

The Neural Correlates of Grapheme-Color Synesthesia: A Meta- Analysis

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Abstract

Grapheme-color synesthesia, wherein achromatic graphemes are experienced as chromatic, presents insights into how the brain integrates subjective experiences. The neural correlates of grapheme-color synesthesia are highly debated, with the field full of inconsistent results. To compile the existing functional magnetic resonance imaging literature on grapheme-color synesthesia, the present thesis combined a systematic review with two coordinate-based Activation Likelihood Estimation meta-analyses. Two separate analyses were conducted to see whether investigating synesthesia through chromatic stimuli and incongruency effects would lead to the same activation patterns as investigating it through achromatic stimuli. Therefore, the main analysis included ten studies and more heterogeneity through chromatic stimuli, while the strict analysis had five studies but only achromatic stimuli and thus less heterogeneity. These analyses found convergent activation in the parietal lobe in the main analysis and the frontal lobe in the strict analysis. Although only limited interpretations of the results can be made, the present meta-analyses provided insights into the current state of research on grapheme-color synesthesia. Because the lack of comparability and methodological consensus in the field of synesthesia is evident, further research efforts are encouraged for the field to reach a state where truly convergent findings can be detected.

Keywords: grapheme-color synesthesia, fMRI, Activation Likelihood Estimation, meta-analysis

Introduction

Imagine a reality where black letters have color, music evokes visual experiences of color and movement, or reading a word leads to a sensation of taste. This is the reality for people with synesthesia, a condition where undergoing one sensory experience causes an automatic, involuntary activation of another sensory experience. The initially activated sensory modality is called the inducer, whereas the sensory modality activated by the inducer is called the concurrent (Grossenbacher & Lovelace, 2001). In one of the most common forms of synesthesia, grapheme-color synesthesia (GCS), written units of language are the inducers that prompt a color experience, the concurrent (Ward, 2013). The synesthesia literature states that the colors associated with each letter and number are individual for every synesthete, meaning that it is unlikely for two synesthetes to have the same exact colors for each grapheme (Grossenbacher & Lovelace, 2001). Non-random color associations among synesthetes have, however, been observed (Simner et al., 2005), meaning that some colors are associated with some letters more often than expected by chance. Nevertheless, specific properties like shade and saturation are individual for each synesthete (Grossenbacher & Lovelace, 2001). We assume that most statements about the characteristics of GCS are based on subjective reports containing precise and detailed descriptions, which can be difficult to quantify.

Even though the grapheme-color pairings vary between synesthetes, they often remain consistent within an individual (Simner, 2012). If the letter A is experienced as blue by a particular synesthete, the synesthetic association likely remains through time. This internal consistency is considered to be one of the defining factors of all synesthesias and provides a tool for identifying synesthetes. Using the standardized online test battery called the Synesthesia Battery (Eagleman et al., 2007), researchers can identify synesthetes by assessing an individual's consistency in a single sitting or through a re-test after a certain period of time.

Grapheme-color synesthetes can also be identified by comparing their reaction times when naming chromatic graphemes corresponding to their synesthetic associations (congruently colored) with chromatic graphemes that do not match (incongruently colored) (Hubbard

& Ramachandran, 2005). In the latter condition, researchers anticipate that synesthetes will exhibit longer response times because of the mismatch between the synesthetic and real colors.

Other defining characteristics are the automaticity and involuntary nature of the phenomenon: the concurrent arises automatically, and the synesthete has no control over it (Ward, 2013). These are the aspects that distinguish synesthesia from mental imagery, in which the onset and content of the imagery can be controlled. The unique, subjective characteristics of synesthesia have intrigued researchers for centuries, with the first documented descriptions dating back to the 1800s (Ward, 2013). With the advancements in brain imaging methods during the past few decades, neuroscientists have made efforts to locate the neural correlates of different synesthesias. The focus has lied especially in GCS, which dominates the neuroimaging literature of synesthesia.

Neuroimaging Literature on GCS

Partly due to the highly subjective nature of synesthesia, there is no consensus about its neural correlates. It is not clear if the neural underpinnings of developmental synesthesia are structural, functional, or maybe both. Developmental synesthesia is experienced throughout an individual's lifespan without a specific starting point and differs from acquired synesthesia, which can result from damage to the brain or be temporarily induced by hallucinogenic drugs (Grossenbacher & Lovelace, 2001; Ward, 2013). Because it is difficult to determine whether acquired synesthesia leads to similar subjective experiences as developmental synesthesia, this thesis focused solely on developmental synesthesia.

A common tool used to study synesthesia is functional magnetic resonance imaging (fMRI). In fMRI studies with synesthetes and controls, graphemes are presented to the participants lying in the scanner. Often, participants either freely view the graphemes or receive a task, such as reporting when the graphemes appear in italic font, to maintain attention. Studies investigating GCS in synesthetes often use inducing graphemes and non-inducing stimuli that do not elicit synesthesia. Such stimuli are pseudographemes (grapheme-like stimuli with

no meaning), symbols (like %), or simply graphemes that do not elicit synesthesia for the synesthete. The inducing stimuli are the graphemes that elicit a synesthetic color experience. If controls are involved, they view the same stimuli as the synesthetes. Using these stimuli, the researchers can create a contrast that reveals the “additional” activation that the synesthetes might display in response to the inducing stimuli.

fMRI studies investigating neural differences between grapheme-color synesthetes and controls in response to graphemes claim to have found enhanced activity in the V4 — the color area located in the fusiform gyrus — and in the parietal lobe in synesthetes (van Leeuwen et al., 2011). Taking a closer look at the literature on GCS, the reported activations vary from study to study. For instance, Hubbard et al. (2005) found an increased BOLD response in synesthetes compared to controls in the V4 when presented with graphemes. Stimulation with graphemes activated the parietal lobes both in synesthetes and controls, and the activation was thus deemed not to be synesthesia-related. Weiss et al. (2005), however, found increased neural activity in the parietal lobe during the experience of GCS but not in the V4. Rich et al. (2006) detected increased activation in the left medial lingual gyrus — located in the occipital lobe — in synesthetes but not in controls. Hupé et al. (2012) failed to detect any activation in the color areas of the fusiform gyri in synesthetes in response to graphemes. O’Hanlon et al. (2013) found a negative BOLD response in synesthetes compared to controls in the inferior parietal lobules (IPL) bilaterally and in the left transverse temporal gyrus in response to graphemes. Gould van Praag et al. (2016) did not find differences in activation in the V4 between synesthetes and controls in response to graphemes. Instead, they found increased activation in the left precentral gyrus and bilaterally in the inferior parietal gyri. Attempting to summarize the neuroimaging results, a review by Rouw et al. (2011) revealed that V4 activation in response to synesthetic color was identified in only five out of thirteen studies investigating synesthesia through fMRI and Positron Emission Tomography (PET). Four out of these thirteen studies had detected activation related to synesthetic color in other parts of the ventral occipitotemporal cortex. Thus, the functional neuroimaging literature on GCS is inconclusive.

Challenges in Studying GCS

Associators and projectors

Although some patterns of activation have been detected in the literature, there seems to be no reliable evidence for consistent activation in any specific area. A possible contributor to this inconsistency is the differences in subjective experience between projector and associator synesthetes (Dixon et al., 2004). A projector sees achromatic graphemes on paper as having color. They “project” the color out in the real world. Conversely, an associator sees achromatic graphemes on paper as having color in their “mind’s eye”. This entails seeing the chromatic grapheme in a mental space or simply knowing the color. The majority of grapheme-color synesthetes are assumed to be associators, making projectors a rarer type.

These differences in subjective phenomenology were explained on the neural level by van Leeuwen et al. (2011), who compared associators and projectors through dynamic causal modeling. Dynamic causal modeling is used to establish directed connectivity between brain regions (Sadeghi et al., 2020). In an fMRI paradigm, van Leeuwen et al. (2011) revealed that the activation of V4 resulted from the activity of distinct networks in the two synesthesia subtypes. Projectors displayed a direct connection from the grapheme area¹ of the fusiform gyrus to V4, while associators displayed a pathway from the grapheme area through the superior parietal lobe (SPL) to V4. Because the distinction of synesthetes into associators and projectors has not been a common practice, such differences in connectivity could explain the vastly inconsistent results in the neuroimaging literature on synesthesia.

Theories of the neural basis of synesthesia. Two theories can explain the results obtained by van Leeuwen et al. (2011). The theories are known as the cross-activation theory and the disinhibited feedback theory (Mulvenna & Walsh, 2006). The cross-activation theory states that synesthetic experiences stem from extra connections between neighboring brain regions (Hupé & Dojat, 2015). The disinhibited feedback theory, however, states that the experiences result from a failure to inhibit the processing pathway from multisensory areas back

¹ The grapheme area (also called the visual word form area or the letter shape area) is involved in the processing of letters and numbers (Hubbard et al., 2011).

to sensory-specific areas (Banissy et al., 2012; Grossenbacher & Lovelace, 2001). In the study by van Leeuwen et al. (2011), the projectors' activation can be explained by the cross-activation theory, while the associators' activity can be explained by the disinhibited feedback theory. Because of the findings of van Leeuwen and colleagues, what was before considered to be competing theories could now coexist. Now, the difficulties in finding the neural correlates of synesthesia could be attributed not only to the subjective reality of the phenomenon but also to the objectively distinguishable differences in brain activation that many researchers had not considered.

Inducers and additional synesthesias

Synesthesia presents a challenge to researchers due to its highly subjective and differential phenomenology across individuals. An additional level of complexity comes from the fact that synesthetes can have multiple types of inducers (e.g., auditory or visual), which are often not reported by researchers (Rouw et al., 2011). It is also common for a synesthete to have multiple types of synesthesias (Ward, 2013). Not considering the types of synesthesias and inducers the participants have when designing an experiment necessarily affects the interpretability of the study results. For example, some auditory-visual synesthetes report synesthetic color experiences induced by the fMRI scanner noise (Neufeld et al., 2012). If a synesthete has both GCS and auditory-visual synesthesia, the activation of color areas resulting from scanner noise can be misinterpreted as activation in response to the stimuli used in the experiment. If such activation, that is not the result of the experimental stimuli, is misinterpreted and published, it can lead to even more variability in future experimentation.

Phenomenology

Other types of differences in phenomenology between synesthetes, such as localization, automaticity, and attention, have been shown to affect the BOLD response in color and other brain areas (Gould van Praag et al., 2016). Localization refers to the tendency to experience the concurrent at a specific location. Automaticity and attention concern how automatically the concurrent occurs without having to pay much attention to the inducer. These aspects are not directly connected to a synesthete's associator or projector status but instead represent

differences in subjective phenomenology among synesthetes. Subsequently, the finding that such qualities can influence BOLD responses in the color areas may explain why V4 activation is inconsistently reported in the GCS literature (Gould van Praag et al., 2016). All the aforementioned matters of individuality bring challenges to designing experimental conditions and stimuli that accurately capture synesthesia.

Methodology and study design

In addition to the phenomenological differences, varying experimental designs and methodologies challenge the interpretability of synesthesia studies. Individual functional neuroimaging studies often lack statistical power, which makes drawing conclusions problematic and difficult (Hupé & Dojat, 2015). The low power resulting from small sample sizes is understandable given the low prevalence of synesthesia in the general population (Carmichael et al., 2015), and the cost of functional neuroimaging studies. The effects of low power can partly be mitigated by paying extra attention to the design of the study. Accordingly, researchers often choose analysis methods tailored to suit the specific objectives of their experiments (Hupé & Dojat, 2015). This, however, creates methodological variability in the field, which makes comparing studies challenging, especially when attempting to synthesize the literature or interpret results across studies. The lack of open data sharing also affects literature synthesis. The risk of bias in a meta-analysis increases when such studies are included where researchers selectively report only the coordinates of significant voxels surpassing a predefined statistical threshold set by those same researchers (Hupé & Dojat, 2015).

Region of Interest analyses

Further problems stem from the use of the region of interest (ROI) analysis, wherein brain regions hypothesized to be involved in synesthesia are selectively examined (e.g., Hubbard et al., 2005; Rich et al., 2006). The ROI method reduces the number of voxel comparisons to only within the selected ROI, which allows researchers to address the low statistical power often present in neuroimaging studies (Hupé, 2015). However, the ROI dataset is often used both to identify interesting voxels and to conduct subsequent tests, which has been argued to

impose a serious problem of circularity (Hupé, 2015). In that case, the investigation relies on an expectation of involved brain areas before it has even begun.

Furthermore, including ROI analyses in a coordinate-based meta-analysis inflates the significance of the ROI regions (Müller et al., 2018). This happens because doing a ROI analysis increases the chances of finding significant activation in that specific region. If many studies that have found significant activation in a specific region are included in a coordinate-based meta-analysis, significant convergence in that region is likely detected. These aspects need to be considered when conducting a meta-analysis (Müller et al., 2018), and we decided to include ROI studies because of the lack of available studies on GCS.

Previous Attempts in Literature Synthesis

Most of the aforementioned issues were already introduced by Hupé and Dojat (2015). They reviewed functional neuroimaging studies on different synesthesias and highlighted the lack of statistical and methodological consensus in the field. In their effort to synthesize the results of the field, only 6 out of 25 studies were found to show significant differences between synesthetes and controls. The review did not, however, include a systematic search or quantify the results. A meta-analysis decreases the number of limitations that are often present in individual studies and can allow, with proper power, the drawing of robust conclusions about the current state of synesthesia research. Therefore, an updated review including a meta-analysis of GCS is necessary.

Aim and Objective

Building upon the groundwork laid by Hupé and Dojat (2015), this thesis proceeded with a systematic literature search and utilized meta-analytical methods. This thesis aimed to quantitatively compile the available fMRI literature on GCS and investigate consistent activations in an exploratory manner. Our examination included studies that investigated graphemes and color, with no predetermined hypotheses regarding the outcomes.

We synthesized the published literature on GCS by utilizing the Activation Likelihood Estimation (ALE) analysis (Eickhoff et al., 2009). The ALE method is a coordinate-based

meta-analysis tool to identify consistent brain activation patterns across multiple neuroimaging studies (Müller et al., 2018). To improve the interpretability of the findings, we conducted two ALE analyses. One analysis had stricter, clearer inclusion criteria for maximized comparability, while the other included additional studies with greater variability in experimental design and stimuli. Two analyses were conducted to see whether using chromatic stimuli and investigating synesthesia through incongruity effects would lead to the same activation patterns as investigating it through achromatic stimuli. If the chromatic stimuli are not matched to the synesthetic associations, the neural activation from such studies could potentially be a result of managing the two competing colors. Studies utilizing synesthetic Stroop tasks² have found activation in the rostral cingulate zone (RCZ) (van der Veen et al., 2014), the left anterior cingulate cortex (ACC), among other areas (Specht & Laeng, 2011), and the dorsolateral prefrontal cortex (DLPFC) (Weiss et al., 2005) in synesthetes in response to incongruently colored stimuli. Because only a few studies with inconsistent results have examined the incongruity effect in synesthetes, no hypotheses about its neural correlates were established. Thus, this thesis aimed to synthesize the existing literature on GCS to identify convergent neural activation during the experience of color concurrents while exploring the possible role of incongruity in that activation.

Methods

Search Strategy

To produce a comprehensive review, our search involved three electronic databases: Web of Science, Scopus, and Medline EBSCO. The search string was the following: (synesthesia OR synaesthesia) AND (fMRI OR "functional magnetic resonance imaging"). The search was done on January 22, 2024. The keyword "synesthesia" was applied instead of "grapheme-color synesthesia" to guarantee that the breadth of the search would not be compromised by differential nomenclatures, such as "color-grapheme synesthesia" (Elias et al., 2003) or the

² A synesthetic Stroop task is often a single-letter version of the classic Stroop task where the graphemes are congruently and incongruently colored.

more general term “linguistic-color synesthesia” (Rouw et al., 2011). Two reviewers independently reviewed the literature, and disagreements in inclusion involved a third reviewer whose opinion helped resolve the disagreement. The results were uploaded into the systematic review web application Rayyan (Ouzzani et al., 2016), where duplicates were automatically detected by the program and then manually removed by the authors. The abstracts of the publications were screened. Subsequently, the remaining publications were assessed for eligibility and examined against the inclusion criteria.

Inclusion Criteria

Studies that met the following criteria were included:

1. They were written in English and published in a peer-reviewed journal.
2. They employed fMRI.
3. They examined synesthetes who experience color in response to graphemes.
4. The stimuli were presented visually.
5. The participants had developmental synesthesia.
6. The participants were healthy, meaning that they had not suffered damage to the brain, for instance.
7. They compared differences in brain activation in synesthetes and non-synesthetes in response to the same stimuli (between-subject design) or in synesthetes by contrasting synesthesia-inducing stimuli with non-inducing stimuli, such as pseudographemes or punctuation symbols (within-subject design).
8. They explicitly reported the peak coordinates in Montreal Neurological Institute (MNI) or Talairach space of the significant voxels in either of the contrasts above.
9. They did not declare to be based on data or subjects from another study.

Data Extraction

All data were manually extracted and double-checked by both authors. The collection of data from the publications comprised activation foci coordinates, sample size, thresholds, and the coordinate space (MNI or Talairach) (see Appendix A for details). Furthermore, the experimental contrasts and stimuli were compiled (Table 1).

Our strict analysis included only studies using achromatic synesthesia-inducing graphemes contrasted with non-inducing graphemes or grapheme-like stimuli (see Inclusion criteria for details). The main analysis included all studies from the strict analysis and studies utilizing chromatic stimuli. Studies using congruent and incongruent trials (i.e., trials where the stimuli were colored according to the synesthetes' grapheme-color pairings or not) were also included in the main analysis.

Some studies had multiple relevant contrasts (including both chromatic and achromatic stimuli) that fit either the main or strict analysis. From such studies, the achromatic contrasts were included in the strict analysis, and all relevant (chromatic and achromatic) contrasts were included in the main analysis. The results from such studies were pooled together and included as one experiment in the main analysis (Gould van Praag et al., 2016; van Leeuwen et al., 2010) to control for repeated measures and to minimize any within-group effects. Studies with the same subject group undergoing multiple contrasts can have a larger impact on the results in a meta-analysis, as they are not independent measures (Turkeltaub et al., 2012). Organizing data by subject groups rather than by experiments accounts for this issue (Müller et al., 2018). In the study by Sperling et al. (2006), the coordinates were individually reported for each participant rather than for the group as a whole. To ensure proper weight for all of the coordinates of the participants, the coordinates were treated as separate experiments.

Activation Likelihood Estimation Meta-Analysis

The present analysis employed the coordinate-based meta-analytical method ALE in the software GingerALE (version 3.0.2) (Brainmap, n.d.). The foci included in the analysis represent specific locations in the brain where researchers observed significant neural activity related to the task or condition that was under investigation (Müller et al., 2018; Wager et al., 2007).

The objective of an ALE analysis is to identify brain regions demonstrating consistent activation patterns across experiments where participants experience the same psychological state (Eickhoff et al., 2009). This is achieved by quantifying the likelihood of convergence in

brain activation across experiments through the calculation of activation peaks within designated brain regions. The aim is to discern significant activation clusters from background activation due to chance, thereby facilitating the identification of brain regions consistently implicated in the studied psychological state (Wager et al., 2007).

The process in the GingerALE software includes the following steps. Initially, the activation foci reported in each experiment are organized into an input file, which is imported into the ALE software. The software does an automatic spatial transformation from Talairach space to the standardized MNI space (Brainmap, n.d.). In the present analysis, three experiments underwent that transformation (O’Hanlon et al., 2013; Sperling et al., 2006; Weiss et al., 2005), and all others reported the coordinates in MNI space. Then, a 3D Gaussian kernel is employed, representing the probability distribution wherein individual activation foci serve as midpoints (Eickhoff et al., 2009). The dispersion around these centers is determined by the full width at half maximum (FWHM) of the kernel to calculate the spatial uncertainty related to each focus. The algorithm adjusts the spatial uncertainty FWHM based on the sample size of the studies (Eickhoff et al., 2009). Consequently, publications with smaller sample sizes yield longer FWHM, generating a wider distribution. For studies with a large sample size, the algorithm produces a shorter FWHM under the assumption that sample size reflects study power. After the implementation of the FWHM, the resulting activation map is compared to the random activation map to reveal which of the voxels have ALE values greater than the set threshold. What is provided as the resulting ALE map are the activations that survived the comparison to the set number of random activation maps (Eickhoff et al., 2012; Turkeltaub et al., 2002).

In line with contemporary recommendations, our analysis was based on the MNI152 coordinate system, with 1000 threshold permutations, a cluster-level threshold of $p < .05$, and a cluster-forming threshold of $p < .001$ (Eickhoff et al., 2016; Müller et al., 2018). The activation clusters that exceeded this threshold in the analysis were considered significant. The resulting activation clusters were then superimposed onto an MNI template Colin27_T1_seg_MNI (Brainmap, n.d.) using the Multi-image Analysis GUI “Mango” (Habes

et al., n.d.). ALE provides two options for mask sizes on the chosen template: a larger and a smaller one. The more conservative, smaller one was used, as it is commonly used with fMRI data. (Brainmap, n.d.). When the input files are opened in ALE, the foci coordinates are cross-referenced against the mask in the chosen template (MNI or Talairach). Any foci outside the mask are reported and normally occur at around 3% of the total number of foci (Brainmap, n.d.). The present data contained two foci located outside the mask (see Appendix A for details), within the expected 3%. All other settings were left at default.

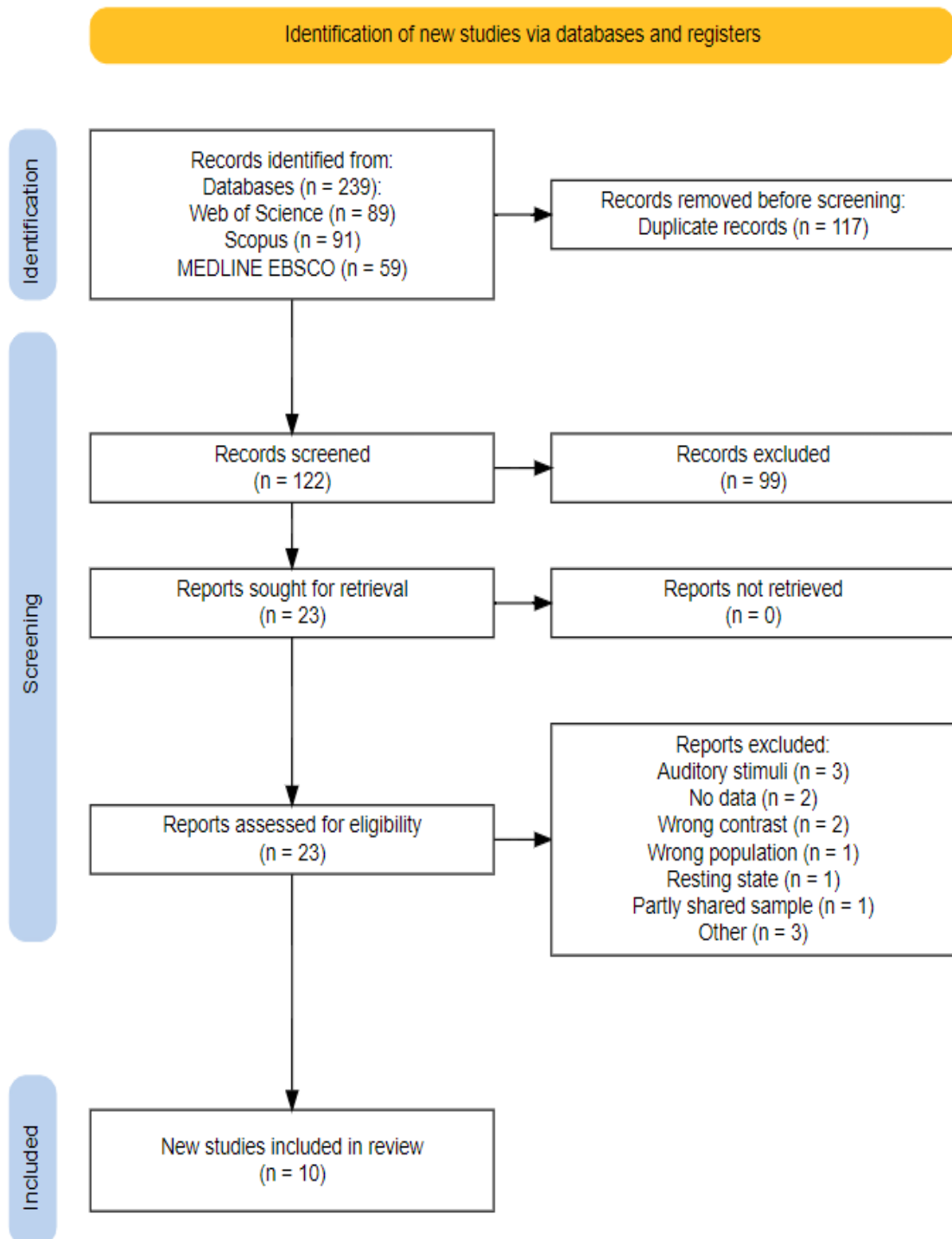
Results

Systematic Search

The database search yielded a total of 239 studies (Figure 1). After the removal of duplicates, 122 studies were left. After the screening of abstracts, 23 studies were left. After the assessment for eligibility and application of the inclusion criteria, ten relevant articles were left for the main analysis (see Table 1 for details). Five of those studies were included in the strict analysis. The ten studies included a total of 143 synesthetes and 104 control participants, resulting in a total of 247 participants. The five studies included in the strict analysis had 103 synesthetes and 69 controls, resulting in 172 participants.

Figure 1

PRISMA Flow Chart Illustrating the Inclusion of Studies



Characteristics of the Included Studies

The included fMRI experiments considered different aspects of the synesthetic experience. Some examined how color and letters form a coherent synesthetic experience in synesthetes (Weiss et al., 2005). Others studied the involvement of color regions in synesthesia within synesthetes by utilizing inducing and non-inducing letters (Sperling et al., 2006), with both achromatic and chromatic or only achromatic letters.

Other investigations compared brain activation resulting from grapheme stimuli between synesthetes and control participants. Some sought the neural correlates of GCS by utilizing achromatic letters that induced a strong, weak, or no color experience in synesthetes (Rouw & Scholte, 2010). Others investigated whether synesthetic color activates the same color regions in the brain as real or imagined color. Such investigations were done by contrasting inducing achromatic and chromatic letters with non-inducing letters (van Leeuwen et al., 2010) or with gray squares (Rich et al., 2006). Sinke et al. (2012) investigated functional connectivity underlying synesthesia by contrasting inducing achromatic and chromatic letters with pseudo-letters. O'Hanlon et al. (2013) contrasted achromatic letters and non-meaningful symbols to investigate structural and functional differences between synesthetes and controls. Gould van Praag et al. (2016) studied how individual differences in synesthetic phenomenology, such as localization, automaticity, and attention, influence activation in color areas. Laeng et al. (2011) explored the binding of color to graphemes in the brain by using congruently and incongruently colored synesthesia-inducing letters and contrasting them to non-inducing color-matched asterisks. Finally, Melero et al. (2014) utilized achromatic and chromatic letters that were either congruently, incongruently, or neutrally colored to investigate the neural basis of GCS and the involvement of color areas in synesthesia.

Table 1*The Characteristics of the Included fMRI Studies in the Meta-Analyses*

Author and Year	Sample Size	Stimuli	Contrast
Gould van Praag et al. (2016)	40	Achromatic letters and punctuation symbols	Inducing vs. non-inducing in synesthetes vs. control participants
Laeng et al. (2011)	2	Achromatic, chromatic letters, and asterisks	Congruent or incongruent inducing letters vs. asterisks within synesthetes
Melero et al. (2014)	20	Achromatic and chromatic graphemes	Congruent vs. incongruent vs. inducing vs. non-inducing letters within synesthetes
O'Hanlon et al. (2013)	24	Achromatic letters and non-meaningful symbols	Inducing vs. non-meaningful symbols in synesthetes vs. control participants
Rich et al. (2006)*	14	Achromatic and chromatic letters and gray squares	Inducing vs. non-inducing in synesthetes vs. control participants
Rouw and Scholte (2010)	61	Achromatic letters	Strongly or weakly inducing vs. non-inducing in synesthetes vs. control participants
Sinke et al. (2012)	36	Achromatic, chromatic letters, and pseudo-letters	Inducing vs. non-inducing in synesthetes vs. control participants

Sperling et al. (2006)*	3	Achromatic and chromatic letters	Inducing vs. non-inducing within synesthetes
van Leeuwen et al. (2010)	38	Achromatic and chromatic letters	Inducing vs. non-inducing in synesthetes vs. control participants
Weiss et al. (2005)	9	Achromatic and chromatic letters	Inducing vs. non-inducing within synesthetes

Note. Studies in **bold** font were included in both analyses (main and strict), whereas studies in normal font were only included in the main analysis. Sperling et al. (2006) had four participants, but data from only three were reported and used. Laeng et al. (2011) included two synesthetes and ten controls, but only the data of the synesthetes was used in this analysis. In Sinke et al. (2012), the colors of the graphemes were not matched to the participants' synesthetic associations, probably leading to incongruently colored stimuli.

* The experimental contrasts were derived from studies employing ROI investigations.

Activation Likelihood Estimation Analysis

Main meta-analysis

The main analysis showed a significant convergence of activation in one cluster (Figure 2). This cluster was located in the left parietal lobe. Most of the cluster was in the inferior parietal lobe, extending to the superior parietal lobe and the precuneus (Table 2) (see Appendix B for details).

Strict meta-analysis

The strict analysis showed a significant convergence of activation in one cluster (Figure 2). The cluster was located in the left frontal lobe. Most of this cluster spanned the precentral gyrus, extending partly to the inferior frontal gyrus (Table 2).

Table 2

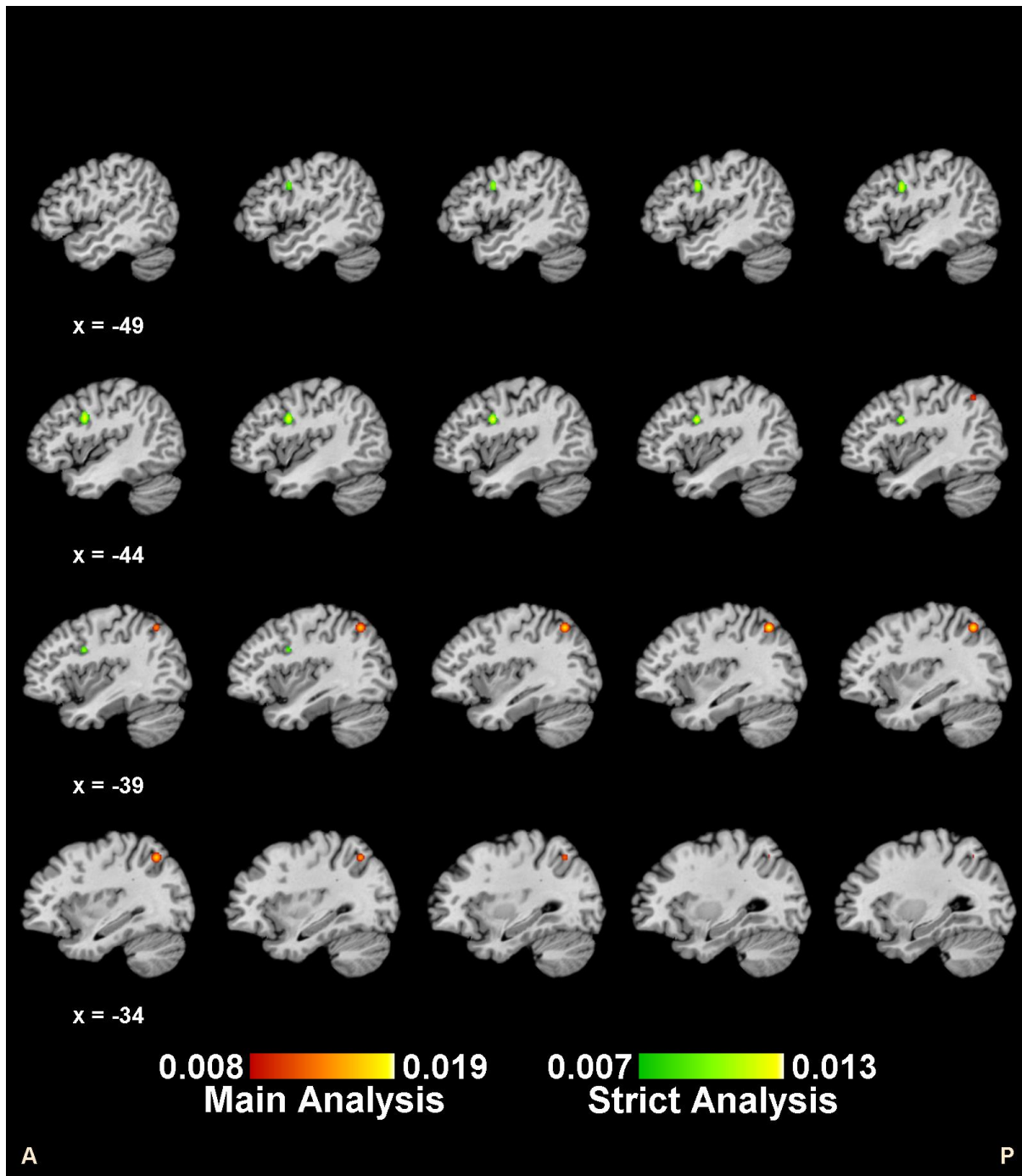
The Results of the Main and Strict Meta-Analyses on Grapheme-Color Synesthesia

Anatomical Label	Cytoarchitectonic Structure	X	Y	Z	ALE Score	Volume (mm³)
Main analysis						
Left Inferior Parietal Lobe	BA39	-36	-62	48	.0188	672
Strict analysis						
Left Precentral Gyrus	BA6	-42	4	28	.0135	808

Note. The coordinates of the cluster centers are reported in MNI space. The analyses had a cluster-forming threshold set at $p < .01$ uncorrected and a family-wise error (FWE)-corrected cluster-level threshold of $p < .05$ (see Appendix B for the output file of the ALE computation).

Figure 2

The Results of the Meta-Analyses of Grapheme-Color Synesthesia



Note. The results of the two meta-analyses were superimposed on an MNI template with sagittal slices. Clusters were thresholded with a cluster-forming threshold of $p < .01$ uncorrected and an FWE-corrected cluster-level threshold of $p < .05$. The intensity of the color reflects ALE scores, with lighter red (main analysis) and lighter green color (strict analysis) corresponding to a higher score.

Discussion

In an attempt to quantitatively synthesize the GCS literature, the present thesis conducted two ALE meta-analyses of fMRI studies on GCS. The main analysis, where chromatic, achromatic, and incongruent stimuli were present, revealed one cluster in the left parietal lobe, spanning the IPL, SPL, and precuneus. The strict analysis, where only achromatic stimuli were included, revealed significant convergence in one cluster located in the left frontal lobe, extending from the precentral gyrus to the inferior frontal gyrus.

The Main Analysis

Associator synesthetes

The studies that contributed to the parietal lobe cluster in the main analysis were Melero et al. (2014) and Sinke et al. (2012). Both studies reported having only associator synesthetes as participants, verified either by subjective descriptions (Sinke et al., 2012) or a questionnaire (Melero et al., 2014). The associator-abundant samples could explain the parietal lobe findings. The phenomenological differences between projector and associator synesthetes were first revealed by Dixon et al. (2004) in a Stroop task paradigm. They found that in projectors, the processes leading to the experience of synesthetic color were more automatic than the processes leading to the normal perception of real color. Additionally, processes leading to synesthetic color were more automatic for projectors than for associators. The neural pathways behind the latter distinction were demonstrated by van Leeuwen et al. (2011). They showed that projectors employed a bottom-up pathway from the letter shape area through V4 to the SPL, while associators displayed a top-down pathway from the letter shape area through the SPL to the V4. Because van Leeuwen and colleagues modeled only the SPL, it is possible that other parts of the parietal lobe are also active in the associators' synesthetic experience. Other parts of the parietal lobe have indeed been reported in the literature (Melero et al., 2014; O'Hanlon et al., 2013; Rouw & Scholte, 2010; van Leeuwen et al., 2010). One possibility is that a larger parietal network than just the SPL or IPL alone mediates synesthesia in associators. Independent or in a network, the IPL activation found in our main analysis could reflect the associator status of the participants. Future studies should investigate the role of other parietal

areas in associator synesthesia. And more importantly, the findings of van Leeuwen et al. (2011) should be replicated.

Feature binding

The parietal lobe is known to be the multisensory hub of the brain, integrating multiple sensory features into meaningful perception. It has therefore been argued to be involved in the binding of perceptual features in synesthesia (Robertson, 2003). The clearest evidence for this comes from Esterman et al. (2006), who applied transcranial magnetic stimulation (TMS) to the right posterior parietal area of grapheme-color synesthetes when presenting congruently and incongruently colored inducing graphemes. Usually, incongruently colored stimuli increase the interference effect by introducing a mismatch between the synesthetic and real colors. Applying TMS decreased the interference effect, which was seen in shorter response times in grapheme-color synesthetes when asked to name the real color of incongruently colored graphemes. The findings by Esterman et al. (2006) showed that synesthetic binding can be disrupted by applying TMS to the right parietal lobe. These findings were later supported by Muggleton et al. (2007), who also created a disruption in synesthetic binding in the right parietal cortex. Therefore, they concluded that the right posterior parietal area is a crucial region for synesthetic binding.

The present analysis, however, revealed convergent activation only in the left hemisphere. Although activity in the left parietal regions has been identified (Rouw & Scholte, 2010; van Leeuwen et al., 2010; Weiss et al., 2005), Muggleton et al. (2007) showed that TMS to the left parietal area does not disrupt synesthetic binding. As both of the studies included only two (Esterman et al., 2006) and five (Muggleton et al., 2007) synesthetes, the potential role of the left parietal lobe in synesthetic binding should not be eliminated. Because of the parietal lobe's unexplained presence in the synesthesia literature, the present analysis can only endorse its existence in the synesthetic experience.

Cognitive control

The parietal and frontal cortices are believed to have a role in cognitive control (Esterman et al., 2009; Rouw et al., 2011). In a repeated TMS study on non-synesthetes, Jin et al.

(2010) showed that the right posterior parietal cortex has a role in spatial attention in a flanker task³, which requires ignoring irrelevant stimuli. Therefore, the competing ink and synesthetic colors resulting from the incongruently colored stimuli could have employed cognitive control mechanisms in the two contributing studies. However, because Jin and colleagues investigated only the right hemisphere, it cannot be concluded that the activation present in our analysis is due to attentional control. Additionally, in the contributing studies, the task was to press a button when a letter or a number appeared (Melero et al., 2014) or to press a button when a question mark appeared (Sinke et al., 2012), meaning that no “ignoring” of the synesthetic color was directly present in the designs.

However, Melero et al. (2014) detected activity in the DLPFC, among other frontal areas. Activity in the DLPFC has been detected before in synesthetes during conflict between real and synesthetic colors (Weiss et al., 2005). So, in one of the contributing studies, both the parietal areas and frontal areas were active, although only the parietal activation remained in our analysis. However, some evidence suggests that synesthetic conflict management does not engage the type of cognitive control mechanisms that are seen in other types of tasks, like Stroop or flanker tasks (Rouw et al., 2013). It is therefore unclear whether the parietal activation present in this analysis could reflect cognitive control mechanisms.

Result bias

Of the two contributing studies, Sinke et al. (2012) provided only one focus, which was located in the IPL. Melero et al. (2014), however, contributed 32 foci, making the study more likely to share findings with other studies in the analysis. Four of the foci from Melero et al. were located in the parietal lobe. Because of the large number of foci, it was enough that one study reported activation in a convergent area for that area to be included in the results. It is thus possible that the results of the main analysis were skewed due to the varying number of foci between studies.

³ In a flanker task, participants are asked to detect a stimulus that is accompanied by flanker stimuli, i.e., stimuli that are either the same as the target (congruent) or other stimuli (incongruent) (Jin et al., 2010). Incongruent flanker stimuli lead to longer reaction times as they encourage the choice of irrelevant stimuli.

The Strict Analysis

The studies that contributed to the cluster located in the frontal lobe in the strict analysis were Rouw and Scholte (2010), Gould van Praag et al. (2016), and Weiss et al. (2005). The convergent activation was mostly in the precentral gyrus and partly in the inferior frontal gyrus.

Localization of concurrents

Motor cortex activation during synesthetic experience is a prevalent, but not fully understood, finding in the literature (Rouw et al., 2011). One explanation is related to how the color concurrent is perceived. Gould van Praag et al. (2016) found a positive, although moderate, correlation between concurrent localization and precentral gyrus activation. Their regression showed that those who tend to experience concurrents at a specific location show a greater BOLD response in the left precentral gyrus, among other areas. The precentral gyrus activation was correlated with the synesthetes' answers on the localization subsection of the questionnaire Coloured Letters and Numbers (CLaN). In this subsection, synesthetes answer questions such as whether they can shift the location of the concurrent or point to it in the outside world (Gould van Praag et al., 2016). Therefore, precentral gyrus activation may reflect a trait across synesthetic individuals that is independent of their projector or associator status.

Comparing the two Analyses

Incongruency

We conducted two analyses to investigate if the type of stimuli could have an impact on the resulting neural activation. In tasks requiring cognitive control, usually, both the parietal and frontal lobes are active (Rouw et al., 2011). Our strict analysis found activation only in the precentral gyrus and not in the ACC, RCZ, or DLPFC, which have been detected during the mismatch of synesthetic and real colors (Specht & Laeng, 2011; van der Veen et al., 2014; Weiss et al., 2005). Instead of cognitive control, the prefrontal gyrus could have a role in differential phenomenology between synesthetes (Gould van Praag et al., 2016). The main analysis found activation mainly in the IPL, which has, according to our knowledge, not been

linked to cognitive control in synesthetic Stroop tasks or the like. It is thus possible that incongruency effects do not affect synesthesia studies utilizing incongruently colored stimuli.

Maybe studying synesthesia through such designs can reveal relevant activations. Sinke et al. (2012) continued with a functional connectivity analysis after having identified seed areas, one of which was included in our analysis. They found a difference in the left IPL between synesthetes and controls only when stimulated with graphemes, not when stimulated with pseudo-letters. The left IPL in synesthetes showed stronger connections to the visual areas, specifically to Brodmann area 18 or V2, which is a part of the secondary visual cortex. These results strengthen the idea that the IPL could have an actual role in synesthesia and not be a result of incongruency effects, at least in associators. What this role is will be an interesting research question for future studies.

Absence of V4 activation

Interestingly, no activation of the color areas was detected in either meta-analysis. Although a seemingly essential finding, the activation of color areas in studies on synesthesia has been inconsistent. As fusiform gyrus activation has often been detected in samples with high projector prevalence (Gould van Praag et al., 2016), maybe the lack of activation in both of our analyses was due to the associator samples. To confirm the role of the fusiform gyrus in projector synesthetes, a future meta-analysis could include only data from projectors. With the available literature, such a meta-analysis cannot be conducted yet. Therefore, we encourage researchers to classify synesthetes into associators and projectors when conducting synesthesia studies.

Limitations

Because of the heterogeneity in the available studies on GCS, our analysis included few studies. The findings of the present analyses are based on a limited set of experiments, a total of ten studies in the main analysis (247 participants in total) and five in the strict analysis (172 participants in total). A small number of experiments subjects any meta-analysis to be driven by the results of individual studies (Müller et al., 2018). To control for such unwanted effects, simulation studies have suggested that ALE analyses should involve at least 17 experiments

(Eickhoff et al., 2016). A sufficient number of studies was, of course, our aim, but unfortunately, there are not enough studies on GCS to conduct a robust meta-analysis. As the number of studies would likely not have reached the recommended amount even while introducing more heterogeneity, we decided to sacrifice power to keep the analysis as homogenous as possible. This meant, for example, only including studies using visual stimuli. The lack of open data sharing also affected the number of included studies. We had to exclude studies and change our initial inclusion criteria from studies utilizing visual or auditory stimuli to only visual stimuli because of the lack of available data or relevant contrasts in many studies.

Ethical Considerations

This thesis adhered to transparency by sharing the used data and output files, describing the systematic review process and the inclusion criteria, and pooling studies with multiple contrasts to maintain the independence of observations (Cooper & Dent, 2011). Two authors extracted and compiled the data independently to ensure methodological accuracy. However, publication bias may affect our results. Studies often report only significant results, resulting in bias in a meta-analysis (Gentili et al., 2021). Including only the significant peak coordinates from individual studies contributes to the selective reporting of significant results that are already overrepresented in the literature. Furthermore, four of the included studies lack declarations of informed consent (Gould van Praag et al., 2016; Laeng et al., 2011; Rouw & Scholte, 2010; Sperling et al., 2006). Although we are not the primary researchers, including data from such studies compromises the ethical validity of our study.

Societal Considerations

Searching for the neural substrates of GCS reveals more about the pathways of visual perception and multisensory integration in the brains of synesthetes and possibly the general public, as synesthesia has been proposed to rely on mechanisms and pathways common to us all (Simner et al., 2005). Studying how color is bound to graphemes in GCS illustrates how the brain sews together a coherent, three-dimensional reality from single features like shape, color, or location. Synesthesia opens up a window into how the brain brings about extremely

subjective experiences and qualia, which are the subjective or qualitative aspects of experiences. We all can imagine what it would be like to see achromatic letters as chromatic, but this imagining lacks the qualia of synesthetic reality. Therefore, synesthesia research is valuable because it teaches us about the binding of qualia in the brain.

Future Directions

The biggest challenges for future research include replicating our meta-analytical findings and, in the case of replication, explaining the parietal and frontal lobe activation in synesthesia. Studies should aim for larger sample sizes, although finding suitable participants can be difficult due to the uncommonness of synesthesia in the general public (Carmichael et al., 2015). As the problems around using ROI analyses in fMRI studies are well-known (Hupé, 2015), we encourage researchers to think twice before utilizing them and to opt for whole-brain investigations when possible. If ROI analyses are used, they should be accompanied by whole-brain investigations (Hupé, 2015). Researchers should aim for open data sharing, reporting even insignificant results, as it could lead to more informative meta-analyses in the future. Because meta-analyses contain more data, they help decrease the limitations of individual studies. Robust meta-analyses are needed as they identify possible patterns of activation, creating pathways for future synesthesia research. The ability to quantitatively synthesize the findings of studies is important for any research field. Only then can clear conclusions be drawn.

Interpretability could also be improved by introducing questionnaires. GCS is evidently not only about color. Some synesthetes report experiencing texture or other material properties (Eagleman & Goodale, 2009). Many report an inherent emotional quality to the experience. A synesthete can feel a sort of “correctness” when their synesthetic colors match with the real colors and can experience discomfort during a mismatch between the two (Callejas et al., 2007). With so many different cognitive aspects packed into one experience, maybe focusing solely on color does not capture the entire synesthetic experience. Gould van Praag et al. (2016) utilized the CLaN questionnaire to investigate how subjective qualities affect brain activation in synesthetes. We believe that combining comprehensive questionnaires

on the subjective qualities of synesthesia with neuroimaging technology is a promising approach toward more interpretable results. The interpretability of study results will be improved when the participants' additional inducers or synesthesias, associator or projector status, and differences in phenomenology are acknowledged.

With the current state of research in the field of synesthesia, no truly robust meta-analyses can be conducted. Future meta-analyses should aim to include at least the recommended 17 studies (Eickhoff et al., 2016). Our study results could benefit from another meta-analysis including a wider variety of synesthesias with color as the concurrent modality. This would, of course, introduce more heterogeneity, but it would be of value to see if such analysis would lead to similar results. The synesthetes in the studies included in this analysis likely had other synesthesias and inducers that were not reported (Rouw et al., 2011). Because of this, a meta-analysis spanning multiple different color synesthesias could help capture the synesthetic experience in the brain without introducing much more heterogeneity than was already present in this analysis.

Conclusions

The main meta-analysis of the fMRI studies on GCS revealed convergent activation in the parietal lobe in response to achromatic and congruently and incongruently colored grapheme stimuli. The strict analysis revealed activation in the frontal lobe in response to achromatic grapheme stimuli. Although these results need to be interpreted with extreme caution due to the evident limitations of our analysis, the meta-analyses emphasize the indisputable inconsistencies within the field. We hope that researchers continue to search for the neural correlates of synesthesia while implementing care and consideration in the decisions concerning experimental design, methods, and reporting results. This way, synesthesia can continue to function as a window into the neural underpinnings of the uttermost subjective experiences of human beings and the pathways of sensory integration in the brain.

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Study	Sample Size	Region	X	Y	Z	Thresholds	Talairach or MNI
O'Hanlon et al. (2013)	24	L inferior parietal lobule/post-central gyrus (BA2/40)	-57	-27	32	Corrected whole-brain p= .01	Talairach
		L declive (cerebellum)	-43	-63	-20	Corrected whole-brain p= .01	Talairach
		L insula	-43	-7	6	Corrected whole-brain p= .01	Talairach
		R inferior parietal lobule (BA40)	56	-28	24	Corrected whole-brain p= .01	Talairach
		R supramarginal/inferior parietal lobe (BA40)	57	-40	33	Corrected whole-brain p= .01	Talairach
		L medial frontal gyrus (BA6)	-3	-12	54	Corrected whole-brain p= .01	Talairach
		R cuneus (BA19)	25	-73	31	Corrected whole-brain p= .01	Talairach
		R superior frontal gyrus (BA6)	25	-2	66	Corrected whole-brain p= .01	Talairach
		L precuneus (BA7)	-7	-59	45	Corrected whole-brain p= .01	Talairach
		R middle occipital gyrus (BA19)	39	-82	13	Corrected whole-brain p= .01	Talairach
		L insula/transverse temporal gyrus (BA41/13)	-45	-19	11	Corrected whole-brain p= .01	Talairach
		R cerebellar tonsil	8	-51	-33	Corrected whole-brain p= .01	Talairach
		R middle frontal gyrus (BA6)	7	-11	71	Corrected whole-brain p= .01	Talairach

Study	Sample Size	Region	X	Y	Z	Thresholds	Talairach or MNI
		L post-central/inferior parietal gyrus (BA2)	-45	-27	43	Corrected whole-brain p= .01	Talairach
Rich et al. (2006)	14	L medial lingual gyrus	-4	-86	-12	Region of interest p = .008	MNI
		L medial lingual gyrus	-2	-82	-6	Region of interest p = .015	MNI
		L medial ventral lingual gyrus	-4	-80	-6	Region of interest p < .001	MNI
		L medial ventral lingual gyrus	-6	-84	-14	Region of interest p = .001	MNI
		L Lateral ventral occipital region	-20	-74	-16	Region of interest p = .011	MNI
Gould van Praag et al. (2016)	40	L precentral cortex**	-46	4	34	Corrected whole-brain p= .05	MNI
		L inferior parietal cortex	-46	-48	50	Corrected whole-brain p= .05	MNI
		R inferior parietal cortex	44	-48	48	Corrected whole-brain p= .05	MNI
Melero et al. (2014)	20	L calcarine sulcus	-4	-94	-10	Corrected whole-brain p= .012	MNI
		L cuneus BA19	-16	-88	26	Corrected whole-brain p= .011	MNI
		L inferior temporal gyrus (BA37)	-58	-54	-14	Corrected whole-brain p < .001	MNI
		R lingual gyrus	-18	-82	-12	Corrected whole-brain p= .007	MNI

Study	Sample Size	Region	X	Y	Z	Thresholds	Talairach or MNI
		L superior temporal gyrus	-52	-4	-2	Corrected whole-brain p= .010	MNI
		L inferior/superior parietal lobe*	-42	-36	34	Corrected whole-brain p< .001	MNI
		R superior parietal lobe*	32	-66	64	Corrected whole-brain p= .025	MNI
		R supramarginal gyrus	68	-32	22	Corrected whole-brain p= .001	MNI
		L precuneus (BA7)*	-22	-72	42	Corrected whole-brain p< .001	MNI
		R precuneus (BA7)	10	-64	50	Corrected whole-brain p= .019	MNI
		L supplementary motor area	-12	-4	64	Corrected whole-brain p < .001	MNI
		R supplementary motor area	8	24	48	Corrected whole-brain p= .021	MNI
		L anterior cingulate gyrus (BA24)	10	-2	48	Corrected whole-brain p= .016	MNI
		R middle frontal gyrus	46	32	38	Corrected whole-brain p< .001	MNI
		R middle frontal gyrus	38	56	2	Corrected whole-brain p= .001	MNI
		L middle frontal gyrus	-46	24	34	Corrected whole-brain p= .002	MNI
		R precentral gyrus (BA6)	12	-22	72	Corrected whole-brain p= .002	MNI

Study	Sample Size	Region	X	Y	Z	Thresholds	Talairach or MNI
		L precentral gyrus (BA6)	-56	-8	40	Corrected whole-brain p= .015	MNI
		R dorsolateral pre-frontal cortex (BA46)	42	46	16	Corrected whole-brain p= .014	MNI
		L orbitofrontal cortex BA10	-36	56	0	Corrected whole-brain p= .026	MNI
		R orbitofrontal cortex (BA10)	28	50	-6	Corrected whole-brain p= .031	MNI
		R insula/inferior frontal gyrus (BA47)	32	20	-4	Corrected whole-brain p= .019	MNI
		L insula (BA13)	-56	-38	20	Corrected whole-brain p= .019	MNI
		R anterior cerebellum	36	-60	-32	Corrected whole-brain p= .001	MNI
		L anterior cerebellum	-32	-42	-28	Corrected whole-brain p= .039	MNI
		R posterior cerebellum	24	-76	-28	Corrected whole-brain p= .012	MNI
		L posterior cerebellum	-38	-72	-30	Corrected whole-brain p= .026	MNI
Sinke et al. (2013)	36	L inferior parietal lobule*	-36	-62	48	Corrected whole-brain p= .05	MNI
Within-subject studies							
Weiss et al. (2005)	9	L caudal intraparietal cortex	-24	-65	51	Corrected whole-brain p= .05	Talairach

Study	Sample Size	Region	X	Y	Z	Thresholds	Talairach or MNI
		L anterior intraparietal cortex	-36	-50	41	Corrected whole-brain p= .05	Talairach
		L premotor cortex	-46	3	27	Corrected whole-brain p= .05	Talairach
Sperling et al. (2006a)	1	Subject 1:					
		L V8	-31	-74	-20	Region of interest p = .05	Talairach
		R V8	30	-68	-20	Region of interest p = .05	Talairach
		L inferior frontal gyrus	-32	48	19	Region of interest p = .05	Talairach
			30	49	19	Region of interest p = .05	Talairach
		L insula	-41	8	10	Region of interest p = .05	Talairach
			44	7	0	Region of interest p = .05	Talairach
		L superior temporal gyrus	-48	10	4	Region of interest p = .05	Talairach
			52	14	-2	Region of interest p = .05	Talairach
		L inferior temporal gyrus	-56	-15	-16	Region of interest p = .05	Talairach
Sperling et al. (2006b)	1	Subject 2:					
		L V8	-27	-70	-14	Region of interest p = .05	Talairach
		R V8	26	-79	-13	Region of interest p = .05	Talairach

Study	Sample Size	Region	X	Y	Z	Thresholds	Talairach or MNI
		L inferior frontal gyrus	-44	19	7	Region of interest p = .05	Talairach
		R inferior frontal gyrus	42	40	18	Region of interest p = .05	Talairach
		R insula	39	3	4	Region of interest p = .05	Talairach
		L superior temporal gyrus	-50	16	0	Region of interest p = .05	Talairach
			52	15	2	Region of interest p = .05	Talairach
		R inferior temporal gyrus	63	-22	-10	Region of interest p = .05	Talairach
Sperling et al. (2006c)	1	Subject 3					
		R inferior frontal gyrus	30	42	19	Region of interest p = .05	Talairach
		R inferior temporal gyrus	63	-11	-21	Region of interest p = .05	Talairach
Laeng et al. (2011)	2	L precentral gyrus	-56	6	40	Whole-brain p= .05	MNI
		L angular gyrus	-36	-62	40	Whole-brain p= .05	MNI
		L inferior parietal lobule	-26	-76	30	Whole-brain p= .05	MNI
		L superior parietal lobule	-28	-68	54	Whole-brain p= .05	MNI
		L inferior occipital gyrus	-50	-72	-12	Whole-brain p= .05	MNI
		L lingual/fusiform gyrus	-36	-82	-18	Whole-brain p= .05	MNI
		L inferior frontal gyrus	-40	4	26	Whole-brain p= .05	MNI

Study	Sample Size	Region	X	Y	Z	Thresholds	Talairach or MNI
		L inferior frontal gyrus*	-46	16	-6	Whole-brain p= .05	MNI
		L rolandic operculum	-60	10	2	Whole-brain p= .05	MNI
		L cerebellum/declive	-42	-70	-24	Whole-brain p= .05	MNI
		L cerebellum/declive	-4	-82	-28	Whole-brain p= .05	MNI
		L medial globus pallidus	-12	2	0	Whole-brain p= .05	MNI
		R precentral gyrus	46	2	30	Whole-brain p= .05	MNI
		R angular gyrus	36	-66	44	Whole-brain p= .05	MNI
		R superior parietal lobule	30	-72	56	Whole-brain p= .05	MNI
		R fusiform gyrus	46	-60	-18	Whole-brain p= .05	MNI
		R fusiform gyrus	46	-70	-14	Whole-brain p= .05	MNI
		R inferior occipital gyrus	46	-60	-18	Whole-brain p= .05	MNI
		R inferior parietal lobule	50	-44	54	Whole-brain p= .05	MNI
		R supramarginal gyrus	50	-44	40	Whole-brain p= .05	MNI
		R inferior frontal gyrus	44	14	28	Whole-brain p= .05	MNI
		R inferior frontal gyrus	46	28	30	Whole-brain p= .05	MNI
		R middle frontal gyrus	38	40	24	Whole-brain p= .05	MNI
		R middle frontal gyrus	36	46	12	Whole-brain p= .05	MNI
		R putamen	2	-4	2	Whole-brain	MNI

Study	Sample Size	Region	X	Y	Z	Thresholds	Talairach or MNI
						p= .05	
		R thalamus	2	-22	10	Whole-brain p= .05	MNI
Total amount	247						

Note. * Contributed to cluster in Main analysis. ** Contributed to cluster in Strict analysis. *** Foci outside of the mask, not included in any analysis.

Appendix B. The appendix illustrates the output of the meta-analyses from GingerALE.

Main analysis

Mask:

Reference Space = MNI152

Dimensions = 91x109x91

Number of within-brain voxels = 228483

Mask Size = More Conservative (Smaller)

Foci:

Coordinate System = MNI

File of foci coordinates = Coordinates MAIN without Rouw 2007.txt

Number of foci = 109

Number of experiments = 12

Total number of subjects = 247

ALE - Random Effects, Turkeltaub Non-Additive (HBM, 2012):

File of ALE voxels = Coordinates MAIN without Rouw 2007_ALE.nii

FWHM minimum value = 8.692140864043681

FWHM median value = 9.574940482272122

FWHM maximum value = 19.072644189655946

Minimum ALE score = 1.1719994E-18

Maximum ALE score = 0.018798599

P Values: Eickhoff (HBM, 2009)

File of P values = Coordinates MAIN without Rouw 2007_P.nii

Minimum P value = 5.9033017E-8

Thresholding:

Threshold Method = Cluster-level Inference

Thresholding Value = 0.05

Thresholding Permutations = 1000

Cluster-Forming Method = Uncorrected P value

Cluster-Forming Value = 0.001

Volume > Threshold = 672 mm³

Chosen min. cluster size = 496 mm³

Thresholded ALE image = Coordinates MAIN without Rouw 2007_C05_1k_ALE.nii

Cluster Analysis:

#1: 672 mm³ from (-40,-66,44) to (-30,-58,52) centered at (-35.8,-62,47.9) with 1 peaks
with a max value of 0.0188 ALE, 5.9033017E-8 P, 5.3 Z at (-36,-62,48)

Labels: (Gray Matter only)

Hemisphere: 100% Left Cerebrum

Lobe: 100% Parietal Lobe

Gyrus: 42.2% Inferior Parietal Lobule, 33.3% Superior Parietal Lobule, 24.4% Precuneus

Cell Type: 48.9% Brodmann area 7, 28.9% Brodmann area 39, 22.2% Brodmann area 19

Experiment Table:

[0 0 0 0 0 1 1 0 0 0 0 0]

Contributors to cluster #1

1 foci from Reference=MNI Melero et al., 2014: chromatic achromatic inducing vs non-inducing vs congruent incongruent

1 foci from Reference=MNI Sinke et al., 2013: black and colored inducing vs pseudo

Strict analysis

Mask:

Reference Space = MNI152

Dimensions = 91x109x91

Number of within-brain voxels = 228483

Mask Size = More Conservative (Smaller)

Foci:

Coordinate System = MNI

File of foci coordinates = Coordinates strict without rouw 2007.txt

Number of foci = 24

Number of experiments = 5

Total number of subjects = 172

ALE - Random Effects, Turkeltaub Non-Additive (HBM, 2012):

File of ALE voxels = Coordinates strict without rouw 2007_ALE.nii

FWHM minimum value = 8.692140864043681

FWHM median value = 8.857805542544007

FWHM maximum value = 10.164010215663069

Minimum ALE score = 1.4E-45

Maximum ALE score = 0.013467629

P Values: Eickhoff (HBM, 2009)

File of P values = Coordinates strict without roww 2007_P.nii

Minimum P value = 1.4666084E-6

Thresholding:

Threshold Method = Cluster-level Inference

Thresholding Value = 0.05

Thresholding Permutations = 1000

Cluster-Forming Method = Uncorrected P value

Cluster-Forming Value = 0.001

Volume > Threshold = 808 mm³

Chosen min. cluster size = 520 mm³

Thresholded ALE image = Coordinates strict without roww 2007_Co5_1k_ALE.nii

Cluster Analysis:

#1: 808 mm³ from (-48,0,24) to (-38,8,36) centered at (-43.5,4.1,29.3) with 1 peaks
with a max value of 0.0135 ALE, 1.4666084E-6 P, 4.68 Z at (-42,4,28)

Labels: (Gray Matter only)

Hemisphere: 100% Left Cerebrum

Lobe: 100% Frontal Lobe

Gyrus: 74.4% Precentral Gyrus, 25.6% Inferior Frontal Gyrus

Cell Type: 84.6% Brodmann area 6, 15.4% Brodmann area 9

Experiment Table:

[1 0 0 1 1]

Contributors to cluster #1

1 foci from Rouw & Scholte, 2010: grayscale strong inducing weak inducing vs non-inducing letters

1 foci from Reference=MNI Gould van Praag et al., 2016: achromatic letters vs achromatic non-inducing symbols

1 foci from Reference=Talairach Weiss et al., 2005: inducing vs non-inducing grayscale