Synesthesia: Sensory System Interactions Producing an Altered Reality

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Abstract

Synesthesia is a neurological condition that involves abnormal sensory system interactions which lead to an altered perception of the world. Recently, there has been substantial progress in the research dedicated to understanding the mechanisms behind synesthesia, and this paper summarizes the current information about the condition from many angles. The first part of this review provides a brief history of synesthesia, followed by a description of its most common forms, with an emphasis on grapheme-colour synesthesia. The next section considers synesthesia's influences on memory, detailing which areas of the brain are active in synesthetes to cause their heightened mnemonic abilities, and is followed by an analysis of the two major theories that describe the cortical mechanisms behind synesthesia, known as cross-activation theory and disinhibited feedback theory. In order to understand the etiology of synesthesia, this paper will examine its genetic aspects, including speculations as to why the synesthesia gene has been conserved throughout evolution, and environmental influences that resulted in cases of synesthesia acquired later in life.

Keywords: synesthesia, grapheme-colour synesthesia, cross-activation, dis-inhibited feedback

Introduction

When it comes to the senses, most people experience a comparable reality. When we read a sentence on a piece of paper, we are seeing the shapes of the letters by using our visual system. While listening to a song on the radio, we hear it by using our auditory systems to perceive a medley of sounds. On the other hand, individuals with the neurological phenomenon known as synesthesia ("synesthetes") experience an extraordinary way of perceiving the world. In synesthesia, the stimulation of one specific sensory modality, such as hearing a sound or seeing a letter, triggers the perception of another non-stimulated sensory modality or percept, such as visualizing a colour (Ward, 2013). In other words, a certain attribute of a stimulus can lead to the perception of an additional attribute that is not physically present. For example, to a person with synesthesia, the letter P may always appear to be a dark shade of green, the name "Steven" may taste of sour keys, a piano playing an E note can appear as a wavy red line extending across the visual field, or the taste of chicken may cause the feeling of small blocks pressing into their hands. Moreover, the perceptual interactions occurring in synesthesia are not always a merging of different sensory systems; in the case of a printed letter evoking the perception of a specific colour, this synesthetic association is restricted to the visual system. In fact, a sensory stimulus that is not physically present, but is instead an internal representation, may be enough to trigger a synesthetic experience. For instance, to a synesthete that can taste certain spoken words, a perceived taste can occur even if the word that triggers it is not accessible, such as one in a tip-

of-the-tongue state (Simner & Ward, 2006). For this reason, Simner (2012) argues that the criteria defining synesthesia should not be limited to only sensory experiences, but also be broad enough to include concepts as well. To date, there are estimated to be 150 distinguishable forms of synesthesia (Cytowic & Eagleman, 2009), but only a fraction of them have been scientifically evaluated (van Campen, 2007). Perhaps the most remarkable aspect of all the categories of synesthesia is that many individuals who have it do not realize that the reality in which they have lived their entire lives is vastly different than "normal"; to the individuals who are aware that they have synesthesia, it is just as remarkable that these kinds of perceptions are not experienced by everyone else. This paper is a general introduction to the phenomenon of synesthesia, focusing on what it means to be synesthetic, how it affects the memory of these individuals, how the brains of synesthetes differ from those of nonsynesthetes, and how the condition arises in the first place.

A Brief History of Synesthesia

It is only in the past decade or so that truly detailed studies of the psychological experiences and neural mechanisms of synesthesia have been scientifically performed, yet it has actually been acknowledged for roughly 200 years (Ward, 2013). In fact, even though there are no documented cases of synesthesia before the 19th century, the idea that the perception of colour may arise from mechanisms other than light entering the eyes and producing vision was considered by renowned scientists as far back as the 17th century (Ward, 2013). For instance, Issac Newton attempted to discover the law of physics that connected the colours of the visible spectrum with seven tonal intervals of the musical octave (Pesic, 2006). The first case of

synesthesia was documented in 1812; this report, originally published in Latin, was a medical dissertation written by Georg Sachs about his own albinism and synesthesia involving colours seen when listening to music (Jewanski, Day, & Ward, 2009). Following this report, Cornaz (1848) interpreted synesthesia as the opposite of colour blindness and gave it its first name, "hyperchromatopsia", meaning the perception of too many colours.

Following Cornaz's observations in 1848, three new cases of letter-colour synesthesia were documented one year later, and after that period, the topic of synesthesia began to enter the mainstream of sciences and arts (Jewanski, Day, & Ward, 2009). Although the explanation given by Cornaz claims that synesthesia is an eye-based phenomenon, with the colour-letter associations arising from within the retina, this idea was quickly replaced by a general agreement that these synesthetic associations were brain-based (Jewanski, Simner, Day, & Ward, 2011). This perspective suggests that perhaps the brains of synesthetes differ from those of individuals without synesthesia in a way that alters the mechanisms of perception. Eventually the condition was renamed "synesthesia", derived from the Greek words *syn,* meaning union, and *aesthesis,* meaning sensation (Ward, 2013). By this period in time, the perceptual associations observed by synesthetes were considered a biological phenomenon rather than a physical one.

The attraction of synesthesia to modern scientists came from Ferdinand Suarez de Mondoza's book entitled *L'audition colorée*, which focused on the colour perceptions associated with the auditory system in 1890 (Jewanski, Simner, Day, & Ward, 2011). Unfortunately, the field of psychology was dominated by Freudian and structuralist views at this time, which did not focus on perceptual processing, so synesthesia was treated more as a medical curiosity than as a psychological or neurophysiological condition (Ione & Tyler, 2004). In fact, a large

proportion of what is currently known about the topic of synesthesia stemmed from research by the psychologist Alexander Luria, who was initially studying the extraordinary memory capacities of his famous subject "S.", now known as Solomon Sherevskii, for over 30 years (Linssen, 2011). S. could memorize a list of 70 words in a total of two minutes, and recall the list without error several months after first learning it (Luria, 1968). Luria (1968) quickly discovered that S.'s incredible mnemonic abilities were accompanied by a case of five-fold synesthesia that integrated all five of his senses; when he heard certain words or saw numbers, they were accompanied by colorful and meaningful perceptions that helped him to remember them. At this point, Luria shifted his studies from memory to synesthesia, in an attempt to link S.'s synesthetic experiences with his incredible memorization abilities; according to Luria, the essence of patient S.'s talent resided in his synesthesia (Linssen, 2011). The resulting descriptions of the perceptual experiences of synesthesia were very helpful in understanding the relationship between sensory and perceptual experiences, but the field of neuroscience at that time was not as developed as it is today; as a result, there was still no explanation for why or how the brains of synesthetes differ from those of nonsynesthetes in cortical development or sensory integration. Evidently, the subject of synesthesia has recently undergone a dramatic increase in research from many angles, including the various forms of the condition, its etiology, and differences in the brains of individuals with and without synesthesia.

Common Forms of Synesthesia

Although it may come as a surprise to many, about five percent of the general population has some form of synesthesia, and individuals that have one form of synesthesia typically have a

50% chance of having a second or third type as well (Cytowic & Eagleman, 2009). As stated above, there are estimated to be 150 different types of synesthesia, and so far, the best studied form is called grapheme-colour synesthesia, which is found in about twenty percent of all synesthetes and is also the most common (Simner et al., 2006). A grapheme is the smallest possible unit in a written language that has meaning; this means that graphemes include all the letters, numbers, and punctuation marks in the English language. When individuals with grapheme-colour synesthesia look at a monochromatic set of graphemes, such as the alphabet typed out in black ink, every letter will be associated with a unique and reliable perceived colour (Rouw & Scholte, 2007), such that the letters observed by this individual appear as though they are in colour rather than in black. An example of what an individual with grapheme-colour synesthesia may see when looking at letters and numbers is shown in Figure 1.

Figure 1. The letters of the English alphabet and the possible digits, as would be seen by a grapheme-colour synesthete when looking at them in black ink.

In the majority of cases, the same letter produces different colours to different synesthetes (Janke, Beeli, Eulig, & Hanggi, 2009), suggesting that individual differences in perception can

be caused by a range of differences in the underlying neural mechanisms of each individual. Some have suggested that these specific grapheme-colour associations are created early in childhood when the individuals are first learning the meanings behind them, such as when playing with coloured-letter refrigerator magnets (Witthoft & Winawer, 2013). Interestingly, the visual stimulus does not have to be physically present; when grapheme-colour synesthetes are presented with a display such as “5+2”, it is sometimes sufficient to trigger an internal representation of the number 7, and can therefor trigger the perceived colour associated with 7 rather than with the numbers 5 or 2 (Dixon, Smilek, Cudahy, & Merikle, 2000). Grapheme-colour synesthesia is generally believed to enhance memory, as will be described in another section below, but this effect is limited. The reason these associations may help with memory is that certain words or numbers will have a specific pattern of colours associated with them, and the colour pattern can be remembered rather than the specific letters. Generally, the colour associations remain stable for a synesthete’s entire life (Cytowic, 2003). Perceiving colours in place of achromatic numbers and letters is usually an experience that synesthetes have for as long as they can remember. Patricia Duffy (2001) explains one of her earliest memories with grapheme-colour synesthesia:

> "'One day,' I said to my father, 'I realized that to make an 'R' all I had to do was first write a 'P' and then draw a line down from its loop. And I was so surprised that I could turn a yellow letter into an orange letter just by adding a line."

Another common form of synesthesia is sound-colour, or auditory-visual, synesthesia. Individuals with this condition experience a range of colours in their visual field that are induced by specific sounds heard in the environment. Every sound, whether simple or complex, evokes a

different pattern of colours to the synesthetic individuals; descriptions of these colours has varied from simple horizontal flashes of light across the visual field to oscillations, a kaleidoscope, and an amoeba-like arrays of colours associated with a specific sound (Jacobs et al., 1981). Ramachandran and Brang (2001) note that synesthesia is seven times more likely to appear in artists, poets, and novelists, and that the majority of these cases include auditory-visual synesthesia. To emphasize this point, the famous musicians Stevie Wonder, Eddie van Halen, Duke Ellington, and Billy Joel, as well as composers Olivier Messaien, Franz Liszt, and Nikolai Rimsky-Korsakov, all have or had auditory-visual synesthesia, perceiving colours with every musical note heard. In many cases, there is a positive correlation between the perceived pitch of a sound and the intensity or brightness of synesthetic colour observed (Vike, Jabbari, & Maitland, 1984), so that high-frequency sounds are associated with brighter colours and low-frequency sounds are associated with dimmer colours.

Other, less common, forms of synesthesia include lexical-gustatory synesthesia, in which particular spoken or heard words and sounds induce the synesthetes to taste specific flavours in their mouths (Simner & Ward, 2006), number-form synesthesia, in which synesthetes visualize numbers in a three-dimensional or spatial way (Cytowic & Eagleman, 2009), and personification, in which numbers or letters are perceived as each having their own personality and gender (Simner & Holenstein, 2007). As awareness about synesthesia spreads, there is a larger and larger estimated synesthetic proportion of the general population, indicating that many individuals with the condition do not realize that their perceptions differ from those of other people until they learn that other people do not experience the world in the same way that they do. These “extra” sensory abilities add an extra dimension to incoming sensory information, but

they generally do not impede on the normal functioning of the affected individuals.

Synesthesia and Memory

Although synesthesia is commonly referred to as a "neurological condition" in the world of research, it is not listed in the DSM IV, the Diagnostic and Statistical Manual of Mental Disorders, because it normally does not interfere with regular functioning on a day to day basis (Hubbard, 2007), and many synesthetes do not choose to refer to synesthesia as a "condition", but rather simply as a trait, such as hair colour or eye colour (Cytowic & Eagleman, 2009). That being said, a definite causal basis of synesthesia has yet to be determined; it is still uncertain whether this condition is psychological and physiological. Interestingly, the renowned neuropsychologist Alexander Luria, who studied the synesthesia and incredible mnemonic abilities of patient S., treated synesthesia more as a disorder than simply a physical trait. In his book, *The Mind of a Mnemonist,* Luria (1968) refers to a synesthete as "a person [who] cannot mature in the same way others do, nor will [their] inner world tend to be like others," (p. 159). His point of view on the effects of synesthesia suggests that perhaps the development of these individuals is impaired or different from normal in some way; according to Luria, despite patient S.'s astounding memory, he had trouble remembering information that had a metaphorical meaning that was different from its literal meaning, as well as trouble recognizing faces (Luria, 1968). However, patient S. was definitely an exceptional case study of memory linked to synesthesia; during the time that Luria was studying S., synesthesia was estimated to be present in roughly one in every 20,000 people (Cytowic & Eagleman, 2009). This means that the sample

size of synesthetic individuals that Luria based his analysis on was much too small to truly represent the effects of synesthesia on the memories and capabilities of these individuals.

It is now known, however, that being a synesthete does not necessarily guarantee and enhanced memory (Linssen, 2011) and Cytowic, an important researcher in the field of synesthesia, claims that 1 in 23 people have some form of synesthesia, whether they are aware of it or not (Cytowic & Eagleman, 2009). Such a dramatic increase in the appearance of synesthesia in the general population, most likely due to a more widespread awareness of it, has provided researchers with larger sample sizes to draw conclusions from. Nevertheless, Shereshevskii's "photographic memory" has been connected to his fivefold synesthesia (Rothen, Meier, & Ward, 2012), but his abnormal sensory experiences may not have been the only causal factor that led to his impressive memory. Recently, Baron-Cohen et al. (2007) suggest that because synesthesia is commonly associated with autism, Shereshevskii may have had autism as well, and that these two conditions together resulted in his ability to remember seemingly anything he wanted to. After all, there have been many autistic savants that appear to have similar memory capacities as Shereshevskii, such as Daniel Tammet, a savant with Asperger Syndrome and grapheme-colour synesthesia that recited the digits of Pi from memory to over 22,000 decimal places (Rothen, Meier, & Ward, 2012). Still, Shereshevskii's limitless memory sparked a wave of research on the effects of synesthetic experiences on the mnemonic abilities of individuals with synesthesia.

The actual extent to which a superior memory is a characteristic associated with synesthesia is still unknown, and so is the mechanism behind this interaction (Yaro & Ward, 2007). Yaro and Ward (2007) demonstrate in their studies that synesthetes tend to have memory capacities that are above average, both in synesthetic and nonsynesthetic situations. A synesthetic

situation can be described as one in which a specific stimulus used elicits a synesthetic perception, whereas in a nonsynesthetic situation, the stimulus does not. Rothen et al. (2012) agree that synesthetes show an enhanced memory relative to controls, and they propose that this increase in memory span can be explained by the "extra" synesthetic perceptions causing richer encoding of memories; for this reason, synesthetes who see colours associated with words and numbers tend to have better visual memory than others. After all, memory is often enhanced when visual imagery is included; a deeper level of encoding a memory into the cognitive system results in easier subsequent recall of that memory (Craik & Lockhart, 1972). It is important to note that the enhanced memories associated with synesthetic abilities are limited to synesthesia-inducing stimuli. For instance, Mills et al. (2006) determined that patient C., a woman with grapheme-colour synesthesia, had an enhanced ability to memorize achromatic digits and letters relative to nonsynesthetic controls, but did not have any mnemonic advantage in a separate test that used ambiguous visual stimuli that did not induce synesthesia. Additionally, when the graphemes to be memorized are either achromatic or correspond with the colours that a synesthete normally associates with them, the recall ability of the synesthete is greatly enhanced (Smilek et al., 2002). In contrast, when the graphemes are presented in colours that are incongruent with the specific grapheme-colours associations that a synesthete normally perceives, their recall ability consistently falls below that seen in the nonsynesthetic control group (Smilek et al., 2002). What this indicates is that although grapheme-colour synesthesia can improve memory in many cases, it can also negatively affect recall ability in others.

A plausible explanation for the improved mnemonic abilities in synesthetes is the increased connections observed in the cortical areas associated with working memory (Linssen,

2011). Using diffusion tensor imaging (DTI), Rouw and Scholte (2007) found a significant increase in white matter within the superior parietal cortex, right inferior temporal (IT) cortex, and frontal cortex of a group of eighteen synesthetes relative to control subjects. This finding is relevant because the superior parietal cortex is critical for the manipulation of working memory (Koenigs et al., 2009). In addition, Wiess and Fink (2009) discovered that grapheme-colour synesthetes generally have a higher volume of gray matter in the left interparietal sulcus, which plays a role in visuospatial memory (Todd & Marois, 2004). To date, there is evidence suggesting that grapheme-colour synesthetes may have superior encoding of memories, rather than an enhanced storage or recall (Gross et al., 2011); this may indeed be a direct result of the additional visual imagery that they experience when observing certain stimuli. Despite the evidence for differences in cortical volume in certain areas of the brain in synesthetes and nonsynesthetes, there is much debate over defining the critical changes in the brains of synesthetes that directly lead to their abnormal sensory abilities. In other words, what is it about the brains of synesthetes that make them synesthetes?

Cortical Mechanisms of Synesthesia

Before delving into the neurological properties and mechanisms of synesthesia, it is important to raise the question of whether the sensations experienced by synesthetes are a result of reflex-like sensory inputs or the result of memories and associations. In a clever experiment designed by Ramachandran and Hubbard (2001) to test whether synesthesia was a perceptual effect or a cognitive effect based on memories, grapheme-colour synesthetes were instructed to look at a display containing a matrix of randomly placed graphemes, such as the number 2. Within this display, a second grapheme that would appear very similar to the first to a

nonsynesthete, such as the number 5, would be embedded in a pattern that creates a certain shape. This display is shown in Figure 2a. To nonsynesthete control subjects, reporting the specific shape that the 5's are making is a difficult task to perform quickly and it requires attention. On the other hand, since grapheme-colour synesthetes saw the 2 and the 5 as completely different colours, the shape being created by the 5's, which could look like Figure 2b, was reported immediately because the shape popped out and did not require attention to see. Since the synesthetes performed significantly better than controls at rapidly detecting the hidden shapes, Ramachandran and Hubbard (2001) concluded that synesthesia is a genuinely perceptual phenomenon. Furthermore, they determined that the evoked colour occurs at an early, preconscious level rather than at a higher cognitive level because when the subjects were not given enough time to recognize what letter they saw, they would say things like, "I can't see that middle letter but it must be an 'O' because it looks blue," (Ramachandran & Hubbard, 2001).

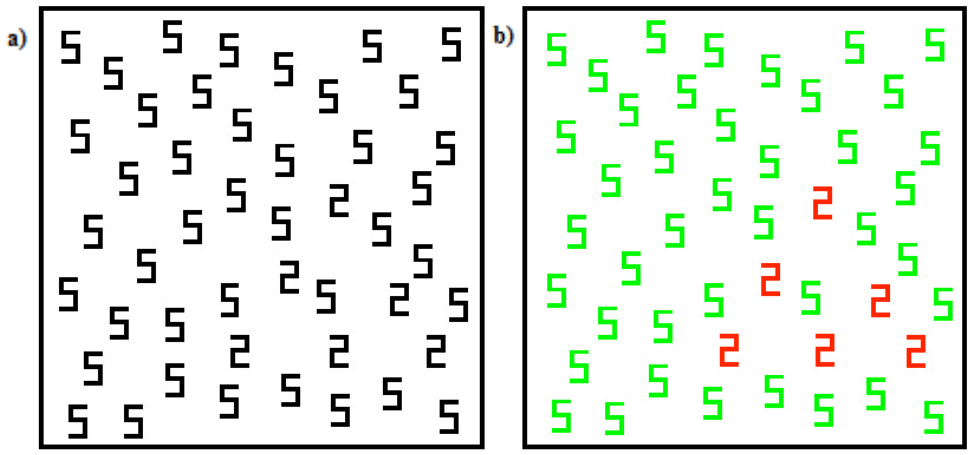

Figure 2. Grapheme display to test the abilities of grapheme-colour synesthetes and control subjects to detect the embedded shapes created by two types of graphemes. a) the achromatic display, as a nonsynesthete would see it. b) an example of the way in which a synesthete would view the display. (Ramachandran & Hubbard, 2001).

Now, it is well known that the automatic merging of sensory experiences that are normally kept separate in individuals with synesthesia is a phenomenon that is completely involuntary and unconscious (Eagleman & Goodale, 2009). Since grapheme-colour is the most common form of synesthesia, the majority of research that has focused on the underlying mechanisms of the brain that cause certain individuals to experience synesthesia has focused mainly on grapheme-colour synesthetes. The two major theories that attempt to describe the neural mechanisms behind synesthesia are the cross-activation theory and the disinhibited feedback theory. These opposing ideas will be discussed and compared.

The cross-activation theory of the development of synesthesia was proposed by Ramachandran and Hubbard (2001), and it states that adjacent cortical areas which both receive sensory input may fail to decrease the synaptic connections between them during neurodevelopment, resulting in simultaneous stimulation of both cortical areas. Based on the discovery that the fusiform gyrus contains both the "colour areas" in the brain, V4 and V8, (Lueck et al., 1989; Hadjikhani et al., 1999) and the "visual grapheme area" of the brain, known as the inferotemporal (IT) cortex (Allison et al, 1994), Ramachandran and Hubbard (2001) suggest that it is not a coincidence that the most common form of synesthesia is grapheme-colour synesthesia, since these two areas are directly beside each other. They propose that this form of synesthesia is the result of the formation of excess cross-connections between the two areas, or from defective pruning of the connections between the two areas early in neurodevelopment. The first idea, that cross-wiring between the colour and grapheme regions of the cortex leads to synesthesia, is similar to the cross-activation of the hand area of the somatosensory strip by the face area after amputation the hand that results in phantom limb syndrome (Ramachandran et al.,

1992). On the other hand, the idea that a defect in pruning of these connections suggests that every individual has synesthetic connections at one point in neurodevelopment, but that they are severed before long-lasting associations between graphemes and colours are made. This theory is supported by the fact that in an immature, prenatal human brain, there are there are many more connections between areas of the brain, such as between the IT cortex and V4, than there are in adults, and that some of these connections are destroyed and removed by pruning (Kennedy et al., 1997). As our brains develop, the many connections that are initially formed are continuously altered; the connections that are used are strengthened, and those that aren't are pruned. This means that, according to this theory, nonsynesthetes would not have these cross-connections in their own brains, and that in order to acquire synesthesia later in life (which can happen, as described in a later section), these connections would somehow have to manifest themselves similarly those present in synesthetes. According to Ramachandran and Hubbard (2001), this theory also supports the strong genetic basis of synesthesia because a mutation in a gene that normally initiates the pruning process could directly result in an excess of cortical connections. In effect, these extra connections within the brains of synesthetes would lead to an excitation of both areas when either one is stimulated.

In contrast to the cross-activation theory, Grossenbacher and Lovelace (2001) propose the disinhibited feedback theory to explain the development of synesthesia. This theory states that the symptoms of synesthesia arise from inadequate inhibition from the neighboring higher order cortical areas, such as a relative association cortex, to lower sensory areas, such as V4 or V8, resulting in signals that influence these early sensory areas more than in unaffected individuals. This is based on the assumption that incoming sensory information makes its way up the sensory

hierarchy to a "higher" cortical area that integrates information from many sensory modalities, which then sends this information down to "lower" areas such as V4. In other words, sensory information being fed to V4 is controlled by top-down mechanisms, and these mechanisms can inhibit certain aspects of the sensory information being perceived. As a result, all people would have these multi-sensory connections present within their brains, but nonsynesthetes would have certain sensory connections "blocked" or inhibited their entire lives, while synesthetes would have the same connections "unblocked" or disinhibited. Unfortunately, an explanation for the genetic basis of synesthesia is not discussed with respect to the disinhibited feedback theory, but it is possible that a mutation in a specific receptor or signalling protein that functions anywhere along the hierarchical pathway to inhibit the synapses between certain sensory areas would lead to a condition similar to synesthesia. What this theory implies about acquiring synesthesia later in life is that no new connections would have to be formed between sensory cortices in the brains of nonsynesthetes; rather, some type of change in the brain, such as one in the neurochemistry or physiology of specific cortical regions, could damage these inhibitory pathways and lead to the development of synesthesia. Thus, this theory indirectly suggests that we all have the potential to be synesthetes.

It should not come as a surprise that the brains of synesthetes differ in significant ways from the brains of others, but a absolute description of the exact differences that exist has not yet been determined. Rouw and Scholte (2007) used diffusion tensor imaging to conclude that the added sensations experienced by grapheme-colour synesthetes are due to hyperconnectivity in the IT cortex of their brains. Building on the fact that hyperconnectivity in the brain leads to synesthesia, Dovern et al. (2012) used fMRI to measure the resting-state functional connectivity

of 12 synesthetes and 12 nonsynesthete controls, and they found that not only do grapheme-colour synesthetes have a significant increase in the intrinsic connectivity between certain brain areas, but the more connections were activated, the stronger the perceived synesthetic experience was in the experimental group. Another study found that grapheme-colour synesthetes have increased cortical density and surface area in the right and left fusiform gyrus (Janke et al., 2009); as previously stated, the fusiform gyrus contains both the colour and grapheme processing areas of the brain, so this finding is consistent with the cross-activation theory of synesthesia. Yet another experiment using functional connectivity fMRI data was performed by Neufeld et al. (2012) to directly test which one of these two theories was correct; to a group of 14 auditory-visual synesthetes and a group of nonsynesthete controls, different simple and complex sounds were listened to while activity in the bilateral auditory cortex and inferior parietal cortex was measured. They found no differences in the connectivity between the auditory cortex and visual cortex in synesthetes and controls, but did find significantly stronger connectivity between the left inferior parietal cortex and the right primary auditory and primary visual cortices in the group of auditory-visual synesthetes. Since the inferior parietal cortex is known to function in the integration of incoming sensory information from different sensory modalities, the results of this experiment support the disinhibited feedback theory as the cause of synesthesia rather than the cross-activation theory. In a recent and similar experiment using grapheme-colour synesthetes, fMRI data revealed that the parietal lobe plays an important role in the synesthetic experience (Sinke et al., 2012), further lending support to the disinhibited feedback theory because it indicates that top-down mechanisms strongly influence the perceived synesthetic colours. Overall, it is clear that there is evidence supporting both theories of the brain mechanisms behind

synesthesia. This does not mean that both theories are correct, but it is certainly possible; there may be many different changes in the structure of the human brain that lead to the various types of synesthesia, and like many other neurological conditions, not all synesthetes have identical brain abnormalities.

There is a difference, however, in the nature of the synesthetic experience among synesthetes; for instance, in the case of grapheme-colour synesthesia, the colour perceived by looking at a number, letter, or word can either be observed as a physical colour associated with the object in the "outside world" or as a colour that's imagined in the mind, and each synesthete generally experiences only one of these types of sensations (Rouw & Scholte, 2010). According to Rouw & Scholte (2010), the type of synesthetic experience is mediated by different neural mechanisms; in particular, using fMRI to view brain activity of nonsynesthetes and synesthetes with either of these two distinct sensory experiences, it was found that those who said they observed synesthetic colours in the outside world experienced enhanced activation in the visual cortex, auditory cortex, and motor cortex when looking at particular objects. This result is reasonable because these cortical areas are normally activated when perceiving and interacting with the outside world. Additionally, they discovered that synesthetes who describe their synesthetic colours as "in their mind" experience activation of the hippocampus and parahippocampal gyrus (Rouw & Scholte, 2010), which are associated with retrieving memories about the past (Buckner, 2010). Moreover, fMRI data showed that individuals with grapheme-colour synesthesia had a significant increase in the levels of activity in the posterior superior parietal lobes, which are involved in the integration of incoming sensory information to the brain, relative to nonsynesthetes (Rouw & Scholte, 2010). What this indicates is that the brains

of individuals with grapheme-colour synesthesia are relatively hyperactive in the regions involved with combining sensory input, as might be expected from people that experience a constant overlap of certain sensory modalities. It is true that the brains of synesthetes differ in significant ways from those of nonsynesthetes, but the reason why these changes occur is far from obvious.

Etiology -- Heredity and Genetics

Not only has there been strong evidence for the cortical connections in the brains of synesthetes differing from those of nonsynesthetes, but recently, there has also been an accumulation of evidence supporting the fact that there is a genetic predisposition associated with developing synesthesia. In general, synesthesia is viewed as a strongly genetic condition based on the failure to specialize cortical regions (Mitchell, 2011). Linkage analysis experiments using family members of individuals with synesthesia has led to the discovery of a 23 mega-base pair region of chromosome 16 in the human genome that contains a gene associated with the development of grapheme-colour synesthesia (Tomson et al., 2011). These linkage analyses included five families within which multiple family members had synesthesia; an example of the pedigrees created to represent the family members is shown in Figure 3. Although there is no definitive conclusion about the dominance relationships of the alleles resulting in synesthesia, it appears from these pedigree examples that the allele in the synesthesia gene that causes this phenotype is recessive, because the development of synesthesia appears to skip across generations. Additionally, the gene appears to be X-linked, or in other words, located on the X chromosome, because it seems as though a mother homozygous for the synesthesia allele

typically gives birth to sons that all have synesthesia. This is possible if the gene was on the X chromosome, because males always receive their X chromosome from their mothers. Interestingly, initial whole-genome scans performed by Asher et al. (2009) on families affected by auditory-visual synesthesia suggested a single-gene X-linked mode of inheritance due to lack of male-male transmission, but subsequent experiments concluded that the gene was in fact autosomal. Also, they concluded that auditory-visual synesthesia is actually a trait produced by two or more genes working together; specifically, it was found that auditory-visual synesthesia is linked to chromosomes 2, 5, 6, and 12 in the human genome (Asher et al., 2009). There are currently no review papers integrating the information about chromosome linkage for different categories of synesthesia, so it is still unknown whether or not these supposed "synesthesia genes" are specific to the type of synesthesia they cause (in other words, one gene causes grapheme-colour synesthesia and another gene causes auditory-visual synesthesia) or if they simply work together to create a change in the brains of affected individuals that can result in any possible type of synesthesia.

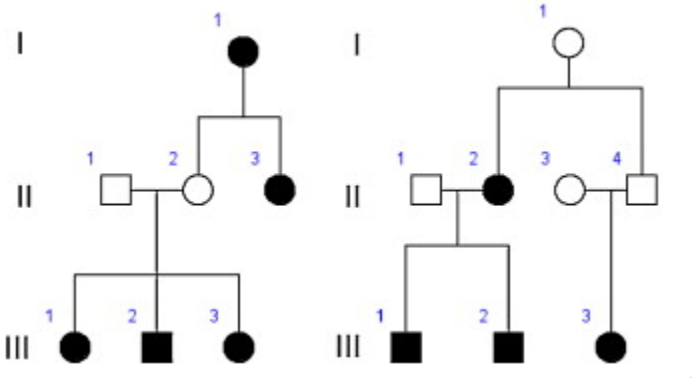

Figure 2. Pedigrees of two families with grapheme colour synesthesia. Squares represent males, circles represent females, and black represents an individual with synesthesia (Tomson *et al.,* 2011).

Since synesthesia doesn't appear to have any negative or harmful effects on the individuals who experience it, it is possible that the gene, or genes, for synesthesia were positively selected for by natural selection throughout human evolution. Of course, this idea assumes that synesthesia provides some sort of advantage to the people who have it. Although most synesthetes describe their sensory experiences as passive, with generally no direct effect that has a positive or negative impact on their daily functioning (Hubbard, 2007), there has been much evidence for an association between enhanced memory and synesthesia, as noted in the section above, and this mnemonic advantage could have perhaps been a positive trait that was selected for. Even though the extent of the enhanced memory that, for instance, grapheme-colour synesthetes have is limited to the words, letters, or numbers that are relative and meaningful to them, it is still quite advantageous to be able to remember graphemes that are meaningful. It is important to keep in mind that not all forms of synesthesia have been associated with memory advantages, though. Additionally, it is very beneficial to be able to link different concepts together when learning something new, and individuals with synesthesia have the advantage of being able to innately form these connections, which can make understanding and memorizing new concepts much easier. In relation to the idea that synesthesia may have been selected for, Ramachandran and Brang (2011) suggest that the survival of the synesthesia gene through evolution may just represent an evolutionary spandrel, which is a phenotype that evolved as a by-product of another trait, and it has also been hypothesized that synesthesia is just an extreme tail end of the normal distribution of the general population's experiences with cross-modality interactions (Ramachandran & Hubbard, 2001). A very interesting point of view on synesthesia

raised by Ramachandran and Hubbard (2001) is that the synesthesia gene may have been selected for because of its potential influences on the creativity of human beings; after all, the creativity and ability to think outside the box of many of the artists, musicians, and other individuals mentioned in this report that had synesthesia may have been largely influenced by their irregular perceptions of the world.

Etiology -- Acquiring Synesthesia Later in Life

The genetic and neurophysiological research on the etiology of synesthesia has been challenged by a few studies which suggest that the neurological "condition" may arise from certain environmental causes, meaning that synesthesia can also be acquired at some point in life in a variety of ways. A recent and influential study in Stanford University reported that the letter-colour associations among eleven individuals with grapheme-colour synesthesia were surprisingly similar; that is, the same letter commonly produced the same perceived colour among the synesthetes being tested (Witthoft & Winawer, 2013). Although this finding contradicts the conclusions from Janke et al. (2009) which suggested that the sensations experienced by synesthetes are generally unique across affected individuals, it has strong implications for a central role of learning and memory in synesthesia because the grapheme-colour associations experienced by these eleven individuals were effectively traced back to their childhood toys containing coloured letters (Witthoft & Winawer, 2013), such as the common mass-produced coloured letter fridge magnets many children grew up with. Interestingly, the English capital letters that are more similar in their synesthetic colour to the capital letters in early fridge magnets are perceptually more saturated in colour (Witthoft & Winawer, 2006). The

fact that synesthesia can be learned suggests that perhaps it is not only a consequence of genetics, but can instead be induced by influences from the environment while the brain is adapting and the meaning of letters and colours is being learned during childhood. Nevertheless, this experiment failed to mention whether a genetic screen was performed for the individuals being tested or their families, in order to determine whether they were genetically susceptible to developing synesthesia. This information would have been an important factor in concluding that synesthesia can be learned simply from the mnemonic and neuroplastic mechanisms of the developing brain, rather than being influenced by a genetic predisposition.

Richard Cytowic (2003), a famous researcher in the field of synesthesia, supports the idea that early associations between sensory stimuli, such as graphemes or sounds with certain colours, can ultimately lead to the development of synesthesia; he claims that once these associations are made in childhood, they remain stable for life. In an attempt to prove that synesthesia can indeed be learned, psychologists Stevenson, Boakes, and Prescott (1998) designed an experiment that allowed them to affect the perceived sweetness of a certain odour by allowing participants to taste varying mixtures of an odor-producing flavourant and sugar. Since the nose does not contain any "sweet" taste receptors, unlike the tongue, they claim that the perception of sweetness that the participants experienced as an association with a specific odour is an example of a learned smell-taste synesthesia (Stevenson, Boakes, & Prescott, 1998). However, it is difficult not to be skeptical about the conclusions made in this experiment, because the senses of taste and smell are already highly integrated in the nervous system in order to produce the experience of flavour; this innate sensory crossover may or may not have contributed to the results. Perhaps a more convincing example of learned synesthesia would be

between sensory modalities that are not normally integrated, such as sound and taste, as experienced in lexical-gustatory synesthesia.

The development of synesthesia has also been documented in case studies of individuals that recovered from brain damage. In one such study, Beauchamp and Ro (2008) observed that the neural plasticity induced by a stroke, which normally repairs connections and recovers the function of certain brain areas, led to the formation of abnormal connections in the brains of three stroke victims with thalamic lesions. Specifically, using fMRI, these individuals showed significantly heightened BOLD responses to sounds in the parietal operculum, which is where the secondary somatosensory cortex is located. In other words, the brain's response to thalamic lesions induced by a stroke led to an increased sensitivity to auditory stimuli in the secondary somatosensory cortex. These accidental connections left the patients with acquired auditory-tactile synesthesia. In this form of synesthesia, specific sounds produce intense tingling sensations along the skin (Beauchamp & Ro, 2008). It is easy to imagine this type of feeling if you can recall the tingling sensation that is usually associated with the sound of nails being scraped along a chalkboard. Since these cross-sensory experiences are said to be caused by the formation of new connections between sensory modalities that are normally separate, this case supports the cross-activation theory of the development of synesthesia. One point of view that the authors did not mention in this paper is that perhaps the auditory-tactile synesthesia that these patients experienced after their strokes is due to the loss of some inhibitory connections between somatosensory and auditory loci within the thalamus that were lesioned during the stroke.

There have also been numerous documented cases of sudden developments of synesthesia that are not due to strokes. In an interesting and unique case study of a woman that

suffered from migraines accompanied by visual auras for many years, Alstadhuaq and Benjaminsen (2010) reported that on several occasions, this individual experienced acquired synesthesia during the visual aura phase of her migraines, in which she experienced an intense taste of lemon whenever staring at a bright light. Since it is unlikely that new cortical connections are being formed during these visual auras and destroyed immediately after, this case study may lend support to the disinhibited-feedback theory of synesthesia development. It is well known that there are cortical changes occurring during the visual aura of a migraine, and perhaps these excitatory or inhibitory changes temporarily disinhibited neural connections between certain visual and gustatory areas of her brain. Also, sound-colour synesthesia and lexical-gustatory synesthesia are common symptoms of LSD use, with users typically reporting "hearing colours", or "seeing sounds" both during their high and long after (Goldfrank, 2011, p. 1172). Perhaps this finding can be used as support for the disinhibited feedback theory as well, because it is more realistic that this psychedelic drug is unblocking or disinhibiting certain neural connections that are normally inhibited in people without synesthesia by binding to specific endogenous receptors that do so, rather than triggering the synthesis of new connections. Synesthetes would normally always have these connections unblocked. Since LSD acts similar to a neurotransmitter in the brain, binding to the 5-HT(2A) receptor that normally binds serotonin (Hanks & Gonzalez-Maeso, 2013), it causes many perceptual effects. The resulting synesthetic experiences may possibly be due to the excitation of certain neural structures, such as area V4 that plays a role in colour perception, by neurotransmitter-like chemicals that are meant to excite a completely different part of the brain, such as the auditory cortex.

Although synesthesia has a strong genetic basis, it is clear that the environment has a strong influence on its development as well. Thus, it appears that synesthesia, along with the vast majority of other neurological conditions, cannot be explained solely by either nature or nurture. This is not surprising, because the environments in which individuals are raised play a critical role in their neurodevelopment, and these experiences can determine the extent to which genetic predispositions are expressed.

Conclusion

Although the work of many researchers has shed light on the neuroanatomy, cognitive mechanisms, and etiology of synesthesia, there is much more work that needs to be done in order to fully understand and appreciate how simple changes in the brain can lead to the phenomenal sensory experiences that synesthetes observe on a daily basis. In order to refine the current data, it is important to continue searching for more synesthetes and conduct genetic analyses of them and their families; once it is known what type of protein is being mutated to produce the cortical changes associated with synesthesia, further research into how this protein functions in the brain and interacts with certain transmission pathways can be extremely insightful into how sensory information is normally integrated. In addition, many of the recent fMRI experiments have focused on the anatomical differences in the brains of synesthetes versus nonsynesthetes, but none so far have directly compared the differences in cortical activity of individuals with different types of synesthesia. It would be interesting to test whether the same region of the inferior parietal cortex and visual cortex, such as V4, are activated when grapheme-colour synesthetes look at words and when auditory-visual synesthetes listen to sounds.

Now that we know for certain that synesthetic experiences are completely out of the control of the individuals who experience them, we can use synesthesia as one way to accept the idea that some people perceive the world in an entirely different way than others, and that differences in the structures of people's brains can truly create an alternative reality for them. There are a vast number of reasons why some people perceive the world differently than others besides having synesthesia; for example, many individuals are red-green colour-blind, but they can spend their entire lives not realizing that they are not perceiving the same colours as other people because the array of colours that they perceive is simply part of the reality that they have always lived in. Our brains adapt to whatever situations we are in and find a way to make sense of the constant incoming sensory stimuli from all around us, and the various forms of synesthesia can be viewed as an example of this neuroplastic ability. As a result, synesthesia is not a mere oddity but is rather an important insight into how our brains normally work. For all we know, every person may perceive the world in different ways, yet we all use the same words to describe our experiences. It is possible that many of us have some undiscovered form of synesthesia without realizing it.

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