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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.

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

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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

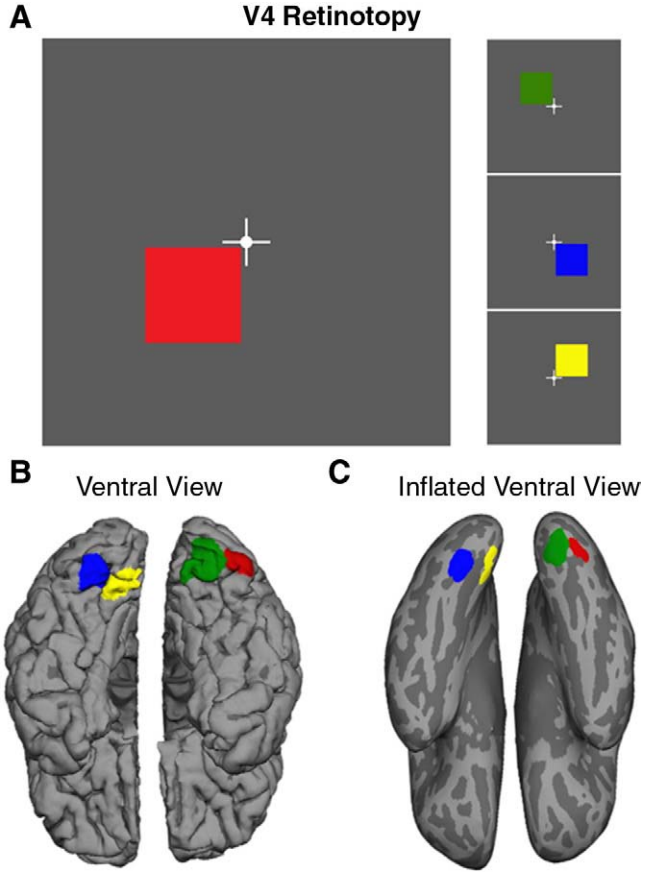

Fig. 1. (A) Square blocks presented randomly in one of four visual quadrants, in order to elicit retinotopy in visual area V4; identical block stimuli were presented in each quadrant, and colored here for presentation. (B–C) MEG activity in response to visual stimulation of either the lower left (red), 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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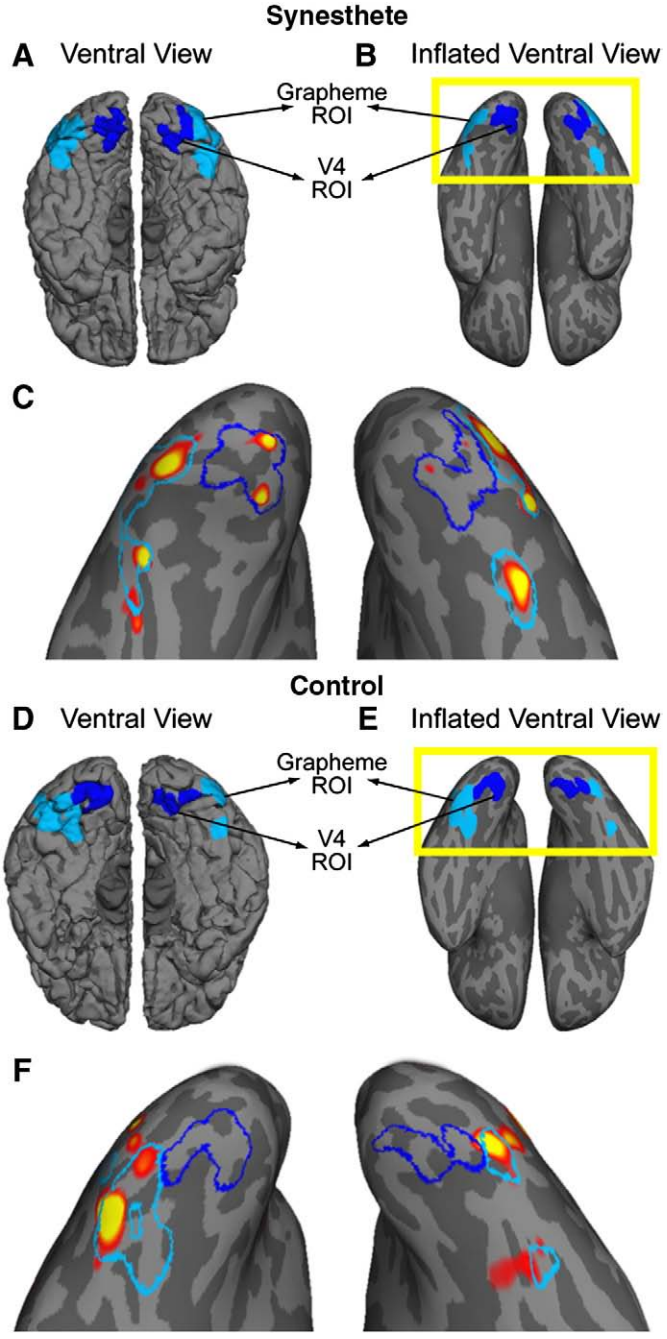

Fig. 2. Representative synesthete's (A–C) and control subject's (D–F) brains. The grapheme ROI is shown in light blue, and V4 ROI in dark blue. A and D show ROIs overlaid on a non-inflated cortical surface. B and E show ROIs overlaid on digitally inflated brains; yellow box highlights region depicted 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). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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

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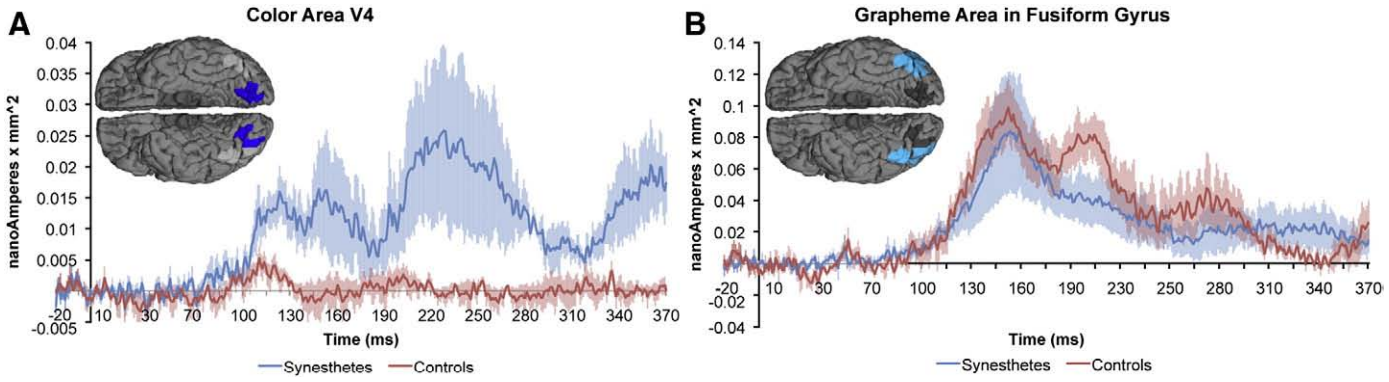

Fig. 3. Synesthetes' and controls' mean activation in (A) the V4 ROI and (B) the Grapheme ROI between −20 and 370 ms. Achromatic letters and numbers evoked significantly more activity in synesthetes compared to controls between 111 and 130 ms in V4 $t(6) = 3.09$, $p < .05$, but not in the grapheme area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

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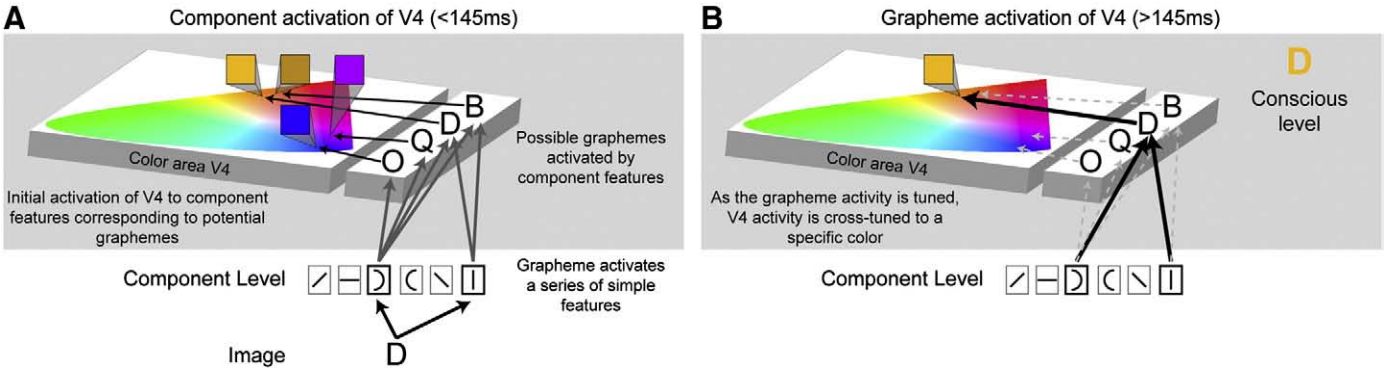

Fig. 4. Cascaded cross-tuning model of synesthesia. (A) Initial processing. As in hierarchical feature models of grapheme processing, visual input prior to 145 ms activates component features (line segments, curves, etc.) and partially activates graphemes comprised of those features (Rey et al., 2009). 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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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