PART V

NEUROLOGICAL BASIS OF SYNESTHESIA

CHAPTER 24

SYNESTHESIA AND FUNCTIONAL IMAGING

EDWARD M. HUBBARD

Introduction

Researchers have debated the neural mechanisms that give rise to synesthesia since the earliest days of synesthesia research (e.g., Flournoy 1893). However, it is only with the advent of sophisticated neuroimaging techniques like positron emission tomography (PET) and, more recently, functional magnetic resonance imaging (fMRI) that these questions could be empirically addressed by examining patterns of brain activation in synesthetes and non-synesthetes alike. Since the first attempt to measure brain activity related to synesthetic experiences over 25 years ago (Cytowic and Stump 1985), our understanding of brain functions and the sophistication of neuroimaging methods has increased dramatically.

These advances have led to a number of neurophysiologically sophisticated models of synesthesia, and to a wealth of studies aimed at testing them. Here, I will not discuss studies using methods such as electroencephalography (Brang et al. 2011; Niccolai, Wascher, and Stoerig 2012) or magnetoencephalography (Brang et al. 2010) although in many cases the findings using these other methods converge with those from neuroimaging methods (for a review of studies using these other methods, see Hubbard et al. 2011; Jäncke, Chapter 28; Ramachandran and Brang, Chapter 48, this volume). Instead, here I focus exclusively on functional neuroimaging studies of various forms of synesthesia (summarized in Table 24.1 at the end of this chapter), in which neural activity is inferred from bloodflow measures of metabolic activity.

Early studies of synesthesia focused primarily on synesthesia involving color, elicited either by auditory words and tones (word/tone-color synesthesia), or by letters and numbers (grapheme-color synesthesia) by contrasting brain responses to stimuli that either did or did not elicit synesthetic experiences. However, more recent studies have moved away from these simple task-based designs to explore functional connectivity in

the synesthetic brain independent of whether participants are experiencing synesthesia or not. One advantage of these "resting state" studies is that they may be less affected by possible demand characteristics or motivational factors that may differ between synesthetes and non-synesthetes. Additionally, the models and methods that were originally developed to explore tone-color synesthesia and grapheme-color synesthesia are now being applied to the exploration of other forms of synesthesia. Here, I describe these studies both in an historical context and as they relate to different neurophysiological models of synesthesia.

MW: The First Neuroimaging Study of Synesthesia

Cytowic and Wood (1982a, 1982b) suggested that synesthesia was due to a *neural linkage* rather than *semantic mediation* based on the distinct, reliable percepts reported by two synesthetic participants, one who experienced taste-shape synesthesia (MW), and the other who experienced music-color synesthesia. Because other neural events including lysergic acid diethylamide (LSD)-induced hallucinations and epileptic seizures were known to induce synesthesia-like experiences, and because these events were associated with reduced cortical blood flow, Cytowic and Wood (1982a) hypothesized that synesthesia might result from cortical inhibition, and suggested that the limbic system might be the locus of synesthesia. Cytowic and Stump (1985) tested this hypothesis by asking MW to inhale radioactive Xenon (Xe^{133}) gas mixed with room air. With this methodology, cerebral blood flow (CBF) is then measured by detectors placed over the scalp that detect the emission of X-rays and gamma rays as a consequence of the decay of the unstable xenon isotopes. Cytowic and Stump found that cortical blood flow decreased during MW's synesthetic experiences, consistent with their model, but because the Xe^{133} method does not provide spatial information and is insensitive to subcortical blood flow, they were unable to directly test their hypothesis that synesthesia depends on limbic structures.

Early Investigations of Auditory Word/Music-Color Synesthesia

After Cytowic and Wood's early investigations of MW's taste-shape synesthesia there were no other neuroimaging investigations of synesthesia for more than 10 years. In these intervening 10 years, another imaging method, PET, became a standard method for the emerging field of cognitive neuroscience through the combined efforts of

cognitive psychologists and radiologists (Petersen et al. 1988). Like Xe^{133}, PET depends on the decay of short-lived radioactive isotopes. For example, radioactive oxygen (O^{15}) or radioactively labeled glucose are injected into the bloodstream, and are then absorbed by active brain regions. When the radioisotope decays, it emits a positron, which travels a short distance before interacting with an electron. The annihilation of the positron and electron generates a pair of gamma rays that travel in opposite directions, which are then detected by sensors placed around the head. Because the gamma rays are detected at the sensors at slightly different times, the relative position along the axis of the sensors can be inferred, and by placing sensors at carefully calculated positions, multiple axes through the body can be measured simultaneously. In this way, PET yields "tomographic" images (slice pictures), and is able to provide detailed spatial information about differences in regional CBF (rCBF) unlike Xe^{133}, which provided only global measurements of cortical blood flow.

Earlier PET studies had demonstrated changes in rCBF in cortical regions when participants viewed colored versus black and white displays, and identified these regions as the "color center" in humans (Lueck et al. 1989). To test the hypothesis that these color selective areas of the cortex were also active during the experience of colors in word-color synesthesia, Paulesu et al. (1995) measured rCBF with PET while six auditory word-color synesthetes listened to words (which elicited synesthetic colors) versus tones (which did not). Also tested on the same task were six non-synesthete controls. 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 participants, but not in controls. However, despite being a tomographic technique, anatomical localization in PET is limited because of the distance positrons travel before interacting with electrons. In addition, the failure to find activity in early visual areas (e.g., V4) may also have been due to limited sensitivity, rather than a true absence of activity.

After this early study, there was again a substantial gap of 7 years before the next imaging study of synesthesia, and in these intervening 7 years, neuroimaging methods again improved, with the discovery of the blood oxygenation level-dependent (BOLD) fMRI signal in 1991 (for a review, see Huettel et al. 2004). Unlike Xe^{133} and PET, which require the use of inhaled or injected radioactive tracers, the BOLD signal depends on the natural magnetic properties of the hemoglobin molecule in blood. Oxygen carrying hemoglobin (oxyhemoglobin) responds more strongly to the strong magnetic fields in MRI than does deoxyhemoglobin. When brain regions are active, the blood supply overcompensates so that the relative concentration of oxyhemoglobin increases, leading to changes in the fMRI signal, allowing researchers to infer the location of neural activity. Because fMRI does not use radioactivity, fMRI scanners do not need to be near cyclotrons which are necessary to create the radioactive isotopes, and is safe for repeated measurements. Although fMRI has relatively slow temporal resolution on the order of 4 to 6 seconds, due to the sluggish hemodynamic response, it has excellent spatial resolution, with typical functional scans being on the order of $3 \times 3 \times 3$ mm (compared with 4 to 8 mm for PET), and higher sensitivity than previous imaging methods.

Using fMRI, Nunn et al. (2002) tested six female, right-handed auditory word-color synesthetes and six matched non-synesthetes. Nunn et al. reported that regions of the brain involved in the processing of colors (including the color center V4 and/or V8) were more active when word-color synesthetes heard spoken words than when they heard tones, but not earlier visual areas such as V1 or V2. No such difference was observed in controls, even when they were extensively trained to imagine specific colors for specific words. Similarly, in a case study of a synesthete who experienced colors for people's names, Weiss et al. (2001) reported that hearing names that elicited synesthetic colors led to activity in left extra-striate cortex (near to V4), but not in V1. However, in another 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 in this single participant.

Grapheme-Color Synesthesia as A Model System

As neuroimaging investigations of word-color synesthesia were yielding striking insights into the neural mechanisms of this form of synesthesia in the early 2000s, behavioral studies were beginning to focus on grapheme-color synesthesia. For example, behavioral studies of grapheme- color synesthesia demonstrated that the synesthetic sensations were automatic using modified Stroop-interference paradigms (Dixon et al. 2000; Mattingley et al. 2001); others demonstrated the perceptual reality of synesthetic colors using a variety of visual search paradigms (Palmeri et al. 2002; Ramachandran and Hubbard 2001a; Smilek et al. 2001; for reviews see Rich and Mattingley, Chapter 14; Kim and Blake, Chapter 15, this volume).

As a model system, grapheme-color synesthesia has several advantages over other forms of synesthesia. First, understanding the perceptual, cognitive and neural mechanisms of reading and color perception has been the topic of substantial research efforts independent of the synesthesia research community. Second, from a methodological perspective, grapheme-color synesthesia is ideally suited to the constraints of MRI environments. These environments are typically very noisy, which complicates effective study of the neural mechanisms of auditory language processing, and because of the presence of the magnetic field all metallic objects should be kept out of the scanner, making it difficult, for example, to create mechanical devices to present tastes, smells, and even controlled tactile stimulation to participants in the scanner. On the other hand, visual presentation in MRI simply requires a computer projector placed outside the scanner environment, a screen, and a mirror to reflect the image into the participant's eyes while they lie on the scanner bed.

Building on this knowledge, when we began to search for a possible neural basis for grapheme-color synesthesia, we were struck by the fact that brain regions involved

in letter and number processing (the "grapheme area" or the "visual word form area"; VWFA) lie adjacent to the V4 color processing area (Ramachandran and Hubbard 2001a, 2001b). Given that synesthesia was known to run in families (Baron-Cohen et al. 1996; Galton 1883; see Johnson, Allison, and Baron-Cohen, Chapter 1, this volume) we suggested that a genetic factor might cause a failure in the neuronal pruning processes that usually take place during childhood development; this failure could give rise to adjacent brain regions in the fusiform gyrus being unusually connected in adult synesthetes, thereby leading to "cross-activation" between these regions (Hubbard and Ramachandran 2003; Ramachandran and Hubbard 2001b). Although this theory shares certain key aspects with the neonatal synesthesia theory, which suggests that everyone is born a synesthete (Maurer 1997) and the breakdown in modularity theory (Baron-Cohen 1996; Baron-Cohen et al. 1993), our original proposal capitalized on our emerging understanding of the neural mechanisms of reading and color perception to go beyond these general notions of hyperconnectivity, and to suggest specific brain regions as the locus for a specific form of synesthesia.

In addition to the cross-activation theory (see Figure 24.1a), two other main classes of model have been proposed to explain synesthetic experiences: the disinhibited feedback model and the re-entrant processing model (for a thorough review of these issues, see Hubbard and Ramachandran 2005). The disinhibited feedback theory (Figure 24.1c) suggests that synesthesia may be due to disinhibited feedback from a "multisensory nexus" such as the temporo-parietal-occipital junction, and that synesthetic concurrents arise because of disinhibited feedback from higher-level visual areas in pathways common to synesthetes and non-synesthetes alike (Grossenbacher and Lovelace 2001).

The re-entrant processing (Figure 24.1b) model posits cross-talk between form and color processing areas in the fusiform (as in the cross activation model), but, as in the disinhibited feedback model, it also suggests that elicitation of synesthetic colors requires neural activity from higher level areas in the temporal lobe (e.g., the anterior inferior temporal lobe) to feed back to V4 (Smilek et al. 2001).

Recently, a fourth model of synesthesia has been proposed, the "hyperbinding" model (Esterman et al. 2006; Robertson 2003). Under normal circumstances, the brain must bind together information from color, form, motion, and so on into a coherent representation of the world (Treisman 1980) and this binding process depends on parietal mechanisms (Robertson 2003). The hyperbinding model suggests that synesthesia arises through an over-activation of these same parietal binding mechanisms (see Alvarez and Robertson, Chapter 16, this volume). While anomalous binding may play an important role in the full explanation of the synesthetic experiences, it is not sufficient to say that synesthesia is a result of anomalous binding, since binding must have features upon which to act. Thus, one of these described mechanisms for generating additional synesthetic experiences may act in concert with over-active binding mechanisms.

It is important to note that a single model may fail to capture the variability in synesthetic experiences. The neural mechanisms may have both a common factor, which is present in all synesthetes, and other variable factors, which influence the strength of the synesthetic experiences, leading to individual differences in their experiences (Dixon

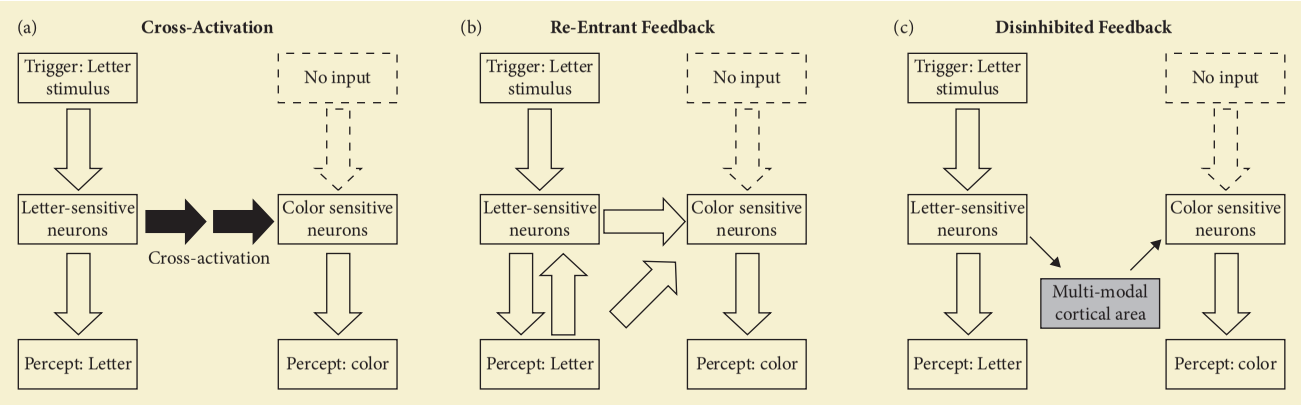


FIGURE 24.1 The main classes of neurophysiological theories of synesthesia. Arrows indicate the flow of information, and boxes indicate processing stages/areas. Solid lines indicate active regions and pathways, while dotted lines indicate non-active regions and pathways. (a) The cross-activation model. Letter input leads to cross-activation of color areas (black arrows), which then leads to both the percept of letters and colors. (b) The re-entrant feedback model. Feedback from higher-order conceptual areas involved in the conscious percept of the letter feeds back both to physical form areas and to color areas, leading to the percept of a color. (c) The disinhibited feedback model. Information propagates up from letter processing to a multi-modal cortical area (gray box) before feeding back to color selective areas. Reprinted from *Trends in Cognitive Sciences*, 10 (8), Catherine M. Mulvenna and Vincent Walsh, Synaesthesia: supernormal integration?, pp. 350–352, Copyright (2006), with permission from Elsevier.

et al. 2004; Hubbard, Arman et al. 2005). In addition, the different models are not necessarily mutually exclusive. Indeed, as mentioned earlier, the hyperbinding account must work in concert with one of the other models to explain the genesis of the features that are bound if we are to explain synesthetic experiences.

It is also possible that different neural theories will account for different types of synesthesia, as the local cross-activation, re-entrant feedback, and hyperbinding theories have focused primarily on grapheme-color synesthesia, while feedback models have focused on word-color and tone-color synesthesia. While it is probable that at the architectural level, different forms of synesthesia will have different neural substrates, the fact that synesthetes within the same family may inherit different forms of synesthesia (Ward and Simner 2005) suggests that the neurophysiological mechanisms may be shared across different forms of synesthesia.

Functional Neuroimaging of Grapheme-Color Synesthesia

With the rise of grapheme-color synesthesia as a model system and improved methods for neuroimaging, the study of the neural mechanisms of synesthesia has truly exploded (for reviews, see Hubbard 2007a; Hubbard and Ramachandran 2005; Hubbard et al. 2011; Rouw et al. 2011). Early investigations focused primarily on the question of whether color selective brain regions were active, even to the extent of collecting functional brain imaging data only from specific regions that were hypothesized to be involved in the generation of synesthetic experiences. More recent investigations have moved beyond this singular focus on color selective regions to more thoroughly investigate network properties in synesthesia (see Rouw et al. 2011).

In an early study of grapheme-color synesthesia, we predicted that viewing black graphemes on a white background would lead to greater activity in color selective region V4. To test this theory, we compared fMRI responses to graphemes against non-grapheme stimuli matched for visual complexity in six synesthetes and six non-synesthetes (Hubbard, Arman, et al. 2005). Color and grapheme regions of interest (ROIs) were defined using a priori methods in a separate scan for each participant. We found greater modulation of V4 activity for graphemes versus non-graphemic stimuli in synesthetes than in non-synesthetes, consistent with our predictions (Figure 24.2a and 24.2b). Importantly, we did not observe differences in the responses to colors in the brains of synesthetes compared with non-synesthetes, and did not observe differences in the response to graphemes outside of V4, arguing against generalized differences in the synesthetes. Interestingly, we also found that performance on an independent perceptual task in which synesthetic colors conferred a behavioral advantage correlated with V4 activation in the synesthetes (Figure 24.2c), supporting the idea of a direct relationship between neural activity and perceptual experience (Hubbard, Arman, et al. 2005). This

pattern of results has important implications for our understanding of the variability observed in behavioral studies (Dixon and Smilek 2005).

A number of subsequent neuroimaging studies of grapheme-color synesthesia have also examined whether color selective regions, including V4, were more active in synesthetes when viewing black-and-white graphemes. Like Hubbard, Arman et al. (2005), Sperling et al. (2006) measured fMRI BOLD response in four synesthetes in retinotopically defined V1 to V4 to graphemes that elicited synesthetic colors versus those that did not. 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.

However, not all studies identified activity in the region of V4. Rich et al. (2006) used whole-brain fMRI and statistical parametric mapping (SPM) to analyse fMRI responses in a group of seven synesthetes and seven controls in three separate imaging paradigms. They first localized color selective ROIs using colored Mondrians versus grayscale images, which should selectively activate V4. They then measured fMRI responses within these ROIs in synesthetes and controls while these participants viewed either colored letters (which also induced synesthesia in the synesthetes) or grayscale letters, while monitoring for a brief disappearance of one of the letters. Rich et al. did not find greater activation of the V4 complex in synesthetes, but instead found activation of more anterior color areas, related to color naming and categorization. In addition, unlike in the previous Nunn et al. (2002) study, they found color imagery was capable of eliciting activation in the V4 complex in both synesthetes and non-synesthetes. Similarly, Weiss et al. (2005) examined fMRI signals in nine grapheme-color synesthetes, using a 2×2 factorial design. Subjects were presented with letters that either did or did not induce colors (many synesthetes report not having colors for all stimuli), with either colored or grayscale letters. Weiss et al. did not observe any significant activation in visual areas, but did observe a significant activation in the left intraparietal sulcus, consistent with the hyperbinding account of synesthesia.

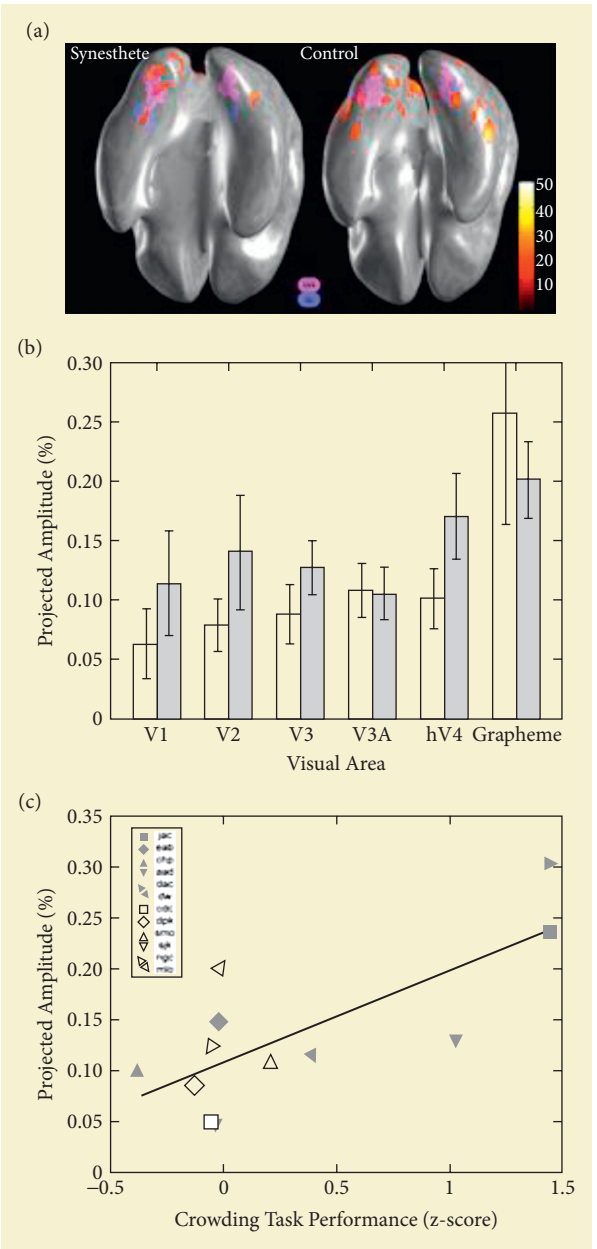
The reasons for these differences in the strength of the findings are still unclear, but may be due to individual differences in the synesthetes tested across the studies (Hubbard, Arman, et al. 2005; Rouw and Scholte 2010). For example, one individual difference comes in the localization of synesthetic colors from synesthete to synesthete: *associator synesthetes* experience their colors internally (often described as being "in the mind's eye") while *projector synesthetes* experience their colors externally, for example, projected onto the written typeface (Dixon et al. 2004). Individual differences such as this might then be responsible for the different outcomes found in past imaging studies. For example, Rouw and Scholte (2010) measured fMRI responses (and voxel-based morphometry: VBM) in a group of 42 grapheme-color synesthetes (16 projectors and 26 associators) to identify: (1) brain regions that showed differences across all synesthetes compared with controls, (2) brain regions that showed differences between the two groups of synesthetes. Across all synesthetes compared with non-synesthetes, the authors found increased activation in a network of regions involved in perceptual binding including parietal and frontal regions, and the parieto-

occipital sulcus near the precuneus. However, when they directly compared activation in the associators versus projectors, they found increased activation in hippocampal regions for the associators compared with the projectors. These results (and the corresponding VBM analyses) suggest that projector synesthesia may arise from more sensory mechanisms, while associator synesthesia may from more cognitive mechanisms including memory processes.

Another important aspect of evaluating these discrepant results is that until recently, most studies of synesthesia were statistically underpowered. Standard whole brain fMRI analyses using SPM and random effects analyses require a minimum of 20 participants in order to allow inferences about both positive and negative findings (Thirion et al. 2007). Analyses using restricted ROIs are less likely to be as severely underpowered, because the restricted number of voxels tested reduces the adverse statistical impact of the multiple comparisons problem. Techniques such as retinotopy which permit delineation of individual participant areas may similarly be less adversely affected because differences in brain anatomy are taken into consideration when examining patterns of activation. Given these considerations, positive findings should be given substantially more weight than negative ones when attempting to develop models of grapheme-color synesthesia.

Consistent with this, studies that examined larger numbers of synesthetic participants typically do find activation of color selective regions near the coordinates of V4 (Rouw and Scholte 2007; van Leeuwen et al. 2010). For example, as part of a larger study of anatomical connectivity (DTI) in synesthesia, Rouw and Scholte (2007) scanned a total of 18 synesthetes and 18 controls when they viewed graphemes that elicited strong, weak, or no synesthetic experiences. They found increased activation for strong and weak synesthetic experiences (compared with no synesthetic experience) across multiple brain regions including frontal regions, parietal regions and fusiform gyrus, near the coordinates of V4. Similarly, van Leeuwen et al (2010) scanned 19 synesthetes and 19 controls, and also found increased activation in a network of regions including superior parietal cortex and color-related areas. Consistent with the possibility that individual differences complicate the interpretation of group-level neuroimaging analyses, projectors showed greater activation in parietal cortex than did associators.

However, power and individual differences are unlikely to fully account for the discrepant results in the literature. In another recent study, Hupé et al. (2012) scanned ten grapheme-color synesthetes compared against 25 non-synesthetes. They used retinotopic mapping methods to define a priori visual ROIs, and also assessed individual differences across synesthetes. Even so, these authors did not find increased activation at a group level for synesthetes compared with non-synesthetes in visual areas related to color experience. Instead, they suggest that the neural mechanisms of grapheme-color synesthesia may be distributed, or may critically depend on brain regions outside the classical color areas. This conclusion is difficult to reconcile with the other studies reviewed here (and converging results from other methodologies) but given the methodological rigor in their study, any coherent model of grapheme-color synesthesia will have to account for these results.



AQ: Please provide better quality figure for "c"

FIGURE 24.2 (a) Activation during grapheme viewing from a representative synesthete and control participant. Retinotopic region V4 is indicated in pink and grapheme responsive areas are indicated in blue. (b) Average projected amplitude for synesthetes and controls across early visual areas, showing significantly greater activation in synesthetes than in controls in area V4. (c) Correlation between activation in V4 during grapheme viewing and performance enhancement on an independent perceptual task. Data reprinted from *Neuron*, 45 (6), Edward M. Hubbard, A. Cyrus Arman, Vilayanur S. Ramachandran, and Geoffrey M. Boynton, Individual differences among grapheme-color synesthetes: Brain-behavior correlations, pp. 975–985 © 2005, Elsevier.

Alternatives to Block-Designs in the Study of Grapheme-Color Synesthesia

These considerations have led a number of authors to move beyond the simple "block-design" methods used in the studies described earlier, in which blocks of synesthesia-inducing stimuli are contrasted with non-synesthesia inducing stimuli. Although these studies still depend on measuring blood flow to infer neural activity, the designs permit stronger inferences about the pattern of neural activity across different conditions, and therefore shed additional light on the neural mechanisms of grapheme-color synesthesia.

For example, taking advantage of the fact that synesthetic Stroop-interference increases with increasing difference between the real text color and the synesthetic color (Nikolic et al. 2007), Laeng et al. (2011) measured parametric modulations of neural activity in response to graphemes that were presented in colors that were either more or less similar to those reported by two grapheme-color synesthetes. They found that activation increased as a function of the color distance between the real and synesthetic colors in both synesthetes, and that the location of this activation was quite close to the coordinates from other studies that examined both real and synesthetic color perception, including V4.

Another method for examining shared neural substrates for real color perception and synesthetic color is the fMRI-adaptation (fMRI-A) method, which takes advantage of the fact that repeated presentations of a stimulus lead to decreased neural responses (Miller et al. 1991) and corresponding decreases in the fMRI BOLD signal. Presentation of stimuli that depend on different populations of neurons leads to a "rebound" effect in which fMRI responses increase to baseline levels or beyond (Grill-Spector and Malach 2001; Naccache and Dehaene 2001).

Several recent studies have applied this logic to the study of grapheme-color synesthesia, but did not find significant adaptation or rebound effects. Van Leeuwen et al. (2010) presented graphemes which elicited synesthetic colors and real color patches, in which the color patches were either congruent with, incongruent with, or neutral with respect to synesthetic colors. The authors predicted decreased fMRI responses when the graphemes and color patches were congruent due to repetition suppression effects on these populations of neurons for those colors fatiguing. No such repetition suppression effect was observed, with fMRI responses being the same for the congruent and incongruent conditions, but lower for both conditions than for the neutral condition. As such, the authors suggest that synesthetic colors do not depend on the same neural mechanisms as real color perception in color selective areas (see also, Hupé et al. 2012).

However, the interpretation of fMRI adaption experiments is fraught with difficulties (Krekelberg et al. 2006). It is known that the BOLD signal includes both spiking and non-spiking activity, and therefore reflects mostly inputs to an area (Logothetis and Wandell 2004). Because in the visual pathway adaptation occurs at multiple levels from

the retina to higher-order visual areas, and because adaptation at early stages of processing is "inherited" at subsequent stages of processing, this inherited adaptation complicates the interpretation of any fMRI adaptation paradigm. In the case of grapheme-color synesthesia, even if real colors and synesthetic colors eventually converge on the same neurons, the pathways would differ for real and synesthetic colors. Real color patches would activate, and therefore cause adaptation at the level of the retina, V1, V2, and eventually color selective areas like V4 while synesthetic colors might only lead to activation of color selective neurons in V4. As such, the absence of measured adaptation in this study might reflect differences in inherited adaptation, rather than a lack of a shared neural substrate for real and synesthetic colors (Krekelberg et al. 2006). As an example of these concerns, an fMRI-adaptation study of orientation tuning found no differences in adaptation in V1 for gratings of the same orientation versus different orientations (Boynton and Finney 2003). Orientation specific adaptation effects were present only in later areas like V2 and V4, despite the well-established fact that V1 neurons are orientation selective. Finally, it is known that adaptation is greater for expected stimuli than for unexpected stimuli (Summerfield et al. 2008). Since van Leeuwen et al. (2010) presented twice as many incongruent stimuli as congruent stimuli, it possible that increased adaptation to the congruent stimuli was countered by increased responses due to the greater novelty of the congruent stimuli. Because of its power to infer neural processes, fMRI-A is an important method, but these methodological issues are critical for designing effective fMRI-A studies.

Localized Differences Versus Network Differences

A growing awareness of the importance of binding and parietal mechanisms led to the introduction of a "two-stage model" of grapheme-color synesthesia (Hubbard 2007a, 2007b). The cross-activation theory proposed that synesthetic experiences are generated via cross-activation in the fusiform gyrus, but assumed that parietal binding and attention mechanisms were similar in synesthetes and non-synesthetes. Conversely, the "hyperbinding" theory of grapheme-color synesthesia suggested that synesthetic experiences depend on increased binding between color and form (Esterman et al. 2006; Robertson 2003).

Although the evidence reviewed earlier clearly demonstrates a critical role for early color-selective visual areas in the genesis of synesthetic experiences, a number of studies have also demonstrated the importance of parietal regions involved in attention and binding. For example, intraparietal regions are consistently more active in synesthetes than in non-synesthetes (Nunn et al. 2002; Paulesu et al. 1995; van Leeuwen et al. 2010; Weiss et al. 2005). Taken together, these results suggest that, while the activation of color specific visual areas may be the origin of synesthetic experiences, these color

experiences must still be bound by (possibly overactive) parietal mechanisms. While anomalous binding may play an important role in the full explanation of the synesthetic experiences, it is not sufficient to say that synesthesia is a result of anomalous binding, since binding must have features upon which to act. We thus suggest that synesthetic colors are first elicited in fusiform regions via cross-activation, but are then bound by parietal mechanisms in the same way as other visual features.

One particularly powerful way to examine these questions depends on the advent of methods to measure "functional connectivity" (FC), especially in the absence of a task (called resting state fMRI or rs-fMRI; Fox and Raichle 2007; Gusnard and Raichle 2001). FC is assessed by measuring the correlation between the time series of any two brain regions. The more strongly correlated the time series is, the more strongly activity in one brain area depends on brain activity in another area, and the more functionally connected those brain regions are. The analysis of correlations can be done either within a hypothesis-driven framework, in which ROIs are defined a priori, or in a data-driven framework, in which spatio-temporal networks are identified through the use of independent components analysis (ICA), or through a combination of both methods. In addition to measuring simple connectivity, by looking at time-lagged correlations it is also possible to infer which brain region is driving which, using modeling techniques like structural equation models (SEM), dynamic causal modeling (DCM), and Grainger causality.

Van Leeuwen et al. (2011) used DCM analyses to examine network connectivity between three regions thought to be involved in the generation of synesthetic experiences: fusiform regions involved in letter-shape analysis (which they refer to as the LSA), V4, and parietal cortex for associators and projectors. For projectors, the LSA directly drives V4 in a bottom-up manner, while for associators, the LSA drives parietal cortex, which in turn drives V4. Critically, they showed the degree to which synesthetes' reports of externally projected experiences was correlated with the degree to which the bottom-up versus top-down models fit the brain imaging data. This suggests that, even if V4 is activated in both groups of synesthetes, the pathways taken for this information may vary.

In another recent study, rs-fMRI and ICA were used to identify intrinsic connectivity networks (ICNs) in 12 grapheme-color synesthetes and 12 matched non-synesthetic controls (Dovern et al. 2012). The authors identified a set of seven "synesthesia-relevant" ICNs, including primary visual cortex, primary auditory cortex and parietal regions and a parieto-frontal network. FC was greater in the synesthetes both within and between these ICNs and FC strength was correlated with the behaviorally assessed consistency in synesthetes' reports. Synesthetes had three times more significant connections between the seven ICNs than did controls. Crucially, synesthetes had stronger connections between both visual networks and the right fronto-parietal network than controls, and color consistency in synesthetes was correlated with connectivity between visual networks and the auditory and right fronto-parietal networks.

Other recent studies have similarly demonstrated the importance of both visual areas and parietal networks in generating synesthetic experience (Sinke, Neufeld, et al. 2012;

Specht and Laeng 2011) and have generally supported the idea that visual and parietal networks are more strongly connected in synesthesia, consistent with a two-stage model of grapheme-color synesthesia (Hubbard 2007a, 2007b; Hubbard et al. 2011). Taken together, these results also demonstrate that increased connectivity between regions might be even more widespread than originally thought. For example, Sinke, Neufeld, et al. (2012) showed that FC was greater in synesthetes even in primary visual areas, suggesting even more widespread differences than predicted in previous models.

Less Studied Variants of Synesthesia

In the past few years, neuroimaging investigations have expanded well beyond grapheme-color synesthesia to include many other forms of synesthesia. Although these investigations are only beginning, we hope to spur future research into these questions, using neuroimaging methods similar to those used in the study of grapheme-color synesthesia. Although a great deal of data has been collected on grapheme-color synesthesia, for most other forms of synesthesia, a great deal more work is needed, and examination of some of these forms may require revising or even rejecting current models. Indeed, additional research may demonstrate that different mechanisms are important to explain different forms of synesthesia, and may even suggest that grapheme-color synesthesia is a non-representative model of how synesthesia works generally.

Sequence-space synesthesia

In another form of synesthesia, numbers and other ordinal sequences including months of the year and days of the week are associated with specific spatial locations (Galton 1880b, 1880a). This often co-occurs with grapheme-color synesthesia (Sagiv et al. 2006; Seron et al. 1992) and has been referred to as *spatial sequence synesthesi*a (SSS; Eagleman 2009), although it is sometimes described with various other terms depending on the particular subvariants under discussion (e.g., described as *number form synesthesia* when triggered by numbers; Hubbard, Piazza, et al. 2005; or as *time-space synesthesia* when triggered by months etc. Smilek, Callejas, et al. 2007). Based on numerous patient and neuroimaging studies, parietal cortex is generally recognized as a key region for numerical and spatial processes (Dehaene et al. 2003; Hubbard, Piazza, et al. 2005; Simon et al. 2002) including processing of non-numerical ordinal sequences, such as letters (Fias et al. 2007) and months (Ischebeck et al. 2008). Building on these observations, we proposed that this form of synesthesia arises through cross-activation in parietal regions (Hubbard, Piazza, et al. 2005; Ramachandran and Hubbard 2001b), and furthermore, that non-conscious numerical-spatial interactions that are present in

everyone (e.g., the SNARC effect Dehaene et al. 1993) are mediated by similar, albeit weaker connections in parietal cortex (Hubbard, Piazza, et al. 2005). An alternative model suggests that temporal regions, rather than parietal regions, are the locus of this form of synesthesia (Eagleman 2009) as sequences are "reified" and thought of as visual objects, which can then be operated on with normal visuo-spatial mechanisms of attention, including panning, zooming, and translating.

Preliminary support for the parietal model comes from fMRI data showing increased posterior parietal activation in number-form synesthetes when they performed a number task that focused on the ordinal position of the number in a sequence ("first" versus "fifth") compared against a task that focused on numerical magnitude ("one" versus "five"; Tang et al. 2008). This focus on numerical sequence is important, as it has been suggested that order and sequence is more important to explain SSS than numerical magnitude (Eagleman 2009; Hubbard et al. 2009; Sagiv et al. 2006). Consistent with this model, a patient who suffered a gunshot wound which entered near the right angular gyrus and lodged near the left temporal-parietal junction complained that his "number plan" for months of the year, days of the week and letters of the alphabet, was no longer distinct (Spalding and Zangwill 1950).

Steven et al. (2006) conducted a single-case study of a synesthetic participant, JF, who had become blind due to retinal degeneration 10 years before the fMRI session. Prior to becoming blind, JF reported both SSS and colors for "time words" (day and month names). Steven et al. showed that V4 could be activated by auditory presentation of time words versus frequency matched non-time words. Similar visual activations were not observed in a non-synesthetic late-blind participant or a non-synesthetic sighted participant, suggesting that the functional differences that lead to synesthesia persist even in the absence of visual input. In a follow-up study, Niccolai et al. (2012) sought to disentangle the effects of SSS and color synesthesia on JF's brain activation patterns. They presented time words that elicited both SSS and colors ("Monday," "February"), time words that elicited only SSS ("morning," "Easter"), and time words that elicit neither SSS nor colors ("season," "year"). Words that elicited SSS and colors led to greater activation of color selective areas near (anatomically defined) V4, while words that elicited only SSS led to greater activation of posterior/inferior parietal cortex, consistent with the parietal model.

Mirror-touch synesthesia

In mirror-touch synesthesia, observing touch to another person's body is felt as touch by the synesthete (Banissy and Ward 2007; Banissy et al. 2009; see Banissy, Chapter 30, this volume). One proposed mechanism for this form of synesthesia is enhanced responsiveness in the tactile mirror neuron system, which has been demonstrated to be active both when being touched and when observing others being touched. To date, there has been only one neuroimaging study of this form of synesthesia (Blakemore et al. 2005). Consistent with predictions, neuroimaging of a single mirror-touch synesthete, C,

compared against 12 non-synesthetes showed enhanced activation in multiple regions of the tactile mirror system, including primary and secondary somatosensory regions. Investigation of the data from each participant demonstrated greater activation in C than in any of the 12 non-synesthetes. To date, there have been no follow-up neuroimaging studies of this form of synesthesia.

Ordinal linguistic personification

Ordinal linguistic personification (OLP) is another form of synesthesia, in which people associate letters and numbers with personalities (e.g., "A" may be thought of as female and "the boss," while "B" might be her toddler son). We suggested that this form of synesthesia depends on cross-activation between brain regions involved in sequence representations, such as the inferior parietal cortex and regions involved in personality attribution (Simner and Hubbard 2006) while other models have suggested numerous anatomical substrates in a "personification network" (Smilek, Malcolmson, et al. 2007) including the angular gyrus, but also including extra-striate and fusiform regions, the amygdala and medial frontal cortex. Recently, a single-case fMRI study examined the neural substrates of this form of synesthesia (Amin et al. 2011). Their participant, AA, reported personifying about half of the letters in the alphabet, but not the others. In this way, the authors were able to directly contrast activations when AA viewed letters she personified versus letters she did not. The authors found a single focus of activation in the precuneus, which leads them to suggest that "OLP may represent an aberration of self-reflection and/or mental imagery" (275), although the authors suggest caution in interpreting the absence of other activations, given the single-case design. Future studies will be needed to better understand the neural mechanisms of OLP in a larger number of participants.

Lexical-gustatory synesthesia

Finally, lexical-gustatory synesthesia involves tasting the flavors of food in response to heard, read, or thought words (Ward and Simner 2003; Ward et al. 2005). Given the role of insular cortex and its adjacency to auditory regions involved in the analysis of auditory words, it seems natural to speculate that lexical-gustatory synesthesia might arise through cross-activation of these regions. In the only neuroimaging study of this form of synesthesia to date, Jones et al. (2011) demonstrated increased activation in the insula and the precuneus in two lexical-gustatory synesthetes. Interestingly, insular activation was related to the emotional valence of the experienced taste (pleasant/unpleasant) while precuneus activation was related to the subjective intensity of the tastes. Whether these findings hold across all synesthetes, and how these different regions interact to yield the full-blown experience of lexical-gustatory synesthesia is still to be determined.

Future Directions

Although the past 25 years have seen great progress in our understanding of the neural basis of synesthesia, there is still much work to be done. First, many different types of evidence have been brought to bear on the neural basis of grapheme-color synesthesia, but similarly intensive studies have not yet been carried out on the other forms of synesthesia, and to date none of the studies demonstrating anatomical and functional differences in other forms of synesthesia have been replicated. Thus, greater efforts to apply the methods developed in the study of grapheme-color synesthesia to other forms of synesthesia will be critical. Indeed, systematic exploration of other forms of synesthesia may lead to the conclusion that different forms of synesthesia depend on different mechanisms, although much of the available evidence appears consistent with the cross-activation theory (Hubbard et al. 2011).

Second, there are no empirical studies of the neural development of synesthesia (but see Mitchell, Chapter 27, this volume, for a discussion). Methods for neuroimaging with children are becoming widespread, and have been applied to a number of questions in cognitive and perceptual development. Similar methods, combined with methods of identifying and tracking children who are synesthetic (e.g., Simner et al. 2009) or who are likely to become synesthetic (e.g., Green and Goswami 2008) will be critical to understanding the development of synesthesia, and how genes and experience interact. One recent proposal (Cohen Kadosh et al. 2009) suggests that both play a role, building on the interactive specialization framework (Johnson 2001, 2011).

However, interactive specialization is intended as a domain-general account of brain development, and as such does not distinguish between evolutionarily ancient systems and modern cultural systems. Why, for example, is grapheme-color synesthesia more common than face-color synesthesia if adjacency and brain wiring are the only factors that count? Perhaps the degree to which cortex must reorganize during learning is greater for novel culturally acquired systems like graphemes (Dehaene and Cohen 2007) and ordinal sequences (Cohen Kadosh et al. 2009) than for items that have a long evolutionary history, like faces or colors. This greater degree of cortical reorganization for novel cultural artifacts might provide greater opportunities for cross-activation in the cortical recycling process.

Finally, we must address the relative absence of neuroimaging data directly testing other neurophysiological models of synesthesia. For example, the evidence that synesthesia arises from altered neurotransmitter balance leading to disinhibition is largely anecdotal. Grossenbacher and Lovelace (2001) note that experiences similar to synesthesia can sometimes be elicited with psychedelics. However, systematic analysis demonstrates numerous important differences between these forms of synesthesia, and suggests that they arise from different neural mechanisms (Sinke, Halpern, et al. 2012).

Additionally, none of these pharmacological hypotheses of synesthesia have been tested with neuroimaging methods such as PET, single photon emission computed tomography (SPECT), or magnetic resonance spectroscopy (MRS). Future studies using these methods will help to identify whether there are any differences in neurotransmitter concentrations, receptor density or other alterations in synthesis or breakdown of specific neurotransmitters involved with cortical inhibition and excitation. Radioactive tracer molecules developed for use with PET and SPECT, called radioligands, show striking specificity, differentially binding to specific neurotransmitter receptors within specific brain regions. Based on the hypothesis that synesthesia results from differences in cortical excitability (Terhune et al. 2011), and in particular, from disinhibited feedback, we might also predict imbalances in the primary neurotransmitter systems involved in cortical excitation and inhibition, glutamate and GABA, respectively. MRS methods are ideally suited to measuring levels of these neurotransmitters, including GABA and glutamate/glutamine. MRS methods have shed considerable light on the processes of glutamate and GABA synthesis use and reuptake (for a review, see Petroff 2002) and could shed similar light on the relative role of these neurotransmitters, if any, in the increased cortical excitability thought to be associated with synesthesia. Future studies using these methods will be critical to evaluating the possibility that differences in neurotransmitter function underlie synesthesia.

Table 24.1 Neuroimaging studies of synesthesia

Study	Form of synesthesia	Method	Participants (syn. versus con.)
Cytowic and Stump 1985/Cytowic 1989/2002	Taste-shape	Xe^{133}	n = 1, within participants
Paulesu et al. 1995	Auditory-word color	PET	n = 6 vs 6
Aleman et al. 2001	Grapheme-color	fMRI	n = 1, within participants
Weiss et al. 2001	Colors for names of personally familiar people	fMRI	n = 1, within participants
Nunn et al. 2002	Auditory word-color	fMRI	n = 13 vs 27
Elias et al. 2002	Grapheme-color	fMRI	n = 1, within participants
Hubbard et al. 2005	Grapheme-color	fMRI with retinotopy	n = 6 vs 6
Blakemore et al. 2005	Mirror touch	fMRI	n = 1 vs 12
Weiss et al. 2005	Grapheme-color	fMRI	n = 9, within participants
Sperling et al. 2006	Grapheme-color	fMRI with retinotopy	n = 4

Table 24.1 *Continued*

Study	Form of synesthesia	Method	Participants (syn. versus con.)
Steven et al. 2006	Auditory-color time words vs non-time words	fMRI	n = 1 late blind vs n = 1 late blind control and n = 1 sighted
Gray et al. 2006	Grapheme-color ACE	fMRI	n = 8 with, n = 7 without, n = 7 controls
Rich et al. 2006	Grapheme-color	fMRI	n = 7 vs 7
Rouw and Scholte 2007	Grapheme-color	fMRI (+DTI)	n = 18 vs 18
Cohen Kadosh et al. 2007	Explicit bi-directional g-c	fMRI	n = 1
Tang et al. 2008	Number forms (SSS)	fMRI	n = 10 vs 10
Beauchamp and Ro 2008	Acquired sound-touch	fMRI	n = 1 vs 9
Rouw and Scholte 2010	Grapheme-color	fMRI (+VBM)	n = 42, 16 projectors vs 26 associators vs 42
Van Leeuwen et al. 2010	Grapheme-color	fMRI + fMRI-A	n = 19 vs 19
Van Leeuwen et al. 2011	Grapheme-color	functional connectivity	n = 19 vs 19 (same participants as van Leeuwen et al., 2010)
Gaschler-Markefski et al. 2011	Auditory word-color	fMRI	n = 7 vs 7
Laeng et al. 2011	Grapheme-color	fMRI color distance	n = 2, within participants
Specht and Laeng 2011	Grapheme-color	fMRI, ICA	n = 2 vs 2 (same participants as Laeng et al., 2011)
Jones et al. 2011	Lexical-gustatory	fMRI	n = 2 vs 10
Amin et al. 2011	Personification	fMRI	n = 1, within participants
Hupé et al. 2012	Grapheme-color	fMRI + fMRI-A with retinotopy	10 vs 25
Neufeld et al. 2012	Auditory-visual	Functional connectivity	n = 14
Niccolai, van Leeuwen, et al. 2012	Blind SSS	fMRI	n = 1, within participants (same as Steven et al. 2006)
Dovern et al. 2012	Grapheme-color	Functional connectivity	n = 12 vs 12
Sinke, Neufeld, et al. 2012	Grapheme-color	Functional connectivity	n = 18 vs 18

References

Aleman, André, Geert-Jan M. Rutten, Margriet M. Sitskoorn, Geraud Dautzenberg, and Nick F. Ramsay. 2001. Activation of striate cortex in the absence of visual stimulation: An fMRI study of synesthesia. *Neuroreport* 12 (13):2827–2830.

AQ: please complete page range at proof stage

Alvarez, Bryan D., and Lynn C. Robertson. 2013. Synesthesia and binding. In *Oxford Handbook of Synesthesia,* ed. Julia Simner and Edward M. Hubbard, XX–XX . Oxford: Oxford University Press.

AQ: please complete page range at proof stage

Amin, Maina, Olufemi Olu-Lafe, Loes E. Claessen, Monika Sobczak-Edmans, Jamie Ward, Adrian L. Williams, and Noam Sagiv. Understanding grapheme personification: a social synaesthesia? *Journal of Neuropsychology* 5 (2):255–282.

Banissy, Michael J. 2013. Synesthesia, mirror-neurons, and mirror-touch. In *Oxford Handbook of Synesthesia*, ed. Julia Simner and Edward M. Hubbard, XX–XX . Oxford: Oxford University Press.

Banissy, Michael J., and Jamie Ward. 2007. Mirror-touch synesthesia is linked with empathy. *Nature Neuroscience* 10 (7):815–816.

Banissy, Michael J., Roi Cohen Kadosh, Gerrit W. Maus, Vincent Walsh, and Jamie Ward. 2009. Prevalence, characteristics and a neurocognitive model of mirror-touch synaesthesia. *Experimental Brain Research* 198 (2–3):261–272.

Baron-Cohen, Simon. 1996. Is there a normal phase of synaesthesia in development? *Psyche* 2 (27).

Baron-Cohen, Simon, Lucy Burt, Fiona Laittan-Smith, John E. Harrison, and Patrick Bolton. 1996. Synaesthesia: prevalence and familiality. *Perception* 25 (9):1073–1079.

Baron-Cohen, Simon, John Harrison, Laura H. Goldstein, and Maria Wyke. 1993. Coloured speech perception: Is synaesthesia what happens when modularity breaks down? *Perception* 22 (4):419–426.

Beauchamp, Michael S., and Tony Ro. 2008. Neural substrates of sound–touch synesthesia after a thalamic lesion. *The Journal of Neuroscience* 28 (50):13696–13702.

Blakemore, Sarah Jayne, Davina Bristow, Geoffrey Bird, Christopher Frith, and Jamie Ward. 2005. Somatosensory activations during the observation of touch and a case of vision-touch synaesthesia. *Brain* 128 (7):1571–1583.

Boynton, Geoffrey M., and Eva M. Finney. 2003. Orientation-specific adaptation in human visual cortex. *The Journal of Neuroscience* 23 (25):8781–8787.

Brang, David, Edward M. Hubbard, Seana Coulson, Minxiong Huang, and Vilayanur S. Ramachandran. 2010. Magnetoencephalography reveals early activation of V4 in grapheme-color synesthesia. *Neuroimage* 53 (1):268–274.

Brang, David, Stanley Kanai, Vilayanur S. Ramachandran, and Seana Coulson. 2011. Contextual priming in grapheme-color synesthetes and yoked controls: 400 msec in the life of a synesthete. *Journal of Cognitive Neuroscience* 23 (7):1681–1696.

Cohen Kadosh, Roi, Avishai Henik, and Vincent Walsh. 2009. Synaesthesia: learned or lost? *Developmental Science* 12 (3):484–491.

Cytowic, Richard E. 1989/2002. *Synesthesia: A union of the* senses. 2nd ed. Cambridge, MA: MIT Press.

Cytowic, Richard E., and David A. Stump. 1985. Reduced cortical blood flow in geometrically-shaped taste synesthesia. *International Neuropsychological Society*.

Cytowic, Richard E., and Frank B. Wood, 1982a. Synesthesia: I. A review of major theories and their brain basis. *Brain & Cognition* 1 (1):23–35.

———. 1982b. Synesthesia: II. Psychophysical relations in the synesthesia of geometrically shaped taste and colored hearing. *Brain & Cognition* 1 (1):36–49.

Dehaene, Stanislas, Serge Bossini, and Pascal Giraux. 1993. The mental representation of parity and numerical magnitude. *Journal of Experimental Psychology: General* 122:371–396.

Dehaene, Stanislas, and Laurent Cohen. 2007. Cultural recycling of cortical maps. *Neuron* 56 (2):384–398.

Dehaene, Stanislas, Manuela Piazza, Philippe Pinel, and Laurent Cohen. 2003. Three parietal circuits for number processing. *Cognitive Neuropsychology* 20 (3/4/5/6):487–506.

Dixon, Mike J., and Daniel Smilek. 2005. The importance of individual differences in grapheme-color synesthesia. *Neuron* 45 (6):821–823.

Dixon, Mike J., Daniel Smilek, Cera Cudahy, and Philip M. Merikle. 2000. Five plus two equals yellow: Mental arithmetic in people with synaesthesia is not coloured by visual experience. *Nature* 406 (6794):365.

Dixon, Mike J., Daniel Smilek, and Philip M. Merikle. 2004. Not all synaesthetes are created equal: projector versus associator synaesthetes. *Cognitive Affective and Behavioral Neuroscience* 4 (3):335–343.

Dovern, Anna, Gereon R. Fink, A. Christina B. Fromme, Afra M. Wohlschläger, Peter H. Weiss, and Valentin Riedl. 2012. Intrinsic network connectivity reflects consistency of synesthetic experiences. *The Journal of Neuroscience* 32 (22):7614–7621.

Eagleman, David M. 2009. The objectification of overlearned sequences: a new view of spatial sequence synesthesia. *Cortex* 45 (10):1266–1277.

Elias, Lorin J., Deborah M. Saucier, Colleen Hardie, and Gordon E. Sarty. 2003. Dissociating semantic and perceptual components of synaesthesia: behavioural and functional neuroanatomical investigations. *Cognitive Brain Research* 16 (2):232–237.

Esterman, Michael, Timothy Verstynen, Richard B. Ivry, and Lynn C. Robertson. 2006. Coming unbound: disrupting automatic integration of synesthetic color and graphemes by transcranial magnetic stimulation of the right parietal lobe. *Journal of Cognitive Neuroscience* 18 (9):1570–1576.

Fias, Wim, Jan Lammertyn, Bernie Caessens, and Guy A. Orban. 2007. Processing of abstract ordinal knowledge in the horizontal segment of the intraparietal sulcus. *The Journal of Neuroscience* 27 (33):8952–8956.

Flournoy, Theodore. 1893. *Des phénomènes de synopsie [On the phenomena of synopsia]*. Genève: Charles Eggimann & Co.

Fox, Michael D., and Marcus E. Raichle. 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience* 8 (9):700–711.

Galton, Francis. 1880a. Visualised numerals. *Nature* 21 (533):252–256.

———. 1880b. Visualised numerals. *Nature* 21 (543):494–495.

———. 1883. *Inquiries into human faculty and its development*. London: Dent & Sons.

Gaschler-Markefski, Birgit, Gregor R. Szycik, Christopher Sinke, Janina Neufeld, Udo Schneider, Frank Baumgart, Oliver Dierks, *et al.* 2011. Anomalous auditory cortex activations in colored hearing synaesthetes: An fMRI-study. *Seeing and Perceiving* 24 (4):391–405.

Gray, Jeffrey A., David M. Parslow, Michael J. Brammer, Susan Chopping, Goparlen N. Vythelingum, and Dominic H. ffytche. 2006. Evidence against functionalism from neuroimaging of the alien colour effect in synaesthesia. *Cortex* 42 (2):309–318.

Green, Jennifer A. K., and Usha Goswami. 2008). Synesthesia and number cognition in children. *Cognition*, 106:463–473.

Grill-Spector, Kalinit, and Malach, Rafael 2001. fMR-adaptation: a tool for studying the functional properties of human cortical neurons. *Acta Psychologica (Amsterdam)* 107 (1–3):293–321.

Grossenbacher, Peter G., and Christopher T. Lovelace. 2001. Mechanisms of synesthesia: cognitive and physiological constraints. *Trends in Cognitive Sciences* 5 (1):36–41.

Gusnard, Debra A., and Marcus E. Raichle. 2001. Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience* 2 (10):685–694.

Hubbard, Edward M. 2007a. Neurophysiology of synesthesia. *Current Psychiatry Reports* 9 (3):193–199.

——. 2007b. A real red-letter day. *Nature Neuroscience* 10 (6):671–672.

Hubbard, Edward M. and Ramachandran, Vilayanur S. 2003. Refining the experimental lever: A reply to Shannnon and Pribram. *Journal of Consciousness Studies* 10 (3):77–84.

——. 2005. Neurocognitive mechanisms of synesthesia. *Neuron* 48 (3):509–520.

Hubbard, Edward M., A. Cyrus Arman, Vilayanur S. Ramachandran, and Geoffrey M. Boynton. 2005. Individual differences among grapheme-color synesthetes: Brain-behavior correlations. *Neuron* 45 (6):975–985.

Hubbard, Edward M., David Brang, and Vilayanur S. Ramachandran. 2011. The cross-activation theory at 10. *Journal of Neuropsychology* 5 (2):152–177.

Hubbard, Edward M., Manuela Piazza, Philippe Pinel, and Stanislas Dehaene. 2005. Interactions between number and space in parietal cortex. *Nature Reviews Neuroscience* 6 (6):435–448.

Hubbard, Edward M., Mariagrazia Ranzini, Manuela Piazza, and Stanislas Dehaene. 2009. What information is critical to elicit interference in number-form synesthesia? *Cortex* 45 (10):1200–1216.

Huettel, Scott A., Allen W. S. Song, and Gregory McCarthy. 2004. *Functional Magnetic Resonance Imaging*. Sunderland, MA: Sinauer Associates.

Hupé, Jean-Michel, Cécile Bordier, and Michel Dojat. 2012. The neural bases of grapheme-color synesthesia are not localized in real color-sensitive areas. *Cerebral Cortex* 22 (7):1622–1633.

Ischebeck, Anja, Stefan Heim, Christian Siedentopf, Laura Zamarian, Michael Schocke, Christian Kremser, Karl Egger, Hans Strenge, Filip Scheperjans, and Margarete Delazer. 2008. Are numbers special? Comparing the generation of verbal materials from ordered categories (months) to numbers and other categories (animals) in an fMRI study. *Human Brain Mapping* 29 (8):894–909.

Johnson, Donielle, Carrie Allison, and Simon Baron-Cohen. 2013. The prevalence of synesthesia: The consistency revolution. In *Oxford Handbook of Synesthesia,* ed. Julia Simner and Edward M. Hubbard, XX–XX . Oxford: Oxford University Press.

Johnson, Mark H. 2001. Functional brain development in humans. *Nature Reviews Neuroscience* 2:475–483.

——. 2011. Interactive specialization: A domain-general framework for human functional brain development? *Developmental Cognitive Neuroscience* 1 (1):7–21.

Jones, C. L., M. A. Gray, L. Minati, J. Simner, H. D. Critchley, and J. Ward. 2011. The neural basis of illusory gustatory sensations: Two rare cases of lexical-gustatory synaesthesia. *Journal of Neuropsychology* 5 (2):243–254.

Kim, Chai-Youn, and Randolph Blake. 2013. Revisiting the perceptual reality of synesthetic colour. In *Oxford Handbook of Synesthesia,* ed. Julia Simner and Edward M. Hubbard, XX–XX . Oxford: Oxford University Press.

Krekelberg, Bart, Geoffrey M. Boynton, and Richard J. A. van Wezel. 2006. Adaptation: from single cells to BOLD signals. *Trends in Neurosciences* 29 (5):250–256.

Laeng, Bruno, Kenneth Hugdahl, and Karsten Specht. 2011. The neural correlate of colour distances revealed with competing synaesthetic and real colours. *Cortex* 47 (3):320–331.

Logothetis, Nikos K., and Brian A. Wandell. 2004. Interpreting the BOLD signal. *Annual Review of Physiology* 66:735–769.

Lueck, Christian J., S. Zeki, K. J. Friston, M. P. Deiber, P. Cope, V. J. Cunningham, A. A. Lammertsma, C. Kennard, R. S. J. Frackowiak. 1989. The colour centre in the cerebral cortex of man. *Nature* 340 (6232):386–389.

Mattingley, Jason B., Anina N. Rich, Greg Yelland, and John L. Bradshaw. 2001. Unconscious priming eliminates automatic binding of colour and alphanumeric form in synaesthesia. *Nature* 410 (6828):580–582.

Maurer, Daphne. 1997. Neonatal synaesthesia: Implications for the processing of speech and faces. In *Synaesthesia: Classic and Contemporary Readings*, ed. Simon Baron-Cohen and John E. Harrison, 224–242. Malden, MA: Blackwell Publishers Inc.

Miller, Earl K., Lin Li, and Robert Desimone. 1991. A neural mechanism for working and recognition memory in inferior temporal cortex. *Science* 254 (5036):1377–1379.

Mitchell, Kevin J. 2013. Synesthesia and cortical connectivity: a neurodevelopmental perspective. In *Oxford Handbook of Synesthesia*, ed. Julia Simner and Edward M. Hubbard, XX–XX . Oxford: Oxford University Press.

Naccache, Lionel, and Stanislas Dehaene. 2001. The priming method: Imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. *Cerebral Cortex* 11 (10):966–974.

Neufeld, Janina, Chris Sinke, Markus Zedler, Wolfgang Dillo, Hinderk M. Emrich, Stefan Bleich, and Gregor R. Szycik. 2012. Disinhibited feedback as a cause of synesthesia: Evidence from a functional connectivity study on auditory-visual synesthetes. *Neuropsychologia* 50 (7):1471–1477.

Niccolai, Valentina, Tessa M. van Leeuwen, Colin Blakemore, and Petra Stoerig. 2012. Synaesthetic perception of colour and visual space in a blind subject: an fMRI case study. *Consciousness and Cognition* 21 (2):889–899.

Niccolai, Valentina, Edmund Wascher, and Petra Stoerig. 2012. Distinct neural processes in grapheme-colour synaesthetes and semantic controls. *The European Journal of Neuroscience* 36 (11):3593–601.

Nikolic, Danko, Philipp Lichti, and Wolf Singer. 2007. Color opponency in synaesthetic experiences. *Psychological Science* 18 (6):481–486.

Nunn, Julia A., L. J. Gregory, M. J. Brammer, S. C. R. Williams, D. M. Parslow, M. J. Morgan, R. G. Morris, E. T. Bullmore, S. Baron-Cohen, and J. A. Gray. 2002. Functional magnetic resonance imaging of synesthesia: Activation of V4/V8 by spoken words. *Nature Neuroscience* 5 (4):371–375.

Palmeri, Thomas J., Randolph Blake, René Marois, Marci A. Flanery, and William Whetsell Jr. 2002. The perceptual reality of synesthetic color. *Proceedings of the National Academy of Sciences of the United States of America* 99:4127–4131.

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

Petersen, Steven E., P. T. Fox, M. I. Posner, M. Mintum, and M. E. Raichle. 1988. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 331 (6157):585–589.

Petroff, Ognen A. C. 2002. GABA and glutamate in the human brain. *The Neuroscientist* 8 (6):562–573.

Ramachandran, V. S., and David Brang. 2013. From molecules to metaphor: Outlooks on synesthesia research. In *Oxford Handbook of Synesthesia*, ed. Julia Simner and Edward M. Hubbard, XX–XX . Oxford: Oxford University Press.

Ramachandran, Vilayanur S. and Hubbard, Edward M. 2001a. Psychophysical investigations into the neural basis of synaesthesia. *Proceedings of the Royal Society Biological Sciences Series B* 268 (1470):979–983.

——. 2001b. Synaesthesia: A window into perception, thought and language. *Journal of Consciousness Studies* 8 (12):3–34.

Rich, Anina N., and Jason B. Mattingley. 2013. The role of attention in synesthesia. In *Oxford Handbook of Synesthesia,* ed. Julia Simner and Edward M. Hubbard, XX–XX . Oxford: Oxford University Press.

Rich, Anina N., Mark A. Williams, Aina Puce, Ari Syngeniotis, Matthew A. Howard, Francic McGlone, and Jason B. Mattingley. 2006. Neural correlates of imagined and synaesthetic colours. *Neuropsychologia* 44 (14):2918–2925.

Robertson, Lynn C. 2003. Binding, spatial attention and perceptual awareness. *Nature Reviews Neuroscience* 4 (2):93–102.

Rouw, Romke and H. Stephen Scholte. 2007. Increased structural connectivity in grapheme-color synesthesia. *Nature Neuroscience* 10 (6):792–797.

——. 2010. Neural basis of individual differences in synesthetic experiences. *The Journal of Neuroscience* 30 (18):6205–6213.

Rouw, Romke, H. Stephen Scholte, and Olivia Colizoli. 2011. Brain areas involved in synaesthesia: a review. *Journal of Neuropsychology* 5 (2):214–242.

Sagiv, Noam, Julia Simner, James Collins, Brian Butterworth, and Jamie Ward. 2006. What is the relationship between synaesthesia and visuo-spatial number forms? *Cognition* 101 (1):114–128.

Seron, Xavier, Mauro Pesenti, Marie-Pascale Noel, Gérard Deloche and Jacques-André Cornet. 1992. Images of numbers: Or 'When 98 is upper left and 6 sky blue'. *Cognition* 44 (1–2):159–196.

Simner, Julia, Jennifer Harrold, Harriet Creed, Louise Monro, and Louise Foulkes. 2009. Early detection of markers for synaesthesia in childhood populations. *Brain*, 132:57–64.

Simner, Julia, and Edward M. Hubbard. 2006. Variants of synesthesia interact in cognitive tasks: Evidence for implicit associations and late connectivity in cross-talk theories. *Neuroscience* 143 (3):805–814.

Simon, Olivier, Jean-François Mangin, Laurent Cohen, Denis Le Bihan, and Stanislas Dehaene. 2002. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron* 33 (3):475–487.

Sinke, Chris, Janina Neufeld, Hinderk M. Emrich, Wolfgang Dillo, Stefan Bleich, Markus Zedler, and Gregor R. Szycik. 2012. Inside a synesthete's head: A functional connectivity analysis with grapheme-color synesthetes. *Neuropsychologia* 50 (14):3363–3369.

Sinke, Christopher, John H. Halpern, Markus Zedler, Janina Neufeld, Hinderk M. Emrich, and Torsten Passie. 2012. Genuine and drug-induced synesthesia: A comparison. *Consciousness and Cognition* 21 (3):1419–1434.

Smilek, Daniel, Alicia Callejas, Mike J. Dixon, and Philip M. Merikle. 2007. Ovals of time: Time-space associations in synaesthesia. *Consciousness and Cognition* 16 (2):507–519.

Smilek, Daniel, Mike J. Dixon, Cera Cudahy, and Philip M. Merikle. 2001. Synaesthetic photisms influence visual perception. *Journal of Cognitive Neuroscience* 13 (7):930–936.

Smilek, Daniel, Kelly A. Malcolmson, Jonathan S. A. Carriere, Meghan Eller, Donna Kwan, and Michael Reynolds. 2007. When '3' is a jerk and 'E' is a king: Personifying inanimate objects in synesthesia. *Journal of Cognitive Neuroscience* 19 (6):981–992.

Spalding, John M. K., and Oliver Zangwill. 1950. Disturbance of number-form in a case of brain injury. *Journal of Neurology, Neurosurgery, and Psychiatry* 12:24–29.

Specht, Karsten, and Bruno Laeng. 2011. An independent component analysis of fMRI data of grapheme-colour synaesthesia. *Journal of Neuropsychology* 5 (2):203–213.

Sperling, Julia M., David Prvulovic, David E. J. Linden, Wolf Singer, and Aglaja Stirn. 2006. Neuronal correlates of graphemic colour synaesthesia: A fMRI study. *Cortex* 42 (2):295–303.

Steven, Megan S., Peter C. Hansen, and Colin Blakemore. 2006. Activation of color selective areas of visual cortex in a blind synesthete. *Cortex* 42 (2):304–308.

Summerfield, Christopher, Emily H. Trittschuh, Jim M. Monti, M.-Marsel Mesulam, and Tobias Egner. 2008. Neural repetition suppression reflects fulfilled perceptual expectations. *Nature Neuroscience* 11 (9):1004–1006.

Tang, Joey, Jamie Ward, and Brian Butterworth. 2008. Number forms in the brain. *Journal of Cognitive Neuroscience* 20 (9):1547–1556.

Terhune, Devin B., Sarah Tai, Alan Cowey, Tudor Popescu, and Roi Cohen Kadosh. 2011. Enhanced cortical excitability in grapheme-color synesthesia and its modulation. *Current Biology* 21 (23):2006–2009.

Thirion, Bertrand, Philippe Pinel, Sébastien Mériaux, Alexis Roche, Stanislas Dehaene, and Jean-Baptiste Poline 2007. Analysis of a large fMRI cohort: Statistical and methodological issues for group analyses. *Neuroimage* 35 (1):105–120.

Treisman, Anne M. 1980. A feature-integration theory of attention. *Cognitive Psychology* 12:97–136.

van Leeuwen, Tessa M., Hanneke E.M. den Ouden, and Peter Hagoort. 2011. Effective connectivity determines the nature of subjective experience in grapheme-color synesthesia. *The Journal of Neuroscience* 31 (27):9879–9884.

van Leeuwen, Tessa M., Karl M. Petersson, and Peter Hagoort. 2010. Synaesthetic colour in the brain: beyond colour areas. A functional magnetic resonance imaging study of synaesthetes and matched controls. *PLoS ONE* 5 (8):e12074.

Ward, Jamie, and Julia Simner. 2003. Lexical-gustatory synaesthesia: linguistic and conceptual factors. *Cognition* 89 (3):237–261.

———. 2005. Is synaesthesia an X-linked dominant trait with lethality in males? *Perception* 34 (5):611–623.

Ward, Jamie, Julia Simner, and Vivian Auyeung. 2005. A comparison of lexical-gustatory and grapheme-colour synaesthesia. *Cognitive Neuropsychology* 22 (1):28–41.

Weiss, Peter H., N. Jon Shah, Ivan Toni, Karl Zilles, and Gereon R. Fink. 2001. Associating colours with people: a case of chromatic-lexical synaesthesia. *Cortex* 37 (5):750–753.

Weiss, Peter H., Karl Zilles, and Gereon R. Fink. 2005. When visual perception causes feeling: Enhanced cross-modal processing in grapheme-color synesthesia. *Neuroimage* 28 (4):859–868.