CHAPTER 48

FROM MOLECULES TO METAPHOR

Outlooks on synesthesia research

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Introduction

The march of science usually takes place incrementally, through the slow painstaking process of acquiring new knowledge and insights. This process, which Thomas Kuhn called “normal science” leads to a “paradigm”; a framework of ideas, methodologies, and theories that is widely accepted and zealously guarded by the priesthood of that discipline. These elders regard themselves as the custodians of that paradigm and if a new observation comes along that threatens to topple the edifice, the standard reaction is to brush it under the carpet—engaging in a form of denial. Kuhn called such observations anomalies. This denial is not necessarily as unhealthy or absurd as it seems. Since most anomalies are false alarms (e.g., spoon bending, telekinesis), one can waste a lifetime pursuing them, when it is often a better idea to ignore them. But if every anomaly were ignored scientific progress would be impossible (e.g., X-rays and continental drift were anomalies in their time). Indeed some anomalies can turn our world view topsy-turvy and generate “paradigm shifts”—steering us in a new direction, opening up whole fields of enquiry.

Neurology and psychiatry, it turns out, are disciplines full of oddities ripe for investigation. One has to be careful in choosing the right anomaly to work on though, since the majority of them are bogus. Consider De Clérambault’s syndrome, which is officially recognized by psychiatrists: a young woman developing a delusion that a famous, rich older man is in love with her but is in denial about it. This is almost certainly a fabricated syndrome. Ironically the converse syndrome in which an older gentleman develops a delusion that an attractive young woman is irresistibly attracted to him but is in denial is perfectly real and much more common (S. M. Anstis, personal communication) but there is no name for it, undoubtedly because most psychiatrists who name syndromes are men.
A genuine anomaly is synesthesia. People with this curious “condition”—the subject of this book—experience jumbled sensory experiences. A stimulus (such as a sound) that would normally evoke a sensation in a single modality (hearing) spontaneously and irrepressibly evokes an unrelated sensation—e.g., vision. So, for example, the individual may experience a specific color for every given note (“C sharp is red”), or every grapheme—printed number or letter—may be tinged with a specific hue (e.g., 5 is red and 3 is green; Figure 48.1). The specificity of evoked colors remains stable over time within any given individual (Baron-Cohen et al. 1996) but the same grapheme doesn’t necessarily evoke the same color in different people (Cytowic 1989).

Synesthesia seems to defy common sense—although the very phrase “common sense” has synesthetic connotations (and this is discussed also by Keeley, Chapter 46, this volume). Recent research by a number of groups has amply confirmed a suggestion we made a decade ago (Ramachandran and Hubbard 2001a) that far from being just another odd perceptual quirk, synesthesia might hold the key to a treasury of insights into higher mental functions such as the neural and genetic basis of creativity and mathematical talent. This view of synesthesia stands in stark contrast with the notion that it is simply based on associative learning, an explanation that not only begs the question of why only some people make such associations (not to mention the selective nature of the associations, e.g., grapheme-color) but is merely a description masquerading as an explanation, taking us back into the murky waters of classical associationist psychology.

**Figure 48.1** Number-color associations for one of our synesthetes. Notice that the numbers 7 and 8 are composed of two colors each.
(that everything the brain does is based on chains of associations—which may well be true but doesn’t explain anything).

Although long regarded as a curiosity, following our two publications (Ramachandran and Hubbard 2001a, 2001b); there has been a tremendous resurgence of interest in the phenomenon. (Blakemore et al. 2005; Dixon et al. 2000; Eagleman et al. 2007; Mattingley et al. 2001; Palmeri et al. 2002; Ramachandran and Hubbard, 2003; Robertson and Sagiv 2005; Simner and Ward, 2006).

One of the first forms of synesthesia described is what Galton called “number forms.” When asked to imagine or visualize numbers (say 1 to 50) most of us have a vague tendency to imagine the numbers laid out sequentially in space in front of us in a left-to-right manner, but this assignment of numbers to spatial location is by no means obligatory or visually compelling. In some individuals, however, this number line is spontaneously evoked and not easily repressed. In these individuals, each number always occupies a specific location in space and even though they are in proper sequence, the imaginary line on which they lie is often elaborately convoluted—sometimes even doubling back on itself so that (for example) 15 might be closer to 5 in visual/geometric space than it is to 13. Examples of these unconventional yet consistent number-lines as visualized by Francis Galton’s synesthetes in 1881 are given in Figure 47.1 (Lynall and Blakemore, Chapter 47, this volume; for other examples see also Figure 7.1, Jonas and Jarick, Chapter 7, this volume).

Beyond identifying this phenomenon as an anomaly worthy of pursuit, Galton also recognized that synesthesia runs in families, providing a 100-year precursor to current genetic work on synesthetes.

Examining this little-studied variant, Ramachandran and Hubbard tried to test the veracity of number lines by measuring reaction times (RTs) on various cognitive tasks pertaining to numbers (such as the “number distance effect”; memory for number locations, etc.). The results were suggestive but not compelling. More recent work has also yielded mixed results (e.g., Brang, Teuscher, et al. 2010; Gertner et al. 2009; Jarick et al. 2009) but, overall, there seems to be a consensus emerging that at least some number-related tasks are indeed influenced by the disposition of the number line, so the phenomenon is perfectly genuine.

Why does the phenomenon arise? No explanation had been proposed since Galton discovered the effect until Ramachandran and Hubbard suggested an evolutionary explanation (Ramachandran and Hubbard 2003) based on the way representation of numbers is mapped on to spatial representations in the brain. Numbers (including concepts of sequence, ordinality, cardinality, magnitude, etc.) are relatively recent inventions in evolution—possibly as recent as a few thousand years. It would have been virtually impossible to evolve a dedicated module in the brain e.g., a “look up table”—to deal with numbers so evolution may have chosen to map numerical concepts such as natural numbers, calendars, etc. on pre-existing spatial maps in the brain that are ubiquitous (as we would on a graph paper). Ordinarily the line may be straight left-to-right but if something goes awry in this one-to-one spatial mapping the result might be a Galtonian convoluted number line; as if the graph paper had been genetically coded.
The more common forms of synesthesia (tone color, grapheme color) cry out for similar neurological explanation, based, for example, on cross-activation between brain maps dedicated to different sensory inputs (Ramachandran and Hubbard, 2001b). One recurring theme in synesthesia research, which we will consider in this article, is the extent to which the phenomenon is based on low-level cross-activation between sensory areas versus high-level associations with possible involvements with memory (and the inevitable question of how one goes about operationally distinguishing the two). As we shall see the phenomenon seems to occur in many variants spanning the whole spectrum, from spontaneous sensory cross-wiring to high-level conceptual associations (e.g., associating the letter D with not only the color green, but also with a specific gender and emotional connotation). Our own research has focused mostly on the “sensory cross-activation” variant for three main reasons. First, it is easier to do psychophysical experiments. Second, sensory variants are easier to relate to the known physiology of visual pathways that has been studied in exquisite detail. Third, they lend themselves more readily to brain imaging (e.g., Brang, Hubbard, et al. 2010; Hubbard et al. 2005). With all three in place, the phenomenon became ripe for more extensive studies.

However, “higher” forms of synesthesia have by no means been neglected, having been studied elegantly by several researchers; most notably Jamie Ward and Julia Simner. Indeed, it is precisely the fact that the phenomenon spans the whole spectrum from low-level sensations to higher-order cognitive associations that makes it so fascinating, and at times frustrating, to study (Ramachandran and Hubbard 2006). If the history of science is any guide, such “borderline” phenomena that straddle the boundary between different realms of discourse or levels of analysis can be particularly fruitful in yielding novel insights and this has certainly been shown to be true for synesthesia.

**Prevalence and Scope of Synesthesia**

Since the time Galton first described it, synesthesia was regarded as a rare condition, but recent estimates suggest an incidence of 4%; one of the most common of which appears to be grapheme-color (Simner et al. 2006). Most individuals report having had the experience for as long back in childhood as they can remember. As Galton himself noted, the condition tends to run in families and recent work suggests a genetic basis (Barnett et al. 2008; Tomson et al. 2011). Synesthesia was previously believed to be six times more common in women than in men according to research that appealed for synesthetes via newspaper ads (Baron-Cohen et al. 1996). However, Simner and colleagues showed no difference between the sexes testing a large population for synesthesia (Simner et al. 2006). Sometimes, sensory deprivation can lead to one sensory input evoking sensations in a different modality. For example, after early visual deprivation due to retinitis pigmentosa, touch stimuli can produce visual phosphenes (Armel and Ramachandran 1999) or after a thalamic lesion leading to a loss of tactile sensation, sounds can elicit touch sensations (Ro et al. 2007). These instances probably occur because the tactile or
auditory sensory input now begins to cross-activate the deprived cortical areas. These could be regarded as a form of acquired synesthesia caused, possibly, by pre-existing back projections becoming hyperactive, or through axonal sprouting, especially given the long period of time (on the order of years) between the loss of sensory input and the onset of the synesthetic experiences.

Dozens of strange forms of synesthesia and descriptions of these can be found in several recent books, reviews and edited volumes (Cytowic 1989; Grossenbacher and Lovelace 2001; Robertson and Sagiv 2005; Ramachandran and Hubbard 2001a). Although these will be mentioned in passing, this short review will mainly emphasize grapheme-color synesthesia rather than attempt a comprehensive survey of the entire field. The reason for this is that grapheme-color is one of the most common forms and also the one on which most psychophysical experiments have been done. Equally important, we have now begun to understand the anatomical and physiological basis of grapheme-color synesthesia to an extent that is not yet possible with the other more exotic variants. As such, it might provide a “model” for how we might experimentally approach the less common types.

Bearing all this in mind, we can ask several important questions—some old and some new—regarding the phenomenon.

- Is the phenomenon authentic ("real") and hence worthy of study? Or are synesthete individuals simply making it up?
- Is it an early sensory process or a high-level cognitive process such as a memory association (e.g., formed by having played with refrigerator magnets in early childhood)?
- Do the evoked colors have "quale?"
- Is it based on genes or upbringing?
- Does it have any function? Or could it be the by-product of something else that has function (The answer is Yes; see later).
- What is its neural basis?
- How does one account for the observation that poetry and art are more likely to be pursued by synesthetes? (Domino 1989; Rich, Bradshaw, Mattingley 2005; Rothen and Meier 2010; Yaro and Ward 2007).
- Does the phenomenon have broader implications?
- What are the critical tests necessary for the future of synesthesia research?

**Sensory Nature of Synesthesia**

Synesthesia is stable (i.e., has test–retest reliability) over several months (Baron-Cohen et al. 1996), which suggests that it is authentic; not confabulatory in origin. The initial evidence that it is an actual sensory process—in some synesthetes at least—rather than
a high-level cognitive one, is suggested by five lines of support (Ramachandran and Hubbard 2001a, 2001b, 2003).

First, some simple observations made on synesthetes (without formal psychophysics or brain imaging) had already suggested to us that at least in some synesthetes, the associations are sensory in nature—produced by a hardware “glitch” (whether caused by axonal cross-wiring or disinhibition or transmitter dysfunction or all three) rather than high-level associations. The old adage in clinical medicine that 90% of the diagnosis can be arrived at by simply talking to the patient has, we have found, special force in the case of synesthesia (Ramachandran and Hubbard 2001a). In these interviews we have found:

1. The same letter can have different portions colored differently, an observation that suggests a “hardware” glitch rather than a cognitive effect.
2. Intensity of synesthetic color can vary as a function of lower and upper case letters and even font; simple memory association wouldn’t be expected to vary based on low-level visual changes that don’t change the meaning of the item.
3. Synesthesia runs in families, and yet the majority of synesthetes report never discussing this condition with anyone in their immediate family.
4. There is a directional bias: synesthetic associations are typically unidirectional.
5. There are instances of blindsight for synesthesia: using illusions that render letters and numbers invisible, we have encountered two synesthetes who can nonetheless “guess” what the synesthetically evoked color is.

In addition to these informal observations there is also a wealth of more formal experimental evidence against a mere memory-association account of synesthesia. First, as the luminance contrast of the grapheme is progressively reduced, the perceived saturation of the color decreases monotonically and disappears at less than 10% contrast even though the grapheme is still clearly visible. If the color is a simple memory association there is no reason why it should be less vivid with lower contrast. The physiological basis of this effect was studied by Hubbard, Manohar, and Ramachandran (2006). Second, evidence against a memory account comes from the fact that the evoked color can lead to texture segregation (Figure 48.2). If several 2s are scattered among a random array of 5s, synesthetes can use the evoked color difference to much more rapidly group and segregate the 2s from the 5s than “normal” non-synesthetes (Palmeri et al. 2002; Ramachandran and Hubbard 2001a). Such segregation strongly suggests that the colors are evoked early in sensory processing; this segregation effect has now been elegantly confirmed by Jamie Ward and colleagues in a large population of synesthetes (Ward et al. 2010).

Third, the synesthetically evoked color can provide an input to apparent motion perception (Kim et al. 2003; Ramachandran and Azoulai 2006; Ramachandran and Hubbard, 2002). Fourth, as noted previously even for a single grapheme different regions can be tinged different colors, an observation that suggests a “hardware” glitch rather than a cognitive effect (see Figure 48.1). Fifth, subjects can adapt to synesthetically induced colors and experience McCollough color after effects (Blake et al. 2005).

Sixth, there is direct brain imaging evidence for perceptual processes (see later).
There is at least one color blind synesthete on record who reported that she could see colors in numbers that she couldn’t see in the real world; referring to them as “Martian colors.” Her color anomaly, caused by deficient cone pigments, allowed her to see only a limited range of real colors. But perhaps the color neurons in V4, having been specified genetically, were largely intact and were being indirectly stimulated by cross-activation via graphemes (Ramachandran and Hubbard 2001a). This again negates the memory association theory and supports the sensory cross-activation theory.

These experiments establish the sensory nature of synesthesia but, as we shall see later, this is only true of a subset of synesthetes (“lower synesthetes”). It should also be added that the view that some types of synesthesia are caused by sensory cross-activation is by no means universal. There are people who still believe—in spite of the evidence cited earlier—that all types of synesthesia are the result of higher-level conceptual or linguistic associations. This harks back to the dark ages of classical “associationist” psychology. Taken collectively all these observations support the “early sensory cross-activation” theory, but what is the underlying physiological basis?

**Physiological Basis**

The visual grapheme area is located in the fusiform gyrus which represents visual appearance and is adjacent to color area V4 in the same gyrus. Since the condition is hereditary, it has been suggested that there is an accidental cross-activation between these areas caused by a gene mutation that causes either defective pruning of axons (Ramachandran
and Hubbard 2001a) or disinhibition (Armel and Ramachandran 1999). This has been called the sensory cross-activation hypothesis. This is consistent with the observation that Roman numerals (e.g., V or VI) are ineffective in evoking the color in some synesthetes; for those individuals, it’s the visual appearance of the numeral that is critical—not the abstract idea of number. As noted earlier, all this appears to be characteristic of only a subset of synesthetes whom we call “lower synesthetes.” A second group called “higher synesthetes” associate the color with more abstract numerical concepts; color is triggered not only by graphemes (visual shapes of numbers) but also by the abstract idea of numerical sequences, even embodied in days of the week or months of the year; so called “calendar synesthetes” or time-space synesthesia (Brang, Teuscher, et al. 2010). It has been suggested that in these higher synesthetes, the cross-wiring occurs higher up in the vicinity of the angular gyrus where more abstract numerical ideas are represented (Ramachandran and Hubbard 2001a). The ratio of “higher” to “lower” synesthesia is not known, but anecdotal evidence suggests that it may be as high as 2:1 reflecting a potentially bimodal distribution (Rouw and Scholte 2010). It should also be noted that in some higher synesthetes the first letter of a word determines the color of that word, suggesting that the grapheme/phoneme-word “package” as a whole evokes the color.

Brain imaging studies (using functional magnetic resonance imaging (fMRI)) which allow precise localization of V4 support the notion that lower synesthetes have cross-activation in the fusiform gyrus between letter and color areas (Hubbard et al. 2005). This result was recently extended using magnetoencephalography (MEG), replicating the activation of V4 color area in synesthetes watching achromatic graphemes (Brang, Hubbard, et al. 2010). Moreover, as magnetoencephalography (MEG) is able to capitalize on temporal aspects of neural processing, Brang and colleagues demonstrated near simultaneous activation of V4 and grapheme regions, beginning as early as 110 ms after stimulus onset.

More compelling evidence for this hypothesis is the recent finding, using diffusion tensor imaging, of an actual increase of connectivity in the fusiform gyrus and the superior parietal lobule of grapheme-color synesthetes (Rouw and Scholte 2007), exactly as we had predicted (Ramachandran and Hubbard 2001a). This finding was also replicated by Jäncze and colleagues (2009), albeit with a more liberal statistical threshold. Such selective “cross-wiring” may be based on transcription factors that lead to selective local expression of the synesthesia gene. Besides studies assessing fractional anisotropy (Rouw and Scholte 2007), voxel-based morphometry (VBM) has also been used to demonstrate that synesthetes have increased gray matter volume compared to non-synesthetes in regions of the inferior temporal lobe, implicated in both grapheme and color processing (Jäncze et al. 2009; Weiss and Fink, 2009). Further, Rouw and Scholte (2010) also demonstrated strong differences in VBM between synesthetes who project the synesthetic colors into the world (projectors) and those who experience the colors only in their minds eye (associators). Critically, projectors relative to associators showed large differences in gray matter volume in the sensory systems (visual cortex, auditory cortex, and motor cortex), consistent with the notion that they experience synesthetic colors as perceptual qualia. Associators, however, differed from projectors in gray matter volume within the hippocampus and parahippocampus, confirming subjective reports from
synesthetes that the experience is associative in nature, more akin to memory recall than a sensory experience.

**Top-Down and Contextual Effects**

Saying that synesthesia involves cross-activation (by which one means the spontaneous inevitable activation of neurons in one map by those in another) doesn’t imply that the process cannot be influenced by top-down processes. For example, in Figure 48.3 which is a large 5 made up of little 2s one can use a mental zoom lens to focus on the big 5 or the little 2s and for synesthetes the color is seen to switch correspondingly (Ramachandran and Hubbard 2001b) which implies that top-down attentional focus can modulate the cross-modal activation in the fusiform gyrus.

The second experiment (Figure 48.4) used an ambiguous grapheme (“A” or “H”) embedded either in between “T” and “E” (as in “THE”) or between “C” and “A” (“CAT”). The color of the grapheme then depended on which letters the central letter was grouped with, proving that the linguistic categorization of the grapheme, based on spelling, can determine the induced synesthetic colors (Ramachandran and Hubbard, 2001b). The role of linguistic effects (including phonemic and semantic effects) has since then been shown by several other groups. Simner and Ward (2006) showed that individuals who experience tastes in response to words (lexical-gustatory synesthetes) actually perceive the taste before they can say the associated word (while the word is still on the tip of the tongue)—demonstrating this gustatory sensation arises from semantic meaning. The significance of semantic activation was recently shown in grapheme-color synesthesia.
using event-related potentials to record synesthetes’ brainwaves (Brang et al. 2008; Brang, Kanai, et al. 2011). In this study, sentences were presented one word at a time, ending with a congruent or incongruent color word (“The sky is BLUE” versus “The sky is RED”) OR ending with a congruent or incongruent synesthetic grapheme (“The sky is 4” versus “The sky is 7”). Brainwaves in the grapheme condition showed that synesthetic colors are processed in the brain for semantic meaning and context more quickly (approximately 150 ms) than color words. In addition to semantic effects in grapheme-color synesthesia, the saturation and luminance of the color experienced with each grapheme seems to be modulated by linguistic factors, specifically the frequency of letter and number use in a language (Beeli, Esslen, and Jäncke 2007; Smilek et al. 2007) and similarly by numerical magnitude (Cohen Kadosh, Henik, and Walsh, 2007).

Finally, some synesthetes report that imagined letters (visualized in the mind’s eye) are, paradoxically more vividly colored than actual printed ones. For example, when you look at a white printed letter, the bottom-up activity in V4 caused by the white “clashes” with the red color induced by cross-activation; but for top-down imagined letters even though the activity in fusiform number nodes is weaker the final experienced color is stronger because there is no contradictory bottom-up information (Ramachandran and Hubbard 2001a).

**Learned or Acquired?**

Despite the overwhelming evidence for a role of genes in synesthesia (as discussed later), one still hears the remark that the phenomenon is acquired through learning. Of course learning *must* play a role given that the shapes of numbers vary from culture
to culture and we are not born with grapheme coding neurons in the fusiform. What is inherited, however, is the predisposition to link certain brain areas (e.g., number and color regions). If synesthesia is present from birth and the exact pattern of letter-to-color mappings is acquired throughout development, what gives rise to synesthetic colors for a nascent grapheme-color synesthete? One of the most promising models proposes that prior to letter specialization, synesthetic associations begin as colors paired with the basic graphemic features (line segments, curves, basic shapes) present in low-level visual centers (Brang, Hubbard, et al. 2010); it is only after this point during development that synesthetic colors are redefined and tuned to individual graphemes. This is clearly the case with luminance, where synesthetes and non-synesthetes alike pair round objects (including the letter O) with white, and jagged lines (including the letter X) with black (Spector and Maurer, 2011). Furthermore, visually similar letter-forms appear to be associated with similar synesthetic colors (Brang, Rouw, et al. 2011). Moreover, this relationship is expressed more strongly in projectors than associators, consistent with our findings that increased connectivity between V4 and grapheme regions is more likely to be present in projectors (Rouw and Scholte 2007). Our findings are consistent with preliminary work by Hubbard and colleagues (2005), who demonstrated greater synesthetic color similarity within the letter-groups “KVWXYZ” or “CUDOPQ” than when compared across the letter-groups, reflecting the pairing of visually similar letters with similar synesthetic colors.

While familial studies suggest that one is predisposed to having synesthesia based on genetic influences, the notion of how the associations develop and which particular synesthesia emerges within an individual likely involve cultural/behavioral factions on top of predispositions. The latter question is a particularly interesting case, in asking what causes one synesthete to see colors with tones and another synesthete to see colors with numbers. The easiest explanation to this difference is that each form of synesthesia is based on unique and independent genes, but this doesn't fit with the well-established finding that having one form of synesthesia increases the likelihood you will have a second or third form as well, suggesting the genetic undertones only impose a predisposition to having synesthesia in general. If the genetic basis for synesthesia is invariant to the specific form, it is an open question of whether the child of two grapheme-color synesthetes could be “made” into a tone-color synesthete with extensive musical training during childhood. However, recent work by David Eagleman and colleagues suggests that there may in fact be “islands” of synesthetes, such that certain types of synesthesias cluster together within and across individuals (Tomson et al. 2011). But even within these clusters this question remains pertinent. As time-space synesthesia (experiencing a spatial layout or spatial-form for months of the year and other time sequences) is tightly linked with grapheme-color synesthesia (Sagiv et al. 2006), would this shared (latent) underlying mechanism allow individuals with only time-space synesthesia to learn grapheme-color correspondences more easily?

While the majority of the work examining how synesthesia is coded (either through inheritance or development/culture) has focused on grapheme-color synesthesia, preliminary work has extended this research to time-space synesthesia. In time-space
synesthesia, months of the year exist in a highly memorable and affect spatial layout, most often in the form of a circle (Brang, Teuscher, et al. 2010; Eagleman, 2009). While the preferred direction may mimic that of a clock, the spatial organization of the months on the circle differs from the pattern on a clock-face (Eagleman 2009). For example, January is no more likely to occur at the 12 or 1 o’clock position than it is to occur at any other position on the clock-face, suggesting that this is not due to imprinting of features from early on in development. Analyzing these circular forms further, however, we find that approximately 75% are arranged in a clockwise direction (with January preceding February according to the layout of a clock) and approximately 25% in a counterclockwise direction. Owing to the strong influence of heredity on this form of synesthesia, Brang and colleagues demonstrated that this difference is mainly driven by the handedness of the individual synesthete, such that 80% of left-handed synesthetes showed a counter-clockwise arrangement, compared to only 17% of right-handed individuals (Brang, Teuscher, et al. 2011).

Consistent with the notion that synesthesia is partially mediated by learning, synesthetes often report that newly acquired languages develop synesthetic colors of their own. While the pattern of this transfer has not been well studied (but see Mills 2002; Witthoft and Winawer 2006), subjective reports suggest that colors transfer due to a combination of phonetic and graphemic similarity. One synesthete who was learning Russian and posted on Sean Day’s Synesthesia List exemplifies this idea:

When there is a letter like P (colored slightly bluish violet), which in Russian is pronounced like R (colored burgundy), the symbol P would take on a reddish-purple tint when in the context of the Cyrillic alphabet. Thus, the same symbol could have a color different from its English look-alike and the English letter it sounds like . . .

Furthermore, recent research has taken the idea of synesthetic transfer into the laboratory setting and shown that the synesthesia can transfer to novel scripts through visual features by mere experience (Mroczko et al. 2009).

**Defining the Limits of Synesthesia**

The term synesthesia has been applied liberally throughout the decades, and no clear consensus exists to draw a line between the form of synesthesia of which this book is about, and other similar phenomena and conditions ranging from metaphorical language to vivid drug-induced hallucinations. Conservative boundaries defining synesthesia require the association to be (1) stable over time, (a 7 experienced as green should always be green), (2) involuntary and automatic (experiences do not require effort), and (3) both memorable and affect-laden (a number printed in the “incorrect” color may make a synesthete uncomfortable; Baron-Cohen et al. 1996; Cytowic 1989). However, many phenomena clearly encapsulate one or more of these qualifications,
but there is too little evidence to fully classify their relationship to “typical” synesthetic phenomena. Specifically, many phenomena maintained as genuine forms of synesthesia occur from either non-developmental origins or appear largely conceptual, removed from the sensory percepts that originally drew so much interest to synesthesia. Indeed many of these modern forms appear dangerously close to what many would describe as simple metaphor.

**Ordinal linguistic personification**

At the edge of this boundary is ordinal linguistic personification, a condition in which individuals report specific, highly memorable and affective personified traits for numbers and/or letters (Simner and Holenstein, 2007). The cross-activation (of brain maps) model explains many aspects of synesthesia, but given the complex reports of some synesthetes that each grapheme has a certain personality and sex (Ramachandran and Hubbard 2006), we are unsure whether it can be generalized to all forms of synesthesia, as personality and gender are broadly distributed processes lacking focal modules. One possibility is that as the brain may tend to binarize the world (black/white, male/female, good/evil, ugly/beautiful, yin/yang, etc.) to simplify cognitive processing, and OLP may reflect an enhancement of the connections between numbers and areas responsible for these binarizations. Further, perhaps certain shapes are more feminine (or masculine) through association even in “normals” and these are made explicit by the enhanced connectivity caused by synesthesia genes. While research in this area is scant, Amin and colleagues (2011) have put forward preliminary evidence using fMRI that OLP experiences rely on the precuneus, which past work has implicated in self-referential processes, but also more generally with imagery. One remaining possibility is that while many of us also make such seemingly random associations from time to time, we don’t get “stuck” with them. In synesthesia, the proclivity to make such Hebbian associations may have a “self-enhancing” tendency—akin to kindling—once they are set in motion, resulting in the firm belief that, say, “8 is female and has a demanding personality; wants to be a larger number than she is and is difficult for the other numbers to be around.”

**Mirror neurons and synesthesia**

A curious form of acquired synesthesia can be observed in patients with phantom limbs. Such patients have undergone amputation although continue to report sensation or even pain in the lost body part. If a system of mirrors is used to optically resurrect the phantom limb and it is made to appear visually that the phantom is being touched with a pencil, the subjects feels her phantom being touched even though no part of her body is being touched at all. This implies that the visual sensations must be feeding back to activate somatosensory maps in the brain (Ramachandran,
Rogers-Ramachandran, and Cobb 1995). Even more remarkably it was noticed that patients with phantom arms will experience their phantom being touched in a precisely localized manner even if they merely observe another person’s intact arm being touched (Ramachandran and Brang 2009). Similarly they experienced their phantom moving if the experimenter put his own hand in the vicinity of the phantom and moved it. Such effects may be mediated by a class of neurons in the premotor cortex and parietal lobes called “mirror neurons” (Rizzolatti et al. 1996). These neurons are activated when a subject moves his hand—as expected. But surprisingly they also fire when the subject watches another person making similar movements. Such activation does not lead a normal observer to experience sensations presumably because the regular somatosensory neurons (i.e., those that are not mirror neurons) signal the absence of real proprioceptive and tactile inputs. When the arm is amputated, however, this normal sensory input is removed, leading the patient to quite literally experience the touch (or proprioceptive) sensations in the phantom (Ramachandran and Brang 2009). The patient also noted that watching another person’s intact hand being rubbed caused relief from his phantom pain. There is anecdotal clinical evidence that synesthesia is more common in temporal lobe epilepsy. This can be explained by assuming that the repeated seizure volleys might indiscriminately strengthen certain brain connections through a process known as kindling. This would lead to pathological cross-activation (Ramachandran and Hubbard 2001a).

**Touch-emotion synesthesia**

Certain rarer forms of “congenital” synesthesia can also be partially explained by the cross-activation model. For example, some people “taste shapes.” For these synesthetes, every taste has a shape which they perceive alongside their gustatory experience (i.e., chicken tastes “pointy,” Cytowic 1989). It has been suggested that this is caused by cross-activation between taste neurons in the insula and S2 somatosensory cortex involved in discerning tactile texture and shape (Ramachandran and Hubbard 2001a). Similarly, in a newly discovered form of synesthesia, tactile textures evoke highly specific emotions (e.g., velvet = guilt). We postulate that there may be enhancement of connections that already exist between tactile textures (S2 cortex) and adjacent insula (emotion) as well as between the insula and the orbito-frontal cortex (Ramachandran and Brang 2008). Not coincidentally, perhaps similar “touch to emotion” activations are also common in cross-sensory metaphors (“rough day,” and “touching remark”) suggesting that metaphors may, speaking statistically, respect the same cross-sensory anatomical constraints as “pathological” synesthesia (Ramachandran and Hubbard 2001a). Enhanced cross-activations are most likely to occur between adjacent brain regions given that such regions are most likely to be already partly connected to begin with. But this isn’t always true because pre-existing connections can also exist (less frequently) between far-flung brain regions that are functionally linked. The synesthesia gene(s) could enhance these connections.
Bidirectionality in synesthesia

By and large, synesthetes report these experiences are unidirectional, such that numbers may automatically elicit colors, yet colors will not cause the automatic percept of a number. While these subjective reports have been accepted for a number of years, mounting evidence from neuroimaging and behavioral studies suggest that synesthesia may be partially, if not unconsciously, bidirectional in grapheme-color synesthesia. Knoch et al. (2005) elegantly showed that synesthetes, but not controls, implicitly activated numerical representations when randomly generating colors. In addition, synesthetes instructed to choose the numerically larger of two numbers (the 5, when 4 and 5 are presented together) showed slowed reaction times if the numbers were colored with a numerically incongruous synesthetic color (4 printed in the color induced by 8, and 5 printed in the color induced by 2; Cohen Kadosh et al. 2005).

Do drug-induced synesthesias utilize the same mechanisms?

Research stemming from the mid nineteenth century has shown that some drugs (e.g., LSD and mescaline) can cause a blending of the senses in typical individuals (for a review, see Cytowic 1989). While these hallucinations are generally believed to be arbitrary and extant experiences, Klüver (1942) and Simpson and McKellar (1955), among others (e.g., Horowitz 1975; Siegel 1977), have shown that the visual experiences elicited by pharmacological agents tend to follow comparable patterns or themes between individuals. Most notably, subjects report similar “form constants”—visual patterns or shapes that are imbued with movement and color—as opposed to viewing complex landscapes or scenes (Klüver 1942). Critically, Cytowic and Eagleman (2009) point out that the visual sensations and form constants produced by LSD and mescaline are markedly similar to the reports of synesthetes, giving way to the hypothesis that drug induced synesthetic experiences may match the psychophysical definitions and neural mechanisms underlying those of developmental synesthesia.

Why Was the Gene Conserved?

While a proven genetic basis for synesthesia remains elusive, the phenomenon tends to run in families, as nearly 50% of synesthetes report a first-degree relative with the phenomenon (Barnett et al. 2008; Baron-Cohen et al. 1996). Importantly, the “type” of synesthesia can vary within families, and the qualitative experience usually differs even between individuals of the same family. Preliminary work by Brang and Ramachandran (2007) suggested previously, based on pharmacological models of synesthesia, that genes on chromosome 13 may be involved in this phenomenon. Two recent genetic
studies (Asher et al. 2009; Tomson et al. 2011) on synesthetes have located various non-overlapping hotspots suggesting either a lack of power from the derived sample sizes, or that the phenomenon is due to several genes.

In asking why any synesthesia gene would be maintained through evolution, one first must consider whether synesthesia is merely epiphenomenal, and the related genes serve some totally unrelated purpose and synesthesia operates as simply a by-product. However, as the causality cannot be known at present, we must assume for the time being that this is not (at least not fully) the explanation. To begin to understand why synesthesia would have been maintained, we can ask whether it is a gift or a curse? Most people who have it claim it enriches their lives. For example, if any letter in a word (but especially the first letter) evokes the same color as the referent of that word (say there happen to be blue letters within the word sea, for example), synesthetes report a pleasing harmony between word and letter, which has great aesthetic appeal. However, subjective enjoyment of the experience is not itself a good argument for the conservation of the gene (presuming of course synesthesia is not merely epiphenomenal). What we can point to, however, are the tangible links between synesthesia and more adaptable traits, and specifically what the general consequences of synesthesia are.

**Consequences of synesthesia: memory**

Many number-form synesthetes have told us (Ramachandran and Hubbard 2006) that they use their number lines to “see hidden relationships” between numbers and numerical calculations, by “wandering the numerical landscape” and adopting multiple allocentric viewpoints of the line. This is most certainly the case for some synesthetes, including Daniel Tammet who, using his synesthesia, memorized pi to 22,514 digits. A clever experiment by Smilk et al. (2002) suggests that synesthesia can enhance memory in all synesthetes, but not to the degree of Tammet’s ability. They asked a grapheme-color synesthete to memorize a random selection of letters which were either randomly colored or colored in a manner consistent with their synesthesia. On subsequent testing they found that the letters with concordant colors were more accurately remembered. Luria (1969) described an individual (“S”) whose prodigious memory was based largely on using synesthetic associations evoked by the things to be memorized. Enhancements of memory based on synesthesia have also been reported more recently by other groups (Brang and Ramachandran 2010; Yaro and Ward 2007).

**Consequences of synesthesia: enhancements in primary sensory processing**

Outside the realm of memory research, there is accumulating evidence of generalized processing benefits in synesthesia, providing a provocative evolutionary hypothesis.
Contrary to notions that synesthesia serves no benefit, recent work suggests synesthesia may alter primary sensory processes. Barnett et al. (2008) show differences in early visual perception and there are studies showing increased (unimodal) perceptual sensitivity in synesthetes (Banissy et al. 2009; Yaro and Ward 2007). Furthermore, research from our own laboratory suggests that grapheme-color synesthetes have lower color detection thresholds in a psychophysically low-level visual task (Wagner et al., in preparation). Taken collectively, these data suggest that synesthesia is associated with enhanced primary sensory processing as well as the integration between the senses. If validated, this idea would suggest that synesthesia serves to enhance normal sensory processing at a general level, better utilizing unisensory and multisensory processes.

Consequences of synesthesia: metaphor

If the gene for synesthesia were more diffusely expressed, the result would be an excess of cross-wiring throughout the brain. If abstract concepts are also represented in specific brain regions, then such diffuse cross-wiring would confer a propensity to link seemingly unrelated concepts represented in far-flung brain areas; the basis of metaphor ("sharp cheese" or "Juliet is the sun"). Hence, we would expect a higher incidence of synesthesia in artists, poets and novelists who all have the ability to link unrelated ideas. This “hidden agenda” might explain the high prevalence of the otherwise useless synesthesia gene (Ramachandran and Hubbard 2001a). This is analogous to the manner in which the sickle cell anemia gene survived in the Mediterranean, despite being lethal in the double recessive form, because the single recessive gene confers immunity from malaria. The gene mutation-based cross-wiring hypothesis also receives support from the fact that if you have one type of synesthesia you are also more likely than chance to have one or two other types (again, this would depend the gene being expressed more widely but in a patchy manner; Ramachandran and Hubbard 2001a).

The nature of the link between synesthesia and metaphor remains elusive given that synesthesia involves arbitrarily (in a conceptual sense) connecting two unrelated things (e.g., color and number) whereas there is a non-arbitrary conceptual connection between Juliet and the sun. One potential solution to this problem comes from realizing that any given word only has a finite set of strong first order associations (sun = warm, nurturing, radiant, bright) surrounded by a penumbra of weaker second order associations (sun = yellow, flowers, beach, etc.) and third and fourth order associations that fade away like an echo. The overlapping region between two halos of associations (e.g., Juliet and the sun; both are radiant, warm and nurturing)—the basis of metaphor—exists in all of us but may be larger and stronger in synesthesia as a result of the cross-activation gene. In this formulation synesthesia is not synonymous with metaphor but the gene that produces synesthesia confers a propensity towards metaphor. A side effect of this may be that associations that are only vaguely felt in all of us (e.g., masculine or feminine letters or good and bad shapes produced by subliminal associations) may become more
explicitly manifest in synesthetes, a prediction that has been tested experimentally (e.g., Ward et al. 2006).

**Future Directions for Research**

As alluded to in the previous sections, some of the most needed research in the field is identifying the relationships between inherited synesthesias (e.g., grapheme-color synesthesia) and other conditions and phenomena that mimic these characteristics. Specifically, what aspects of synesthesia are based on pharmacology (intensity of the experience, numbers of synesthesia, or simply possessing synesthesia in general), and how does altering these neurotransmitters affect the experience of synesthesia in the normal population as well as in synesthetes; i.e., does a synesthete who has taken LSD experience novel forms and/or an enhancement of their current synesthesia? Similarly, what is the relationship between synesthesia and typical cross-modality interactions seen in the general population? As noted throughout the twentieth century, information presented in one sensory modality will alter processing in a second unrelated modality in all individuals (e.g., Hershenson, 1962). Preliminary evidence from our own lab suggests that synesthetes show a generalized increase in communication between the senses, suggesting that synesthesia may have piggy-backed on these phylogenetically old mechanisms (Brang, Williams, and Ramachandran 2012). Lastly, what are the genetic mechanisms underlying synesthesia, and what effect do they promote in the general population (i.e., what is the *normal* purpose of these genes). Do family members of synesthetes who themselves are not synesthetic (i.e., carriers) show latent synesthetic associations or an enhanced ability to make synesthesia-like associations?

**Conclusion**

In summary, these experiments conducted by several groups in the last decade have spawned a new era of investigation into this strange phenomenon that so intrigued Galton. While the topic has been discussed for over a century, the exact definition of synesthesia and what constitutes a “true” form of the phenomenon remains open to debate. Such semantic distinctions aside (as Francis Crick once said its best not to get preoccupied with definitions too early in the game; “That's best left to philosophers”), few would disagree that studies on synesthesia in the last decade have taken us on a journey—not in any particular order—from genes (affecting S2a receptors, perhaps) to anatomy (e.g., fusiform and angular gyri) to psychophysics (texture segregation/contrast effects/apparent motion/McCollough effect/Stroop interference) to metaphor. They suggest that far from being a “fringe” phenomenon as formerly believed (or that it
is purely “conceptual” or associative in nature), synesthesia can give us vital clues toward understanding some of the physiological mechanisms underlying some of the most elusive yet cherished aspects of the human mind.

References


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