Patterns of Verbal Long-Term and Working Memory Performance Reveal Deficits in Strategic Processing in Children with Frontal Infarcts Related to Sickle Cell Disease

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Frontal brain regions are thought to mediate strategic processes that facilitate memory. We hypothesized that children with frontal cerebral infarcts related to sickle cell disease (SCD) would exhibit impairments in long-term and working memory as a result of disruptions in strategic processing. Word list learning and digit span tasks were used to assess verbal memory and strategic processing in 21 children with SCD without infarcts (controls) and 10 children with SCD with frontal infarcts. On the word list learning task, children with frontal infarcts performed more poorly in terms of learning and free recall, although recognition and cued recall were adequate; this pattern suggested intact encoding and storage but impaired retrieval. Children with frontal infarcts performed more poorly on backward digit span, although forward digit span was adequate; this pattern suggested intact maintenance but impaired manipulation of information in working memory. Overall, these findings support the notion that disruptions in strategic processing contribute to memory impairments in children with frontal infarcts.
Unfortunately, in a number of the studies just cited, the presence or absence of clinical strokes was used to classify children rather than the presence or absence of cerebral infarcts as evidenced by magnetic resonance imaging (MRI). This is problematic because a substantial number of children with SCD experience silent cerebral infarcts (Moser et al., 1996). Silent infarcts are not accompanied by motor abnormalities, and therefore are not typically detected during the course of standard neurological examinations. Children with silent infarcts may not be diagnosed with stroke, but they may have significant neuropsychological impairments resulting from damage to brain regions other than motor cortex (Armstrong et al., 1996; Craft et al., 1993; DeBaun et al., 1998). Of particular relevance to the present study, SCD-related infarcts often occur in the distribution of the anterior cerebral artery and/or the anterior distribution of the middle cerebral artery (Moser et al., 1996; Serjeant, 1992), thereby damaging frontal brain regions that subserve executive abilities (Stuss, 1992).

Previous research has shown that frontal brain regions play a significant role in supporting two executive aspects of memory: organizational strategy use in long-term memory (Incisa della Rocchetta & Milner, 1993; Gershberg & Shimamura, 1995; Moscovitch, 1992; Stuss et al., 1994) and manipulation of information in working memory (Casey et al., 1995; Jonides et al., 1993; Luciana & Nelson, 1998; Thome et al., 1999). In terms of long-term memory, Moscovitch suggested a model in which posterior brain regions subserve simple associative processing and long-term storage. Frontal brain regions, however, mediate strategic control processes that facilitate the efficient organization of complex information, which in turn facilitate the formation of robust memory traces (Moscovitch, 1992; Moscovitch & Umilta, 1990, 1991). This model has been supported by neuroimaging findings of frontal cortex involvement in long-term encoding and retrieval (Buckner & Petersen, 1996; Kapur et al., 1994; Nyberg, Caeza, & Tulving, 1996; Petrides, 1995). Turning to working memory, posterior brain regions also are thought to subserve the simple maintenance of information in working memory, whereas frontal brain regions appear to mediate the strategic manipulation of information (for an overview, see Petrides, 1995).

From a developmental perspective, research suggests that maturation of the frontal cortex is accompanied by an increase in the use of executive strategies (Dempster, 1992; Gathercole & Baddeley, 1993). Results of studies with children having damage to frontal brain regions support this notion, as such injury results in impaired use of organizational strategies (Levin et al., 1996; White, Nortz, Mandernach, Huntington, & Steiner, 2001) and working memory (White, Nortz, Mandernach, Huntington, & Steiner, 2002; White et al., 2000). In spite of the clear importance of executive abilities in performing everyday tasks (Burke, Zencius, Wesolowski, & Doubleday, 1991), learning new tasks (Sohlberg, Mateer, & Stuss, 1993), and generally enhancing higher order cognition (Shallice & Burgess, 1991; Stuss, 1992), very little research within this neuropsychological domain has been conducted with children with SCD-related infarcts. The aim of our investigation was to build on existing research to evaluate the hypothesis that the use of strategic, executive processes facilitating verbal learning and memory are disrupted in children with SDC-related frontal infarcts. Two aspects of frontally-mediated executive processing are particularly relevant to this endeavor: (1) the use of organizational strategies to facilitate long-term episodic memory and (2) the ability to manipulate information in working memory. We assessed these two aspects of executive ability in children with SCD-related frontal infarcts by examining patterns of performance on word-list learning and verbal memory span tasks.

**METHOD**

**Participants**

The study sample included 31 African American children who were recruited through the Division of Hematology/Oncology in the Department of Pediatrics at St. Louis Children’s Hospital. The recruited children comprised two study groups. Group classifications were made on the basis of the presence or absence of cerebral infarcts affecting frontal brain regions as evidenced by T1- and T2-weighted MRI without contrast. Infarcts were classified as frontal if confined to the anterior cerebral artery territory or anterior distributions of the middle cerebral artery. There were 21 children with SCD who had no history of stroke or observable infarcts (control group) and 10 children with cerebral infarcts affecting frontal brain regions (infarct group).

Demographic information for each group is listed in Table 1. There were no significant differences between the groups in terms of gender, years of age, years of education, or estimated Verbal IQ (based on the Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999). There were no children in the sample with histories of major medical disorders or learning disorders (e.g., dyslexia or Attention Deficit Hyperactivity Disorder) unrelated to SCD.
Procedure

Tests of learning and memory were administered as components of a larger neuropsychological battery requiring approximately three hours for administration.

*Long-term episodic learning and memory.* The California Verbal Learning Test–Children’s Version (CVLT–C; Delis, Kramer, Kaplan, & Ober, 1994) was used to assess long-term episodic learning and memory of a 15-item word list (List A). This test was designed for administration to children through 16 years of age. In the present study the test was administered to children through 17 years of age. The inclusion of a control group in our study, however, allowed interpretation of findings without referring to the normative data accompanying the test. In addition, no ceiling effects were observed in our study, indicating that the test was sufficiently challenging for the 17-year-old children in our study.

Each of the 15 words on the word list belonged to one of three semantic categories (things to play with, things to wear, and fruits). Children listened as an examiner read List A aloud over five learning trials; after each trial, children were asked to recall as many words as possible. A 15-word distractor list (List B) was then presented for recall. Immediately following recall of List B, children were again asked to recall as many words as possible from List A (short-delay free recall), without hearing the list again. Children were then given a cued recall test of List A (short-delay cued recall) in which they were provided with the three semantic categories and were asked to recall as many words as possible belonging to each category. A 20-minute delay followed the short-delay cued recall trial. After this delay, free recall and cued recall of List A were again assessed. This was followed by a recognition trial during which children indicated whether or not each of 45 words (15 targets and 30 non-targets) was present in List A. In addition to these variables, the use of semantic clustering on Trials 1 and 5 was assessed. One point was awarded each time a child consecutively recalled two words belonging to the same semantic category. A semantic cluster ratio was calculated by dividing the cluster score by the number of words recalled on Trials 1 or 5.

*Working Memory.* The Digit Span subtest from the Children’s Memory Scale (CMS; Cohen, 1997) was used to assess the ability to briefly maintain and manipulate information in working memory. In the first condition of this subtest, forward digit span, children were asked to listen and then repeat lists of digits in serial order. In the second condition of this subtest, backward digit span, children were asked to listen and then recall lists of digits in reverse serial order. In both conditions, presentation began with a pair of lists comprising two digits. The number of digits presented in subsequent pairs of trials increased by one digit (e.g., 3-1, 5-7; 4-9-2, 5-8-1; etc.). Children attempted recall of each list of digits immediately following presentation. Each condition was discontinued when both trials of a given number of digits were incorrectly recalled. Digit span was recorded as the number of digits in the longest series correctly recalled in forward or reverse order. One child with SCD-related frontal infarct did not complete the digit span subtest due to an interruption in testing.

**Results**

Study variables were subjected to analysis of covariance variance (ANCOVA). Group (control and infarct) served as the between-subjects variable in all analyses. Although age and estimated Verbal IQ were not significantly different between our groups, children in the control group tended to be younger and to have higher estimated Verbal IQs. Because small differences in these variables can have substantial effects during early development, age and estimated Verbal IQ were included as covariates in all analyses.

**Long-Term Episodic Learning and Memory**

To assess learning and recall over repeated trials, we compared the number of words on Trials 1 and 5 that were correctly recalled by the control and infarct...
groups. Mixed model ANCOVA, with condition (Trial 1 and Trial 5) as the within-subjects variable, revealed a significant interaction between group and condition, $F(1, 27) = 5.55, p < .05$; the effects of group and condition were not significant. Additional analyses were performed to determine the nature of the interaction. On Trial 1, there was no significant difference between the groups, indicating that initial learning of List A was approximately equivalent for the control and infarct groups. On Trial 5, however, the infarct group recalled significantly fewer words than the control group after controlling for the contribution of initial learning on Trial 1, $F(1, 26) = 6.06, p < .05$. Thus, although initial learning and recall were equivalent, children with SCD-related cerebral infarct failed to learn and recall as many words as control children over repeated trials.

Differences in semantic clustering, encoding, storage, and retrieval were examined as possible reasons for the between-group difference in learning and recall over repeated trials. To evaluate possible differences in semantic clustering, mixed model ANCOVA was used, with condition (semantic cluster ratio on Trials 1 and 5) as the within-subjects variable. The effects of group and condition were not significant, and there was no significant interaction between group and condition ($p > .05$ in all instances). Possible differences in encoding, storage, and retrieval were evaluated by examining the pattern of performance on recognition, short-delay free recall, short-delay cued recall, long-delay free recall, and long-delay cued recall trials. ANCOVA revealed no significant between-group difference in terms of recognition discriminability ($p > .05$). In examining free and cued recall following short- and long-delays, recall on Trial 5 was used as an additional covariate to control for differences in performance following the last presentation of List A. For both short-, $F(1, 26) = 5.19, p < .05$, and long-delay free recall, $F(1, 26) = 5.18, p < .05$, the infarct group recalled fewer words than the control group. There were, however, no significant differences in cued recall following either the short- or long-delay ($p > .05$ in both instances). Taken together, this pattern reflects adequate recognition and cued recall accompanied by poor free recall. This suggests that encoding and storage were intact, but retrieval was impaired for children with SCD-related cerebral infarcts.

**Working Memory**

Mixed model ANCOVA, with condition (forward and backward digit span) as the within-subjects variable, revealed a significant interaction between group and condition, $F(1, 26) = 7.38, p < .05$; the effects of group and condition were not significant. Additional analyses were performed to determine the nature of the interaction. ANCOVA revealed that forward digit span was not significantly different between the groups ($p > .05$). Backward digit span, however, was significantly poorer for the infarct group after controlling for the contribution of simple maintenance as measured by forward digit span, $F(1, 25) = 8.66, p < .01$. Thus, simple maintenance was intact for children with SCD-related infarcts, but their ability to manipulate information in working memory was impaired.

**DISCUSSION**

We examined the hypothesis that children with SCD-related infarcts affecting frontal brain regions demonstrate impairments in the use of strategic, executive processing to facilitate verbal long-term and working memory. Our findings provided support for this hypothesis. With regard to long-term episodic learning and memory, in comparison with children with SCD who had no evidence of

**TABLE 2**

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<th>Control</th>
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<td>M</td>
<td>SD</td>
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<tr>
<td>California Verbal Learning Test - Children's Version</td>
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<tr>
<td>Trial 1 (words correct)</td>
<td>6.38</td>
<td>2.44</td>
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<td>Trial 5 (words correct)</td>
<td>12.10</td>
<td>1.87</td>
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<td>Trial 1 semantic cluster score</td>
<td>1.62</td>
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<td>Trial 5 semantic cluster score</td>
<td>5.29</td>
<td>3.20</td>
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<tr>
<td>Short delay free recall (words correct)</td>
<td>10.95</td>
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<tr>
<td>Short-delay cued recall (words correct)</td>
<td>11.33</td>
<td>2.11</td>
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<tr>
<td>Long delay free recall (words correct)</td>
<td>11.48</td>
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<tr>
<td>Long-delay cued recall (words correct)</td>
<td>11.40</td>
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<td>Recognition discriminability %</td>
<td>96.62</td>
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<th>Children's Memory Scale</th>
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<td>Forward digit span</td>
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<td>Backward digit span</td>
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were comparable for the infarct and control groups.

In his model of long-term memory, Moscovitch (1992) postulated that frontal brain regions mediate strategic, executive aspects of memory, whereas medial temporal brain regions mediate associative aspects of memory. The pattern of performance exhibited by children with SCD-related frontal infarcts in our study is consistent with this model. Associative aspects of memory were intact, as demonstrated by the fact that the recall of children with SCD-related frontal infarcts improved to the level of control children when they were provided with compelling retrieval cues. These children were, however, either unable to spontaneously generate strategies for recall or unable to spontaneously implement strategies for recall. The fact that semantic clustering was comparable for the control and infarct groups provides support for the later hypothesis. That is, children with infarcts spontaneously generated a semantic clustering strategy that appeared to facilitate encoding and storage; they did not, however, make use of this strategy to facilitate retrieval unless external support for doing so was provided.

In addition, in assessing working memory with forward and backward digit span tasks, we found that the ability to simply maintain information was intact in children with frontal infarcts, although their ability to actively manipulate information in working memory was impaired. It has been shown that frontal brain regions are the primary underpinnings of strategic, executive aspects of working memory, whereas posterior brain regions play the primary role in the simple maintenance of information (see Petrides, 1995). The pattern of performance exhibited by children with SCD-related frontal infarcts is consistent with these findings. Although simple span was comparable to that of controls, a dramatic reduction in span occurred when children with infarcts were required to actively manipulate information in working memory.

Taken together, our findings argue against concerns that the differences in memory performance between our two study groups were due to attention problems in children with SCD-related frontal infarcts. Attention problems may cause variability in memory performance, but a pre-existing diagnosis of ADHD was an exclusionary criterion for this study. Furthermore, it was observed that the numbers of intrusion and perseverative errors, as well as forward digit span, were comparable for the infarct and control groups.

Our findings suggest several possibilities for future research to more fully elucidate the nature of strategic memory processing deficits in children with SCD-related frontal infarcts. First, we are currently collecting data using the Rey-Osterrieth Complex Figure (Osterrieth, 1944; Rey, 1941) to determine if our findings with verbal materials generalize to nonverbal materials. Second, it will be of interest to examine possible age-related changes in strategic memory processing in children with SCD-related frontal infarcts; the restricted age range of children in the present study, however, precluded such analyses. Third, a more refined analysis of the correspondence between lesion location, lesion size, and strategic memory processing will be informative. Fourth, it will be of interest to compare the strategic memory processing abilities of children with SCD-related frontal infarcts with those of children with damage to frontal brain regions related to other medical etiologies (e.g., traumatic brain injury or epilepsy), as well as conducting comparisons with children with posterior brain damage. Overall, through the inclusion of children across a range of ages, lesion locations, and etiologies, we will achieve the most refined level of analysis of strategic memory processing following early brain injury. In turn, this will forward the development of more refined assessment tools and more specific methods for rehabilitating strategic processing impairments in children.

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REFERENCES


