Systematic review

# Brain morphofunctional changes associated with pain in children, adolescents and young adults with sickle cell disease

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**ABSTRACT | INTRODUCTION:** Neuroimaging has been widely used to investigate the brain signature in patients with pain, but the results are heterogeneous, especially when the brain is under development, and in specific health conditions. Sickle cell disease (SCD) is often associated with chronic pain that starts in infancy, and there is a need to understand the brain of such children. **OBJECTIVES:** This systematic review aims to summarize the findings in the literature on brain morphofunctional changes in children, adolescents, young adults, and young adults with SCD. **METHODS**: Data search was performed in PubMed, LILACS, and SciELO, and results were organized to identify brain regions that showed significant structural and functional changes assessed through structural or functional MRI, or electroencephalography. **RESULTS:** The synthesis of five studies showed that children with SCD present decreased cerebral cortex thickness, and increased functional connectivity, mainly concentrated in the precuneus and anterior cingulate cortex, regions that make up the default mode network (DMN), and/or the pro-nociceptive network. **DISCUSSION:** These alterations were related to the frequency of pain and hospitalizations, and the increased connectivity in structures of the antinociceptive network is associated with a decrease in the frequency of pain crises and their consequences. **CONCLUSION:** Children, adolescents and young adults with SCD have decreased thickness and connectivity in the anterior cingulate cortex and precuneus.

**KEYWORDS:** Neuroimaging. Brain Morphofunctional Changes. Children. Adolescents. Young Adults. Sickle Cell Disease.

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## 1. Introduction

Sickle cell disease (SCD) is a genetic hemoglobinopathy resulting from a mutation in the β-globin gene characterized by hemolytic anemia, vaso-occlusive pain, and progressive organ failure. Vaso-occlusion is a multifactorial process involving the occlusion of small blood vessels by sickled red blood cells (RBCs), polymorphonuclear neutrophils, platelets, and activated endothelial cells. This blood vessel occlusive process leads to hypoxia and then ischemia, which is associated with local inflammation and pain.[1] Most children with SCD experience at least one pain crisis per year, and these have significant negative impacts, such as poor quality of life, more frequent school absences, depression, and damaged relationships.[2]

Pain is defined as an unpleasant sensory and emotional experience associated, or similar to that, with actual or potential tissue damage.[3] In SCD it can be acute or chronic, but frequently episodes of acute pain occur in the presence of chronic pain.[4] A recent consensus of experts suggests subdividing chronic pain in SCD into that associated with another identifiable cause, or that without an identified cause.[4] Acute pain episodes are abrupt in onset, unpredictable, and account for the largest number of emergency room admissions, although these episodes are often managed at home.[5] They increase in frequency with age, and chronic pain syndrome develops in 30% to 40% of adolescents and adults with SCD.[5]

Chronic pain involves several processes of neuronal plasticity that have not yet been decoded in terms of the involvement of specific circuits and cause-effect relationships[6], especially in the developing brain. An important feature of chronic pain is its sustained nature, which may involve brain regions related to cognitive and affective coping responses, in addition to sensory-discriminatory processes.[7] There is a consensus based on imaging studies that the origin of the painful sensation is not restricted to a single area, but that pain results from the integration of brain areas, forming specific brain networks.[8] Human studies of brain networks, or brain connectivity, began in the 1990s with the development of structural and functional techniques such as tractography[9], structural (MRI), and functional (fMRI) magnetic resonance imaging.[10] However, although they have special characteristics such as high fidelity to show brain structure in MRI and tractography and high spatial resolution in fMRI, they have none to a low possibility of showing brain activity with good temporal resolution.[10] Because of that, the brain imaging field has included other tools, such as quantitative electroencephalography (qEEG).[11] These techniques have been extensively used to assess the brain in pain, and are considered in this review.

The results of previous studies suggest that pain in children is associated with structural changes in the gray matter and that the magnitude of these structural changes is associated with the duration of pain.[9,12] Several brain regions must be involved, such as the posterior and anterior cingulate cortex, medial prefrontal cortex, precuneus, lateral temporal lobe, hippocampus, parahippocampus, medial prefrontal cortex, and insula. Furthermore, specific networks may be involved, such as the emotion regulation network (ERN), the sensorimotor network (SMN), and the default mode network (DMN).[13] However, categorizing patients just by having pain is too general, as each pain condition and associated factor can strongly influence brain imaging. Previous studies have investigated brain alterations associated with SCD pain in general[8,9,12,14,15], but no synthesis has been made on the alterations of brain structure and function in SCD children, which is an important gap in the literature. Particularities should be revealed to help in the understanding of the pathophysiology of SCD pain in children and to support more adequate treatments. Hence, the aim of this study is to summarize the results of brain imaging studies that used MRI, fMRI, EEG, or MEG to assess the brain characteristics of children with SCD pain.

## 2. Data collection and synthesis

### 2.1. Literature research process

A systematic review of the literature was carried out in PubMed, Latin American and Caribbean Literature in Health Sciences (LILACS), and Scientific Electronic databases. Library Online (SciELO) from March 2019 to December 2022. In addition, a manual search was performed by two reviewers in the references of the included studies. There was no date or language limitation. The following descriptors were used: sickle cell disease, child, brain connectivity, functional connectivity, and pain. This systematic review was previously registered under the number INPLASY2022120022 and with the DOI 10.37766/inplasy2022.12.0022.

### 2.2. Eligibility criteria and study selection

Studies were included in the current systematic review if they met each of the following eligibility criteria: a) they included children (0-9 years), adolescents (10-19 years old), young adults (20-24 years old), and young adults (25-29 years old) with SCD following the WHO/PNJ classification criteria[16]; b) examined pain intensity/frequency/duration and/or functional impairment of pain; c) examined brain connectivity; d) examined brain thickness; e) were quantitative studies; f) use magnetic resonance imaging, functional magnetic resonance imaging, electroencephalography, and magnetic resonance angiography as evaluation measures. Non-empirical articles (e.g., review articles, commentaries, practice guidelines, book chapters, case reports, dissertations, and conference abstracts) were excluded.

### 2.3. Data collection and extraction

The search and analysis of articles was performed independently by two reviewers (CVPM and LL). After the titles and abstracts of the studies were evaluated, those that did not meet the eligibility criteria were excluded, and disagreements were resolved by a third reviewer (AFB). The studies that met the predetermined criteria had their full text acquired for detailed analysis and data extraction. An electronic data extraction file was created to organize the relevant extracted data from each study. The extracted data pertains to the demographics of the participants, as well as the evaluated variables and the measures used.

### 2.4. Evaluation of the quality of the studies and risk of bias

To assess the risk of bias, the selected articles were analyzed following the Newcastle-Ottawa Scale with an assessment of eight items, categorized into three groups: 1) selection of study groups; 2) comparability of groups; 3) verification of the outcome of interest. The scale score ranges from four (minimum) to nine (maximum).[17]

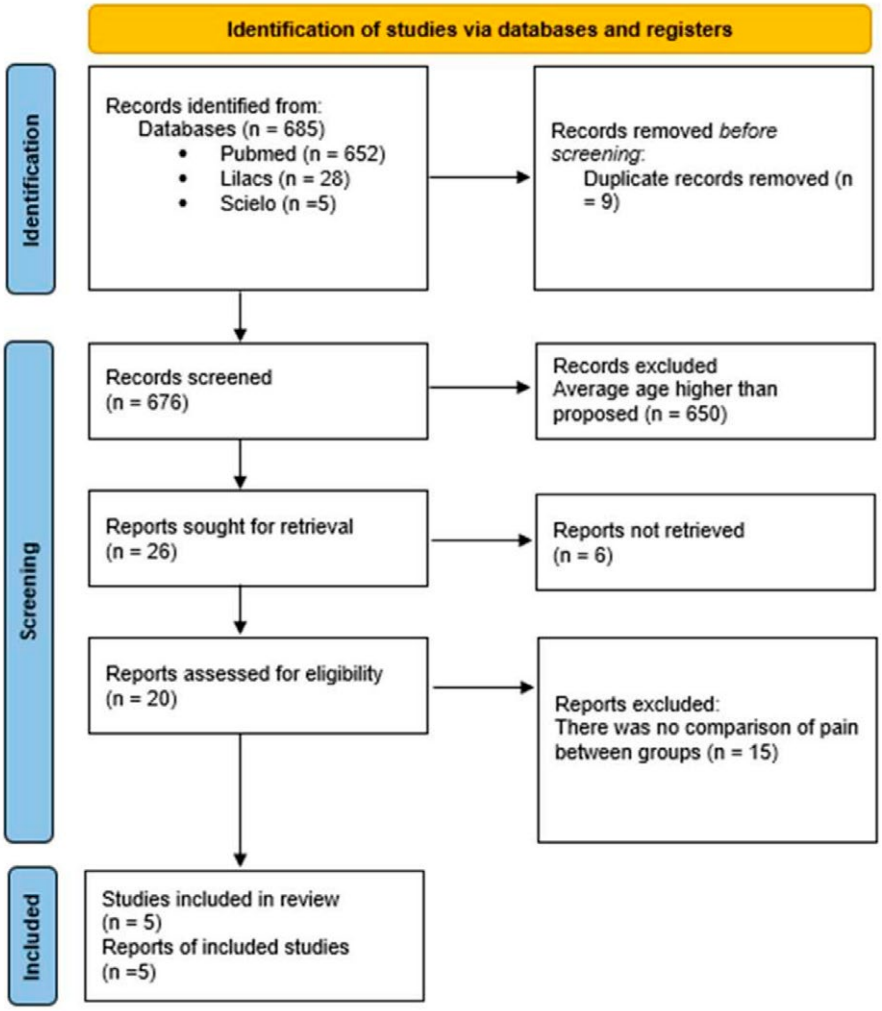
### 2.5. Literature synthesis

In the current review we identified brain regions that showed significant functional or structural changes in patients compared to control participants, or within patients between affected and unaffected sites. The reported brain regions were categorized into 14 regions of interest (ROIs) that are associated in previous studies with pain processing: anterior cingulate cortex, posterior cingulate cortex, ventromedial frontal cortex, insular cortex, primary motor cortex, right primary somatosensory cortex, subcortical pattern mode network, supratemporal gyrus, parahippocampus, right precuneus, posterior precuneus, medial prefrontal region, right prefrontal region, posterior calcarine region. Categorization was performed separately for positive changes (e.g., increased thickness, activity, or connectivity vs. control subjects) and negative changes (e.g., decreased thickness, activity, or connectivity in patients vs. control subjects).

## 3. Results

According to the search criteria, we initially identified 685 studies. Of these, 20 were selected for analysis after reading the abstract. We excluded others due to the presence of exclusion criteria, leaving a total of five studies that we selected for discussion. Bibliographic information on the articles selected for review and the reasons for excluding the studies are available in Figure 1.

**Figure 1.** Flow chart of selected studies




Source: the authors (2023).

Eligible articles were published between 2009 and 2021, using a cross-sectional design (100%), with good quality, ranging from 8 to 9 on the New-Casttle-Ottawa scale (Box 1). The funding source was reported in 100% of citations. The largest sample size was 40 children[12], and the lowest was 12[15] (25.4±12.95 children/study). In total, 127 children, adolescents and young adults with SCD, and 44 controls were evaluated. Girls (64.5%) were assessed more frequently than boys (Box 2). Box 2 describes the main characteristics of the five included studies. Functional Magnetic Resonance Imaging (fMRI) was the most frequently used modality, corresponding to 80% of the studies, and using full brain coverage. EEG, MRI, and MR angiography were also used. As covariates, the studies used age, gender, laboratory tests, amount of hemoglobin (Hb) in blood samples, correlation with fetal Hb, oxygen saturation ($SatO_2$), number of transfusions, use of hydroxyurea, cognitive assessment, number of hospitalizations in the last 12 months, history of stroke, vasculopathy or painful events, economic status, quality of life and type of SCD.

The authors proposed differences in brain regions related to pain perceptions (pro-nociceptive) and pain endogenous control (anti-nociceptive) (Box 3) between the control group, and the group of children, adolescents, and young adults with SCD. Measures involved basically cerebral cortical thickness and connectivity (Figure 1).

Box 1 shows the results of the quality assessment and risk of bias for the studies included in this review. Study scores ranged from 8 to 9.

**Box 1.** Results of the quality assessment of the studies and risk of bias using the Newcastle Ottawa Scale

| ARTICLE | SELECTION | COMPARISON BETWEEN GROUPS | RESULT | TOTAL |
|---|---|---|---|---|
| Colombatti, 2016 | 4 | 2 | 3 | 9 |
| Darbari, 2015 | 4 | 2 | 3 | 9 |
| Wang, 2021 | 4 | 1 | 3 | 8 |
| Case, 2019 | 4 | 1 | 3 | 8 |
| Zempsky, 2017 | 4 | 2 | 3 | 9 |

Source: the authors (2023).

**Box 2.** Experimental design of the included studies and neuroimage findings

| STUDY | SAMPLE (N) | AGE (mean ± SD) | GENDER | BRAIN IMAGING MODALITY | SIGN / technique | KEY FINDINGS |
|---|---|---|---|---|---|---|
| Colombatti et al., 2016 | DF (40)<br>Control (16) | DF (8.08 ± 2.83)<br>Control (9.98 ± 2.8) | DF (21M, 19F)<br>Control (5M, 11F) | fMRI at rest with DMN assessment | BOLD/ICA | ↑ connectivity on the precuneus |
| Darbari et al., 2015 | Low pain (14),<br>high pain (8) | Low pain (17 [12–20]),<br>High pain (18.5 [13–22]) | Low pain (5M, 9F),<br>High pain (2M, 6F) | fMRI at rest | BOLD/ICA | Participants with more severe pain had ↑ connectivity of the dorsolateral/medial ACC (pro-nociceptive network) to default mode network structures (right precuneus and inferior parietal lobe). Participants with less severe/frequent pain had ↑ connectivity in the subgenual cingular cortex and somatosensory cortex<br>(anti-nociceptive network) |
| Wang et al., 2021 | DF (38) | 11.45±3.31 | 14M, 24F | MRI | Voxel based morphom etry | pACC GMV was negatively associated with pain crisis frequency. The subgroup with pain crisis in the last year had ↓ GMV in the left supratemporal gyrus in comparison with the group without pain crisis. There was a negative correlation between pACC and sACCv, GMV and the frequency of pain crises. |
| Case et al., 2019 | DF (15),<br>Controls (16) | less severe (21.4±5.7)<br>more severe (21.7±6.3) | severe 8F, 7M;<br>more severe 7F, 9M | EEG e fMRI | theoretic al analysis graphs | fMRI: The most severe group had lower local efficiency and the clustering coefficient was decreased in the Beta-1 band in patients, compared to the control group. These results were more pronounced in patients with more severe pain. Path length was positively correlated with the number of hospitalizations, while small-world and global efficiency showed the opposite correlation. More severely ill patients resulted from decreased crowding throughout the brain, including regions in the frontal cortex, temporal cortex, parietal cortex, occipital cortex, and subcortical regions. SCD patients demonstrate altered network behavior in memory-related regions, such as the cerebellum, parahippocampus and prefrontal cortex, cerebellum, parahippocampus, prefrontal cortex |
| Zempsky et al., 2017 | DF (12),<br>Controls (12) | DF 22.8 (4.3),<br>Controls 20.5 (4.6) | 3M, 9F | fMRI | BOLD/ICA | Abnormalities in SCD patients in the brain's somatosensory network, salience network and default mode network during an unstructured resting state |

Abbreviations: ACC - Anterior Cingulate Cortex; BOLD - Blood Oxygen Level-Dependt; EEG - electroencephalography; GMV - gray matter volume; ICA - Independent Component Analysis; fMRI functional Magnetic Ressonance Imaging; MRI - magnetic resonance imaging; pACC - perigenual anterior cingulate cortex; sACC - subgenaul anterior cingulate cortex.
Source: the authors (2023).

**Box 3.** Brain Connectivity versus cortical thickness

| STUDIES ON THICKNESS | FINDINGS |
|---|---|
| Wang, 2021 | 1. Thickness of the anterior cingulate cortex was negatively associated with frequent bouts of pain 2. Decreased gray matter in the left supratemporal gyrus in the pain group 3. Decreased gray matter in the parahippocampus |
| Case, 2019 | 1. Decreased white and gray matter compared to the control group |
| **CONNECTIVITY STUDIES** | **FINDINGS** |
| Colombatti, 2016 | 1. Increased Default Mode Network connectivity in posterior precuneus in patients compared to controls<br>2. Increased connectivity in the Default Mode Network in the medial prefrontal region, in patients with normal verbal IQ compared to controls<br>3. Increased Default Mode Network connectivity, in the right prefrontal region, in normal MRI patients compared to controls<br>4. Increased connectivity in the posterior calcarine sulcus in patients with 97% SaO2 compared to patients with higher ox |
| Darbari, 2016 | 1. Increased central connectivity compared to the low pain group between the dorsal anterior cingulate cortex and the precuneus D; between the secondary somatosensory cortex and the left precuneus; between the inferior parietal lobe and the middle cingulate cortex; between the right posterior insular cortex and the right primary somatosensory cortex<br>2. The standard mode network showed greater negative connectivity (anti-correlation) with the anterior insula in the low-pain group compared to the high-pain group<br>3. The network emphasizes less negative connectivity with the perigenual anterior cingulate cortex in the low-pain group compared to the high-pain group 4. The low pain group exhibited a negative correlation between HbF% and connectivity between the secondary somatosensory cortex and the left precuneus<br>4. The low pain group had a positive correlation between the level of connectivity between the salience network and the perigenual anterior cingulate cortex and fetal hemoglobin levels |
| Case, 2019 | 1. Pain intensity related to lower clustering coefficient and local efficiency<br>2.EEG source imaging demonstrated that controls differed significantly from patient groups in the beta1 band.<br>3.Altered network behavior in memory-related regions such as the cerebellum, parahippocampus and prefrontal cortex |
| Zempsky, 2017 | Change in precuneus and CCA in addition to other regions of the standard mode, salience and somatosensory network |

Source: the authors (2023).

**Box 4.** Brain regions with connectivity alteration in children, adolescents and young adults with SCD (to be continued)

| BRAIN REGION | **Wang 2021** | **Case 2019** | **Colombatti 2016** | **Darbari 2015** | **Zempsky 2017** |
|---|---|---|---|---|---|
| **Network Standard Mode** | | | | | |
| MEDIAL CINGULAR CORTEX | | | | | ↓ |
| ANTERIOR CINGULAR CORTEX | ↓ | | | ↑ | ↑ |
| PRECUNEUS RIGHT | | | ↑ | ↑ | ↓ |
| PRECUNEUS LEFT | | | ↑ | ↑ | ↓↑ |
| LEFT ANGULAR TURN | | | | | ↑ |
| UPPER LEFT FRONT SWING | | | | | ↓↑ |
| UPPER RIGHT FRONT TURN | | | | | ↑ |
| LOWER LEFT FRONT TURN | | | | | ↓ |
| LEFT MEDIAL FRONT TURN | | | | | ↑ |
| LOWER FRONT TURN | | | | | ↓ |
| RIGHT MEDIAL TEMPORAL TURN | | | | | ↑ |
| RIGHT MEDIAL TEMPORAL TURN | | | | | ↑ |
| UPPER RIGHT MEDIAL TURN | | | | | ↑ |
| CALCARINE TURN | | | ↑ | | ↑ |
| PARAHIPOCAMPO | | ↓ | | | |
| RIGHT INSULA | | | | | ↓ |
| **Saliência Network** | | | | ↑ | |
| ÍNSULA ANTERIOR | | | | ↑ | |
| DORSAL ANTERIOR CINGULATED CORTEX | | | | ↑ | |
| RIGHT MEDIAL FRONT TURN | | | | | ↓↑ |
| LOWER LEFT FRONT TURN | | | | | ↑ |
| RIGHT SUPRAMARGINAL TURN | | | | | ↓ |

**Box 4.** Brain regions with connectivity alteration in children, adolescents and young adults with SCD (conclusion)

| BRAIN REGION | **Wang 2021** | **Case 2019** | **Colombatti 2016** | **Darbari 2015** | **Zempsky 2017** |
|---|---|---|---|---|---|
| UPPER LEFT MEDIAL GROUP | | | | | ↑ |
| LEFT INFERIOR PARIETAL LOBE | | | | ↑ | ↓ |
| **Somatosensorial Network** | | | | | |
| LEFT PRE-CENTRAL TURN | | | | | ↓ |
| RIGHT PRE-CENTRAL TURN | | | | | ↓ |
| LEFT MEDIAL FRONT TURN | | | | | ↑ |
| LEFT LOWER/MEDIAL FRONT TURN | | | | | ↑ |
| RIGHT SUPRAMARGINAL TURN | | | | | ↑ |
| ROLANDIC OPERCULUM | | | | | ↓ |
| **DlPFC *** | ↑ | ↓ | ↑ | | |
| **Cerebelum** | | ↓ | | | |
| **White substance** | | ↓ | | | |
| **Gray matter** | ↓ | ↓ | | | |

Source: the authors (2023).

As a secondary finding, we observed that the greater the age of the child, the greater the reported intensity of pain for adolescents with SCD. Generally, in adolescence, there is an increase in the frequency of painful crises, longer hospital stays, and the onset of chronic pain.

## 4. Discussion

This study sought to identify patterns of structure and/or abnormal functional activity in the brain of children, adolescents, and young adults with SCD through a systematic review of the literature. The results of cross-sectional studies show a decrease in cortical thickness and an increase in functional connectivity mainly concentrated in the precuneus and anterior cingulate cortex, regions that make up the Default Mode Network (DMN) and/or the Pro-nociceptive Network. These alterations are related to the frequency of pain and hospitalizations and the increased connectivity in structures of the Antinociceptive Network is associated with a decrease in the frequency of pain crises and their consequences.

From the point of view of brain networks, the precuneus and the anterior cingulate cortex are included in the DMN. The precuneus is a region often associated with pain processing[18] showing a decrease in its thickness in individuals with SCD and frequent pain crises.[8,12] This region is involved in sensorimotor, cognitive and visual coding and is related to individual differences in pain sensitivity.[19] As precuneus connectivity is able to reflect the brain maturation that occurs from childhood to adulthood[20] and the studies included in this review compared participants with and without PD, with and without pain complaints, it is possible to suggest that the presence of pain can increase connectivity in this region through neurodevelopment. This can also characterize a specific signature for this type of clinical condition and a possible target for interventions. Alterations in the thickness, activity and connectivity of the anterior cingulate cortex are present in both acute and chronic pain in general[21], being eminently involved in affective processing and coding of pain intensity.[22] Synaptic changes in this region seem to be crucial for the transition from acute to chronic pain.[23] Its link with pain control areas such as the periaqueductal gray suggests that, in addition to being able to contribute to negative modulation, it may also contribute to endogenous pain control.[23] Being an area in the executive control of attention, emotions and social cognition[24] its maturation is especially important in the first or second decade of life.[25] The abnormal development of this area has already been associated with neurodevelopmental disorders, such as attention deficit hyperactivity disorder[26] and autism[27], which highlights the possibility that the presence of pain since childhood in individuals with PD may have negative impacts. Far beyond suffering but involving fundamental cognitive and emotional functions for a quality life.

The findings of this study may suggest differences between the brains of adults and children/adolescents with PD and chronic pain. In adults with chronic pain, more brain networks are compromised, such as the salience network, more areas of the default mode network, and the sensorimotor network. Adults with PD who experience high levels of pain and hospitalizations have shown increased functional connectivity at rest between the salient structures (SLN), in the default mode network (DMN) and sensorimotor network (SMN) when compared to individuals with low pain levels and hospitalizations.[28] Zempsky et al.[15] demonstrated hyperconnectivity of several regions of the frontal lobe, more specifically in the precuneus and posterior cingulate cortex; and Case et al.[14] also demonstrated that DMN increased connectivity with sensory regions in individuals with SCD. In the study carried out by Veldhuijzen[29], brain responses to painful stimuli and cognitive tasks did not show variation during the menstrual cycle with the precuneus, the PCC and the inferior parietal cortex. Comparison of brain alteration findings between adults and children/adolescents with SCD and pain suggests that there is less brain impairment in children compared to adults, which needs to be demonstrated in longitudinal studies.

Finally, this study shows that functional connectivity has the potential to aid in the diagnostic classification of different pain conditions, which can predict individual responses to specific therapeutic interventions and serve as a gateway to personalized medicine.[30] The small number of studies and their cross-sectional designs limit the assertion that all brain alterations found in our study are a consequence of pain in this specific population. Furthermore, it is very difficult to group children, adolescents, young adults, and young adults with SCD with a history of pain in the same study. Another limitation is related to the neuroimaging methods used. Most of the included studies used structural and functional magnetic resonance imaging as an investigation method and only one study, with a mean age corresponding to young adults, used EEG. Due to the heterogeneity of the studies, it was not possible to carry out a quantitative synthesis of the results of the included studies through a meta-analysis. It is suggested that future studies use strategies such as quantitative electroencephalography and near-infrared spectroscopy to assess brain activity in children, as well as to longitudinally assess alterations in the presence of pain in individuals with SCD.

## 5. Conclusion

Children, adolescents, and young adults with SCD have decreased thickness and connectivity in the anterior cingulate cortex and precuneus.

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## Authors' contributions

Marques C worked in the elaboration of the research question, literature search, article selection, data extraction, methodological quality assessment, evidence quality assessment, manuscript writing and submission. Lopes L participated in the literature search, article selection and data extraction. Lucena R contributed to the elaboration of the research question and final review of the manuscript. Baptista A worked in the elaboration of the research question, literature search, assessment of the quality of evidence, writing and in the submission of the manuscript.

## Conflicts of interest

Abrahão Baptista and Rita Lucena are members of the Brain Imaging and Stimulation editorial team.

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