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Tasting Sounds: A Review of Synesthesia Mechanism Theories

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Introduction

Synesthesia is a neural phenomenon in which stimulus in one sensory modality activates sensory perception within another sensory pathway, or within another aspect of the same sensory modality[19]. For example, reading the word "house" could cause the perception of the taste of cinnamon, the letter A could consistently appear red, or hearing a B-flat note could cause the appearance of a red dot in the person's vision. The term "inducer" is used to refer to the stimulus that initiates the abnormal sensory event, while "concurrent" refers to the induced perception[10]; in the first example above, the word "house" would therefore be the inducer, and the taste would be the concurrent. Persons with this condition are referred to as "synesthetes"[10].

This condition can arise from several sources: first, it may begin in early childhood as a result of genetic influences; second, it has observed to occur following during rare instances of brain injury; and lastly, a variant of the condition has also been induced by hallucinogens. Respectively, these forms are called developmental synesthesia, acquired synesthesia, and pharmacological synesthesia[10]. This review will primarily focus on developmental synesthesia, as acquired synesthesia is comparatively rare and less studied, and both pharmacological and acquired synesthesia do not result from intrinsic neural differences that may provide understanding into typical neural processing. As such, all further references to synesthesia in this paper are in regard to developmental synesthesia unless otherwise stated.

In this review, I provide a general overview of recent findings regarding synesthesia with special focus on findings pertaining to the neural mechanisms of synesthesia, and the implications this condition presents for the general understanding of the nervous system. For the sake of brevity, this review will focus on studies concerning two commonly researched forms of synesthesia that relate to intriguing aspects of the condition: grapheme-color, and sequence-space synesthesia. However, studies focusing on other forms of synesthesia may be mentioned in order to understand the implications these studies present. First, this review will give an overview of synesthesia classifications, and describe the types that have been studied intensively. Second, the aspects of synesthesia that distinguish it from explicit memory recollection or other mechanisms will be detailed. Third, the review will give an overview of current theories of what neural mechanisms could give rise to synesthesia. Lastly, an explanation of developmental mechanisms that could give rise to these synesthesia mechanisms will be provided, alongside several genetic studies that could lend further insight into the developmental mechanisms. The conclusion will provide a summary of the findings of this paper, and the implications these findings present for understanding the condition.

Types of Synesthesia

At least 60 different types of synesthesia have been identified[24]. Synesthetes are typically and simply classified by the inducer and concurrent associated with their synesthesia; for example, a music-taste synesthete has a form of synesthesia in which music triggers a taste sensation[29]. Based on this classification, many variations have been identified, including sequence-space, lexical-gustatory, and auditory-tactile synesthesia. These categories can also further subdivided; for example, time-space synesthesia is considered a subset of sequence-space synesthesia[5].

One of the most commonly studied types of synesthesia is grapheme-color synesthesia[14], in which synesthetes perceive written letters, digits, or words as various colors particular to the graphemes (Figure 1a). Some grapheme-color synesthetes perceive a word as a single color, rather than a series of letters of varying colors; these types of perceptions are classified as word-level, or “lexical” coloring[29].

Sequence-space synesthetes associate sequential concepts such as weeks, numbers, and even musical tones with specific spatial areas[8]. Sequence-space synesthesia has many subsets which fall under it; one such subset is time-space synesthesia, a form in which synesthetes experience sequential time units like months and years as a spatial layout in peripersonal space, or in the inner mind[4,19] (Figure 1c). Another intriguing subset is musical-space synesthesia, where musical pitches are associated with a particular spatial position[1]. Though not quite as commonly studied as grapheme-color synesthesia, the studies of this type of synesthesia could present unique insights into other aspects of synesthesia, such as how spatial awareness relates to sensory perception.

Though there are many parallels between synesthetes that allow broad categories to identified, the synesthetic responses are still highly idiosyncratic in some aspects. Synesthetic experiences can vary in terms of what dimension synesthetes experience the extra sensory stimuli, and these varying types of experiences have been broken up into two groups: associators and projectors. While associators simply have their synesthetic experience perceived as a strong mental association, projectors actually perceive the synesthesia in external space[14]; these classifications are not clear-cut however, as some synesthetes have reported an experience between the two classifications, where in the instance of grapheme-color synesthesia the colors are “projected onto a ‘mental screen’ in peripersonal space”[14].

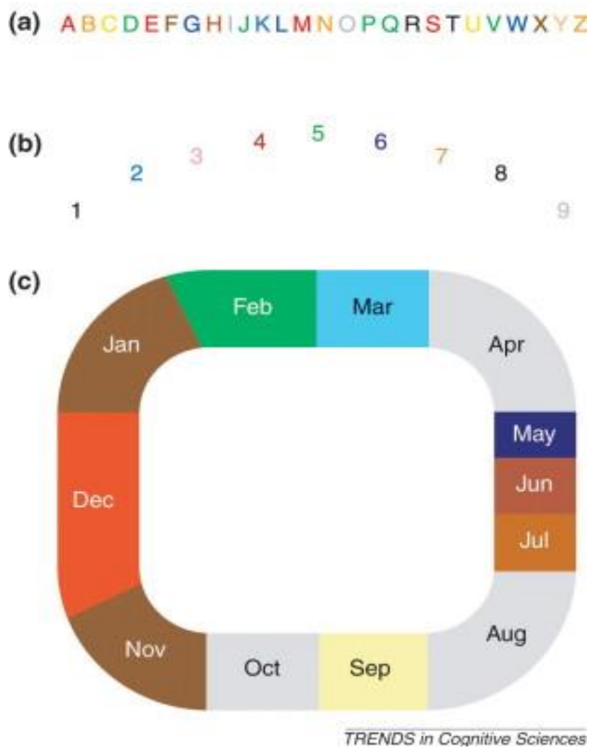

Figure 1. This diagram depicts examples of synesthetic experiences. a) Example of grapheme-color synesthete's associations; b) Associations of a synesthete with grapheme-color and sequence-space synesthesia, with this spatial representation appearing before her; c) Sequence-space synesthete experience, with this ring appearing around her in space. (Adapted from Grossenbacher & Lovelace, 2001)

Distinguishing Aspects of Synesthesia

It should be noted that synesthesia varies distinctly from phenomenon such as recalling implicit memories associated with sensory stimuli. Knowing what features of synesthesia make it unique from typical sensory experiences can lend insight into understanding the underlying neural mechanisms of synesthesia. One of the first noted characteristics of synesthesia is the consistent nature of the associations. The varying responses between the different stimuli in the inducer sense (i.e., a grapheme-color synesthete may observe the letter A as green, but the letter C is blue) tend to be consistent over long spans of time, even potentially over the lifetime of the individual[15], though the responses of some forms have been noted to evolve and change slightly over time[13]. In fact, this characteristic has been used to identify genuine synesthetes for experiments[7].

Synesthesia is also characterized as being an automatic[1,9] and irrepressible[29] response, though some synesthetes report that through concentration they can increase the intensity of their experience[22]. Akiva-Kabiri et al., 2014 found that musical-space synesthetes have involuntary and irrepressible reactions to auditory cues that activate a synesthetic response, causing synesthetes to direct their attention to the spatial region that was stimulated by the cue even if they were told to repress the reaction. The rapid reaction time observed in response to the synesthesia-inducing stimuli further implicated the automatic nature of the response. These findings suggest that the response is a result from some inherent neural circuitry rather than an explicit memory being recalled and then associated to the stimulus.

Another intriguing facet of synesthesia is that these varying responses tend to be idiosyncratic[3], though it has been observed that some responses to inducers may be similar across synesthetes as well[1,4,28]. For instance, it has been observed that time-space synesthetes commonly perceive time units such as months as an oval or circle about them[4], and that most grapheme-color synesthetes will perceive the letter C as yellow[28]. The reason for the slight uniformity between concurrent responses is still being investigated, though it may be due to exposure to common semantic associations learned during childhood[28].

Neural Mechanism Theories

Many varying and interweaving schools of thoughts currently exist regarding the neural mechanisms that underlie synesthesia. In this section, several popular theories will be introduced along with current research findings regarding the validity of these theories. These theories will be discussed first in terms of what brain regions may be involved in synesthesia, and then how these regions may interact with one another.

Many of the perceptions associated with synesthesia are affiliated with the higher-order aspects of the associated sensory systems which reside within the cortex[3,29]. As such, many imaging studies have been conducted on cortical regions, as they are potentially where synesthesia cross-activation may take place[3,29]. For example, in grapheme-color synesthesia some possible areas involved include the letter shape area (LSA), the color area V4 within the occipital cortex, and the superior parietal lobe (SPL)[14].

There are many ways to classify all the different models that have been proposed by research. One model that is common across many theories is the cross-activation model[4], which is also known as the bottom-up model[14]. The cross-activation model suggests that hyperconnectivity between two particular cortical regions could cause stimulation in one cortical region to activate a connected cortical region, causing the dual sensory experience. Because it may be tempting to postulate that only adjacent cortical areas could participate in cross-activation, it should be noted that while cortical areas involved in common forms of synesthesia are in fact adjacent, it has also been shown that this cortical adjacency is not necessary for cross-activation to occur[3].

A study conducted by Yokoyama et al. (2014) lends some insight into the cortical regions involved with grapheme-color synesthesia. In particular, several brain regions they believed were involved with three subsets of grapheme-color synesthesia were imaged: first-letter dependent coloring, ordinal-dependent coloring, and semantic coloring. First-letter dependent coloring occurs when the first letter of a word decides what color the whole word will be. If a synesthete with this type associates “H” with purple, then the whole word “hand” would appear purple. Synesthetes with ordinal-dependent coloring have particular color associations with sequential orders; for instance, these types of synesthetes might associate words that start with “S” with blue, but Saturday and Sunday would instead have distinct colors, such as red and green.

Semantic coloring seems to result from semantic knowledge that sways the associations. In the Yokoyama et al. (2014) study, the synesthete perceived the word “banana” as yellow, and the word “melon” as green, likely due to this form of association.

To better understand what mechanisms may lead to these varied responses, Yokoyama et al. (2014) conducted brain imaging by magnetencephalography (MEG) on a synesthete who reported all three types of grapheme-color synesthesia, and recorded her neural activity when presented with words that corresponded to the three types. These experiments revealed that the perception of first-letter dependent words cause neural responses within the occipito-temporal region, which contains the V4 area, the letter-form area (PTGA), and the word-form area (VWFA). The V4 region is responsible for color processing, and due to its close location to the PTGA and VWFA, it is possible that this synesthesia may result from cross-activation of these areas. For imaging of sequence-dependent perceptions, it was found that the left parietal cortex was activated along with V4; the left parietal cortex is implicated in numerical processing, which may be why this ordinal preference exists alongside the abnormal color processing. However, these regions do not lie adjacent to each other, which further supports the thought that cortical regions activated during synesthesia do not need to be adjacent to be activated together. Semantic-dependent words were shown to increase activity in the left inferior frontal and anterior temporal areas of the subject’s brain, regions which have been implicated in semantic processing. Due to the delay in neural response with semantic-dependent perception that was not exhibited in the other two subtypes, the authors suggest that a more complex neural network may be in place for this synesthesia subtype[29]. This implies that even within one category of synesthesia, multiple mechanisms may be responsible for various subtypes, thus complicating the identification of precise neural substrates that underlie synesthesia.

Bargary & Mitchell, 2008 summarize current theories on synesthesia origins by showing how these theories tend to differ based on two parameters: first, whether the inducer region activates the concurrent region directly or indirectly; and second, whether this cross-activation is a result of structural/anatomical differences or functional differences. With theories relating to structural differences, it is postulated that synesthetes possess excitatory neural connections to the concurrent region that non-synesthetes lack. On the other hand, theories relating to functional differences claim that non-synesthetes and synesthetes alike possess excitatory connections between the inducer and concurrent region, but non-synesthetes possess inhibitory connections alongside these that prevent the concurrent region from becoming activated (Figure 2). Normally, feedback exists in the brain to help strengthen the neuronal activity that is associated with the expected stimulus, while it also inhibits neural firing associated with another sensory modality[25]. It should be considered that these two schools of thought may not be exclusive, and it may be that one model could cause the other[6].

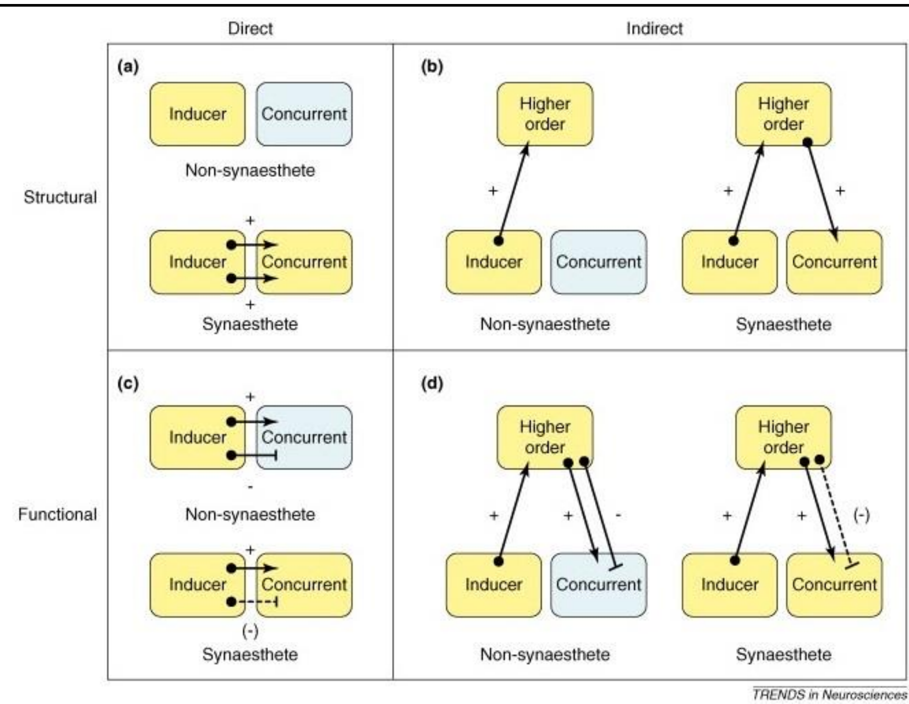

Figure 2. Possible connections leading to cross-activation. Yellow areas are active. Excitatory connections given by arrows, inhibitory connections given by blunt-ended arrows. (Adapted from Bargary & Mitchell 2008)

One popular model that fits within the parameters established by Bargary & Mitchell, 2008 is the disinhibited feedback model—also known as the top-down theory[14]—which suggests that synesthetic brains lack certain feedback mechanisms from high cortical areas that, in neurotypical adults, should suppress the activation of lower cortical areas in other sensory systems[10] (Figure 2d). This model has been applied to grapheme-color synesthesia, suggesting that the multimodal SPL area sends abnormal feedback to lower regions like the V4 region[14].

Several studies have indicated that differences in structure exist in synesthetes when compared to controls, and therefore structural components may be in part responsible for synesthesia. Rouw & Scholte, 2007 utilized diffusion tensor imaging (DTI) imaging to identify increased white matter within the fusiform gyrus using BOLD-MRI analysis. White matter is made up of myelinated axon pathways that connect different neural regions; therefore, the presence of increased white matter indicates increased connectivity in this region. It is intriguing to note that this study found only an increase in white matter connectivity within the temporal cortex near V4, but does not seem to show connections to any other areas[3].

Both structural and functional neuroimaging studies that have been conducted thus far have provided highly variable results even within the same phenotype of synesthesia. Functional MRI (fMRI) studies analyzing grapheme-color synesthesia, for instance, typically support the involvement of V4[4,29], while other studies find more correlation with the parietal cortex instead[16,20,21,24]. Due to this, O'Hanlon et al., 2013 suggest that these varied results may stem simply from the differences in brain connections within individual synesthetes, such as grapheme-color synesthetes that are considered projectors versus associators. This proposition further complicates the pursuit for a common cause of all forms of synesthesia and suggests there is no one common cause for the different forms of this condition. In the study, the authors employed diffusion tensor imaging (DTI) on synesthetes and control individuals to assess for structural brain differences between the two study groups. Some noted structural differences found between synesthetes and controls include a higher volume of white matter and gray matter in certain brain regions. Another proposed model postulates that there's two stages involved in the processing of the senses that leads to synesthesia, the first being the perception of the synesthetic color that takes place in the fusiform gyrus and V4, and the second is the projection or association of the synesthetic color to the grapheme, which could take place in the parietal cortex[12]. An imaging study utilizing fMRI imaging found an increase in blood-oxygenated-level-dependent (BOLD) response in these areas at the hypothesized time points, indicating neural activity that further supports this theory[14].

The increased gray matter found in the Rouw & Scholte, 2010 study could play a role in the models associated with projector vs. associator and cross-activation vs. disinhibited feedback model. Grey matter consists of neuronal cell bodies and dendrites, and is where sensory information converges and is processed. If these extra structural variations exist in sensory regions, it could strengthen the cross-activation model seen in projectors, while increased connections in the memory-related areas would reinforce the findings associating the disinhibited-feedback model with associators.

Van Leeuwen et al., 2011 have also compared the two populations of projector and associator grapheme-color synesthesia in terms of the cross-activation and disinhibited-feedback model. It was found that the bottom-up model was the more likely cause of projectors, while the top-down model was likely occurring in associators (Figure 3). So while similar areas of the brain may be connected depending on the type of synesthesia, individual variations within a specific type of synesthesia may be due to varying connections between the regions, and merely impact the phenomenal perception[14]. It is suggested that these different pathways between projectors and associators may be similar to the mechanisms seen when neurotypical adults mentally picture something vs. actually view it; while viewing something activates a feedforward mechanism to higher sensory areas, mental imaging causes feedback from higher sensory areas down to lower sensory areas. What's intriguing is that mental imagery and actually viewing an object in the external environment also activate the same cortical areas. However, due to the fact that projector and associator classification should be considered as a continuum rather than two distinct taxonomies, it is likely not the case that projectors only exhibit the cross-activation model and vice versa, but rather that these synesthetes may be considered stronger in regards to one model vs the other[14].

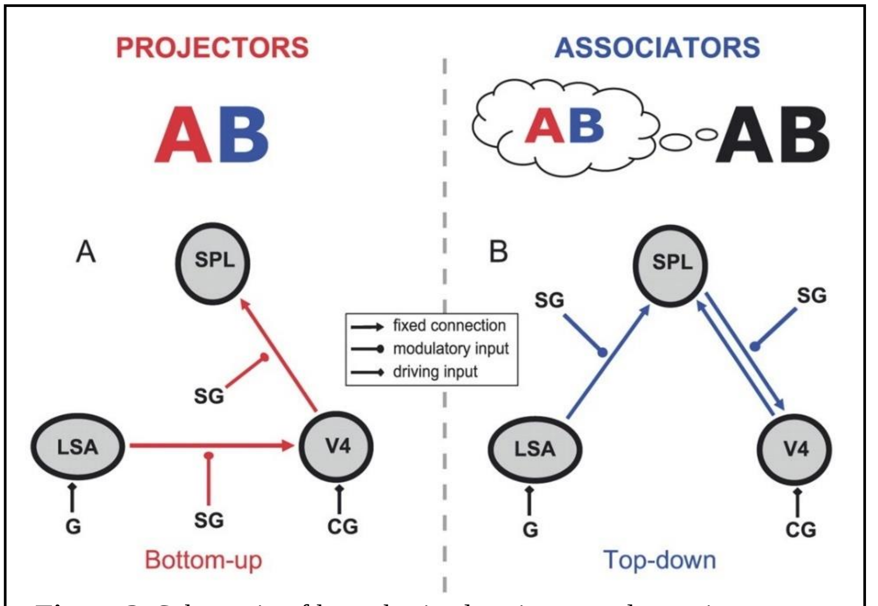

Figure 3. Schematic of hypothesized projector and associator pathways in grapheme-color synesthesia. G stands for where the grapheme is interpreted, and SG stands for where the synesthesia-inducing graphemes act as modulatory inputs in the path, and CG stands for where colored-graphemes are interpreted. (Adapted from van Leeuwen et al. 2011)

The existence of a variation of mechanisms within one form of synesthesia can be also seen in sequence-spatial synesthesia. Even the idiosyncratic differences found between synesthetes that have the same type of synesthesia likely result from different neural pathways acting. In the instance of sequence-spatial synesthesia, individual synesthetes seem to vary in how they experience their synesthesia spatially versus visually. For example, if a synesthete is considered low in the spatial dimension, their spatial experience with have low spatial quality, while synesthetes that are high in this dimension can experience higher qualities of spatial synesthesia, and capable of having multiple viewpoints in their spatial experience[13]. It has been theorized that differences may result from higher activation in the dorsal stream of visual perceptions –which correlates with spatial and movement awareness—or the ventral stream—which correlates with more superficial distinctions[13].

Developmental Origins and Genetics

The origin of the hyperconnectivity believed to exist in synesthetes is another target of current research. At present, several hypotheses have been posed to resolve this debate. One hypothesis claims that the anomalous interaction between cortical regions is due to decreased inhibitory actions between the two regions, which seems to support the disinhibited-feedback model. Another hypothesis suggests that the excess connections may be due to insufficient thinning (commonly referred to as “pruning” in these studies) of connections that are typically removed during development[17]; this sort of development is likely associated with the cross-activation model[25].It has also been theorized that alterations in cortex border formation due to mutations in molecule gradients could play a role[3].

Many studies claim that synesthesia results from the remnants of developmental processes that were abnormally ungroomed during development. Transient cross-modal connections have previously been observed in animal models and older studies have also implicated these kind of connections in juvenile adults[25], which could lend credence to the lack of pruning theory of synesthesia origin. No underlying mechanism for this excess of connections has been identified yet, but it is likely genetic in origin. The theory regarding a decrease in normal inhibitory networks could possibly also depend on the lack-of-pruning theory, as this gives extra connections that could act excitatory to boost the activation of the additional sensory area.

However, other mechanisms could cause a decrease in inhibitory networks that also allow the concurrent sense to fire[25].

Synesthesia can also lend understanding to how humans psychologically develop as well as physiologically. It has been shown that the culture and language a synesthete is brought up in plays a role in some of the concurrent responses they experience, though they still remain highly idiosyncratic[4,5]. It should also be clarified that cultural norms only sway what kind of concurrent response is elicited by the inducer, not whether synesthesia is presented or not[28]. In the instance of time-space synesthesia, the cultural perception of months occurring in a typically left to right manner is preserved in the clockwise and left to right spatial layout of months in the synesthetes[4]. The study conducted by Rich et al. (2005) also provides evidence that semantic knowledge may also influence synesthetic perception; an example used in the Yokoyama et al. (2014) study is the perception of green when viewing the word MELON and yellow when viewing the word BANANA.

Because synesthesia has been noted to run in families since the condition was originally identified, it has long been theorized that synesthetic mechanisms may be genetic in origin[26], and several studies have been conducted into the possible genetic basis of synesthesia. A genetic analyses conducted by Tomson et al., 2011 found a gene in the 16q12.2-23.1 region as a likely candidate for some forms of colored-sequence synesthesia, though it was associated with two of the five families used in the study, implicating that colored-space synesthesia has locus heterogeneity. This study corroborated the findings on an earlier genetic analyses of auditory-visual synesthetes, which found four possible regions wherein mutation could lead to synesthesia[2]. The findings of both of these studies lead to the belief that some forms of synesthesia may be due to multiple gene mutations. It is interesting to note that in the Asher et al., 2009 study, the regions that were identified had been previously associated with genes that could be associated with synesthesia mechanisms. For instance, the D2S142 region of chromosome 8 was potentially linked to synesthesia, and this region possesses a gene *TBR1*, which transcribes a gene called reelin that regulates the development of the cortex[11]; therefore, a mutation in region could impact cortical organization and possibly lead to synesthesia.

Conclusion

At present, a large body of evidence from various types of neural testing implicates several theories regarding the possible mechanisms of synesthesia. These theories attempt to explain both the associated cortical regions, and the manner in which these areas are connected. However, even within one type of synesthesia—such as grapheme-color synesthesia—imaging studies reveal varying findings[16]; these variations are likely due to individual differences between synesthetes, such as whether or not they are considered a projector or associator.

The main caveat of attempting to discover the precise neural mechanisms that give rise to synesthesia is this large scope of heterogeneity amongst types of synesthetes, meaning that the results of studies conducted on specific types of synesthesia only provide conclusive evidence regarding that specific subset of synesthesia. Therefore, in order to gain a comprehensive understanding of all the possible mechanisms that could play roles in the many forms of synesthesia, it seems that the best course of action would be to perform the variety of tests discussed in this paper (e.g. MEG, DTI, etc.) on specific forms in order to understand the associated cortical regions and the possible pathways that connect these regions.

Even though synesthesia does not exhibit any inherently negative side effects besides the abnormal sensory perception[19], and therefore does not require a treatment to be found for it, conducting research into synesthesia is still crucial for both the appreciation of this condition and others. Because of its developmental origins, understanding the mechanisms of synesthesia could lend insight into how people normally perceive sensory input, as well as how different brain regions communicate amongst one another in conditions such as autism or schizophrenia[26].

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