Neurophysiology of Synesthesia

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Synesthesia is an experience in which stimulation in one sensory or cognitive stream leads to associated experiences in a second, unstimulated stream. Although synesthesia is often referred to as a "neurological condition," it is not listed in the *DSM IV* or the *ICD* classifications, as it generally does not interfere with normal daily functioning. However, its high prevalence rate (one in 23) means that synesthesia may be reported by patients who present with other psychiatric symptoms. In this review, I focus on recent research examining the neural basis of the two most intensively studied forms of synesthesia, grapheme → color synesthesia and tone → color synesthesia. These data suggest that these forms of synesthesia are elicited through anomalous activation of color-selective areas, perhaps in concert with hyperbinding mediated by the parietal cortex. I then turn to questions for future research and the implications of these models for other forms of synesthesia.

Introduction

Synesthesia is an experience in which stimulation in one sensory or cognitive stream leads to associated experiences in a second, unstimulated stream. The stimulus that elicits a synesthetic experience is called the inducer, the additional sensations are called concurrents, and various forms of synesthesia are identified in the form of X → Y, in which X is the inducer and Y is the concurrent. For example, in one common form of synesthesia, known as grapheme → color synesthesia, letters or numbers are perceived as if viewed through a colored overlay [1•,2], whereas in ordinal linguistic personification, numbers, days of the week, and months of the year evoke personalities [3,4•]. In sequence → space synesthesia, numbers, months of the year, days of the week, and other ordered sequences are experienced as corresponding with precise locations in space, such as a three-dimensional view of a year as a map [5,6,7••]. "Colored hearing," which includes auditory word → color and music → color synesthesia [8–10], involves linkages that are truly cross-modal and are often considered the paradigmatic examples of synesthesia, despite being less common than the previously mentioned forms.

One problem that until recently has hindered synesthesia research is a lack of clarity in the use of the term. For example, cross-sensory metaphors are sometimes described as "synesthetic," despite the fact that they have no sensory experience associated with them. Similarly, additional sensory experiences brought on under the influence of psychedelic drugs, after a stroke, or as a consequence of blindness or deafness are sometimes considered to be forms of synesthesia. Synesthesia that arises from such nongenetic events is referred to as adventitious synesthesia to distinguish it from the more common congenital forms of synesthesia. In this review, I will focus on congenital synesthesia, which occurs in slightly more than 4% of the population (1 in 23 persons) across all of its various forms [11••]. Congenital synesthesia runs strongly in families [5,11••,12], possibly inherited as an X-linked dominant trait [13,14].

Although it is often referred to as a "neurological condition," synesthesia is not listed in either the *DSM IV* or the *ICD* classification, as it generally does not interfere with normal daily functioning. Indeed, most synesthetes report that their experiences are neutral or even pleasant [15]. Rather, like color blindness or perfect pitch, synesthesia is a difference in perceptual experience and is referred to as a neurological condition to reflect the brain basis of this perceptual difference.

The unusual reports of synesthetes may lead clinicians to think of synesthesia as a symptom of a psychiatric disorder. Its high prevalence rate means that congenital synesthesia sometimes may be found in patients who present with psychiatric conditions. However, recent research has suggested that there is no association between congenital synesthetic experience and other neurological or psychiatric conditions [16], despite case reports of impairments in spatial and numerical cognition [17] and improved memory [18,19] in these individuals. On the other hand, adventitious synesthesia occasionally may appear as a symptom of epilepsy [20] or other neurological syndromes. In order to help clinicians distinguish between congenital synesthesia and other potential psychiatric complaints, synesthesia researcher Chris Lovelace has developed a flowchart suggesting the appropriate questions and branchpoints to determine whether such reports constitute symptoms of some other psychiatric complaint

or are merely indicative of congenital synesthesia (http://cas.umkc.edu/psyc/research/scnl/syn-clinician.html).

Broadly speaking, the experiences of synesthetes are consistent across the lifespan, idiosyncratic, automatic, and involuntary, and they occur without any conscious effort on the part of the synesthete [17]. Indeed, many synesthetes report that they assumed that everyone experienced the world the same way they do and were shocked to find that others do not share these experiences. Conversely, some synesthetes report negative reactions from others upon reporting their experiences, leading them to harbor a secret fear that they were "crazy." Given the lack of information, both for individuals with synesthesia and for clinicians who might encounter them, a broader understanding of the existence and neural mechanisms of this unusual phenomenon is clearly desirable.

Neural Models of Synesthesia

In the past 5 years, a number of behavioral and functional MRI (fMRI) results have demonstrated the reality of synesthesia (for reviews, see [1•,2]). In this review, I will focus on various models of synesthetic experiences and neuroimaging studies that have been conducted to examine these proposals. To date, all neuroimaging research into the neural basis of synesthesia has been conducted on forms of synesthesia in which auditory, visual, or tactile presentation of linguistic stimuli elicits the experience of colors. However, most synesthesia researchers expect that neural models derived from these test cases may generalize to other forms of synesthesia and may thereby provide valuable insights into this fascinating phenomenon.

Neural models of synesthesia can be described at either a neurophysiologic level or an architectural level [1•]. At the neurophysiologic level, models of synesthesia differ depending on whether they suggest that synesthetic experience arises from incomplete neural pruning [21,22••] or are due to a failure to inhibit feedback in the visual system [23]. In short, the distinction might be framed as one of connections versus communication. In the pruning model, there is thought to be increased connectivity between brain regions, leading to stronger inputs in synesthetes compared with nonsynesthetes, whereas in the disinhibited feedback models, the degree of connectivity is assumed to be identical in synesthetes and nonsynesthetes, but neural communication is thought to be increased between brain regions due to a lack of inhibitory processes. Although this is an interesting debate in its own right, current fMRI methods do not allow us to distinguish between these models. After reviewing current neuroimaging data, I will return to ways in which future research, using both anatomical techniques such as diffusion tensor imaging (DTI) and voxel-based morphometry (VBM) and functional techniques such as event-related potentials or magnetoencephalography (MEG), might help to distinguish between these accounts.

Theories at the architectural level have concerned themselves with the neural mechanisms that might lead to synesthesia. Currently, there are four architectural models, which are referred to as "cross-activation," "long-range feedback," "re-entrant processing," and "hyperbinding." I will briefly discuss each of these models in turn here (for more details, see [1•]).

Cross-activation

When we began our work on synesthesia, we were struck by the fact that a key brain region for recognizing letters and numbers, the visual word form area (for a review, see [24]), lies adjacent to color-processing region hV4 [25]. Based on this observation, we proposed that grapheme → color synesthesia may arise from cross-activation between these adjacent brain regions [21,22••,26] and suggested that one potential mechanism for this would be increased retention of connections between inferior temporal regions and area V4 [27]. Given the presence of a genetic factor in synesthesia, we suggested that this factor may lead to decreased pruning of these prenatal pathways so that connections between the number grapheme area and V4 would persist into adulthood, leading to the experience of color when viewing numbers or letters. Although being adjacent to each other increases the likelihood of brain regions being connected to each other, our model suggests that it is the presence or absence of such early connections that is important, not the fact that brain regions are adjacent per se.

Long-range disinhibited feedback

Other researchers have suggested that grapheme → color may be due to disinhibited feedback from a "multisensory nexus" such as the temporo-parietal-occipital junction [23,28,29]. One finding usually taken as support for the disinhibited feedback theory is that at least some people report synesthetic experiences while under the influence of psychedelics (see [30]). However, it is unclear whether the experiences of drug-induced synesthesia, despite some superficial similarities to the experiences of congenital synesthetes, arise from the same mechanisms. In particular, the experiences of congenital synesthetes are typically generic, including color and movement, but not complex scenes or visualizations [17]. Unlike these synesthetic experiences, the experiences generated by psychedelics are often complex, including visualizations of animals and complex scenes [30]. Of course, if synesthesia is mediated by differences in neurotransmission, it may lead to unusual medication effects of which clinicians should be aware.

Re-entrant processing

A third model is something of a hybrid, in which grapheme → color synesthesia has been suggested to be due to aberrant re-entrant processing (perhaps consistent with models of disinhibited feedback) [31,32]. Smilek et al. [31]

propose that, in addition to the forward sweep of activity from V1 through V4 to posterior and then anterior inferior temporal regions (PIT and AIT, respectively), aberrant neural activity from AIT feeds back to representations in PIT and V4, leading to the experience of synesthetic colors. The main evidence used to argue in favor of the re-entrant theory over the cross-activation theory is the fact that visual context and meaning influence the experienced colors in synesthesia [32,33]; see also [21,34]. However, such top-down influences can be accounted for by appropriately specified versions of either the cross-activation or re-entrant model [1•]. Current neuroimaging data are too coarse to distinguish with certainty between these models. One source of potentially useful evidence could come from electroencephalogram (EEG) or MEG studies that examine the time course of activations in grapheme → color synesthesia. By temporally decomposing the stages of processing involved in the generation of synesthetic experiences, it may be possible to disentangle these two models. Given the relatively small distances between these brain regions, MEG might be an ideal technique for such studies.

Hyperbinding

Recently, a fourth model of synesthesia has been proposed, the "hyperbinding" model [35,36••]. Under normal circumstances, the brain must bind together information from color, form, motion, etc. into a coherent representation of the world [37], and this binding process depends on parietal mechanisms [35]. The hyperbinding model suggests that synesthesia arises through an overactivation of these same parietal binding mechanisms. Although 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, as binding must have features upon which to act. Thus, one of the previously described mechanisms for generating additional synesthetic experiences may act in concert with overactive binding mechanisms.

Multiple neural mechanisms

It also should be borne in mind 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 [22••,38]. In addition, the different models are not necessarily mutually exclusive. Indeed, as mentioned previously, 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.

Another possibility is 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, whereas feedback models have focused on word → color and tone → color synesthesia. Although 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 [14] suggests that the neurophysiologic mechanisms may be shared across different forms of synesthesia.

Neuroimaging Studies

Although there have been numerous neuroimaging studies of synesthesia, they have tended to yield somewhat inconsistent results. One thing to bear in mind when evaluating these discrepant results is that all current studies have been statistically underpowered. Standard whole-brain random effects analyses require a minimum of 20 subjects in order to allow inferences about both positive and negative findings [39]. Analyses using restricted regions of interest (ROIs) are less likely to be as severely underpowered because testing of fewer voxels reduces the adverse statistical impact of multiple comparisons. Techniques that permit delineation of individual subject areas, such as retinotopy, may similarly be less adversely affected because differences in brain anatomy are taken into consideration when examining activation patterns. Given these considerations, positive findings should be given substantially more weight than negative ones when attempting to develop models of synesthesia.

Word → color synesthesia

In the first study of synesthesia, Paulesu et al. [9] used positron emission tomography (PET) to determine whether color-selective areas of the cortex were active when auditory word → color synesthetes reported seeing colors. Subjects were presented with blocks of either pure tones or single words. Paulesu et al. [9] found that areas of the posterior inferior temporal cortex and parieto-occipital junction—but not early visual areas V1, V2, or V4—were activated during word listening more than during tone listening in synesthetic subjects but not in controls. In a follow-up, Nunn et al. [10] tested six female, right-handed auditory word → color synesthetes and six matched nonsynesthetes using fMRI, which has better spatial resolution and sensitivity than PET. Nunn et al. [10] report that left hemisphere regions involved in the processing of colors (V4/V8) are more active when word → color synesthetes hear spoken words than when they listen to tones, but not earlier visual areas such as V1 or V2. No such difference was observed in control subjects, even when they were extensively trained to imagine specific colors for specific words. Gray et al. [40] replicated these findings in another group of word → color synesthetes and found additional activations in hippocampal regions during a synesthetic color conflict situation (the "alien color effect").

Similarly, in a case study of a synesthete who experiences colors for people's names, Weiss et al. [41] report that hearing names that elicited synesthetic colors led to activity in left extra-striate cortex (near V4) but not V1. However, in another case study of an auditory word → color synesthete, Aleman et al. [42] report activation of (anatomically defined) primary visual cortex but were unable to determine if area V4 was active in this single subject.

Grapheme → color synesthesia

Hubbard et al. [22••] obtained both behavioral performance and fMRI measurements in six grapheme → color synesthetes and six nonsynesthetic controls to determine whether grapheme → color synesthesia arises as a result of activation of color-selective region hV4 in the fusiform gyrus. We used standard retinotopy techniques to identify individual visual areas and then presented subjects with black and white letters and numbers, compared against nonlinguistic symbols that did not elicit colors. We observed larger fMRI responses in color-selective area hV4 in synesthetes compared with control subjects. Importantly, we also found a correlation within subjects between our behavioral and fMRI results; subjects with better performance on our behavioral experiments showed larger fMRI responses in early retinotopic visual areas (V1, V2, V3, and hV4), consistent with claims of important individual differences among synesthetes [22••,38,43••].

Another recent study using similar methods found broadly similar results [44]. Sperling et al. [44] 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. Steven et al. [45] showed that Braille stimulation can lead to activation of V4 in a synesthete even after he or she had become blind due to retinal degeneration, suggesting that such functional differences persist in the absence of visual input.

Two other recent neuroimaging studies have used whole-brain fMRI to explore the neural bases of grapheme → color synesthesia [46,47]. Rich et al. [46] measured fMRI responses in a group of seven synesthetes and seven controls in three imaging paradigms. They first localized ROIs using colored Mondrians versus grayscale images, which should selectively activate color-selective areas. They then measured fMRI responses within these ROIs in synesthetes and controls while they 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. Unlike the two studies mentioned previously, Rich et al. [46] 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. [10] study, they found that color imagery was capable of eliciting activation in the V4 complex in both synesthetes and nonsynesthetes.

Similarly, Weiss et al. [47] examined fMRI signals in nine grapheme → color synesthetes using a two-by-two factorial design. Subjects were presented with letters that did or did not induce colors (many synesthetes report not having colors for all stimuli), with either colored or grayscale letters. Weiss et al. [47] did not observe any significant activation in early visual areas but did observe a significant activation in the left intraparietal sulcus consistent with the hyperbinding account of synesthesia. In addition, two recent transcranial magnetic stimulation (TMS) studies have shown that stimulation at parietal sites previously implicated in binding color and form disrupts the synesthetic Stroop effect [36••,48]. Interestingly, both TMS studies found a consistent effect only in the right hemisphere, whereas the fMRI study by Weiss et al. [47] found differences only in the left hemisphere.

An Integrated Model

Taken together, these results suggest that a network of brain areas is involved in the generation of synesthetic experience. Although not all studies find activation of V4, it should be noted once again that statistical power in all of the studies conducted to date was low. Because word processing involves ventral visual areas adjacent to the V4 complex [24], these areas would be constantly activated in studies of grapheme → color synesthesia, leading to a constant factor being removed from the fMRI signals when visual input was used but not when auditory input was used. This suggests that V4 activation might be more robust than would appear on a cursory examination of the published papers to date.

In addition to activation of V4, numerous studies have found activations in other regions that are specific to synesthesia. The most important of these are anterior lingual gyrus regions [9,45] involved in color naming and categorization, and intraparietal sulcus regions [9,10,46] involved in attention, binding, and multisensory processes. Especially given the converging evidence from TMS studies [36••,46], the role of parietal cortex in the genesis of synesthesia needs to be taken quite seriously.

Taken together, these results suggest that activation of color-specific visual areas (both V4 and more anterior regions) may be the origin of synesthetic experiences, which are then bound by (possibly overactive) parietal mechanisms. Alternatively, the parietal activations might reflect involvement of a "multisensory nexus" [23] that, via disinhibition, leads to synesthetic experiences. Identifying the order in which these activations occur is critical to adjudicate between these theoretical models. However, the relative order of these processes cannot be determined with fMRI, so future studies using EEG and MEG will be crucial to disentangling these hypotheses. In addition,

future EEG and MEG studies examining the time course of synesthetic experiences may help to distinguish among cross-activation, disinhibited feedback, and re-entrant models of synesthesia. DTI and VBM methods also will be useful in identifying potential anatomical differences between synesthetes and nonsynesthetes. The presence of anatomical differences would be consistent with the cross-activation theory but would not necessarily rule out the involvement of other processes such as disinhibition or hyperbinding. Clearly these are exciting days for synesthesia researchers, as there are many unanswered questions still to be explored.

Other Forms of Synesthesia

As mentioned at the outset, much of the current research has focused on grapheme → color and tone → color synesthesia. However, it should be stressed that there are quite a number of other forms of synesthesia, and it is hoped that the lessons learned from detailed investigations of grapheme → color and tone → color synesthesia will generalize to other forms. Recently, we revised and expanded our previous hypotheses concerning the neural basis of sequence → space synesthesia [21,49]. We suggest that cross-activation in the parietal cortex, particularly in the region of the angular gyrus, the ventral intraparietal area, and the lateral intraparietal area, may explain this form of synesthesia, in which ordinal sequences are experienced as having specific locations in space.

Similarly, auditory word-to-taste synesthesia may arise through cross-activation between insular regions involved in taste processing and superior temporal and/or frontal regions involved in auditory word comprehension and production [50], whereas lexical → gustatory synesthesia may arise from cross-activation between these same insular regions and somatosensory cortex in the parietal lobe. We also have suggested that ordinal linguistic personification might arise from cross-activation between regions of the left parietal cortex, including the angular and supramarginal gyri that are involved in sequence representations and adjacent regions involved in personality perception [4•]. These extensions to other forms of synesthesia have led us to suggest that anatomically constrained cross-activation may constitute a "Grand Unified Theory" of synesthesia (Hubbard et al., Unpublished data). Many future investigations will be needed to test these proposals, but it is clear that synesthesia no longer should be thought of as an anomaly or a symptom of psychiatric disease. Rather, it is an unusual experience that may even shed light on a variety of perceptual and cognitive processes.

Conclusions

Although synesthesia has been known about for more than 100 years, it has only recently become the topic of renewed scientific investigations. Although it is not a clinical disorder, it is important that clinicians be aware of synesthesia, as its high prevalence means that many individuals who come to mental health practitioners also may report synesthetic experiences. Recent research has only begun to explore the neural mechanisms that are involved in synesthesia. An emerging consensus suggests that synesthesia arises through anomalous activation of brain regions involved in certain perceptual and conceptual representations, although the exact manner by which this anomalous activation occurs remains an open question for future research. Future studies using other anatomical neuroimaging methods and evoked electrical activity will be essential to further exploration of these questions. Examining other forms of synesthesia will begin to allow us to see how general the conclusions arrived at from the study of word → color and grapheme → color synesthesia are. Finally, understanding the mechanisms whereby anomalous synesthetic experiences arise may be a useful tool to understand the neural mechanisms of other unusual sensory experiences, including such phenomena as Charles Bonnet syndrome and other forms of hallucinations.

Acknowledgments

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
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1.• Hubbard EM, Ramachandran VS: **Neurocognitive mechanisms of synesthesia.** *Neuron* 2005, **48:**509–520.

In this recent review, we discuss behavioral evidence demonstrating the reality of synesthesia and examine neural models in more detail. We also discuss a variety of open questions about synesthesia, such as whether it is uni- or bidirectional, the role of individual differences in synesthesia, and the methodological implications of such differences.

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This is the first behavioral study to compare two different models of individual differences in grapheme → color synesthesia, the higher/lower distinction proposed by Ramachandran and Hubbard and the project/associator distinction proposed by Dixon et al. The authors demonstrate that the two distinctions are not entirely overlapping and provide independent replication of both factors in understanding synesthetic experiences.

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