Relationship of Structural Magnetic Resonance Imaging, Magnetic Resonance Perfusion, and Other Disease Factors to Neuropsychological Outcome in Sickle Cell Disease

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Objective To investigate the relationship between neuropsychological functioning and radiographic findings in children with sickle cell disease (SCD) with no history of clinical neurological events. Methods Thirty-one patients with SCD randomly selected from a regional treatment center underwent neuropsychological and disease severity assessments. Of these, 22 also had structural magnetic resonance imaging and magnetic resonance perfusion studies performed. Results Forty-five percent of the imaged subgroup showed imaging abnormalities that were found to be correlated with disease severity but not neuropsychological level of performance indices. A significant relationship, however, was found between imaging abnormalities and increased variability in neuropsychological performance. Conclusions These results corroborate the high rate of rheologic and vascular pathology in SCD and underscore the importance of representing neuropsychological functioning in multiple ways.

Key words sickle cell disease; neuropsychological functioning; imaging, disease severity.

Sickle cell disease (SCD) is the most common type of genetic disease affecting African Americans, with an estimated incidence of approximately 1 in every 500 African American newborns (Charache, Lubin, & Reid, 1992). The SCD genotypes include homozygous sickle cell anemia (hemoglobin [Hgb]SS), the most common form, and a variety of compound heterozygous states in which HgbS is paired with another abnormal hemoglobin, including HgbSC, sickle cell–β° thalassemia (Sβ°thal), sickle cell–β± thalassemia (Sβ±thal), and sickle cell–β+ thalassemia (Sβ+thal). In general, compared with the other genotypes, children with HgbSS and HgbSβ-thal have lower Hgb levels, an earlier onset of clinical symptoms, and more frequent pain episodes and are more likely to have complications such as overwhelming sepsis, growth retardation, acute chest syndrome, and stroke (Charache et al., 1992). However, there is also considerable heterogeneity within genotype, as children with the same SCD genotype commonly differ dramatically in the severity and nature of their symptoms.

Vaso-occlusive episodes are common in SCD and can affect all major organs, including the central nervous system (CNS). Although the reported risk of cerebral vascular accident (CVA) in children with SCD is variable, in most studies it falls in the range of 5–10% in children with HgbSS disease, which is 225 to 400 times the risk in the general population (Balkaran et al., 1992; Ohene-Frempong, 1991; Powars, Wilson, Imbus, Pegelow, & Allen, 1978). Although the risk for stroke is highest for patients with HgbSS disease, strokes have been reported in patients with HgbSC and HgbSβthal disease as well (Ohene-Frempong, 1991; Powars et al., 1978). Ischemic stroke is most common in children, whereas hemorrhagic
stroke is most common in adults, a reversal of the usual age pattern for CVAs (Powars et al., 1978). Evidence from postmortem exams, angiographic studies, computed tomography, magnetic resonance imaging (MRI), and transcranial Doppler ultrasound studies indicates that the majority of cases of CVA in SCD involve multiple stenoses of the distal internal carotid and proximal anterior and middle cerebral arteries (Adams et al., 1992; Kugler et al., 1993; Rothman, Fulling, & Nelson, 1986; Stockman, Nigro, Mishkin, & Oski, 1972). The blood vessels usually show evidence of intimal proliferation, fibrosis, and fragmentation, and in some cases there is formation of thrombi.

Research consistently indicates severe neuropsychological deficits following stroke (defined clinically, not radiographically) in children with SCD (Armstrong et al., 1996; Cohen, Branch, McKie, & Adams, 1994; Powars et al., 1978; Wilimas, Goff, Anderson, Langston, & Thompson, 1980). These studies document cognitive functioning at the low borderline to mildly and even moderately retarded levels. Neurocognitive deficits are usually broad-ranging, although some lateralizing patterns corresponding to the affected hemisphere have been reported (Cohen et al., 1994). Cognitive functioning is especially likely to be severely impaired following multiple CVAs in comparison with single CVAs.

There is growing evidence that children with SCD who have never had a clinical stroke are at risk for cognitive deficits and learning problems. Recent studies have consistently reported neuropsychological dysfunction in patients with SCD and no history of CVA (Brown et al., 1993; Fowler et al., 1988; Noll et al., 2001; Swift et al., 1989; Wasserman, Wilimas, Fairclough, Mulhern, & Wang, 1991). Several of these studies found lower overall IQs for children with SCD relative to controls on the Wechsler Intelligence Scale for Children–Revised (WISC-R), with the magnitude of the difference between groups ranging from approximately one third of a standard deviation (Noll et al., 2001; Wasserman et al., 1991) to a full standard deviation (Swift et al., 1989). In addition, researchers have found evidence of specific deficits in academic skills (Brown et al., 1993; Fowler et al., 1988; Swift et al., 1989), attention (Brown et al., 1993; Fowler et al., 1988; Noll et al., 2001), short-term memory skills (Noll et al., 2001; Swift et al., 1989; Wasserman et al., 1991), and visual-motor coordination (Fowler et al., 1988).

Recent research indicates that an important phenomenon associated with SCD is silent stroke, which is defined as the presence of abnormalities on relevant neuroimaging studies, such as MRI, in the absence of overt clinical symptoms (Craft, Schatz, Glauser, Lee, & DeBaun, 1993). Data from the Cooperative Study of Sickle Cell Disease (CSSCD), which provide perhaps the best available evidence regarding the incidence of silent stroke, have indicated a rate of from 12 to 22% in children with SCD (Armstrong et al., 1996; Craft et al., 1993; Moser et al., 1996; Pegelow et al., 2002; Wang et al., 2001). The data from the CSSCD suggest that silent stroke is more prevalent in children with the HgbSS genotype than the HgbSC genotype and is more common in children with low hematocrit levels.

The evidence regarding the effects of silent stroke on neuropsychological functioning in children with SCD is not entirely consistent. Kugler et al. (1993) did not find significant differences on a variety of neuropsychological measures between a group of eight patients with abnormal MRI scans and a matched control group of eight patients with normal MRI scans. Similarly, Watkins et al. (1998) found that patients with silent stroke did not differ significantly from patients with normal MRI scans and controls on index scores from the WISC-R, design memory and paired associate memory tasks, and the Wisconsin Card Sorting Test. In contrast, several studies have provided evidence that silent stroke is associated with significant neuropsychological deficits. Craft et al. (1993) found that three patients with silent strokes involving anterior lesions made significantly more intrusion errors on the Children’s Auditory Verbal Learning Test than did a sibling control group. Three children with silent strokes involving diffuse lesions scored significantly lower than sibling controls on the Block Design and Object Assembly subtests from the WISC-R. Data from Armstrong et al. (1996) indicated that patients with silent strokes had lower IQ scores than those with normal MRIs (WISC-R full-scale IQ [FSIQ] = 82.8 vs. 90.0). Steen et al. (1998) found a significantly lower WISC FSIQ for patients with abnormal MRI scans compared with patients with normal MRI scans. Brown et al. (2000) reported impaired neuropsychological functioning of patients with silent strokes compared with healthy controls, though this achieved significance on only one measure (Trail Making Test B, Time to Completion) in their battery. Wang et al. (2001) reported that children with HgbSS and silent infarcts had significantly lower scores for FSIQ, verbal IQ, performance IQ, and reading and math achievement compared with children with normal MRI studies. A study by Bernaudin et al. (2000) indicated that silent stroke in children with SCD was associated with reduced
scores on the vocabulary and similarities subtests from the Wechsler Preschool and Primary Scale of Intelligence–Revised and WISC-III. Interestingly, in this latter study, the relationship between silent stroke and IQ was mediated by low hematocrit and thrombocytosis. Steen et al. (2003), on the other hand, found that in patients with SCD without a history of clinical stroke, MRI abnormalities and low hematocrit independently predicted decreased performance on the cognitive factors assessed by the Wechsler scales.

Sample size may be a critical factor in explaining the variability in the research findings to date, as studies which have found a significant relationship between silent stroke and reduced neuropsychological functioning have tended to have a larger sample size compared with those which have found no relationship. While the bulk of the evidence thus suggests that children with SCD who have silent stroke are at increased risk for neurocognitive deficits, it would also appear from the Bernaudin et al. (2000) study that this relationship is not straightforward.

The study reported here is part of an ongoing, prospective investigation of the psychosocial functioning of children with SCD. An earlier publication (Noll et al., 2001) presented the neuropsychological functioning of the sample as compared with matched classroom controls. In the portion of the research presented in this paper, we investigated the relationship of neuropsychological functioning in children with SCD to an array of biological variables, including disease status and neuroimaging studies. We hypothesized that imaging abnormalities would be associated with decrements in neuropsychological functioning. Unlike previous research which has emphasized “level of performance” on neuropsychological measures (i.e., score levels on standardized tests), our study also examined whether “intra-individual variability,” or the degree of variability in performance across neuropsychological domains within each patient, was related to disease factors in SCD (Ris et al., 1996).

**Methods**

**Participants**

The subjects include 31 children with SCD. Initially, 36 eligible children with SCD ages 9 to 16 years were randomly selected from 80 children who met study criteria being treated at the Cincinnati Comprehensive Sickle Cell Clinic, Children’s Hospital Medical Center (due to fiscal constraints, the size of our sample was limited, and random sampling was used to reduce selection bias). Of these 36, 5 patients did not participate in the study; 2 could not be located, and the parents/guardians of 3 declined to participate. This medical center has the only inpatient pediatric facility within the region and virtually every child with a sickle hemoglobinopathy in the area is followed here. Confirmation of the hemoglobin phenotype was obtained by cellulose acetate (pH = 8.6) gel electrophoresis. Inclusion criteria for the study were that children must not be in fulltime special education placement and not have a history of CVA or other detectable neurological disorder. No children were excluded from the study because of these criteria. Approximately half of the children with SCD had HgbSS (n = 15), and the remainder had HgbSC (n = 9), HgbSβthal (n = 6), or HgbSβthal (n = 1). The sample included 12 boys and 19 girls with a mean age of 11.9 years (SD = 1.4). The subsample of children with imaging studies was similar to the overall sample in age (mean = 11.8, SD = 1.6), but for this subgroup there was a bias toward females (6 boys, 16 girls). All participants were African American. Demographic information suggested that the children’s primary caregivers had occupational roles predominantly in clerical, service, and semiskilled-laborer positions. Each subject with SCD was matched case-by-case with a child without SCD who was in the same classroom, of the same race and gender, and closest in date of birth. Although data from the classroom controls are not included in this report, they were used in some of the data reduction procedures which are described below. Noll et al. (2001) should be consulted for relevant results comparing the neuropsychological functioning of children with SCD with the classroom controls.

**Procedures**

Prior to completing any of the neuropsychological evaluations and imaging studies, informed consents were obtained from the parents/guardians. Separate consents were obtained for the neuropsychological and imaging studies. Testing was completed at a time and location convenient for the family (most commonly in the home) by a trained graduate student in clinical child psychology or a psychometrist who was blind as to the disease status and imaging results. Families were reimbursed $100 for their participation in this phase of the study. Flexibility in scheduling and place of testing and reimbursement ensured high rates of participation. The study was approved by the Children’s Hospital Medical Center institutional review board.
Neuropsychological Measures
Each subject was administered a neuropsychological battery. General intellectual skills were assessed by administration of all subtests of the WISC-R (Wechsler, 1974). The reading, spelling, and arithmetic subtests from the Wide Range Achievement Test–Revised (WRAT-R) (Jastak & Wilkinson, 1984) were used to assess academic skills (the more recent editions of the WISC and WRAT, i.e., the WISC-III and WRAT-3, were not available when we began our data collection). Immediate verbal and visual memory skills were assessed by administration of the sentence memory and design memory subtests from the Wide Range Assessment of Memory and Learning (WRAML) (Sheslow & Adams, 1990), which have been shown to load the highest on its verbal and visual factors, respectively. The Beery Visual Motor Integration Test–Third Revision (VMI) was used to measure visual-motor skills (Beery, 1989). The Matching Familiar Figures Test (MFFT) is a matching-to-sample test which was selected because it has been designed to measure the impulsivity-reflectivity dimension of children’s cognitive styles (Kagan, 1966) and has been used in previous research on SCD (Fowler et al., 1988). The Purdue Pegboard Test was administered to assess fine motor dexterity in both upper extremities (Gardner & Bro- man, 1979).

Disease Severity
To objectively document disease severity, a systematic and comprehensive review of the medical record of each child with SCD was completed to generate two clinical severity indices, one based upon symptoms experienced during the 6 months prior to the neuropsychological assessment (6-month severity), and the second based upon symptoms during the entire life of the child (lifetime severity) (Cameron, Christian, Lobel, & Gaston, 1983). The severity scores were based on a variety of clearly defined factors, including the occurrence of hospitalizations, pain episodes, organ involvement, and growth velocity. Since the two disease severity indices were highly correlated, only the lifetime severity index was retained for further analyses. In addition, each patient’s average hemoglobin level during the 6-month period prior to the neuropsychological evaluations was recorded. These objective indices of disease severity have been shown to be significantly correlated with medical providers’ perceptions of disease severity (Cameron et al., 1983).

Neuroimaging Studies
Conventional MRI and MR perfusion studies were obtained from 22 of the children with SCD. Data for 9 of the initial sample of 31 children with SCD were not available because of poor bolus effect (N = 2), incomplete attainment of images (N = 1), failure of patient to sit still (N = 1), lost data (N = 4), and failure of family to participate (N = 1). Twelve of the children with SCD who participated in this part of the study had HgbSS, 6 had HgbSC, and 4 had HgbSβthal. Conventional and perfusion-weighted MRIs were performed on an MR system operating at 1.5 T (GE Medical Systems, Milwaukee, Wisconsin). Imaging consisted of an initial sagittal T1-weighted localizer sequence (800/15/2 excitation), followed by spin echo T2-weighted imaging (2500/30–100/1 excitation/259 × 192/8 MHz) in the axial projection. Perfusion imaging was performed at the level of the basal ganglia at a single slice location (n = 9) or as a dual slice location through the basal ganglia and at the midcentrum semiovale (n = 13). The technique used for the perfusion sequence was that which has been previously described by Tzika et al. (1993). Briefly, MR perfusion is a relatively new procedure that involves administration of a rapid and compact intravenous bolus of MRI contrast agent. Analysis of the diffusion of the contrast provides relevant information about blood perfusion in the brain (Tzika et al., 1993).

Neuroimaging studies and neuropsychological testing were completed within 1 month of each other for 16 of the children, and within 2, 3, 4, 5, 7, and 8 months of each other for the remaining 6 children. The variability in duration between completion of neuroimaging studies and neuropsychological testing was due to the need to reschedule appointments because of cancellations by several families.

Data Analysis
Neuropsychological Measures
In order to reduce Type 1 error, scores from the neuropsychological evaluations were reduced to five level-of-performance scores: verbal (information, similarities, vocabulary, and comprehension subtests from the WISC-R), achievement (reading, spelling, and arithmetic subtests from the WRAT-R), spatial/constructional (picture completion, picture arrangement, block design, object assembly, and maze subtests from the WISC-R and the VMI), attention/memory (coding, arithmetic, and digit span subtests from the WRAML; sentence and design memory subtests from the WRAML; and error and latency scores from the MFFT), and motor
(scores for dominant, nondominant, and both hands from the Purdue Pegboard). These five scores were also summed to yield an overall level-of-performance score. Formation of the five above summary variables was similar to the procedures outlined by Capaldi and Patterson (1991), which involves use of a combination of rational and empirical criteria. Details of our construct-building procedure are available in our earlier publication (Noll et al., 2001).

We also decided a priori to derive intra-individual variability scores in order to characterize the degree of variability in each subject’s neuropsychological profile. Seven indicators of variability were developed: FSIQ versus achievement scores; verbal IQ versus performance IQ; FSIQ versus memory (sentence plus design memory) scores; verbal memory (sentence memory) versus visual memory (design memory) scores; achievement versus memory scores; dominant- versus nondominant-hand fine motor scores; and error + latency scores on the MFFT versus FSIQ. Variability scores were computed by using the results of a regression analysis to predict the values of one variable from those of the other (based on the actual correlations between variables in our full sample of 62 subjects, i.e., including the children with SCD and their classroom controls), subtracting the actual from the predicted value, and dividing by the standard error. Larger scores indicate a greater degree of variability in performance. The advantage of this method in computing discrepancy scores as compared with single-cutoff-point or simple difference methods is that the regression approach takes into account the degree of correlation between two variables. The seven indicators of variability were also summed to yield an overall intra-individual variability index, which provided a summed variability score for each subject.

Neuroimaging Studies

A two-component scoring system was devised for evaluating the structural and MR perfusion studies. First, findings on conventional T2-weighted MRI in the axial projection were scored to evaluate major structural features of the brain and to quantify the degree of abnormality of impairment. Specifically, the structural features which were scored included ventricular enlargement, asymmetry of the lateral ventricles, prominent extra-axial fluid spaces, number of white matter lesions, size of the largest well-defined lesion, white-versus gray-matter involvement, number of cerebral lobes with lesions, and presence of lesions in brain-stem, cerebellar, and basal ganglia locations. Second, findings on MR T2-weighted perfusion imaging were examined in order to identify areas of altered tissue perfusion of brain parenchyma that might indicate early changes of vascular compromise. Specifically, perfusion studies were scored with respect to presence of hemispheric asymmetries in perfusion patterns and number of lobes which demonstrated decreased perfusion. This was based on visual inspection by neuroradiologists who had experience in the use of this technique, which in turn was informed by calculation of relative perfusion values (e.g., between hemispheres) and review of studies obtained locally on children with and without evidence of CNS disease (see Tzika et al., 1993, for more complete discussion). Each element of the scoring system was designed to express a trend in severity, whereby a higher score indicated an increase in clinical severity.

The neuroimaging studies for each patient were independently scored by two pediatric neuroradiologists. The developer of the system (W.B.) trained the second neuroradiologist in the use of the system using imaging from children who were not part of this study. Interrater agreement for the scoring system was excellent; agreement between the two raters was perfect for every category in the system except the number of lesions present, on which the raters differed only by a single lesion in three patients.

A total abnormality score was computed for each patient by summing scores across all categories in the scoring system. An item analysis of the scoring system was conducted excluding the categories of brain-stem and cerebellar involvement because no abnormalities were detected in these areas. The results indicated that the scoring system possessed a high degree of internal consistency; the correlations of items to total score ranged from .57 to .92 for all of the items in the scoring system except ventricular enlargement and ventricular symmetry, which were not significantly correlated with total scores. The coefficient α for the entire set of items was .90, indicating a high degree of internal consistency. Total scores were also derived separately for the structural and perfusion ratings by computing individual scores for each of the items in these two separate domains and then summing these to obtain total scores. Both of the resulting measures were significantly correlated with the total imaging abnormality score ($r = .96, p < .05$, for the structural rating score; and $r = .69, p < .05$, for the perfusion rating score). The correlation between the structural and perfusion rating scores was also significant, but lower in magnitude ($r = .47, p < .05$), suggesting that the structural and perfusion ratings were
assessing somewhat independent characteristics. Additional reliability and validity data regarding this scoring procedure are available from the authors.

**Results**

Sickle cell genotype was not related to children’s neuropsychological performance. Comparisons contrasting the performance of children with more severe genotypes, HgbSS and HgbSBthal (N = 16), with that of children with less severe genotypes, HgbSC and HgbSBthal (N = 15), were not statistically significant for any level-of-performance or intra-individual variables (Table I). Similarly, none of the correlations between disease severity (lifetime severity and Hgb level) and neuropsychological measures (i.e., level and variability indices) were significant (Table II), with the exception of a modest positive correlation between lifetime severity and the motor composite. However, the reliability of this association is questionable given that it could be accounted for by Type I error, and the direction of the association is counterintuitive (i.e., higher disease severity associated with better fine motor ability). Incidentally, these findings were the same when only those patients with MRIs (N = 22) were considered.

Ten children (45% of the sample with available data) exhibited abnormalities on the neuroimaging studies. Of these, two had structural abnormalities only, five had perfusion abnormalities only, and three had both structural and perfusion abnormalities. The structural abnormalities consisted primarily of small but numerous and diffuse punctate lesions in the white matter, and the perfusion abnormalities consisted primarily of areas of hypoperfusion, especially in the frontal lobes.

<table>
<thead>
<tr>
<th>Table I.</th>
<th>Genotype Contrasts on Neuropsychological Variables</th>
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<tr>
<td></td>
<td>HgbSS and HgbSBthal (N = 16)</td>
</tr>
<tr>
<td>Composite scoresa</td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>89.0 ± 8.12</td>
</tr>
<tr>
<td>Spatial</td>
<td>91.4 ± 10.26</td>
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<tr>
<td>Achievement</td>
<td>84.4 ± 13.67</td>
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<tr>
<td>Attention/memory</td>
<td>92.7 ± 8.11</td>
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<tr>
<td>Motor</td>
<td>80.1 ± 11.83</td>
</tr>
<tr>
<td>Overall scores</td>
<td></td>
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<tr>
<td>Level of performance</td>
<td>96.0 ± 11.13</td>
</tr>
<tr>
<td>Intra-individual variabilityb</td>
<td>104.3 ± 16.77</td>
</tr>
</tbody>
</table>


a Standard scores, mean = 100, SD = 15.

b Higher scores on this index are associated with greater variability within subjects.

The presence of neuroimaging abnormalities was strongly correlated with greater clinical disease severity and lower Hgb levels (Table III). Spearman’s rho was used in these analyses because of the marked skewness in the distributions of the imaging variables. The total abnormality score was of primary interest because of its greater reliability as a function of the larger number of subjects with imaging abnormalities (N = 10) in contrast to the structural (N = 5) and perfusion (N = 8) scores, and this is reflected in our analytic strategy. Anecdotally, patients who exhibited neuroimaging abnormalities seemed to be at increased risk for clinical stroke in that all three patients who demonstrated both structural and perfusion abnormalities subsequently developed overt clinical symptoms of stroke. Neuroimaging abnormalities were not significantly correlated with level of neuropsychological performance (i.e., IQ and level-of-performance scores) (see Figure 1) but were positively related to the amount of variability or unevenness in performance across different neuropsychological domains (see Figure 2 and Table III). Analysis of the seven component scores constituting the overall variability index indicated that the primary contributor to this significant relationship was the variable which compared performance on the memory tasks (WRAML sentence and design memory) with FSIQ. Mean scores on the level-of-performance and intra-individual summary variables for children with and without abnormalities of any kind on structural or perfusion studies considered separately were not significantly different (p > .05 in all cases).

<table>
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<tr>
<th>Table II.</th>
<th>Pearson Correlations Between Disease Severity (DS) and Neuropsychological Variables (N = 31)</th>
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<tbody>
<tr>
<td>Composite scores</td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>.17</td>
</tr>
<tr>
<td>Spatial</td>
<td>−.07</td>
</tr>
<tr>
<td>Achievement</td>
<td>.14</td>
</tr>
<tr>
<td>Attention/memory</td>
<td>.21</td>
</tr>
<tr>
<td>Motor</td>
<td>.32*</td>
</tr>
<tr>
<td>Overall scores</td>
<td></td>
</tr>
<tr>
<td>Level of performance</td>
<td>.20</td>
</tr>
<tr>
<td>Intra-individual variability</td>
<td>.14</td>
</tr>
</tbody>
</table>

*p < .05, one-tailed. For overall scores, the significance level was adjusted to p = .025, one-tailed, based on a Bonferroni testwise correction (i.e., p = .05/2).

The presence of neuroimaging abnormalities was strongly correlated with greater clinical disease severity and lower Hgb levels (Table III). Spearman’s rho was used in these analyses because of the marked skewness in the distributions of the imaging variables. The total abnormality score was of primary interest because of its greater reliability as a function of the larger number of subjects with imaging abnormalities (N = 10) in contrast to the structural (N = 5) and perfusion (N = 8) scores, and this is reflected in our analytic strategy. Anecdotally, patients who exhibited neuroimaging abnormalities seemed to be at increased risk for clinical stroke in that all three patients who demonstrated both structural and perfusion abnormalities subsequently developed overt clinical symptoms of stroke. Neuroimaging abnormalities were not significantly correlated with level of neuropsychological performance (i.e., IQ and level-of-performance scores) (see Figure 1) but were positively related to the amount of variability or unevenness in performance across different neuropsychological domains (see Figure 2 and Table III). Analysis of the seven component scores constituting the overall variability index indicated that the primary contributor to this significant relationship was the variable which compared performance on the memory tasks (WRAML sentence and design memory) with FSIQ. Mean scores on the level-of-performance and intra-individual summary variables for children with and without abnormalities of any kind on structural or perfusion studies considered separately were not significantly different (p > .05 in all cases).

**Discussion**

MRI abnormalities occurred at a high rate in our sample of children with SCD despite the fact that patients were
initially selected on the basis of a negative history of clinical neurological events. The presence of imaging abnormalities was associated with a greater amount of variability or unevenness in neuropsychological development rather than with a distinct profile or a deficit in overall level of performance. The potential sensitivity of indices of variability or difference scores is supported by neurodevelopmental models that have been advanced regarding the effects of early lesions (e.g., Dennis, 1988). Irregularities across neuropsychological domains (beyond level of performance) have also proven to be revealing in studies of other disorders, such as preclinical Alzheimer’s (Jacobson, Delis, Salmon, & Bondi, 2002; Mitrushina, Uchiyama, & Satz, 1995).

Although several studies have examined the relationship between silent stroke and level of neurocognitive functioning (Armstrong et al., 1996; Bernaudin et al., 2000; Brown et al., 2000; Craft et al., 1993; Kugler et al., 1993; Steen et al., 2003; Steen et al., 1998; Tzika et al., 1993; Wang et al., 2001; Watkins et al., 1998), our study appears to be the first to examine the relationship to the variability of children’s neuropsychological functioning. Thus, the finding that neuroimaging abnormalities were related to increased variability in neuropsychological functioning is intriguing and bears replication. Possibly children affected by SCD-related neuropathological changes develop a pattern of enhancement of some cognitive skills to offset or compensate for weak skills that have been adversely affected by these changes, thus increasing ability “scatter” while preserving overall level of functioning on omnibus measures. Or perhaps inconsistent cognitive performance is a reflection of frontal-executive dysfunction as found by Brown et al. (2000). Our data suggest that the increased intra-individual variability in neuropsychological performance for children with silent imaging abnormalities may be particularly related to increased variability in memory skills with respect to indices of general cognitive ability (i.e., FSIQ); that is, they demonstrate greater discrepancy between their level of functioning on measures of memory compared with general intellectual skills than do children with SCD who do not have silent imaging abnormalities. It is important to note, though, that our memory tasks assessed primarily immediate memory (e.g., sentence repetition) rather than long-term memory processes (such as delayed recall of story information).

In our earlier paper (Noll et al., 2001) we found that children with SCD differed significantly from controls on level of performance but not on variability scores, a finding that would appear inconsistent with the results reported in the current study. However, the Noll et al. (2001) study and the results reported herein pertain to two different sources of variability (between-group and within-group) which do not necessarily follow the same pattern of relationships.

Our failure to find a significant relationship between MRI abnormalities and level of neuropsychological performance is consistent with the results of Kugler et al. (1993) and Watkins et al. (1998), but is contradicted by the findings of several studies (Armstrong et al., 1996; Bernaudin et al., 2000; Craft et al., 1993; Steen et al., 2003; Steen et al., 1998; Wang et al., 2001; Watkins et al., 1998) which found that silent stroke was associated with greater impairment in terms of performance. Several factors may potentially explain these discrepant findings. Sample size clearly appears to be a relevant factor, as the samples tended to be smaller in the studies which found null results compared with those which

| Table III. Spearman Correlations of Magnetic Resonance Imaging Clinical Ratings with Disease Severity (DS) Variables and Neuropsychology Composite Scores (N = 22) |
|-----------------|-----------------|-----------------|
|                | Abnormality Scores |                |
|                | Total            | Structural      | Perfusion      |
| DS-Lifetime    | .63*             | .58*            | .64*           |
| Hemoglobin     | −.63*            | −.32            | −.60*          |
| Level of performance | .08            | .06             | .10            |
| Intra-individual variability | .44*           | .31             | .34            |

*p < .025, one-tailed, with significance level adjusted by Bonferroni testwise correction separately for the two disease and two neuropsychological variables (p = .05/2).
found significant relationships. A related concern in our study was that there was limited variability in our neuroimaging variables: 12 of the 22 children with available neuroimaging studies had no structural or perfusion abnormalities and thus received identical scores on the neuroimaging variables. However, despite this restricted variability, the neuroimaging variables, particularly the perfusion scores, were strongly related to the independently derived disease severity variables, and the structural scores were significantly related to intra-individual variation in neuropsychological performance. Thus, there was strong evidence to indicate that the neuroimaging variables assessed reliable variance. Nevertheless, the restricted variation in these scores may have obscured more subtle but genuine relationships with the neuropsychological level of performance variables. We should also note that each of our major neuropsychological construct variables represented contributions from several specific tasks. We deemed it essential to develop the construct variables in order to control for Type I error associated with the very large number of specific neuropsychological variables which were included in our study; however, it is possible that this may have obscured the presence of significant relationships between the neuroimaging data and more specific neuropsychological variables. Other factors that may be relevant to explaining the inconsistent results regarding the neurocognitive effects of silent stroke include differences across studies in (a) sampling approach and attrition, (b) the comprehensiveness of the neuropsychological battery (particularly in regard to frontal-executive functions), and (c) the chronicity of these imaging abnormalities.

The neuroimaging data from our study suggest that structural and perfusion abnormalities may reflect different mechanisms of pathology rather than simply being different facets of the same underlying disease process. Specifically, structural and perfusion scores were only weakly correlated with each other; and perfusion scores were correlated with Hgb levels, whereas structural scores were not. In addition, 23% of our sample (5 of 22 patients with available neuroimaging studies) were identified as having abnormal MRI studies on the basis of perfusion abnormalities, even though their conventional MRI studies were normal. And although the sample size was small, children who demonstrated both perfusion and structural abnormalities, in contrast to those with only structural or only perfusion abnormalities, were highly vulnerable to subsequent stroke. These findings are consistent with those of previous research suggesting that children with SCD who have a negative history of stroke may nevertheless exhibit a variety of CNS abnormalities which are only partially captured by conventional MRI studies (Powars et al. 1999; Steen et al., 1998).

In summary, silent stroke is a common and important phenomenon in children with SCD, the neuropsychological implications of which remain to be fully elucidated. We found a significant correlation between neuroimaging abnormalities and disease severity variables, suggesting that changes in brain structure and function, even before a clinical event, are associated with broad-based indicators of compromised physical health in children with SCD. Furthermore, our data as well as that of Pegelow et al. (2002) suggest that the CNS in these children may be under severe challenge because of an increased risk for future stroke, which is clearly associated with significant neuropsychological impairment.

Though not evident in our data, the bulk of the literature suggests that silent stroke is associated with at least mild reduction in neurocognitive functioning. Corresponding to our finding that structural and perfusion MRI variables appeared to be related to at least somewhat different disease processes, functional imaging studies, such as those by positron emission tomography and functional MRI, may be particularly enlightening with respect to elucidating the relationships between silent stroke and neuropsychological performance. Finally, our data indicating that neuroimaging abnormalities were related to increased intra-individual variability in neurocognitive performance
suggest that silent stroke may be associated not only with less efficient cognitive functioning, but also with increased variability or unevenness across domains of cognitive skills.

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