Published in final edited form as:

Adv Med Sci. 2017 March ; 62(1): 151–157. doi:10.1016/j.advms.2016.09.002.

Brain morphometric analysis predicts decline of intelligence quotient in children with sickle cell disease: a preliminary study

Rong Chen^{a,*}, Jaroslaw Krejza^{a,*}, Michal Arkuszewski^b, Robert A. Zimmerman^{c,d}, Edward H. Herskovits^a, and Elias R. Melhem^a

^aDepartment of Diagnostic Radiology and Nuclear Medicine, University of Maryland, Baltimore, USA ^bDepartment of Neurology, Medical University of Silesia, Katowice, Poland ^cDepartment of Radiology, the Children's Hospital of Philadelphia, Philadelphia, USA ^dDepartment of Radiology, the Raymond and Ruth Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA

Abstract

Purpose—For children with sickle cell disease (SCD) and at low risk category of stroke, we aim to build a predictive model to differentiate those with decline of intelligence-quotient (IQ) from counterparts without decline, based on structural magnetic-resonance (MR) imaging volumetric analysis.

Materials and Methods—This preliminary prospective cohort study included 25 children with SCD, homozygous for hemoglobin S, with no history of stroke and transcranial Doppler mean velocities below 170 cm/sec at baseline. We administered the Kaufman Brief Intelligence Test (K-BIT) to each child at yearly intervals for 2-4 years. Each child underwent MR examination within 30 days of the baseline K-BIT evaluation date. We calculated K-BIT change rates, and used rate of change in K-BIT to classify children into two groups: a decline group and a non-decline group. We then generated predictive models to predict K-BIT decline/non-decline based on regional gray-matter (GM) volumes computed from structural MR images.

Results—We identified six structures (the left median cingulate gyrus, the right middle occipital gyrus, the left inferior occipital gyrus, the right fusiform gyrus, the right middle temporal gyrus, the right inferior temporal gyrus) that, when assessed for volume at baseline, are jointly predictive of whether a child would suffer subsequent K-BIT decline. Based on these six regional GM volumes and the baseline K-BIT, we built a prognostic model using the K* algorithm. The accuracy, sensitivity and specificity were 0.84, 0.78 and 0.86, respectively.

*Correspondence authors: Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland, 22 South Greene Street, Baltimore, Maryland 21201, USA, Tel.: 001-410-7063284; rchen@umm.edu (R. Chen); Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland, 22 South Greene Street, Baltimore, Maryland 21201, USA, Tel.: 001-410-7082820. jkrejza@me.com (J. Krejza).

Conflict of interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusions—GM volumetric analysis predicts subsequent IQ decline for children with SCD.

Keywords

sickle cell disease; cognitive decline; magnetic resonance; biomarker; predictive modeling

1. Introduction

Children with sickle cell disease (SCD) are at high risk of cognitive impairment [1, 2]. Early identification of those at highest risk of cognitive decline is crucial for preventive management [3-5]. Timely intervention could significantly improve the quality of life, and reduce direct and indirect non-health related costs. Therefore a reliable determination of the risk of cognitive decline is needed, as these children may benefit from preventive measures if they are implemented early.

The two main pathophysiological processes for SCD are chronic hemolytic anemia and vaso-occlusion [6]. Chronic hemolytic anemia may lead to hypoxia, and vaso-occlusion may cause strokes. Thus, both processes can lead to central nervous system damage. Research has consistently linked stroke to severe neurocognitive impairment in children with SCD [7, 8]. However, children with SCD who never had symptomatic cerebrovascular accidents and are at low risk category of stroke, determined with blood flow velocity below 170 cm/s as measured with transcranial Doppler ultrasound in the middle cerebral or terminal internal carotid arteries, still suffer from neurocognitive deficits [1] and lower intelligence quotient (IQ) [9, 10]. A recent study showed that children with SCD at low risk of stroke and stable hemodynamics still experience ongoing (chronic, intermittent) cerebral ischemia that leads to global or focal brain damage [11].

MR-based gray matter volumetric studies reported morphometric changes in the brains of children with SCD. For example, Kirk et al. [12] analyzed cortical thicknesses in SCD children (ages 12-21 years) who had no magnetic resonance (MR) abnormality, and those of controls. They found statistically significant cortical thinning in several regions in children with SCD, with the largest regions of thinning occurring in the precuneus and the posterior cingulate. A recent study [13] compared children with SCD and silent infarct (n=13), children with SCD without silent infarct (n=13), and controls (n=20), and reported volumetric differences in the hippocampus, amygdala, pallidum, caudate, putamen, thalamus, and cerebellum.

However, few studies have addressed IQ decline in low-risk children with SCD (without overt stroke and transcranial Doppler mean velocities below 170 cm/sec at baseline). Furthermore, no studies have investigated whether MR-based gray matter volumetric analysis can predict subsequent IQ decline. For children with SCD and at low risk category of stroke, we aim to build a predictive model to differentiate those with decline of IQ from counterparts without decline, based on baseline gray-matter volumetric analysis.

2. Materials

The study population was drawn from the Comprehensive Sickle Cell Center at the Children's Hospital of Philadelphia (year 2005-2010). Institutional Review Board of the Children's Hospital of Philadelphia approved the protocol of this study (IRB approval number 801588) that was also compliant with Health Insurance Portability and Accountability Act. Written informed consent was given by subjects' parents (with assent for subjects seven years and older).

2.1 Inclusion and exclusion criteria

Inclusion criteria were: 1) sickle cell anemia genotype: homozygous SS, confirmed by isoelectric focusing with DNA-based confirmatory testing or parental studies, 2) no deficits on neurological examination, 3) no history of stroke, 4) transcranial Doppler mean velocities below 170 cm/sec on a screening routine examination.

Exclusion criteria were: 1) history of major head injury requiring visit to an emergency department, 2) history of seizure disorder requiring anticonvulsant therapy, 3) chronic transfusion therapy, 4) occurrence of sickle cell anemia pain episode, acute chest syndrome or other significant medical problem in the period between laboratory blood testing, neuropsychological testing, and sonographic studies, 5) history of prenatal or perinatal hypoxic-ischemic brain injury, 6) evidence of HIV infection.

2.2 Intellectual assessment

We used the Kaufman Brief Intelligence Test (K-BIT) [14] to assess intelligence of children with SCD. Tests were conducted in controlled environment under the supervision of an experienced neuropsychologist. Average test duration was 30 minutes. Test scores were standardized, and expressed as *t*-scores with mean 100 and standard deviation 15.

The children reported here were the 25 who had a minimum of two yearly intelligence assessments, including a baseline evaluation. Among them, 13 children had two intelligence assessments; 9 children had three intelligence assessments; and 3 children had four intelligence assessments. The recruitment diagram is shown in Figure 1.

2.3 Image acquisition

All subjects underwent MR examination using a 3 Tesla Siemens Trio scanner (Siemens, Erlangen Germany) at the Children's Hospital of Philadelphia. The MR examination date was within 30 days of the baseline K-BIT evaluation date. The MR protocol included T1-weighted, T2-weighted, and fluid attenuation inversion recovery (FLAIR) sequences. For T1-weighted MR imaging, TR/TE/TI = 1380/2.15/800 ms, matrix 256×256, voxel size 1×1×1 mm. We acquired whole brain volumetric T2-weighted (TR/TE = 3500/180 ms, matrix 256×256, voxel size 1×1×1 mm) and FLAIR (TR/TE/TI = 5000/193/1800 ms, matrix 256×256, voxel size 1×1×1 mm) sequences to detect Silent Cerebral Infarction (SCI). A silent cerebral infarct is defined as area of abnormal hyperintensity on FLAIR images and which was at least 3mm in diameter and visible in at least two perpendicular planes.

2.4 Demographic and socioeconomic variables

We recorded four demographic and socioeconomic variables: age, sex, income, and maternal education. We determined maternal education levels and the socioeconomic backgrounds of patients' families on the basis of questionnaires completed by parents. Family income was encoded into six categories: 1 -below \$10K, 2 – \$10-20K, 3 – \$20-30K, 4 – \$30-40K, 5 – \$40-50K, 6 - above \$50K. We encoded maternal education into five categories: 1 – less than high school, 2 - high school graduate or equivalent, 3 - post-high school training, less than completing a 4-year college, 4 - 4- year college degree, 5 - post-graduate academic work.

3. Methods

3.1 IQ change rate

The primary outcome variable of interest was the rate of change in IQ. In this study, IQ was measured at baseline and followed at several time points. We used the variable TIME to represent the number of years since baseline (i.e., TIME = 0 was the baseline). Adopting an individual growth model in which a change is a linear function of TIME, we describe the model for individual change as

$$IQ_{ij} = \pi_{0i} + \pi_{1i} \cdot \text{TIME}_{ij} + \varepsilon_{ij}, \quad (1)$$

where IQ_{ij} is the value of IQ for subject i at time j ; the intercept, π_{0i} , represents child i 's IQ at baseline, the slope, π_{1i} , is the rate at which individual i changed over time, and ε_{ij} is the noise in measurements. π_{1i} , the rate of change in IQ, is the primary outcome variable.

After computing the rate of change in IQ, we classified children with SCD into two (decline and non-decline) groups. We classified a child as suffering decline in IQ if the change rate was at least a half standard-deviation (SD) below the sample mean; otherwise, we classified that child as having no decline. We denote this group-membership variable as C . We selected the threshold to be half SD below the mean [15] because this threshold is neither too conservative nor too liberal. If the threshold is too conservative (for example, 1 SD below the mean), then some children who are at risk of neurocognitive decline and need preventive measures will be ignored. If the threshold is too liberal (for example, equal to the sample mean), then we may advocate unnecessary preventive measures for children who demonstrate marginal IQ changes.

3.2 MR data analysis

We computed regional gray-matter volumes from T1-weighted MR images. Our image-processing procedure consisted of three steps: skull-stripping, segmentation and registration, and regional volume calculation.

First, we used the brain extraction tool to exclude non-brain tissues [16]. Then we used SPM5 to perform joint tissue segmentation and registration. In the joint tissue segmentation and registration steps, we segmented the image volume into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF); and normalized the subject's T1-weighted MR image

to the Montreal Neurological Institute (MNI) space, simultaneously. We then used the software package called “individual brain atlases found in statistical parametric mapping” [17] to parcellate the brain into 90 Automated Anatomical Labeling (AAL) structures [18], and we visually inspected the brain-parcellation results. Based on the results of tissue segmentation and brain parcellation, we calculated total GM volume, total WM volume, total brain volume (defined as the summation of GM and WM volumes), and regional GM volumes for the 90 AAL structures. For regional GM volumes, we were interested in regional, rather than global, effects; therefore, we adjusted regional GM volumes by each subject's total brain volume in the same MR image. For each brain structure, we defined relative volume as $10,000 * (V / (\text{total brain volume}))$, where V is the raw regional volume of this structure. We multiplied the fraction $V / (\text{total brain volume})$ by 10,000 because $V / (\text{total brain volume})$ was typically a very small number, and not stable under numerical procedures. These relative regional volumes are relative measurements and are dimensionless. This image-analysis pipeline had been used in other studies of pediatric populations [19-21].

For each subject, two experienced neuroradiologists reviewed the MR examination and identified SCI, defined as area of abnormal hyperintensity on FLAIR images and which was at least 3 mm in diameter and visible in at least two perpendicular planes. The binary variable SCI represents whether or not there were silent cerebral infarcts in a subject's MR examination.

3.3 Predictive model generation

Our goal was to predict C based on baseline biomarkers. The candidate markers to predict C included features extracted from MR images, as well as demographic and socioeconomic variables.

The first step is variable selection. Our candidate marker set includes 90 regional GM volumes, total GM, WM, and brain volumes, SCI, baseline K-BIT, age, sex, income, and maternal education. The total number of variables is 99; however, we have only 25 subjects. In this case, if the model-generation method does not incorporate feature selection or regularization [22], the resulting predictive model will have poor generalizability, and parameter estimation will become difficult. One approach to solving this problem is to select a subset of features to train the predictive model.

For continuous predictor variables, we used the Wilcoxon rank sum test (for continuous variables) or Fisher's exact test (for categorical variables) to determine whether there were differences between the decline and non-decline groups. We set the cutoff value to 0.1. Thus, if the p-value was below 0.1, we considered this variable to be predictive of C , and included it in the final model.

We used the K^* algorithm [23] to construct the predictive model. The K^* algorithm generates an instance-based learner based on Kolmogorov complexity. On many real datasets, it performed well against other classification methods [23]. Model parameters were tuned by using five-fold cross-validation.

To assess prediction performance, we computed prediction accuracy, defined as $N_{\text{corr}}/N_{\text{total}}$, where N_{corr} and N_{total} represent the number of correctly labeled subjects and the total number of subjects in the study, respectively. Sensitivity is the fraction of children who had IQ decline and were labeled as having IQ decline by the predictive model. Specificity is the fraction of children who did not have IQ decline and were labeled as non-decline by the predictive model. We evaluated the generated predictive models based on leave-one-out cross validation, in which we partition the data set into N_{total} data sets. For each data set, one child is left out to test the predictive model, and a model is generated based on the remaining subjects. The overall performance is the average across all N_{total} data sets.

4. Results

4.1 Rate of change in K-BIT

The mean rate of change in K-BIT was 1.27 (SD = 4.6). This rate of change in K-BIT and the histogram were depicted in Figure 2. We divided the 25 children in our cohort into decline and non-decline groups, using the threshold of 0.5 SD below the mean (threshold = -1.035). Thresholding yielded two groups: decline ($n = 9$) and non-decline ($n = 16$). The mean rates of change of the decline and non-decline group were -4.94 (SD 1.08) and 2.82 (SD 3.79), respectively. There was a significant difference in the mean rate of change (p-value < 0.001). None of these children was on hydroxyurea.

The mean baseline ages of the decline and non-decline group were 9.67(SD 1.41) and 9.38 (SD 2.94), respectively. There was no significant difference in the mean baseline age (p-value = 0.742). The number of female participants of the decline group was 9 (total number of subjects in the group = 16); and that of the non-decline group was 4 total number of subjects in the group = 9). There was no significant difference in the proportion of female participants (p-value = 0.688). There was no significant difference in hemoglobin concentration (g/dL) (p-value = 0.688 based on the two-sample t-test). There was no significant difference in red blood cells (millions/uL) (p-value = 0.658 based on the two-sample t-test).

4.2 Variable selection

Among the potential predictor variables, we found 7 predictor variables that had p-values less than 0.1; Table 1 lists these variables. Six of these predictor variables were structural imaging based, and one was clinical (baseline K-BIT). Figure 3 shows these six brain regions overlaid on the AAL template. As shown in Table 1, subjects in the decline group had lower baseline GM volumes for 5 out of the 6 selected predictor brain structures.

We found that the proportion of children with silent cerebral infarcts in the decline group (7/9) was higher than that in the non-decline group (7/16). However, this proportion difference is not statistically significant (Fisher's exact test p-value = 0.21).

4.3 Prognostic models

We generated prognostic models to predict K-BIT decline based on the selected predictor variables (baseline K-BIT, and gray matter volumes of the right middle occipital gyrus, the

left inferior occipital gyrus, the right fusiform gyrus, the right middle temporal gyrus, the right inferior temporal gyrus, and the left median cingulate gyrus). The accuracy was 0.84. The 95% confidence interval (CI) was [0.65 0.94]. The sensitivity was 0.78 (95% CI: [0.45 0.94]); the specificity was 0.88 (95% CI: [0.64 0.97]); the positive predictive value (PPV) was 0.78 (95% CI: [0.45 0.94]); the negative predictive value (NPV) was 0.88 (95% CI: [0.64 0.97]). Adding variable SCI to the prognostic model didn't improve the prediction performance (accuracy=0.80).

We used one-sample test for a Binomial proportion to assess the chance of observing the results we have. Random guessing achieved accuracy = 0.64 (16/25). For our predictive model, we tested the null hypothesis: accuracy = 0.64 versus alternative hypothesis accuracy = 0.64. P-value was 0.03789. We found that our predictive model's performance was significantly different from that of random guessing.

For the comparison purpose, we constructed a predictive model using all five clinical variables in the study: age, sex, income, maternal education, and baseline K-BIT. This model included no imaging-derived variables. The classification accuracy, sensitivity, specificity, PPV and NPV were 0.64 (95% CI: [0.45 0.80]), 0.66 (95% CI: [0.35 0.88]), 0.63 (95% CI: [0.39 0.82]), 0.5 (95% CI: [0.25 0.75]), 0.78 (95% CI: [0.50 0.92]), respectively.

To assess whether the 7 predictor variables in our model (baseline K-BIT, and gray matter volumes of the right middle occipital gyrus, the left inferior occipital gyrus, the right fusiform gyrus, the right middle temporal gyrus, the right inferior temporal gyrus, and the left median cingulate gyrus) are jointly predictive of K-BIT decline, we built a predictive model using each individual predictor, and generated 7 predictive models. The accuracies, sensitivities, specificities, PPVs, and NPVs of these models are listed in Table 2. The mean accuracy, mean sensitivity, and mean specificity of these models are 0.68 (SD 0.04), 0.44 (SD 0.07), and 0.82 (SD 0.04), respectively. The predictive model with all predictors had accuracy = 0.84, sensitivity = 0.78 and specificity = 0.88. The model with all predictors had significant improvements in accuracy and sensitivity, relative to models with individual predictors.

5. Discussion

We found that features from structural MR examination measured at baseline, along with baseline KBIT, accurately predict K-BIT decline in low risk children with SCD.

In this longitudinal study, 9 of 25 children with SCD suffered K-BIT decline. We identified six brain structures that, when assessed for volume at baseline, are jointly predictive of whether or not a child would suffer subsequent K-BIT decline. These structures are: the left median cingulate gyrus, the right middle occipital gyrus, the left inferior occipital gyrus, the right fusiform gyrus, the right middle temporal gyrus, the right inferior temporal gyrus. Based on these six regional GM volumes, and the baseline K-BIT, our prognostic models had accuracy = 0.84, sensitivity = 0.78 and specificity = 0.88.

We found the baseline status of the decline group is characterized by more baseline disease severity. Children in the decline group had smaller baseline GM volumes in 5 out of 6

selected brain regions. Children in the decline group were more likely to have silent cerebral infarcts at baseline. These two findings suggest that children in the decline group had more disease severity at baseline. Our findings suggest that children may be at risk for K-BIT decline if their MR imaging demonstrates that they have more disease severity (tissue loss and silent cerebral infarct).

Children in the decline group were characterized by regional GM volume reduction. In a related longitudinal study [24], Chen et al. analyzed T1-MR images of the brains of 28 children with SCD and found that 35 brain structures demonstrated age-related GM volume reduction. The findings in our study and that in Chen et al. [24] are in accordance. A possible explanation of the observed regional GM volume reduction in SCD children with cognitive decline is the effect of SCD on the brain. SCD is characterized by abnormal hemoglobin which has reduced oxygen affinity and low solubility in its deoxygenated form. Hemodynamic disturbances during brain development might lead to ischemic brain injury and the reduction of GM volume. Therefore, the decline group may have more hemodynamic disturbances.

Cognitive decline in children with SCD is a complex process, one with many contributory factors. First, we found that the decline group had a relatively higher baseline K-BIT. A higher baseline K-BIT suggests a better cognitive reservoir which could be a protective mechanism for cognitive decline. However, disease severity (tissue loss and silent cerebral infarct) could have a greater impact on cognitive performance. Therefore, our findings suggest that SCD children may be at risk for K-BIT decline if their MR imaging demonstrates that they have more disease severity, although their current K-BIT performances are relatively high. Second, we focused on the baseline regional GM volumes in this study. Brain development is a temporal process. A temporal process is characterized by the baseline state and the state transition function. The baseline regional volumes characterize the baseline state, and a measure such as the rate of change in regional GM volume can be used to characterize the state transition function. Modeling the state transition function in a temporal process is a challenging task and requires longitudinal MR data. The state transition function could be a contributing factor to cognitive decline. We plan to investigate this in our future work.

We found that six brain structures were predictive of K-BIT decline in children with SCD. These brain structures are: the right middle occipital gyrus, the left inferior occipital gyrus, the right fusiform gyrus, the right middle temporal gyrus, the right inferior temporal gyrus, and the left median cingulate gyrus. The inferior and middle temporal gyri (Brodmann Areas (BA) 20-21) are involved in high-level visual processing, recognition memory, auditory processing, and language. These two brain structures are known to be correlated with general intelligence in healthy adults [25]. For the left median cingulate gyrus, different functions have been ascribed to the median cingulate gyrus including attention-for-action [26], working memory [27], and response selection [28]. The middle and inferior occipital gyrus (BA 18 and 19) and the fusiform gyrus (BA 37) are involved in recognition, imagery and elaboration of visual inputs. Jung and Haier [29] reviewed 37 neuroimaging studies and proposed the parieto-frontal integration theory of intelligence. These three brain structures are included in the parieto-frontal integration model.

The neuroanatomical basis of cognitive decline is also reported in other clinical conditions. For example, Chen et al. [30] found that a machine learning based predictive model accurately differentiates mild cognitive impairment (MCI) converters and non-converters, based on the five baseline regional GM volumes. In this study, MCI converters were MCI patients who progressed to Alzheimer's disease within 5 years. Relative to non-converters, MCI converters had accelerated cognitive decline.

The results in Table 1 don't argue against the positive correlation between IQ and brain volumes. In Table 1, we observed that the decline group had lower regional GM volume, and higher IQ. However, only brain regions which demonstrated significant differences across decline/non-decline groups were included in Table 1. Based on all subjects, we calculated the Pearson correlation coefficient between the baseline total brain volume and baseline IQ to be 0.11. The weak positive correlation may have resulted from the small sample size. This finding suggests a positive correlation between IQ and total volumes.

In one of our previous studies of brain morphometry in children with SCD [31], we reported that regional gray matter volumes accounts substantially for variability in the K-BIT score among children with sickle cell disease, who have no magnetic resonance visible infarcts. There are two major differences between the previous study by Chen et al. [31] and the current study. First, the previous study by Chen et al. [31] is cross-sectional and measured the variability of K-BIT in a single time point. The current study is longitudinal, and has several K-BIT measurements. Second, the previous study by Chen et al. [31] is an association study to find association between regional gray matter volumes and K-BIT. It did not generate a predictive model. The current study generates a predictive model which can provide a risk score for each subject.

We developed a model to predict K-BIT decline in low risk children with SCD using machine learning algorithms. Relative to building clinical decision support systems based on expert knowledge, constructing such systems using machine learning algorithms [22, 32, 33] is automated and unbiased. Generating predictive models using machine learning algorithms is an effective method to detect diagnostic or prognostic biomarkers, predict treatment responses, or select a specific group of patients for a treatment.

One of the limitations of this study is that we used the K-BIT, a brief, individually-administered measure of verbal and nonverbal intelligence for IQ assessment, rather than a full-length instrument such as the Wechsler Intelligence Scale for Children. We selected the K-BIT primarily because of its short administration time (15-30 minutes). Since intelligence testing was one part of a more-comprehensive neuropsychological battery that had to be completed in a single sitting by even the youngest subjects, the short administration time of K-BIT was crucial. While some precision of measurement is lost moving from a full-length to abbreviated intelligence measure, the use of K-BIT is justified by its construct validity [34], and worked well in our previous study [31]. The second limitation is small sample size. Although the generated predictive model was accurate (accuracy = 0.84, sensitivity = 0.78 and specificity = 0.86), this model is generated using a data set with small sample size. However, our study group was carefully selected and homogenous in terms of hemodynamic status, hematologic parameters, and presence of vascular abnormalities. As a result, the

groups with and without IQ decline in our study were well comparable in terms of several hemodynamic, clinical and anatomical parameters to maintain internal validity of the study. It should be noted that during 5 years (2005-2010) of the project, despite significant effort on the part of the entire team, we were able to recruit only 25 from 218 initially screened children with SCD (Figure 1), who underwent baseline neuroimaging and several psychometric tests. The recruitment problem in the population of children with SCD is common. We plan to evaluate the predictive model generated in this study in a cohort with a larger sample size. The third limitation is this study is based on regional GM volumes. Due to the small sample size, we cannot investigate other variables such as the transcranial Doppler based variables. Building a predictive model based on a large number of variables and a small sample size may lead to an unstable model with poor generalizability [22, 30]. We plan to construct a predictive model for cognitive decline in SCD based on structural and functional MR variables, transcranial Doppler based variables, and hemodynamic variables in a cohort with larger sample size.

6. Conclusion

In this preliminary pilot study, we generated a predictive model to differentiate children with SCD who will suffer subsequent IQ decline from those who will not, based on baseline structural-MR measurements of regional GM volumes, and baseline K-BIT. Using our model, we are able to identify children with SCD who are at a high risk for subsequent IQ decline.

Acknowledgments

Financial disclosure: Rong Chen and Edward H. Herskovits were supported by National Institutes of Health grant R01 AG13743, R03 EB-009310, the American Recovery and Reinvestment Act. Rong Chen was supported by ITMAT fellowship, University of Pennsylvania. Jaroslaw Krejza, Michal Arkuszewski, and Elias R. Melhem were supported by National Institutes of Health grant R01 NS 046717.

References

1. Berkelhammer LD, Williamson AL, Sanford SD, Dirksen CL, Sharp WG, Margulies AS, et al. Neurocognitive Sequelae of Pediatric Sickle Cell Disease: A Review of the Literature. *Child Neuropsychology*. 2007; 13(2):120–131. [PubMed: 17364569]
2. Kral MC, Brown RT, Hynd GW. Neuropsychological aspects of pediatric sickle cell disease. *Neuropsychol Rev*. 2001; 11(4):179–96. [PubMed: 11883668]
3. Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ, et al. Prediction of adverse outcomes in children with sickle cell disease. *N Engl J Med*. 2000; 342(2):83–9. [PubMed: 10631276]
4. Quinn CT, Lee NJ, Shull EP, Ahmad N, Rogers ZR, Buchanan GR. Prediction of adverse outcomes in children with sickle cell anemia: a study of the Dallas Newborn Cohort. *Blood*. 2008; 111(2): 544–8. [PubMed: 17909076]
5. Quinn CT, Shull EP, Ahmad N, Lee NJ, Rogers ZR, Buchanan GR. Prognostic significance of early vaso-occlusive complications in children with sickle cell anemia. *Blood*. 2007; 109(1):40–5. [PubMed: 16940426]
6. NHLBI. Management and Therapy of Sickle Cell Disease: NIH. 1995 Report No.: NIH Publication No. 95-2117.
7. Armstrong FD, Thompson RJ, Wang W, Zimmerman R, Pegelow CH, Miller S, et al. Cognitive functioning and brain magnetic resonance imaging in children with sickle cell disease. *Pediatrics*. 1996; 97(6):864–870. [PubMed: 8657528]

8. Powars D, Wilson B, Imbus C, Pegelow C, Allen J. The natural history of stroke in sickle cell disease. *Am J Med.* 1978; 65:461–471. [PubMed: 717414]
9. Swift AV, Cohen MJ, Hynd GW, Wisenbaker JM, McKie KM, Makari G, et al. Neuropsychologic impairment in children with sickle cell anemia. *Pediatrics.* 1989; 84(6):1077–85. [PubMed: 2587138]
10. Knight S, Singhal A, Thomas P, Serjeant G. Factors associated with lowered intelligence in homozygous sickle cell disease. *Archives of Disease in Childhood.* 1995; 73:316–320. [PubMed: 7492195]
11. Quinn CT, McKinsty RC, Dowling MM, Ball WS, Kraut MA, Casella JF, et al. Acute silent cerebral ischemic events in children with sickle cell anemia. *JAMA Neurol.* 2013; 70(1):58–65. [PubMed: 23108767]
12. Kirk GR, Haynes MR, Palasis S, Brown C, Burns TG, McCormick M, et al. Regionally specific cortical thinning in children with sickle cell disease. *Cereb Cortex.* 2009; 19(7):1549–56. [PubMed: 18996911]
13. Kawadler JM, Clayden JD, Kirkham FJ, Cox TC, Saunders DE, Clark CA. Subcortical and cerebellar volumetric deficits in paediatric sickle cell anaemia. *Br J Haematol.* 2013; 163(3):373–6. [PubMed: 23889205]
14. Kaufman, AS., Kaufman, NL. Manual for the Kaufman Brief Intelligence Test. Circle Pines, MN: American Guidance Service; 1990.
15. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care.* 2003; 41(5):582–92. [PubMed: 12719681]
16. Smith SM. Fast robust automated brain extraction. *Human Brain Mapping.* 2002; 17(3):143–155. [PubMed: 12391568]
17. IBASPM. IBASPM. 2011. <http://www.thomaskoenig.ch/Lester/ibaspm.htm>
18. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *NeuroImage.* 2002; 15:273–289. [PubMed: 11771995]
19. Tzarouchi LC, Astrakas LG, Xydis V, Zikou A, Kosta P, Drougia A, et al. Age-related grey matter changes in preterm infants: an MRI study. *Neuroimage.* 2009; 47(4):1148–53. [PubMed: 19348950]
20. Yamashita K, Yoshiura T, Hiwatashi A, Noguchi T, Togao O, Takayama Y, et al. Volumetric asymmetry and differential aging effect of the human caudate nucleus in normal individuals: a prospective MR imaging study. *J Neuroimaging.* 2011; 21(1):34–7. [PubMed: 19659682]
21. Widjaja E, Yeung R, Geibprasert S, Mahmoodabadi SZ, Snead OC 3rd, Smith ML. Longitudinal brain volumes in children with intractable partial seizures. *Pediatr Neurol.* 2010; 42(5):315–9. [PubMed: 20399383]
22. Chen R, Herskovits EH. Machine-learning techniques for building a diagnostic model for very mild dementia. *Neuroimage.* 2010
23. Cleary JG, Trigg LE. K*: An Instance-based Learner Using an Entropic Distance Measure. *IProceedings of the 12th International Conference on Machine Learning;* 1995. 1995:108–114.
24. Chen R, Arkuszewski M, Krejza J, Zimmerman RA, Herskovits EH, Melhem ER. A prospective longitudinal brain morphometry study of children with sickle cell disease. *AJNR Am J Neuroradiol.* 2015; 36(2):403–10. [PubMed: 25234033]
25. Coloma R, Haiarb RJ, Headb K, Álvarez-Linerac J, Quirogad MÁ, Shiha PC, et al. Gray matter correlates of fluid, crystallized, and spatial intelligence: Testing the P-FIT model. *Intelligence.* 2009; 37(2):124–135.
26. Posner MI, Petersen SE, Fox PT, Raichle ME. Localization of cognitive operations in the human brain. *Science.* 1988; 240(4859):1627–31. [PubMed: 3289116]
27. Petit L, Courtney SM, Ungerleider LG, Haxby JV. Sustained activity in the medial wall during working memory delays. *J Neurosci.* 1998; 18(22):9429–37. [PubMed: 9801381]

28. Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE. Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. *J Neurosci.* 1991; 11(8):2383–402. [PubMed: 1869921]
29. Jung RE, Haier RJ. The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. *Behav Brain Sci.* 2007; 30(2):135–54. discussion 154-87. [PubMed: 17655784]
30. Chen R, Young K, Chao LL, Miller B, Yaffe K, Weiner MW, et al. Prediction of conversion from mild cognitive impairment to Alzheimer disease based on bayesian data mining with ensemble learning. *Neuroradiol J.* 2012; 25(1):5–16. [PubMed: 24028870]
31. Chen R, Pawlak MA, Flynn TB, Krejza J, Herskovits EH, Melhem ER. Brain morphometry and intelligence quotient measurements in children with sickle cell disease. *J Dev Behav Pediatr.* 2009; 30(6):509–17. [PubMed: 19898248]
32. Chen R, Herskovits EH. Graphical-model based morphometric analysis. *IEEE Transaction on Medical Imaging.* 2005; 24(10):1237–1248.
33. Chen R, Herskovits EH. Network analysis of mild cognitive impairment. *NeuroImage.* 2006; 29(4): 1252–1259. [PubMed: 16213161]
34. Kamphaus, RW. Clinical assessment of child and adolescent intelligence. second. Allyn and Bacon; 2001.

Figure 1. A diagram of the recruitment workflow

Figure 2. IQ rate of change. (a) The sorted IQ rates of change for all subjects. (b) The histogram of the IQ rate of change

Figure 3. The brain structures used to predict K-BIT decline, overlaid on the AAL template, in radiological convention

Table 1
The selected predictor variables

	DECLINE GROUP (N=9)	NON-DECLINE GROUP (N=16)	P-VALUE
Left median cingulate gyrus	86.9 (SD 4.4)	83.2 (SD 4.7)	0.03
Right middle occipital gyrus	80.5 (SD 5.1)	85.1 (SD 5.7)	0.03
Left inferior occipital gyrus	38.0 (SD 3.4)	41.0 (SD 2.5)	0.04
Right fusiform gyrus	112.0 (SD 6.6)	116.6 (SD 7.3)	0.08
Right middle temporal gyrus	184.6 (SD 6.9)	193.5 (SD 9.5)	0.01
Right inferior temporal gyrus	143.4 (SD 8.2)	149.3 (SD 7.4)	0.07
Baseline K-BIT	97 (SD 9)	85 (SD 13)	0.05

Table 2
Accuracies, sensitivities, specificities, PPVs and NPVs of individual predictor variables

	ACCURACY	SENSITIVITY	SPECIFICITY	PPV	NPV
Left median cingulate gyrus	0.52 (95% CI [0.33 0.70])	0.11 (95% CI [0.01 0.43])	0.75 (95% CI [0.51 0.90])	0.20 (95% CI [0.01 0.62])	0.60 (95% CI [0.39 0.78])
Right middle occipital gyrus	0.80 (95% CI [0.61 0.91])	0.56 (95% CI [0.27 0.81])	0.94 (95% CI [0.72 1.00])	0.83 (95% CI [0.44 0.99])	0.79 (95% CI [0.57 0.91])
Left inferior occipital gyrus	0.80 (95% CI [0.61 0.91])	0.67 (95% CI [0.35 0.88])	0.88 (95% CI [0.64 0.97])	0.75 (95% CI [0.41 0.93])	0.82 (95% CI [0.59 0.94])
Right fusiform gyrus	0.72 (95% CI [0.52 0.86])	0.44 (95% CI [0.19 0.73])	0.88 (95% CI [0.64 0.97])	0.67 (95% CI [0.30 0.90])	0.74 (95% CI [0.51 0.88])
Right middle temporal gyrus	0.64 (95% CI [0.45 0.80])	0.44 (95% CI [0.19 0.73])	0.75 (95% CI [0.51 0.90])	0.50 (95% CI [0.22 0.78])	0.71 (95% CI [0.47 0.87])
Right inferior temporal gyrus	0.76 (95% CI [0.57 0.89])	0.56 (95% CI [0.27 0.81])	0.88 (95% CI [0.64 0.97])	0.71 (95% CI [0.36 0.92])	0.78 (95% CI [0.55 0.91])
Baseline K-BIT	0.56 (95% CI [0.37 0.73])	0.33 (95% CI [0.12 0.65])	0.69 (95% CI [0.44 0.86])	0.38 (95% CI [0.14 0.69])	0.65 (95% CI [0.41 0.83])
Mean (SD)	0.68 (0.04)	0.44 (0.07)	0.82 (0.04)	0.58 (0.09)	0.73 (0.03)