

Research Article

Can Synesthesia be Caused by Neurocysticercosis? Any Drug Therapy? Systematic Review

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Abstract

Introduction: We searched the medical literature, following the guidelines outlined in the PRISMA statement. From 01st, January 2010 to 31st, May 2025, the authors searched the scientific databases, Scopus, Embase, Medline, and PubMed Central using the following searches: “Synesthesia” OR “synaesthesia” OR “Aetiology of synesthesia” OR “mirror-touch”, OR “neurocysticercosis”

Results: After screening the full-text articles for relevance, 101 articles were included for final review. However, no article was found when we searched for synesthesia related to neurocysticercosis or synesthesia responding to drug therapy.

Conclusions: To our best knowledge, there are no studies that correlate synesthesia and neurocysticercosis has been published up to date. Therefore, there is not any relationship between synesthesia and NCC and drug therapy for synesthesia does not exist.

Keywords: Synesthesia/Synaesthesia; Individual differences; Multisensory/Cross-modal processing; Hearing-motion; Mirror-touch; Personification

Introduction

The medical terminology synesthesia (Sth) arises from a combination of two words, “together” and “perception”, which describe a spontaneous reaction where one triggering stimulus results in another atypical specific experience. There are many different modalities of synesthesia, one of which is the case of Mirror-Touch Synesthesia (MTS), which is also known as vision-touch synesthesia, which happens when a person consciously feels a tactile sensation at the time they see other people being touched [1,2].

Some authors have established that “Synesthesia” or “synaesthesia” has its roots in the Greek language, which means “syn-like union” and “aesthesia,” referring to the union of the senses. According to the most accurate

investigation into the prevalence of synesthesia, the authors reported that it affects 4.4% of the world’s population [3]. At the same time, other authors report that 2% of the population lives with MTS [4].

Banissy et al. documented on the involuntary association of different senses, where individuals, in response to the stimulation from another, then experience one sensory modality. Sth has many different modalities for individuals, grouping the issue into about sixty different subcategories [5]. Although it is not included in the list of clinical disorders, many people ask whether synesthesia might be either beneficial or detrimental to memory and learning. Bremer and colleagues documented that most people consider their Sth as a personal benefit or gift that does not interfere with their everyday life but rather enriches it [6]. However, other reported cases manifest that Sth did not enrich their senses and creativity and feel the reverse word synesthesia with debilitating rather than enriching performance [7].

From the critical review of the neuroimaging literature on Sth made by Hupé and Dojat in 2015, it has been taken into account that Sth, rather than being a neurological condition caused by any structural or functional brain disorder, could be reconsidered as a special type of childhood memory, whose signature in the brain it is out of reach of the current brain imaging techniques [8].

In 2021, van Leeuwen et al. proposed that Sth shows hypersensitivity to senses, which interferes with daily living; therefore, it is linked to autism spectrum disorder [9].

Unfortunately, there is no known pathophysiology for this condition. However, Arend and colleagues have suggested that grapheme-colour synesthesia might be associated with increased grey matter in the left angular gyrus [10].

In 2019, Riečanský and Lamm suggested that sensorimotor activations in response to others' pain are best conceptualized as reflecting the expression of defensive responses in alignment with the sense of pain, thereby modulating the body's protective mechanisms against external harm [11]. Yaro et al. gathered a large group of people who performed memory tasks, concluding that these synesthetes might have better memory than non-synesthetes [12]. This study and its hypotheses aim to delve deeper into the intricacies of Sth, based on our investigations into its connection to declarative memory.

In 2024, a group of investigators guided by Anash studied grapheme-colour synesthesia, which has been described as the involuntary perception of specific colours or colour associations when thinking or seeing certain symbols, letters, or numbers. These researchers explore the performance of declarative memory tasks in people with grapheme-colour synesthesia. These authors conducted a comprehensive search of controlled clinical trials published between 2014 and 2024 in the PubMed and Google Scholar databases. These researchers found that cases presenting Synesthesia were shown to outperform non-synesthetes in visual memory tasks. Nevertheless, synesthetes showed better recall of shape-colour associations, paired patterns, and visual grids compared to control groups. However, the influence of synesthesia on word memory remains unclear [13].

Taenia Solium Taeniasis/Cysticercosis (TSTC) is a preventable foodborne, zoonotic, neglected tropical disorder predominately seen in persons living or visiting low and middle-income endemic countries, at the same time, Neurocysticercosis (NCC) is the consequence of invasion by the same cestode of the brain, optic nerves or the spinal cord which is identified as the larva form of the pig tapeworm *Taenia solium* (Ts). The most typical clinical features of this condition are Epilepsy (EP), Epileptic Seizures (ES) and headache, among other problems.

Pigs act as intermediate hosts of cysticercosis while humans are the definitive hosts. Taeniasis, i.e., intestinal infection with mature *T. solium* in the human host, occurs after ingesting undercooked meaty pork infected with the larval stage (porcine cysticercosis). Cysticercosis in human beings occurs after humans ingest *T. solium* eggs or proglottids. NCC is the principal aetiology of secondary epilepsy in endemic areas [14-18]. ES and Ep are the most common symptoms of Cerebral Cysticercosis (CC). In the past, we conducted more than a dozen epidemiological studies in rural areas around Mthatha, confirming that CC, also known as Neurocysticercosis (NCC), is the primary aetiology of secondary epilepsy. Most ES and Ep respond well to first-line Antiepileptic Drugs (AEDs) and Antiseizure Medications (ASM) [19-27]. The most prescribed ASM is benzodiazepine, and the most used

AEDs are valproic acid and carbamazepine [28-45].

One of the aims of this systematic review is to answer the following research questions. May the NCC in the parietal and temporal lobes lead to any synesthesia? Therefore, the main goal of this review is to obtain accurate information that enables us to support or reject the notion that synesthetic experiences may result from structural brain alterations, such as those induced by NCC.

Materials and Methods

Methods

A comprehensive search was conducted through two databases: PubMed and Google Scholar. In Google Scholar, the search terms “grapheme-colour synesthesia” AND/OR “grapheme-colour synaesthesia” AND “memory” were used. In PubMed, additional MeSH terms were used, which included (grapheme-colour Synesthesia (MeSH Terms)) AND (memory (MeSH Terms)).

Both databases were searched using filters “past 10 years” and controlled trials only, yielding 58 records from Scopus, Embassy and 43 from PubMed and Google Scholar. Records from both databases were combined, and 57 duplicates were removed, resulting in a total of 44 unique results.

Of those 44 results, each article was individually screened for eligibility. A total of 44 records were excluded because they did not measure declarative memory, and they did not correlate synesthesia with NCC. Among them seven records were excluded because they did not study grapheme-colour synesthesia. Additionally, 12 articles were excluded because they did not pertain to the hypothesis in any other way. In total, no articles were eligible for analysis (Figure 1).

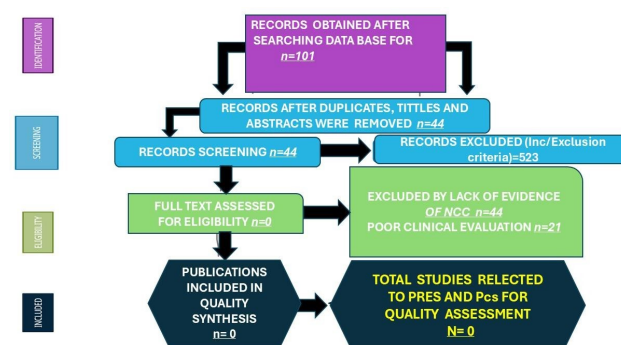


Figure 1: Following the PRISMA guidelines, this graphic shows a flow diagram of the selected publications

Search strategy

The PRISMA guidelines conducted this review. The databases searched included Scopus, Medline, and Embase. The search strategy encompassed terms related to Sth and NCC. Studies were selected if they were peer-reviewed publications examining Sth, excluding non-English, non-Spanish, and non-Portuguese publications, letters to the editor, editorials, and articles without appropriate primary endpoints. Data on demographics and clinical features,

imaging findings, drug therapy regimes, and prognosis were extracted. To minimise the risk of bias, the Joanna Briggs Institute tool for case reports was utilised.

In this study, no attempt was made to identify individuals and no original patient data were collected from the literature review. The systematic review is conducted by the ethical principles outlined in the Declaration of Helsinki.

We systematically searched for a combination of terms, including “synesthesia”, “neurocysticercosis”, “pathophysiology of Sth”, “treatment of Sth”, “management of Sth”, and medical subject headings and their relevant synonyms.

Discrepancies among the authors were resolved through scientific analysis and discussion.

The full-text manuscripts selected for analysis were then assessed based on the pre-established inclusion and exclusion criteria. The extracted data included the year of publication, the author’s name, the patient’s clinical symptoms, sex, age, radiographic findings, medical treatment, and outcomes.

Applying the Joanna Briggs Institute (JBI) tool for case reports, the risk of bias in included case reports was assessed by two authors (Ibanez and Foyaca). This tool evaluates the clarity of the diagnosis, various dimensions of bias, the precision of the reported intervention, and the validity of the outcomes [8]. Descriptive statistics were implemented to summarise the findings.

From January 1, 2010, to May 31, 2025, we searched the databases Embase, Medline, Scopus, and PubMed Central using the search terms mentioned earlier. After removing duplicates, two reviewers (LDFIV and HFS) independently screened all titles and abstracts. They evaluated the full texts based on the inclusion criteria. Any disagreement between the reviewers involved in the literature search was resolved through discussion with all authors to reach a consensus.

Selection criteria

Exclusion criteria were as follows:

- Inaccessibility to full text.
- Articles with unclear description of synesthete.
- Lack of relevant clinical data.
- Non-original studies (*i.e.*, editorials, letters, conference proceeding, book chapters);
- Animal model studies.
- Non-/Spanish/Portuguese/English studies as before mentioned.

The papers were thoroughly assessed, and duplicates were removed.

Data extraction and quality assessment

All selected data were tabulated in an electronic Excel database. That information included pathogenesis, drug

management, initial clinical presentation, evaluation of PRES after treatment, follow-up, and status at the latest evaluation. The quality of the studies was categorized as good, poor, fair, or reasonable, in agreement with the National Institutes of Health criteria.

Quality and risk of bias: Using the JBI tool for case series and case reports, the risk of bias in all selected articles was assessed. This program served to evaluate several dimensions of bias, including the precision of the reported intervention, the clarity of diagnosis, and the validity of the reported results.

Of the 101 case reports and series selected for this review, most studies were found to have a low risk of bias. Specifically, 61 cases were rated as having a low risk of bias, 30 cases were found to have a moderate risk of bias, and 10 publications were rated as having a high risk of bias. The presence of studies with moderate and high risk of bias (despite many studies being rated as high quality) highlights the need for more standardized and comprehensive reporting in future research on Sth.

Statistical analysis

Statistical analyses were performed using XLSTAT (add-on for Microsoft Excel, version 2021.4.1, Addinsoft SARL) and RStudio (version 4.3.1, <https://www.rstudio.com/>). Variations in continuous variables were assessed using the Mann–Whitney U-test. We presented descriptive statistics for continuous variables as median (95% Confidence Interval (95% CI)). All situations were evaluated using the Kaplan–Meier method to identify relevant prognosticators. A model of multivariable Cox proportional hazards with a priori selection of covariates was used to check for independent prognostic effects.

Results and Discussion

A total of 44 titles were selected from the literature after removing duplicates and excluding records. One hundred and one relevant articles were examined. Seventy-nine studies were unavailable for retrieval. After including seven additional articles identified from citation searching, 44 were excluded for they did not match any relationship with NCC. A total of zero records were identified from these searches which comply all requirements.

Series description and differences among groups

All the selected studies were relevant to the subject of this systematic review. None of the articles included were randomized controlled trials or prospective studies; all the articles were case reports and case series. Median age was 17.8 (range 8–81) with significant differences between age groups ($p < 0.001$). We did not find remarkable variations in gender ($p = 0.064$), although females presenting Sth were noticeably more frequent and slightly more prevalent.

For the selection process in this review, zero papers fit the inclusion and exclusion criteria. Some of these studies demonstrated an advantage in declarative memory recall for those with grapheme-colour synesthesia, depending on

the type of memory being tested.

The difference in results was analyzed using Analyses of Covariance (ANCOVA) and partial eta-squared (η^2). The accuracy of paired pattern recall of each picture was observed, and the measurement of accuracy was defined as the hit rate. The increased number of runs had a significant effect on the contribution to the hit rate for dissimilar pairs ($p < 0.001$, $\eta^2 = 0.401$).

Comments and final remarks

From our systematic review, we did not find any publication concerning the role played by NCC in the pathogenesis of Synesthesia (St), as is shown in the Flow diagram of Figure 1.

Synesthesia (from Greek meaning syn—union, aithesis—sensation) is a perceptual mechanism in which the stimulation of one kind of sensory modality (the inducer) involuntarily triggers a different kind of sensory modality sensation (the concurrent) [46-48].

In this review, we identified 165 different associations between possible inducers and concurrent conditions (Figure 2).

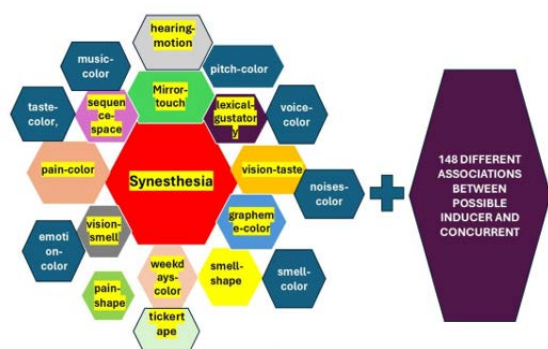


Figure 2: Shows the most relevant associations reported in the medical literature to date

The most remarkable modalities of Sth include mirror-touch, lexical-gustatory, grapheme-colour, and others. In the case of grapheme-colour synesthesia, it involves the association of colours with specific numbers or letters. This study includes mirror-touch synesthesia, grapheme-colour Synesthesia, and declarative memory due to restrictions on the length of this publication.

Declarative memory refers to the recall of events through long-term memory. Some in this group involuntarily perceive colour associations or specific colours when they see or think about certain numbers, letters, or symbols. For example, some grapheme-colour synesthetes will say the letter D is brown while the number six is red. The association of colour to a letter or number is subjective and can change between individuals. Mirror-touch synesthesia occurs when one person watches another being physically touched and feels as though they are being touched as well. In cases of lexical-gustatory synesthesia, a person hears or reads certain words and then perceives them as having a corresponding taste. Never those, Sth only blends sensory perceptions, creating a diverse number of subtypes.

Synesthesia was first identified around the mid-1700's, when Johann Gottfried Herder, a renowned philosopher and poet, reported his confusing experience with the condition. In 1848, a French physician named Charles-Auguste-Édouard Cornaz described Synesthesia as the opposite of colour blindness.

From history, we identified Solomon Shereshevsky, a famous synesthete of the 1920's, who could recall lists of numbers, street names, digits, and more in a matter of minutes. Alexander Luria, a famous neurophysiologist, followed him for 30 years and concluded that Solomon Sth was linked to better memory [49].

Anash and collaborators established that the medical term synesthesia is related to the involuntary association of multiple senses when people perceive one sensory modality in response to stimulation from another person. It means that a synesthete can perceive colours when reading certain numbers or even associate specific flavours with particular words. Some people can feel pain when they have seen another person suffering from pain. Other people may vomit when watching another person vomiting or can feel a remarkable pain when they see somebody being stabbed in the hand. Nevertheless, synesthesia may present differently for people who group the condition into various subcategories, such as sound-to-colour, lexical-gustatory, grapheme-colour, mirror-touch, and many others [13].

We want to emphasize that some people with Sth may present unusual, elicited experiences, so that, for example, numbers may elicit words, and colours may elicit tastes. Sth emerges in childhood or possibly even earlier and is related to a persistent "condition" or trait that affects a few per cent of the population [3].

Other investigators have established that the cross-activation process also involves cross-activation in area V4 (associated with colour perception), in addition to other distinct processing areas of the brain, including the inferior temporal cortex [50]. Other investigators suggest that grapheme-colour synaesthesia can be developed while learning colours and letters during childhood. Children, learning colours and letters simultaneously, tend to associate the two. Other investigators suggest that people with Sth have hyperconnectivity between different sensory regions of the brain [51]. The pathophysiological mechanisms of Sth have been investigated since the beginning of the nineteenth century, but numerous scientific limitations have hindered progress. However, from the early 2000's, the link between Sth and memory has been studied mainly by looking at synesthetes individually and their tested memory. In this sense, Smilek et al. tested a case in her memory capacities to recall coloured digits successfully [52].

Bankieries and Aslin concluded that grapheme-colour synesthetes learn and recall visual images more quickly and effectively in both the short and long term. These authors also considered that synesthetes performed better at memory tasks, and the age of persons was not implicated

as a confounding factor, suggesting that these memory tasks are impressive; however, it is unknown how they may translate to everyday situations [53].

Other investigator and their collaborators used the previous procedure (three-by-three grid to conduct their studies, obtaining similar results [54]. These investigators established that when participants were asked to recall the grids, they had to recognise whether they were presented with those specific colours and shapes before categorising them as “new” or “old”. Therefore, this test confirmed that there was no significant difference between Sth and its protective effects on memory decline, which suggests that there is no relation between synesthesia and memory, or that synesthesia’s effect on memory is more of a minor enhancement than a significant advantage. In another

investigation, the same authors found that grapheme-colour synesthetes performed faster and better in memory tasks than their control group. However, this study was statistically irrelevant due to the small sample size.

Another group pf participant was tested with letter span tasks by the same team of researchers whom after being verbally with a sequence of letters, they were required to orally recall as many of those letters as they could and the investigators did not find no difference between synesthetes and high memory controls [54, 55].

In a 2018 study conducted by Lunke and Meier [56], participants were asked to memorize a series of words. However, they were allowed to associate colours of their choice with the words, providing a grapheme-colour stimulus, as shown in Table 1 [57-66].

Table 1: Summary of study findings.

Author and reference	Objective	Study design	Level of evidence	Study population	Therapy or exposure	Results summary
Nunn JA et al. (2002) [57]	Grapheme- color evaluation	Cross-section	2	21 synesthete and a group of control	Memory test	Expression of V1-V2
Weiss PH (2009) [58]	To assess grapheme-color Sth	Clinical trial	2	Ten synesthete and control group	Recognition of memory test	Activated adjacent areas responsible for color perception, like area V4 in the calcarine visual cortex
Jäncke L (2011) [59]	Processing in speech-color Sth		2	Sixteen synesthete and twenty control	Memory test	High expression of area V2, V3 and V41
Bankieris and Aslin (2016) [60]	To assess whether synesthetes demonstrate superior short-term memory tasks in recalling snowflake-color pairings	Contro trial	2	14 synesthetes and 15 non-synesthetes from the Rochester area	Snowflake color pairings	Synesthetes learned snowflake-color pairings more quickly than controls. Synesthetes demonstrated better color recall than their peers
Chin and Ward (2017) [61]	To study childhood memory recall in exnsthetes and non-synesthetes	Contro trial	2	44 grapheme-color synesthetes and 40 non-synesthetes in the University of Sussex	Autobiographical memory tests	Synesthetes reported sharper childhood memories as compared to non-synesthetes reported more vivid memories from adulthood
Lunke and Meier (2018) [62]	To assess memory recall in grapheme- color synesthetes when given color stimuli	Contro trial	2	52 grapheme-color synesthetes and matched them to 52 controls according to age, gender, and level of education	Color and word recognition in random order	The results showed a memory benefit with color stimuli in those with grapheme-color synesthesia
Lunke and Meier (2020) [62]	To evaluate long-term recall in grapheme-color synesthetes compared to their control counterpart	Contro trial	2	19 grapheme-color synesthetes recruited via the synesthesia-check on the website of the University of Bern and 76 healthy control-participants matched for age, gender and education participated	Recognition memory tests	The advantage for memorizing color shown by grapheme-color synesthetes was persistent after one year compared to their matched controls
Mealor et al. (2019) [63]	To evaluate protective effects of memory in grapheme-color synesthetes compared to non-synesthetes	Contro trial	2	17 older synesthetes, 29 older control, 22 young synesthetes, 20 control	Recognition memory tests	Grapheme-color synesthesia does not have a protective effect against memory decline in aging

Pfeifer et al. (2014) [64]	To compare memory advantage in grapheme-color synesthetes compared to non-synesthetes in young and old age groups.	Control trial	2	14 young synesthetes, 14 young, and 14 computer older adults.	Visual associative learning computer program	The results show subtle associative memory advantage in synesthetes for non-synesthesia inducing stimuli, which can be detected against older adults
Simner and Bain (2018)	To evaluate enhanced abilities in performing tasks in Sth compared to their control counterpart.	Control trial	2	Group of randomly sampled child synesthetes age 10 and 11 years.	Cognitive memory tests	Synesthetes demonstrated above-average performance in a processing speed task and a near significant advantage in a letter-span task
Raminta Bartulienė (2025) [66]	To test sound-color synesthetes	Control trial	2	One female	Color and sound recognition randomly	sound-color synesthesia was related to specific voice features by using a feed-forward deep neural network and fMRI algorithm

Synesthesia is a sporadic brain cortical situation in which stimulation of one sensory modality provokes an immediate response in another sensory modality that is not being stimulated at the time.

However, in cases presenting grapheme-colour synesthesia, there is an activation of the visual processing areas associated with letters (such as the fusiform gyrus) that may inadvertently activate adjacent areas responsible for colour perception, like area V4 in the calcarine visual cortex [57]. High functional connectivity between the parietal and auditory cortex has also been reported in resting-state EEG studies by other authors, as well as greater V4/V8 expression during speech processing in speech-colour synesthetes [58, 59].

Therefore, cross-activation in coloured-hearing Synesthesia may occur when hearing signals are indirectly processed *via* integrative hubs, such as the IPC, offering a mechanistic account of the involuntary and consistent qualities of synesthetic perceptions, or directly engage colour-processing areas (V4/V8) by following these core characteristics, including automatic occurrence and stability over time. The current investigation seeks to determine whether specific hearing features of human voices are systematically associated with distinct synesthetic colour experiences in a case of sound-colour synesthesia. Other cases reported about grapheme colour synaesthesia are included in Table 1 [60-65].

Recently, Bartulienė, et al. [66] demonstrated that voice signal features determine the voice-evoked colour in individuals with poor visual acuity, and that certain vocal qualities are associated with sound-colour synesthesia. They identified the voice features that have the most significant impact on predicting synesthetic colour. These investigators also demonstrated that sound-colour synesthesia is related to specific voice features by utilizing a feed-forward deep neural network and the mRMR algorithm. They also documented that specific voice parameters and sound energy play a crucial role in colour perception, and that the tone, pitch, and energy of a person's voice all contribute

to specific colour perception. They investigated a female patient presenting with sound-colour synesthesia and impaired vision, and found that a person's voice pitch, tone, and energy changes different colour perceptions [66].

This research demonstrated a remarkable advantage in their memory performance. However, further investigations are needed to assess this phenomenon and to place too much focus on how stimuli can trigger and enhance the memory advantage in synesthetes. On the other hand, Chin and Ward provided participants with different cue words to determine whether they triggered memories differently in grapheme-colour synesthetes compared to non-synesthetes, to test autobiographical memory. They found sharper childhood memories in synesthetes compared to non-synesthetes, as well as more vivid childhood memories in synesthetes [67].

Based on our comprehensive review, to date, there is no accurate explanation as to why childhood memories are clearer. We hypothesized that it can be explained by exposure to cartoons and vibrant colours of toys, which may trigger synesthesia. We also hypothesized that Synesthesia may be a learned phenomenon involving the parietal-occipital cortex and deeper anatomical structures related to the limbic system.

Finally, we concluded that synesthetes showed better recall of paired patterns, visual grids, and shape-colour associations compared to control groups. They propose that the influence of all subtypes of synesthesia on memorizing words remains unclear.

Ward and Simner documented that it remains unclear whether Sth is a single condition or multiple conditions, and it may have a single cause or multiple independent causes. They speculated that modulatory feedback pathways from the concurrent to inducers play a crucial role in the emergence of Sth. These authors also speculated that modulatory feedback pathways (from the concurrent to inducer) may play a crucial role in the emergence of Sth [68].

We hypothesised that mirror-touch could have clustered

with music-touch, and tickertape could have clustered with the visualised sensations or language-colour. In contrast, Hearing-motion could have clustered with many other auditory concurrent events.

The investigators focused on a standard form called chromesthesia a type of synesthesia in which sounds trigger additional colour sensations, with a prevalence rate of 4% and a 1:1 female-to-male ratio [69].

We hypothesized that synesthetic phenomena surge from an elevated interaction and connectivity between neighbouring parietal areas involved in processing both the inducer and the concurrent percept, based on the results delivered by some authors [70] which is graphically represented in Figure 3.

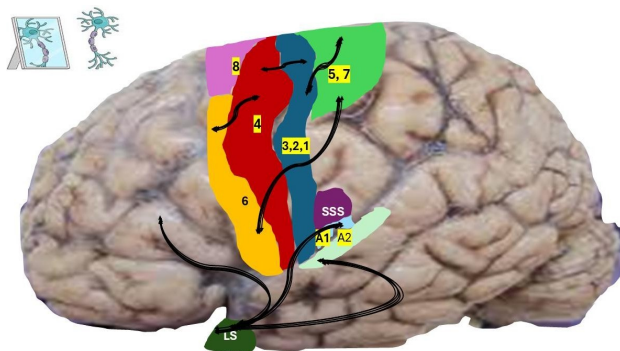


Figure 3: We graphically represent the interconnection between different areas in the somatosensory cortex involved in Sth. 3,2,1) Primary somatosensory cortex, 4) Primary motor cortex, 5,7) Parietal association cortex, 6) Premotor cortex, 8) Supplementary motor area. A1-A2-Secondary somatosensory area (in parietal operculum). LS-Limbic System

It is well known that the parietal cortex modulates the integration of visual and auditory inputs, leading to the consistent and vivid experiences reported by synesthetes. Therefore, it is particularly evident in investigations done that demonstrate enhanced connectivity between visual and auditory networks in people with synesthesia, indicating a neural basis for the cross-modal associations they experience [71].

We also hypothesized a theory for brain connectivity in synesthesia based on insufficient neural pruning, which is the process by which the brain eliminates synaptic connections that are rarely used or under-stimulated. While other authors consider that it is fair during early brain development [72]. In the meantime, other investigations using anatomical and neural imaging of infants' brains have found signs of excellent connectivity, which allow cross-modal perception, leading to experiences like that of Sth [73].

Another investigator suggested that synesthetic experiences can happen not from increased structural connectivity, but from a lack of inhibition of feedback signals rising from higher-order associative areas and then influencing sensory cortical regions not directly activated by the initial stimulus [74].

Notwithstanding, we hypothesized that the neural

mechanisms and their cognitive processes play a crucial role in Sth because many forms of Sth involve culturally learned elements. Therefore, synesthetic experiences typically develop later, mainly at the time when language skills are emerging, a finding supported by recent studies [75]. The semantic mechanisms hypothesis may support the idea that the associations formed in Sth may be modulated by higher-order cognitive mechanisms, such as conceptual understanding and language used in reading, writing, and calculation. More than 20 years ago, other researchers supported it, adding that the meaning of a grapheme may trigger a specific colour based on learned associations rather than purely sensory interactions [75].

Seems that most evidence for the neural basis of synesthetic perception still arrives from investigations on grapheme-colour Synesthesia-colour based on the findings reported by some authors [76] which supports some differences in coloured-hearing syndrome, including enhanced structural connectivity between visual and auditory association areas and the frontal cortex. People with coloured-hearing syndrome present distinct hemispheric patterns of subcortical integrity in the Inferior Fronto-Occipital Fasciculus (IFOF), a major pathway linking sensory areas with frontal regions [76].

Consistency in association for specific stimulation over time should be considered a hallmark of Sth, and it will serve as the primary goal of most experimental validation procedures [66].

Currently, the phenomenon of Sth has drawn the attention of investigators in the field of artificial intelligence, leading to the development of machine learning models based on Sth, including a cross-Sth-aware image-music model. To reach this goal, they combined image databases and emotional music, creating pairs of images and music with emotional labels [58]. Other authors found that their selected methods were effective in linking the similarities between image-sound emotions [77].

In Figure 3, we also represent the most important regions of the auditory system, where sounds are processed selectively, and where their association with different colours may indicate specific neural imaging characteristics. It is well known that almost all different acoustic properties are decoded in different places in the auditory cortex of the temporal lobe: Frequency, amplitude, and temporal structure simple acoustic features are processed at the primary auditory cortex-A1 while more complex structures, voice timbre, and phonemic characteristics are processed at the secondary auditory areas-A2 (superior temporal gyrus and planum temporale). On the other hand, the prefrontal cortex and some of the components of the limbic system are involved in subjective perceptions and the formation of emotions such as "sharpness" or "warmth" of voices [78].

Spectral roll-off identifies the perception of sharpness in sound within the auditory cortex [79] while spectral entropy indicates how the brain cortex rerecognizes chaotic and structured sounds [80].

Brief comments on mirror-touch synesthesia

The modality of Sth known as Mirror-Touch Synaesthesia (MTS) is characterized by a tactile sensation perceived by a person on their own body when they see another person being touched. In other words, MTS is the conscious phenomenon of a light touch induced by seeing someone else touched. MTS has been confirmed more often in a non-Western (Chinese) population comparable to Western peoples under the identical stimuli. Nevertheless, this Sth requires the involvement of another human being; therefore, it has specific attributes which make a difference [81].

Some authors have demonstrated that individuals presenting with MTS can be influenced by others' emotions, as observed in a well-designed qualitative research study [82].

While some people with MTS are better at detecting subtle facial expressions of emotion, as supported by behavioural evidence [83].

Banissy et al. investigate identity recognition abilities and facial expressions in a rare group of participants who exhibit facilitated sensorimotor simulation (MTS), which involves experiencing touch on their own body when observing touch in another person. These authors suggest that these experiences are linked to heightened sensorimotor simulation in the shared-touch network, and they also believe that this implies a role for sensorimotor simulation processes in re-experiencing affective states, but not facial identity [76].

In 2013, Maister et al. suggested that observing touch on other people not only elicits a conscious experience of touch in MTS but also leads to a blurring of the self-other boundary and a change in the mental representation of the self. It is consistent with a multisensory account of the self; whereby integrated multisensory experiences maintain or update self-representations [84].

Banissy and Ward established two spatial subtypes of MTS. In the commonest one, the synesthetic experience is evoked as though looking in a mirror in this case the persons observing a light touch to the left part of the face evokes tactile sensations on the contralateral side of the synesthete's face and in the less common, anatomical subtype, the synesthetic experience is mapped anatomically, it means the person seeing touch on the left part of the face evokes tactile sensations on the left side of the synesthete's face. The same investigators also support the theory that developmental MTS is a function of atypical brain excitability within the neural network supporting normal somatosensory mirroring. For this variant of MTS, self-other blurring happened in the absence of felt touch being applied to their face, implying that merely viewing touch on others evokes a modification in self-representations in MTS [85].

On the other hand, Chun and Hupé studied the relationship between Sth with ticker tape experiences and phenomenal traits of mirror-touch, as well as the representation of these three phenomena in the population, domain of work or study, and across gender. Considering ticker tape as

an automatic visualization of thoughts or spoken words, such as a teleprompter. They described this experiment as follows: As the time an individual talks, a ticker tape might see mentally the spoken words displayed as coming out of the speaker's mouth or in front of their face. Then, to assess the associations between synesthesia and these phenomena, they examined a large number of people ($n=3743$). They did not identify differences across gender or domain of work and study in prevalence of Sth, MTS or ticker tape. However, they confirmed that grapheme-personification was the most common subtype of Sth, estimated at around 12% [86].

Cioffi et al. wrote that the sense of agency (SoAg) refers to the sensation of control over one's actions and forms an integral component of our cognitive and social lives; according to their example, the recognition of oneself as the element of an action plays a crucial role in self-awareness. The importance of SoAg is proved by the striking modifications in this experience associated with various neurological (e.g., cortico-basal degeneration) and psychiatric (e.g., schizophrenia) disorders. Considering that MTS is primarily a "disorder" of ownership, it can bring consequences for SoAg, potentially worsening ownership disturbances, despite its most probable speculation, which current confidential research has not yet proven.

Previous authors have documented that two brain cortical areas are deeply implicated in SoAg/MTS, specifically the Temporo-Parietal Junction (TPJ) and the anterior insula. It has been confirmed that the anterior insula is strongly linked with self-other discrimination and highly activated in agency attribution tasks. On the other hand, numerous investigations into the comparison between externally produced sensory signals and self-generated ones have found expression in the right hemisphere, as evidenced by a meta-analysis of fMRI studies on the TPJ and its mirror-touch network hyper-expression. Finally, these authors concluded that there is enough accurate evidence to consider that MTS is linked to a blurring of self-other representation [87].

As previously cited, there are two important theoretical fundamentals for MTS. The first is the threshold theory, which links MTS to hyperactivity in the parietal-frontal mirror neuron system. The second attributes MTS to impaired self-other representations in the temporal-parietal junction and medial prefrontal cortex. However, Kuang proposes that these two postulates can be merged under a unified social motor cognition postulate, which states that action observation engages two complementary levels of cognitive processing mechanisms: an abstract mental level regarding attribution of mental states, which supports inferring others' minds and self-other distinctions.

Moreover, a lower-level, physical process regarding fundamental motor and sensory aspects of the action, which supports motor imitation and goal understanding, and this investigator concluded that MTS is caused by disturbed mirroring and mentalizing functions that represent the two complementary aspects of cognition process with shared

predictive coding during the process when the Synesthete is seeing someone is touched [88].

Synaesthetes are people who have synaesthesia. Those with MTS are referred to as MT synaesthetes; they can understand and identify facial expressions and have enhanced social awareness. Some synaesthetes become distressed and overwhelmed by their feelings because of others' experiences; this is called sensory overload. Therefore, sensory overload is described as receiving excessive input from all five senses, which your brain struggles to cope with [89]. According to Kassan et al., fMRI of the brain reveals that the activated areas (SI and SII) in the brains of synaesthetes and individuals acting are the same; however, the SII in the parietal operculum of the synaesthete's brain has more grey matter. fMRI also confirmed that the expression of SI and SII was related to increased stimulation of the mirror-touch network. Furthermore, the tactile mirror system, which links empathy and MTS, enables synaesthetes to feel what others are feeling [82] physically.

Mirror neurons are motor or visuomotor cells located in Broca's area, the primary motor cortex, and the inferior parietal cortex. They are highly specialized cells that can help us better understand human behaviours and emotions, with the capacity to replicate sensory experiences that occur at a heightened level in synaesthetes. These neurons are activated when we perform an action and when we observe others and are part of an extensive mirroring network [90, 91].

Visuomotor refers to the coordination between the motor and visual aspects of the brain cortex, mainly the upper and lower limbs and the eyes [89]. A long time ago, some investigators have proven that a visual stimulus would activate visuomotor mirror neurones, which results in a motor response such as movement of the limb [92].

In other words, when a person replicates an action, the mirror neuron fires like it would have fired for the person who acted [93].

Some people cringe when someone has fallen, because the mirror network crosses the threshold between subconscious and conscious thinking, making you feel as though you have fallen as well. The mirroring event intensifies and is a more conscious phenomenon [89].

Dr Joel Salinas, a well-known neurologist who wrote a book about Synesthesia, also suffered from MTA. Based on his personal experiences and investigations, he documented that all humans have a mirror network in their brains, but synaesthetes have a more extensive and hyper-activated network.

He defined it as a rare neurological trait that gave him the ability to feel the physical and emotional experiences of other people literally. From the medical wards of Massachusetts General Hospital to his own life, Salinas delivered to interested readers a remarkable insight into his trait, its often-unforgiving complications, and its gifts, allowing us a better understanding of how our brain, in

all its wonder, continues to offer limitless chances for compassion and human potential. Beautifully described and wholly original, MTA is a condition of an exceptional mind that challenges our understanding of what it means to be human, everything it means to feel, think, and be [89].

MTS is a physical feature of empathy, which could be perceived as a superpower. Understanding one another in more empathetic ways could help us to better take care of one another [89].

Although not related to MTS, we see people presenting nausea or vomiting after smelling/washing someone who vomited, like a tendency to reproduce the observed states of other people on one's internal GIT representations in the brain. It may involve somatosensory mirror systems, previously reported by other researchers [94,95].

We hypothesized that this mechanism is regulated by the Temporoparietal Junction (TPJ), as it is involved in directing attention between the self and others, and 'theory of mind' more generally, as has been postulated by other authors under different circumstances [96].

We also considered that mirror pain is linked to different neurons, as documented by voxel-based morphometry, a finding that has been reported by other authors in various scenarios [96,97].

To support the involvement of mirroring mechanisms, some authors have performed functional MRI of the brain during the observation of touch and pain, confirming the important expression of the somatosensory cortex [84].

Some authors have established that some countries in Asia, such as Korea and China, have a more "somatization culture" compared to Western countries; therefore, different diagnostic criteria for some diseases should be applied [98].

Based on the previous postulates, the tendency of people from China to express depression somatically is broadly acknowledged and currently a crucial finding in cultural psychopathology must be considered. The same author hypothesizes that people with MTS will have modifications in brain cortex volume in somatosensory areas and rTPJ, replicating those in Western samples and concluded that this reflects cross-cultural differences in self-construal and differences in somatization of psychological phenomena due to that the Chinese people are more prompt to incorporate others in their self-concept leading to more vicarious experiences [74].

Pitcher and colleagues postulated that future face perception network models must consider interhemispheric asymmetries in the functional connections of different face-selective brain areas [99]. Kujala and collaborators investigate the role of the amygdala, dorsomedial prefrontal cortex and posterior superior temporal sulcus into the interactional position of the observed people and distinguished humans facing toward from humans facing away and concluded that the amygdala did not differentiate the humans facing away, it was most sensitive to face-to-face interaction and involved in the assessment of the proximity between two other persons [100].

Drug therapy for synesthesia

Unfortunately, there is no treatment for synesthesia. However, many people enjoy perceiving the world in a way that differs from the general population. Despite some synesthetes feeling that their condition isolates them from other people. Notwithstanding, synesthetes have trouble explaining their sensorial phenomenon because they are very different.

Talking with the management team, including all mental health professionals, may also help these individuals see the value that synesthesia can add to their lives, and they may find that both sides of their brain harmonise as they pursue work, they are passionate about. Many famous personalities lived whole and everyday lives with synesthesia. In other words, many successful people experience this phenomenon, including Kanye West, Pharrell Williams, Mary J. Blige, Tori Amos, Duke Ellington, Lorde, Vladimir Nabokov, Vincent van Gogh, and Joan Mitchell.

Ward and Banissy consider that MTS consist in a hyper-activity within a mirror system for pain and/or touch although it cannot explain the whole pattern (e.g., performance on some tests of social cognition; structural brain differences outside of this system) or the mechanism of disorder in the ability to distinguish the self from others [101].

Brief comments on sequence-space synesthesia

Sequence-space Synesthesia (SSS) is a condition characterized by the perception of ordinal sequences, such as letters of the alphabet, months, or numbers, occupying spatial locations in the mind's eye, extrapersonal, or peripersonal space [102].

For better understanding, imagine someone thinking about January; this may evoke a visuospatial impression of a circular arrangement of January, or hearing a numeral may elicit a specifically shaped number line. SSS are consistent over the time, also idiosyncratic presenting a lot of different shapes of complexity in the mind's eyes or outside the body and Its visuospatial nature is well known which is quite complex verifying from visual impression of their forms to detailed visual content such as color, texture, written text, and associated visual images.

We hypothesized that this variation may reveal the distinction between (1) Spatial imagery of explicit spatial relationships, which is complex and detailed, sometimes taking the aspect of a spatial map with flexible viewpoints, and (2) Visual imagery that more holistically represents visual surface properties, depicting visual appearance. Different behavioural tests can tap all these complementary aspects of visuospatial imagery *vs.* ventral streams of visual processing.

Spatial and visual dimensions would independently reflect an emphasis on ventral versus dorsal stream activation in mediating synaesthetic imagery [90].

The spatial dimension represents the extent to which spatial forms can be built up as spatial models where affected

people have explicit introspective access to the relative positions of sequence members. Therefore, synesthetes with low spatial dimensions exhibit low spatial resolution. In contrast, those with high spatial dimensions possess a more explicit spatial model, and they have a better capacity to facilitate spatial transformations, allowing forms to be viewed from multiple viewpoints [90].

Finally, these authors concluded that for synesthetes with limited visual experience, their spatial forms appear to occupy space but lack a depictive visual quality. In contrast, those with increased visual experience "see" their spatial type in visual detail from a specific viewpoint in their mind's eye, or extrapersonal or peripersonal space.

Brief comment on structural correlates of synesthesia

In this systematic review, we did not find evidence to establish a correlation between brain structural alterations caused by *T. solium* in the CNS and Sth. Previously, Hupé and Dojat studied structural alterations on the brain using MR imaging in two different ways: (1) Structural morphometry to study whether Sth would be associated with local changes of brain cortex volume caused by any organic lesion of the brain looking specifically into the white matter and gray matter or fractional anisotropy changes and (2) Connectivity to investigate whether Sth would be associated with abnormal connections between specific brain regions. After reviewing eleven investigations, including two MRI modalities for searching structural differences between synesthetes and the control group, such as diffusion tensor imaging for probabilistic fibre tractography and FA analysis, including T1-weighted MRI imaging for voxel-based morphometry analysis/cortical surface analysis, to identify atrophy or the presence of nervous tissue expansion between groups of people. The synesthetic experience was consistently reported as involving colour in all studies. Graphemes and tones elicited it, but they could not confirm whether structural changes might affect the function of colour centres, and no differences were found in synesthetes compared with controls. In conclusion, there is currently no firm evidence of structural differences between synesthetes and controls, particularly in the grey matter, and no observed differences in the vicinity of colour centres.

Regarding the experience of Sth related to connectivity changes based on structural fMRI and EEG recording, the studies searched did not reach a valid conclusion [103].

Therefore, there is no clear evidence of structural brain changes in synesthetes, including differences in connectivity or local differences, despite most investigations using incorrect statistical models.

However, it is well established that there is no conclusive evidence to date regarding the neural correlates of the subjective experience of synesthesia, and the brain cortex of synesthetes is structurally and functionally like that of non-synesthetes [91].

Ward and Simner documented that it remains unclear whether Sth is one single condition or many, and it may

have a single cause or multiple independent causes, and they speculated that modulatory feedback pathways from the concurrent to inducers play a crucial role in the emergence of Sth [68] Dubová et al. studied ten healthy young people *via* sLORETA imaging obtained from EEG data converted into the sLORETA program and an accurate statistical model, and the results indicate that the summation of stimuli secured by interpersonal haptic contact changed by mirror illusion can activate the brain regions integrating sensory, motor, and cognitive functions, further areas related to communication and understanding processes, including the mirror neuron system [104].

An investigation performed with fMRI by Zhou et al. showed that the right supramarginal gyrus, left precentral gyrus, bilateral postcentral gyri, bilateral middle temporal gyri, and left supplementary motor area were significantly activated during sensory observation or somatosensory stimulation. These authors concluded that sensory observation can activate mirror neurons and sensorimotor network-related brain regions in healthy subjects, like somatosensory stimulation.

Conclusion

We afford some limitations for this systematic review that must be acknowledged. The main limitations were related to most of the data obtained from case reports and series, which may limit the generalizability of the findings and introduce bias.

We also found significant variability in the description of the pathogenesis of Sth. Therefore, this heterogeneity complicates the drawing of definitive conclusions based on the synthesis of data. The presence of bias towards reporting cases with severe or unusual presentations, leading to an overrepresentation of specific drug therapy associations with Sth in the literature.

Some limitations can arise in studying grapheme-colour Sth, irrespective of the design of the investigation. Self-reported Sth is a standard limitation across all publications. A remarkable proportion of the population may not be aware of their Sth. Participants in the investigation who are aware of their status may introduce bias to the study. They may consciously create their synesthetic mnemonics during the investigation, which can lead to skewed results. Memory performance can be affected by factors outside of Sth, such as cultural background, level of intelligence, and social factors.

Additionally, Sth is not a linear experience. Although many cases of grapheme-colour synesthesia exist, individuals may not experience it in the same way. Limitations also arise in this review structure. There were only xx studies that met the criteria. Further reviews should expand the criteria. Finally, most of the primary articles included in this review were conducted by the same or overlapping research groups.

Author Contributions

Both investigators have read and agreed to the published

version of the manuscript.

Conflict of Interest Statement

The authors declare they have no conflicts of interest.

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Ethics Statement

The study was conducted using the principles of the Helsinki Declaration, the Italian and US privacy and sensitive data laws, and the internal regulations for retrospective studies of the Otolaryngology Section at Padova University and Brescia University.

Informed Consent Statement

This review did not require informed consent.

Data Availability Statement

The corresponding author will make the raw data supporting this article's conclusions available upon request.

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