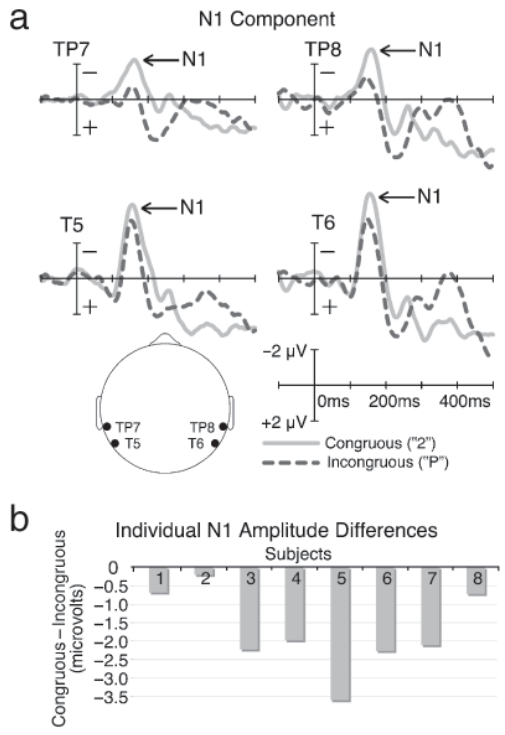


Fig. 3. The N1 observed in synaesthetes (n = 8). The upper panel (a) shows grand-average event-related potentials to congruous and incongruous graphemes at four electrode sites. For purposes of display (but not analysis), these data were digitally low-pass-filtered at 20 Hz. Negative voltage is plotted upward. The lower panel (b) presents the difference in N1 amplitude between congruous and incongruous graphemes for each synaesthete individually.

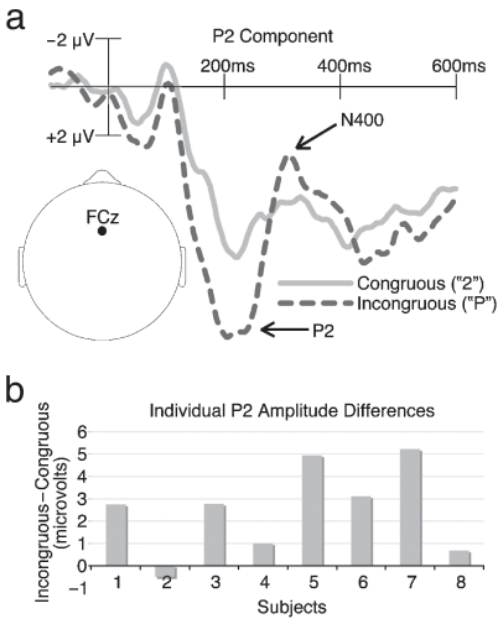


Fig. 4. The P2 observed in synaesthetes (n = 8). The upper panel (a) shows grand-average event-related potentials to congruous and incongruous graphemes at FCz. For purposes of display (but not analysis), these data were digitally low-pass-filtered at 20 Hz. Negative voltage is plotted upward. The lower panel (b) presents the difference in P2 amplitude between congruous and incongruous graphemes for each synaesthete individually.

review, see Vogel & Luck, 2000). Observed N1 effects in the present study may reflect enhanced visual processing of contextually appropriate graphemes, as semantic expectations engendered by the preceding sentence context served to facilitate form discrimination of expected graphemes and synaesthetic color induction arising from them.[2]

The P2, a frontal positivity evident between 150 and 250 ms after stimulus onset, was modulated by congruity in synaesthetes, but not in control subjects (see Table 3). In synaesthetes, the mean amplitude of the P2 was approximately 2.5 μV larger for incongruous graphemes than for congruous ones (Fig. 4). In control subjects, P2 amplitude was similar for congruous and incongruous graphemes, differing only by 0.5 μV (see Table 3).

[2]In a case study of a grapheme-color synaesthete, Sagiv and Ward (2006) also observed that N1 amplitude in response to graphemes differed depending on whether the graphemes' printed color was consistent or inconsistent with their induced color.

The frontal positivity we observed is partially consistent with results of a prior electrophysiological study of grapheme-color synaesthetes using a target-detection paradigm (Schiltz et al., 1999). Although the experimental manipulation in that study did not modulate P2 amplitude, both target and nontarget stimuli elicited larger positivities in synaesthetes' than control subjects' ERPs between 200 and 300 ms after grapheme onset.

Though the neural generators for the anterior P2 component are currently unknown, Kranczioch, Debener, and Engel (2003) argued that this component reflects perceptual processing. The P2 has previously been observed in target-detection paradigms that address the role of spatial attention in vision. In these paradigms, the P2 is larger for targets than nontargets (Hillyard & Münte, 1984; Kenemans, Kok, & Smulders, 1993). Because the P2 has been shown to be enhanced for targets defined by orientation, size, or color, Luck and Hillyard (1994) argued that it reflects a multidimensional feature-detection process. In view of its sensitivity to attentional manipulations (Kranczioch et al., 2003; Luck, Vogel, & Shapiro, 1996) and to multiple distinct visual attributes, the P2 observed in our synaesthetes' ERPs to graphemes may index processes relevant to the synaesthetic

binding of shape and induced color. The observed congruity effect, then, might reflect the difficulty of generating the synaesthetic percept when contextual cues prime a different color.

This explanation receives partial support from ERP data reported by Beeli, Esslen, and Jäncke (2008) from a study of color-hearing synaesthetes, in whom spoken words and letters give rise to concurrent color sensations. Beeli et al. found that the P2 elicited by spoken letters was smaller in synaesthetes than in control subjects, and during the 10 ms surrounding the P2 peak, Beeli et al. observed brain activity in synaesthetes in left superior frontal gyrus, left precuneus, and right intraparietal sulcus. Though such localization claims about EEG activity should always be approached with caution, these activations are consistent with brain areas putatively involved in perceptual binding. However, the precise relationship between the auditory potentials reported by Beeli et al. and the visual potentials observed in the present study is unknown, and further work will be required to ascertain the functional significance of observed P2 congruity effects in grapheme-color synaesthetes.

In sum, contextual congruity of synaesthetic colors altered synaesthetes' brain response to achromatic graphemes beginning 100 ms postonset, affecting form-recognition, perceptual, and meaning-integration processes. The early effects observed in this study support accounts of synaesthesia as caused by nonstandard neuroanatomy, such as altered connectivity in the visual system (Ramachandran & Hubbard, 2001; Rouw & Scholte, 2007) or disinhibited feedback (Grossenbacher & Lovelace, 2001), and further support the idea that synaesthesia is perceptual in nature. The present study expands the notion of synaesthesia as a psycholinguistic phenomenon in which many inducer stimuli are linguistic (Simner, 2007), by showing that synaesthetic colors are subject to linguistically mediated contextual-priming effects. In addition, these results support the suggestion that there are bidirectional connections between colors and numbers in synaesthetes (Cohen Kadosh et al., 2007; Knoch et al., 2005), as the conceptual expectation of colors, evoked by the sentence frames, successfully mediated the processing of graphemes at multiple levels. The observed N1 effects (100 to 150 ms) are particularly remarkable, as they indicate that the sentence contexts (e.g., "Looking very clear, the lake was the most beautiful hue of . . .") successfully modulated visual discrimination of graphemes presented in black. However, our findings do not indicate whether these bidirectional mappings in synaesthetes result from cross-activation between V4 and fusiform gyrus or are mediated by higher-level areas.

Indeed, our results have implications beyond synaesthesia, extending to the flexibility of multimodal meaning-integration processes. Participating in a conversation, for example, often requires combining linguistic information in speech with contextually salient visual information, such as an image on a television or computer screen, the affective facial expressions of interlocutors, and information in cospeech gestures. Our demonstration that synaesthetic colors were integrated into participants' representation of sentence meaning is consistent with recent evidence that the brain simultaneously integrates information from spoken words and cospeech gestures (Ozyurek, Willems, Kita, & Hagoort, 2007).

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Contextual Priming in Grapheme–Color Synesthetes and Yoked Controls: 400 msec in the Life of a Synesthete

David Brang, Stanley Kanai, Vilayanur S. Ramachandran, and Seana Coulson

Abstract

■ Grapheme–color synesthesia is a heritable trait where graphemes ("2") elicit the concurrent perception of specific colors (red). Researchers have questioned whether synesthetic experiences are meaningful or simply arbitrary associations and whether these associations are perceptual or conceptual. To address these fundamental questions, ERPs were recorded as 12 synesthetes read statements such as "The Coca-Cola logo is white and 2," in which the final grapheme induced a color that was either contextually congruous (red) or incongruous ("…white and 7," for a synesthetes who experienced 7 as green). Grapheme congruity was found to modulate the amplitude of the N1, P2, N300, and N400 components in synesthetes, suggesting that synesthesia impacts perceptual as well as conceptual aspects of processing. To evaluate whether observed ERP effects required the experience of colored graphemes versus knowledge of grapheme–color pairings, we ran three separate groups of controls on a similar task. Controls trained to a synesthete's associations elicited N400 modulation, indicating that knowledge of grapheme–color mappings was sufficient to modulate this component. Controls trained to synesthetic associations and given explicit visualization instructions elicited both N300 and N400 modulations. Lastly, untrained controls who viewed physically colored graphemes ("2" printed in red) elicited N1 and N400 modulations. The N1 grapheme congruity effect began earlier in synesthetes than colored grapheme controls but had similar scalp topography. Data suggest that, in synesthetes, achromatic graphemes engage similar visual processing networks as colored graphemes in nonsynesthetes and are in keeping with models of synesthesia that posit early feedforward connections between form and color processing areas in extrastriate cortex. The P2 modulation was unique to the synesthetes and may reflect neural activity that underlies the conscious experience of the synesthetic induction. ■

INTRODUCTION

Synesthesia is a neurological condition in which stimulation in one cognitive or perceptual stream results in additional experiences more typically associated with stimulation of a different domain (Hubbard, 2007). An extreme example can be found in S, the subject of the classic case study by Luria. Presented with a 50-Hz tone, S simultaneously heard the tone, experienced the taste of a strong beet soup, and saw a brown stripe against a dark background surrounded by a red rim (Luria, 1969). A more common variety of this condition is grapheme–color synesthesia, in which printed numbers and letters induce particular colors (for a review, see Ramachandran & Brang, 2008). For example, 5 might always appear to be indigo, whereas 7 might appear to be green. In grapheme–color synesthesia then, graphemes (such as the digit 5 or the letter "A") are the *inducers*, and the experience of color (i.e., indigo) is the *concurrent*.

Synesthetic associations are idiosyncratic, differing from synesthete to synesthete; however, within an individual each synesthetic association is highly consistent over time (Simner & Logie, 2007; Baron-Cohen, Burt, Smith-Laittan, Harrison, & Bolton, 1996; Cytowic, 1989). Thus, although different synesthetes typically experience the number 7 as different colors, an individual synesthete will associate 7 with (say) the exact same shade of green throughout their life span. In fact, qualifying characteristics of synesthesia require the association to be (a) stable over time (a 7 experienced as green should always be green), (b) involuntary and automatic (experiences do not require effort), and (c) both memorable and affect-laden (a number printed in the "incorrect" color may make a synesthete uncomfortable). As even nonsynesthetes experience synesthesia-like associations to some degree (Ward, Moore, Thompson-Lake, Salih, & Beck, 2008), uncovering the cognitive and neural basis of synesthesia has potential implications for the mechanisms underlying the categorization of sensory experience and the integration of information from different neural processing streams.

One proposed explanation of synesthesia is that it is a heritable condition that results from an excess of neural connections (Ramachandran & Hubbard, 2001). According to the *cross-activation* model, a genetic factor in synesthetes decreases neural pruning between interconnected

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areas leading to an abnormal increase in connectivity between brain areas that underlie the processing of inducers and concurrent sensations (Ramachandran & Hubbard, 2003). In grapheme–color synesthesia, for example, incomplete neural pruning during development results in increased connectivity between color processing area V4 and the nearby visual word form area in the fusiform gyrus (Ramachandran & Hubbard, 2001, 2003). Consequently, when graphemes activate the visual word form area they also excite neurons in V4 giving rise to the concurrent sensation of color. Alternatively, the *disinhibited feedback* proposal provides that synesthetic concurrents arise because of disinhibited feedback from higher level visual areas in pathways common to synesthetes and nonsynesthetes alike (Grossenbacher & Lovelace, 2001). A hybrid, the *reentrant processing* model posits hyperconnectivity between form and color processing areas in the fusiform (as in the cross-activation model), but, as in the disinhibited feedback model also suggests that synesthetic colors require neural activity from higher level areas in the temporal lobe (e.g., anterior inferior temporal and posterior inferior temporal) to feedback to V4 (Smilek, Dixon, Cudahy, & Merikle, 2001).

Although grapheme–color synesthesia has received a good deal of attention of late (e.g., the special issue of *Cortex* 2006 on synesthesia), researchers continue to debate some fundamental issues regarding the cognitive properties of synesthetic associations and their underlying neural substrate (for a review, see Hubbard, 2007). Cognitively, researchers have questioned whether the connection between inducer and concurrent is meaningful and connects to other information in the semantic memory system or is simply an arbitrary, isolated association (Brang, Edwards, Ramachandran, & Coulson, 2008); whether synesthetic associations are perceptual or conceptual (Ramachandran & Hubbard, 2001); and whether synesthetic connections operate in only one direction (Cohen Kadosh, Cohen Kadosh, & Henik, 2007; Cohen Kadosh et al., 2005; Knoch, Gianotti, Mohr, & Brugger, 2005). Relatedly, researchers have tested whether synesthetic colors result from feed-forward activation (Brang et al., 2010; Hubbard, Arman, Ramachandran, & Boynton, 2005), feedback from higher level visual areas (Grossenbacher & Lovelace, 2001), or a combination of feed-forward and feedback connections (Smilek et al., 2001). Moreover, synesthesia researchers continue to dispute whether connectivity differences between synesthetes and neurotypicals are fundamentally anatomical (Weiss & Fink, 2008; Rouw & Scholte, 2007), reflecting incomplete pruning during development, or physiological because of the lack of inhibitory processes (Grossenbacher & Lovelace, 2001).

Focusing on the cognitive issue of whether concurrent color sensations in grapheme–color synesthesia are available to conceptual processes, Brang et al. (2008) recorded event-related brain potentials as eight grapheme–color synesthetes read sentence fragments that suggested a particular color as a sentence-final word. For example, "The Coca Cola logo is white and" suggests "red" as the final word (or at least it did so to 75/75 participants in our normative sentence completion study). Each sentence ended either with a "congruous" grapheme that induced the contextually appropriate color (e.g., "2," which for synesthete LS induced red) or an "incongruous" grapheme that induced a contextually inappropriate color (where "7" induced green). Relative to the incongruous graphemes, congruous graphemes elicited larger amplitude N1, smaller P2, and reduced N400 components in synesthetes but not age-matched naive control subjects.

Because reduced N400 for congruous relative to incongruous sentence completions is conventionally understood as resulting from contextual integration processes (Van Berkum, Hagoort, & Brown, 1999; Holcomb, 1993), the N400 effect in synesthetes was argued to support the automaticity of the color-induction process in grapheme–color synesthesia and to suggest that the concurrent color sensation is treated by the brain as a meaningful stimulus. However, as is common practice in synesthesia research, the control group tested by Brang et al. (2008) was naive to the synesthetes' associations—and those participants were surely bewildered as to why they were reading sentences ending in isolated letters and numbers.

This raises the question of whether ERP effects reported by Brang et al. (2008) reflect the synesthetes' altered experience of graphemes as colored objects or whether they merely reflect their knowledge of the correspondences between particular graphemes and their assigned colors. Indeed, previous research has demonstrated that training nonsynesthetic individuals on synesthetic associations can produce markedly similar behavioral performance between synesthetes and controls on the synesthetic Stroop task (Meier & Rothen, 2009). Thus, the relative import of synesthetes' altered perceptual experience versus conceptual knowledge of the grapheme–color mappings is at issue in the N400 context effect, P2 effect, and N1 effect reported by Brang et al.

The Present Study

The goal of the present study was, first, to partially replicate contextual priming effects in grapheme–color synesthetes' ERPs described in Brang et al. (2008) and, second, to elucidate their functional significance via the testing of three different groups of neurotypical controls. As in Brang et al., we collected data from grapheme–color synesthetes as they read sentences (e.g., "The Coca Cola logo is white and") that ended in color words, color patches, or achromatic graphemes (see Figure 1). Three groups of neurotypical controls were also tested on variations of the original paradigm: colored grapheme controls, trained controls, and explicit visualization controls. The colored grapheme controls were tested to identify ERP effects related to the perceptual experience of viewing colored graphemes. Consequently, each member of this group of

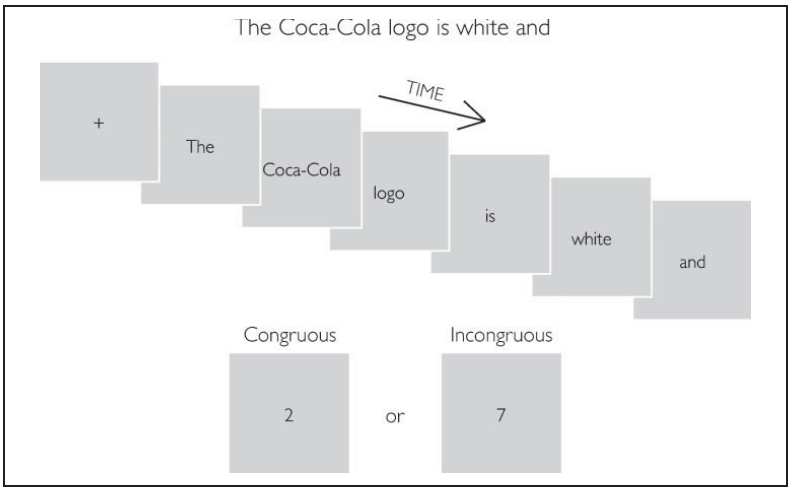


Figure 1. Example trial illustrating the display sequence. Depending on the condition, the final display ended with a congruous/incongruous color word, color patch, or grapheme.

naive nonsynesthetes viewed sentences ending in color words, color patches, or graphemes colored to mimic the perceptual experience of one of our synesthetes. The trained controls were included to test whether any of the contextual priming effects observed in synesthetes could be attributed to conceptual knowledge of the mappings between graphemes and their concurrent colors. These neurotypical controls were first trained on one grapheme–color synesthete's associations and then had ERPs recorded as they viewed the same sentences as their synesthete.

In addition to the conceptual knowledge of grapheme–color pairings, synesthetes' greater familiarity with these mappings may have affected the way they performed this task. That is, as soon as they realized the upcoming color ending, they may have begun to anticipate the associated congruous grapheme. To test whether ERP effects observed in the synesthetes resulted from anticipation of the form of the expected grapheme (viz., its shape), explicit visualization controls were trained on a synesthete's grapheme–color associations and given an explicit visualization task. These participants were told that as soon as they realized which grapheme should appear at the end of the sentence (i.e., 2 at the end of "The Coca Cola logo is white and"), they should explicitly visualize that grapheme on the monitor in front of them.

The present study was aimed to test for group differences in the cognitive and neural processes invoked by our task and to assess the time course of any such differences between synesthetes and neurotypical controls. In particular, we hoped to explore whether processing differences between the groups would arise during a timeframe associated with perceptual versus conceptual aspects of processing. ERPs were employed because they are a direct measure neural activity with a high degree of temporal resolution.

The inclusion of the three control groups was intended to determine which of the previously reported ERP context effects (N1, P2, and N400) result from synesthetes' knowledge of the mappings between graphemes and colors and which result from the subjective experience of seeing colored graphemes. The observation of ERP effects in the trained controls would show that the mere knowledge of the conceptual mappings of synesthetic associations is sufficient to elicit previously reported ERP effects in synesthetes. Of the ERP components listed above, the N400 is most likely to be affected by knowledge of the grapheme–color mappings given that it has been linked to the access of information in semantic memory (Kutas & Federmeier, 2000). Earlier, perceptual effects such as the N1 and P2 might be driven by the way that synesthetes approach the task. For example, if synesthetes anticipate the shape of the expected grapheme, we might expect to see these effects in the explicit visualization controls. Alternatively, if perceptual experience is required for the elicitation of these ERP effects, we would expect to see N1 and P2 effects only in the colored grapheme controls.

METHODS

Participants

Data were collected from four grapheme–color synesthetes and combined with those from the eight synesthetes reported in Brang et al. (2008). Grand-average ERP data from synesthetes thus includes a total of 12 synesthetic participants. Thirty-six nonsynesthetic controls also participated, none of whom participated in the previous study. All participants were fluent English speakers, had normal or corrected-to-normal vision, and none had any history of psychiatric or neurological disorder. The 12 synesthetes ranged in age from 18 to 30 years (mean age = 19.7 years,

SD = 1.5 years) and included 10 women. The 12 colored grapheme controls ranged in age from 19 to 24 years (mean age = 20.7 years, *SD* = 1.6 years) and included 9 women. The 12 trained controls' age ranged from 19 to 28 years (mean age = 21.6 years, *SD* = 2.8 years) and included 4 women. The 12 explicit visualization controls' age ranged from 19 to 29 years (mean age = 21.2 years, *SD* = 2.8 years) and included 11 women.

Handedness was assessed via the Edinburgh Inventory (Oldfield, 1971), which yields a laterality quotient ranging from +1 (strongly right-handed) to −1. The majority of our participants were right-handed: synesthetes, 10 right, 2 left, average laterality quotient of +0.40; colored graphemes controls, 11 right, 1 left, average laterality quotient of +0.69; trained controls, 10 right, 2 left, average laterality quotient of +0.44; explicit visualization controls, 11 right, 1 left, average laterality quotient of +0.55. Synesthetes were recruited via fliers posted on the UCSD campus as well as similar ads on the Web. Synesthesia was confirmed by means of consistency matching as well as RT testing for color congruency, standardized by Eagleman, Kagan, Nelson, Sagaram, and Sarma (2007). All participants gave signed informed consent before the experiment and participated either for cash or in fulfillment of a course requirement. None of the control participants reported any known forms of synesthesia.

Materials and Procedure

Synesthetic participants, colored grapheme controls, and trained controls read 80 sentences that ended in text, 80 in color patches, and 80 in graphemes. Multiple stimulus lists were employed so that although no individual participant saw the same sentence twice, across participants each sentence ended an equal number of times with a color term, a color patch, or a grapheme. To control for surprise effects due to the introduction of nonlinguistic stimuli into sentence contexts, sentence-ending forms were presented in a blocked format. Blocks were pseudorandomized for each subject, such that two blocks of the same type were not presented sequentially. Block order was counterbalanced between subjects. Half of the sentences in each block ended as expected (congruous completions) and half with an unexpected color word, color patch, or a grapheme that induced an unexpected color (incongruous completions). Explicit visualization controls read 240 sentences that ended in graphemes (half ended congruously, half incongruously).

General Procedure

All participants were seated in a comfortable chair at a distance of 37 in. from the monitor in a sound-attenuated room. Sentences were visually presented one word at a time at the rate of two words per second. Unless noted otherwise, all words and graphemes were presented in black against a gray background. Each sentence-final word, color patch, or grapheme was presented for 200 msec followed by 1300 msec of blank screen (Figure 1). Participants were instructed to silently read experimental materials and to refrain from eye movements from the time the sentence-final stimulus appeared until the fixation cross appeared on the screen. Congruity of sentence-final words was established in a separate normative study.

Synesthetes

The stimulus material and the experimental design were identical to those used in Brang et al. (2008). Stimuli consisted of 240 sentences ending in one of three forms: text, color patch, or grapheme. In the grapheme condition, sentences ended with an achromatic grapheme known to induce either a congruous concurrent color ("2" for a synesthetes for whom 2 appears red) or an incongruous one ("7" for a synesthetes for whom 7 appears green). Sentence-final graphemes were adapted for each of our 12 synesthetes to match 11 possible color terms (red, orange, yellow, green, blue, purple, black, brown, white, gray, and pink) when possible. However, as some synesthetes did not experience grapheme–color associations for each of these color terms, the number of associations varied slightly between individuals (range = 9–11 grapheme–color associations, average = 10).

Colored Grapheme Controls

The experimental materials and procedure were identical to those applied to the synesthetes, with the exception of sentence-final stimuli in the grapheme condition. Whereas synesthetes viewed achromatic (black) graphemes, colored grapheme controls viewed graphemes written in a colored font matched to the subjective experience of a particular synesthete. Each member of this control group was yoked to a different synesthetic participant.

Trained Controls

Each participant in this group was yoked to a different synesthete and taught that synesthete's mappings between graphemes and colors via the use of a computerized training program. Each trained control thus learned a distinct set of 10 grapheme–color associations, in which each of the 10 graphemes corresponded to one of the 10 colors used in the study: red, orange, yellow, green, blue, purple, black, brown, white, and pink.

On a given trial, the training program displayed one achromatic grapheme in the center of the screen, surrounded by 10 colored blocks (location of each color was randomized on each trial). Subjects proceeded to click one of the colors in a guess-and-check fashion and received feedback on whether their grapheme–color pairing was correct. Participants were not allowed to advance to the EEG portion of the study until they correctly identified the associated color with each of the 10 graphemes twice

in a row without any errors. Training took approximately 15 minutes.

During the EEG recording session, each participant in the trained control group viewed the exact same stimuli as had their yoked synesthete. Experimenters quizzed them verbally about the color of each grapheme immediately before beginning the recording session and during a break at the session's midpoint.

Explicit Visualization Controls

Differing from the synesthetes and other two control groups, explicit visualization controls viewed a grapheme at the end of all 240 sentences (120 with a grapheme associated with the contextually congruous color and 120 with an incongruous color); that is, there were no text or color blocks. As with trained controls, explicit visualization controls began with a brief training session in which they learned the grapheme–color associations of a particular synesthete. Using the computer program described above, training on pairings between letter/number and color proceeded via a process of guess and check followed by feedback. Participants were not allowed to advance to the EEG portion of the study until they correctly identified the associated color with each of 10 graphemes twice in a row without any errors.

For the ERP study, these participants were asked to anticipate the sentence-final item and to visualize it on the screen. That is, participants were told that as soon as they realized a 2 would appear at the end of "The Coca Cola logo is white and," they were to imagine a 2 on the monitor in front of them. As in the trained control group, participants were quizzed verbally about the color of each grapheme immediately before beginning the recording session and during a break at the session's midpoint.

Electroencephalographic and Electrooculographic Recording

Participants' EEG was monitored with a commercial electrode cap with 29 scalp sites arranged according to the International 10–20 system (Ebner, Sciarnetta, Epstein, & Nuwer, 1999). Horizontal eye movements were measured with a bipolar derivation of electrodes placed at the outer canthi. Vertical eye movements and blinks were monitored with an electrode under the right eye. All electrodes were referenced on-line to the left mastoid, and all impedances were maintained below 5 kΩ. The EEG at a band pass of 0.01 and 100 Hz was amplified with SA Instruments 32-channel bioamplifiers (Stony Brook, NY), digitized at 250 Hz, and stored on a computer hard disk for later averaging.

Analysis of ERPs

ERPs were time locked to the onset of the sentence-final stimuli, and signals were averaged with a time window of −100 to 920 msec around an event. The 100-msec period preceding the onset of the target item served as the baseline. Epochs containing artifacts were rejected before averaging. Rejection values for each artifact were modified on a subject-by-subject basis, yet rejection values were applied uniformly throughout a given subject. Epochs were rejected for thresholds exceeding on average 292 μV for blinks, 337 μV for eye movements, 493 μV for amplifier drift, or 15 msec for blocking. Unless noted otherwise, analysis involved mean amplitude measurements of each participant's ERPs elicited between 150 and 200 msec post-sentence-final stimulus onset (intended to capture the N1 component), 150 and 250 msec post-sentence-final stimulus onset (intended to capture the P2 component), between 250 and 350 msec post-sentence-final stimulus onset (intended to capture the N300 component), and between 350 and 450 msec post-sentence-final stimulus onset (intended to capture the N400 component). Measurements were subjected to repeated measures ANOVA, with the within subject factors of congruity (congruous/incongruous) and scalp distribution factors as follows: N1 analysis included posterior electrodes (TP7, CP3, CPz, CP4, TP8, T5, P3, Pz, P4, TP7, O1, Oz, O2), and P2 and N400 analyses included all electrode sites (FP1, FPz, FP2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, C3, Cz, C4, TP7, CP3, CPz, CP4, TP8, T5, P3, Pz, P4, TP7, O1, Oz, O2). Although the original degrees of freedom have been maintained for clarity, where appropriate, p values were subjected to Greenhouse–Geisser correction (Greenhouse & Geisser, 1959).

RESULTS

Text Condition

The final word of sentences in the text condition elicited ERPs typical of visually presented words: N1, P2, and N400, observed in synesthetes, trained controls, and colored grapheme controls. ERPs to sentences ending in color words can be seen in Figure 2. As predicted, the congruity manipulation reliably affected the amplitude of the N400 because congruous sentence completions elicited less negative N400 than did incongruous ones, Congruity, $F(1, 33) = 30.46$, $p < .0001$. Neither the amplitude nor the distribution of the congruity effect varied as a function of group, Group × Congruity, $F(2, 33) = 0.11$, $p = .90$; Group × Congruity × Electrode, $F(56, 924) = 1.74$, $p = .11$.

Follow-up analyses in each group revealed a similar-sized congruity effect in synesthetes (2.04 μV), $F(1, 11) = 14.39$, $p < .01$, colored graphemes (naive controls; 1.75 μV), $F(1, 11) = 6.89$, $p < .05$, and trained controls (2.14 μV), $F(1, 11) = 10.86$, $p < .01$; Congruity × Electrode, $F(28, 308) = 3.23$, $p < .05$ (see Figure 2).

Color Patch Condition

Rectangular color patches elicited ERPs that were similar to the color words in the text condition, including N1, P2, and N400 components. ERPs to congruous and incongruous

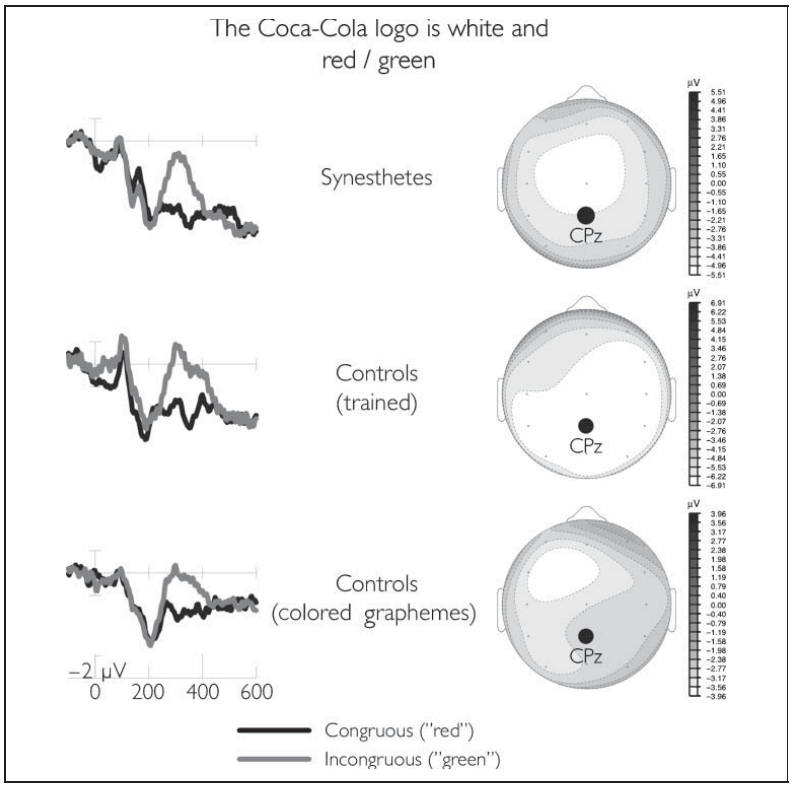


Figure 2. (Left) Grand-average ERPs at posterior electrode CPz to congruous (black line) and incongruous (gray line) sentences ending in a color word. N400 amplitude between 350 and 450 msec was larger for incongruous compared with congruous words. (Right) Spline-interpolated topographic maps show the scalp distribution of the N400 congruity effect. Congruity effects were derived by subtracting the waveform elicited by congruous graphemes from incongruous graphemes. Results are shown separately for synesthetes (n = 12), controls trained to a particular synesthete's associations (n = 12), and controls who viewed physically colored graphemes (n = 12). Controls in the explicit visualization condition did not read sentences ending in color words.

color patches in each group are shown in Figure 3. As in the text condition, color patches elicited less negative N400 when they served as congruous than incongruous sentence completions, Congruity, $F(1, 33) = 14.74$, $p < .001$. Moreover, the color patch congruity effect did not differ as a function of group, Group × Congruity, $F(2, 33) = 0.60$, $p = .55$; Group × Congruity × Electrode, $F(56, 924) = 0.82$, $p = .59$. N400 congruity effects were reliable in synesthetes, $F(1, 11) = 6.36$, $p < .05$, and colored graphemes (naive controls), $F(1, 11) = 6.82$, $p < .05$, and trended toward significance in trained controls, $F(1, 11) = 3.28$, $p = .10$.

Grapheme Condition

Synesthetes' ERPs to sentence-final graphemes are shown in Figure 4. As in the text and color patch conditions, graphemes elicited N1 and P2 potentials. However, whereas text and color patches elicited a monophasic (single peaked) negativity in the latency window of the N400, sentence-final graphemes elicited a biphasic negativity with a peak at 320 msec—presumed to be the N300 component—and a second peak at 380 msec representing the classic N400 component.

N1

The N1 elicited by graphemes is shown for each group in Figure 5. Omnibus analysis revealed a main effect of Congruity, $F(1, 44) = 4.45$, $p < .05$, as well as a Group × Congruity interaction, $F(3, 44) = 3.30$, $p < .05$. Preplanned analyses of the congruity effect in each group revealed a reliable congruity effect only in synesthetes, as the N1 component elicited by congruous graphemes was 1.57 μV more negative than that elicited by incongruous graphemes (see Table 1). This pattern of N1 congruity effects was apparent in 10 of our 12 synesthetes. A similar pattern was observed in 9 of the 12 naive controls who viewed colored graphemes, resulting in a nonsignificant trend in the colored graphemes control group (see Table 1). No congruity effects were found either in trained controls or in trained controls given the explicit visualization task (see Table 1).

P2

The P2 elicited by congruous and incongruous graphemes is shown for each group in Figure 6. Figure 6 suggests that incongruous graphemes elicited more positive P2 than congruous ones in synesthetes but in none of the control groups. This was borne out by a reliable Group × Congruity interaction, $F(3, 44) = 4.10, p < .05$, as well as the results of preplanned analyses of each group. Grapheme congruity reliably affected P2 amplitude in the synesthetes but in none of the control groups (Table 1).

N300

Consistent with other researchers who report both N300 and N400 (McPherson & Holcomb, 1999; Holcomb & McPherson, 1994), incongruous stimuli elicited more negative ERPs than congruous, with the earlier peak being largest over anterior sites, and the later peak largest over posterior sites (see Figure 4). Figure 7 shows that the biphasic N300/N400 complex was evident in synesthetes and in the controls given an explicit visualization task. To confirm the presence of the N300/N400 in synesthetes and explicit visualization controls we conducted a post hoc analysis of the mean amplitude of ERPs comparing between-participants factor group (synesthetes, trained controls, explicit visualization controls, and colored number controls) and within-participant factors latency window (250–350 and 350–450 msec), congruity (congruous, incongruous), and electrode (12 medial electrodes). This analysis revealed a significant interaction of group, latency window, congruity, and electrode, $F(33, 484) = 2.16, p < .05$, suggesting the distribution patterns of the N300 and N400 did indeed vary as a function of group.

N400

Omnibus analysis of ERPs in the N400 window revealed a main effect of Congruity, $F(1, 44) = 33.89, p < .001$, as congruous graphemes elicited less negative N400 than did incongruous ones. However, this congruity effect did not vary as a function of group, Group × Congruity, $F(3, 44) = 0.50, p = .69$. Results of preplanned analyses of the N400 congruity effect in each group are shown in Table 1. Synesthetes, naive controls who viewed colored graphemes, and trained controls given the explicit visualization task all showed robust congruity effects; trained controls

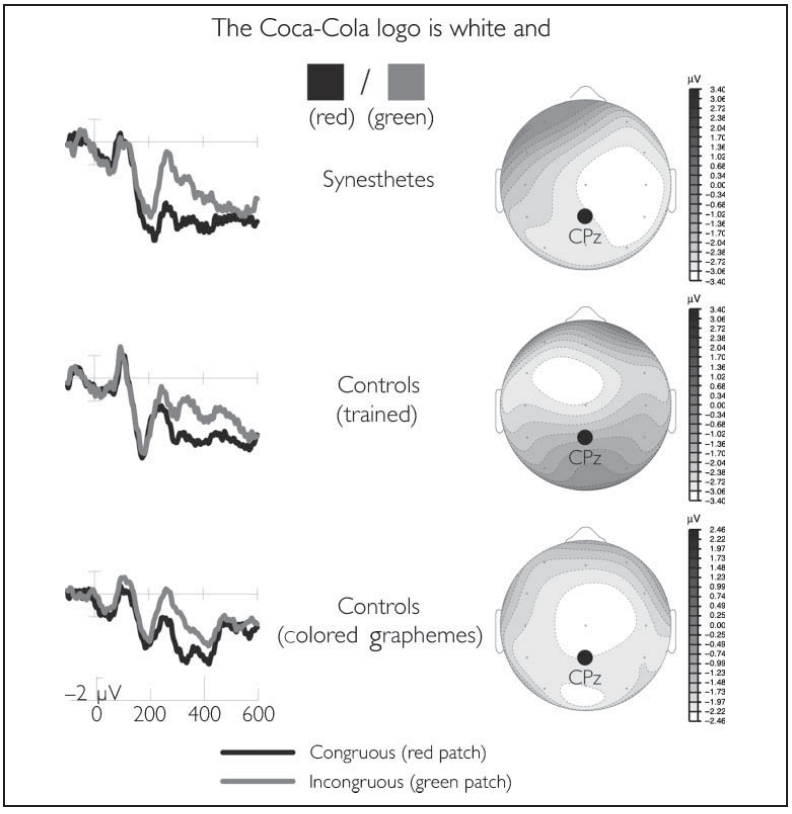


Figure 3. (Left) Grand-average ERPs at posterior electrode CPz to congruous (black line) and incongruous (gray line) sentences ending in a color patch. N400 amplitude between 350 and 450 msec was larger for incongruous compared with congruous words. (Right) Spline-interpolated topographic maps show the scalp distribution of the N400 Congruity effect. Congruity effects were derived by subtracting the waveform elicited by congruous graphemes from incongruous graphemes. Results are shown separately for synesthetes ($n = 12$), controls trained to a particular synesthete's associations ($n = 12$), and controls who viewed physically colored graphemes ($n = 12$). Controls in the explicit visualization condition did not read sentences ending in color patches.

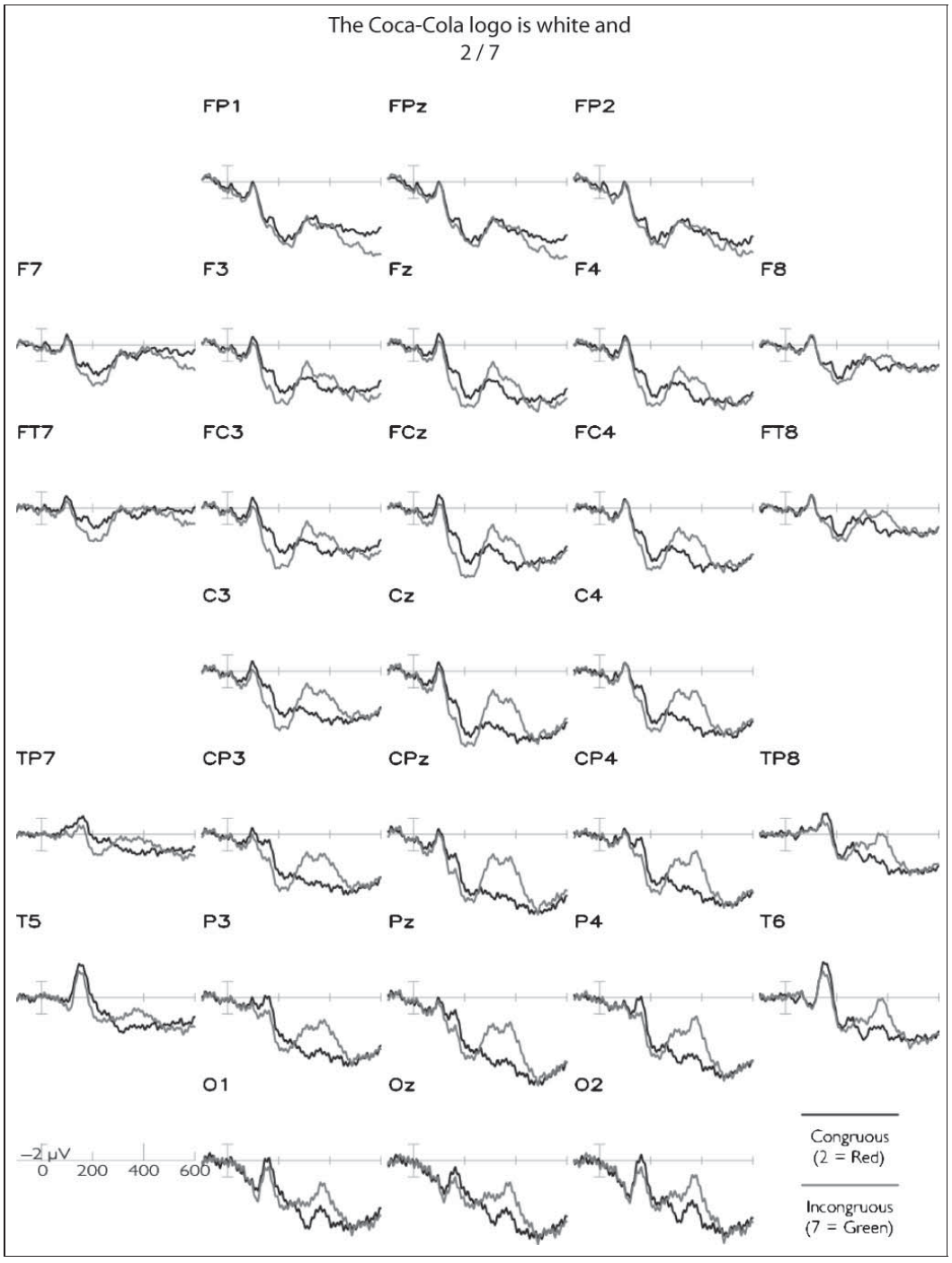


Figure 4. Synesthete's grand-average ERPs at all electrode sites to congruous (black line) and incongruous (gray line) sentences ending in a grapheme.

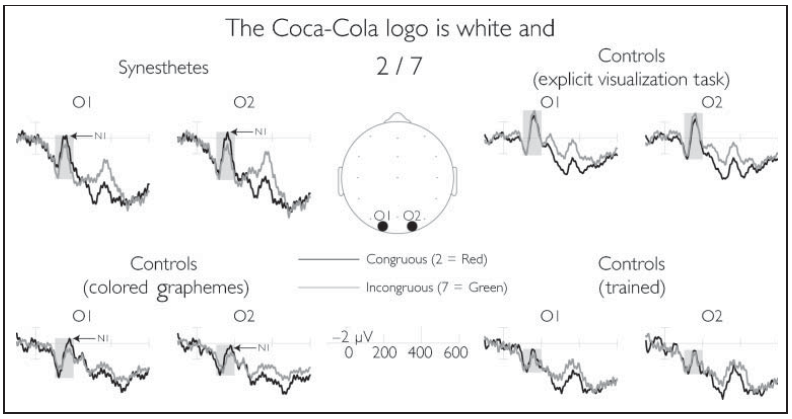


Figure 5. The N1 effect observed in synesthetes (n = 12) and who viewed physically colored graphemes (n = 12) but not seen in controls trained to a particular synesthete's associations (n = 12) or trained controls given an explicit visualization task (n = 12). Grand-average ERPs at posterior electrodes O1 and O2 to congruous (black line) and incongruous (gray line) sentences ending in a grapheme. N1 amplitude between 170 and 190 msec was larger (more negative) for congruous compared with incongruous graphemes. Shaded region encapsulates measured window.

showed a smaller difference that did quite not reach significance (see Table 1).

DISCUSSION

To test whether synesthetic associations in grapheme–color synesthesia are treated by the brain as arbitrary associations versus potentially meaningful connections, scalp-recorded ERPs were recorded as 12 grapheme–color synesthetes read sentences that evoked the concept of a particular color. Sentences ended either with a color word, a color patch, or a grapheme that induced a color. For example, "The Coca Cola logo is white and" ended with either a congruous target (such as the word "red," a red color patch, or with a grapheme such as 2 known to elicit the concurrent sensation of red) or an incongruous target

Table 1. Grapheme Condition

	Synesthetes	*Controls (Colored Graphemes)*	*Controls (Trained)*	*Controls (Explicit Visualization)*
N1				
Amplitude difference	−1.57 μV	−0.81 μV	−0.01 μV	0.38 μV
Congruity	$F(1, 11) = 6.41$, $p < .05$	$F(1, 11) = 3.35$, $p = .09$	$F(1, 11) = 0.00$, $p = .98$	$F(1, 11) = 1.85$, $= .20$
Congruity × Electrode	$F(12, 132) = 1.01$, $p = .39$	$F(12, 132) = 2.03$, $p = .12$	$F(12, 132) = 1.30$, $p = .29$	$F(12, 132) = 0.93$, $p = .44$
P2				
Amplitude difference	−1.41 μV	0.24 μV	−0.06 μV	0.57 μV
Congruity	$F(1, 11) = 5.59$, $p < .05$	$F(1, 11) = 0.68$, $p = .43$	$F(1, 11) = 0.02$, $p = .90$	$F(1, 11) = 6.78$, $p < .05$
Congruity × Electrode	$F(28, 308) = 1.02$ $p = .39$	$F(28, 308) = 2.10$ $p = .13$	$F(28, 308) = 0.69$ $p = .52$	$F(28, 308) = 1.13$ $p = .34$
N400				
Amplitude difference	1.95 μV	1.40 μV	1.24 μV	2.06 μV
Congruity	$F(1, 11) = 6.88$, $p < .05$	$F(1, 11) = 7.02$, $p < .05$	$F(1, 11) = 4.48$, $p = .06$	$F(1, 11) = 32.74$, $p < .001$
Congruity × Electrode	$F(28, 308) = 5.02$ $p < .01$	$F(28, 308) = 0.82$ $p = .50$	$F(28, 308) = 3.74$ $p < .05$	$F(28, 308) = 4.03$ $p < .05$

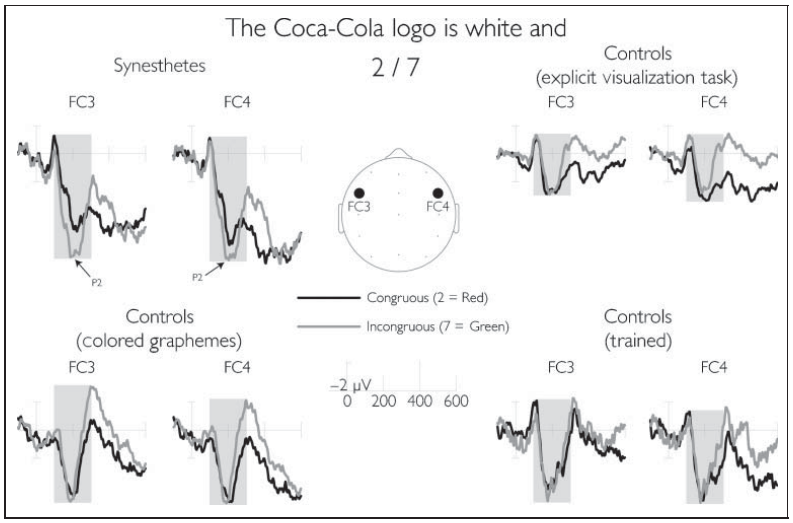


Figure 6. The P2 observed in synesthetes (n = 12) but not controls trained to a particular synesthete's associations (n = 12), trained controls given an explicit visualization task (n = 12), or controls who viewed physically colored graphemes (n = 12). Grand-average ERPs at anterior electrodes FC3 and FC4 to congruous (black line) and incongruous (gray line) sentences ending in a grapheme. P2 amplitude between 150 and 250 msec was larger (more positive) for incongruous compared with congruous words. Shaded region encapsulates measured window.

(such as the word "green," a green color patch, or with a grapheme such as 7 known to elicit the concurrent sensation of green).

The congruity manipulation in the text and color patch conditions resulted in the well-known contextual priming effect on the N400 component in the ERP. N400 contextual priming effects were also observed in the grapheme condition, indicating that synesthetic associations are available for integration with linguistically activated concepts. Moreover, the congruity manipulation affected the amplitude of the N1, P2, and N300 components elicited by graphemes.

Three neurotypical control groups were tested in a similar paradigm to elucidate the functional significance of these ERP effects. For example, to identify effects attributable to conceptual knowledge of the correspondences between graphemes and their concurrent colors, trained controls were taught these mappings and subsequently read sentences ending in achromatic graphemes. To identify effects attributable to task strategy, explicit visualization controls were taught grapheme–color mappings and asked to anticipate the appearance of the expected grapheme at the end of the sentence. Finally, to identify ERP effects attributable to the experience of colored graphemes, *colored grapheme* controls read sentences ending with colored graphemes.

Grapheme congruity modulated the N400 in synesthetes and all three control groups (Figure 3). Congruity modula-

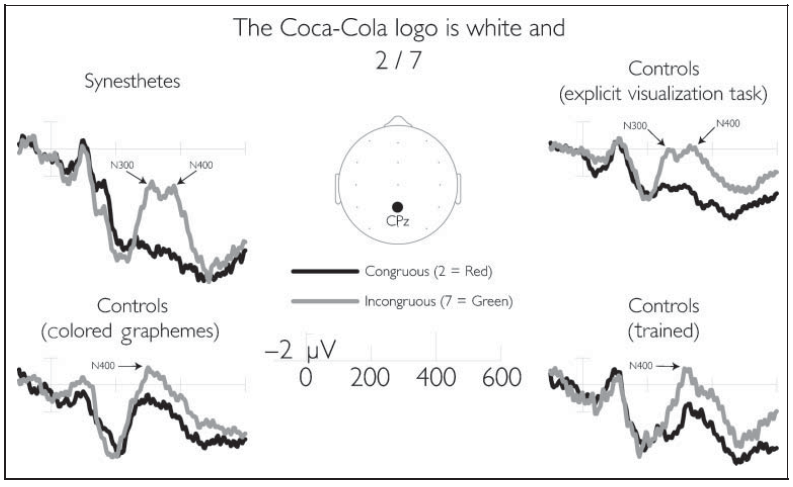


Figure 7. The N300 and N400 observed in synesthetes (n = 12) and trained controls given an explicit visualization task (n = 12) and only the N400 seen in controls trained to a particular synesthete's associations (n = 12) and controls who viewed physically colored graphemes (n = 12). Grand-average ERPs at posterior electrode CPz to congruous (black line) and incongruous (gray line) sentences ending in a grapheme. N300 and N400 amplitudes between 250–350 and 350–450 msec, respectively, were larger (more negative) for incongruous compared with congruous graphemes.

tion of the N300 was observed in synesthetes and explicit visualization controls (Figure 7). Congruity effects on the P2 were observed only in synesthetes (Figure 6). Finally, congruity modulation of the N1 was observed in synesthetes and colored grapheme controls (Figure 5).

N400

Contextual priming effects on the N400 component were thus the most consistent finding in the study, as the amplitude of this component was reduced by congruous sentence contexts for color words in synesthetes and in both the naïve and trained neurotypical control groups (Figure 2). The amplitude of the N400 elicited by color patches was also reduced in congruous relative to incongruous sentence contexts in synesthetes as well as for neurotypical controls (see Figure 3). Most importantly, similar N400 contextual priming effects were found for achromatic graphemes in synesthetes, for trained controls doing an explicit visualization task, and for colored graphemes viewed by naive control participants (see Figure 7).

These data suggest that the perceptual experience of colored graphemes is sufficient but not necessary for the elicitation of grapheme priming effects in this paradigm. Given that similar grapheme congruity effects on the N400 were observed in synesthetes and trained controls, effects in the synesthetes presumably stem from knowledge of the correspondences between particular letters or numbers and their corresponding colors. This knowledge could arise from the experience of graphemes as colored objects (as in the synesthetes and the naive controls who viewed colored graphemes) or from a short training period on the mappings.

Beyond synesthesia, these data speak to the flexibility of multimodal meaning-integration processes as conceptual expectations about color displayed a remarkably similar impact on ERPs 350–450 msec postonset, irrespective of whether the eliciting event was a color word, a color patch, a colored grapheme, or a grapheme recently associated with a color. The rapid integration of color information with participants' representation of sentence meaning may reflect the import of combining information from different modalities in face-to-face communication and in keeping with recent evidence that the brain simultaneously integrates information from spoken words and cospeech gestures (Ozyurek, Willems, Kita, & Hagoort, 2007; Wu & Coulson, 2007a, 2007b).

Another possibility is that perceived colors are rapidly integrated into sentences about color because the neural representation of color words recruits brain regions important for color perception, as in the cell assembly model proposed by Pulvermuller (2001). According to this model, word meanings are established via associative learning mechanisms linking information about word forms and the things they represent. Subsequently, word forms activate a distributed cortical network that includes associated sensorimotor activations. The model is supported by data showing that the comprehension of words related to olfactory experience (e.g., garlic) involves the activation of olfactory cortex (Gonzalez et al., 2006) and that understanding action verbs involves somatotopic activation of motor and premotor cortex (Pulvermuller, Shytrov, & Ilmoniemi, 2005).

The cell assembly model thus suggests that any neural activity correlated with the occurrence of "2" will be incorporated into its meaning and become available for integration with other activated conceptual information. Although the neural activity underlying the (for example) redness of a synesthete's 2 is irrelevant to its numeric referent, it nonetheless functions as part of its meaning. As a result, contextual congruity of the normally irrelevant concurrent had a facilitative effect on the meaning integration processes indexed by the N400 component.

N300

In view of the similarities between our four groups' ERPs to contextual priming of color words and color patches, the differences in their ERPs to graphemes subjected to the very same contextual priming paradigm are all the more remarkable. For example, the N300/N400 complex was evident in synesthetes and in the explicit visualization controls but not in trained controls without the visualization task or in untrained controls viewing colored graphemes (see Figure 7).

More typically reported in studies of picture priming (e.g., Hamm, Johnson, & Kirk, 2002; McPherson & Holcomb, 1999), this complex consists of an anteriorly distributed negative peak (N300) evident 250–350 msec poststimulus onset, thought to reflect object recognition, followed by a more broadly distributed negativity, the N400, thought to reflect more general, multimodal semantic processing (for a review, see Wu & Coulson, 2007a). The N300 is more negative for pictures of unidentifiable objects than for identifiable objects, and like the N400, its amplitude is reduced by the prior presentation of a picture of a related object (McPherson & Holcomb, 1999). N300 amplitude has also been shown to be reduced by contextual congruity, evoked by either linguistic (Federmeier & Kutas, 2002) or pictorial (West & Holcomb, 2002) contexts.

Although not typically elicited by graphemes, the observation of N300 effects in the present study is not particularly surprising given that graphemes are especially complex objects for synesthetes, eliciting color and even texture from form. Perhaps more puzzling is our failure to observe N300 effects in ERPs elicited by color patches (see Figure 3) or in ERPs elicited by colored graphemes (see Figure 7). These findings suggest that color per se is not sufficient to engage the object recognition processes that underlie the N300. Rather, N300 elicitation in controls was confined to participants asked to explicitly visualize expected graphemes, suggesting this ERP effect was related either to the anticipation of particular graphemes in sentence-final position or to the instruction to engage in mental

imagery (or both). The latter suggestion is consistent with the report that synesthetes exhibit superior visual imagery abilities than do nonsynesthetic controls (Barnett & Newell, 2008).

P2

Congruity effects, revealed by an enhanced positivity on the anterior P2, were observed in synesthetes but neither of the control groups (see Figure 6). By all appearances, this effect is unique to synesthetes' processing of graphemes in sentence contexts. Moreover, although anterior P2 effects have occasionally been reported for words in sentence contexts, it is typically contextually congruous (expected) words that elicit a larger positivity than incongruous words (e.g., Federmeier, Mai, & Kutas, 2005). In contrast, the anterior P2 in the synesthetes was more positive for incongruous than congruous graphemes (see also Brang et al., 2008).

Citing Luck and Hillyard's (1994) suggestion that the functional significance of the anterior P2 is in multidimensional feature detection, Brang et al. (2008) interpreted the observed anterior P2 effect in grapheme–color synesthetes as indexing the binding of form information with synesthetically induced color presumed to underlie the synesthete's conscious percept of an achromatic 2 as a red 2. In keeping with this suggestion, the time course of the observed P2 effect is consistent with electrophysiological investigations of feature binding. Schoenfeld et al. (2003) report a positive ERP deflection beginning 230–240 msec postonset for attended dots in a moving dot display when the dot had a task-irrelevant color. Schoenfeld et al. localized the source of this effect to ventral V4 and suggested it was important for the feature binding process underlying the perceptual unity of attended objects.

Anterior positive components in this time window have been also been identified with inhibitory processes, such as the suppression of irrelevant visual features (Guillem, Bicu, & Debruille, 2001) and the inhibition of auditory distractors (Melara, Rao, & Tong, 2002). Bles, Alink, and Jansma (2007) have shown that the anterior P2 elicited in word recognition paradigms is sensitive to the need to suppress salient alternative lexical candidates, with larger P2 being associated with greater inhibitory demands. Synesthetes' generation of a larger P2 for contextually incongruous graphemes may thus reflect inhibitory processes needed to suppress or limit the engagement of synesthetically induced colors.

If the anterior P2 indexes inhibition, it appears that the inhibition of synesthetically induced colors imposes a greater demand than the inhibition of colors that are perceptually perceived. If the anterior P2 indexes the demands of binding of form and color information, it suggests that synesthetically induced colors are more negatively impacted than are colors that are perceptually perceived. In fact, these two explanations are not mutually exclusive and both point to an important role for contextual expectations in the processes underlying the induction of synesthetic colors.

Irrespective of the precise characterization of the processes underlying the P2, results of the present study indicate that they were not engaged by expectations about grapheme form, as suggested by their absence in the explicit visualization group. Nor were they engaged by expectations about grapheme color, as suggested by their absence in the colored grapheme group. Indeed, they were not engaged by color apprehended via normal perceptual processes, as suggested by their absence in the color patch condition in controls and synesthetes alike. The implication is that synesthetic induction of color from an achromatic grapheme involves slightly different cognitive and neural processes than does the perception of stimulus color information. In keeping with this suggestion, synesthetes report that the colors induced by graphemes often have an intangible quality that sets them apart from other colors, including the presence of unique hues (e.g., a "blueness" that exists only for 32), textures (a "metallic green"), and appearances, such as subtle tinges or halos emanating from the graphemes.

N1

N1 effects were not observed in any group in sentences ending with color words (see Figure 2) or with color patches (see Figure 3). In the grapheme condition, N1 effects were seen only in synesthetes who viewed achromatic graphemes and neurotypical controls who viewed colored graphemes (see Figure 5), further supporting the notion that synesthetically colored graphemes are processed similarly to physically colored graphemes in nonsynesthetic subjects. Importantly, trained controls given an explicit visualization task showed no modulation of the N1 component, suggesting that the expectation of grapheme form was not sufficient to modulate early components of the ERP. Of course, given that both the trained and the explicit visualization controls underwent a relatively short period of training on the color–grapheme correspondences, we cannot rule out the possibility that N1 effects might have been observed in controls who engaged in a more extensive training regime.

As the N1 is thought to index visual discrimination processes (Vogel & Luck, 2000), its elicitation in our contextual priming paradigm suggests that the conceptual expectations about color engendered by the sentence context facilitated visual processing of the appropriately colored grapheme. Findings in the present study thus replicate earlier work which suggests that synesthetically induced colors can influence the perception of digits (Smilek et al., 2001).

To test whether the N1 effect in synesthetes differed in size or scalp distribution from the N1 effect observed in controls who viewed physically colored graphemes, we conducted a post hoc analysis of the mean amplitude of ERPs measured 150–200 msec poststimulus onset, with

between-participants factor Group (synesthetes and colored grapheme controls) and within-participants factors Congruity and Electrode site. This analysis revealed a main effect of Congruity, $F(1, 22) = 9.76. p < .01$, but critically no interaction between Group and Congruity, $F(1, 22) = 0.98$, $p = .33$, nor between Group, Congruity, and Electrode sites, $F(12, 264) = 0.50$, $p = .69$. Results of this analysis are thus consistent with the conclusion that the N1 grapheme congruity effect had similar neural sources in synesthetes who viewed achromatic graphemes and controls who viewed colored graphemes. However, null results of this sort must always be interpreted with caution (see Urbach & Kutas, 2003). Moreover, this particular analysis was post hoc and did not involve high-density recording best suited for addressing claims of this sort.

Nonetheless, if taken at face value, the similar N1 response in these two groups suggests achromatic graphemes engage similar visual processing networks, as do colored graphemes in nonsynesthetes. This finding is thus consistent with fMRI results that argue for synesthetes' activation of color processing networks in response to achromatic graphemes (Sperling, Prvulovic, Linden, Singer, & Stirn, 2006; Hubbard et al., 2005).

The strength of electrophysiological measures used in the present study, however, lies not in their spatial precision but rather in their temporal resolution. Although our analysis revealed no evidence for group differences in the topography of the N1 component, we did find evidence for group differences in the timing of the brain response. As the amplitude of the N1 itself was measured between 150 and 200 msec poststimulus onset, we assessed N1 onset by measuring the mean amplitude of ERPs elicited in the 50-msec interval before this window (i.e., 100–150 msec poststimulus onset), with between-participants factor group (synesthetes and colored grapheme controls) and within-participants factors congruity and electrode site. This analysis revealed an interaction between group and congruity, $F(1, 22) = 6.05, p < .05$, indicating that our experimental manipulation of color expectations had an earlier impact on the synesthetes' brain response than on that of controls who viewed colored graphemes. Indeed, generalized differences in synesthetes' visual processing mechanisms have been argued to occur as early as between 65 and 85 msec (Barnett et al., 2008), providing a basis for these findings of early synesthetic engagement.

Generalized Waveform Differences

In addition to notable differences between groups with respect to congruity manipulations, synesthetes also showed strikingly more positive ERP waves compared with each of the control groups in text, color, and grapheme conditions. Although the interpretation of standing waveform differences between groups must be considered with caution, this generalized positivity in synesthetes has now been shown in other ERP studies on synesthesia by different research groups, using different synesthetes, and critically with different tasks (Beeli, Esslen, & Jancke, 2008; Schiltz et al., 1999). Compared with trained controls and controls who viewed physically colored numbers, synesthetes showed significantly more positive waveforms starting between 200 and 250 msec, notably encompassing the window of the P2, which we have argued reflects processing unique to synesthetes, $F(2, 33) = 3.47, p < .05$ (Figure 8).

These standing differences in the waveforms may reflect structural differences in the brains of synesthetes and neurotypical controls, such as greater neural connectivity among synesthetes. Besides producing the enhanced sensory experiences associated with synesthesia, greater connectivity could also serve to enhance the amplitude of ERP components such as the P2 that reflect coordinated activity across multiple distributed neural generators. Analogous explanations have previously been suggested to explain the larger amplitude P3 response observed in left- relative to right-handers; namely, larger corpora callosa in left-handers affords greater interhemispheric transmission needed for the generation of the P3 (Polich & Hoffman, 1998). Diffusion tensor imaging has shown greater connectivity in synesthetes than nonsynesthetes, and moreover, the degree of connectivity has been shown to correlate with the "depth" of synesthesia (Rouw & Scholte, 2007). More recently, Weiss and Fink (2008) have shown that synesthetes have more gray matter (measured by volume) than nonsynesthetes, specifically in parietal cortices, which they suggest reflects the hyperbinding of the synesthetic concurrent. To date, few investigators have considered whether generalized differences between the neural organization of synesthetes and nonsynesthetes reflect any phenotypical traits besides the synesthetic experience (Brang, Williams, & Ramachandran, under review). The question of whether altered connectivity presumed to underlie synesthesia has implications for other aspects of cognitive or perceptual processing is thus an issue deserving of further study.

Implications for Models of Synesthesia

As for whether the associations in grapheme–color synesthesia reflect conceptual or perceptual connections, results of the present study suggest that both sorts of connections are important. N400 grapheme priming effects were observed in synesthetes as well as both groups of trained controls, suggesting they reflect conceptual knowledge of the relationship between particular graphemes and particular colors. N300 grapheme priming effects were observed both in synesthetes and in the explicit visualization controls, suggesting that these effects index processes of visual imagery. Besides the synesthetes, N1 grapheme priming effects were observed only in the control group who viewed colored graphemes. These data strongly suggest a perceptual connection between inducers and concurrents in synesthesia and indicate that the integration of color and form information in synesthesia

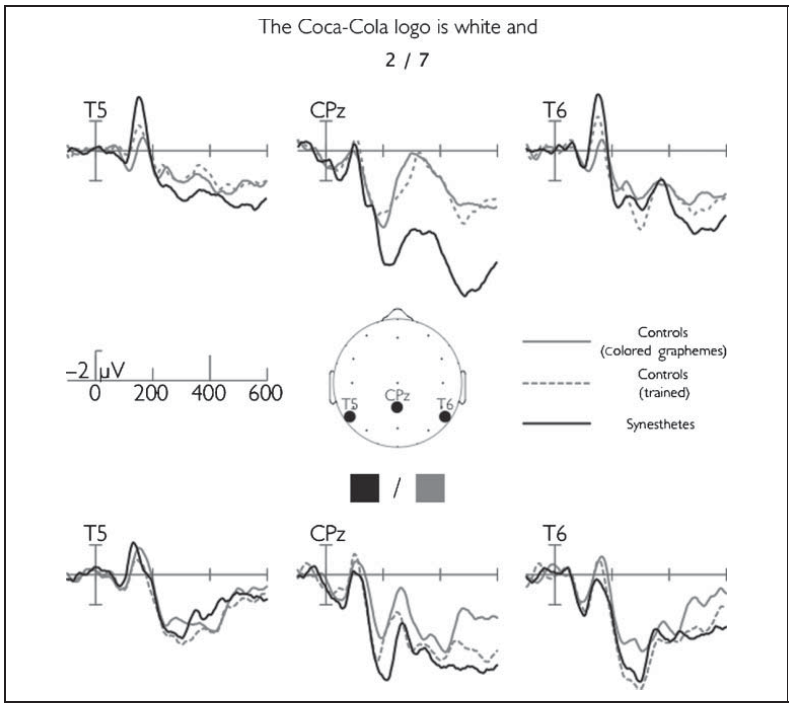


Figure 8. Overall positivity differences observed in synesthetes (n = 12; black line) compared with controls who viewed physically colored graphemes (n = 12; gray line) and controls trained to a particular synesthete's associations (n = 12; gray dotted line). Grand-average ERPs at electrodes T5, CPz, and T6 to sentences ending in a grapheme (top) or a color patch (bottom) regardless of congruity. In grapheme and color patch conditions, notice the more positive waveform elicited by synesthetes along the central electrode.

recruits the neural substrate of form-color integration in neurotypicals individuals. Moreover, the fact that the onset of N1 effects was earlier in synesthetes who viewed achromatic graphemes than it was in controls who viewed colored graphemes is consistent with models of synesthesia that posits early feed-forward connections between form and color processing areas in extrastriate cortex.

Previous research has shown that top–down factors (which in our paradigm were manipulated via the meaning of sentential stimuli) can affect feature based attention, such that stimuli presented in the attended color receive enhanced processing, even when they are in an unattended location (Zhang & Luck, 2008; Giesbrecht, Woldorff, Song, & Mangun, 2003). As no group showed N1 modulation in response to congruous/incongruous color patches, it can be inferred that the observed contextual priming effects required the focused attention needed to recognize a grapheme. The posterior N1 component observed in the present study has previously been localized to sources in dorsal extrastriate cortex of the middle occipital gyrus (Di Russo, Martínez, Sereno, Pitzalis, & Hillyard, 2002). Moreover, attentional modulation of this ERP component has been argued to arise from activity in the ventral occipital region of V4v and adjacent regions of the fusiform gyrus, including V4/V8 (Di Russo, Martinez, & Hillyard, 2003). Activity in this time frame likely reflects a combination of both feed-forward and feedback connections (Martínez et al., 2001). Our results of early activation are consistent with the reentrant model of synesthesia, such that higher cognitive streams can affect lower level visual processing.

Results of the present study also have implications for the issue of whether connections in synesthesia are bidirectional. Subjectively, synesthetes report that their associations are unidirectional. That is, although 7s consistently induce the experience of green, green does not induce the appearance of a 7. But although putative connections between color and grapheme processing areas do not affect conscious experience, careful testing has indicated that the visual experience of colors can affect numerical cognition in synesthetes (Cohen Kadosh et al., 2005).

The report by Brang et al. (2008) that the expectation of a particular color term affected the processing of graphemes also appears consistent with bidirectional connections in synesthesia. However, our observation of similar effects on the N400 in nonsynesthetes suggests that the increased neural connectivity in synesthesia is not necessary for expectations about color to affect semantic processing of graphemes. Likewise, our finding of N300 effects in the nonsynesthetes who performed an explicit visualization task and the N1 effects in controls who viewed colored graphemes further limit the notion that observed effects in synesthetes reflect bidirectional connections unique to grapheme–color synesthesia. This is perhaps unsurprising considering the degree of interconnectivity in the primate

visual system (Callaway, 1998; Felleman & Van Essen, 1991) and the importance of reentrant connections for attentional modulation of visual processing (Lamme & Roelfsema, 2000; Martínez et al., 1999). Nonetheless, observed amplitude modulation of the P2—present in the synesthetes but neither in naive controls tested by Brang et al. nor by any of the control groups tested in the present study—may reflect bidirectional connections between brain regions important for grapheme recognition and those that mediate knowledge of colors.

In sum, graphemes that elicit synesthetic colors were shown to modulate the ERP as early as 100 msec poststimulus onset, affecting the amplitude of the N1, P2, N300, and N400 components. Although N1, N300, and N400 effects were all observed in neurotypical control groups, the P2 modulation was unique to the synesthetes and may reflect neural activity that underlies that conscious experience of the synesthetic induction, including the subjective qualia of this phenomenon. These data argue against an account of synesthetic mappings reflecting isolated associations, pointing instead to connections at both the conceptual and the perceptual levels. Furthermore, this set of studies highlights the need for synesthesia researchers to use appropriate control groups in their experiments, as some previously reported effects on grapheme processing in synesthetes were attributable to knowledge of the inducer-concurrent mappings and task-specific behaviors.

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Magnetoencephalography reveals early activation of V4 in grapheme-color synesthesia

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ABSTRACT

Grapheme-color synesthesia is a neurological phenomenon in which letters and numbers (graphemes) consistently evoke particular colors (e.g. A may be experienced as red). The cross-activation theory proposes that synesthesia arises as a result of cross-activation between posterior temporal grapheme areas (PTGA) and color processing area V4, while the disinhibited feedback theory proposes that synesthesia arises from disinhibition of pre-existing feedback connections. Here we used magnetoencephalography (MEG) to test whether V4 and PTGA activate nearly simultaneously, as predicted by the cross-activation theory, or whether V4 activation occurs only after the initial stages of grapheme processing, as predicted by the disinhibited feedback theory. Using our high-resolution MEG source imaging technique (VESTAL), PTGA and V4 regions of interest (ROIs) were separately defined, and activity in response to the presentation of achromatic graphemes was measured. Activation levels in PTGA did not significantly differ between synesthetes and controls (suggesting similar grapheme processing mechanisms), whereas activation in V4 was significantly greater in synesthetes. In synesthetes, PTGA activation exceeded baseline levels beginning 105–109 ms, and V4 activation did so 5 ms later, suggesting nearly simultaneous activation of these areas. Results are discussed in the context of an updated version of the cross-activation model, the cascaded cross-tuning model of grapheme-color synesthesia.

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Introduction

In synesthesia, stimulation of one processing stream (e.g. hearing) elicits concurrent experiences in a second, unstimulated stream (e.g. visual colors). In one of the most common forms, viewing numbers or letters (graphemes) elicits the percept of a specific color (Cytowic and Eagleman, 2009; Baron-Cohen et al., 1996), known as grapheme-color synesthesia. For example, to synesthete JC the number 2 always appears green, irrespective of its actual color. Synesthetic experiences begin in early childhood and remain extremely consistent over the lifespan. Further, synesthesia runs in families (Baron-Cohen et al., 1996; Ward and Simner, 2005; Asher et al., 2009), suggesting it is a heritable trait. Although psychophysical experiments have demonstrated the reality of synesthetic experiences (Hubbard et al., 2005b; Ramachandran and Hubbard, 2001a; Dixon et al., 2000; Smilek et al., 2001; Mattingley et al., 2001), the neural mechanism remains a matter of contention (for reviews see Hubbard and Ramachandran, 2005, and Hubbard, 2007).

Two main classes of models have been proposed to explain the neural basis of synesthesia: the cross-activation model and the cortical disinhibited feedback model. The cross-activation model suggests that the experience of colored letters in grapheme-color synesthesia reflects hyperconnectivity between posterior fusiform areas involved in grapheme processing and adjacent color area V4 in the fusiform gyrus and lingual sulcus, which arises due to decreased axonal pruning during development (Ramachandran and Hubbard, 2001a). The main tenet of this theory proposes that the hyperconnectivity between these areas leads to their cross-activation in grapheme processing and thus the experience of synesthetic colors from simple graphemes (Ramachandran and Hubbard, 2001b). Consistent with this suggestion, a number of studies have demonstrated anatomical differences in the inferior temporal lobe, near regions related to grapheme and color processing in synesthetes, including increased fractional anisotropy as assessed by diffusion tensor imaging (Rouw and Scholte, 2007, but see Jancke et al., 2009), and increased gray matter volume, as assessed by voxel-based morphometry (Jancke et al., 2009; Weiss and Fink, 2009). Moreover, functional neuroimaging studies have demonstrated increased activation in color-selective regions, including V4, in grapheme-color synesthetes relative to non-synesthetic controls (Hubbard et al., 2005b; Rouw & Scholte, 2007; Sperling et al., 2006).

In contrast, the disinhibited feedback model was originally proposed to explain certain forms of acquired synesthesias (Armel and Ramachandran, 1999) and subsequently extended to include the

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congenital variants (Grossenbacher and Lovelace, 2001). Whereas the cross-activation model suggests altered connectivity as the origin of synesthetic processing, the disinhibited feedback model posits normal connectivity patterns in synesthetes and suggests that synesthesia results from disinhibited feedback from higher-level cortical areas in the visual processing hierarchy, a process common to synesthetes and non-synesthetes alike (Grossenbacher and Lovelace, 2001; Grossenbacher, 1997; Brang and Ramachandran, 2008). This model is supported by pharmacological studies showing that synesthetic percepts can be induced in neurotypical individuals (Simpson and McKellar, 1955), suggesting that synesthesia results from disinhibition of normally inhibited feedback connections to V4 from higher-level areas in the temporal lobe (e.g. anterior inferior temporal and posterior inferior temporal) and parietal lobe (Grossenbacher and Lovelace, 2001). Critically, this theory suggests that graphemes are processed in their entirety before subsequent activation of the color (Grossenbacher and Lovelace, 2001) and requires the engagement of higher cortical areas where grapheme and color information converge (Grossenbacher, 1997; Grossenbacher and Lovelace, 2001).

A key difference between these two models is the existence of local connections (what Grossenbacher and Lovelace, 2001 describe as "horizontal" connections) between posterior temporal grapheme processing areas (PTGA) and color processing area V4 and their implications for the time course of neural activity in V4. The cross-activation theory posits increased local connectivity and consequently predicts the activation of V4 during the initial sweep of activity in PTGA (Ramachandran and Hubbard, 2001a). The disinhibited feedback theory argues against "abnormal" local connectivity in synesthesia (Grossenbacher and Lovelace, 2001, p. 40) and instead proposes that synesthesia arises as a consequence of feedback from areas involved in "pathway convergence" such as the STS (Grossenbacher and Lovelace, 2001). In this model, information propagates through multiple stages of the visual hierarchy before arriving at a convergence site and then finally feeding back to V4. The disinhibited feedback theory thus predicts that differential activation of V4 should not occur on the feed-forward sweep, but rather only on the feedback sweep, after substantial cortical processing. These two theories cannot be distinguished on the basis of extant fMRI and behavioral studies, as these methods lack the temporal resolution needed to identify the relative sequence of cortical activations in synesthesia; that is, whether activations in V4 occur nearly simultaneously with activity in PTGA, as predicted by the cross-activation theory, or whether such activations occur only after substantial processing as predicted by the disinhibited feedback theory.

Given that electrophysiological techniques are capable of recording neural activity with millisecond resolution, studies using event-related potentials (ERPs) have attempted to distinguish between these theories. For example, semantic modulation of synesthetically engaged colors can begin as early as 100–150 ms after viewing graphemes (Brang et al., 2008; Brang et al., in press) or hearing words (Beeli et al., 2008). However, as event-related potentials lack the required spatial resolution for resolving activity between PTGA and color area V4, these findings demonstrate only that grapheme-color synesthesia is engaged quickly and leave open the question of whether color processing area V4 contributes to ERP effects observed in synesthetes.

To test the relative timing of activation among inferior temporal regions in synesthesia, we used magnetoencephalography (MEG), a neuroimaging technique capable of recording magnetic activity elicited by the firing of large numbers of neurons on a millisecond time scale with sufficient spatial resolution to distinguish V4 from PTGA. First, MEG was recorded from four grapheme-color synesthetes and four age-, gender-, and handedness-matched controls as they viewed stimuli designed to define two regions of interest (ROIs) within each subject: V4 and PTGA. Localization of the neural generators of the MEG signal was constrained by the use of high-resolution anatomical magnetic resonance images (MRI) to reconstruct the cortical surface for each subject. Besides increasing the spatial resolution of MEG, this method allows us to estimate the signal in each brain area as it unfolds in time (Dale and Halgren, 2001). To investigate the relative timing of brain activity induced by graphemes, anatomically constrained MEG was recorded as these same subjects performed an upright versus italic letter discrimination task (see Hubbard et al., 2005b). The cross-activation theory of synesthesia predicts activity in V4 and PTGA will have similar onset times in synesthetes, while the disinhibited feedback theory predicts that increased activity in V4 will occur substantially after activation of PTGA.

Methods

Participants

Participants included four grapheme-color synesthetes and four non-synesthetic controls, all of whom were native English speakers with normal or corrected-to-normal vision and no history of psychiatric or neurological disorders. Synesthetes ranged in age from 19 to 32 (mean age = 26.3 years, SD = 5.4) and included 1 woman; controls ranged in age from 21 to 33 (mean age = 26.8 years, SD = 5.1) and included 1 woman. Group ages did not differ reliably $t(6) = 0.13$, $p = .90$. Three of the four participants in each group were right-handed, and the remaining participants were left-handed, as assessed via the Edinburgh Inventory (Oldfield, 1971). Synesthesia was confirmed by means of consistency matching as well as reaction time testing for color congruency, standardized by Eagleman et al. (2007). All 4 synesthetes experienced synesthetic colors "projected" out into the visual world. All participants gave signed informed consent prior to the experiment and participated for monetary compensation. None of the control participants reported any known forms of synesthesia.

Materials and procedure

Grapheme presentation

Using methods similar to those of Hubbard et al. (2005b), synesthetes and controls were presented with graphemes and non-graphemic stimuli in a randomly intermixed presentation format. Stimuli were 2.2° tall white letters, numbers, and non-graphemic characters (courtesy of Mauro Pesenti; see Pesenti et al., 2000) on a neutral gray background square of 12°. The remainder of the screen was black. At least 100 upright and 100 italic letter/number and 200 non-graphemic (100 upright, 100 italic) stimuli (for a total of 400 trials) were presented in a randomly intermixed order for 500 ms each followed by a 1-s blank screen. We used online averaging of the MEG, which allowed us to reject trials that contained blinks or other artifacts as they occurred, and randomly re-presented those trials in the remaining portion of the trial sequence. We therefore continued recording until there were at least 100 stimulus presentations in each of the four conditions, and the number of stimuli in each condition therefore may vary by one to five stimuli in order to achieve a total of 100 valid trials per stimulus condition. Total run duration was ~11 min, divided into two blocks of 5 min each. Italic number/letter stimuli were used to control for attention during the experimental run and to define the grapheme-selective ROIs during a separate run conducted in the same testing session. Responses were measured from the upright number/letter stimuli. Subjects' task was to indicate which stimuli were shown in italic font via a button press.

Data acquisition and analysis

The MEG imaging in this study was conducted with the University of California, San Diego's whole-head Elekta Neuromag 306-channel system in an enhanced multi-layer magnetically shielded room. The

system records brain responses simultaneously from the entire scalp and samples the magnetic field with 510 separate pick-up loops configured into 204 gradiometers and 102 magnetometers. The combined usage of magnetometers and gradiometers allows for accurate detection of sulcal and even some gyral sources (Hillebrand and Barnes, 2002). Four head position indicator coils were used for anatomical digitization. Vertical eye movements and blinks were monitored with a set of electrodes above and below the left eye. The data-sampling frequency was 1000 Hz. The data were run through a high-pass filter with a 0.1-Hz cutoff and a notch filter (58–62 Hz) to remove 60 Hz power-line noise.

Trials were time locked to the onset of each target, and signals were averaged online with a time window of −500 to 800 ms around an event. The 500-ms period preceding the onset of the target item served as the baseline. Epochs containing blinks, eye movements, large baseline drifting, or signal saturation were rejected online. After online averaging, MEG data were analyzed using our high-resolution MEG source imaging technique: the vector-based spatial–temporal analysis using an L1-minimum-norm (VESTAL) approach (Huang et al., 2006). The MEG source grid used by VESTAL was based on the gray-white matter boundary, and MEG forward calculation was based on the real-shape boundary element method. All tissue boundaries used in MEG data analysis were obtained from the cortical reconstruction and volumetric segmentation of each subjects' MRI was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/; Fischl et al., 1999; Dale et al., 1999). Freesurfer also provides tools for accurately visualizing VESTAL results based on individual differences in gyri/sulci. Despite its excellent temporal and spatial resolution, MEG remains unreliable in imaging deep brain structures that are away from the cortical convexity (Hämäläinen et al., 1993). To eliminate sources from deep structures, activation patterns localized to subcortical regions were extracted post-analysis.

After MEG recording, subjects underwent a T1-weighted structural MRI scan (General Electric 1.5 T, MP-RAGE), for subsequent integration with MEG data.

Grapheme ROI. Grapheme ROIs were created from a separate run using similar methods as those in the Grapheme Presentation run. Synesthetes and controls viewed graphemes presented in colors congruous with each synesthetes' grapheme-color association, and subjects completed the same upright vs. italic discrimination task as in the grapheme presentation run. ROIs were derived from vertices that showed significantly greater MEG signal 70–170 ms after stimulus onset than during baseline from posterior temporal regions neighboring but excluding visual area V4 and occipital pole regions.

V4 ROI. Consistent with previous research demonstrating V4 localization using MEG, subjects were presented with red squares subtending 3.1° presented in one of four visual quadrants (upper left, bottom left, upper right, and bottom right; Yokoyama et al., 2004). Squares were presented for 200 ms followed by a blank screen ranging in time from 200 to 248 ms. Approximately 200 trials in each of the four locations were presented pseudo-randomly, such that the quadrant of presentation was not immediately repeated. In line with prior work, V4 was localized between 90 and 110 ms post-stimulus onset, and ROIs were constructed from the peak activation within this time-range in posterior temporal regions. Activation patterns were required to demonstrate topographic mapping (requiring localization of the upper quadrant more medial along the temporal lobe than the lower quadrant). We used these regions as *a priori* defined ROIs for each individual subject for subsequent V4 analysis in the Grapheme Presentation study.

Analysis of grapheme region distribution. Each subjects' distribution of grapheme processing activity was defined by vertices showing activation to upright and italic graphemes between 90 and 170 ms (each subjects' threshold set at 0.03 $\mu A \times mm^2$). Grapheme distributions were restricted to anatomical locations within the posterior temporal lobe defined via the automated labeling process in Freesurfer as the medial occipital-temporal sulcus and lingual sulcus, posterior collateral transverse sulcus, lateral occipital-temporal gyrus or fusiform gyrus, lateral occipital-temporal sulcus, and inferior occipital gyrus and sulcus.

Results

Independent tasks were used to define two regions of interest (ROIs) within each subject: V4 and the posterior temporal grapheme areas (PTGA). Retinotopic maps of V4 were identified through stimulation of upper and lower visual quadrants (Yokoyama et al., 2004; Fig. 1A). V4 ROIs were defined as posterior temporal lobe regions that showed a topographic response profile to stimulation of the upper and lower visual field (Fig. 1B and C). Grapheme ROIs were created from a separate run in which subjects performed the upright versus italic letter discrimination task used in the main experiment. PTGA ROIs were defined as posterior temporal lobe areas activated by graphemes between 70 and 170 ms, excluding visual area V4 (see Fig. 2). PTGA ROIs identified in this way were consistent with fMRI research showing letter

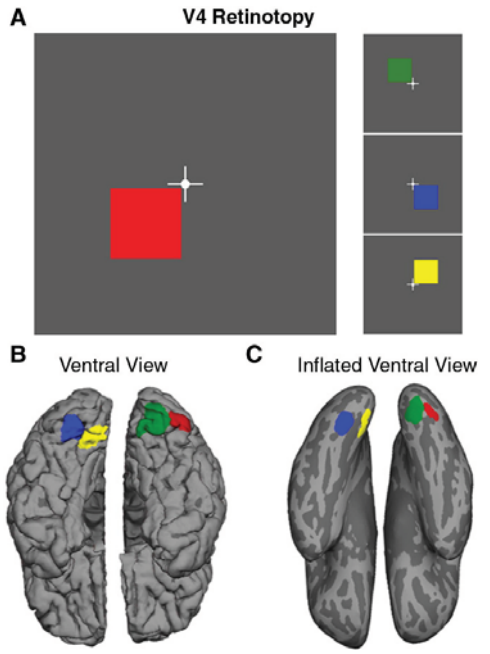


Fig. 1. (A) Square blocks presented randomly in one of four visual quadrants, in order to elicit retinotopy in visual area V4; identical block stimuli were presented in each quadrant, and colored here for presentation. (B–C) MEG activity in response to visual stimulation of either the lower left (red), upper left (green), lower right (blue) or upper right (yellow) quadrant of the visual field, overlaid on non-inflated (A) and inflated (B) cortical surfaces of a representative subject. Retinotopy was seen in each subject, such that lower-field stimulation activated more lateral portions of the temporal lobe than upper-field stimulation.

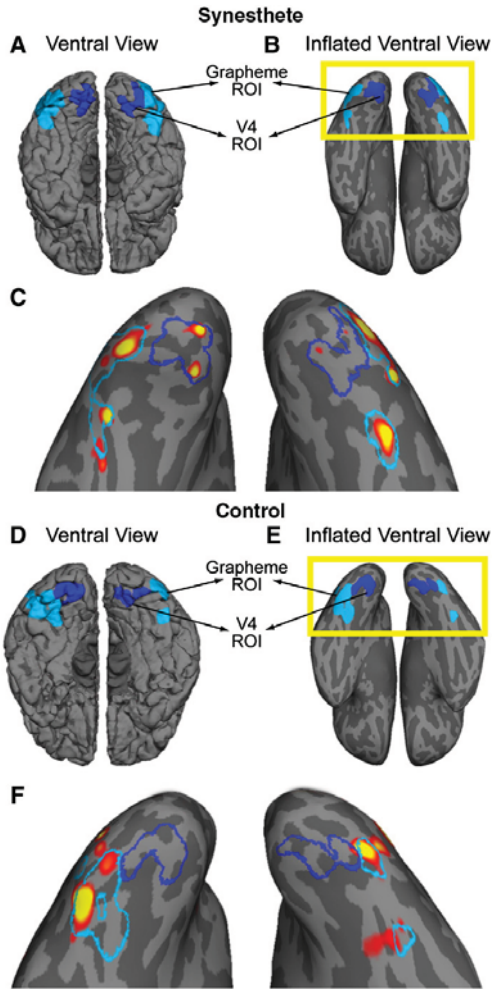


Fig. 2. Representative synesthete's (A–C) and control subject's (D–F) brains. The grapheme ROI is shown in light blue, and V4 ROI in dark blue. A and D show ROIs overlaid on a non-inflated cortical surface. B and E show ROIs overlaid on digitally inflated brains; yellow box highlights region depicted in C and F. When presented with achromatic letters and numbers, synesthetes showed significant activation in both the grapheme ROI (light blue) and the V4 ROI (dark blue) (C). Controls, however, showed significant activation only in the grapheme ROI (light blue) (F).

perception activates both posterior and anterior areas of the ventral occipitotemporal cortex extending to the medial temporal lobe (Joseph et al., 2006; Vinckier et al., 2007; for a review see Grainger et al., 2008).

Results of the main experiment involving the letter discrimination paradigm are presented in Fig. 2. When presented with achromatic letters and numbers, synesthetes showed significant activation in both the Grapheme ROI (shown in the area outlined in light blue) and the V4 ROI (shown in the area outlined in dark blue). Controls, however, showed significant activation only in the Grapheme ROI (outlined in light blue in Fig. 2, panel F). MEG data reported here are thus consistent with prior work in our laboratory using fMRI to show that achromatic graphemes elicit greater V4 activity in synesthetes than non-synesthetic controls (Hubbard et al., 2005b).

To compare the relative degree of activity in these ROIs in synesthetes versus controls, *t*-tests were conducted at four successive 20-ms windows between 90 and 170 ms in keeping with studies showing the processing of single letters within this time frame (Rey et al., 2009). Achromatic graphemes elicited significantly more activity in color area V4 in synesthetes compared to controls between 111 and 130 ms [$t(6) = 3.09$, $p < .05$, Cohen $d = 2.19$] and between 131 and 150 ms [$t(6) = 2.86$, $p < .05$, Cohen $d = 1.89$; Fig. 3A]. Crucially, however, no difference was observed between these groups within the grapheme area for any 20-ms time bin tested (all *p*-values greater than .75; Fig. 3b), arguing against attentional or motivational differences in the two groups and against generalized processing differences in activation levels in synesthetes and controls.

To compare the relative onset of activation in grapheme and V4 regions, single-tail *t*-tests were conducted at successive 5-ms time windows beginning at 90 ms for both synesthetes' and controls' PTGA and V4 ROIs. In synesthetes, activity in the grapheme ROI reached significance between 105 and 109 ms $t(3) = 3.14$, $p = .05$, with activity in the V4 ROI reaching significance between 110 and 114 ms $t(3) = 3.61$, $p < .05$, suggesting V4 engagement occurs nearly simultaneously with processing of graphemes in PTGA. Additionally, activation levels in PTGA and V4 were compared in the first significant time window (105–109 ms); no significant differences were found [paired *t*-test $t(3) = 1.10$, $p = .35$].

In controls, the first window of significant activation in the grapheme ROI occurred between 115 and 119 ms ($t(3) = 3.62$, $p < .05$). However, activity in the V4 ROI failed to reach significance at any point between 90 and 370 ms (all *t*-values < 2.4). Comparing activation levels between PTGA and V4 in the first significant time window (115–119 ms), activation in PTGA was significantly greater than that in V4 [paired *t*-test $t(3) = 3.07$, $p = .05$].

In order to further confirm that the co-activation of V4 and PTGA in synesthetes could not be attributed to less specialized or focal patterns of activity in general (such that synesthetes may simply activate more regions of the cortex neighboring the fusiform gyrus), we compared the extent of the significant activation comprising the PTGA in both groups. Overall, the mean area of activation within the PTGA was not significantly different between synesthetes (709.5 mm^2) and controls (1356.9 mm^2) $t(6) = 1.74$, $p = .13$, with synesthetes activating 65.0% of the vertices activated by controls, confirming that enhanced activation of V4 in synesthetes is not part of a general pattern of overall increased activity.

Discussion

These data provide the strongest evidence to date that grapheme-color synesthesia involves direct communication between V4 and grapheme processing areas in the posterior temporal lobe (PTGA). The near-simultaneous activation of color area V4 and PTGA between 105 and 115 ms argues strongly against the cortical disinhibited feedback model of grapheme-color synesthesia which predicts activation of V4 only after substantial processing has occurred. The similar onset latencies we observed for increased activity in synesthetes' grapheme (105–109 ms) and color (110–114 ms) ROIs suggest the rapid exchange of information between these areas, in keeping with the report of increased connectivity between V4 and the posterior fusiform in synesthetes' brains (Rouw and Scholte, 2007).

Results of the present study are more consistent with the cross-activation model of grapheme-color synesthesia and suggest that correlated activity in PTGA and V4 may be the first step in the generation of the synesthetic experience. Previous research using ERPs has demonstrated processing differences within similar time

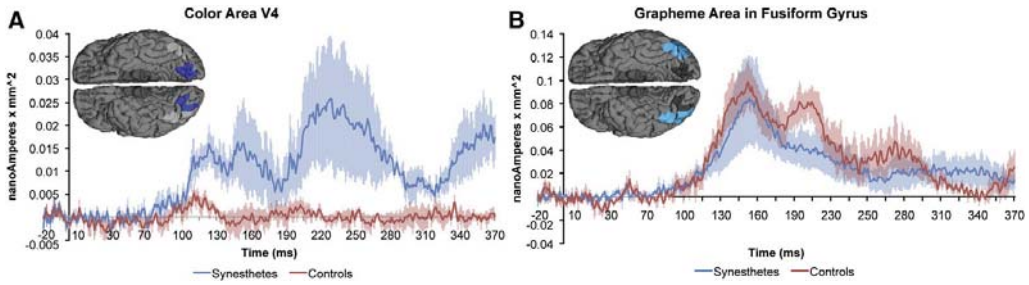


Fig. 3. Synesthetes' and controls' mean activation in (A) the V4 ROI and (B) the Grapheme ROI between −20 and 370 ms. Achromatic letters and numbers evoked significantly more activity in synesthetes compared to controls between 111 and 130 ms in V4 $t(6) = 3.09$, $p < .05$, but not in the grapheme area $t(6) = 0.06$, $p = .95$. Error bars represent standard error of the mean.

windows between synesthetes and controls (Brang et al., 2008; Brang et al., in press; Beeli et al., 2008; Goller et al., 2009), but as volume conduction of electrical signals limits the spatial resolution of electroencephalography (EEG) from dissociating signals from V4 or the neighboring PTGA, the precise loci of cortical generators of observed ERP effects are unclear. In light of the present findings, however, modulation of early components in synesthetes' ERPs likely reflects parallel activation in V4 and PTGA.

Cascaded cross-tuning model of grapheme-color synesthesia

In view of the results reported here, we propose an updated version of the cross-activation model that incorporates recent findings on the cognitive and neural substrate of grapheme processing. In Ramachandran and Hubbard's (2001a) original cross-activation proposal for grapheme-color synesthesia, the interacting regions were described broadly as V4 cross-activating the "visual number grapheme" area in the fusiform gyrus. Furthermore, the model tacitly assumed a template-matching model of grapheme processing widely accepted at the time; in the intervening years, however, cognitive neuroscientists have increasingly come to view grapheme recognition as a process of hierarchical feature analysis (see Grainger et al., 2008 and Dehaene et al., 2005 for reviews). As in the original Pandemonium model (Selfridge, 1959), hierarchical feature models posit a series of increasingly complex visual feature representations and describe grapheme recognition as resulting from the propagation of activation through this hierarchical network. In the initial stages of letter processing, visual input activates component features of the letter (line segments, curves, etc.) and results in the partial activation of letters containing some or all of the component features. Grapheme identification occurs over time via a competitive activation process involving some combination of excitatory and inhibitory connections both within the grapheme level and between the grapheme level and other representational levels, both bottom–up and top–down.

This Pandemonium model of letter perception is supported by a wealth of studies on letter recognition, indicating that the number of component features shared by a pair of letters predicts the likelihood of those letters being confused (Geyer and DeWald, 1973). Integrating these behavioral measures with the neuro-anatomical models of visual perception, careful examination of the brain response to pseudo-letters (non-letter shapes visually matched to the component features comprising real letters) as well as infrequent and frequent letters shows a cascading hierarchy of processing within the PTGA, proceeding from posterior to anterior regions (Vinckier et al., 2007). Further, ERP studies of letter processing (e.g., comparing the brain response to letters and pseudo-letters) suggest feature-level processing occurs before 145 ms, and letter-level processes occur thereafter (Rey et al., 2009).

We suggest that in projector synesthetes, local connectivity between V4 and PTGA are such that the initial feed-forward activations in PTGA give rise to partial activations in V4 soon thereafter, in keeping with our finding that V4 activity in synesthetes diverged from the baseline between 110 and 114 ms. In synesthetes, cascaded activation between feature- and letter-level processes gives rise both to low-level activations of letter representations and to low-level activations of color representations in V4 (Fig. 4A). The range of synesthetic colors initially activated by the visual components is fine-tuned in the course of subsequent processing and identification of the grapheme (Fig. 4B). The cascaded cross-tuning model thus suggests the existence of numerous horizontal and feedback connections to V4. Activation propagated via these connections serves to gradually tune both color and letter-level activations until they are sufficient to support the emergence of the unified conscious percept.

Our finding of early interaction of color and form information fits with grapheme-color synesthetes' reports that shapes and non-orthographic stimuli sometimes also elicit the sensation of color (Ramachandran and Hubbard, 2001b). Moreover, cross-activation during the component stage of processing would provide a putative mechanism for the acquisition of new synesthetic percepts, as when synesthete JC reported that particular characters in the false fonts developed by Pesenti et al. (2000) began to appear colored after repeated fMRI testing sessions with the characters (Hubbard et al., 2005b). Further confirmation of this model can be gleaned from testing whether similarly shaped graphemes produce similar synesthetic colors within a particular individual through the use of regressions between letter-confusion matrices and evoked synesthetic colors, preliminary results of which have been presented elsewhere (Hubbard et al., 2005a). Consistent with this prediction, Simner et al. (2005) report that among the grapheme-color synesthetes they have surveyed, pairs of letters that are mirror images of one another are similarly colored, such as *q* and *p* which are most often colored pink and *b* and *d* which are most often blue or brown.

In addition to the cross-activation and cortical disinhibited feedback models of synesthesia, an additional third account has been proposed, suggesting that synesthetic induction is mediated by abnormal feedback connections from the anterior temporal lobe and posterior inferotemporal (PIT) cortex to V4 (reentrant processing model; Smilek et al., 2001). Similar to the disinhibited feedback model, Smilek and colleagues suggested that synesthetic activation of V4 would not precede a grapheme being processed for meaning, but instead that letter recognition may elicit partial activation of V4, leading to disambiguation by meaning and context in more anterior inferotemporal regions receiving input from multiple areas within the anterior temporal lobe and PIT. Accordingly, the reentrant processing

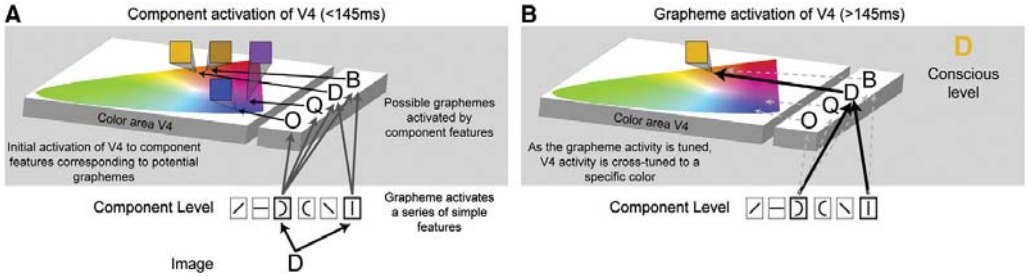


Fig. 4. Cascaded cross-tuning model of synesthesia. (A) Initial processing. As in hierarchical feature models of grapheme processing, visual input prior to 145 ms activates component features (line segments, curves, etc.) and partially activates graphemes comprised of those features (Rey et al., 2009). Horizontal connections between grapheme units and V4 afford partial activations of associated colors. (B) Subsequent processing. A competitive activation process results in the activation of the grapheme most consistent with bottom–up and top–down activations as well as its associated color. The synesthete's conscious experience of an orange D reflects only the final stage of activation.

model would predict waves of activity within V4 corresponding to each level of grapheme processing where the meaning of the grapheme is changed (e.g. seeing O as a letter in HOUSE, or as a number in 8O374). However, the present data demonstrate V4 activity in response to the feature-level of grapheme processing, presumably followed by a tuning of V4 activity to each stage of grapheme processing (letter-level and context). Furthermore, our cascaded cross-tuning model would suggest multiple waves of activity in V4 even in cases where the meaning of the grapheme was unchanged by context or top–down effects, and the hierarchical "tuning" of V4 would occur in response to each processing stage regardless, narrowing in on the consciously perceived color. Even though the current data demonstrate the level at which V4 activates in response to grapheme processing, subsequent modulation of that activity, via modulatory tuning processes or reentrant activation, remains a matter for future research.

Conclusions

In sum, the present study is the first to demonstrate near-simultaneous activation of V4 and PTGA to achromatic letters and numbers in projector synesthetes. These findings suggest that direct communication between these brain areas mediates the initial processing stage in grapheme-color synesthesia and support the importance of neuronal cross-activation in other forms of this condition (Ramachandran and Hubbard, 2001b). However, as projector synesthetes make up only a subset of the synesthetic population, an examination of the timing and relative activation of V4 in associator synesthetes (those experiencing synesthetically evoked colors only in their mind's eye) is a critical next step in this research. Further, the extent to which the cascaded cross-tuning model of synesthesia applies to other variants of the condition (e.g. Hänggi et al., 2008) or instances of acquired synesthesia requires further investigation.

Lastly, as this research speaks only to the timing and relationship between the PTGA and V4, it leaves open the question of whether later, reentrant connections from anterior temporal cortex affect V4 activity as a function of top–down processes (Smilek et al., 2001), presumably feeding backward through the same cascading model discussed above. Indeed, previous research in our laboratory has shown the influence of high-level contextual and meaning processes on synesthetes' behavioral (Ramachandran and Hubbard, 2001b) and neural (Brang et al., 2008) response to achromatic graphemes, suggesting that the initial activation of V4 demonstrated here may be necessary but not sufficient to explain the broad spectrum of synesthetic qualia.

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Brief communication

Similarly shaped letters evoke similar colors in grapheme–color synesthesia

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ABSTRACT

Grapheme–color synesthesia is a neurological condition in which viewing numbers or letters (graphemes) results in the concurrent sensation of color. While the anatomical substrates underlying this experience are well understood, little research to date has investigated factors influencing the particular colors associated with particular graphemes or how synesthesia occurs developmentally. A recent suggestion of such an interaction has been proposed in the cascaded cross-tuning (CCT) model of synesthesia, which posits that in synesthetes connections between grapheme regions and color area V4 participate in a competitive activation process, with synesthetic colors arising during the component-stage of grapheme processing. This model more directly suggests that graphemes sharing similar component features (lines, curves, etc.) should accordingly activate more similar synesthetic colors. To test this proposal, we created and regressed synesthetic color-similarity matrices for each of 52 synesthetes against a letter-confusability matrix, an unbiased measure of visual similarity among graphemes. Results of synesthetes' grapheme–color correspondences indeed revealed that more similarly shaped graphemes corresponded with more similar synesthetic colors, with stronger effects observed in individuals with more intense synesthetic experiences (projector synesthetes). These results support the CCT model of synesthesia, implicate early perceptual mechanisms as driving factors in the elicitation of synesthetic hues, and further highlight the relationship between conceptual and perceptual factors in this phenomenon.

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1. Introduction

Grapheme–color synesthesia is a neurological condition in which viewing numbers or letters (graphemes) results in the concurrent sensation of color (Baron-Cohen, Burt, Smith-Laittan, Harrison, & Bolton, 1996; Cytowic & Eagleman, 2009). In a given synesthete, the associations between graphemes and colors are very specific, in that each grapheme corresponds to a particular hue that is largely consistent across the lifespan. However, the particular associations between individual graphemes and colors differ across individuals, and synesthetes further differ in the degree to which these associations are perceptual or conceptual (Ramachandran & Hubbard, 2001). The majority of synesthetes, known as *associators*, report that the concurrent color sensation is present in their "mind's eye", whereas *projectors* experience the concurrent color as an intrinsic feature of the grapheme (Dixon, Smilek, & Merikle, 2004). Here we address the factors that mediate associations between particular graphemes and colors in synesthesia, and how they differ as a function of the projector–associator continuum.

While it was previously believed that the associations in grapheme–color synesthesia were random pairings between graphemes and hues (e.g. Jordan, 1917), studies examining large groups of synesthetes have shown some commonality in associations between individuals (e.g. A is typically red across multiple synesthetes; Simner et al., 2005). Furthermore, careful analyses of synesthetic correspondences demonstrated that the frequency of the stimulus predicted the relative intensity of the concurrent synesthetic experience. That is, higher frequency letters often pair with higher frequency color names (Simner et al., 2005), vowels tend to elicit more luminant and 'intense' colors than consonants in grapheme–color synesthesia due to their relative frequency (Beeli, Esslen, & Jancke, 2007; Smilek, Carriere, Dixon, & Merikle, 2007), and common words elicit more intense flavors than infrequent words in lexical-gustatory synesthesia (Simner & Haywood, 2009; Ward, Simner, & Auyeung, 2005). Although these studies failed to explain the factors driving the particular grapheme–hue pairings within a single individual, the common report of a non-arbitrary relationship between objective properties of the inducing stimuli (such as the frequency of graphemes) and subjective aspects of the concurrent sensations is in keeping with the cross-activation model of synesthesia (Ramachandran & Hubbard, 2001), and a more recent version of the model known as the cascaded cross-tuning (CCT) model of grapheme–color synesthesia (Brang et al., 2010).

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1.1. Cross-activation and the cascaded cross-tuning (CCT) model of synesthesia

In these models of grapheme–color synesthesia, the perceptual experience of colored graphemes reflects increased connectivity between brain regions underlying grapheme and color processing, respectively (Brang et al., 2010; Ramachandran & Hubbard, 2001). The proposal follows that greater structural connectivity between adjacent color and grapheme areas in the fusiform gyrus increases the probability that cells mediating grapheme processing will fire in synchrony with those representing color, thereby resulting in Hebbian connections between particular graphemes and particular hues. Among associator synesthetes, for whom grapheme–color associations are more conceptual, the increased connectivity (relative to non-synesthetes) is in frontal, parietal, and anterior temporal lobe structures, perhaps explaining the more associative and less perceptual experience of color. In projector synesthetes, who experience the concurrent color sensations as inherent perceptual properties of the graphemes, the increased connectivity extends to color processing area V4 and nearby posterior temporal lobe structures involved in the earliest stages of grapheme processing.

In an important test of this model, Rouw and Scholte (2007) compared structural connectivity in grapheme–color synesthetes and non-synesthetic controls using diffusion tensor imaging, and found greater connectivity in the frontal, parietal, and inferior temporal cortices of synesthetes than controls (but see Jancke, Beeli, Eulig, & Hanggi, 2009). Moreover, connectivity in the inferior temporal lobes was correlated with synesthetes' scores on the projector–associator continuum, as individuals with more characteristics of projector synesthetes show higher inferior temporal lobe connectivity. Besides studies assessing fractional anisotropy (Rouw & Scholte, 2007), voxel-based morphometry (VBM) has also been used to demonstrate that synesthetes have increased grey matter volume compared to non-synesthetes in regions in the inferior temporal lobe, implicated in both grapheme and color processing (Jancke et al., 2009; Weiss & Fink, 2009). Further, Rouw and Scholte (2010) also demonstrated strong differences in VBM between projector and associator synesthetes. Critically, projectors relative to associators showed large differences in grey matter volume in the sensory systems (visual cortex, auditory cortex, and motor cortex), consistent with the notion that they experience synesthetic colors as perceptual qualia. Associators, however, differed from projectors in grey matter volume within the hippocampus and parahippocampus, confirming subjective reports from synesthetes that the experience is associative in nature, more akin to memory recall than a sensory experience.

Consistent with the CCT model, studies have shown that reading or thinking about simple numbers or letters is associated with the activation of posterior temporal lobe grapheme areas (PTGA) in controls, but with engagement of both the PTGA and color processing area V4 in synesthetes (e.g. Hubbard, Ambrosio, Azoulai, & Ramachandran, 2005; Hubbard, Arman, Ramachandran, & Boynton, 2005; Sperling, Prvulovic, Linden, Singer, & Stirn, 2006, but see Rich et al., 2006; Weiss, Zilles, & Fink, 2005). This result was recently extended using magnetoencephalography (MEG), replicating the activation of PTGA in controls, and that of PTGA and color processing area V4 in projector synesthetes (Brang et al., 2010). Moreover, as MEG is able to capitalize on temporal aspects of neural processing, Brang et al. (2010) demonstrated near simultaneous activation of V4 and the PTGA in projector synesthetes, beginning as early as 110 ms after stimulus onset. Studies of synesthetes using event-related brain potentials (ERPs) from the electroencephalogram (EEG) also reveal the impact of synesthetic colors at a very early stage of grapheme processing, 100–150 ms post-stimulus (Brang, Edwards, Ramachandran, & Coulson, 2008; Brang, Kanai, Ramachandran, & Coulson, in press). Taken together, these data suggest the importance of cross-activation during the initial stages of letter processing.

The CCT model incorporates recent insights on the neural underpinnings of grapheme recognition in neurotypical individuals into cross-activation accounts of synesthesia. Recent accounts in neurotypical individuals describe grapheme recognition as a process of hierarchical feature analysis (see Dehaene, Cohen, Sigman, & Vinckier, 2005; Grainger, Rey, & Dufau, 2008 for reviews). In the initial stages of letter processing, visual input activates component features of the letter (line segments, curves, etc.), and results in the partial activation of letters containing some or all of the component features. Grapheme recognition occurs over time via a competitive activation process involving some combination of excitatory and inhibitory connections both within the grapheme level, and between the grapheme level and other representational levels, both bottom-up and top-down.

Hierarchical feature analysis models are supported by a wealth of studies on letter recognition, indicating that the number of component features shared by a pair of letters predicts the likelihood of those letters being confused (Geyer & DeWald, 1973). Integrating these behavioral measures with the neuro-anatomical models of visual perception, careful examination of the brain response to pseudo-letters (non-letter shapes visually matched to the component features comprising real letters), as well as infrequent and frequent letters shows a cascading hierarchy of processing within the PTGA, proceeding from posterior to anterior regions (Vinckier et al., 2007). Further, ERP studies of letter processing (e.g., comparing the brain response to letters and pseudo-letters) suggest feature level processing occurs prior to 145 ms, and letter-level processes occur thereafter (Rey, Dufau, Massol, & Grainger, 2009).

In light of these findings, the CCT model suggested that in synesthetes, connections between PTGA and V4 play a computational role in the competitive activation process. In projector synesthetes, interactions between color and grapheme processing begin during component level activations, as visual input activates not only component features of the letter, but also associated regions in V4. Just as activation of components at the feature level results in partial activation of a number of compatible candidates at the letter level, in synesthetes such activations are hypothesized to result in the partial activation of a range of colors within area V4, and later tuned to the correct color only after the letter has been subjected to further processing.

1.2. The present study

A key prediction follows from the CCT model claim that cross-activation between V4 and PTGA begins during the component stage of processing: at least in projector synesthetes, letters that share component features are more likely to activate similar hues in color space than are letters that do not share features. That is, for an individual synesthete, 'b' and 'd' should be closer in color space than say 'b' and 'm' as the latter share very few visual features.

The present study was designed to test this prediction of the CCT model. Accordingly, we tested the import of visual similarity on synesthetic colors evoked by letters. To this end we calculated color similarity matrices for each synesthete's set of letter–color correspondences, and examined the extent to which they correlated with visual letter confusability. To assess whether letters with similar visual features evoke similar hues, we regressed each synesthete's color similarity matrix against a letter confusability matrix. For a given synesthete, a strong correlation with visual similarity would suggest the importance of brain areas mediating component level processing of graphemes, consistent with the CCT model.

Table 1
Information on projector and associator synesthetes' correlations between visual similarity and hue similarity. Positive scores reflect a stronger impact of shape on synesthetic hues.

	Projectors ($n = 16$)	Associators ($n = 36$)
Average Fisher's corrected r	.145	.054
Minimum Fisher's corrected r	−.044	−.119
Maximum Fisher's corrected r	.600	.300
Number of significant correlations at the individual level	9 (56.2%)	16 (44.4%)

2. Methods

2.1. Participants

Data were collected from 52 English-fluent grapheme–color synesthetes (all possessing letter–color associations; 16 projectors, 36 associators), recruited via fliers posted on the UCSD campus, as well as similar ads on the web, and through a database of synesthetes at the University of Amsterdam. Synesthesia was confirmed by means of consistency matching as well as reaction-time testing for color congruency, standardized by Eagleman, Kagan, Nelson, Sagaram, and Sarma (2007).

2.2. Procedure and analysis

Synesthetes were presented with black letters (A–Z) and numbers (0–9) randomly, and instructed to pick the corresponding color from a color-picker palette via synesthete.org (see Eagleman et al., 2007 for additional details on data acquisition). Colors were registered in RGB color-space for subsequent analysis. Synesthetes also provided answers to Rouw and Scholte's associator/projector questionnaire, shown to correlate with the amount of connectivity in the inferior temporal lobe.

Colors were converted from RGB to CIE Lab color space to calculate color distances in a perceptual color space. Individual subject matrices were computed by comparing the distance between synesthetic colors (Euclidean distance between L, a, and b channels of Lab color space) for each of the possible letter combinations (yielding up to 325 color–distance values per subject). Some subjects reported that synesthetic colors did not exist for all letters, so such letters were excluded where appropriate. Each individual's set of color–distances was subsequently correlated to Courrieu, Farioli, and Grainger (2004) measure of visual similarity. In order to assess visual similarity, data were extracted from Courrieu et al.'s study investing values in response to same-different judgments of visually presented letters (325 combinations; 2004), with positive correlations suggesting more similar colors pair with more visually similar letters.

As the sampling distribution of Pearson's r is not normally distributed, Fisher's z' transformations must be applied when testing for group correlations or significant differences between correlations (Fisher, 1915). In instances where this transform has been applied, we refer to the values as Fisher corrected.

3. Results

Table 1 shows projector and associator synesthetes' average correlations for shape similarity; as a group, synesthetes showed an average correlation of $r = .082$ (Fisher corrected). While this correlation is small at the group level, the impact of shape similarity on synesthetic color, as assessed by Fisher corrected correlations, was highly significant for both projectors [one-sample t-test $t(15) = 3.64$, $p < .01$] and associators [one-sample t-test $t(35) = 3.73$, $p < .001$]. Furthermore, as predicted by the CCT model grapheme–color synesthesia, the effect of shape on color similarity was greater in projector synesthetes compared to associators, $t(50) = 2.63$, $p < .05$.

As the intensity of synesthetic experiences exist along a continuum, it is possible to quantify where along the projector–associator gradient each subject lies using a simple survey (Rouw & Scholte, 2007). Scores from the projector/associator survey ranged from −4 (associator classification) to +4 (projector classification). Results of this survey were compared to each synesthete's correlation between color similarity and visual similarity. Consistent with the group-level analysis, projector/associator scores showed a moderate positive correlation with color/shape correlations ($r = .300$, $t(50) = 2.214$, $p < .05$; Fig. 1), suggesting that the greater number of projector characteristics a synesthete showed, the greater their correlation between the relevant grapheme and color similarity metrics.

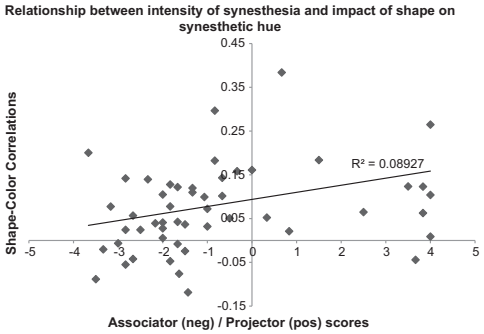


Fig. 1. Associator/projector scores for each synesthete reflecting the intensity of each synesthetes' experiences, compared against shape–color correlations (Fisher corrected). The positive correlation suggests that similarly shaped letters pair with similar synesthetic colors, with particularly strong an impact in projector synesthetes.

4. Discussion

The cascaded cross-tuning (CCT) model of grapheme–color synesthesia suggests that the concurrent sensation of color is evoked by graphemes due to cross-activation of grapheme and color processing areas in the posterior temporal lobes. In projector synesthetes, cross-activation begins during the initial feed-forward processing sweep involving feature component level processing of the graphemes. The present study was designed to test the prediction of the CCT model that letters sharing component features will be more likely to evoke similar synesthetic colors compared to letters that do not.

In keeping with this prediction, we have shown that in synesthetes, visually similar letter-forms were indeed associated with similar synesthetic colors. Moreover, this relationship was expressed more strongly in projectors than associators, consistent with the CCT model's claim that increased connectivity between V4 and PTGA is more likely to be present in the former group of synesthetes. Our findings are consistent with preliminary work by Hubbard, Ambrosio, et al. (2005) and Hubbard, Arman, et al. (2005), who demonstrated greater synesthetic color similarity within the letter-groups "KVWXY" or "CUDOQ" than when compared across the letter-groups, reflecting the pairing of visually similar letters with similar synesthetic colors. Furthermore, the present study is also consistent with preliminary results from multi-dimensional cluster analyses showing similar synesthetic colors tend to cluster around graphemes with similar low-level visual features (Eagleman, 2010), as well as basic feature analyses (round vs. angular, open vs. closed; Jürgens, Mausfeld, & Nikolić, 2010).

While the CCT may well explain the pattern of similar synesthetic colors between graphemes for projector synesthetes, this explanation may be incomplete for the associator form of grapheme–color synesthesia, which has been argued to rely less on low-level visual features, and tend to operate through conceptual processes (Ramachandran & Hubbard, 2001). Indeed, it is likely that some of the remaining variance in grapheme–color associations, that is, variance that is not accounted for by visual letter similarity, is due to linguistic (Simner et al., 2005) and cultural factors (Witthoft & Winawer, 2006). Moreover, it remains possible that some pairings are, as originally postulated, truly arbitrary.

Finally, these results, in conjunction with the CCT model, are in keeping with a developmental account of synesthesia in which the condition emerges before children begin to read. One tentative prediction made by the CCT model suggests that synesthesia might pre-date literacy, with colors initially elicited by basic shapes; it is then during development that synesthetic colors are redefined and tuned to individual graphemes. However, the notion of when during development synesthesia emerges remains a matter for future research.

In conclusion, grapheme–color synesthetes demonstrated a significant correlation between the visual similarity of graphemes and that of their associated synesthetic colors. This correlation was largest in projector synesthetes, implicating a stronger impact of early perceptual mechanisms. Further, the relationship between visual similarity and color similarity was a graded one, highlighting the intertwined relationship between conceptual and perceptual factors in synesthesia. Overall, these data support the CCT model of grapheme–color synesthesia, in which concurrent color experiences arise from cross-activation between brain areas important for processing graphemes (PTGA) and color (V4), as well as the notion that grapheme–color synesthesia emerges in development prior to the onset of literacy.

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Note

Grapheme-color synesthetes show enhanced crossmodal processing between auditory and visual modalities

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ABSTRACT

Synesthesia is an involuntary experience in which stimulation of one sensory modality triggers additional, atypical sensory experiences. Strong multisensory processes are present in the general population, but the relationship between these 'normal' sensory interactions and synesthesia is currently unknown. Neuroimaging research suggests that some forms of synesthesia are caused by enhanced cross-activation between brain areas specialized for the processing of different sensory attributes, and finds evidence of increased white matter connections among regions known to be involved in typical crossmodal processes. Using two classic crossmodal integration tasks we show that grapheme-color synesthetes exhibit enhanced crossmodal interactions between auditory and visual modalities, suggesting that the experience of synesthesia in one modality generalizes to enhanced crossmodal processes with other modalities. This finding supports our conjecture that the atypical sensory experiences of synesthetes represent a selective expression of a more diffuse propensity toward 'typical' crossmodality interactions.

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1. Introduction

Synesthesia is an involuntary experience in which stimulation of one sensory modality produces additional, atypical sensory experiences in either the same or a separate modality. In one of the most common forms, viewing numbers or letters (graphemes) elicits the percept of a specific color (grapheme-color synesthesia; Cytowic and Eagleman, 2009; Baron-Cohen et al., 1996). For example, to one of our synesthetes the number 2 always appears bright red, irrespective of its actual color. Synesthetic experiences typically begin early in childhood and remain extremely consistent over the lifespan. Further, synesthesia runs in families (Baron-Cohen et al., 1996; Ward and Simner, 2005; Asher et al., 2009), suggesting it is a heritable trait. Although researchers have studied this phenomenon for well over a century (Galton, 1880), it has long been considered a curiosity and only recently has there been a resurgence of interest in synesthesia, along with attempts to discover the underlying mechanisms.

The neural substrates of synesthesia have been thoroughly studied using both psychophysical tests and neuroimaging techniques (e.g., Palmeri et al., 2002; Nunn et al., 2002; Hubbard et al., 2005; Goller et al., 2009; Brang et al., 2008, 2011; Beeli et al., 2008). When viewing achromatic numbers or letters, grapheme-color synesthetes show co-activation of grapheme regions in the posterior temporal lobe and color

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area V4, giving rise to the concurrent sensation of color (Hubbard et al., 2005; Sperling et al., 2006; Brang et al., 2010). Ramachandran and Hubbard (2001) proposed that this cross-activation is driven by an excess of neural connections in synesthetes, possibly due to decreases in neural pruning between typically interconnected areas. Confirming this suggestion, a number of studies have demonstrated anatomical differences in the inferior temporal lobes of synesthetes, near regions related to grapheme and color processing, including increased fractional anisotropy as assessed by diffusion tensor imaging (DTI; Rouw and Scholte, 2007), and increased gray matter volume, as assessed by voxel-based morphometry (VBM; Jancke et al., 2009; Weiss and Fink, 2009).

Extending the cross-activation theory of synesthesia, Hubbard (2007) proposed a two-stage model to explain how synesthesia is bound into a sensory experience. In this model, synesthetic sensations are initially activated by direct connections between the senses, then are subsequently bound together into a conscious percept via 'hyperbinding' mechanisms in the parietal lobes (Robertson, 2003). This model is consistent with studies showing enhanced parietal lobe activity associated with synesthetic concurrents (e.g., Weiss et al., 2005), as well as studies using transcranial magnetic stimulation (TMS) demonstrating that parietal lobe inhibition weakens the synesthetic experience (Esterman et al., 2006; Muggleton et al., 2007). Moreover, DTI and VBM studies on grapheme-color synesthetes show altered morphology of parietal regions compared to controls, with increased fractional anisotropy in the superior parietal lobe (Rouw and Scholte, 2007) and increased gray matter volume in the left superior parietal lobe (Rouw and Scholte, 2010) and left intraparietal sulcus (Weiss and Fink, 2009). Taken collectively, these studies suggest that synesthesia operates through both direct communications between the senses as well as integration of information at multisensory nexuses in parietal areas.

By definition, synesthesia is a process that activates additional sensory information (e.g., color) that was not present in the original sensory signal (e.g., the sound of C-sharp). The existence of connections between the senses is indeed not unique to synesthetes, and has been empirically studied in non-synesthetic participants within the field of multisensory processing (Spence et al., 2009). In typical multisensory processes, stimulation of any particular sensory modality can affect how information is processed by the other senses. One well-popularized example of how visual cues can affect auditory processing is the Ventriloquist illusion, in which individuals perceive a Ventriloquist's voice as originating from the location of his puppet's mouth due to visual cues 'capturing' the auditory information (Pick et al., 1969). A striking demonstration that auditory stimulation affects visual perception is the double-flash illusion (Shams et al., 2000), wherein two auditory beeps paired with a single visual flash is actually perceived as two distinct visual flashes. This percept of an additional "flash" is correlated with specific neural activity (Bhattacharya et al., 2002) and could be viewed as a semi-synesthetic experience observed in non-synesthetes. These visual illusions exemplify the processing costs and perceptual errors that can result from the presentation of incongruent multisensory stimulation. Conversely, researchers have shown that being presented with congruent information from multiple modalities confers an advantage for speed and accuracy of processing (for review see Loveless et al., 1970). For example, in a target detection task reaction times are faster when auditory and visual cues are presented simultaneously compared to a cue in a single modality (Hershenson, 1962). Along similar lines, Frens et al. (1995) showed participants have faster saccades to a visual target when an irrelevant auditory cue is spatially and temporally aligned with the target. Interestingly, research into crossmodal integration in the normal population yields surprisingly consistent results with those of synesthesia studies: activation in parietal regions as well as direct co-activation of early sensory areas (e.g., Kayser and Logothetis, 2007; Driver and Spence, 2000; Foxe and Schroeder, 2005; Watkins et al., 2006, 2007).

The shared characteristics of synesthesia and multisensory processing paired with the established finding that feature binding in typical individuals relies on parietal lobe activity (e.g., Friedman-Hill et al., 1995; Critchley, 1953) have led several groups to suggest that synesthesia is an exaggeration of the crossmodal processes present in typical individuals (Robertson, 2003; Mulvenna and Walsh, 2005; Hubbard, 2007; Cohen Kadosh and Henik, 2007; Ward et al., 2006; for a review see Sagiv and Robertson 2005). Indeed, inhibitory parietal lobe TMS disrupts the binding of form and color similarly for non-synesthetes (Esterman et al., 2007) and synesthetes (Esterman et al., 2006; Muggleton et al., 2007) alike. If synesthesia is an exaggeration of typical multisensory processes, we would predict that synesthetes as a group will show an enhanced ability to integrate information from different sensory modalities, resulting in enhanced effects of crossmodal processing. While many studies have highlighted this possibility and the need for research in the area, no study to date has directly examined whether synesthetes show increased crossmodal processing between sensory modalities unrelated to the synesthetic experience. This increased, automatic binding should be observed regardless of whether it increases perceptual errors in the form of visual illusions in response to incongruent multimodal cues, or promotes enhanced processing of congruent multisensory stimuli. To this end, we compared the performance of 7 synesthetes to that of 25 controls on two psychophysical tasks that quantify an individuals' integration of crossmodal information: the double-flash illusion (Shams et al., 2000) and intersensory facilitation of reaction time (Hershenson, 1962).

2. Experiment 1: double-flash

The double-flash illusion is a striking example of crossmodal interactions in which a single white disk presented very briefly, yet unambiguously, is actually perceived as two flashes when accompanied by two auditory beeps (Shams et al., 2000). This illusion critically demonstrates that an auditory stimulus is capable of altering a visual experience, operating via crossmodal links, with quantifiable differences between illusion and non-illusion trials at the neural level (Bhattacharya et al., 2002). Consistent with our view that synesthesia is an enhanced variant of normal crossmodal processes, we expect synesthetes to show increased

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susceptibility to this illusion, which would be indicative of increased automatic crossmodal integration.

2.1. Methods: Experiment 1

2.1.1. Participants

Seven synesthetes ranging in age from 19 to 22 [mean age = 20.1 years, standard deviation (SD) = 1.1, 5 women] and 25 control subjects ranging in age from 18 to 23 (mean age = 20.3 years, SD = 1.4, 16 women) were recruited. All were healthy fluent English speakers with normal color vision, and none reported any history of psychiatric or neurological disorder. Synesthetes reported the experience of colors in response to viewing letters and/or numbers, and claims were confirmed by means of consistency matching (on-line testing with the Synesthesia Battery; Eagleman et al., 2007), including reaction time testing for color congruency.

2.1.2. Materials and procedure

Subjects were seated in front of a PC screen (refresh rate 60 hz) with their eyes 57 cm from the center of the screen. During each trial, a combination of 0, 1, or 2 auditory beeps and 0, 1, or 2 visual flashes were shown to the subject. Each visual flash was a uniform white disk (2 cm subtending 2 degrees of visual angle) shown very briefly at eccentricity (9 degrees of visual angle below fixation) on a black background. Each auditory beep was a 3.5 khz tone and lasted 7 msec. Subjects were instructed to only report the number of flashes seen by pressing 0, 1, or 2 on the PC keyboard. On each trial a variable number of flashes and beeps were presented for a total of 7 experimental conditions. For the main analysis we are most interested in contrasting the 'illusion' condition, in which a single flash is surrounded by two beeps, with a well-matched 'control' condition, in which a single flash follows two beeps by 300 msec. Both the illusion and control condition are composed of identical elements (1 flash, 2 beeps), but the temporal separation in the control condition fails to induce the illusion, allowing us to rule out a simple difference in response bias between our groups. The additional five conditions were included to prevent subjects from predicting the number of flashes or beeps and to ensure subjects were not incorrectly responding to the auditory cues (0 flashes 2 beeps), were accurately able to identify the visual cues presented in isolation (1 flash 0 beeps, 2 flashes 0 beeps), and that both groups had similar response patterns to other multisensory cue combinations (1 flash 1 beep and 2 flashes 1 beep). Each flash of the disk lasted 17 msec, with 50 msec interstimulus interval in the two-flash condition. Trials were initiated by the participant with a spacebar press followed by a 1 sec fixation cross and the onset of the trial. Subjects were acclimated to the task with an initial practice block. Participants completed 6 blocks of 77 trials (7 practice trials, one from each condition, and 10 of each trial type) for a total of 60 trials/condition.

None of the synesthetes experienced a synesthetic percept for any of the auditory or visual targets used. By utilizing stimuli that caused no synesthetic experiences, we can be confident that group differences reflect generalized processing, as opposed to differences driven by synesthetic percepts.

2.2. Results

Results from all seven conditions are presented in Fig. 1. As noted in the Methods section above, incidence of the illusion is quantified by the comparison between the two critical conditions with the additional five conditions preventing response biases and quantifying unisensory perception in both groups. Accuracy data from the critical illusion and control conditions were subjected to a 2 × 2 repeated measures analysis of variance (ANOVA) with factors of Group (synesthetes/controls) and Condition (2 beep 1 flash illusions, 2 beep 1 flash control), yielding a main effect of Condition [$F(1,30) = 74.5$, $p < .001$] and a significant interaction of Group × Condition [$F(1,30) = 7.76$, $p < .01$]. Orthogonal planned contrasts were conducted to compare synesthetes' and controls' relative accuracy in the illusion and control conditions. In the 2 beep 1 flash illusion condition, synesthetes' average accuracy rate of 10.5% (range: 3.3–23.3%) was significantly lower than that of control subject's average accuracy rate of 37.4% [range: 3.3–98.3%; $t(30) = 2.28$, $p < .05$], indicating a higher incidence of the double-flash illusion in synesthetes. In the 2 beep 1 flash control condition, however, synesthete's average accuracy rate of 82.8% (range: 48.3–100%) did not significantly differ from control subject's average accuracy of 74.4% [range: 28.3–100%; $t(30) = .89$, $p = .38$].

Providing additional confirmation that these results are not the product of a few outliers, we examined synesthetes' accuracy as a function of z-scores relative to the distribution of performance by controls; individual synesthetes' z-scores ranged from −1.12 to −.48 SDs from the mean accuracy of controls (synesthete's average z-score: −.88). Fig. 2 presents subjects' individual score in the illusion condition and demonstrates noticible overlap between the groups, even though all seven synesthetes showed low performance (high incidence of the illusion); it is possible this overlap is due to task-specific variability, floor effects, or veridical overlap between the groups. Further confirming the specificity of this difference between synesthetes and controls in only the illusion condition, no significant group differences were found for any of the five additional control conditions using two-tailed t-tests (uncorrected): 0 flashes 2 beeps $t(30) = .29$, $p = .78$; 1 flash 0 beeps $t(30) = .84$, $p = .41$; 2 flashes 0 beeps $t(30) = .74$, $p = .47$; 1 flash 1 beep $t(30) = .83$, $p = .41$; 2 flashes 1 beep $t(30) = 1.48$, $p = .15$. Lastly, in the critical illusion condition subjects on average incorrectly reported perceiving zero flashes on .55% of trials, confirming that these results are driven by the illusory perception of two-visual flashes and not reduced performance due to lack of attention or other reasons.

2.3. Discussion

The double-flash illusion was more pronounced in synesthetes compared to controls, reflected by their reduced accuracy in the critical illusion condition. This illusion represents an instance where subjects' visual perception is modulated by the incongruence of a sound pairing, in turn reducing veridical perceptual judgments. We suggest that synesthetes' increased susceptibility to the illusion represents increased crossmodal processing relative to controls. This notion is further supported by the specificity of the difference between

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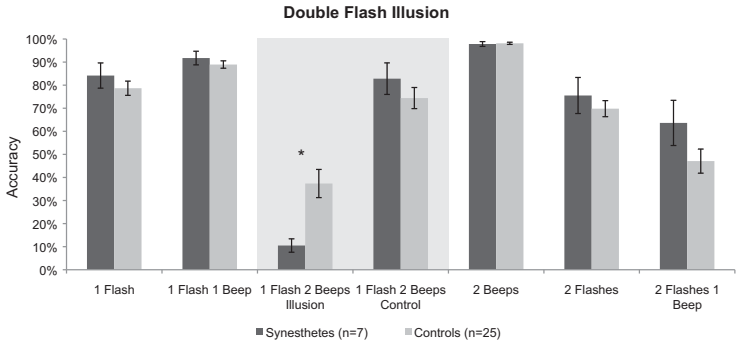


Fig. 1 – Accuracy in reporting the number of flashes in response to varying flash/beep conditions. Shaded region highlights the illusion condition (1 flash paired with 2 beeps, no delay) and the control condition (1 flash spaced 300 ms between 2 beeps). Error bars represent standard error of the mean. Asterisk reflects $p < .05$.

the groups; synesthetes showed reduced accuracy in only the critical illusion condition, and none of the control conditions. Interestingly, however, of the six control conditions, the only one to approach a marginally significant difference between the groups was the 2 flashes 1 beep condition, which some have argued is a multisensory illusion in itself (Mishra et al., 2008). It is important to note that while this illusion operates through audio and visual communication, none of our subjects experiences a form of synesthesia in which visual cues trigger auditory concurrents, or vice versa. Accordingly, as synesthesia was not engaged during this task, the increased crossmodal processing seen in synesthetes can be interpreted as a generalized increase in crossmodal interactions between auditory and visual centers.

3. Experiment 2 – intersensory facilitation of reaction time

As a test of crossmodal integration between congruent auditory and visual cues we quantified intersensory facilitation of reaction time for both our groups. Intersensory facilitation of reaction time is a well-documented behavioral effect first reported by Hershenson (1962), in which reaction times to multimodal stimuli (e.g., auditory and visual presented simultaneously) are reduced compared to *either* unimodal stimulus alone. Multiple studies (e.g., Miller, 1982, 1986; Laurienti et al., 2006) have found that this speeding of reaction times in the multimodal condition is above and beyond what would be expected by statistical summation of the two targets, and is thought to reflect genuine facilitation between multiple sensory cues originating from the same source. Accordingly, multisensory stimuli that are spatially and temporally coincident typically result in behavioral and/or perceptual enhancements. Hershenson (1962) concluded that the two senses interact in a beneficial manner, reflecting crossmodal processes present in us all. This test of multisensory response utilizes reaction time measures to evaluate the degree of crossmodal integration within each individual by comparing response time on a target detection task between a multimodal condition (a paired visual and auditory stimulus) and the unimodal conditions (visual alone or auditory alone). While previous research has shown responses in the multimodal condition to be faster than those in the unimodal in the general population, we expected this facilitation to be even greater in synesthetes, owning to increased crossmodal processes.

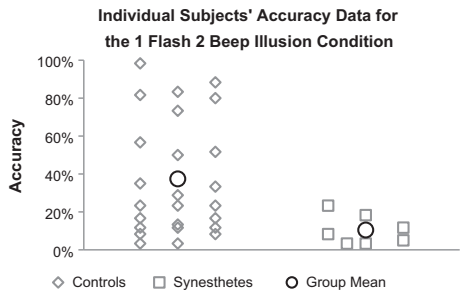


Fig. 2 – Controls' and synesthetes' individual percent-accuracy scores in the 1 flash 2 beep illusion condition.

3.1. Methods

3.1.1. Participants

The same group of synesthetes and controls from Experiment 1 participated in Experiment 2.

3.1.2. Stimuli

Participants were seated in front of a PC screen (refresh rate 60 hz) with their eyes 57 cm from the center of the screen. The experiment was programmed in E-Prime software (Psychology Software Tools, Inc.). Participants pressed the spacebar on a PC keyboard to start each trial. Trials began with a 1.5 sec fixation cross followed by a variable random delay (500–1500 msec) by either a visual stimulus – a red letter X printed in Times New Roman font, 12 pt, subtending

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.7 degrees of visual angle, presented for 100 msec, an auditory stimulus – a brief, 100 msec tone presented binaurally via headphones, or both targets simultaneously in the multimodal condition. Blank trials were also included to discourage anticipatory responding. Participants were instructed to press the "K" key of a PC keyboard with the index finger of their preferred hand (right hand for all participants) as quickly as possible when they detected a visual and/or auditory cue. There were 4 blocks of 74 trials; each block began with 4 randomly selected trials that were treated as practice trials and excluded from analysis, followed by 20 trials in each condition (auditory, visual, and multimodal) plus 10 blank catch trials. As such, each participant generated 80 reaction times for each experimental condition.

3.1.3. *Analysis*

The multimodal condition presents participants with two redundant targets compared to the single target presented in either the auditory or visual conditions. Thus, some of the speeding of reaction time to multimodal targets is attributable to the advantage of having two independent stimuli contributing to response generation and execution. To calculate the extent of multisensory benefit in addition to that which is predicted by the redundant nature of the multimodal condition (e.g., two stimuli as opposed to one), the independent race-model was used as a comparison for multisensory benefits compared to the joint probability of responses from either sensory stimulus alone (Miller, 1982, 1986; Laurienti et al., 2006). The independent race-model utilizes cumulative distribution functions (CDFs) to compare relative probabilities for a response within grouped 1 msec time windows. A race-model is constructed from the joint probabilities of the auditory alone and visual alone conditions [(Pr Auditory + Pr Visual) – (Pr Auditory × Pr Visual)]. If the CDF for the multimodal condition exceeds that which would be predicted by the race-model, then the model is violated. These violations of the race-model are thought to reflect true multisensory integration at the neural level (Miller, 1982; Laurienti et al., 2006). Accordingly, each subjects' data was divided into 1 msec reaction time bins, used to create individual CDFs for each condition (auditory, visual, and multimodal). Next, the race-model predictions at each time bin were computed for each subject based on the auditory and visual CDFs. Finally, average race-model predictions were calculated for each subject from the mean of the response times in the race-model CDFs for comparison against the raw multimodal response times.

3.2. *Results*

Results are presented in Table 1. Data were subjected to repeated measures ANOVA with factors of Group (synesthetes, controls) and Condition (multimodal, race-model). ANOVA revealed main effect of Condition [$F(1,30) = 49.3$, $p < .001$], suggesting that multimodal response times across groups exceeded those predicted by the race-model, confirming the benefit of multisensory information, and the presence of crossmodal enhancement. Follow-up paired t-tests comparing multimodal and race-modal conditions within each group confirmed the presence of this effect in both synesthetes [two-tailed $t(6) = 6.29$, $p < .001$] and controls [two-tailed $t(24) = 5.18$, $p < .001$]. Critically, repeated measures ANOVA revealed a marginal Group × Condition interaction [$F(1,30) = 3.87$, $p = .058$], such that synesthetes demonstrated more benefit from multimodal stimuli over race-model predictions compared to control subjects (Fig. 3). Even though each subjects' race-model prediction serves as a within subject baseline, numerical differences in this baseline could superficially be argued to drive group differences. However, synesthete's mean reactions times did not differ from control's on either visual alone trials [two-tailed $t(30) = .85$, $p = .40$] or auditory alone trials [two-tailed $t(30) = .91$, $p = .37$].

Table 1 – Intersensory facilitation of reaction time (Experiment 2) response times for synesthetes and controls. Race-model predictions calculated from joint probability of responses from auditory and visual conditions, and serve as the baseline for multimodal response times.

	Auditory response times	Visual response times	Race-model predictions	Multimodal response times
Synesthetes ($n = 7$)	440 msec	442 msec	380 msec	348 msec
Controls ($n = 25$)	409 msec	422 msec	358 msec	340 msec

To test whether the enhanced cross-modal processing in synesthetes operates as a general group effect or reflects multisensory benefits differing between individuals, we tested the relationship of synesthetes' performance on these two tasks using a Pearson r correlation. While this is a small sample size and so the results must be considered with caution, a robust relationship was found for synesthetes' accuracy on the double-flash task and response time benefit to a multimodal response compared to race-model predictions [$R = -.77$, $t(5) = -2.74$, $p < .05$]. Notably, the negative correlation yielded here reflects an increase in multisensory processing in both tasks; i.e., reduced performance on the double-flash is associated with decreased response time (heightened benefit) in the detection task (Experiment 2).

3.3. *Discussion*

Individuals with grapheme-color synesthesia were shown to benefit more from a multimodal stimulus, a sound and a simple visual cue presented simultaneously, than normal controls. As no subjects included in this study experienced synesthetic concurrents between visual and auditory modalities, we suggest that synesthesia is associated with enhanced crossmodal processing in modalities outside those related to their conscious synesthetic experiences. Crucially, as each subject serves as his or her own baseline, it is unlikely that these results are due to response biases, as that bias would be uniform throughout the conditions.

4. General discussion

To our knowledge, these studies provide the first evidence of enhanced crossmodal interactions in synesthesia beyond

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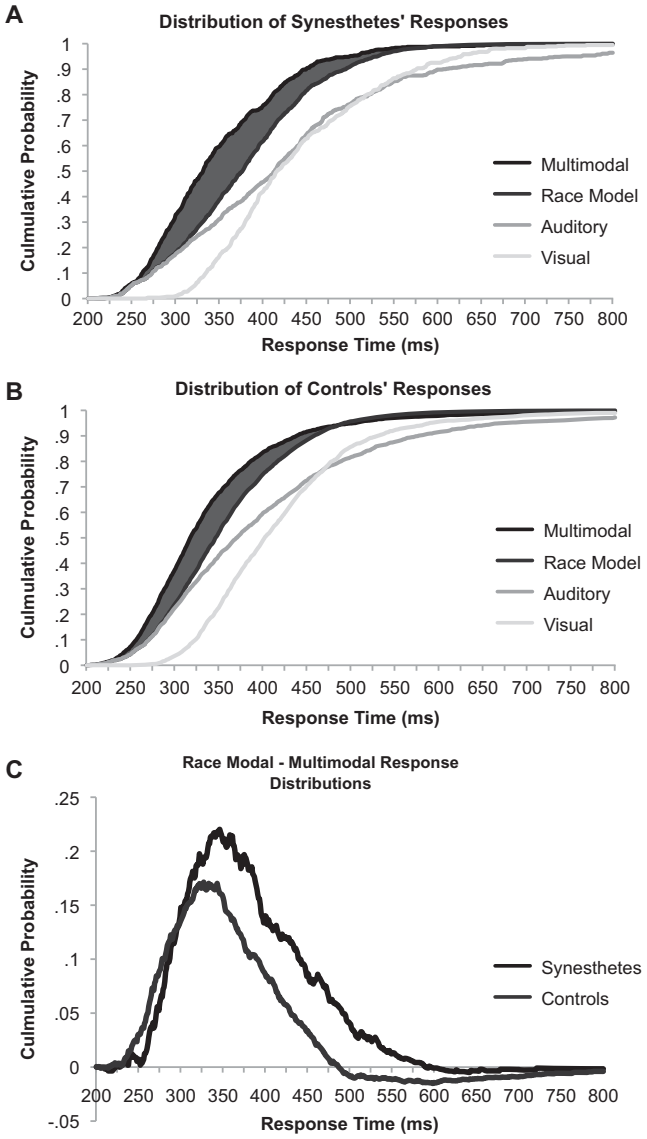


Fig. 3 – CDFs for synesthetes' and control subjects' response times to auditory, visual, and multisensory stimuli. The independent race-model represents summed probability for auditory and visual responses. Shaded area between the curves represents multisensory benefit over race-model distributions. Note the increased shaded area in synesthetes compared to controls.

modalities involved in the synesthetic experience, suggesting that synesthesia may build upon the same mechanisms underlying typical crossmodal processes. These two studies used very different tasks and each point toward synesthetes possessing increased communication between auditory and visual areas compared to controls. Synesthetes showed reduced performance in Experiment 1 (higher incidence of illusion trials) and increased performance in Experiment 2

(more reaction time benefit) suggesting these effects are not merely driven by performance biases in the synesthetes. Furthermore, synesthetes did not statistically differ from controls in their unisensory response times in Experiment 2 (auditory alone and visual alone trials); indeed, numerically they were slower in these conditions compared to controls. However, it remains possible to test whether these effects are specific to crossmodal tasks or reflect some general speeding in synesthetes to increasingly complex or additive stimuli. One experiment well suited to rule out this alternative explanation would be the redundant target effect (Miniussi et al., 1998) in which subjects are faster to indiscriminatingly respond to two-visual cues as opposed to one, which is thought to be mediated by early visual areas as opposed to crossmodal processes. In such a task we would expect no difference between synesthetes and controls.

While preliminary, the correlation of synesthetes' performance between the two crossmodal tasks employed in this study suggests that not only do synesthetes show increased crossmodal processing compared to controls at the group level, but also that crossmodal enhancement is a generalizable and reliable aspect of the individual differences between synesthetes. One speculative possibility is that the strength of synesthesia or perceptual reality of the each synesthetes' experiences relates to the degree of crossmodal enhancement. Indeed, research suggests that synesthetes with more perceptually 'real' experiences display improved performance on tasks that utilize synesthetic experiences (Hubbard et al., 2005). However, as the current group of synesthetes were not classified according to their strength of synesthetic perceptions, this question will remain a matter for future research.

As the results presented here address only the behavioral output of crossmodal processing, further research is required to clarify the relationship between synesthesia, crossmodal mechanisms, and connectivity and activation patterns both between the individual sensory systems and within parietal areas. Indeed, this study fills one of the putative links in this matrix, such that synesthetes have been shown to possess increased connectivity between the senses and in the parietal lobes (Rouw and Scholte, 2007), and these results demonstrate increased crossmodal processing in synesthetes in tasks that are expected to engage similar networks. The missing critical value to aid in our understanding of multisensory processing in the general population is to examine how crossmodal performance on behavioral tasks relates to connectivity both between the senses and to the parietal lobes.

This study also adds to accumulating evidence of generalized processing benefits in synesthesia, providing a provocative evolutionary hypothesis (assuming of course synesthesia is not merely epiphenomenal). Contrary to notions that synesthesia serves no benefit, recent work suggests synesthesia may alter primary sensory processes. Barnett et al. (2008) show differences in early visual perception and there are studies showing increased (unimodal) perceptual sensitivity in synesthetes (Banissy et al., 2009; Yaro and Ward, 2007). Furthermore, research from our own laboratory suggests that grapheme-color synesthetes have lower color detection thresholds in a psychophysically low-level visual task (Wagner et al., in prep.). Taken collectively, these data suggest that synesthesia is associated with enhanced primary sensory processing as well as the integration between the senses. However, as these sensory enhancements could also be due to synesthetes' increased experience with sensory percepts due to synesthetic concurrent experiences, the causality of this relationship will remain a matter for future studies.

In conclusion, while the mechanisms supporting this enhanced crossmodal processing still require careful examination, the current study provides the first direct link between synesthesia and crossmodal processes in the general population. Further, while this initial result is based off of auditory and visual crossmodal tasks tested in only one form of the condition, subsequent studies are encouraged to examine additional types of synesthesia, crossmodal tasks across additional modalities, as well as the relationship between connectivity and crossmodal processing in all individuals.

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CONCLUSION

In Experiment 1, we investigated whether the brain treats synesthetic associations in grapheme-color synesthesia as arbitrary associations versus potentially meaningful connections, via scalp-recorded event-related potentials (ERPs) recorded as eight grapheme-color synesthetes read sentences that evoked the concept of a particular color. Sentences ended either with a color word, color patch, or a grapheme that induced a color. For example, "The Coca Cola logo is white and" ended with either a congruous target, (such as the word "red", a red color patch, or with a grapheme such as 2 known to elicit the concurrent sensation of red for a particular synesthete), or an incongruous target (such as the word "green", a green color patch, or with a grapheme such as 7 known to elicit the concurrent sensation of green). The congruity manipulation in the text and color patch conditions resulted in the well known contextual priming effect on the N400 component in the ERP. Furthermore, N400 contextual priming effects were also observed in the grapheme condition, indicating that synesthetic associations are available for integration with linguistically activated concepts. Moreover, the congruity manipulation also affected the amplitude of the N1, P2, and N300 components elicited by graphemes, reflecting earlier perceptual activation. While this effect demonstrated the quick latency of synesthetic colors and their similarity to perceptual colors, it remained possible that the early perceptual effects remained causally related to semantic knowledge of the associations as opposed to the experience of synesthesia itself.

In order to address this issue, in Experiment 2 three neurotypical control groups were tested in a similar paradigm to elucidate the functional significance of synesthetes' ERP components. For example, to identify effects attributable to conceptual knowledge of the correspondences between graphemes and their concurrent colors, trained controls were taught these mappings and subsequently shown sentences ending in achromatic graphemes. To

identify effects attributable to task strategy, explicit visualization controls were taught grapheme-color mappings and asked to anticipate the appearance of the expected grapheme at the end of the sentence. Finally, to identify ERP effects attributable to the experience of colored graphemes, colored grapheme controls were presented sentences ending with colored graphemes. Grapheme congruity modulated the N400 component in all three control groups, revealing conceptual processing and understanding in synesthetes and trained controls alike. Additionally, effects on earlier perceptual effects was revealed in only controls who viewed physically colored graphemes, as this group most closely mirrored the perceptual experience of color described by synesthetes.

Electroencephalography (EEG) measurements suffer from limited spatial resolution due to the volume conduction of electrical signals through the scalp. In order to more precisely localize the anatomical origin of the activity observed in studies 1 and 2, we utilized magnetoencephalography (MEG) with four synesthetes and four naïve controls during a simple grapheme processing task. In addition to determining the origin and onset of synesthesia, this design also allowed the comparison of competing models in synesthesia. Results were largely consistent with the cross-activation model, and suggested that correlated activity in posterior temporal lobes and V4 may be the first step in the generation of the synesthetic experience.

Adding additional support to our evidence that the posterior temporal lobes play a critical role in grapheme-color synesthesia, in Experiment 4 we sought out the existence of patterns in individual synesthetes' array of grapheme-color associations. In this study we demonstrated that the selection of particular hues in synesthesia relies in part on visual similarity between graphemes, such that visual similar letters and numbers tended to elicit similar synesthetic colors. This finding argues against the notion that synesthetic colors are

simply random associations, and instead suggests they arise via predicted functional mechanisms in the inferior temporal lobe.

While studies 1 – 4 highlight the role of early visual mechanisms in grapheme-color synesthesia to explain the perceptual effects of the conditions, extensive research suggests the phenomenon is associated with global changes to the brains of synesthetes. In order to examine the hypothesis that these global changes reflect alterations to multisensory processes in synesthetes, Experiment 5 tested the relationship between synesthesia and multisensory processes present in the general population. Across two distinct tasks, synesthetes demonstrated enhanced multisensory processing in a modality separate from their synesthetic experiences, suggesting that synesthesia may be an extreme form of normal multisensory processing, and establishing a long absent link between these two fields. Critically, in addition to providing a functional mechanism for the emergence of synesthesia, these findings allow the field as a whole to more directly impact our understanding of normal cognition.

In sum, the findings from these five studies suggest a direct route of communication between early perceptual centers mediates the initial processing stage in grapheme-color synesthesia. Furthermore, these early mechanisms may partially overlap with those present in the general population, utilized in typical multisensory processes. However, as demonstrated in Experiment 2, simply training non-synesthetes to make these associations is insufficient for the utilization of these networks allowing dissociation between authentic synesthetic experiences and many of the component traits induced in non-synesthetes. This work clarifies the mechanisms that underlie this interesting condition, and provides a roadmap to using synesthesia as a tool to better understand perceptual and conceptual processes present in all individuals.

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