Neurocognitive Mechanisms of Synesthesia

Review

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Synesthesia is a condition in which stimulation of one sensory modality causes unusual experiences in a second, unstimulated modality. Although long treated as a curiosity, recent research with a combination of phenomenological, behavioral, and neuroimaging methods has begun to identify the cognitive and neural basis of synesthesia. Here, we review this literature with an emphasis on grapheme-color synesthesia, in which viewing letters and numbers induces the perception of colors. We discuss both the substantial progress that has been made in the past fifteen years and some open questions. In particular, we focus on debates in the field relating to the neural basis of synesthesia, including the relationship between synesthesia and attention and the role of meaning in synesthetic colors. We propose that some, but probably not all, of these differences can be accounted for by differences in the synesthetes studied and discuss some methodological implications of these individual differences.

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 feeling tactile shapes while tasting foods (Baron-Cohen and Harrison, 1997; Cytowic, 1989). One of the most common, and intensely studied, forms of synesthesia is grapheme-color synesthesia (Day, 2005), in which viewing letters or numbers elicits the experience of colors. For our synesthete JAC, looking at the letter E will elicit the experience of a red photism, or colored overlay, while viewing an O elicits a blue percept. Other synesthetes report that they do not actually see these colored photisms but rather just "know" that a particular letter is a particular color, whereas still others report experiencing specific colors but say that the color is experienced somewhere within their "mind's eye" (Dixon et al., 2004; Flournoy, 1893; Ramachandran and Hubbard, 2001b).

Although synesthesia was first investigated over one hundred years ago (Galton, 1880a, 1880b, 1883), the study of synesthesia has since been largely treated as a curiosity in psychology and neuroscience (for a historical overview, see Marks [1975]). Recently, this trend has reversed, and a new generation of psychologists and neuroscientists has begun to take notice of synesthesia (Ramachandran and Hubbard, 2001b; Rich and Mattingley, 2002; Robertson and Sagiv, 2005). In this review, we will focus on four major topics: (1) genetic, cognitive, and perceptual studies that have been conducted in the past fifteen years; (2) neural models of synesthesia; (3) functional imaging studies of synesthesia; and (4) the role of individual differences in explaining some of the apparently contradictory results in the perceptual and neuroimaging literature.

Genetic Components of Synesthetic Experience

Early research demonstrated that synesthesia is a familial trait (Baron-Cohen et al., 1996; Galton, 1883) and suggested that it is more common in women than in men (Baron-Cohen et al., 1996), perhaps through an X-linked dominant mode of inheritance (Bailey and Johnson, 1997). However, the exact genetic loci remain to be identified, and preliminary results from a molecular genetic study of synaesthesia indicate that synaesthesia may not be solely X linked (J.E. Asher, personal communication). When large-scale random sample studies are carried out, there is no gender bias, suggesting that early studies suffered from an underreporting by male subjects (J. Simner, personal communication). Other recent findings, including a pair of monozygotic twins who were discordant for synesthesia (Smilek et al., 2002) and data suggesting that synesthesia can skip generations (Hubbard and Ramachandran, 2003) are hard to reconcile with dominant transmission. In sum, recent data suggest that the genetic mechanisms underlying synesthesia may be more complex than the straightforward X-linked dominant account proposed by early researchers.

Similarly, the estimated prevalence of synesthesia has varied dramatically, between as many as 1 in 20 (Galton, 1883) and as few as 1 in 25,000 (Cytowic, 1989). The most widely cited study to date suggests that synesthesia occurs in at least 1 in 2000 people (Baron-Cohen et al., 1996), although this is now generally regarded as an underestimate. Our own informal samples have suggested that the prevalence of grapheme-color synesthesia might be between 1 in 200 (Ramachandran and Hubbard, 2001b) and 1 in 100 (Mulvenna et al., 2004). Subsequent large-scale studies have suggested that the prevalence of synesthesia might be as high as 1 in 20 across all forms and 1 in 100 for grapheme-color synesthesia (J. Simner, personal communication). This high prevalence argues against the notion that synesthesia is merely a "benign cognitive variant" (see Ward and Mattingley, 2005) and instead suggests that it is a widespread phenomenon that may provide novel insights into the neural basis of the mind (Ramachandran and Hubbard, 2001b).

Test-Retest Consistency in Synesthesia

In addition to showing that synesthesia is a familial trait, early behavioral studies indicated that individual synesthetes are consistent across time in their color associations (greater than 90% consistent over test-retest intervals of up to one year) and that their color associations tend to be highly specific (Baron-Cohen et al., 1993, 1996; Mattingley et al., 2001). Recently, using a "Revised Test of Genuineness" (TOG-R), Asher et al. (2005) have further demonstrated the reliability of

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synesthetic color reports. Using calibrated color samples that allow a quantitative measurement of the match between testing sessions, they demonstrated that consistency measures for synesthetes and controls formed two distinct nonoverlapping populations. These measures thereby provide an objective method for identifying synesthetes, although whether this should be treated as a definitional feature or an associated one remains open to debate (Ward and Mattingley, 2005).

Cognitive Studies of Synesthesia

Although studies of consistency are useful in differentiating between synesthetes and nonsynesthetes, they are too coarse to allow exploration of the cognitive, perceptual, and neural bases of synesthesia. Consistency tells us that there is some difference between synesthetes and nonsynesthetes, but it does not tell us exactly what that difference is. In the past five years, there has been an explosion of studies examining these questions with more sophisticated behavioral techniques. With modified Stroop interference paradigms, recent research has shown that synesthesia is automatic and perhaps obligatory (Dixon et al., 2000; Lupiañez and Callejas, 2005; Mattingley et al., 2001; Mills et al., 1999; Odgaard et al., 1999; Wollen and Ruggiero, 1983). In the standard Stroop paradigm, color names are presented in colored ink, such as the word RED printed in either red or green ink ("congruent" and "incongruent," respectively). Responses in the incongruent condition are typically much slower than in the congruent condition. Because the task has nothing to do with reading the word, the interference shows that reading the word is automatic (MacLeod, 1991).

Similarly, in the "synesthetic Stroop" paradigm, graphemes are presented in either congruent or incongruent ink colors for each synesthete. For a synesthete who sees 7 as yellow, a 7 presented in yellow would be congruent, and a 7 presented in any other color would be incongruent. The consistent finding that synesthetes are slower in the incongruent condition than in the congruent condition demonstrates that synesthetic colors are automatic and not under voluntary control. Subsequent research has shown that synesthetic Stroop interference can be induced simply by thinking about or imagining the eliciting stimulus when it is the solution to a math problem (Dixon et al., 2000; Jansari et al., 2005) and can be eliminated by masking the target grapheme before presenting a colored grapheme (Mattingley et al., 2001). One open question is the degree to which suppression of synesthetic colors is possible, as measured by negative priming (Lupiañez and Callejas, 2005; Odgaard et al., 1999).

Psychophysical Studies of Grapheme-Color Synesthesia

Although Stroop interference demonstrates automaticity, interference alone does not distinguish between perceptual or conceptual processes (MacLeod, 1991) because it can be induced through trained associations (Elias et al., 2003; MacLeod and Dunbar, 1988). To address the question of whether synesthetic colors are perceptual or conceptual, numerous groups have designed perceptual experiments in which synesthetic colors may be expected to either help or hinder performance, depending on the exact design. Although the number of paradigms has increased recently, the most extensively utilized methods fall into two broad categories: search-related and masking-related paradigms.

Search-Related Paradigms

The most commonly used strategy to test synthetic colors is to adapt a visual search task. In our previous research, we adapted a texture segregation task to present subjects with displays in which one of four shapes (4-AFC) composed of a target grapheme was embedded in a background of distracter graphemes. In this task, synesthetes were significantly more accurate than control subjects in identifying which of the target shapes was presented (see Figure 1A). We initially tested two synesthetes (Ramachandran and Hubbard, 2001a) and later expanded this sample to six synesthetes in an improved design (Hubbard et al., 2005a). We find that, in five out of six subjects, their synesthetic colors aid in performance on this task, consistent with the idea that synesthetic colors are evoked early in perceptual processing.

In another early study, Smilek et al. (2001) report two experiments that demonstrate that a number is harder to identify and localize when the background color is congruent with the synesthetic color than when it is incongruent. For example, a "blue" 4 is detected faster when presented against a red background than against a blue background (Figure 1B). This interference effect also suggests that synesthetic colors must be elicited at early stages of perceptual processing in order for the color to interfere with the detection of the target grapheme.

Subsequently, Palmeri et al. (2002) showed that synesthetic colors can aid in the detection of a singleton grapheme in a traditional visual search paradigm, in which reaction times were measured as a function of the number of distracters (Figure 1C). When synesthetic colors differed between target and distracter (searching for a 2 among 5s), their synesthetic subject was much more efficient in his visual search. When the target and distracter elicited similar colors (searching for a 6 among 8s), search was much less efficient. In control subjects, no such difference was observed.

However, in another recent study, 14 synesthetes and matched controls were tested on a visual search task similar to that employed by Palmeri et al., but none of them demonstrated parallel search (Edquist et al., 2005). Two of the synesthetes showed a degree of perceptual enhancement, but none of their subjects demonstrated truly preattentive search functions. These results suggest that previous results showing strong perceptual pop-out may not be true of all synesthetes but rather only a small proportion of synesthetes (see below).

Two other recent studies have suggested that the relationship between attention and synesthesia may be more complex than originally thought. Laeng et al. (2004) tested a single synesthete in a synesthetic visual search paradigm. When slopes were calculated as a function of number of distracters, they found evidence of improved search efficiency for the synesthete relative to controls. However, when reaction times were analyzed as a function of eccentricity, the search time advantage occurred only for eccentricities of less than 10°, suggesting that perceptual enhancement might occur only within the "functional field of attention." In another variant of the visual search paradigm, Sagiv et al. (2005)

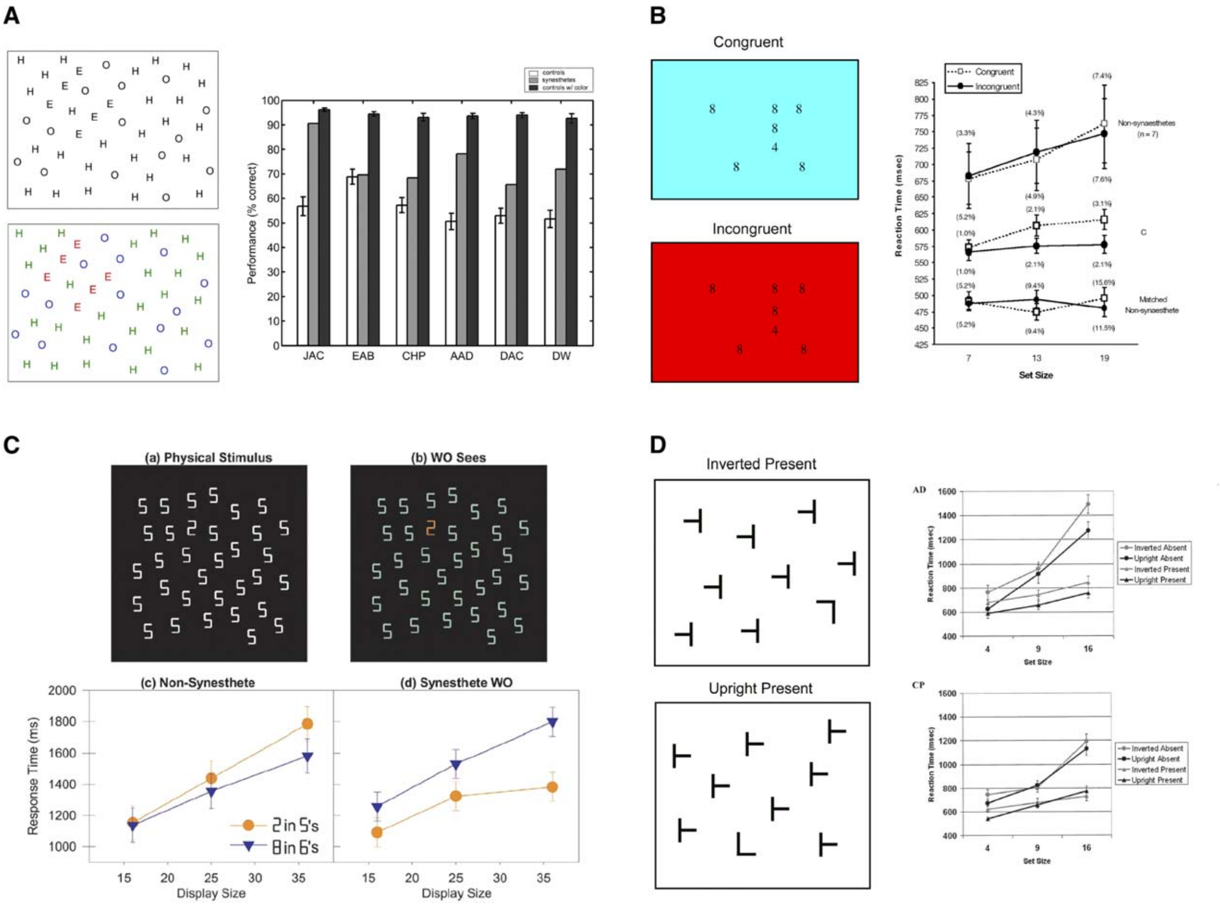

Figure 1. Visual Search Paradigms in Synesthesia

(A) The left panel shows a representative screen shot illustrating stimuli and our rendition of what it may have appeared like for subject JAC. The right panel shows behavioral performance for our six synesthetes. 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 (from Hubbard et al. [2005a]).

(B) A visual search paradigm in which the background could either be congruent or incongruent with the synesthete's experienced colors. As can be seen here, synesthete C shows a clear difference in her search performance as a function of background color, although no such difference was observed for controls. Error bars indicate the SEM (adapted from Smilek et al. [2001]).

(C) Another visual search paradigm in which search for graphemes that elicited dissimilar colors (a 2 among 5s) was differentially improved compared for a search for graphemes that elicited similar synesthetic colors (an 8 among 6s). Error bars indicate the SEM (from Palmeri et al. [2002]).

(D) Data showing that at least some of the improvement found in previous studies may come from faster rejection of distracters. In the upright conditions (both target present and target absent), absolute search times were improved for synesthete AD, whereas no such difference was observed for synesthete CP. Note that AD and CP in this panel are referred to as AAD and CHP in (A). Error bars indicate the SEM (adapted from Sagiv et al. [2005]).

presented two synesthetes with targets that elicited synesthetic colors against a background of rotated letters that did not induce synesthetic colors (Figure 1D). In this "inverted" condition, they found no perceptual enhancement in either of the two subjects, although they found improved performance in synesthete CP in the upright condition, suggesting that at least part of the enhancement observed in early studies was due to faster rejection of the distracters, rather than detection of the target.

Masking-Related Paradigms

Studies of synesthesia have also used a variety of masking paradigms to explore the level at which synesthetic colors are elicited. Using a crowding paradigm, we investigated whether synesthetic colors could aid in the identification a peripheral target grapheme under conditions where control subjects were unable to identify the target (Ramachandran and Hubbard, 2001b). Graphemes presented in the periphery are difficult to identify when crowded by other, flanking graphemes, an effect known as crowding (Bouma, 1970; He et al., 1996). This effect is attenuated by presenting the target in a different color than the flankers (Kooi et al., 1994). We originally reported that two synesthetic subjects were significantly better at identifying the target grapheme than controls (Ramachandran and Hubbard, 2001b). However, subsequent research with a sample of six synesthetes demonstrated that these effects may not generalize to all synesthetes (Hubbard et al., 2005a).

Contrary to these findings, Mattingley et al. (2001) showed that synesthetic Stroop interference was eliminated when conscious awareness of the grapheme was eliminated by pattern masking (for critiques, see Blake et al. [2005] and Smilek et al. [2005]). They tested a group of 15 synesthetes on a modified synesthetic Stroop paradigm, by presenting a forward pattern mask, a target grapheme, and then a backward pattern mask composed of six colored symbols that were either congruent or incongruent with the synesthetic colors experienced by their synesthetes for the target grapheme. The graphemes were presented for different durations such that subjects either could (at 500 ms) or could not (at 28 and 56 ms) identify the grapheme. When graphemes were presented for 500 ms, a clear Stroop interference was observed. However, when graphemes were presented for 28 or 56 ms, no such interference was observed.

However, Wagar et al. (2002) have shown that object substitution masking, which occurs late in processing (Enns and Di Lollo, 1997), does not eliminate the experience of synesthetic colors, even though it does eliminate conscious recognition of graphemes in control subjects. In a single synesthetic subject, C, the deleterious effect of object substitution masking on identifying a masked grapheme was much less than in any of their eight control subjects. One important difference is that recognition of graphemes seems to require focused attention to bind the elements together, whereas color is generally thought of as a basic feature (e.g., Triesman and Gelade [1980]).

Potential Explanations of These Contradictions

Overall, these studies demonstrate the perceptual reality of synesthetic colors; however, almost every published study has been met by a counter study that produces apparently contradictory results with a different group of synesthetes and a different paradigm. There are at least three possible interpretations of these results. First, a growing body of evidence suggests that there is substantial variability in synesthetes (Dixon et al., 2004; Hubbard et al., 2005a; Smilek and Dixon, 2002) and that these differences are likely to account for some of the conflicting results in the literature. We suggest that the reality of substantial individual differences needs to be taken into consideration in evaluating "failures" to replicate or partial replications (see also Dixon and Smilek [2005]). This is especially important given that perhaps only 10% of synesthetes are "projector" synesthetes (Dixon et al., 2004), in whom we would expect to find these low-level perceptual effects (see below). The same synesthetes need to be tested with different paradigms to determine whether some of the contradictory results in the literature are due to individual differences between synesthetes or differences in experimental paradigms.

To date, there is only one example where the same synesthetes have been tested with the different paradigms by different investigators. Four of the six synesthetes we tested with our behavioral and fMRI paradigms (Hubbard et al., 2005a) have also been tested by Sagiv and colleagues with ERPs (Sagiv et al., 2003), and two of them have been tested by behavioral methods (Sagiv et al., 2005). In this case, data from several paradigms (crowding task, fMRI BOLD signal, and ERP signals; see below) correlated, whereas other measures (the embedded figures task and visual search with rotated distracters) did not (compare Figures 1A and 1D). Despite the diverging conclusions these two studies reached about the role of attention synesthetic visual search, the pattern of differences is stable between the two studies, with AAD showing a greater behavioral advantage than CHP. Although these results suggest that individual differences will not resolve all of the contradictory results in the literature, until this is tested more explicitly, it is premature to decide whether contradictory results are due to differences in synesthetes, differences in testing methods, or some combination of both.

Second, even for those rare subjects in whom synesthetic colors occur relatively early in visual processing, they may not be strictly preattentive. Paradigms that test strict preattentive processing may fail to find effects of synesthetic colors, whereas paradigms that test for early visual processes, such as texture segregation, may find effects of synesthetic colors (Treisman, 2005). This may help to reconcile much of the contradictory literature by suggesting that although they are elicited early in processing, synesthetic colors are not equivalent to real colors in the external world. This is consistent with our findings that synesthetic colors were not as effective as real colors in enhancing performance on our embedded figures and crowding tasks (Hubbard et al., 2005a).

Finally, it is possible that the dichotomous view of attentional processes as either pre- or postattentive is too simple, and synesthesia simply highlights the inadequacies of the dichotomous distinction. Both psychophysical (Pashler, 1998; Wolfe, 1994) and neuroimaging studies (for a review, see Kastner and Pinsk [2004]) suggest that attention may operate at multiple levels. We suggest that some measure of distributed attention may be required to elicit synesthetic experiences but perhaps not the same degree required to bind highly confusable letter segments. Future studies will have to investigate the possibility that hybrid models of attention, such as Guided Search (Wolfe, 1994), will better explain the apparent contradictions in the psychophysical literature.

Neural Models of Synesthesia

Based on these and other results demonstrating the reality of synesthetic experiences, it becomes natural to speculate about its neural basis. To date, there have been two, somewhat parallel discussions concerning the neural substrate of synesthesia. The first of these discussions has taken place at the neurophysiological level and has centered on the question of whether synesthetic experience arises from a failure of neural pruning or some form of disinhibition (compare Ramachandran and Hubbard [2001a] and Grossenbacher and Lovelace [2001]). The second discussion has taken place at the architectural level. Three architectural models have been proposed to date, which we will refer to here as "local crossactivation," "re-entrant processing," and "long-range disinhibited feedback." These two orthogonal questions might be best thought of as a two by three table, illustrated in Table 1.

Despite their logical independence, not all combinations of possible mechanisms have been proposed. Although we have suggested that our model could involve disinhibition of feedback, we have tended to think in terms of excess anatomical connections, which are normally pruned in development (Hubbard and Ramachandran, 2003; Hubbard et al., 2005a; Ramachandran and Hubbard, 2001a, 2001b). At the other end of the spectrum, the long-range feedback theory tends to be

Table 1. Theories of the Neural Basis of Synesthesia

	Local Crossactivation	Re-Entrant	Feedback
Anatomical connections	Ramachandran and Hubbard, 2001a; Hubbard et al., 2005; Maurer, 1997	Smilek et al., 2001	Armel and Ramachandran, 1999
Disinhibition		Smilek et al., 2001	Grossenbacher, 1997; Grossenbacher and Lovelace, 2001

Along the rows are the neurophysiological mechanisms proposed to account for synesthesia, and the columns indicate the architectural accounts. References in individual cells indicate representative publications that have advocated these positions.

couched in terms of disinhibition of feedback (Grossenbacher, 1997; Grossenbacher and Lovelace, 2001), although an unusual case of acquired synesthesia because of blindness might be due to axonal sprouting, given the long time required for the emergence of this form of synesthesia (Armel and Ramachandran, 1999). Finally, re-entrant processing models are neutral as to the possible low-level neurophysiological substrates but could be reconciled with either excess connectivity or with disinhibited feedback.

Local Crossactivation

Based on the fact that the visual word form area (VWFA; for a review, see Cohen and Dehaene [2004]) lies adjacent to color processing region hV4 (Wade et al., 2002), we have proposed that grapheme-color synesthesia may arise from direct crossactivation between these adjacent brain regions (Hubbard et al., 2005a; Ramachandran and Hubbard, 2001a, 2001b). Our hypothesis builds on previous work suggesting that phantom limb sensations may arise through cortical reorganization in amputees (Ramachandran and Hirstein, 1998; Ramachandran et al., 1992). Crucially, these cortical-to-cortical connections led to systematic perceptual experiences of having the missing limb stimulated through stimulation of the still-present facial nerves, and these novel perceptual experiences were reproducible and involuntary. We suggest that synaesthesia arises through a mechanism of crossactivation similar to that observed in phantom limb patients, and this crossactivation leads to reproducible, involuntary, systematic perceptual experiences (Hubbard and Ramachandran, 2003).

One potential mechanism for this would be the observed prenatal connections between inferior temporal regions and area V4 (Kennedy et al., 1997; Rodman and Moore, 1997). In the fetal macaque, approximately 70%–90% of the connections are from higher areas (especially TEO), whereas in the adult, approximately 20%–30% of retrograde-labeled connections to V4 come from higher areas (Kennedy et al., 1997). If a genetic mutation were to lead to a failure of pruning of these prenatal pathways, connections between the VWFA and hV4 would persist into adulthood, leading to the experience of color when viewing numbers or letters (see also Baron-Cohen et al. [1993] and Maurer [1997]). Although being adjacent to each other increases the likelihood of brain regions being connected to each other, we suggest that it is the presence or absence of such early connections that is important, not the fact that brain regions are adjacent per se.

Long-Range Disinhibited Feedback

Other studies have suggested that synesthesia may be due to disinhibited feedback from a "multisensory nexus" such as the temporo-parietal-occipital junction (Armel and Ramachandran, 1999; Grossenbacher, 1997; Grossenbacher and Lovelace, 2001). One piece of evidence in favor of the long-range model comes from the study of a patient, PH, who became blind at the age of 40 because of retinitis pigmentosa (Armel and Ramachandran, 1999). After a period of 2 years of blindness, PH began reporting that tactile stimuli elicited the subjective impression of seeing visual movement. Interestingly, the intensity of the tactile stimulation required to induce synesthetic photisms was greater when his hand was held in front of his face than when it was held behind his face, suggesting some sort of top-down multisensory activation, perhaps mediated by parietal structures.

Another piece of evidence in favor of the disinhibited feedback theory is that at least some people report synesthetic experiences while under the influence of psychedelics (see e.g., Shanon [2002]). However, the experiences of congenital synesthetes, despite some superficial similarities with the experiences in drug-induced synesthesia, may arise from different mechanisms (Hubbard and Ramachandran, 2003). In particular, the experiences of congenital synesthetes are typically generic (Cytowic, 1989), whereas the experiences generated by psychedelics are often complex (Shanon, 2002). Similarly, the effects of psychedelics tend to be systemic, whereas congenital synesthesia typically involves highly precise mappings (like the letter A being a very specific shade of red). In the absence of some mechanism to account for these phenomenological differences, we find it difficult to see how congenital and drug-induced synesthesia could arise from a common mechanism.

Re-Entrant Processing

Finally, something of a hybrid model has been suggested (Myles et al., 2003; Smilek et al., 2001), in which grapheme-color synesthesia has been suggested to be due to aberrant re-entrant processing (perhaps consistent with models of disinhibited feedback). Smilek et al. propose that in addition to the forward sweep of activity from V1 to V4, to posterior and then anterior inferior temporal regions (PIT and AIT, respectively), aberrant neural activity from AIT feeds back to representations in PIT and V4, leading to the experience of synesthetic colors. The main evidence used to argue in favor of this theory over the crossactivation theory is the fact that visual context and meaning influence the experienced colors in synesthesia (Dixon and Smilek, 2005; Myles et al., 2003; see also Ramachandran and Hubbard [2001b] and Rich and Mattingley [2003]).

However, the presence of behavioral top-down modulations cannot distinguish between the local crossactivation and re-entrant models of synesthesia because neither model has been specified with sufficient

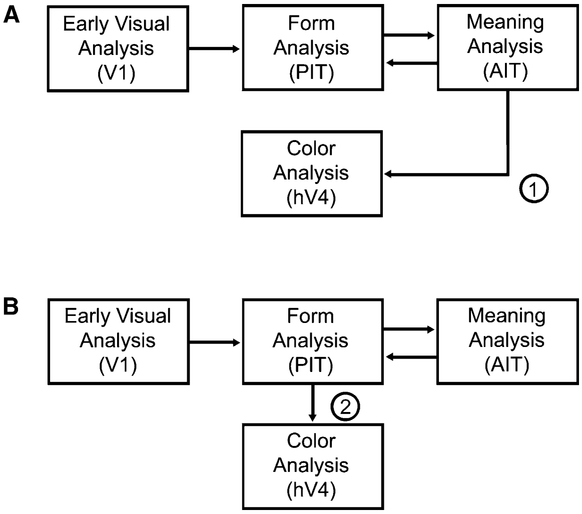

Figure 2. Mechanisms whereby Feedback Could Affect Synesthetic Colors

In (A), suggested by Smilek et al. (2001), meaning (processed in AIT) directly influences synesthetic colors via direct feedback connections to V4 (circle 1). In (B), as suggested here, meaning indirectly influences synesthetic colors, only after it has biased form analysis in PIT (circle 2).

precision (see Figure 2). Feedback is ubiquitous in the visual system (Felleman and Van Essen, 1991); the main difference between the models is how feedback is thought to modulate synesthetic colors. To account for the presence of contextual modulations, the reentrant model suggests that neural signals propagate back to V4 (labeled 1 in Figure 2A), and in parallel, this activation influences the recognition of the grapheme in PIT thereby leading to the influence of meaning on synesthetic colors. The crossactivation model can account for these contextual modulations by assuming that the same feedback mechanisms that are already present, and that can account for top-down modulations in nonsynesthetic observers (McClelland and Rumelhart, 1981), are also present in synesthetes. Once those mechanisms are in place, activation from AIT can directly bias the firing of neurons in PIT, such that the responses of these neurons differ. The different pattern of PIT (VWFA) neuronal firing will crossactivate a different population of V4 neurons, leading to both the percept of a different grapheme and a different synesthetic experience (labeled 2 in Figure 2B).

Multiple Neural Mechanisms

Of course, these proposals are not necessarily mutually exclusive. One instructive lesson may come from studies of phantom limbs, in which a similar debate between "unmasking" and "sprouting" occurred (see Ramachandran and Hirstein [1998] for a review). In some cases, phantoms sensations are experienced less than 24 hr after amputation, implying the unmasking of existing, previously inhibited connections (Borsook et al., 1998). However, longitudinal studies of amputees show that the organization of the point-to-point correspondence between facial trigger zones and phantom limb sensations in the arm develops slowly after amputation, suggesting the development of new neural connections (Ramachandran and Hirstein, 1998). A similar interplay between preserved connectivity and disinhibited feedback may be present in synesthesia, leading to the observed mixture of occasional synesthetic effects in the general population and the specificity of the experiences of congenital synesthetes.

Different Neural Mechanisms for Different Synesthetes

Another possibility is that a "one size fits all" approach may fail to capture the variability in synesthetic experiences. Different neural theories have focused on different types of synesthesia, with the local crossactivation and re-entrant feedback theories focusing on grapheme-color synesthesia, whereas the feedback models have focused on word-color and tone-color synesthesia. It is quite likely, given that graphemes, phonemes, music, and colors are processed by different brain regions, that forms of synesthesia have different architectural substrates. However, the fact that synesthetes within the same family may inherit different forms of synesthesia (Ward and Simner, 2005) suggests that common neurophysiological mechanisms may be shared across different forms of synesthesia.

Functional Imaging Studies

Although there have been numerous neuroimaging studies of synesthesia, they have yielded somewhat inconsistent results. Using PET, Paulesu et al. (1995) presented 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. In a follow-up fMRI study, Nunn et al. (2002) tested six female, right-handed, word-color synesthetes and six matched nonsynesthetes. They 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 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. In a case study of a synesthete who experiences person-color synesthesia, hearing names that elicited synesthetic colors led to activity in left extra-striate cortex (near V4), but not V1 (Weiss et al., 2001). Another case study of a word-color synesthete reports activation of anatomically defined V1 but the authors were unable to determine if V4 was active (Aleman et al., 2001). Yet another recent study failed to find increased activation in the fusiform gyrus during synesthetic experiences but did find enhanced activity in the intraparietal sulcus (Weiss et al., 2005), a region thought to be crucial for binding of color and form (Robertson, 2003).

In sum, most studies of 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, remains unclear. These conflicting results may be due to methodological differences between the studies, differences between synesthetes studied, or differences in the strength of the colors experienced by the different synesthetes. To investigate this question, we obtained both

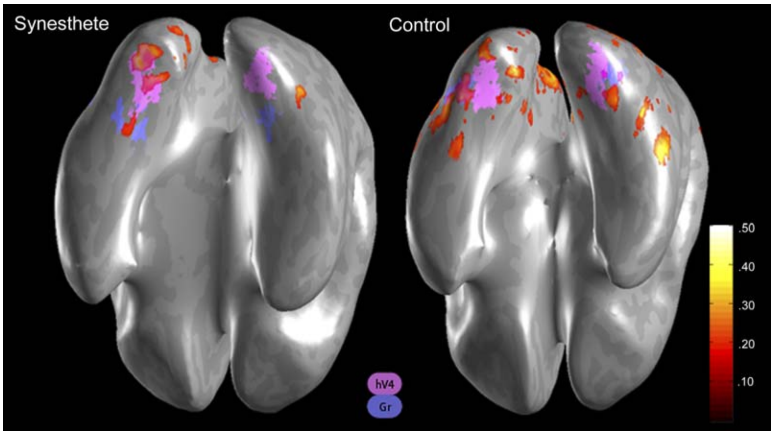

Figure 3. FMRI Data from Representative Control and Synesthetic Subject

Ventral view of two inflated brains, with hV4 indicated in purple and the grapheme area indicated in blue. 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. For details see Hubbard et al. (2005a).

behavioral 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 (Hubbard et al., 2005a). In our behavioral experiments, described above, we found that a subject's synesthetic experience can aid in texture segregation and reduce the effects of crowding. We then used standard fMRI retinotopic mapping techniques to identify individual visual areas in six synesthetes and controls. When presented with white on gray letters and numbers, compared against nonlinguistic symbols that did not elicit colors, we observed larger fMRI responses in hV4 in synesthetes compared with control subjects (Figure 3). Importantly, we found a positive correlation within subjects between the behavioral and fMRI results (Figure 4). Subjects with better performance in the behavioral experiments showed larger fMRI responses in early retinotopic visual areas (V1, V2, V3, and hV4). Importantly, the variability we observed here is not purely random noise. Rather, our behavioral crowding task correlates not only with our embedded figures task but also with our fMRI responses measured in hV4 and ERP measurements collected on a subset of the subjects tested here. The stability of these differences across different paradigms argues for stable individual differences, which may help to explain some of the contradictory results in the literature.

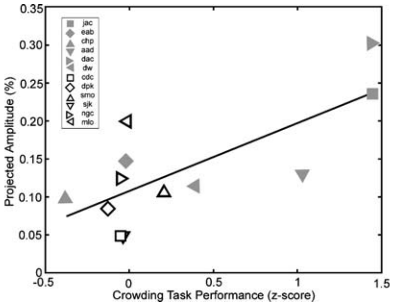

Figure 4. Correlation between Behavioral Performance on the Crowding Task and fMRI Responses in hV4

Filled symbols indicate synesthetic subjects, whereas open symbols indicate control subjects. As can be seen here, synesthetes showed substantial variability in both behavioral and performance and fMRI response. Controls, on the other hand, performed universally poorly and showed overall lower responses in hV4 (from Hubbard et al. [2005a]).

Another recent study measured fMRI BOLD responses in four synesthetes in retinotopically defined V1–V4 to graphemes that elicited synesthetic colors versus those that did not (Sperling et al., 2005). Overall, they found greater activation in V4 when synesthetes were presented with graphemes that caused them to report seeing colors than when presented with graphemes that did not. Interestingly, Sperling et al. report a hint of individual differences but in the opposite direction from what we find. Those synesthetes that report the most spatially localized photisms showed less activation than those who reported diffuse photisms. However, unlike our study in which we restricted our analysis to only voxels that responded to the same retinal location where stimuli were presented, Sperling et al. measured responses across the entire retinotopic region, raising the possibility that a few highly active voxels were averaged with many other nonactive voxels for those synesthetes who report strong focal experiences, leading to a reduced mean response in those subjects with the most localized photisms.

Activation of Early Retinotopic Areas in Grapheme-Color Synesthesia

Our behavioral and fMRI results suggest not only that synesthetic colors affect behavioral performance in a manner similar to real colors but also that they also activate color-selective regions of cortex in a manner similar to real colors. As mentioned above, we find that across subjects, improved psychophysical performance is positively correlated with fMRI responses in retinotopic visual areas, including hV4. Although this brain-behavior correlation did not reach significance in early visual areas, such as V1 and V2, it is interesting to note that subjects that showed the greatest behavioral performance in our crowding task also showed the greatest degree of activation in these early visual areas. These results are consistent with three alternative proposals.

First, these results could be due to increased specificity of color processing in the ventral visual stream, consistent with models of color processing that suggest an increasing neural specialization for color processing from V1 blobs through V2 thin stripes to V4 (Livingstone and Hubel, 1984, 1987; Tootell et al., 2004). Alternatively, it could be that the neural mechanisms of synesthesia involve two components: local crossactivation between grapheme regions and hV4 and top-down feedback pathways with early visual areas. If so, the increased activation in V1 (presumably mediated by feedback pathways) might be important for explaining the synesthetic performance observed here. In synesthetes who were experiencing more highly spatially localized photisms, the degree of target localization (and corresponding behavioral performance) would increase, consistent with the idea that V1 may serve as a high-resolution buffer for spatial information in perception (Lee et al., 1998) and imagery (Kosslyn and Thompson, 2003). Finally, it must be noted that the strength of the synesthetic experience (presumably elicited in hV4), which varied between synesthetes, might evoke differential attention to the synesthetic colors, which would itself activate V1 (Gandhi et al., 1999; Martinez et al., 1999). Unfortunately, given the temporal resolution of current techniques, these are questions that cannot be answered definitively with our data. Future studies will need to examine these questions more precisely.

Uni- or Bidirectional?

Related to the question of feedback is the question of whether synesthesia is uni- or bidirectional. Although conscious synesthetic experiences are manifestly unidirectional (e.g., from numbers to colors) (Ramachandran and Hubbard, 2003), two recent studies have investigated the question of whether there might be some bidirectionality in synesthetic activation, even if it is insufficient to reach conscious awareness (Cohen-Kadosh et al., 2005; Knoch et al., 2005). Cohen-Kadosh et al. took advantage of the numerical distance effect, in which numbers that are far apart (large magnitude difference) are responded to more quickly than numbers that are close together, and a synesthetic congruity effect. By presenting a pair of numbers that are far in distance but are presented in colors associated with a closer pair of numbers ("small color distance"), responses should be slowed in the synesthete group (but not the control group) if numerical magnitude is automatically activated. Similarly, for pairs that are numerically close but are presented in colors associated with a farther pair ("large color distance"), responses should be facilitated in the synesthete group but not the control group. In two synesthetic subjects, responses were facilitated by a large color distance in the small number condition but were not interfered with by the small color distance in the large number condition.

Although intriguing, further research will be required to link these findings up with detailed neuroanatomical models of synesthesia. For example, given that numerical magnitude information is represented in the region of the left angular gyrus and bilateral IPS (see e.g., Dehaene et al., 2003), would these effects be found only in "higher" synesthetes? Another question raised by these findings is why synesthetic experience is uniformly unidirectional, despite the implicit bidirectionality demonstrated here. Two possible explanations suggest themselves. First, it may be that an object of some sort is required to bind the synesthetic experiences (Ramachandran and Hubbard, 2003; Robertson, 2003). For example, when a number evokes a color, there is something in the visual image to which the color can be ascribed. On the other hand, were a color to evoke a number, the number may not be able to be represented as a stimulus with physical properties of size, distance, and the like. By using numerical tasks, the studies described above may have provided an object for the activation to bind to, if only a cognitive one. Second, it may be that the connections leading to synesthetic experience are of the appropriate strength or form to reach conscious awareness, whereas the connections that support bidirectional effects are not. How, and why, certain neural activity becomes conscious is being actively investigated (Crick and Koch, 1998; Dehaene and Naccache, 2001). Competing proposals suggest that activity reaches conscious awareness when activity in either early sensory areas or in a global neural workspace exceeds a certain threshold. Future studies will be required to further clarify these issues.

Common or Special Mechanisms?

One final question is whether synesthesia depends on mechanisms shared by everyone or whether it depends on special mechanisms that are unique to synesthetes (Blakemore et al., 2005; Ward et al., 2005). Ward et al. have shown that tone-color associations share common mechanisms with nonsynesthetic pitch-lightness associations, replicating prior work (Hubbard, 1996; Marks, 1975). Based on this, they argue that synesthesia depends on mechanisms of auditory-visual correspondence common to us all not on pruning of neonatal pathways (e.g., Baron-Cohen et al. [1993]). Similarly, Blakemore et al. (2005) have reported a case of synesthesia in which observed touches are experienced as felt touches on the corresponding body part. Using fMRI, they were able to measure activity in cortical networks related to the mirror neuron system involved in self-other mapping. The synesthete showed activity in the same regions as the nonsynesthetes but showed greater activity in this network than any of the eight control subjects, leading Blakemore et al. to also suggest that this form of synesthesia depends on mechanisms present in us all but that they are active to a greater degree.

As we have noted previously, the same mechanisms present in synesthetes are likely to be present to a lesser degree in nonsynesthetes and could account for the "conceptual rightness" of certain cross-sensory mappings, such as mapping a jagged visual shape with a jagged sound (Ramachandran and Hubbard, 2001b) or associating high pitches with bright lights (Hubbard, 1996; Marks, 1975). Perhaps there is some degree of pruning of perinatal pathways, but the degree of pruning differs between synesthetes and nonsynesthetes (recall that even in the normal adult macaque, the pruning is not all or none). If the pathways are only slightly pruned, the activity would be greater and, therefore, could enter into conscious awareness. However, if the pathways are heavily pruned only a residual activation may remain, which may be sufficient for establishing cross-sensory mappings but insufficient to reach conscious awareness.

Individual Differences in Synesthetes

Based on our recent brain-behavior correlations and the behavioral results by Dixon and colleagues, we argue that the experiences of different synesthetes are systematically different (Dixon et al., 2004; Hubbard et al., 2005a; Ramachandran and Hubbard, 2001b; Smilek and Dixon, 2002). Smilek and Dixon refer to differences in the locus of the experienced colors as either "out in space" or "in the mind's eye," which they term projector and associator synesthetes, respectively. They show that synesthetes grouped into the two different categories on the basis of self-report also show different patterns of Stroop interference. Specifically, for projector synesthetes, naming the color of the ink in which a grapheme was presented induced greater Stroop interference than naming the photism color, whereas for associator synesthetes, the opposite pattern was observed (Dixon et al., 2004).

We have proposed an alternative classification of these synesthetes (Ramachandran and Hubbard, 2001b; Hubbard et al., 2005a), based not only on differences in the experience of where the synesthetic concurrent is experienced but also on the basis of differences in the triggers, or inducers, of synesthetic experience. We suggest that there might be two groups of synesthetes, which we term "lower" (referring to lower perceptual processes) and "higher" (referring to higher cognitive processes) synesthetes, in whom the different forms of synesthesia arise at different stages of processing. Much as memory research gradually fractionated from a unified concept of "memory" into the now widely accepted "multiple memory systems" view that allowed these processes to be better tied to neural substrates (for a recent historical review, see Squire [2004]), we believe that advances in understanding synesthesia will require a further fractionation of our concepts of synesthesia.

Given the already existing neurocogntive models of processes such as reading and numerical cognition, two of the most common triggers of synesthetic experience, we may be able to predict what this deeper understanding of synesthesia will look like. The Dual-Route Cascade model for reading (Coltheart et al., 2001) and the Triple-Code model of numerical cognition (Dehaene, 1992; Dehaene et al., 2004) each contain less than a half-dozen nodes, connected by approximately a dozen pathways. By combining these models of synesthetic triggers with the known neural basis of synesthetic concurrents, we may be able to constrain potential neural substrates of synesthesia to a small subset of these nodes and thereby explain the individual differences observed in synesthesia. Although we have previously focused on the neural substrates of numerical cognition (Ramachandran and Hubbard, 2001b), our higher-lower distinction shares much with the neurocognitive model developed by Rich and Mattingley (2002) based on models of cognitive and neural processes involved in reading. The main difference between these two proposals is that we suggest different nodes as the site of crossactivation for different synesthetes, whereas Rich and Mattingley remain agnostic about potential subtypes and their neural correlates.

If our hypothesis about the importance of adjacency is correct, then we would predict that different classes of inducers would lead to different classes of synesthetic concurrents. For example, perceptual processing of graphemes may elicit strong, externally projected photisms, whereas processing of numerical concepts may elicit internally experienced sensations of color. In lower synesthetes, we suggest that crossactivation may occur between adjacent regions of the fusiform gyrus involved in letter recognition and color processing, whereas higher synesthesia may arise from crossactivation in the parietal cortex, particularly in the region of the angular gyrus, the ventral intraparietal area, and the lateral intraparietal area (Hubbard et al., 2005b). We suggest that crossactivation in the region of the parietal lobe may explain synesthetic number forms, in which numerical (and other ordinal sequences) are experienced as having specific locations in space, in addition to colors (Hubbard et al., 2005b; Ramachandran and Hubbard, 2001b).

One prediction of this model is that for lower synesthetes but not higher synesthetes, synesthetic color intensity should be modulated by low-level visual properties of the inducer, such as contrast and font, which we have recently observed in a single synesthete (Hubbard et al., 2005). Crucially, this synesthete, JAC, performed best in our psychophysical tasks and showed the greatest activation of early visual areas in our imaging paradigm (Hubbard et al., 2005a). Another prediction is that different synesthetes should show different patterns of fMRI and ERP responses. Recently, a late-blind synesthete who experienced colors both for letters and for months of the year was tested using fMRI (Steven et al., 2005). When presented with Braille letters that elicited synesthetic colors, activation was found in the fusiform gyrus in the synesthete but not in a late-blind control subject. In a second task, Steven et al. showed that when (for example) "March" was used to refer to months, it elicited increased activation in the region of the angular gyrus, but not in the fusiform gyrus, in the synesthetic subject. Similarly, preliminary ERP data with a mismatch paradigm on four of the six synesthetes tested by Hubbard et al. (2005a) further suggest qualitative differences between synesthetes (Sagiv et al., 2003). The earliest ERP differences mirrored the pattern of psychophysical and fMRI responses observed in our study (see Hubbard et al. [2005a] for details).

Finally, it should be noted that the extent to which the projector/associator and lower/higher distinctions map onto each other is an open empirical question. One possibility is that higher synesthetes would be more likely to experience colors in their mind's eye and, therefore, demonstrate weaker perceptual effects. We would therefore predict that higher synesthetes would be more likely to be classified as associators. Another possibility is that the projector/associator distinction captures differences in the strength of experiences within what we would refer to as lower synesthetes. It is even possible that these dimensions are orthogonal, such that there could be a "higher" synesthete with strong externally projected photisms, although we consider this unlikely. Additional research will be needed to answer these questions.

Methodological Considerations

We would also like to comment briefly on the subject of single-case versus group studies. These methodological questions are linked to the question of individual differences because single-case approaches are more likely to highlight differences, whereas group studies are more likely to highlight commonalities. We believe that synesthesia research can profit from using both single-case and group approaches. However, we must be cautious when interpreting the results of these approaches. Results from a single case may not generalize to other synesthetes (especially given the rarity of some of the stronger manifestations of synesthesia), and indeed, most of the studies that report strong synesthetic effects have used a small number of self-referred synesthetes. However, a failure to find an effect in a group study should be equally treated with caution. If a sample is composed of several subtypes of synesthetes, the variability in the sample may lead to a failure to find significant results, such as in fMRI studies that use random effects analyses. Similarly, if there is only one synesthete in a sample of ten who demonstrates the hypothesized strong manifestations, then a group study will miss a real but rare effect.

We used a third approach, which might best be termed a “multiple-case study” approach, to demonstrate that the positive results found for certain synesthetes were not simply statistical artifacts, observable under specific circumstances with specific subjects (Hubbard et al., 2005a). Rather, the differences we observed were stable across two behavioral paradigms and two brain-imaging techniques (our fMRI results and the ERP results of Sagiv et al. [2003]). Given these converging data showing the stability of these individual differences, we believe that both generalizing from a limited sample or simply lumping all (superficially similar) synesthetes together will lead to contradictory results and failures to replicate (see also Dixon and Smilek [2005]).

One final question raised by this focus on individual differences is if projector or lower synesthetes are so unusual (Dixon et al., 2004), why were they so disproportionately represented in early studies of synesthesia? One factor that may have brought them to researchers' attention is just that unusualness. That is, because their experiences were particularly strong, the synesthetes were more aware of them and, therefore, were more likely to approach researchers (see Palmeri et al. [2002], Ramachandran and Hubbard [2001a], and Smilek et al. [2001]). However, studies that recruit synesthetes from the population at large, such as the larger studies of Mattingley and colleagues (2001), may include a mixture of stronger and weaker synesthetes, leading to the contradictory results discussed above.

Conclusions

Although the study of synesthesia has recently undergone resurgence, a great number of open questions remain. In this review, we have focused on specific questions concerning the behavioral consequences and neural correlates of one form of synesthesia, grapheme-color synesthesia. However, there are a number of other questions that we do not have space to address here. For example, other recent research has begun to address the cognitive consequences of synesthesia for creativity (Mulvenna et al., 2004) and memory abilities (Mills et al., 2005; Smilek et al., 2002). These studies have, to date, been conducted with small samples, and future research will be needed to determine how general these findings are. Additionally, although much of the current research has focused on grapheme-color and tone-color synesthesia, there are many other forms of synesthesia that are just beginning to be explored. We believe that the crossactivation model may be able to explain these other forms as well. For example, auditory word to taste synesthesia may depend on crossactivation between insular regions involved in taste processing and superior temporal and/or frontal regions involved in auditory word comprehension and production (Ward and Simner, 2003), and feeling tactile shapes in response to tastes (Cytowic, 1989) may arise from cross-activation between insular regions and primary somatosensory regions. The neural basis of other forms of synesthesia, such as experiencing personalities for letters and numbers or experiencing temperatures to sounds, remains to be explored. We hope that our explorations into the neural basis of grapheme-color synesthesia will also help to shed light on these other forms of synesthesia.

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References

Aleman, A., Rutten, G.J., Sitskoorn, M.M., Dautzenberg, G., and Ramsey, N.F. (2001). Activation of striate cortex in the absence of visual stimulation: an fMRI study of synesthesia. Neuroreport *12*, 2827–2830.

Armel, K.C., and Ramachandran, V.S. (1999). Acquired synesthesia in retinitis pigmentosa. Neurocase *5*, 293–296.

Asher, J., Aitken, M.R.F., Farooqi, N., Kurmani, S., and Baron-Cohen, S. (2005). Diagnosing and phenotyping visual synaesthesia: a preliminary evaluation of the revised Test of Genuineness (TOG-R). Cortex, in press.

Bailey, M.E.S., and Johnson, K.J. (1997). Synaesthesia: is a genetic analysis feasible? In Synaesthesia: Classic and Contemporary Readings, S. Baron-Cohen, and J.E. Harrison, eds. (Oxford, England: Blackwell), pp. 182–207.

Baron-Cohen, S., and Harrison, J.E., eds. (1997). Synaesthesia: Classic and Contemporary Readings (Malden, MA: Blackwell Publishers, Inc.).

Baron-Cohen, S., Burt, L., Smith-Laittan, F., Harrison, J., and Bolton, P. (1996). Synaesthesia: prevalence and familiality. Perception *25*, 1073–1079.

Baron-Cohen, S., Harrison, J.E., Goldstein, L.H., and Wyke, M. (1993). Coloured speech perception: is synaesthesia what happens when modularity breaks down? Perception *22*, 419–426.

Blake, R., Palmeri, T.J., Marois, R., and Kim, C.-Y. (2005). On the perceptual reality of synesthetic color. In Synesthesia: Perspectives from Cognitive Neuroscience, L. Robertson, and N. Sagiv, eds. (Oxford: Oxford University Press), pp. 47–73.

Blakemore, S.J., Bristow, D., Bird, G., Frith, C., and Ward, J. (2005). Somatosensory activations during the observation of touch and a case of vision-touch synaesthesia. Brain *128*, 1571–1583.

Borsook, D., Becerra, L., Fishman, S., Edwards, A., Jennings, C.L., Stojanovic, M., Papinicolas, L., Ramachandran, V.S., Gonzalez, R.G., and Breiter, H. (1998). Acute plasticity in the human somatosensory cortex following amputation. Neuroreport *9*, 1013–1017.

Bouma, H. (1970). Interaction effects in parafoveal letter recognition. Nature *226*, 177–178.

Cohen-Kadosh, R., Sagiv, N., Linden, D.E.J., Robertson, L.C., Elinger, G., and Henik, A. (2005). When blue is larger than red—implicit activation of magnitude in synesthesia. J. Cogn. Neurosci. *17*, 1766–1773.

Cohen, L., and Dehaene, S. (2004). Specialization within the ventral stream: the case for the visual word form area. Neuroimage *22*, 466–476.

Coltheart, M., Rastle, K., Perry, C., Langdon, R., and Ziegler, J. (2001). The DRC model: a model of visual word recognition and reading aloud. Psychol. Rev. *108*, 204–258.

Crick, F., and Koch, C. (1998). Consciousness and neuroscience. Cereb. Cortex *8*, 97–107.

Cytowic, R.E. (1989). Synaesthesia: A Union of the Senses (New York: Springer-Verlag).

Day, S. (2005). Some demographic and socio-cultural aspects of synesthesia. In Synesthesia: Perspectives from Cognitive Neuroscience, L. Robertson, and N. Sagiv, eds. (New York, NY: Oxford University Press).

Dehaene, S. (1992). Varieties of numerical abilities. Cognition *44*, 1–42.

Dehaene, S., and Naccache, L. (2001). Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. Cognition *79*, 1–37.

Dehaene, S., Piazza, M., Pinel, P., and Cohen, L. (2003). Three parietal circuits for number processing. Cognit. Neuropsychol. *20*, 487–506.

Dehaene, S., Molko, N., Cohen, L., and Wilson, A.J. (2004). Arithmetic and the brain. Curr. Opin. Neurobiol. *14*, 218–224.

Dixon, M.J., and Smilek, D. (2005). The importance of individual differences in grapheme-color synesthesia. Neuron *45*, 821–823.

Dixon, M.J., Smilek, D., Cudahy, C., and Merikle, P.M. (2000). Five plus two equals yellow: mental arithmetic in people with synaesthesia is not coloured by visual experience. Nature *406*, 365.

Dixon, M.J., Smilek, D., and Merikle, P.M. (2004). Not all synaesthetes are created equal: projector versus associator synaesthetes. Cogn. Affect. Behav. Neurosci. *4*, 335–343.

Edquist, J., Rich, A.N., Brinkman, C., and Mattingley, J.B. (2005). Do synaesthetic colours act as unique features in visual search? Cortex, in press.

Elias, L.J., Saucier, D.M., Hardie, C., and Sarty, G.E. (2003). Dissociating semantic and perceptual components of synaesthesia: behavioural and functional neuroanatomical investigations. Brain Res. Cognit. Brain Res. *16*, 232–237.

Enns, J., and Di Lollo, V. (1997). Object substitution: a new form of masking in unattended visual locations. Psychol. Sci. *8*, 135–139.

Felleman, D.J., and Van Essen, D.C. (1991). Distributed hierarchical processing in the primate cerebral cortex. Cereb. Cortex *1*, 1–47.

Flournoy, T. (1893). Des Phénomènes de Synopsie [On the Phenomena of Synopsia] (Genève: Charles Eggimann & Co.).

Galton, F. (1880a). Visualised numerals. Nature *21*, 252–256.

Galton, F. (1880b). Visualised numerals. Nature *22*, 494–495.

Galton, F. (1883). Inquiries into Human Faculty and Its Development (London: Dent & Sons).

Gandhi, S.P., Heeger, D.J., and Boynton, G.M. (1999). Spatial attention affects brain activity in human primary visual cortex. Proc. Natl. Acad. Sci. USA *96*, 3314–3319.

Grossenbacher, P.G. (1997). Perception and sensory information in synaesthetic experience. In Synaesthesia: Classic and Contemporary Readings, S. Baron-Cohen, and J.E. Harrison, eds. (Malden, MA: Blackwell Publishers, Inc.), pp. 148–172.

Grossenbacher, P.G., and Lovelace, C.T. (2001). Mechanisms of synesthesia: cognitive and physiological constraints. Trends Cogn. Sci. *5*, 36–41.

He, S., Cavanagh, P., and Intriligator, J. (1996). Attentional resolution and the locus of visual awareness. Nature *383*, 334–337.

Hubbard, E.M., Manohar, S., and Ramachandran, V.S. (2005). Contrast affects the strength of synesthetic colors. Cortex, in press.

Hubbard, E.M., Arman, A.C., Ramachandran, V.S., and Boynton, G.M. (2005a). Individual differences among grapheme-color synesthetes: brain-behavior correlations. Neuron *45*, 975–985.

Hubbard, E.M., Piazza, M., Pinel, P., and Dehaene, S. (2005b). Interactions between number and space in parietal cortex. Nat. Rev. Neurosci. *6*, 435–448.

Hubbard, E.M., and Ramachandran, V.S. (2003). Refining the experimental lever: a reply to Shannnon and Pribram. J. Consciosness Stud. *9*, 77–84.

Hubbard, T.L. (1996). Synesthesia-like mappings of lightness, pitch, and melodic interval. Am. J. Psychol. *109*, 219–238.

Jansari, A.S., Spiller, M.J., and Redfern, S. (2005). Number synaesthesia: when hearing "four plus five" looks like gold. Cortex, in press.

Kastner, S., and Pinsk, M.A. (2004). Visual attention as a multilevel selection process. Cogn. Affect. Behav. Neurosci. *4*, 483–500.

Kennedy, H., Batardiere, A., Dehay, C., and Barone, P. (1997). Synaesthesia: implications for developmental neurobiology. In Synaesthesia: Classic and Contemporary Readings, S. Baron-Cohen, and J.E. Harrison, eds. (Malden, MA: Blackwell Publishers, Inc.), pp. 243–256.

Knoch, D., Gianotti, L.R., Mohr, C., and Brugger, P. (2005). Synesthesia: when colors count. Brain Res. Cognit. Brain Res. *25*, 372–374.

Kooi, F.L., Toet, A., Tripathy, S.P., and Levi, D.M. (1994). The effect of similarity and duration on spatial interaction in peripheral vision. Spat. Vis. *8*, 255–279.

Kosslyn, S.M., and Thompson, W.L. (2003). When is early visual cortex activated during visual mental imagery? Psychol. Bull. *129*, 723–746.

Laeng, B., Svartdal, F., and Oelmann, H. (2004). Does color synesthesia pose a paradox for early-selection theories of attention? Psychol. Sci. *15*, 277–281.

Lee, T.S., Mumford, D., Romero, R., and Lamme, V.A.F. (1998). The role of the primary visual cortex in higher level vision. Vision Res. *38*, 2429–2454.

Livingstone, M.S., and Hubel, D.H. (1984). Anatomy and physiology of a color system in the primate visual cortex. J. Neurosci. *4*, 309–356.

Livingstone, M.S., and Hubel, D.H. (1987). Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. J. Neurosci. *7*, 3416–3468.

Lupiañez, J.C., and Callejas, A. (2005). Automatic perception and synaesthesia: evidence from colour and photism naming in a Stroop negative priming task. Cortex, in press.

MacLeod, C.M. (1991). Half a century of research on the Stroop effect: an integrative review. Psychol. Bull. *109*, 163–203.

MacLeod, C.M., and Dunbar, K. (1988). Training and Stroop-like interference: evidence for a continuum of automaticity. J. Exp. Psychol. Hum. Percept. Perform. *14*, 126–135.

Marks, L.E. (1975). On colored-hearing synesthesia: cross-modal translations of sensory dimensions. Psychol. Bull. *82*, 303–331.

Martinez, A., Anllo-Vento, L., Sereno, M.I., Frank, L.R., Buxton, R.B., Dubowitz, D.J., Wong, E.C., Hinrichs, H., Heinze, H.J., and Hillyard, S.A. (1999). Involvement of striate and extrastriate visual cortical areas in spatial attention. Nat. Neurosci. *2*, 364–369.

Mattingley, J.B., Rich, A.N., Yelland, G., and Bradshaw, J.L. (2001). Unconscious priming eliminates automatic binding of colour and alphanumeric form in synaesthesia. Nature *410*, 580–582.

Maurer, D. (1997). Neonatal synaesthesia: implications for the processing of speech and faces. In Synaesthesia: Classic and Contemporary Readings, S. Baron-Cohen, and J.E. Harrison, eds. (Malden, MA: Blackwell Publishers, Inc.), pp. 224–242.

McClelland, J.L., and Rumelhart, D.E. (1981). An interactive activation model of context effects in letter perception: part I. An account of basic findings. Psychol. Rev. *89*, 60–94.

Mills, C.B., Boteler, E.H., and Oliver, G.K. (1999). Digit synaesthesia: a case study using a Stroop-type test. Cognit. Neuropsychol. *16*, 181–191.

Mills, C.B., Innis, J.A., Westendorf, T., Owsianiecki, L., and McDonald, A. (2005). Influence of a synesthete's photisms on name recall. Cortex, in press.

Mulvenna, C., Hubbard, E.M., Ramachandran, V.S., and Pollick, F. (2004). The relationship between synaesthesia and creativity. J. Cogn. Neurosci. Suppl. *16*, 188.

Myles, K.M., Dixon, M.J., Smilek, D., and Merikle, P.M. (2003). Seeing double: the role of meaning in alphanumeric-colour synaesthesia. Brain Cogn. *53*, 342–345.

Nunn, J.A., Gregory, L.J., Brammer, M., Williams, S.C.R., Parslow, D.M., Morgan, M.J., Morris, R.G., Bullmore, E.T., Baron-Cohen, S., and Gray, J.A. (2002). Functional magnetic resonance imaging of synesthesia: activation of V4/V8 by spoken words. Nat. Neurosci. *5*, 371–375.

Odgaard, E.C., Flowers, J.H., and Bradman, H.L. (1999). An investigation of the cognitive and perceptual dynamics of a colour-digit synaesthete. Perception *28*, 651–664.

Palmeri, T.J., Blake, R.B., Marois, R., Flanery, M.A., and Whetsell, W.O. (2002). The perceptual reality of synesthetic color. Proc. Natl. Acad. Sci. USA *99*, 4127–4131.

Pashler, H.E. (1998). The Psychology of Attention (Cambridge, MA: MIT Press).

Paulesu, E., Harrison, J.E., Baron-Cohen, S., Watson, J.D.G., Goldstein, L., Heather, J., Frackowiak, R.S.J., and Frith, C.D. (1995). The physiology of coloured hearing: a PET activation study of colour-word synaesthesia. Brain *118*, 661–676.

Ramachandran, V.S., Rogers-Ramachandran, D., and Stewart, M. (1992). Perceptual correlates of massive cortical reorganization. Science *258*, 1159–1160.

Ramachandran, V.S., and Hirstein, W. (1998). The perception of phantom limbs: the D.O. Hebb lecture. Brain *121*, 1603–1630.

Ramachandran, V.S., and Hubbard, E.M. (2001a). Psychophysical investigations into the neural basis of synaesthesia. Proc. R. Soc. Lond. B. Biol. Sci. *268*, 979–983.

Ramachandran, V.S., and Hubbard, E.M. (2001b). Synaesthesia: a window into perception, thought and language. J. Consciousness Stud. *8*, 3–34.

Ramachandran, V.S., and Hubbard, E.M. (2003). The phenomenology of synaesthesia. J. Consciousness Stud. *10*, 49–57.

Rich, A.N., and Mattingley, J.B. (2002). Anomalous perception in synaesthesia: a cognitive neuroscience perspective. Nat. Rev. Neurosci. *3*, 43–52.

Rich, A.N., and Mattingley, J.B. (2003). The effects of stimulus competition and voluntary attention on colour-graphemic synaesthesia. Neuroreport *14*, 1793–1798.

Robertson, L.C. (2003). Binding, spatial attention and perceptual awareness. Nat. Rev. Neurosci. *4*, 93–102.

Robertson, L.C., and Sagiv, N. (2005). Synesthesia: Perspectives from Cognitive Neuroscience (Oxford: Oxford University Press).

Rodman, H., and Moore, T. (1997). Develpment and plasticty of extrastriate visual cortex in monkeys. In Cerebral Cortex, K.S. Rockland, J.H. Kaas, and A. Peters, eds. (New York, NY: Plenum Press), pp. 639–672.

Sagiv, N., Heer, J., and Robertson, L.C. (2005). Does binding of synesthetic color to the evoking grapheme require attention? Cortex, in press.

Sagiv, N., Knight, R.T., and Robertson, L.C. (2003). Electrophysiological markers of synesthesia. J. Cognit. Neurosci. Suppl. *15*, 153.

Shanon, B. (2002). Ayahuasca visualizations: a structural typology. J. Consciousness Stud. *9*, 3–30.

Smilek, D., and Dixon, M.J. (2002). Towards a synergistic understanding of synaesthesia: combining current experimental findings with synaesthetes' subjective descriptions. http://psyche.cs.monash.edu.au/v8/psyche-8-01-smilek.html.

Smilek, D., Dixon, M.J., Cudahy, C., and Merikle, P.M. (2001). Synaesthetic photisms influence visual perception. J. Cogn. Neurosci. *13*, 930–936.

Smilek, D., Dixon, M.J., Cudahy, C., and Merikle, P.M. (2002). Synesthetic color experiences influence memory. Psychol. Sci. *13*, 548–552.

Smilek, D., Moffatt, B.A., Pasternak, J., White, B.N., Dixon, M.J., and Merikle, P.M. (2002). Synaesthesia: a case study of discordant monozygotic twins. Neurocase *8*, 338–342.

Smilek, D., Dixon, M.J., and Merikle, P.M. (2005). Binding of graphemes and synaesthetic colors in grapheme-color synaesthesia. In Synesthesia: Perspectives from Cognitive Neuroscience, L. Robertson, and N. Sagiv, eds. (Oxford: Oxford University Press), pp. 74–89.

Sperling, J.M., Prvulovic, D., Linden, D.E.J., Singer, W., and Stirn, A. (2005). Neuronal correlates of graphemic colour synaesthesia: a fMRI study. Cortex, in press.

Squire, L.R. (2004). Memory systems of the brain: a brief history and current perspective. Neurobiol. Learn. Mem. *82*, 171–177.

Steven, M.S., Hansen, P.C., and Blakemore, C. (2005). Neural activity associated with visual synesthesia elicited by different levels of analysis of the inducing stimulus. J. Cogn. Neurosci. Suppl. *17*, 216.

Tootell, R.B., Nelissen, K., Vanduffel, W., and Orban, G.A. (2004). Search for color 'center(s)' in macaque visual cortex. Cereb. Cortex *14*, 353–363.

Treisman, A.M. (2005). Synesthesia: implications for attention, binding and consciousness—a commentary. In Synesthesia: Perspectives from Cognitive Neuroscience, L. Robertson, and N. Sagiv, eds. (Oxford: Oxford University Press), pp. 239–254.

Triesman, A.M., and Gelade, G. (1980). A feature-integration theory of attention. Cognit. Psychol. *12*, 97–136.

Wade, A.R., Brewer, A.A., Rieger, J.W., and Wandell, B.A. (2002). Functional measurements of human ventral occipital cortex: retinotopy and colour. Philos. Trans. R. Soc. Lond. B Biol. Sci. *357*, 963–973.

Wagar, B.M., Dixon, M.J., Smilek, D., and Cudahy, C. (2002). Colored photisms prevent object-substitution masking in digit-color synesthesia. Brain Cogn. *48*, 606–611.

Ward, J., and Mattingley, J.B. (2005). Synaesthesia: an overview of contemporary findings and controversies. Cortex, in press.

Ward, J., and Simner, J. (2003). Lexical-gustatory synaesthesia: linguistic and conceptual factors. Cognition *89*, 237–261.

Ward, J., and Simner, J. (2005). Is synaesthesia an X-linked dominant trait with lethality in males? Perception *34*, 611–623.

Ward, J., Huckstep, B., and Tsakanikos, E. (2005). Sound-colour synaesthesia: to what extent does it use cross-modal mechanisms common to us all? Cortex, in press.

Weiss, P.H., Shah, N.J., Toni, I., Zilles, K., and Fink, G.R. (2001). Associating colours with people: a case of chromatic-lexical synaesthesia. Cortex *37*, 750–753.

Weiss, P.H., Zilles, K., and Fink, G.R. (2005). When visual perception causes feeling: enhanced cross-modal processing in grapheme-color synesthesia. Neuroimage, in press.

Wolfe, J.M. (1994). Guided search 2.0: A revised model of visual search. Psychol. Bull. *1*, 202–238.

Wollen, K.A., and Ruggiero, F.T. (1983). Colored-letter synesthesia. J. Ment. Imagery *7*, 83–86.