The underlying mechanisms of altered visual perception in synesthesia and autism spectrum disorder

Bachelor's Thesis Neurosciences Research
Lisa Bouwman
S3445062
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Supervisor: M.J.H. Kas

Abstract

Synesthesia is a condition in which a stimulus, the inducer, triggers a second perceptual experience, the concurrent. The most common form of synesthesia is grapheme-color synesthesia, in which the perception of a letter or number triggers the perception of a color, either as an association or as an actual projection. The underlying neurobiological mechanisms of synesthesia are still largely unknown. Interestingly, the prevalence of synesthesia seems to be higher in autism spectrum disorder (ASD). Alterations in sensory perception, like preference for local perception and superior perception of details, are common characteristics of ASD. However, the reason for co-occurrence of synesthesia and ASD is still unknown. In this review, the characteristics of altered visual perception in both synesthesia and ASD are compared, ranging from visual pathways to candidate genes. Evidence from different types of studies suggests that developmental synesthesia is caused by hyperconnectivity between different brain areas, which might be the consequence of a deficit in the pruning of connections during neurodevelopment. Multiple studies have shown that both synesthesia and ASD are biased towards local processing (focus on details) rather than global processing (focus on the context). Furthermore, deficits in motion perception have been found in both conditions. The MT/V5 area, involved in the magnocellular pathway, seems to be altered in both synesthesia and ASD. This might explain the deficit in motion perception. Furthermore, both synesthesia and ASD seem to show deficits in multisensory integration. Genetic studies have highlighted chromosome 2q as a potential gene involved in both synesthesia and ASD. When looking at neurotransmitters, both synesthesia and ASD seem to show increased excitability, either caused by increased glutamate release or reduced GABA release. Another important neurotransmitter involved in both synesthesia and ASD is serotonin. The role of serotonin in synesthesia is supported by acquired synesthesia after brain injury, in which serotonin levels increase, as well as drug-induced synesthesia, in which serotonin receptors are stimulated by drug-intake. Furthermore, individuals with ASD often show increased blood serotonin levels. An interesting finding is that the prevalence of synesthesia in ASD is around the same percentage as the prevalence of elevated blood serotonin levels in ASD. Future studies could measure the prevalence of synesthesia in autistic individuals with elevated blood serotonin levels in order to investigate whether there might be a causal relationship between serotonin increase and the development of synesthesia.

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Introduction

Synesthesia is an involuntary experience in which the perception of a stimulus (the inducer) activates a second perceptual experience (the concurrent) (Grossenbacher & Lovelace, 2001). Synesthesia was first described in 1880 by F. Galton, and has gained a lot of interest by neuroscientists and psychologists over the past century. There are various types of synesthesia, in which different combinations of inducer and concurrent are possible. The inducer and concurrent can be unisensory (like letter-color) or multisensory (like sound-color). One of the most common types of synesthesia is grapheme-color synesthesia, in which the vision of a letter or number induces the perception of color. The color usually doesn't change over time. For example, if a synesthete perceives the letter 'A' as blue, this person will still perceive 'A' as blue a year later. There are differences in the severity of synesthesia. In grapheme-color synesthesia for example, some synesthetes might see this text as black while associating the letters or words with colors, while more severe synesthetes might actually see the colors projected on the letters (Dixon et al., 2004).

Since synesthesia usually does not interfere with normal functioning, it has not been taken up in the Diagnostic and Statistical Manual of Mental Disorders (DSM). However, there is evidence that synesthesia often co-occurs in patients with neurodevelopmental disorders, especially in autism spectrum disorder (ASD). The rate of synesthesia is around 20% in adults with ASD, compared to 7% in non-autistic adults (Baron-Cohen et al., 2013). Furthermore, altered sensory processing is one of the criteria for the diagnosis of autism spectrum disorder according to the DSM-5 (DSM 5; American Psychiatric Association, 2013). Multiple studies have investigated altered sensory processing in synesthesia and ASD, and these studies suggest that synesthesia and ASD do indeed share the same alterations in sensory processing (Van Leeuwen et al., 2019; Ward et al., 2017; Ward et al., 2018). This raises the question whether altered sensory processing in synesthesia and ASD are caused by the same neurobiological mechanisms. Finding a connection between altered visual processing in synesthesia and ASD might explain the high prevalence of synesthesia in ASD, and might give us insights in the neurobiological mechanisms underlying synesthesia.

In this review, altered sensory processing in both synesthesia and ASD will be discussed. Studies on visual processing, brain areas, neurotransmitters and genes that might be involved in altered sensory processing in synesthesia and ASD will be discussed. Furthermore, altered visual perception in synesthesia and ASD will be compared, to see if synesthesia and ASD might indeed share the same neurobiological mechanisms. Since most types of synesthesia involve visual perception, this review will mainly focus on visual perception in synesthesia and ASD.

1. Visual processing in the healthy brain

Before investigating altered visual perception in synesthesia and ASD, it is important to know how visual perception is regulated in the healthy brain. A schematic representation of visual perception can be seen in figure 1.

When looking at an object, light first hits the photoreceptors in the retina. The photoreceptors will give a signal to the retinal ganglion cells (RGCs). There are three types of ganglion cells in the retina: parasol RGCs, midget RGCs and bistratified RGCs. Signals from the RGCs go to the lateral geniculate nucleus (LGN). In the LGN, the signals from the different types of RGCs are separated in different layers of the LGN. Parasol RGCs give information to the magnocellular layers, midget RGCs give information to the parvocellular layers, and bistratified cells give information to the koniocellular layers. The information will then go into different layers of the primary visual cortex (V1). Magnocellular layers give information to the 4Cα layer, parvocellular layers to the 4Cβ layer and koniocellular layers to layers 2/3. From the V1 area, information from parvocellular layers and koniocellular layers will go to the V4 area and the inferotemporal cortex, while information from the magnocellular layers will go to the medial temporal area (MT/V5) and the parietal cortex. The inferotemporal cortex plays an important role in object recognition and color perception. The parietal cortex is mainly responsible for space and motion perception (Yantis & Abrahams, 2017).

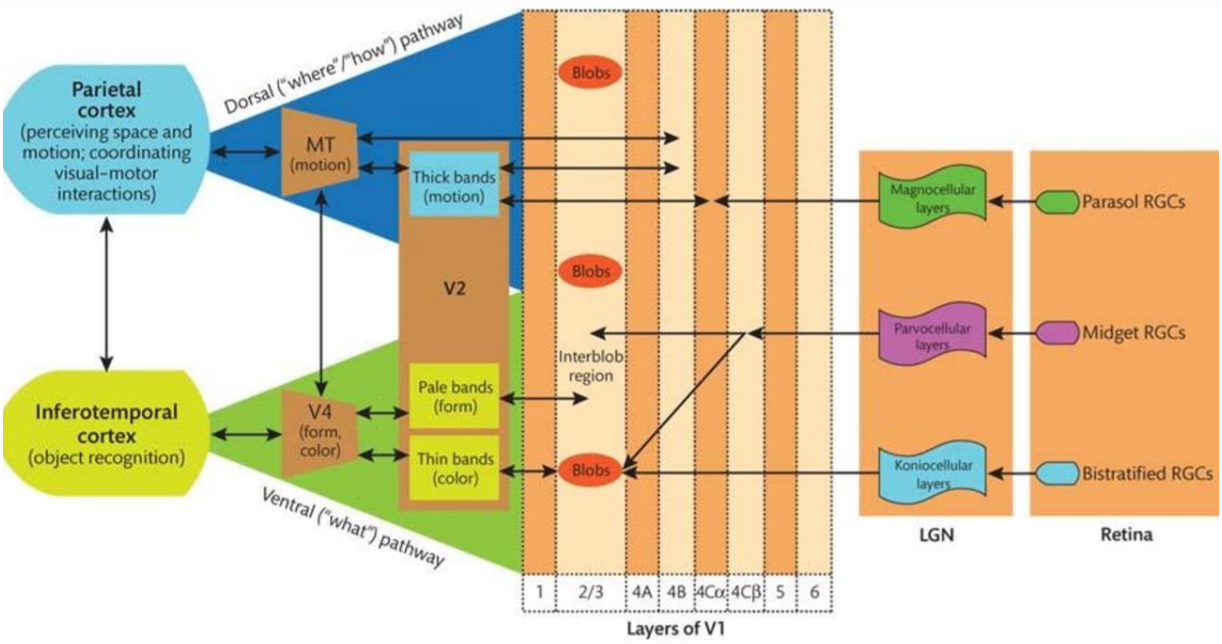

Figure 1. Schematic representation of the magnocellular, parvocellular and koniocellular pathways*. At the right side of the figure, the different RGCs in the retina can be seen. These RGCs give information to the LGN, which is divided into magnocellular, parvocellular and koniocellular layers. From the LGN, information goes to the different layers of the V1 area. The magnocellular layers give information to the 4Cα layer, which is connected to the thick bands in the V2 and the MT area. The parvocellular layers give information to the 4Cβ layer. Information from this layer goes to the blobs and interblob regions of the 2/3 layer. The interblob regions are connected to the pale bands of the V2 area. The blobs are connected to the thin bands. Both the pale bands and thin bands from the V2 area are connected to the V4 area. The V2 area is in contact with the parietal cortex, responsible for motion perception. The V4 area gives information to the inferotemporal cortex, which is responsible for shape and color perception. Adapted from Yantis & Abrahams (2017).*

2. Visual processing in synesthesia

Although there are many types of synesthesia, and different combinations of inducer and concurrent are possible, color is the most prevalent concurrent. The perception of color in synesthesia suggests enhanced color perception in synesthetes. Indeed, Banissy et al. (2009a) found that synesthetes who experience color as a concurrent show enhanced color perception, but no enhanced perception of other senses. Furthermore, synesthetes seem to have superior color working memory compared to controls (Terhune et al., 2013). In contrast to color perception, motion perception seems to be reduced in color synesthetes (Banissy et al., 2013; figure 2).

There is also growing evidence that local and global perception is different in synesthetes. Local perception is the perception of details, global perception is the perception of the context as a whole. Individuals with synesthesia seem to outperform control groups on tasks that require local perception. (Janik McErlean et al., 2016; Ward et al., 2018). Furthermore, Banissy et al. (2013) found that grapheme-color synesthetes had a higher motion-coherence threshold, indicating that they have a deficit in global perception. However, since few studies have focused on local/global processing in synesthesia, more research is needed to investigate whether there is a link between enhanced local perception and synesthesia.

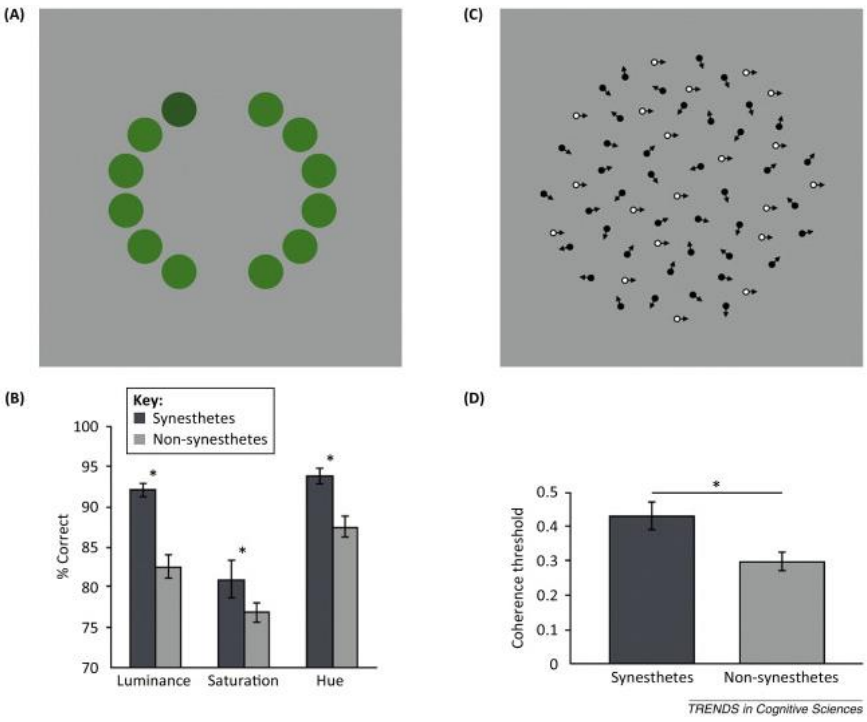

Figure 2. Visual search task and random-dot kinematogram display*. In figure A, a color-visual search task is seen, in which the participants had to seek out the slightly different coloured circle after the circles were observed for a very short time. Figure B shows the results of this experiment. In figure C, a sample random-dot kinematogram display is seen, in which all dots move in a different direction. The results are seen in figure D. Adapted from McCarthy& Caplovitz (2014), original results from Banissy et al. (2013).*

2.1. Hyperconnectivity and disinhibition

Enhanced color perception in synesthetes might explain the perception of color as concurrent. However, enhanced color perception does not explain the connection between the inducer and the concurrent. There seems to be interaction between different senses, or between different domains within the same sense (e.g. the perception of a letter induces the perception of color). There are three theories that try to explain the connection between the inducer and concurrent: the theory of cross-activation, the theory of cortical disinhibition, and the theory of re-entrant processing (figure 3).

The cross-activation theory suggests that number-color synesthesia is caused by hyperconnectivity between brain areas that are responsible for color and numbers (Ramachandran & Hubbard, 2001). If a grapheme-color synesthete reads a letter, letter-sensitive neurons are activated. If there is hyperconnectivity between these neurons and neurons responsible for color perception, color-sensitive neurons might be activated without any color being present. This might cause the perception of color as concurrent. Hyperconnectivity in synesthesia might be caused by a genetic mutation, that causes defects in the pruning of connections between different brain areas. The place of selective expression of this gene in the brain might explain the different types of synesthesia.

The second theory that might explain the connection between the inducer and the concurrent is the theory of cortical disinhibition (Cohen Kadosh & Walsh, 2008). Information from many different sensory pathways comes together in the brain. Normally, a feedback mechanism is caused by top-down information, which is cognitive information that can influence the perception of a stimulus (Gilbert & Li, 2013). This feedback causes only the inducer to activate the brain, which will prevent perception of other sensory pathways. However, in synesthetes, there might be disinhibition of the concurrent pathway (Grossenbacher & Lovelace, 2001). Information from the inducer pathway might activate neurons in the brain area where information from the inducer and concurrent pathway come together. If there is no inhibition of the concurrent pathway, this might lead to perception of the concurrent.

The re-entrant processing theory is a combination between the cross-activation theory and the cortical disinhibition theory. It suggests that there is crosstalk between brain areas responsible for graphemes and colors (like the cross-activation theory), as well as the requirement of higher level brain activity for synesthetic experiences (like the cortical disinhibition theory) (Smilek et al., 2001; Hubbard et al., 2011). This theory was proposed by Smilek et al. (2001), when they found that a grapheme-color synesthete was less successful in localizing graphemes on a background that was congruent with the concurrent of that grapheme, while this was not the case in non-synesthetes. This shows that the perception of a grapheme can induce a synesthetic experience, while the synesthetic experience can also influence the perception of the grapheme.

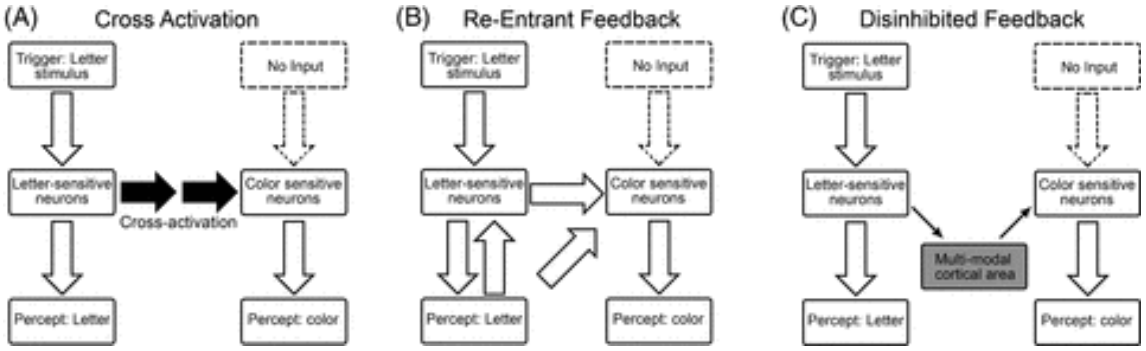

Figure 3. Schematic representations of the cross-activation theory, the re-entrant feedback theory, and the disinhibited feedback theory. *According to the cross-activation theory (A), hyperconnectivity between letter-sensitive neurons and color-sensitive neurons causes the activation of color perception when a letter is perceived. The re-entrant feedback theory (B) states that color-sensitive neurons are indeed activated by letter-sensitive neurons, but that there is also feedback on color-sensitive neurons by higher brain areas responsible for the perception of the letter. The disinhibited feedback theory (C) suggests that there is no direct connection between letter- and color-sensitive neurons, but that information from both pathways comes together in another brain area, where a lack of inhibition causes the perception of color. Adapted from Hubbard et al. (2011).*

2.2. Brain areas involved in synesthesia

As mentioned before, the place of hyperconnectivity or disinhibition in the brain could determine the type of synesthesia that occurs. Therefore it is interesting to know which brain areas are involved in synesthesia. One of the brain areas that plays an important role in color vision is the V4 area in the fusiform gyrus (FG). The cross-activation model suggests that the experience of coloured letters in grapheme-color synesthesia reflects hyperconnectivity between posterior fusiform areas involved in grapheme processing and area V4 in the FG and lingual sulcus (Ramachandran and Hubbard, 2001). Brang et al. (2010) used magnetoencephalography (MEG) to measure the activation of the V4 area and posterior temporal grapheme areas (PTGA) in grapheme-color synesthetes. They found that activation of V4 was significantly increased in synesthetes, whereas activation in PTGA did not significantly differ from the control group (figure 4). Furthermore, they found that activation of V4 and PTGA happened at almost exactly the same time. This finding supports the theory of cross-activation rather than the theory of disinhibition, which states that V4 is activated after the initial stages of grapheme processing. fMRI studies on grapheme-color synesthetes show that color synesthesia arises as a result of activation of V4 (Hubbard et al., 2005), and that activation of V4 was greater when the synesthetes were presented with graphemes that caused them to report seeing colors compared to graphemes that did not (Sperling et al., 2006). Sinke et al. (2012a) found that there is altered brain activity in the left parietal lobe of grapheme-color synesthetes. However, they did not find activation of the V4 area. This might be due to the fact that this study controlled for vividness of visual imagery. There seem to be differences in the vividness of visual imagery between synesthetes and non-synesthetes (Barnett & Newell, 2008). Increased V4 activation in synesthetes might be due to the fact that they have more vivid visual imagery, and it has been shown that visual imagery can activate visual areas (Ganis et al., 2004). The comparison of color synesthetes to non-synesthetes with the same vividness of visual imagery might explain why Sinke et al. did not find a significant increase in V4 activation. It is thus not clear if enhanced activation of the V4 area has a direct association with synesthesia, or that the enhanced activation is only the result of increased vividness.

However, V4 is not the only brain area that has been studied in synesthetes. Whole-brain studies report increased activation in both left and right superior parietal lobe in response to synesthetic color experiences (Laeng et al., 2011; Paulesu et al., 1995; Weiss et al., 2005). Colizoli et al. (2017) let non-synesthetes read texts in which letters were specifically coloured for several weeks. When viewing a black text after these weeks of reading, activity of the right angular gyrus of the parietal lobe was directly related to the strength of the learned letter–color associations, which indicates that the right angular gyrus plays a role in grapheme-color synesthesia as well. Hupé et al. (2012) showed that in grapheme-color synesthetes, white matter was increased in the retrosplenial cortex, a brain area that receives input from visual areas and that seems to play an important role in sensory integration (Vogt & Miller, 1983; Fournier et al., 2020). Another brain area that seems to have increased activation in grapheme-color synesthesia is the left fusiform grapheme processing area (Volberg et al., 2017). Banissy et al. (2012) observed that synesthetes showed an increase in gray matter volume in left posterior FG and a decrease in anterior regions of the left FG and left MT/V5, which also supports the findings of enhanced color perception and reduced motion perception in synesthesia.

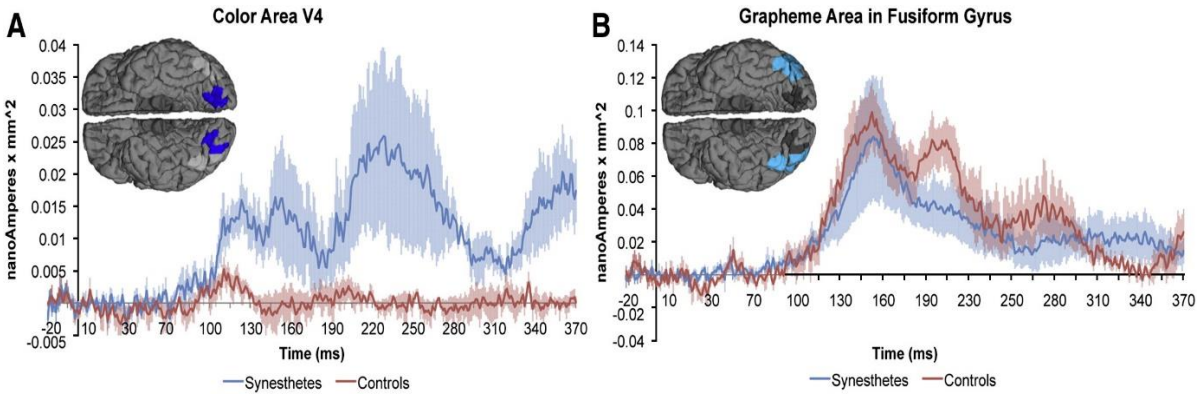

Figure 4. Activation of V4 and grapheme area. *Mean activation of color area V4 (A) and the grapheme area in the fusiform gyrus (B) in synesthesia and controls. Mean activation of the V4 area was significantly enhanced in synesthetes, but there was no difference in activation of the grapheme area between synesthesia and controls. Adapted from Brang et al. (2010).*

3. Synesthesia on a molecular level

3.1 Neurotransmitters involved in synesthesia

Although the direct cause of the development of synesthesia is not clear, it is likely that synesthesia is caused by a defect in neurodevelopment, and that it has a genetic basis. However, there are also people who acquire synesthesia somewhere later in life. This cannot be explained by defects in development of the brain.

Synesthesia can be acquired after brain injury, like a stroke or traumatic brain injury (Ro et al., 2007). It can also occur during migraine (Alstadhaug & Benjaminsen, 2010) or a seizure (Jacome & Gumnit, 1979). Ro et al. (2007) suggest that acquired synesthesia can be caused by reorganization of the sensory systems after brain injury, which results in increased connectivity. How this

reorganization happens is still unclear. However, there is increasing evidence that neurotransmitters play an important role in this process. Hinzman et al. (2010) found that tissue damage in brain injuries might eventually lead to excessive release of excitatory neurotransmitters, particularly serotonin and glutamate. They used enzyme-based microelectrode arrays (MEAs) to measure the amount of glutamate in the brains of rats 2 days after brain injury, and found that extracellular glutamate levels were significantly increased in the dendate gyrus and dorsal striatum (figure 5). Busto et al. (1997) performed micro-dialysis on rats during brain injury, and found that serotonin increased within the first 10 minutes after the brain injury. The question remains how this increase in excitatory neurotransmitters leads to synesthesia. One hypothesis is that the elevated neurotransmitter levels down-regulate serotonin receptors in the ipsilateral hemisphere, which will eventually lead to decreased serotonin levels (Brogaard, 2013). Studies on ASD have shown that down-regulation of the serotonergic system in one hemisphere may result in an upregulation of the serotonergic system in contralateral brain regions (DeLong, 1999; Takeuchi et al., 2012). This might cause functional changes in the brain that eventually lead to the development of synesthesia (Brogaard, 2013).

Another form of synesthesia that is not caused by a deficit in neurodevelopment is drug-induced synesthesia. In drug-induced synesthesia, different perceptions are mixed up after intake of drugs (Sinke et al., 2012b). One of the drugs that is known to cause synesthesia is lysergic acid diethylamide (LSD) (Schmid et al., 2015; Terhune et al., 2016). LSD selectively activates 5-HT2a receptors (serotonin receptors), which supports the statement that serotonin plays a role in drug-induced synesthesia (Brang & Ramachandran, 2007). 5-HT2a receptors can also increase glutamate release, which could contribute to increased excitability in synesthesia (Ceglia et al., 2004). Furthermore, Yanakieva et al. (2019) reported a case of synesthesia induced by 2C-B, a potential 5-HT2a receptor agonist. This case supports the role of serotonin in drug-induced synesthesia as well.

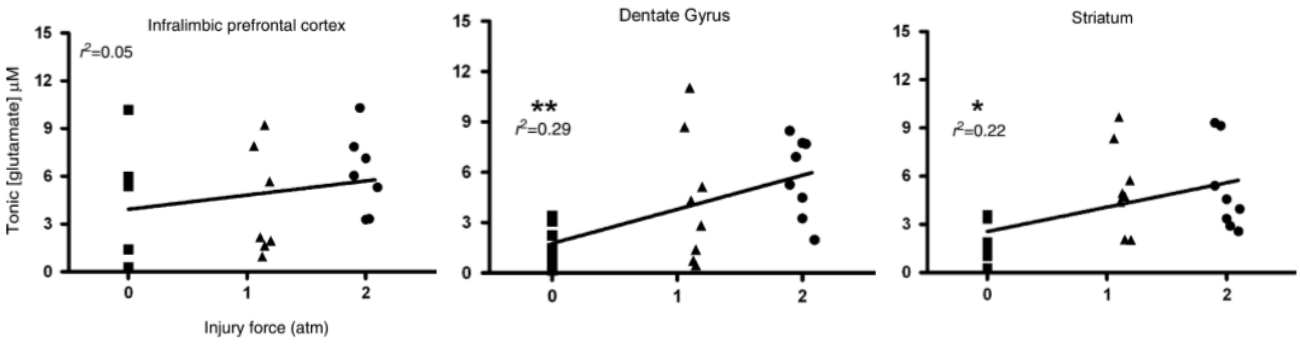

Figure 5. Glutamate levels after brain injury. *Correlations of tonic glutamate levels with injury force in the prefrontal cortex, dentate gyrus, and striatum of the rats. A significant correlation between injury force and tonic glutamate levels in the dendate gyrus and striatum can be seen. Adapted from Hinzman et al. (2010).*

3.2 Genes involved in synesthesia

As discussed before, synesthesia might occur due to defects in pruning during neurodevelopment, which might be caused by mutations. There is strong evidence that synesthesia has a genetic basis (Baron-Cohen et al., 1996). There seems to be a prevalence of synesthesia of more than 40% among first-degree relatives of synesthetes (Barnett et al., 2008). The question remains which genes are responsible for the development of synesthesia. Since synesthesia is hard to test in animals, it is impossible to study mutations that might be required for the development of synesthesia. However, since synesthesia is often found in many individuals within the same family, whole-genome studies of families have been done to find genes that might be responsible for synesthesia. Tilot et al. (2018)

identified 3 families with auditory-visual synesthesia. They found rare genetics variants that fully co-segregate with synesthesia in each family. Gene ontology analysis highlighted six genes: COL4A1 (13q34), ITGA2 (5q11.2), MYO10 (5p15.1), ROBO3 (11q24.2), SLC9A6 (Xq26.3) and SLIT2 (4p15.31). All these genes are associated with axonogenesis and are expressed during early childhood, which supports the role of hyperconnectivity in synesthesia. Asher et al. (2009) did a whole-genome scan in 43 families with auditory-visual synesthesia. They found significant linkage to chromosome 2q24, and suggestive linkage to chromosomes 5q33, 6p12 and 12p12. They did not find any linkage to the X chromosome, and even found two cases of male-to-male transmission of synesthesia. Tomson et al. (2011) performed a genetic analyses and found that coloured sequence synesthesia is linked to a gene in the 16q12.2-23.1 region. However, since only two of the five families they tested showed linkage to this region, synesthesia might be a heterogeneous condition. Furthermore, studies on monozygotic twins found that sometimes only one of the twins experienced synesthesia, which suggests that synesthesia is partly influenced by extragenic factors (Smilek et al., 2002; Smilek et al., 2005; Bosley & Eagleman, 2015).

4. Visual perception in ASD

Altered sensory processing is a common characteristic of autism spectrum disorder, and is one of the criteria for ASD according to the DSM 5 (DSM 5; American Psychiatric Association, 2013). Patients with ASD can show both hyper- and hypo-sensitivity to visual stimuli. These symptoms are often seen in the behaviour of people with ASD. Individuals with hyper-sensitivity often look at tiny objects (like dust or tiny particles) and are oversensitive to bright light, while hypo-sensitive patients are often attracted to light and shiny objects, and like to move objects in front of their eyes (Bogdashina, 2003). Therefore, it is interesting to take a look at the alterations in visual processing in ASD.

4.1 Local and global processing

One important aspect of altered visual processing in ASD is the difference in local and global perception. The first evidence of altered local/global processing came from a study by Shah & Frith (1983), who found that autistic children performed significantly better on the embedded figures task (a task in which they had to find a hidden shape in a figure) than the control group, which indicates improved local processing. Furthermore, patients with ASD often show superior processing of fine detail (Dakin & Frith, 2005), which also supports increased local processing. In contrast to local processing, global processing seems to be reduced in individuals with ASD. A recent meta-analysis has shown that individuals with ASD show a small deficit in global processing, independent of the paradigm, task, dependent variable, age or IQ (Van der Hallen et al., 2019). A study by Bölte et al. (2017) has shown that individuals with ASD show decreased gestalt perception (the perception of structures as a whole), which indicates a local perception bias. Interestingly, Bertone et al. (2005) found that autistic individuals showed impaired perception of complex orientation, while they showed superior perception of simple orientations. They suggest that this is caused by enhanced lateral inhibition, which is the result of atypical neural connectivity.

There are two theories that try to explain the changes in local and global perception in ASD: the enhanced perceptual functioning (EPF) theory and the weak central coherence (WCC) theory (Brown & Crewther, 2017). The EPF theory suggests that there is an over-development of low-level perceptual operations, which leads to superior performances on low-level cognitive tasks (Mottron et al., 2006). It assumes that patients with ASD show superiority of local processing without failure of global processing. The WCC theory, in contrast, suggests that there is a deficit in global perception in

ASD, which makes patients with ASD appear to be superior in local processing (Happé, 1999). However, this theory has been modified after research had shown that autistic individuals are able to perform normal on global processing tasks when told to do so, but that they prefer local processing over global processing (Mottron et al., 2006; Happé & Frith, 2006). This theory is also supported by the findings of altered gestalt perception in ASD (Bölte et al., 2017). Patients with ASD seem to have a bias towards local perception instead of global perception, which could be the reason why they seem to outperform controls on local perception tasks.

4.2 Magnocellular and Parvocellular responses

As discussed earlier, magnocellular and parvocellular responses play an important role in visual perception. Parvocellular responses are mainly responsible for color perception, whereas magnocellular responses are mainly responsible for motion perception. Magnocellular and parvocellular pathways seem to have different latencies. Human VEP studies have shown that the magnocellular pathway activates the primary visual cortex (V1) a few milliseconds earlier than the parvocellular pathway (Baseler & Sutter, 1997; Klistorner et al., 1997). This phenomenon is called the magnocellular advantage (Laycock et al., 2007). Delay in primary visual cortical processing is seen in ASD, and this delay might diminish the magnocellular advantage, which appears to be associated with impaired global perception (Sutherland & Crewther, 2010). Jackson et al. (2013) showed that autistic individuals performed worse when they were forced to indicate the direction of a group of moving dots (that was presented only 80 milliseconds), requiring global processing. Brown & Crewther (2017) used VEP to measure magnocellular and parvocellular responses in patients with ASD, and found that patients with ASD show a lower parvocellular response, which is a sign of a more efficient parvocellular pathway. In contrast, Fujita et al. (2011) found that individuals with ASD show prolonged VEP responses to chromatic stimuli, which is associated with a deficit in the parvocellular pathway. Furthermore, children with autism seem to be less accurate at color perception than the non-autistic children (Franklin et al., 2008). The changes in parvocellular responses in ASD are thus not fully understood yet.

Multiple studies have investigated changes in activity in visual brain areas in ASD. Alaerts et al. (2017) found that the superior temporal sulcus responded less to biological motion in individuals with ASD compared to the control group. There is also evidence that people with ASD have larger receptive fields in the extrastriate areas of the visual cortex (Schwarzkopf et al., 2014). V1 and MT responses were reduced in ASD when looking at low-strength motion signals (Robertson et al., 2014). An fMRI study by Herrington et al. (2006) found significantly less activity in the inferior, middle and superior temporal regions (including MT/V5) in individuals with ASD during motion perception. In contrast, a MEG study by Peiker et al. (2015) showed increased responses of the MT/V5 area during motion perception, which suggest an enhanced response gain. Takarae et al. (2014) found that the V5 area was overactive in individuals with ASD in tasks that involved bottom-up information, but that V5 activation was reduced in tasks that required top-down control. Activity of the MT/V5 area might be dependent on the task. However, these studies suggest that activity of the MT/V5 area is altered in ASD.

4.2. Multisensory processing in ASD

The studies previously discussed show alterations in visual perception in ASD. However, these are only focussed on one sense. Individuals with ASD seem to show alterations in multisensory processing as well. One aspect of altered multisensory integration in ASD is reduced susceptibility to the McGurk effect (Smith & Bennetto, 2007; Stevenson et al., 2014). The McGurk effect is the creation of an illusionary perception, when two stimuli from different senses do not match (for example, when you see someone saying a word, but you hear another word) (McGurk & MacDonald, 1976). Reduced susceptibility to the McGurk effect indicates a deficit in multisensory integration. Russo et al. (2010) showed that there was a deficit in multisensory integration in the ASD group when perceiving a multisensory auditory–somatosensory stimulus. Individuals with ASD only seem to show integration of visual cues when the cues are congruent, whereas non-autistic individuals show integration of incongruent cues as well (Bedford et al., 2016). Brandwein et al. (2013) found that children with ASD show less effective neural integration. Another interesting finding is that serotonin transporter (SERT) mutated mice, a mouse model for ASD, were not able to show learned behavioural gains under multisensory conditions (Siemann et al., 2017). Mice were trained to respond to either auditory or visual stimuli, and were tested under multisensory conditions (figure 6). The results of this experiment can be seen in figure 7. This study suggests that serotonin plays an important role in multisensory processing, as well as in ASD. The role of serotonin in ASD will be discussed later in this paper.

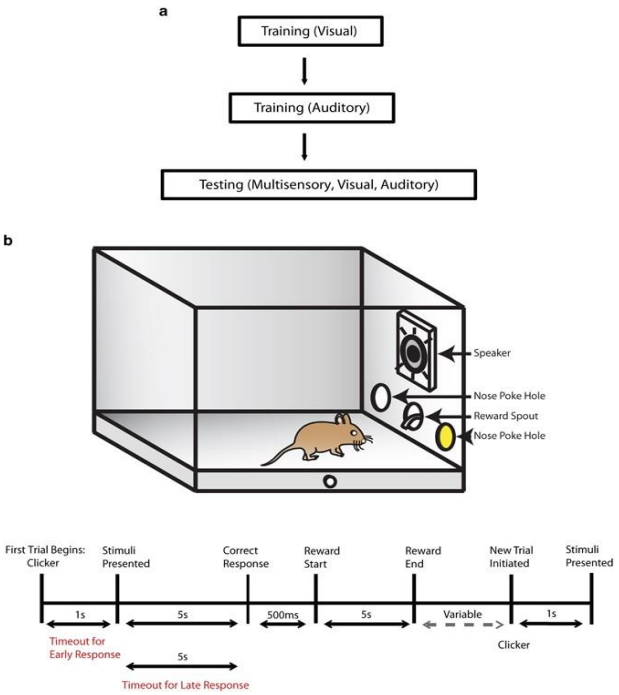

Figure 6. Behavioral paradigm for multisensory processing in mice. *In this behavioural paradigm, mice were first trained to respond to visual and auditory stimuli separately for a liquid reward. After the unisensory training, the mice were tested in sessions where visual, auditory and congruent audio-visual (multisensory) stimuli were presented. Adapted from Siemann et al., 2017.*

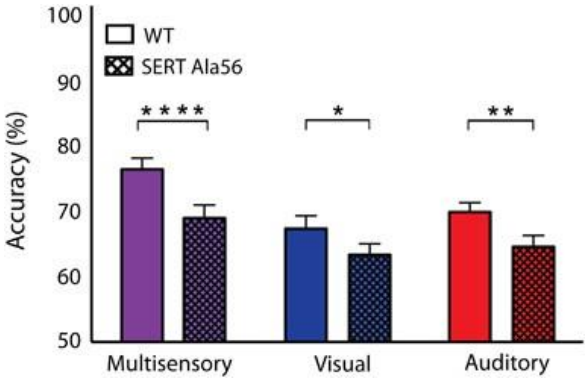

Figure 7. Accuracy of behaviour. *Here the results of the behavioural paradigm are presented. Behavioural accuracies were significantly decreased in the SERT mutated group during multisensory conditions. Adapted from Siemann et al., 2017.*

5. ASD on a molecular level

5.1 Neurotransmitters involved in ASD

Although a large part of altered visual perception in ASD still remains unknown, there seem to be changes in the brain of individuals with ASD. Since neurotransmitters play an important role in neurodevelopment, changes in brain structure in ASD might be caused by changes in neurotransmitter levels. Furthermore, one third of all patients with ASD shows seizures, which indicates a disbalance between inhibitory and excitatory neurotransmitters (Brooks-Kayal, 2010).

Takarae et al. (2016) found that ASD patients show greater increases in visual responses over contrast manipulation, which suggests higher excitability in the sensory cortex. Magnetic resonance spectroscopy (MRS) showed that there are changes in the relationship between cortical GABA concentrations and visual perceptual performance in ASD, which suggests reduced action of GABA in ASD (Robertson et al., 2016). Post-mortem studies found a 50% reduction of GAD65/67, the enzymes responsible for conversion of GABA, in the cerebellum and parietal cortex of individuals with ASD (Fatemi et al., 2002). Since GABA is an inhibitory neurotransmitter, reduced action of GABA results in increased excitability. Furthermore, GABA mediates calcium signalling during embryonic development, which regulates a variety of different developmental processes like cell proliferation, migration, differentiation, synapse maturation, and cell death (Owens & Kriegstein, 2002). Therefore, changes in GABA levels during embryonic development might cause alterations in brain structures, which might lead to neurodevelopmental disorders.

Another neurotransmitter that seems to play an important role in ASD is serotonin. Blood serotonin levels seem to be elevated in 25% of the ASD population (Schain & Freedman, 1961; Gabriele et al., 2014). Hérault et al. (1996) found that blood serotonin levels were positively correlated with the severity of ASD. Furthermore, an increase in both serotonin levels and serotonin transporters (SERT) has been found in ASD, as well as a correlation between these increased levels and the severity of ASD (Abdulamir et al., 2018). ASD also seems to be associated with rare SERT variants, which all have elevated serotonin transport function (Prasad et al., 2009). In BTBR mice (a mouse model for ASD), the density of serotonin neurons was reduced in the hippocampus, but increased in the caudal dorsal raphe and the median raphe, which indicates that there are region-dependent abnormalities in serotonin signalling (Guo & Commons, 2017). These region-dependent changes in serotonin levels are also seen in studies using PET scans, which have shown that serotonin synthesis is often suppressed in the left hemisphere and increased in the right hemisphere in ASD (Chandana et al., 2005). Taken together, these studies suggest an important role for serotonin in the development of ASD.

5.2 Genes involved in ASD

There are multiple studies that suggest a strong genetic factor in ASD. Twin studies have suggested that monozygotic twins have a 60–90% chance to develop ASD when the other twin is diagnosed with autism, compared to a risk of 0–24% in non-identical twins (Bailey et al., 1995, Steffenburg et al., 1989). Studies have found several chromosomal loci associated with ASD, including 2q (Buxbaum et al., 2001, Shao et al., 2002), 5 (Philippi et al., 2007; Ma et al., 2009; Weiss et al., 2009), 7q (Cukier et al., 2009), 15q (Nurmi et al., 2001; Sutcliffe et al., 2003; Kim et al., 2008) and 16p (Barnby et al., 2005; Kumar et al., 2008). Two genome-wide linkage and association mapping studies found that single-nucleotide polymorphisms (SNPs) located at 5p14.1 and 5q15 were associated with ASD (Ma et al., 2009, Weiss et al., 2009). Chromosome 16 linkage results show a peak at 16p11–13, which strongly suggests loci in this region may contribute to the risk of developing ASD (Shinawi et al., 2010, Kumar et al., 2008). Another gene that seems to have a strong connection with ASD is 15q, especially 15q11-13 (Cook et al., 1998; Buxbaum et al., 2002; McCauley et al., 2004). Interestingly, the 15q11-13 part contains genes coding for subunits of the $GABA_A$ receptor, which further supports the role of GABA in ASD (Coghlan et al., 2012).

The X chromosome seems to be associated with ASD as well. Skuse et al. (1997) found an increased incidence of ASD in women with Turner syndrome, a syndrome in which only one X chromosome is present. Petit et al (1996) found a different allele distribution of the DXS287 marker on the X chromosome in ASD, correlated with the severity of autistic behaviours. Furthermore, deletions in the Xp22.2 to Xp22.3 region seem to be associated with autistic features (Chung et al., 2011). The fact that autistic symptoms often occur in fragile X syndrome, a syndrome caused by a mutation on the X chromosome, further supports the role of the X chromosome in ASD (Farzin et al., 2006; Hayes & Matalon, 2009).

6. Connection between synesthesia and ASD

As mentioned in the introduction, there is a high prevalence of synesthesia in individuals with ASD. Previous studies have found that there is a positive correlation between autistic traits and synesthesia (Burghoorn et al., 2019; Mealor et al., 2016). In this review, the different aspects of altered sensory perception in both synesthesia and ASD have been discussed. The question remains whether there is an overlap between altered sensory perception in synesthesia and ASD, and if this might explain the high prevalence of synesthesia in ASD.

In the previous paragraphs, the characteristics of altered visual perception in synesthesia and ASD have been described. Furthermore, some studies on involved neurotransmitters and genes have been discussed. In table 1, the findings of this review are summarized. Although not every characteristic of altered visual perception in synesthesia and ASD has been studied extensively, and not all studies agree on some of the findings, there seem to be some shared features between synesthesia and ASD. These shared features will be discussed below the table.

Table 1. Overlap between synesthesia and ASD. *Here, a summary and comparison of different findings on altered visual perception and underlying mechanisms in synesthesia and ASD is presented.*

Alteration	***Synesthesia***	***ASD***	***Overlap***
Visual processing	Local perception ↑ Global perception ↓ Motion perception ↓ Color perception ↑	Local perception ↑ Global perception ↓ Motion perception ↓	Reduced motion perception, reduced global perception, increased local perception
Brain areas	V4 ↑ MT/V5 ↓ Left parietal lobe ↑ Right angular gyrus ↑ Fusiform grapheme processing area ↑	V1 ↓ MT/V5 ↓ Superior temporal sulcus ↓	Reduced activation of MT/V5
Neurotransmitters	Serotonin ↑ Glutamate ↑	Serotonin ↑ GABA ↓	Increase in serotonin, increased excitability.
Genes	2q24 5p15.1 5q11.2 5q33 6p12 12p12 13q34 16q12-23	2q 5q14-15 7q 15q11-13 16p11-13 X	2q

6.1 Shared visual processing

It is clear that altered visual processing is a feature of both synesthesia and ASD. First of all, both synesthesia and ASD seem to have a bias towards local processing and reduced global processing, although few studies have focused on local and global processing in synesthetes. Furthermore, motion perception seems to be impaired in both synesthesia and ASD. There is evidence that there is a deficit in the magnocellular pathway in both synesthesia and autism. However, the functioning of the parvocellular pathway is still not clear. While the parvocellular pathway seems to be upregulated in color synesthetes, studies have found both upregulation and deficits in the parvocellular pathway in ASD.

Another feature that is shared by synesthesia and ASD is altered multisensory processing. Multisensory processing has only been discussed in ASD, since this review only focussed on visual perception in synesthesia. However, studies have shown alterations in multisensory processing in synesthesia as well. Sinke et al. (2014) found that synesthetes show weaker integration of vision and audition, which is comparable to the reduced susceptibility to the McGurk effect in ASD. Bargary et al. (2009) tested the McGurk illusion in speech-color synesthetes, and found that the colors induced by the McGurk illusion were different from the colors induced by the auditory-only components of the stimuli. This indicates that synesthesia is linked to late perceptual processing instead of early perceptual processing. It might be possible that synesthesia is the effect of a deficit in multisensory integration, and that synesthesia might be more prevalent in individuals with ASD who have deficits in multisensory integration. However, multisensory integration does not explain the prevalence of grapheme-color synesthesia in ASD, since there is only one sense involved in this type of synesthesia. More research is needed to investigate whether multisensory processing might be an underlying cause of synesthesia.

6.2 Shared brain areas

Both synesthesia and ASD show changes in the activation of brain areas when looking at objects. Decreased activation in the MT/V5 area has been found in both synesthesia and ASD, which is related to reduced motion perception. However, not all studies show this decrease in MT/V5 in ASD, and there is still a lot unclear about the link between synesthesia, ASD and brain activity. It is also not clear if changes in activity in these brain areas are the cause of synesthesia, or that these changes in activity are the consequence of altered sensory processing in synesthesia.

6.3 Shared neurotransmitters

Both synesthesia and ASD seem to show increased excitability. In synesthesia, this is mainly caused by an increase in glutamate, while in ASD, there is more evidence of a decrease in GABA.
One neurotransmitter that seems to be elevated in both synesthesia and ASD is serotonin. Serotonin plays an important role in developmental processes such as cell proliferation, migration and differentiation (Muller et al., 2016). Furthermore, serotonin seems to play an important role in the sensory system (Salichon et al., 2001; Esaki et al., 2005). The elevation of serotonin levels in ASD might be one explanation of the increased prevalence of synesthesia in the ASD population. Furthermore, serotonin seems to play a role in multisensory processing, suggested by the fact that SERT mutated mice fail to show behavioural gains under multisensory conditions. Multisensory integration is often impaired in ASD, which further supports the role of serotonin in the development of ASD.

6.5 Shared genes

Although there are multiple candidate genes for synesthesia and ASD, no single gene has been found to be responsible. Furthermore, environmental factors also seem to play a role. It is not clear which genes play the most important roles in synesthesia and ASD. The only gene that seems to be involved in both synesthesia and ASD is 2q. In synesthesia, a link with a mutation in 2q24 has been found. Several case studies have indicated a mutation in these gene in ASD as well (Celle et al., 2013; Chong et al., 2018; Nickel et al., 2018). 2q24 contains the SCN2A gene, which encodes for the alpha-subunit of voltage-gated sodium channel Nav1.2. A mutation of this gene can cause severe developmental disorders in childhood (Chong et al., 2018), which might explain why this gene is associated with both developmental synesthesia and ASD. Another gene that seems to play an important role in ASD is the X chromosome. Some studies suggest that the X chromosome is involved in synesthesia as well, but since Asher et al. (2009) found two cases of male-male transition of synesthesia, it is debatable whether the X chromosome is actually involved in synesthesia.

Discussion

Although synesthesia has gained increased interest of neuroscientists over the past decades, the underlying neurobiological mechanisms that cause synesthesia are still largely unknown. Since synesthesia is a cognitive experience, it is hard to test it in animal models. However, psychological tests and measurements of brain activity have been able to show some of the mechanisms of altered visual processing in synesthesia. Furthermore, the underlying mechanisms on a molecular level have been investigated by studying cases of patients with acquired or drug-induced synesthesia. Whole-genome studies in families with a high prevalence of synesthesia have highlighted several candidate genes involved in synesthesia. However, there are more studies needed to determine the actual causes of synesthesia, and the differences between the different types of synesthesia.

It has been known for a long time that altered visual perception is a common characteristic in ASD, but only in the 5th edition of the DSM it has been incorporated as one of the criteria for the diagnosis ASD. Individuals with ASD seem to show either hyper-sensitivity, which makes them avoid certain stimuli, or hypo-sensitivity, in which the individual seeks for stimuli. Altered visual perception in ASD is often associated with enhanced detail perception and reduced global perception. Furthermore, synesthesia seems to be more prevalent in ASD than in the non-autistic population. This suggests that there are common mechanisms underlying both synesthesia and ASD.

The most interesting aspect of synesthesia is the perception of the concurrent. Somehow, synesthetes perceive a stimulus that is not present. Furthermore, the concurrent seems to be strongly linked to a specific inducer (e.g. in grapheme-color synesthesia, every letter is connected to a color, and this connection doesn't change over time). This raises the question how the perception of the inducer leads to the perception of the concurrent. As mentioned before, there are three theories that try to explain the occurrence of synesthetic experiences: the cross-activation theory, the cortical disinhibition theory and the re-entrant feedback theory. Support for the cross-activation theory is given by results of multiple studies, like the association of genes involved in axogenesis with synesthesia, alterations in neurotransmitter levels and the simultaneous activation of V4 and PTGA in synesthesia. However, since studies suggest that synesthetic experiences can influence the perception of the inducer as well, the cortical disinhibition theory is not excluded. This seems to support the re-entrant feedback model, which combines the idea of hyperconnectivity between brain areas with the lack of inhibition from higher brain areas in synesthesia. therefore, the re-entrant feedback model seems like a good explanation of the different findings on synesthetic experiences.

Both synesthesia and ASD seem to have a bias towards local perception. Synesthetes seem to outperform non-synesthetes on tasks that require local perception, but show deficits in global perception. The same results have been found in ASD. Furthermore, both synesthesia and ASD seem to show a deficit in the magnocellular pathway, the pathway that is involved in motion perception. However, there is still some discussion on whether autistic individuals have a deficit in global perception or only a bias towards local processing instead of global processing. Furthermore, it is still not clear whether the parvocellular pathway is upregulated or downregulated in ASD. More studies on parvocellular and magnocellular processing are needed to find a link between parvocellular and magnocellular processing in synesthesia and ASD.

The MT/V5 area, which is involved in motion perception, seems to be downregulated in both synesthesia and ASD. This can be linked to a deficit in motion perception. However, not all studies seem to be able to find reductions in activity in these brain areas. Furthermore, there is evidence that the activity of the V5 area depends on the task.

Another feature of altered sensory perception that seems to be reduced in both synesthesia and ASD is multisensory integration. Just like autistic individuals seem to focus on details rather than the whole picture, they also seem to focus on separate features rather than the whole context. Deficits in multisensory processing have been found in synesthesia as well. Altered multisensory processing might explain the occurrence of synesthesia in ASD, but only for types of synesthesia that involve multiple senses.

When looking at candidate genes, there are several genes that could possibly be linked to synesthesia and ASD. However, there are not many genes that seem to be linked to both synesthesia and ASD. One gene that seems to be associated with both conditions, however, is a gene on chromosome 2q, specifically 2q24. This chromosome contains genes that code for subunits of a sodium channel that is involved in neurodevelopment. Mutations in these subunits seem to be responsible for several neurodevelopmental disorders, like ASD. Since developmental synesthesia is thought to be caused by a defect in synaptic pruning during neurodevelopment, it might be possible that 2q24 plays a role in synesthesia as well.

Another interesting finding is that serotonin seems to play an important role in both synesthesia and autism. Since serotonin is known to play an important role in neurodevelopment, it is possible that changes in the brain caused by elevated serotonin levels might eventually lead to the development of synesthesia. As discussed before, synesthesia can be acquired after use of LSD or after brain injury. This is thought to be caused by increased serotonin levels, which might lead to altered connections in the brain. Blood serotonin levels seem to be elevated in 25% of the ASD population. If the elevated serotonin levels cause hyperconnectivity in brain areas that are involved in sensory perception, we can suggest that this might be one of the reasons why the prevalence of synesthesia is higher in the ASD population. Since serotonin cannot pass the blood-brain barrier, the levels of serotonin in the blood are not a good predictor for the levels of serotonin in the brain. However, high serotonin levels in the blood of individuals with ASD might indicate high levels of serotonin in the brain of these people during development, since the blood-brain barrier is not fully closed till the age of two (Brogaard, 2013).

As mentioned in the introduction, the prevalence of synesthesia in ASD is around 20%. Since the prevalence of elevated blood serotonin levels in ASD is around 25%, there might be a correlation between blood serotonin levels and synesthesia in ASD. If the high prevalence of synesthesia in ASD would indeed be caused by high serotonin levels, you would expect that the prevalence of synesthesia among the 25% of ASD patients with elevated blood serotonin levels is extremely high. In order to gain more evidence for a causal relationship between serotonin levels and synesthesia, it would be interesting for future studies to measure the prevalence of synesthesia in the part of the ASD population that has elevated blood serotonin levels.

Although this review shows that there are some shared underlying mechanisms between synesthesia and ASD, it is important to mention that this review only focused on color synesthesia, especially on grapheme-color synesthesia. However, there are many different types of synesthesia, and not all of them involve visual perception. One example of non-visual synesthesia is mirror-touch synesthesia, in which the synesthetes experiences touch when seeing another person being touched (Banissy et al., 2009b). Non-visual types of synesthesia are caused by other mechanisms than described in this review, and might have other shared features with ASD that have not been discussed here. Furthermore, this review has focused on ASD as one disorder, while there are different types of ASD. These different types show different symptoms, and not all types of ASD might share the same alterations in visual processing. Furthermore, the severity of symptoms can differ between individuals with the same type of ASD.

In summary, this review shows that synesthesia and ASD do indeed share some underlying neurobiological mechanisms in altered visual perception. The shared characteristics of visual perception in synesthesia and ASD are a bias towards local perception, reduced global perception and a deficit in motion perception. Furthermore, both synesthesia and ASD seem to show reduced multisensory integration. One neurotransmitter that seems to play a very important role in both synesthesia and ASD is serotonin. Increased serotonin levels in synesthesia and ASD might explain hyperconnectivity and deficits in multisensory integration. Future studies could focus on the prevalence of synesthesia in autistic individuals with elevated blood serotonin levels, to investigate whether there might be a causal relationship between serotonin levels and synesthesia.

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