Alteration of grey matter volume is associated with pain and quality of life in children with sickle cell disease

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Pain is the most common symptom experienced by patients with sickle cell disease (SCD) and is associated with poor quality of life. We investigated the association between grey matter volume (GMV) and the frequency of pain crises in the preceding 12 months and SCD-specific quality of life (QOL) assessed by the PedsQL™ SCD module in 38 pediatric patients with SCD. Using voxel-based morphometry methodology, high-resolution T1 structural scans were preprocessed using SPM and further analyzed in SPSS. The whole brain multiple regression analysis identified that perigenual anterior cingulate cortex (ACC) GMV was negatively associated with the frequency of pain crises (r = -0.656, P = 0.003). A two-group t-test analysis showed that the subgroup having pain crisis/crises in the past year also showed significantly lower GMV at left supratemporal gyrus than the group without any pain crisis (p=0.024). The further 21 pain-related regions of interest (ROI) analyses identified a negative correlation between pregenual ACC (r = -0.551, P = 0.001), subgenual ACC (r = -0.540, P = 0.001) and the frequency of pain crises. Additionally, the subgroup with poorer QOL displayed significantly reduced GMV in the parahippocampus (left: P = 0.047; right: P = 0.024). The correlations between the cerebral structural alterations and the accentuated pain experience and QOL suggests a possible role of central mechanisms in SCD pain. (Translational Research 2022; 240:17–25)

Abbreviations: SCD = sickle cell disease; MRI = magnetic resonance imaging; GMV = grey matter volume; QOL = quality of life; VBM = voxel-based morphometry; SPM12 = Statistical Parametric Mapping; DARTEL = diffeomorphic anatomical registration through exponentiated lie algebra; ROI = region of interest; IPL = inferior parietal lobule; MCC = middle cingulate cortex,; MIC = mid insula cortex; PIC = posterior insula cortex; pgACC = perigenual anterior cingulate cortex; PCC = posterior cingulate cortex; SCI = silent cerebral infarcts; sgACC = subgenual anterior cingulate cortex

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At A Glance Commentary

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Background

Pain is the most common morbidity associated with sickle cell disease (SCD), which remains inadequately treated. Improved understanding of mechanisms and identification of novel endpoints is needed to develop better pain management strategies for patients with SCD.

Translational Significance

Pathobiology of SCD affects brain, however its relationship with pain has not been fully evaluated. Present study provides the evidence that pain and quality of life in SCD youth is associated with brain morphological changes. Changes we describe in this report points to pathways involved in SCD pain experience and may have potential to serve as objective endpoints to be used in SCD pain research.

INTRODUCTION

Pain, both acute and chronic, is one of most common complications observed in patients with sickle cell disease (SCD). Episodes of acute pain can start as early as 6 months of age and are commonly known as vaso-occlusive pain crises. Starting in adolescence, some individuals with SCD develop chronic pain and can also continue to experience recurrent episodes of acute pain superimposed on background of chronic pain. While most episodes of acute pain are managed at home, severe pain crises may require a visit to an acute care facility such as an infusion center, emergency department or hospitalization for pain management. The high frequency of pain in SCD is associated with poor quality of life (QOL)[1-3] Despite recent advances in SCD management, pain control primarily relies on opioids and remains inadequate for many patients. An improved understanding of the mechanisms of pain in SCD is needed to develop targeted therapies and improve the QOL of individuals with SCD. Additionally, there is a need for novel endpoints which can be used to evaluate the effectiveness of pain-directed therapies.[4]

Similar to many chronic pain disorders, central mechanisms of pain have been proposed to play an important role in pain in SCD.[5] Experimental studies in an SCD mouse model have also shown amplified central sensitization in the spinal cord.[6] Neuroimaging studies exploring functional resting state brain activity/connectivity have observed alterations in several brain regions in SCD[7-9] and many of these regions such as the primary and secondary somatosensory cortex, default mode network, and insula have been implicated in experimental and clinical pain conditions with underlying central sensitization mechanisms.[10-13] Our earlier study showed that patients with SCD with higher frequency of pain crises display greater functional connectivity in pronociceptive areas, whereas patients with lower frequency of pain crises display more activity in antinociceptive structures including perigenual and subgenual cingulate cortex.[14]

Morphological changes in neuroimaging studies have been observed in pain conditions such as chronic back pain, phantom limb pain, head and facial pain, fibromyalgia, and neuropathic pain.[15,16] A wide range of grey matter structural changes have been reported in pain syndromes as well, primarily involving cingulate cortex, the orbitofrontal cortex, the insula, dorsal pons, bilaterally thalamus, basal ganglia, and parahippocampus.[15,17] Voxel-Based Morphometry (VBM) is an imaging technique used to assess changes in brain anatomy[18] that has been used to study a variety of pain conditions. This methodology has provided considerable insight into structural brain reorganization among subjects suffering from chronic pain.[15,19,20] The results of previous VBM studies suggest that chronic pain induces grey matter structural changes and the magnitude of structural changes is associated with pain duration.[21] In addition to functional changes, structural brain alterations, especially in grey matter volume (GMV), have been observed across multiple pain conditions.[22] Structural alterations of the brain and their association with pain outcomes have not been thoroughly examined in pediatric SCD; however, there is evidence to suggest structural changes occur in this population. For instance, one study showed that individuals with SCD with silent cerebral infarcts (SCI) had widespread bilateral white matter volumetric abnormalities.[23] Therefore, given that SCD carries independent risk for neurologic injury as well as development of chronic pain, SCD presents a unique model for exploring associations between brain structure and pain outcomes.

In the present study, we investigated structural alterations in GMV and their association with the number of pain crises in the preceding 12 months (frequency of pain crisis) and QOL in a group of children and adolescents with SCD. We hypothesized that morphological alteration of GMV is associated with the frequency of pain crisis and QOL score.

MATERIALS AND METHODS

Study population and eligibility criteria. Data for the current investigation were extracted from two prior

studies involving youth with SCD who participated in a computerized cognitive training intervention.[24] Participants were recruited from a hematology clinic in a large urban pediatric hospital in the eastern United States. Only baseline data (prior to intervention) were used in the current analyses. All participants were in steady state at enrollment. No patients were experiencing acute pain episodes at the time of MRI acquisition or completion of patient/parent-reported questionnaires. To be eligible for the original studies, participants were required to have a diagnosis of SCD and be between ages 7 and 16 years (n = 112). Other eligibility criteria for the studies included: 1) no significant visual, motor, or auditory impairment that would interfere with ability to complete computer-based cognitive tests, 2) no recent (30 days) initiation or dose adjustment of a stimulant medication. For the current analyses, participants were only included if they had undergone a steady state brain MRI scan within 12 months before or after study enrollment. In cases where more than one MRI scan had been conducted, the scan closest to study enrollment was used. Data from 38 participants were included for final analyses (Fig 1). The study was approved by the Institutional Review Board at Children's National Hospital and conformed to the relevant ethical guidelines for human subjects' research. All parents provided written informed consent.

ASSESSMENT OF PAIN CRISES AND SCD-RELATED QUALITY OF LIFE

In the present study, parents of the participants reported the number of SCD-related pain crises that their children had experienced in the past 12 months and this variable was used as the primary outcome.[25] Vaso-occlusive pain crises are viewed as the hallmark symptom of SCD. Individual pain experiences as well as the management of pain in SCD can be quite varied. Many acute pain events in patients with SCD are managed at home without physician contact, thus using caregiver reports of the number of crises allowed us to quantify experiences of pain that were treated in the ED or an inpatient unit as well as those episodes managed at home.

SCD-related QOL was used as the secondary outcome which was measured using the child-report version of the PedsQL™ SCD Module. Individuals with

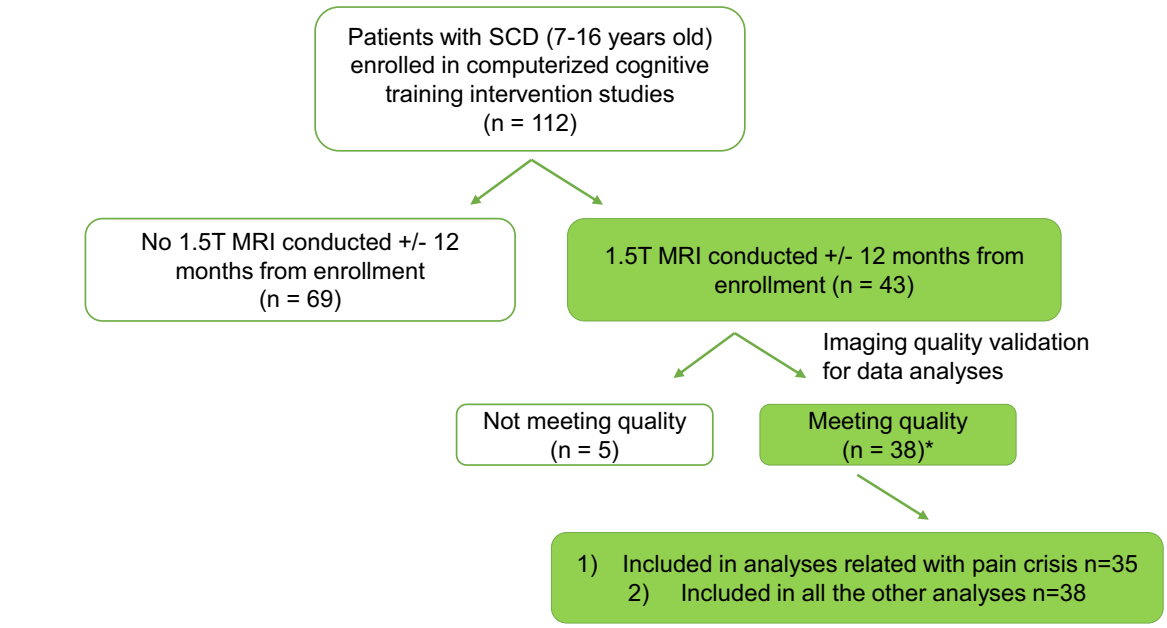

Fig 1. Schematic flow of participants enrollment and data analyses. Data from 38 participants with SCD were adopted for final analyses. The 38 participants were screened from the 43 of initially 112 enrolled participants who were enrolled in earlier larger computerized cognitive training interventional studies and met the criteria of study eligibilities. The 43 participants extracted from electronic health record had either received or were eligible to receive 1.5 T MRI scan(s) within 12 months before and after the enrollment. There are additional 5 participants' T1 weighted imaging datasets were excluded due to the quality of images during the MRI acquisition, as well as missing reports of the number of pain crisis in 3 subjects. Abbreviations: SCD = sickle cell disease.

SCD have varied pain experiences that can be either acute or chronic in presentation or a combination of acute and chronic pain[26]; pain is known to negatively impact both physical and psychosocial functioning and reduce QOL in SCD.[27] In addition, evidence suggests potential consequences of long-term opioid usage on QOL.[28] We therefore used the PedsQL^{TM} SCD Module total score to assess the impact of SCD and pain on QOL and examined its correlations with brain structural changes in GMV. The PedsQL^{TM} SCD Module evaluates QOL across functional domains primarily related to pain (e.g., the frequency of pain crisis, pain interference with daily activities, difficulty controlling pain, pain-related anxiety), and also asks about other SCD-related issues, such as problems with emotions, worries, and communication.[4] A total of 9 domains are used to calculate an overall QOL score (QOL Total) for the PedsQL^{TM} SCD Module, with higher scores representing better QOL and, depending on the domain, fewer pain-related difficulties.

MRI acquisition. Images were obtained in a 1.5-T GE Discovery MR450 whole-body magnetic resonance imaging scanner (GE Healthcare, Milwaukee, WI) with one 60 cm another 70 cm bore, 32-channel optical RF-receiver chain, gradient system of 50 mT/m amplitude and 200 T/m/s slew rate, and a 8-channel receive-only head coil array (GE Healthcare, Milwaukee, WI).

Structural high-resolution data were acquired using a 3-dimensional inversion-prepared fast spoiled gradient echo T1-weighted pulse sequence (TR/TE = 11.4/5.2 milliseconds, inversion time = 500 milliseconds, flip angle = 20°, FOV = 512 × 512 mm^2, acquisition matrix = 512 × 512, voxel size = 0.43 × 0.43 × 1.5 mm^3, and 124 slices).

Data preprocessing. Voxel based morphometry T1-weighted images were first oriented to the anterior-posterior commissure, then bias corrected to correct for inhomogeneity of spatially varying artifact that modulates the intensity of the image, and finally segmented into grey matter (GM), white matter (WM), and cerebral spinal fluid using the segment function in SPM12 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK) software package running under MATLAB 2018a (MathWorks Inc, Natick, MA). Resulting GM segmented images were then processed using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) toolbox in SPM12.[29] DARTEL increases accuracy of inter-subject alignment by modeling the shape of each participant's brain using millions of parameters (three parameters per voxel). DARTEL works by aligning GM among the images, while simultaneously aligning white matter. Thus, an increasingly high-resolution average template was created to which the data were then aligned.[29] Data were then normalized to a standard brain in Montreal Neurological Institute space. Spatial normalization expands and contracts some brain regions, thus the images were modulated involving scaling by the amount of contraction, so that the total amount of GM in the modulated image remains the same as it would be in the original images. Normalized, modulated images were then smoothed with a Gaussian kernel of 8 mm full-width, half-maximum.

Data analyses summarization. In the present study, the primary outcome is the parents' reported frequency of pain crisis. The child-reported PedsQL^{TM} SCD Module total score was used as the secondary outcome for assessing SCD-related QOL. For the whole brain two-sample t-test using the primary outcome, we divided participants into two subgroups: with or without pain crisis in the past 12 months. For the whole brain two-sample t-test using the secondary outcome, we used a median split to divide participants into two subgroups: high or low QOL. Using a dichotomization rather than trichotomy (high-intermediate-low QOL score) classification conserved more power for each group due to the small sample size.

To explore the correlation of GMV and pain-related outcomes, we performed the following major analyses: 1) whole brain multiple regression analyses with 5 predictors (one predictor was GMV and four covariates included age, gender, presence of infarct and total intracranial brain volume) and 1 variable of primary outcome using SPM (Fig 2A), 2) whole brain two-sample t-test for the with or without pain crisis subgroups using SPM (Fig 2B), 3) Pearson correlation analyses between each of the 21 pain-related ROIs (*supplementary Table 2*) and the primary outcome using SPSS (Fig 3), and 4) whole brain two-sample t-test for the higher or lower QOL subgroups using SPM (Fig 4)

Whole brain GMV and association with the number of reported pain crises. A whole brain multiple regression analysis was performed by regressing GMV on frequency of pain crises with age, gender, presence of infarct and total intracranial brain volume as covariates. Smoothed, modulated, and warped GM images were entered into a multiple regression model in SPM12 with the previously mentioned covariates. An absolute threshold mask of 0.1 (that is voxels with GM values <0.1 were excluded from the analysis) and was applied to avoid possible edge effects around the border between GM and WM and to include only relatively homogeneous voxels.

We then chose to perform a small volume correction for the hippocampus as it has been previously shown to have decreased GMV in patients with SCD compared to controls.[30] Small volume correction was applied using bilateral hippocampus seeds as defined by the

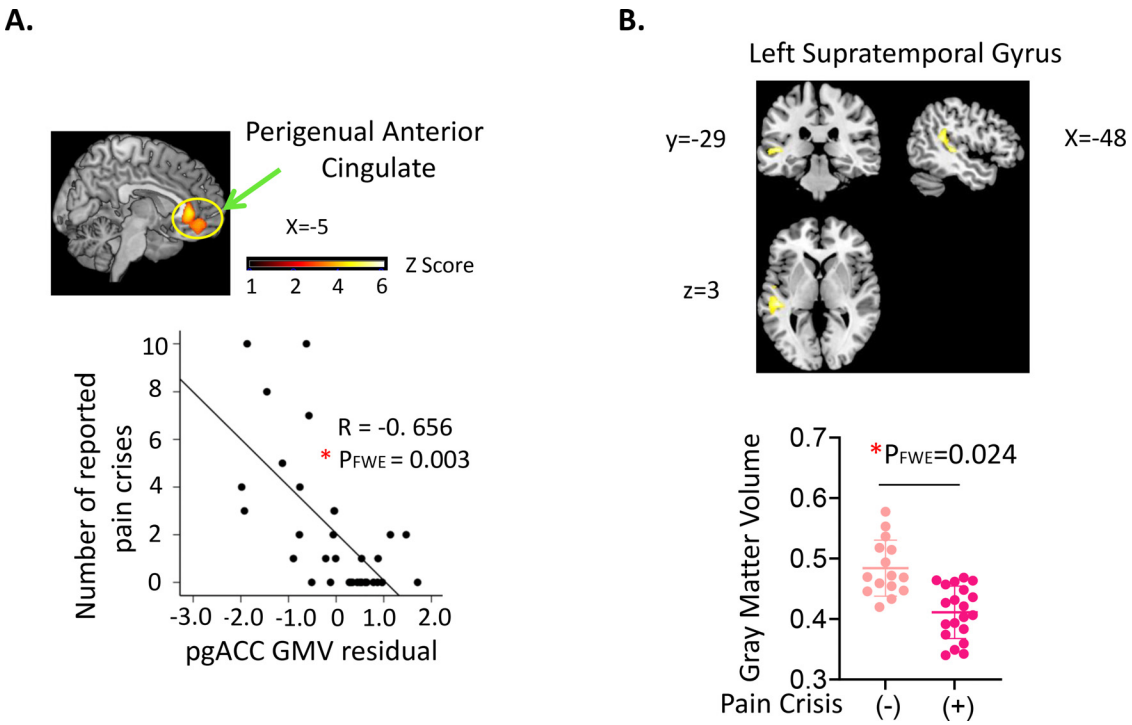

Fig 2. Correlation between whole-brain volume pattern and the number of reported pain crises. (**A**) Correlation between the frequency of pain crisis and whole-brain GMV was analyzed using multiple regression analysis with including age, gender, presence of infarct and total brain volume as covariances. The region pgACC shows less volume when patients report having pain crises more frequently. A negative correlation is shown between pgACC and the frequency of pain crisis (r =-0 .656, P_{FWE} = 0.003). (**B**) Further whole-brain GMV analysis between the two groups with (Pain Crisis (+)) or without (Pain Crisis (-)) reported pain crisis is significantly differentiated in left supratemporal gyrus (P = 0.024). Abbreviations: GMV = grey matter volume; pgACC = perigenual anterior cingulate cortex. Results for whole brain analyses were considered as significant at P-value < 0.05.

Aseg atlas from FreeSurfer[31] and also used in our previous study[32] Results were deemed significant corrected for multiple comparisons with a cluster level family-wise error (FWE) p < 0.05 derived from a voxel level uncorrected P-value < 0.001.

Furthermore, a two-group t-test whole brain analysis was performed in SPM by dividing the subjects into subgroups with (n = 20, with average age of 11.85 ± 3.12 years) or without (n = 15, with average age of 10.46 ± 3.35 years) the occurrence of pain crisis in the

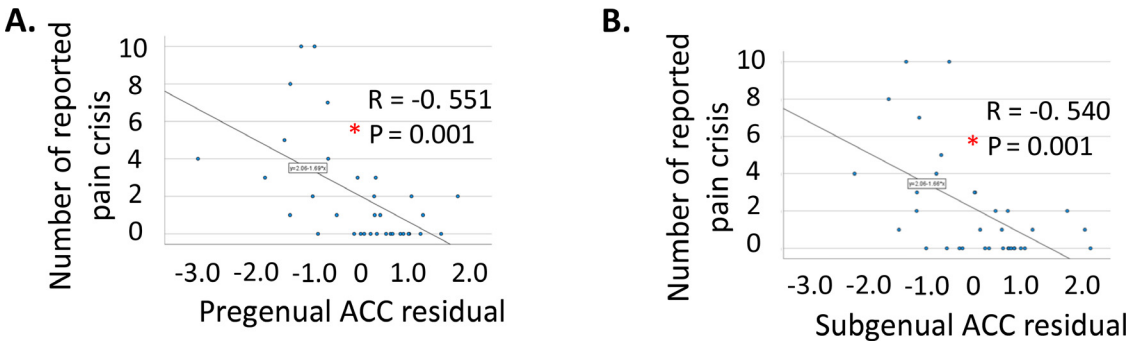

Fig 3. Gray matter volume in targeted ROIs negatively associates with the number of reported pain crises. The correlation between the frequency of pain crisis and the brain volume of priori seed regions at 21 ROIs spherical seeds with 5 mm radii were analyzed using multiple regression with including age, gender, presence of infarct and total brain volume as covariances. A significantly negative correlation was observed in 2 ROIs including (**A**) the pregenual ACC (x = 0, y = 40, z = 0) and (**B**) subgenual ACC (x = -3, y = 32, z = -8). Results for ROI analyses were considered as significant at P -value < 0.0024 with Bonferroni correction.

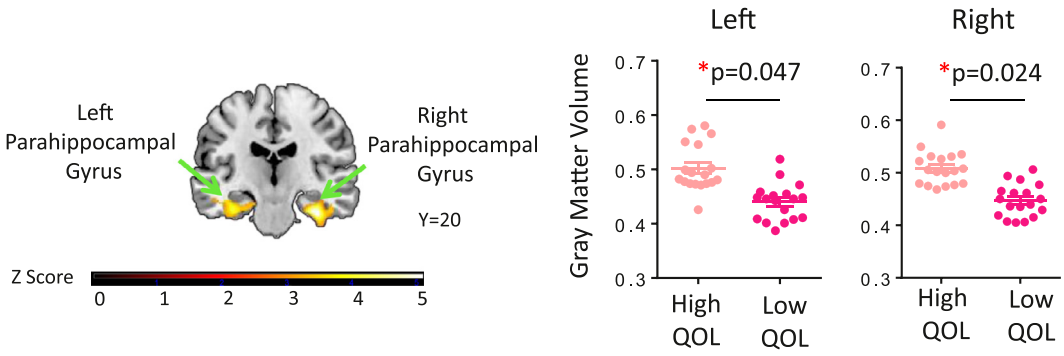

Fig 4. Grey matter volume in parahippocampal gyrus is reduced in children with SCD with lower QOL. Participants were grouped into high or low SCD-related QOL subsets using median split according to the child-reported PedsQL-SCD Module. The whole brain analysis with two-sample t-tests (unpaired, two tailed) showed significant difference between the two groups at the regions of left (P = 0.047) and right (P = 0.024) parahippocampal gyrus in participants with less pain. Results for whole brain analyses were considered as significant at P-value < 0.05. Abbreviations: QOL, quality of life.

past 12 months to explore the regions with volumetric change possibly due to the reoccurrence of pain crisis.

Seed-based region of interest (ROI) correlates of the number of reported pain crises. A priori seed-based ROI analyses were performed using 21 regions with 5mm radius spheres reported in our previous investigations in patients with SCD or fibromyalgia.[14,32-35] These regions include the left and right precuneus, right primary somatosensory cortex, middle cingulate cortex (MCC), three anterior cingulate cortex (ACC, including the ventral ACC, the pregenual ACC and subgenual ACC) regions, left and right amygdala, left and right anterior insula cortex (AIC), two left and two right dorsolateral prefrontal cortex (DLPFC) regions, left and right mid insula cortex (MIC), left and right posterior insula cortex (PIC), left inferior parietal lobule (IPL) and posterior cingulate cortex (PCC). GMV were extracted using the MarsBar ROI toolbox for SPM[36] and correlated using bivariate correlations with pain measures in SPSS controlling for age, gender, presence of infarct, and total brain volume as covariates.

We used Bonferroni's correction to control the familywise type-1 error rate at 0.05 for investigating 21 ROIs. Results for all the ROI analyses were thus corrected as significant at P-value < 0.0024.

Discovering GMV correlates of SCD-related quality of life score. A whole brain multiple regression analysis was performed by regressing GMV on the child-reported QOL score with age, gender, presence of infarct, and total intracranial brain volume as covariates. Results deemed significant were corrected for multiple comparisons with a cluster level PFWE < 0.05 derived from a voxel level uncorrected P -value < 0.001. Participants were then divided into high (n = 19, with average age of 11.51 ± 3.05 years) and low (n = 19, with average age of 11.39 ± 3.63 years) SCD-related QOL groups via a median split. A two-sample t-test whole brain analyses using a general linear model in SPM12 was performed between high and low SCD-related QOL groups with age, gender, total brain volume, and presence of infarct as covariates. In further analyses, we also explored the GMV differences of the 21 targeted ROIs mentioned above between groups with higher or lower QOL scores.

RESULTS

Patient demographics. 43 among the initially enrolled 112 participants underwent a T1 weighted brain MRI scan within 12 months before or after study enrollment. Assessment of imaging quality further excluded scans from 5 participants (Fig 1). Qualified data from the remaining 38 participants (ages 7−16 years) with an average age of 11.45 ± 3.31 years (Table 1) were used for final analyses. Among the 38 participants, data for pain crisis frequency were missing in 3 participants (n = 35 for the frequency of pain crisis). Due to the large variations in participants' numbers of pain crises, we assessed the normality with Kolmogorov-Smirnov and Shapiro-Wilk, and also performed Grubbs' test for outlier. One parent who reported 25 crises in the past 12 months was considered as the sole outlier. The data of that participant was excluded from the multiple regression whole brain analyses (Fig 2A) and all the correlation analyses (Fig 3), but we kept it in two-sample t-test analysis (Fig 2B).

GMV association with the number of reported pain crises. A whole brain multiple regression analysis with age, gender, presence of infarct and total brain volume as covariances showed a negative correlation between perigenual anterior cingulate cortex (pgACC) GMV and the frequency

Table 1. Demographics

Subjects Characteristics (n = 38)	
Age (mean ± SD, years) (range)	11.45 ± 3.31 (6.7 - 17.25)
Females, n (%)	24 (63)
Height (cm) (mean ± SD) (range)	142.82 ± 16.41 (121.3 - 169)
Weight (kg) (mean ± SD) (range)	40.17 ± 18.72 (21 - 104)
SCD genotype (HbSS or HbS-Beta0 thalassemia), n (%)	36 (95)
Hgb, g/dL (mean ± SD) (range)	9.05 ± 1.23 (7.00 – 12.30)
Silent Cerebral or other infarct, n (%)	20 (53)
Chronic transfusion therapy, n (%)	18 (47)
Average years of transfusion therapy (mean ± SD) (range)	4.4 ± 2.61 (0.8 – 8.89)
Hydroxyurea treatment, n (%)	18 (47)
Parent-reported number of pain crisis in the preceding 12 months (mean ± SD, *n* = 35) (range)	2.71 ± 4.81 (0 - 25)
Child-reported sickle cell disease-related quality of life total score (median / IQR) (range)	65.00 / 27.18 (30.23 - 100)

of pain crisis (r =-0.656, $P_{FWE} = 0.003$) – that is less GMV in the pgACC was associated with an increased number of pain crises (Fig 2A). The GMV of the two groups with or without reported pain crisis was significantly differentiated in left supratemporal gyrus ($P = 0.024$, Fig 2B).

ROI analyses with 21 regions of GMV including MCC, right S1, right and left precuneus, ventral ACC, pregenual ACC, subgenual ACC, left and right amygdala, left and right anterior insula cortex AIC, two left and two right dorsolateral prefrontal cortex (DLPFC), left and right mid insula cortex (MIC), left and right PIC, left inferior parietal lobule (IPL) and posterior cingulate cortex (PCC) that were selected from our recent fMRI study in patients with SCD[14] as well as our earlier studies in patients with fibromyalgia.[32-35] All the ROIs used in this study were listed in *Supplementary Table 2*. We found significantly strong associations between 2 (perigenual/subgenual ACC) among 21 ROIs and the number of reported pain crises (Fig 3).

GMV association with the SCD-related quality of life. A whole brain two group analysis with higher (high QOL) or lower (low QOL) QOL scores was performed with age, gender, presence of infarct and total brain volume as covariables. We identified significantly decreased GMV in the low QOL group at both left ($P = 0.047$) and right ($P = 0.024$) parahippocampal gyrus regions (Fig 4).

DISCUSSION

The present study utilized VBM for brain structural analyses and explored the association of GMV with the frequency of pain crisis and SCD-related QOL in children and adolescents with SCD and showed the association between the frequency of pain crises and GMV changes in targeted brain regions involved in pain response such as ACC and parahippocampus. The ACC plays an important role in pain perception as it integrates multiple facets of the pain response, including affective, anticipatory, and cognitive components.[37,38] Anatomically, dorsal ACC, MCC, bilateral IC, and supplementary motor area constitute salience network whereas the pgACC, and sgACC are part of Default Mode Network (DMN) region. Both of these networks have been implicated in pain experience. Our finding of a negative correlation between GMV in pgACC/sgACC and the number of pain crises is suggestive of the activated antinociceptive signaling in the targeted region. Functionally, rostral ACC–Insula cortex connectivity reflects synchronized antinociceptive "effort" whereas structures between anterior cingulate and DMN reflect more pronociceptive function.[33] Furthermore, the targeted ROIs showed significant correlations among pgACC/sgACC areas which were shown to have altered connectivity that correlated with the frequency of pain crisis in our previous study.[14] Our findings suggest that the increased frequency of pain crisis in SCD could result in both functional and structural changes across these pain processing regions that are also seen in other chronic pain conditions such as fibromyalgia.[12,39,40] and irritable bowel syndrome.[13] Our finding of decreased GMV associated with pain is similar to other chronic pain conditions where these changes have been described and speculated to reflect reduced excitatory neurotransmitters neuronal atrophy associated with inflammatory processes and/or excitotoxicity.[41]

Previous studies have described brain volumetric changes in sickle patients with SCI showing distinct volumetric reduction in hippocampus, amygdala, pallidum and cerebellar cortex compared with control subjects without SCI.[30] Of note, in our recent study we observed a progressively reduced GMV in pediatric SCD with SCI and blood transfusion over a follow-up of 3.4 years.[42] In the present study, however, we did not observe statistical difference of GMV between the subgroup with infarct and subgroup without infarct. Furthermore, the observed negative correlation between the frequency of pain crisis and the GMV at pgACC remains with or without including subjects with overt stroke (n=4) as an additional covariable in addition to age, gender, total brain volume and presence of infarct. It needs to be noted that this result might be restricted with

our small sample size, as well as the scanning timepoint when the GMV loss could still be progressing due to infarct or overt stroke in these subjects. We also observed a significant GMV reduction at bilateral parahippocampus in patients with lower QOL scores. Furthermore, we found that the QOL score was negatively correlated with the frequency of pain crisis (r = -0.364, P = 0.034; data not shown), further confirming that the QOL scores were reflective of the impact of SCD pain and associated experiences on QOL.

Our findings need to be viewed in light of limitations. This study is a pilot study involving a small sample size without follow up evaluation or imaging. Given the small sample size and stringent Bonferroni's correction, the likelihood of committing a type II error was high. In our analysis, the absolute values of correlations were between 0.3 and 0.6. We conducted post hoc power analysis based on these results. Specifically, we controlled the familywise error rate at 0.05 by adjusting for 21 tests for 21 ROIs. Given our sample size of 35 patients, our post hoc power analysis indicated that our study was only powered to detect large effects (that is,for $|r|\geq 0.6$). A sample size of 160 would be needed to detect medium effects (that is, for $|r|\geq 0.3$). We expect the associations can be validated in future studies with larger sample sizes. Patients continued their SCD therapies including chronic red cell transfusion, hydroxyurea and other ongoing treatments for managing pain which may have potential to impact GMV and should be explored in larger prospective studies. The hemoglobin values could also be impacted by compliance with those concurrent treatments. Hence, the impact of hematological parameters on brain morphological changes should be explored in future longitudinal studies. Furthermore, participants were not evaluated by a full scale of pain phenotyping and related outcomes such as fatigue, sleep disturbance, memory difficulties, anxiety and depression. The QOL questionnaire assessed the impact of SCD on physical, psychological, and social functions, but did not fully assess all potential co-morbidities of chronic pain. These limitations could have introduced potential confounders and affected our results. Further research into the mechanisms of cerebral morphological changes with larger population-controlled longitudinal studies could provide a more comprehensive and nuanced perspective on these findings in SCD.

In conclusion, this study provides new findings of associations of brain volumetric changes with pain and QOL in SCD. These findings add to our observations of functional brain activity/connectivity in a transgenic mouse model with SCD[9] and human subjects with SCD and can be utilized for further investigations of neurobiological brain mechanisms as they relate to GMV alterations in targeted ROIs. Future clinical and translational research is needed to explore directionality of these changes however given the objective nature of these brain volumetric changes these findings have a potential to be explored as biomarkers of SCD pain.

AUTHOR STATEMENT

The manuscript has been reviewed and approved by all the authors. All authors have read the journal's authorship agreement and policy on disclosure of potential conflicts of interest. D.S.D serves as consultant/advisory board for Novartis, Global Blood therapeutics and Hilton Publishing. R.E.H has consulted for Pfizer, Aptinyx Inc. and has received grant funding from Pfizer, Aptinyx, Cerephex. and National Institutes of Health (NIH). The remaining authors declare no competing interests.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.trsl.2021.08.004.

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