

Individual Differences among Grapheme-Color Synesthetes: Brain-Behavior Correlations

Edward M. Hubbard,^{1,2,*} A. Cyrus Arman,¹
Vilayanur S. Ramachandran,²
and Geoffrey M. Boynton¹

¹Salk Institute for Biological Studies
Systems Neurobiology Laboratory - B
10010 North Torrey Pines Road
La Jolla, California 92037

²Center for Brain and Cognition
University of California, San Diego
9500 Gilman Drive
La Jolla, California 92093

Summary

Grapheme-color synesthetes experience specific colors associated with specific number or letter characters. To determine the neural locus of this condition, we compared behavioral and fMRI responses in six grapheme-color synesthetes to control subjects. In our behavioral experiments, we found that a subject's synesthetic experience can aid in texture segregation (experiment 1) and reduce the effects of crowding (experiment 2). For synesthetes, graphemes produced larger fMRI responses in color-selective area human V4 than for control subjects (experiment 3). Importantly, we found a correlation within subjects between the behavioral and fMRI results; subjects with better performance on the behavioral experiments showed larger fMRI responses in early retinotopic visual areas (V1, V2, V3, and hV4). These results suggest that grapheme-color synesthesia is the result of cross-activation between grapheme-selective and color-selective brain areas. The correlation between the behavioral and fMRI results suggests that grapheme-color synesthetes may constitute a heterogeneous group.

Introduction

Synesthesia is a relatively rare condition in which sensory stimuli cause unusual additional experiences. These additional experiences often occur between modalities, such as seeing colors while listening to music or (more rarely) feeling tactile shapes while tasting foods (Baron-Cohen and Harrison, 1997; Cytowic, 2002). However, other forms of synesthesia occur intramodally. For a large number of synesthetes, viewing letters and numbers elicits the experience of colors (grapheme-color synesthesia). Because grapheme-color synesthesia is relatively common, affecting 68% of synesthetes (Day, 2005), and it involves both visual triggers and experiences, it is well-suited for in-depth perceptual and neuroimaging investigations (for reviews, see Ramachandran and Hubbard, 2001b; Rich and Mattingley, 2002; Robertson and Sagiv, 2005).

In general, psychophysical studies have demonstrated that synesthetic colors have perceptual consequences, and neuroimaging studies have shown greater activation in early visual areas in synesthetes than controls. However, different studies yield conflicting results on the exact nature of the perceptual consequences and neural substrates of synesthesia. For example, our previous research has demonstrated that grapheme-color synesthesia is a perceptual experience, which may occur preattentively (Ramachandran and Hubbard, 2001a; Ramachandran and Hubbard, 2001b). First, synesthetic subjects performed significantly better than controls in identifying which of four shapes composed of graphemes was embedded in a display containing other, distracting graphemes (Ramachandran and Hubbard, 2001a; see experiment 1 below). For example, if presented with a triangle composed of 2s against a background of 5s, synesthetes were significantly more accurate than control subjects in identifying the target shapes created by the 2s. Second, synesthetic experience appears to aid performance in a crowding task (Ramachandran and Hubbard, 2001b). Numbers or letters presented in the periphery are difficult to identify when surrounded by other, flanking graphemes, an effect known as crowding. In nonsynesthetic observers, the crowding effect is attenuated by presenting the target graphemes in a different color than the flanking graphemes (Kooi et al., 1994). When we presented crowded graphemes that elicited different colors to synesthetic subjects, they were significantly better at identifying the target grapheme than controls. These results suggest that synesthetic colors, like real colors, reduce the magnitude of the crowding effect (see experiment 2 below), and further suggest that synesthetic colors may be evoked at an early stage of perceptual processing.

Other groups have reported similar results suggesting that synesthetic colors are evoked early in visual processing. Smilek et al. (2001) report that a number is harder to identify when the background color is congruent with the synesthetic color than when it is incongruent. For example, a “blue” 4 is identified more accurately when presented against a red background than against a blue background. Palmeri et al. (2002) showed that synesthetic colors can aid in the detection of a singleton grapheme in a visual search task. When synesthetic colors differed between target and distractor (searching for a 2 among 5s), their synesthetic subject was much more efficient in his visual search (search slopes were about 15 ms/item). When the target and distractor elicited similar colors (searching for a 6 among 8s), search was much less efficient (search slopes were about 28 ms/item). In control subjects, no such difference was observed. Finally, Wagar et al. (2002) have shown that synesthetic colors can reduce the magnitude of object substitution masking.

However, other studies have questioned just how early in perceptual processing synesthetic colors arise. Laeng, Svartdal, and Oelmann (Laeng et al., 2004), using a visual search task, have suggested that the

*Correspondence: edhubbard@gmail.com

synesthetic advantages described above occur only within the window of attention. Using pattern masking, [Mattingley et al. \(2001\)](#) have shown that synesthetic Stroop interference is eliminated when stimuli are not consciously perceived (for critiques of these claims, see [Blake et al., 2005](#); [Smilek et al., 2005](#)), contrary to the results of [Wagar et al.](#), using object substitution masking. These conflicts may be due to methodological differences, the complex relationship between synesthesia and attention (see [Treisman, 2005](#)), or differences in the synesthetes tested in the different studies.

One potential mechanism for these grapheme-color associations is cross-activation between adjacent regions of the fusiform gyrus ([Ramachandran and Hubbard, 2001a](#); [Ramachandran and Hubbard, 2001b](#)) that are involved in color processing (V4 [[Lueck et al., 1989](#); [Zeki and Marini, 1998](#)], V8 [[Hadjikhani et al., 1998](#)], or human V4 [[Wade et al., 2002](#)]) and regions involved with visual recognition of number graphemes ([Dehaene, 1992](#); [Rickard et al., 2000](#); [Pesenti et al., 2000](#)) and visual words ([Cohen et al., 2000](#); [Polk and Farah, 2002](#); [Polk et al., 2002](#); for a review see [Cohen and Dehaene, 2004](#)). We have suggested that this cross-activation may arise in a manner similar to the cross-activation that leads to phantom limb experiences ([Ramachandran et al., 1992](#); [Ramachandran and Hirstein, 1998](#)). However, we propose that cross-activation occurs between different cortical maps instead of between different portions of the same cortical map (see [Hubbard and Ramachandran, 2003](#)) and that these connections arise not from neural changes following deafferentation, but instead are due to a failure of pruning of perinatal connections between temporal regions involved in object recognition and area V4 ([Kennedy et al., 1997](#); [Rodman and Moore, 1997](#)).

Alternatively, it may be that disinhibited cortical feedback is involved in cases of acquired synesthesia ([Armel and Ramachandran, 1999](#)) or drug-induced synesthesia ([Grossenbacher, 1997](#); [Grossenbacher and Lovelace, 2001](#)), or synesthetic colors may arise through a combination of cross-activation and feedback, in a re-entrant manner (see [Smilek et al., 2001](#)). While the current experiments cannot distinguish between local cross-activation, disinhibited cortical feedback, or re-entrant processes, they can clearly test the hypothesis that cortical regions normally involved in the perception of color are active when synesthetes view letters and numbers.

Several studies have used brain-imaging techniques to examine the neural basis of synesthesia, again with somewhat contradictory results. [Paulesu et al. \(1995\)](#) presented auditory word-color synesthetes with blocks of either pure tones or single words. In this study, areas of the posterior inferior temporal cortex and parieto-occipital junction—but not early visual areas V1, V2, or V4—were activated during word listening more than during tone listening in synesthetic subjects, but not in controls. One possible interpretation is that while activation in the fusiform gyrus may have been present, the use of the PET technique did not provide sufficient power to detect it. Consistent with this, [Paulesu et al.](#) report that weak activation of V4 was observed, but was discounted due to low statistical magnitude and

the fact that similar activation was seen in control subjects.

Recently, [Nunn et al. \(2002\)](#) have published results that support this speculation. Using fMRI, they tested six female, right-handed auditory word-color synesthetes and six matched nonsynesthetes. [Nunn et al.](#) report that regions of the brain involved in the processing of colors (V4/V8) are more active when word-color synesthetes hear spoken words than when they listen to tones, but not in earlier visual areas such as V1 or V2. No such difference was observed in control subjects, even when they were extensively trained to imagine specific colors for specific words. Similarly, in a synesthete who experiences colors for people's names, [Weiss et al. \(2001\)](#) report that hearing names that elicited synesthetic colors led to activity in left extrastriate cortex (near V4), but not V1. However, in a case study of an auditory-word color synesthete, [Aleman et al. \(2001\)](#) report activation of (anatomically defined) primary visual cortex but were unable to determine if area V4 was active.

Thus, most studies of word-color synesthesia suggest that color-selective region V4 is involved in synesthetic colors, but the functional significance of this activation and the degree to which other areas are involved remain unclear. These conflicting results may be due to numerous methodological differences between the studies, differences between different types of synesthetes studied, or differences in the strength of the colors experienced by the different synesthetes. One way to address the possibility that the differing results may be due to important individual differences between synesthetes is to collect both behavioral and neuroimaging data in the same subjects, which provide independent measures of the strength of synesthetic colors.

In this study we obtained both behavioral performance and fMRI measurements in six grapheme-color synesthetes and six nonsynesthetic controls to test the hypotheses that (1) grapheme-color synesthesia arises as a result of activation of color-selective region hV4 in the fusiform gyrus and (2) the behavioral improvements seen in our psychophysical paradigms are mediated by this activation in hV4. Additionally, because of the extensive testing of individual subjects, our data may help to resolve some of the conflicting results in the literature.

Results

Experiment 1: Embedded Figures Task

In our first experiment, we determined if a subject's synesthetic experience aids in texture segregation. We created displays in which one of four different shapes—square, rectangle, triangle, or diamond—composed of small target graphemes was embedded in a matrix of distracting graphemes. Subjects were asked to name the shape defined by the embedded target graphemes. This task tests whether synesthetic colors are indeed perceptual by showing that synesthetic colors aid in texture segregation. Various psychophysical paradigms have demonstrated that texture segregation is an early perceptual process and may be a measure of preattentive processing ([Beck 1966](#); [Julesz 1981](#); [Treisman and](#)

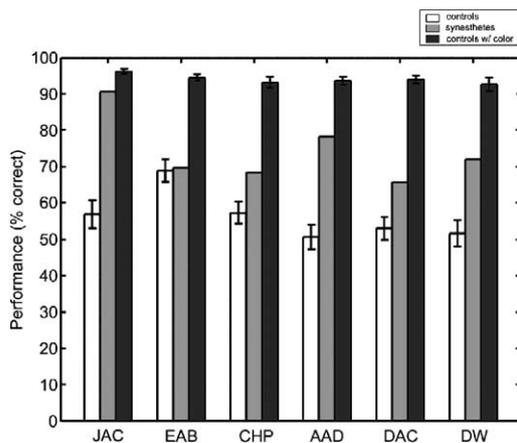


Figure 1. Performance on Embedded Figures Task

Control subjects ($n = 20$ per synesthete) are indicated by white bars, synesthetes by medium gray bars, and control subjects presented with colored displays ($n = 20$ per synesthete) by dark gray bars. Error bars indicate the SEM. Five out of six synesthetes perform better than their respective control populations, but none of the synesthetes perform as well as if they had been presented with real colored displays.

Gelade 1980), although it does not seem to measure exactly the same preattentive process as pop-out in visual search (Wolfe, 1992).

Data from the six synesthetes and their respective control subjects are presented in Figure 1. White bars indicate control subjects viewing black graphemes on a white background, medium gray bars indicate synesthetes (black graphemes on white background), and dark gray bars indicate control subjects viewing colored graphemes. An overall ANOVA yielded a significant main effect of group (synesthete versus controls) ($F_{(1,124)} = 7.41$, $p < 0.01$), with synesthetes performing significantly better ($74.00\% \pm 9.11\%$, mean \pm SD) than controls ($56.29\% \pm 15.76\%$). Control subjects presented with colored displays ($93.92\% \pm 5.67\%$) also performed significantly better than control subjects who had been presented with the black and white displays ($F_{(1,238)} = 605.51$, $p < 0.0001$). However, synesthetes performed significantly worse than control subjects presented with colored displays ($F_{(1,124)} = 66.24$, $p < 0.0001$), suggesting that synesthetic experiences were not as effective as real colors in improving performance.

Because different graphemes were used for each synesthete, there is the possibility of differences in performance between groups of controls. We tested this with an overall ANOVA ($F_{(6,113)} = 3.39$, $p < 0.01$). A Tukey HSD post hoc test showed that the group difference was driven by the control group for EAB performing better than other control groups. However, the presence of this group difference in control performance will only serve to increase the within-group variability of the controls and therefore make it more difficult to detect a between-groups difference between synesthetes and controls.

In order to examine our results in more detail, we

compared the performance of each individual synesthete against the performance of his or her respective control group, using a series of independent, one-sample, two-tailed t tests (see Figure 1). These tests show that five of the six synesthetes (with the exception of EAB) performed better than their respective control populations when viewing the black and white displays (all t s > 3.5 , $df = 20$, $p < 0.005$). However, each of the synesthetes performed worse than their respective control population when nonsynesthetes were presented with colored displays (all t s > 7 , $df = 20$, $p < 0.001$). Overall, these results suggest that synesthetic colors were able to improve performance on the embedded figures task, consistent with previous literature (Palmeri et al., 2002; Ramachandran and Hubbard, 2001a; Ramachandran and Hubbard, 2001b; Smilek et al., 2001). However, comparing the performance advantage conferred by synesthetic colors with that conferred by real colors suggests that synesthetic colors are not as effective as real colors in enhancing performance, consistent with the subjective reports of synesthetes.

Experiment 2: Crowding Task

In experiment 2, we took advantage of the crowding effect to determine if synesthetic colors aid in the identification of crowded graphemes, similarly to nonsynesthetic colors (Kooi et al., 1994). Under normal viewing conditions, a single grapheme presented in the visual periphery is relatively easy to identify (provided it is scaled for eccentricity). However, identification is much more difficult if that same grapheme is presented with additional graphemes surrounding it (Bouma, 1970; He et al., 1996). When crowded graphemes are presented with the target in a different color from the flankers, identification performance improves (Kooi et al., 1994). We tested whether synesthetic colors might also lead to improvements in identification of crowded graphemes in the visual periphery. Because it is thought that crowding may result from limitations in later stages of processing, such as attentional limitations (Intriligator and Cavanagh, 2001; He et al., 1996), these results would suggest that synesthesia may arise prior to attention. We have described preliminary results from this experiment previously (Ramachandran and Hubbard, 2001b).

Data from the six synesthetes and their respective control subjects are presented in Figure 2. White bars indicate control subjects viewing black graphemes on a white background, medium gray bars indicate synesthetes, and dark gray bars indicate control subjects viewing colored graphemes. An overall ANOVA revealed no main effect of group (synesthete versus controls) ($F_{(1,79)} = 1.69$, $p > 0.15$), with synesthetes performing slightly better ($61.58\% \pm 10.18\%$) than controls ($54.80\% \pm 12.42\%$). It is possible that this lack of significance was due to significant differences in performance of the different control groups ($F_{(6,65)} = 5.58$, $p < 0.0001$). Tukey HSD post hoc tests showed that the control population for synesthete DAC performed worse than the controls for both AAD and EAB, while the control group of EAB performed better than the control groups for CHP, DAC, and DW. Overall, these

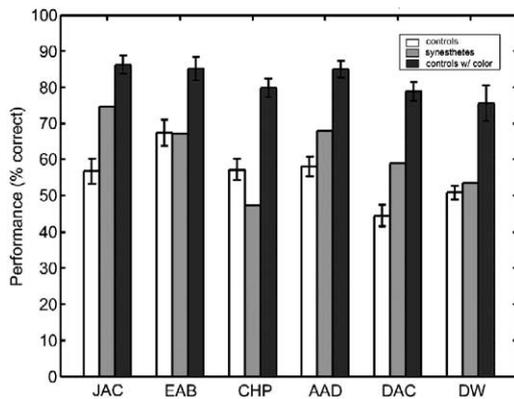


Figure 2. Performance on Crowding Task

Control subjects ($n = 12$ per synesthete) are indicated by white bars, synesthetes by medium gray bars, and control subjects presented with colored displays ($n = 12$ per synesthete) by dark gray bars. Error bars indicate the SEM. Three out of six synesthetes (JAC, AAD, and DAC) perform better than their respective control populations, but none of the synesthetes perform as well as if they had been presented with real colored displays. Overall performance for control subjects is about equal between the crowding task and the embedded figures task, but colors (both synesthetic and real) improve performance less in this task than in the embedded figures task.

two control groups roughly offset the effect on the mean (54.80% with, versus 54.21% without) but nearly doubled the between-groups variability (7.84% with, versus 3.74% without).

To determine whether these differences in control subject performance masked differences between synesthetes and controls, we compared the performance of each synesthete against their respective control groups. Individual subject comparisons revealed that three of synesthetes (JAC, $t(12) = 5.04$, $p < 0.001$; DAC, $t(12) = 4.97$, $p < 0.001$; and AAD, $t(12) = 3.56$, $p < 0.01$) performed better than controls on this task. However, the other three synesthetes showed no performance difference (EAB, $t(12) = -0.05$, ns; CHP, $t(12) = -1.33$, ns; and DW, $t(12) = 1.34$, ns).

An analysis of the crowding data showed that control subjects presented with colored displays performed significantly better than control subjects presented with black and white displays ($F_{(1,142)} = 185.86$, $p < 0.0001$), replicating previous research (Kooi et al., 1994). When we compared performance on the colored displays, we found no group differences in performance ($F_{(5,66)} = 1.64$, $p > 0.05$), suggesting that the effect of colors was strong enough to reduce the differences in difficulty due to the different graphemes used. When we compared the performance of our synesthetes versus the performance of control subjects presented with colored displays, we found that synesthetes performed significantly worse than controls ($F_{(1,76)} = 17.93$, $p < 0.0001$), again suggesting that the effect of synesthetic colors is weaker than the effect of real colors.

Interestingly, those synesthetes who performed better than controls on this crowding experiment show a trend toward better performance on the embedded figures task (experiment 1) ($r = 0.60$, $p = 0.16$; see Figure

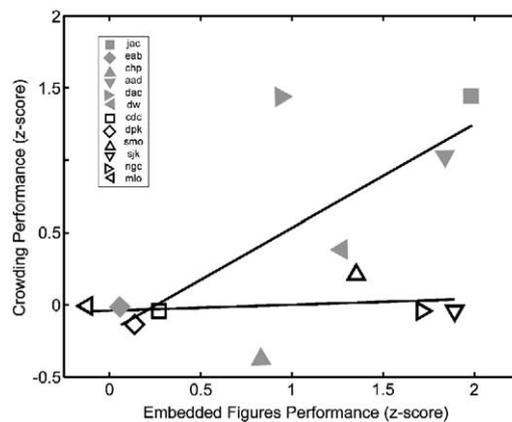


Figure 3. Correlation between Behavioral Measures in Synesthetes and Controls

The x axis indicates performance on the embedded figures task (as a z score), while the y axis indicates performance on the crowding task (as a z score). Gray symbols indicate synesthetes, compared against their respective control groups, while open symbols indicate the control subjects who participated in both the psychophysical and imaging experiments compared against the same control group as the synesthetes. Each symbol indicates one subject (see legend), and corresponding symbols indicate subjects who participated in the same version of the experiment. Synesthetes show substantial variability in both the embedded figures and crowding tasks, which is highly correlated. Control subjects, on the other hand, uniformly perform poorly on the crowding task, despite substantial variability on the embedded figures task.

3), suggesting that the two tasks may be assessing the same underlying psychological process in these synesthetes. Because correlations with small sample sizes tend to be overestimates, and this is only a trend, this correlation should be treated with caution. However, the data from the crowding task suggest a separation of synesthetes into two groups: those that perform significantly better than nonsynesthetes, and those that do not. While the data from the embedded figures task suggest a more continuous gradient of performance (and perhaps underlying experience), it should be stressed that those that perform well on one task also perform well on the other, a topic we will return to in the Discussion.

One concern is that these two tasks may indeed be tapping into a common process, but that it may have nothing to do with synesthesia. Perhaps those who perform better than controls simply have better perceptual abilities, and this would lead to improved performance on visual tasks, irrespective of whether or not the subject experiences synesthesia. In order to rule out this alternative explanation, we tested two of our synesthetes (JAC and EAB) on a variant of our embedded figures task, in which we present them with figures composed, not of graphemes, but of nonlinguistic symbols, such as “&,” “\$,” and “#,” which do not elicit colors for any of our synesthetes. Neither of them showed any differences from control subjects on this task (data not shown).

Experiment 3: fMRI Measurements of Synesthetic Experience

In experiment 3, we tested the hypothesis that grapheme-color synesthesia arises through cross-activation

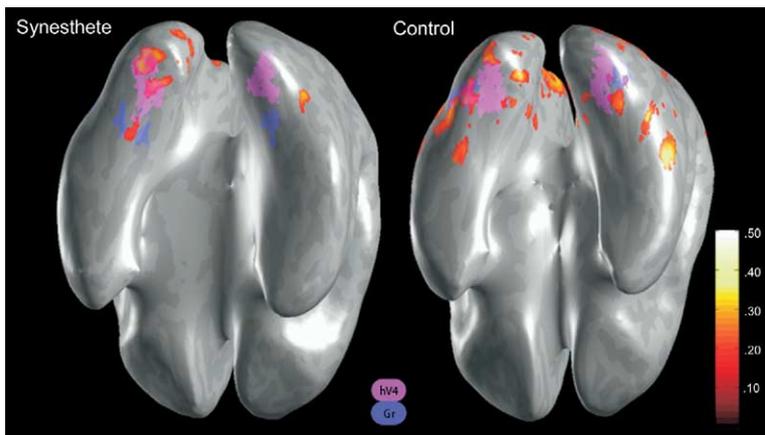


Figure 4. fMRI Ventral Surface Activation in Synesthetes and Controls to Graphemic versus Nongraphic Stimuli

Inflated cortex of a representative synesthete and a representative control subject showing color-selective area hV4 in purple and the grapheme region of interest in blue. Average BOLD signal correlation from eight letter/number scans is shown. Only data with a correlation greater than 0.20 ($p < 0.05$) are shown. Spatial blurring of activity was done only for purposes of data visualization; blurring was not performed on raw BOLD data during analysis (see Figure 5). Data from the synesthete and the control both show activation in the grapheme region. In addition to the grapheme activation, the synesthete shows clear activation of hV4, which is absent in the control subject.

of color-selective areas through the use of fMRI. If grapheme-color synesthesia depends on color-selective area hV4, we would expect to find significant activity in these areas when synesthetes, but not control subjects, view graphemes compared with viewing non-linguistic symbols. We compared fMRI responses in six synesthetes and six nonsynesthetic control subjects in four separate scans, (1) retinotopic mapping, (2 and 3) defining and measuring responses in grapheme-selective regions, and (4) measuring color responses.

Grapheme Scans: Behavioral Results

In our scans defining grapheme-selective areas, we measured behavioral performance on an upright versus italic discrimination (see Experimental Procedures). Overall behavioral performance in the scanner was very good, with nonsynesthetes ($99.37\% \pm 0.91\%$) performing slightly better than synesthetes ($98.76\% \pm 1.30\%$). Although this difference is significant ($F_{(1,142)} = 10.59$, $p < 0.01$), this is probably due to a ceiling effect, which led to extremely low variability for both groups. Furthermore, this difference is opposite to that observed in the fMRI data (see below), arguing against the possibility that the observed differences in BOLD activation are a result of these differences in behavioral performance. No differences were observed between letters ($99.06\% \pm 1.17\%$), numbers ($99.34\% \pm 1.40\%$), and nonlinguistic stimuli ($98.81\% \pm 0.78\%$) or between italic ($99.11\% \pm 1.08\%$) and nonitalic ($99.03\% \pm 1.23\%$) stimuli, arguing that the activations observed below are not due to differences in task difficulty or attention. No interactions between group, font, or symbol type were observed, further arguing against the possibility of modulations of attention or task difficulty, although task difficulty was too low to completely rule this out.

Grapheme Scans: Imaging Results

Inflated brains for one representative control subject and one synesthete are presented in Figure 4. Area hV4 is indicated in purple, and the grapheme ROI is indicated in blue. Note that in the synesthete there is activity in both the grapheme ROI and in hV4 (predominantly in the left for this subject) while for the control subject, there is activity in the grapheme ROI, but not in hV4. This does not seem to be due to overall differences in activation, as numerous other areas were active in the control subject.

Average projected amplitude for all six synesthetes

and six controls is shown in Figure 5. Overall, synesthetes show more activation than nonsynesthetes across all areas ($F_{(1,60)} = 4.30$, $p < 0.05$), and the magnitude of the activation increases across areas ($F_{(5,60)} = 3.17$, $p < 0.05$), with V1 showing the least activation, and the grapheme area showing the greatest activation. Although raw signal amplitude was somewhat greater for synesthetes in all ventral visual areas (V1, V2, V3, and hV4), comparisons of individual ROIs demonstrate that the only area showing significantly greater activation in synesthetes than in nonsynesthetes is area hV4 (bootstrap, $p < 0.05$). In area V3A, along the dorsal visual pathway, we find no difference in activation, arguing against the possibility that synesthetes are simply showing more activation overall. Crucially, we also find no difference in activation in the grapheme ROI between synesthetes and control subjects.

We also find that the magnitude of the BOLD signal correlates with behavioral performance for the crowding task only in hV4 ($r = 0.66$, $p < 0.05$, see Figure 6), but not in the grapheme area ($r = 0.17$) or in area V3A ($r = 0.01$). In early retinotopic areas, there is a trend

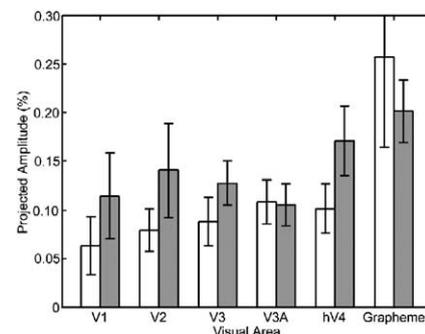


Figure 5. Overall BOLD Response to Graphemes versus Nonlinguistic Symbols

BOLD responses (projected amplitude) for controls, indicated by white bars, and synesthetes, indicated by gray bars, are presented for each region of interest (ROI). Error bars indicate one standard deviation. Areas V1, V2, and V3 include both the ventral and dorsal subdivisions. Area V3A represents an entire hemifield in the dorsal visual pathway. HV4 shows more activation in synesthetes than in nonsynesthetes ($p < 0.05$, bootstrap), while the difference between synesthetes and controls is not significant in other visual areas.

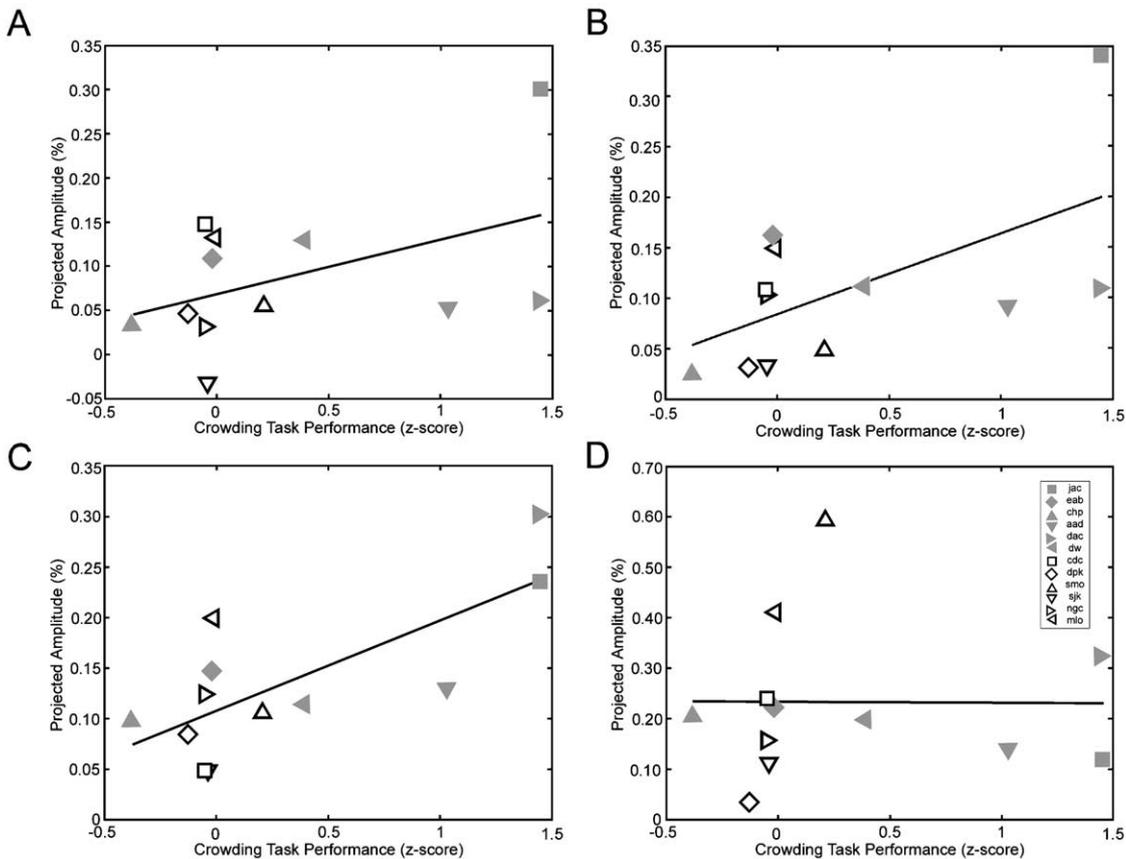


Figure 6. Correlation between Performance on the Crowding Task and fMRI BOLD Responses

Each panel represents a different visual area: V1 (A), V2 (B), hV4 (C), and the grapheme area (D). There is a positive correlation between behavioral performance and BOLD signals in early visual areas, but not in the grapheme area. Synesthetes are indicated by gray symbols, and controls by white symbols.

toward subjects who show better behavioral performance showing greater activation (V1, $r = 0.43$; V2, $r = 0.43$; and V3, $r = 0.50$), with the magnitude of this correlation increasing with increasing level along the visual hierarchy.

Finally, we observed activity in the parietal lobe (especially in the region of the intraparietal sulcus). Visual inspection of the data does not indicate clear differences in the magnitude of the activation between synesthetes and nonsynesthetes, suggesting that this difference may be due to processes that were common between control subjects and synesthetes, as opposed to synesthetic experiences per se. We feel it is premature to make strong claims about the significance of these activations, since this region of the parietal has been variously implicated in orthography-to-phoneme conversion (e.g., Fiez and Petersen, 1998), numerical magnitude processing (e.g., Dehaene et al., 2003; Naccache and Dehaene, 2001), and shifts of attention (for a review see Corbetta and Shulman, 2002). One recent study finds a region of the IPS that is activated by calculation, saccadic eye movements, and orthography-to-phoneme conversion (Simon et al., 2002), suggesting that it is difficult to disentangle the neural loci of these diverse functions using fMRI. Our stimuli al-

ternated between either alphabetic or numeric graphemes, and nonlinguistic symbols. While our use of a behavioral task in the scanner minimizes the possibility of large attentional differences, task difficulty was low enough that there may have been small differences in attention or task difficulty. Therefore, all three parameters may have varied in our study, any of which could have caused the observed parietal activation.

Color Scans

BOLD signal from the average of seven color scans (red-teal gratings alternating with black-white gratings) for synesthetes and controls is shown in Figure 7. Control subjects are indicated by white bars and synesthetes by gray bars. As can be seen here, area hV4 was strongly activated by colors in both synesthetes and controls, while early visual areas were less activated, consistent with previous literature and consistent with our findings of greater activation in those synesthetes who show the best behavioral performance. Finally, we find no differences between synesthetes and controls in their responses to colors ($F_{(1,60)} = 1.81$, $p > 0.15$), arguing against the possibility that our finding of activation of hV4 by graphemes in synesthetes reflects gross anatomical or functional differences in the neural substrate of color processing.

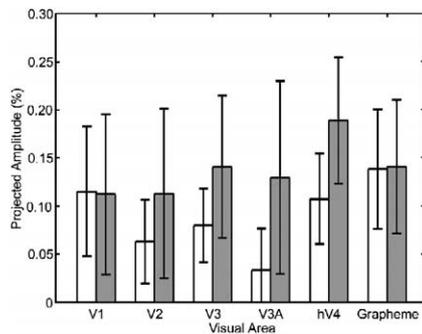


Figure 7. Overall BOLD Response to Colored versus Luminance Gratings

Projected amplitude for controls, indicated by white bars, and synesthetes, indicated by gray bars, are presented for each region of interest (ROI). Error bars indicate one standard deviation. As can be seen here, there are no significant differences in responses to colors between synesthetes and controls.

Discussion

Although synesthesia has been known for centuries (e.g., Galton, 1883), early research on the phenomenon often proceeded simply by classifying the experiences of synesthetes. With the rise of behavioristic approaches in psychology, the purely introspective, subjective reports of synesthetes were ignored by mainstream psychology. However, with increased interest in consciousness and its neural basis (see, e.g., Crick, 1994; Crick and Koch, 1998; Churchland, 2002), the study of synesthesia has once again become scientifically respectable (for discussion of the philosophical implications of synesthesia, see Gray et al., 1997; Gray et al., 2002). A growing body of evidence suggests that, at least for some synesthetes, their synesthetic colors are real, that they have verifiable perceptual consequences (Palmeri et al., 2002; Ramachandran and Hubbard, 2001a; Smilek et al., 2001), and that their brains respond differently than nonsynesthetes' brains when hearing words (Nunn et al., 2002; Paulesu et al., 1995) or when viewing graphemes (current study).

In this study, we tested the perceptual reality of synesthetic colors using a combination of behavioral and neuroimaging techniques. Our results suggest that not only do synesthetic colors lead to improved behavioral performance in a manner similar to real colors, but they also activate color-selective regions of cortex in a manner similar to real colors. Because this study uses both psychophysical and neuroimaging measures in the same subjects in the study of synesthesia, we are able to examine specific aspects of synesthetic experience that previous studies have not been able to address. At a group level, we find that two independent metrics of synesthetic colors, psychophysical metrics, as measured through behavioral performance improvements, and neural metrics, measured through the level of fMRI responses in color-selective hV4, both support the claim that synesthetic colors are evoked at a perceptual stage of processing. Second, the strong correlation on an individual subject basis suggests that it is the

degree of hV4 activation that leads to the synesthetic colors and that the strength of this activation directly influences the strength of the synesthetic colors. These results suggest that hV4 is the neural locus of the colors perceived by grapheme-color synesthetes and furthermore add indirect support to the cross-activation hypothesis that we have previously proposed (Ramachandran and Hubbard, 2001a; Ramachandran and Hubbard, 2001b).

Finally, we find greater activity in early visual areas in synesthetes than controls, but this is highly variable across synesthetes. Although this activation did not reach significance at the group level (consistent with Nunn et al., 2002), some synesthetes show significantly greater activation in V1 to graphemes than to nonlinguistic symbols (consistent with the single case results of Aleman et al., 2001). These results suggest that the contradictory results in the literature regarding the presence of activity in V1 may be due to important differences between synesthetes.

One concern is that our neuroimaging results reflect attentional modulation, rather than color-selective effects, since stimuli were easily discriminable, and some attentional resources may have been available to paying attention to synesthetic color percepts. This was a design decision made early in this study. In general, paradigms seeking to control attention (e.g., Saenz et al., 2002) vary the stimulus intensity (e.g., color saturation) for each subject to obtain 80% correct performance. This type of manipulation allows careful control of attention and permits the use of within-subjects, between-conditions comparisons, but would confound the between-subjects comparisons we wanted to make here. That is, we could have gained greater control of the subject's attentional state only at the cost of between-subjects stimulus differences, which themselves might have led to different levels of BOLD signal change.

However in addition to finding no difference between controls and synesthetes in V3A, where we expected to find no difference, we also find no difference between synesthetes and controls in the grapheme areas. Given that this region is further along the ventral pathway than hV4 and that it is likely the most task-relevant area, we would predict that grapheme areas should be more strongly modulated if our results were due to attention.

Additionally, while numerous studies have shown increased responses in the ventral visual pathway when subjects attend to external colors (e.g., Barrett et al., 2001; Corbetta et al., 1990), top-down processes such as mental imagery fail to induce similar modulations in the absence of a physical stimulus (Howard et al., 1998). Since there was no colored stimulus in our grapheme scans, it seems unlikely that our hV4 activation is due to these top-down processes. Similarly, Nunn et al. (2002) examined the possibility that the difference in V4v/V8 activation in their synesthetes and control subjects was due to word-color associations. However, even with extensive training, their control subjects failed to show activation of V4v/V8, further arguing against the possibility that differences between synesthetes and controls is due to top-down influences.

In addition to finding an overall group difference between synesthetes and controls, we also find that

across subjects, improved psychophysical performance is positively correlated with fMRI responses in retinotopic visual areas, with the magnitude of the correlation becoming stronger at higher levels of the cortical hierarchy. This correlation may arise for two different reasons. First, it is possible that these two different metrics tap into common underlying differences in the strength of synesthetic colors. That is, perhaps some synesthetes simply experience stronger colors than others, and these two different metrics both demonstrate this difference in the strength of synesthetic colors (and indeed, suggest that hV4 is the specific neural locus for their origin).

Second, it is possible that these data represent small samples from two different subtypes of synesthetes, which we have previously dubbed “higher” and “lower” synesthetes (Ramachandran and Hubbard, 2001b) and which Smilek and Dixon (2002) have called “associator” and “projector” synesthetes. In higher/associator synesthetes, it may be the numerical *concept* that is critical for eliciting the synesthetic colors, while in lower/projector synesthetes, it is the *percept* of the physical grapheme that is critical for eliciting the synesthetic colors. Phenomenological reports from synesthetic subjects in our crowding paradigm are consistent with this division (see Ramachandran and Hubbard, 2001b). Synesthete JAC, for example, reported that although he could not identify the crowded grapheme, he was able to identify it on the basis of the perceived color. However, other synesthetes, such as EAB, who did not show a behavioral improvement on either perceptual task, reported that she did not experience her synesthetic colors until after she had identified the target letter, and so therefore was not able to use her synesthetic colors to aid her performance on this task.

Preliminary ERP data using a mismatch paradigm on four of the six synesthetes tested here (JAC, CHP, AAD, and DAC) further suggest qualitative differences between synesthetes (Sagiv et al., 2003). Sagiv et al. presented one of two letters in either the congruent or incongruent color. By averaging ERP responses to congruent and incongruent stimuli (irrespective of letter or color) they were able to determine the time course of the mismatch responses in these four synesthetes. Interestingly, the earliest differences mirrored the pattern of psychophysical and fMRI responses observed in this study. JAC and DAC both showed the earliest ERP divergence, at about 90 ms post-stimulus onset, while AAD showed a divergence at around 170 ms post-stimulus onset, and CHP at around 300 ms post-stimulus onset.

These data argue against the possibility that the differences we have reported in this study are simply a result of differences in the strength of activation across synesthetes, but instead suggest that synesthetes may constitute a highly heterogeneous group. However, given the relatively small sample size, it is premature to assert that synesthetes fall into two distinct groups. Our data may represent the endpoints on a continuum, or a sample from three or even four different groups. This heterogeneity has profound implications for studies of synesthesia that simply group together data from multiple synesthetes and treat them as if they all come from a homogenous population. The use of single

case studies in synesthesia is also of concern because the results obtained with one synesthete may not generalize to other synesthetes. Future studies of synesthesia will need to take into consideration this variability.

Experimental Procedures

Subject Recruitment

Synesthetic subjects were recruited via newspaper advertisements in the UCSD Guardian and other San Diego area newspapers. Synesthetic subjects were also recruited through cross-campus collaboration with Noam Sagiv and Lynn Robertson in the UC Berkeley Psychology Department. Advertisements were kept intentionally nonspecific to reduce the probability of confabulation. Control subjects were UCSD undergraduate students. Subjects were paid or were provided partial course credit for each hour of their time. This method of recruiting subjects allowed us to control for age, education level, and other relevant subject variables. Experiments 1 and 2 were approved by the UC San Diego IRB/HRPP program, and experiment 3 was approved by both the UC San Diego IRB/HRPP and the Salk Institute Human Subjects Program.

Validating Self-Reports of Synesthetic Experience

The most common and currently accepted method for assessing the validity of self-reports of synesthesia is to ask for color-matching judgments at two widely separated times (e.g., 6 months to 1 year). Consistency for synesthetic observers overall is approximately 90% (some synesthetes were perfect), while it is on the order of 20%–30% for control subjects (Baron-Cohen et al., 1993; Mattingley et al., 2001). The reliability of synesthetic reports indirectly suggests that they are validly reporting some experience that is different from nonsynesthetes.

We assessed self-reports by asking each synesthete to match color chips to the colors experienced when presented with various letters or numbers. Each synesthete was retested approximately 6 months from the date of the first interview, without prior warning. Synesthetic subjects chose the same or very similar colors after the 6 month period (data not shown). The low probability of remembering the synesthetic associations means that it is unlikely that any of our synesthetic observers are confabulating. This high level of consistency, and the subject's willingness to participate, were the only criteria that we used to include subjects in this study.

Experiment 1: Embedded Figures Task

Displays composed of 44 to 48 black graphemes (each $0.6^\circ \times 0.8^\circ$) on a white background were presented for 1 s. Because we have previously found that synesthetic colors can be modulated by the presence of the monitor edge (Ramachandran and Hubbard, 2001a), the display did not make use of the full screen, but instead used the central $13.2^\circ \times 10.0^\circ$ area, indicated by a black outline. Embedded forms, composed of six to eight graphemes that elicited red, green, blue, or yellow percepts, were presented in randomly selected locations within the central portion of the screen and were approximately 6° to 7° wide and 4° to 5° high.

Stimuli were presented on a Sony ViewSonic E773 17 inch monitor (1024×768 , 75 Hz), using Macromedia Director 8.5. Subjects were seated 24 inches (60 cm) from the screen in a chair with armrests, which limited lateral movement. Because we have previously found that contrast affects the strength of synesthetic colors (Hubbard et al., 2005) we presented all stimuli at high contrast (black characters, 0.0 cd/m^2 on a white background 65.3 cd/m^2 , measured with a Tektronix J18 photometer).

Subjects were presented with 8 blocks (two of each target grapheme) of 32 trials for a total of 256 trials. Within each block of trials, the target shape appeared randomly at one of eight locations (from the top left to the bottom right corner). For each block of the same target graphemes, displays were different, such that the exact position of the target form and distractor graphemes differed. Order was counterbalanced between control subjects using a simplified Latin square design (five subjects per order), while all synesthetes were arbitrarily run in the first order.

Subjects were instructed at the beginning of each block which grapheme would compose the embedded figure (i.e., their search target) and were told to indicate the shape formed by this target letter (square, diamond, rectangle, or triangle) by pressing the appropriate key on the keyboard (s, d, r, or t) using their left hand. They were also shown a sample display, but were not provided with practice trials. Prior to each trial, a warning cross was presented, although subjects were not required to fixate throughout the trial.

For each of the six synesthetes, 20 control subjects were tested on the same task to determine baseline performance and to assess potential differences in task difficulty. An additional 20 control subjects per synesthete were tested to assess the magnitude of the perceptual enhancement expected as a result of the synesthetic colors. We presented displays identical to those used in the black and white condition, except that now each grapheme was presented in the color selected by each synesthete as the best match to his or her experience.

Experiment 2: Crowding Task

In order to assess the magnitude of crowding, subjects were presented with a cross composed of five graphemes. Graphemes were chosen so that they elicited red, green, yellow, or blue color experiences in each of our synesthetes. Crosses were composed of one central target grapheme and four flanking graphemes (above, below, and on both sides of the target grapheme). On any given trial, all four flanking graphemes were identical, but because we used a complete 4×4 factorial design, the identity of the flankers provided no information as to the identity of the target grapheme.

Displays were randomly presented either to the left or right of fixation (7.1°). Since it has been shown that crowding occurs equally well for both short and long presentation durations, we presented displays for 100 ms to reduce the possibility of eye movements, after which the screen was blanked for 250 ms to avoid any masking effects. Graphemes were presented in Arial font and subtended a visual angle of $1.2^\circ \times 1.6^\circ$, with edge-to-edge spacing of 0.2° . Center-to-center spacing of the letters averaged 1.4° . Based on these parameters, we can be relatively certain the target grapheme was strongly crowded (cf. Chung et al., 2001).

Subjects identified the grapheme at the center of the cross by making a four-alternative forced-choice response via key press on the computer keyboard and were not given feedback. Each subject participated in 8 blocks of 32 trials each (16 stimulus combinations on both sides of fixation) for a total of 256 trials. No practice trials were provided. Since different graphemes were used for each of our synesthetes, we tested a separate group of 12 unselected undergraduate subjects for each of the six synesthetes. All other aspects of this experiment (monitor, viewing distance, etc) were identical to those in experiment 1.

Experiment 3: fMRI Measurements of Synesthetic Experience

fMRI Data Acquisition

Functional MRI data were acquired using a Siemens Vision 1.5 T scanner at University of California, San Diego's Thornton hospital, using a small flex coil and a low-bandwidth echo-planar imaging sequence. During each scan, 140 temporal frames were acquired over 280 s (TR 2 s, flip angle 70° , 3×3 mm in-plane resolution, 16 coronal slices of 3 or 4 mm thickness). The first 20 temporal frames (40 s) were discarded to avoid magnetic saturation effects and to make certain that subjects were in a consistent behavioral state during scanning. Six to eight scans were acquired from each subject during each scanning session. Each scanning session ended with an anatomical scan, used to align all functional data across multiple scanning sessions to a reference volume, allowing us to identify predefined ROIs in each data set. Stimulus presentation was synchronized with fMRI data acquisition using a custom-made phototransistor-based trigger that detects a light indicator on the scanner keyboard.

Retinotopic Mapping Experiments

In the first scanning session, we used traditional retinotopic stimulation and cortical flattening techniques (Engel et al., 1994; Sereno et al., 1995) to identify early, retinotopically organized visual areas (V1, V2, etc.) for each subject. We measured fMRI responses to black and white contrast reversing rotating wedge and expanding

ring stimuli and marked the reversals in the direction of movement of the induced wavefronts of activity. Based on previous literature, we define the human homolog of macaque V4 as hV4, which consists of a full 180° representation of the contralateral hemifield (see the Supplemental Data available with this article online). The locations of the boundaries can be measured across repeated experiments to an error of 2–4 mm of cortex (Engel et al., 1997).

fMRI data from subsequent scanning sessions were then registered with the subject's high-resolution anatomical images using a least-squares fitting procedure, which determines the optimal rotation and translation matrices. This registration, when combined with the map from the gray matter to the flattened representation, provided a mapping between a session's fMRI data and the flattened map. This map is one-to-one so that a subject's visual areas, defined in the flattened representation, can be projected into the in-plane images from a given scanning session. Thus, fMRI data from pixels that define a region of interest, such as area V1, can be easily manipulated. We used these predefined regions as our ROIs for each individual subject for all subsequent scans.

Defining Grapheme-Selective Areas

In two subsequent scanning sessions, we localized and measured responses in grapheme-responsive regions for both control and synesthetic subjects using methods similar to those used by Pesenti et al. (2000). The first session was used to define the grapheme-selective regions, while the second was used to measure responses. fMRI responses to graphemes and nongraphic stimuli were measured using a standard block-design paradigm. Stimuli were 2.15° tall white (670 cd/m^2) letters, numbers, and nonlinguistic characters (courtesy of Mauro Pesenti, see Pesenti et al., 2000) on a neutral gray background (330 cd/m^2) square of 11.13° . The remainder of the screen was black (5.5 cd/m^2). In one half of each block (counterbalanced within and across subjects, eight scans per session), letter or number stimuli were presented at a rate of one every 2 s for a total of 20 s. Nongraphic stimuli were presented every 2 s in the other half of each block. Six 40 s blocks were repeated for each scan, lasting a total of 4 min. To control for attention and arousal, 50% of the stimuli (graphemic and nongraphic) were presented in italic font. Subjects indicated which stimuli were shown in italic font via button press. All subjects ran in at least four practice blocks on the behavioral task prior to scanning. fMRI responses in phase with the presentation of graphemic stimuli were shown on flattened representations of each subject's occipital lobe. We defined the grapheme areas as regions that showed a significantly positive response to graphemes, but which lie outside the boundaries of classical retinotopically organized visual areas.

Measuring Color Responses

In a fourth scanning session, we identified brain regions that respond to color modulations using methods and stimuli similar to those of Hadjikhani et al. (1998). All subjects participated in a single session comprising seven scans (one subject participated in eight scans). Subjects were presented with six 40 s blocks, repeated for each scan, lasting a total of 4 min. Slowly rotating isoluminant teal-red radial sinusoidal gratings (mean chromaticity, white) were presented for 20 s alternating with black-white gratings (10 cd/m^2 to 645 cd/m^2) for 20 s. For each subject, isoluminance for the chromatic gratings was determined using heterochromatic flicker photometry (Boynton, 1988; Boynton and Kaiser, 1968) using the same projector and screen that were used in the subsequent color scans. Mean luminance of the chromatic grating varied between subjects (range 301 – 382 cd/m^2), but was near to the mean luminance of the black-white grating (327 cd/m^2). Activity maps showing responses in phase with the color stimuli were then shown on flattened representations of each subject's occipital cortex.

Response Amplitude

A sequence of functional images was acquired while the two conditions alternated for six 40 s cycles (240 s). Functional MR response was quantified by (1) dividing each voxel's time series by its mean intensity, (2) subtracting any linear trend from each voxel's time series, (3) averaging the time series over a set of voxels corresponding to a particular brain region, and (4) calculating the amplitude of the response relative to a fixed 35° phase delay, which is equivalent to a 4 s delay in a 40 s period (Boynton et al., 1996). Additionally, since the stimuli did not cover the entire visual field, we further restricted our ROI by presenting a black and white con-

trast reversing checkerboard stimulus matched to the size of the stimuli. This reference scan also served as a baseline response to assess hemodynamic lag (phase) and to measure maximal response (amplitude) for each visual area. All reference scan phases were near to 35° (0° difference), thus confirming the appropriateness of the fixed delay (see [Supplemental Data](#) section 2).

We then measured the magnitude of the hemodynamic response as a result of letter and number stimulation in these predefined, restricted ROIs. Responses in phase with the number/letter stimuli would indicate brain regions that responded preferentially to the number/letter stimuli, while responses out of phase with the number/letter stimuli would indicate brain regions that responded more strongly to the nonlinguistic stimuli. Since these stimuli were equated for low-level visual complexity, we predicted that we would see little or no activity in early visual areas. Additionally, since the stimuli were white on a gray background, we would predict no color-specific activity in color-selective region hV4 in controls.

Supplemental Data

The Supplemental Data that accompanies this article can be found at <http://www.neuron.org/cgi/content/full/45/6/975/DC1>.

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