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Systematic Review

Cognitive Function in Sickle Cell Disease Across Domains, Cerebral Infarct Status, and the Lifespan: A Meta-Analysis

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Abstract

Objective To provide a comprehensive quantitative review of neurocognitive function in sickle cell disease (SCD) across multiple domains, cerebral infarct status, and the lifespan. **Methods** One hundred and ten studies were identified in PubMed, MedLine, and PsycINFO involving 110 studies of 3,600 participants with SCD and 1,127 sibling or health controls. **Results** Meta-analytic findings indicate significant deficits across all neurocognitive domains, age groups, and infarct status. Significant deficits relative to the normative mean ranged from Hedges' $g = -.39$ to $g = -.63$ in preschool children, $g = -.83$ to $g = -1.18$ in school-aged children and adolescents, and $g = -.46$ to $g = -.86$ in adults. Deficits in full scale IQ (FSIQ), verbal reasoning, perceptual reasoning, and executive function increased from preschool to school-aged samples. However, findings also showed that deficits were smaller in adult samples relative to school-aged samples, likely due to sampling bias in adult studies. Findings across infarct status in sickle cell anemia showed that deficits ranged from $g = -.54$ to $g = -.65$ in samples without infarcts, $g = -.52$ to $g = -1.03$ in samples with silent cerebral infarct, and $g = -1.35$ to $g = -1.82$ in samples with stroke. Deficits in each domain increased in magnitude from no infarct or stroke, to silent cerebral infarct, to overt stroke. **Conclusion** Individuals with SCD are at risk for cognitive deficits across domains, infarct status, and the lifespan. More research is necessary to determine unbiased effects for cognitive function in adults with SCD.

Key words: age; cerebral infarct; cognitive function; sickle cell disease; stroke; preschool; school-age; adult.

Introduction

As a function of disease and social-environmental factors, individuals with sickle cell disease (SCD) are at increased risk for deficits in cognitive functioning compared with their typically developing peers (Kawadler, Clayden, Clark, & Kirkham, 2016; King et al., 2014; Schatz, Finke, Kellett, & Kramer, 2002). The primary focus of this meta-analytic review is to provide the first comprehensive quantitative analysis of cognitive function in SCD across multiple domains of cognitive function, cerebral infarct status, and the lifespan from infancy and early childhood to adulthood.

SCD is a group of hemoglobin disorders in which there is either a homogenous pair of the sickle hemoglobin (HbS) or a heterogeneous pair of HbS and a different abnormal hemoglobin gene. SCD is one of the most common genetic hemoglobin disorders, occurring

in approximately 1 in 400 to 500 African Americans in the United States (Hassell, 2010). The most common subtype, HbSS, occurs in 60–65% of those with the disease; followed by HbSC (25–30%); HbSβ^+ Thalassemia (8–10%); and HbSβ^0 Thalassemia (2–10%; Hassell, 2010; Ware, de Montalembert, Tshilolo, & Abboud, 2017). HbSS, also known as sickle cell anemia (SCA), and HbSβ^0 Thalassemia have more severe biological characteristics (Jordan & DeBaun, 2018). Due to the clinically indistinguishable phenotypic expressions and clinical risks associated with HbSS and HbSβ^0 (Estcourt et al., 2017), randomized controlled trials for SCA include both genotypes (e.g., DeBaun et al., 2014; Lee et al., 2006). Therefore, HbSS and HBSβ^0 Thalassemia are both classified as SCA in the current review in order to stay consistent with the clinical field. Common sequelae of the disease include chronic anemia, systemic ischemia, silent cerebral infarcts (SCIs), and overt strokes (Ohene-Frempong et al., 1998), all of which have significant influence on cognitive development (Kawadler et al., 2016).

Previous Reviews of Cognitive Function in SCD

Several narrative reviews have integrated findings from studies on cognitive function in children with SCD (e.g., Berkelhammer et al., 2007; Kral, Brown, & Hynd, 2001), and there have been three meta-analyses to date that have assessed the degree of cognitive deficits in this population (Kawadler et al., 2016; King et al., 2014; Schatz et al., 2002). First, Schatz et al. (2002) reported on findings from 17 published studies on cognitive function in school-aged children with SCD without a history of cerebral infarctions relative to healthy or sibling controls. The mean FSIQ across studies was 86.4, which was significantly lower than that of sibling or healthy controls (4.3 IQ points; $d = -0.31$) and national norms (13.6 IQ points; $d \approx -0.91$[1]). Categorical moderator analyses showed that the difference in FSIQ in children with SCD relative to healthy siblings or controls increased with age across late childhood and early adolescence spanning ages 9–13 years old. Schatz et al. also provided a narrative review of deficits in specific areas of cognitive functioning. Seventy-one percent of the investigated studies found that children with SCD were significantly impaired relative to controls in domains of attention, executive functioning, memory, and language; however, these domains of cognitive function were not quantitatively assessed.

Second, King et al. (2014) conduced a meta-analysis of the effect of SCI on FSIQ in school-aged children and adolescents with SCA. Using 10 studies, this meta-analysis found that children with SCA and SCI scored significantly lower (4.76 IQ points, $d \approx -0.32$) than children with SCA without a SCI; however, both groups scored significantly lower than the normative mean (no SCI FSIQ: 86.53, $d \approx -0.90$; SCI FSIQ = 82.17, $d \approx -1.19$).

Finally, Kawadler et al. (2016) recently published a meta-analysis that built upon prior analyses in this population. While Schatz et al. (2002) assessed FSIQ functioning in children with SCD without SCI or stroke relative to sibling or healthy controls, and King et al. (2014) assessed FSIQ in children with SCA with and without SCI, Kawadler et al. reported on FSIQ in children with SCD across three levels of comparison: (a) children with SCD without a history of SCI or stroke relative to healthy or sibling controls, (b) children with SCD with SCI relative to those without infarcts, and (c) children with SCD with overt stroke relative to SCI. Kawadler et al. also limited their analyses to only include studies that reported FSIQ as measured by a Wechsler intelligence scale. Findings were consistent with those in prior meta-analyses, as children with SCD score significantly lower (7 IQ points, $d \approx 0.46$) than healthy or sibling controls, and children with SCD and a history of SCI scored significantly lower (6 IQ points, $d \approx 0.40$) than those without SCI. Finally, children with SCD and a history of stroke scored significantly lower (10 IQ points, $d \approx 0.66$) than those with SCI.

Limitations of Previous Meta-Analyses

Although prior meta-analyses have presented important findings on the effect of SCD and cerebral infarcts on cognitive function, there have been several limitations. First, prior reviews have primarily focused on deficits in FSIQ. Schatz et al. (2002) qualitatively described studies that examined deficits in other domains; however, the review did not include a quantitative analysis of effect sizes across specific domains of cognitive function. Kawadler et al. (2016) only included studies that reported Wechsler FSIQ, which further limited the broader understanding of deficits across domains of functioning in this population by omitting other standardized tests of cognitive function. Although FSIQ is a reliable estimate of general intelligence, understanding and determining a pattern of deficits are clinically important when identifying mechanisms and designing interventions to mitigate the maladaptive effect of the disease on cognition. Determining mean effect sizes across studies is of critical importance. Thus, a primary aim of the current meta-analysis is to assess cognitive function in SCD across multiple domains.

Second, prior meta-analyses have only assessed cognitive function in school-aged children and

1 Cohen's *d* of cognitive function relative to the normative mean in Schatz et al. (2002), and all Cohen's *d* reported here for King et al. (2014) and Kawadler et al. (2016) were estimated using $SD = 15$ because neither Cohen's *d* nor weighted standard deviations were reported within these meta-analyses.

adolescents, and a quantitative analysis of cognitive function in preschool and adulthood has been neglected within the literature. It is important to investigate cognitive function in young children in order to determine how early deficits in cognitive function emerge. Further, it is similarly important to understand the long-term trajectory of cognitive function in adults with SCD, along with potential socioeconomic and biological consequences. In addition, previous research has identified negative relation between age and cognitive function found in school-aged samples (Schatz et al., 2002), and it is not clear if trajectory begins in infancy and preschool or if it continues into adulthood at the same rate. Another aim of the current meta-analyses is to determine whether there is a continued negative association of age with cognitive function in the adult population, or if the negative trend shown in school-aged children plateaus.

Finally, when assessing cognitive function in individuals with SCD, there are a series of comparisons that can be made based on different reference groups. Prior meta-analyses have only included comparisons relative to sibling or healthy controls or other children with SCD to determine the specific influence of the disease on cognition (Kawadler et al., 2016; King et al., 2014; Schatz et al., 2002); however, this approach may minimize the true degree of deficits in this population, as controls may also differ from the standardized normative mean. For example, sibling or healthy controls in the Schatz et al. (2002) meta-analysis also scored significantly lower (9.3 IQ points) than the normative mean. Several meta-analyses assessing cognitive function within pediatric samples have used the normative population mean as a comparison in order to clarify the magnitude of deficits (Compas, Jaser, Reeslund, Patel, & Yarboi, 2017). The current meta-analysis aims to assess deficits relative to the normative mean in addition to sibling and healthy controls.

Meta-Analytic Aims

A comprehensive analysis across a wide range of domains of cognitive function individuals with SCD across the lifespan is important when conceptualizing the deficits with which they are faced. In addition to this, it is important to take disease genotype and cerebral infarct status into account due to their association with cognitive function. Finally, both absolute and relative comparisons are necessary to understand the deficits with which individuals with SCD are faced. The first aim of the current meta-analysis is to assess cognitive function across three age groups (infancy and preschool-age children, school-age children, and adults) in samples of individuals with SCD. We also aim to assess cognitive function across cerebral infarct status (no infarcts, SCI, overt stroke) in samples of individuals with SCA. Finally, we aim to assess cognitive function across multiple domains of cognitive function in individuals with SCD relative to the normative mean and sibling or healthy controls.

Methods

Literature Search

PubMed, PsycINFO, and MedLine were searched for empirical studies reported prior to September 2018 to identify articles that examined cognitive function in children, adolescents, and adults with SCD using standardized assessments. There was no lower limit for publication date in order to include all studies reported in prior narrative reviews and meta-analyses and studies that may have been excluded due to the restricted inclusion criteria used in previous reviews (i.e., studies assessing cognitive domains other than FSIQ, without a control group, or in preschool children or adults). The initial systematic literature search was conducted using PubMed and MedLine, with the specific search terms (*cognition* OR *cognitive function* OR *intelligence*) AND (*sickle cell disease*). Studies were then screened for empirical reports that assessed cognitive function in humans with SCD. Initial screening was completed by two independent raters with 98% agreement. A secondary search in PubMed using more specific search terms of (*neuropsychologic* OR *intellectual impairment* OR *sustained attention* OR *executive function* OR *inhibitory control*) AND (*sickle cell*) was conducted to identify other studies that may not have been captured within the first search. A final search was conducted in PsycINFO filtered specifically for unpublished doctoral dissertations to mitigate concerns for publication bias. Finally, five additional studies from prior meta-analyses and reviews and one dissertation available on a university server that were not found in any search described above were included. Based on the inclusion criteria outlined below, a total of 110 studies (73 independent samples) with 4,727 participants, including 3,600 participants with SCD and 1,127 siblings or healthy controls were deemed eligible for inclusion in the quantitative meta-analysis (see Supplementary Table 1 for complete list studies and study characteristics).

Inclusion criteria for the meta-analysis:

1. Studies were included if they assessed cognitive function in a human sample of any age diagnosed with any SCD genotype.
2. Studies were included if they used a standardized performance-based measure of cognitive function with available reliability and validity statistics.
3. Studies were included if they reported a standardized score for any domain of cognitive function based on a national standardized sample (i.e., standard score, scaled score, or *T*-score), and if the study reported adequate statistics to calculate effect sizes.

Exclusion criteria for the meta-analysis:

1. Studies were excluded if they only report questionnaire-based assessments of cognitive function.
2. Studies were excluded if they only report raw total scores instead of standardized scores.
3. Studies were excluded if they involved experimental manipulation of cognitive function (e.g., intervention studies). However, if pre-intervention tests of the cognitive function were reported, these were included in the meta-analysis.

Study Quality Assessment

Criteria from the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Heart, Lung, and Blood Institute, 2014) were adapted for the current review, excluding items that were irrelevant to or inconsistent with the aims and inclusion/exclusion criteria. Studies were assigned one point per each criterion met, which were summed for a total quality score of 0 to 6 (0 indicating lowest quality and 6 highest quality). Information about quality ratings for included studies are depicted in Supplementary Table 1 and Figure 1. Study quality ranged 2 to 6 ($M = 4.00$, $SD = 1.00$).

Data Coding Procedure

The following information was extracted from each study where available: (a) sample disease characteristics (i.e., percentage of sample with SCA, cerebral infarct status); (b) domains and measures of cognitive function; (c) sample size; and (d) summary statistics for the calculation of effect sizes. Cognitive function scores were categorized into one of five domains:

1. FSIQ, defined as "the aggregate or global capacity of the individual to act purposefully, to think rationally, and to deal effectively with his or her environment" (Wechsler, 1939).
2. Verbal reasoning, defined as "the ability to access and apply acquired word knowledge. The application of this knowledge involves verbal concept formation, reasoning, and expression" (Wechsler, 2014).
3. Perceptual reasoning, defined as "the ability to evaluate visual details and to understand visual spatial relationships to construct geometric designs from a model... and to detect the underlying conceptual relationship among visual objects and to use reasoning to identify and apply rules" (Wechsler, 2014).
4. Executive function and attention defined as "inhibiting dominant responses, updating working memory representations, and shifting between task sets" (Friedman et al., 2008).
5. Processing speed, defined as "the speed and accuracy of visual identification, decision-making, and decision implementation" (Wechsler, 2014).

Cognitive tasks were coded into each domain based on how they aligned with the definition. For example, baseline processing speed tasks on the Delis-Kaplan Executive Function System were included in processing speed, whereas the shifting tasks on this assessment were coded into executive function and attention (see Supplementary Table 3 for complete list of measures within categories). Wechsler composite scores were the most common across each domain. When presented with both subtests and composites, only composite scores were included. Although more specific domains of cognition are often utilized by neuropsychologists, the current review aimed to assess a consistent set of domains of cognition across age groups and infarct status in order to maintain structure and quantitatively compare effect sizes. Due to the limited number of studies in this population, and the format of the reported data in the included studies, which predominately used Wechsler scales (75.5%), these broader domains of analyses were chosen.

Studies were coded into one of three age groups: infants and preschool children, school-aged children and adolescents, and adults. Children ages 2 months to 6 years old were categorized into the preschool-age group. Children ages 6–18 years were categorized into the school-aged group. Adolescent and young adult samples with a mean age below 18 years were coded into school-aged group; adolescent and young adult samples with a mean age over 18 years of age were coded into the adult group. Samples of participants that were exclusively 18 years and above were also coded into the adult age group. A random sample of 25 studies were coded independently by two raters in order to determine if the neurocognitive domains measured on the Wechsler scales were sufficient in coding the cognitive assessments within studies, and discrepancies were resolved through discussion. Once the organization and coding structure of cognitive domains were finalized, all other studies were coded by a single rater.

Finally, due to the more significant medical complications and the increased risk for both silent infarcts and overt strokes within SCA relative to other disease genotypes, and to create a clinically meaningful comparison group of samples without infarcts, SCA-only samples were included in the assessment of cognitive function across infarct status. Studies that included only participants with SCA (referred to in this study as having HbSS and HbSβ^0 Thalassemia) or reported separate effects for a subsample of those with SCA were categorized by cerebral infarct status. Studies or subsamples were coded into the "no infarct" group if authors explicitly stated that the participants were screened and assessed for neurological events, with no evidence of cerebral infarction on a Magnetic Resonance Imaging (MRI) scan. Studies that reported that participants were screened for overt strokes with no evidence, but did not mention SCI, were not included in the no infarct group. The SCI group included

studies in which the authors explicitly reported that participants had a history of an SCI based on MRI evidence. Finally, studies were categorized into the stroke group if authors explicitly reported that participants had a history of overt stroke as evidence by MRI and neurological exam. Studies that included participants with a range of cerebral infarct statuses, but did not report separate scores on cognitive assessments, were not coded into these groups.

Computation of Effect Sizes

All analyses were conducted with the Comprehensive Meta-Analysis Program version 3 (Borenstein, Hedges, Higgins, & Rothstein, 2015) using random effects models. The mean effect size for each study (Hedges' *g*) was used as the level of analysis. When authors published different studies using the same sample or a smaller subset of the same sample (e.g., studies from the Cooperative Study of Sickle Cell Disease, CSSCD; $k = 10$, $k' = 1$), the largest sample was used to calculate effect size for each domain when identical measures were reported; however, some effect estimates were generated by averaging different measures across studies. Effect sizes were computed using the measure's standardized norms and normative sample size as the comparison. If a study included a sample of sibling or healthy controls, separate analyses were conducted to determine the mean effects relative to controls. All mean effects, regardless of significant differences, were extracted from each study. Effect sizes in meta-analyses based on very small number of studies are subject to problems in data synthesis (Davey, Turner, Clarke, & Higgins, 2011); however, because there were few studies within different domains, age groups, and infarct statuses, a minimum of three studies ($k = 3$) was set to estimate effect sizes.

Weighted mean effect sizes (Hedges' *g*), 95% confidence intervals, and estimated heterogeneity statistic (Q) were calculated for each cognitive domain relative to the normative mean and sibling or healthy controls. Sample size across studies of SCD differ greatly; therefore, Hedges' *g* was used as opposed to Cohen's *d*. By convention, Hedges' *g* magnitudes of .2, .5, and .8 are considered small, medium, and large, respectively (Cohen, 1998). Because Hedges' *g* is an estimate of standard deviation from the mean, it can be used to estimate the mean standard score of each domain. Standardized differences in cognitive function based on standard scores (Δ SS; based on a normal distribution where $M = 100$, $SD = 15$) were calculated by multiplying Hedges' *g* by $SD = 15$. The 95% confidence interval on effect size represents the range in which the mean effect size falls in 95% of cases. A mean effect is considered significant when the confidence interval does not include zero. A significant Q statistic indicates that there is significant heterogeneity within the studies contributing to the overall effect size (Borenstein, Hedges, Higgins, & Rothstein, 2009).

Group Comparisons

Comparisons across age group (i.e., preschool, school-age, and adult) and cerebral infarct status (i.e., no SCI or stroke, SCI, stroke) were assessed by using each level as categorical moderators of the mean differences in cognitive function (i.e., Hedges' *g*) relative to the normative mean and sibling or healthy control. Age groups and infarct status groups were analyzed in separate mixed effects models when enough data was available. A significant mixed effects total between groups factor (Q_b) indicates that effect size of a particular domain differs significantly between groups.

Publication Bias

In addition to including unpublished dissertations, we examined funnel plots for each effect and calculated Egger's tests, which is a statistical test used to detect funnel plot asymmetry (Egger, Smith, Schneider, & Minder, 1997); however, Egger's test has been reported to have lower power when used for effects with fewer than 10 studies (Higgins & Green, 2011). Second, we conducted trim and fill analyses (Duval & Tweedie, 2000) to determine how many studies would need to be included above or below the meta-analytic mean to make the funnel plot symmetrical. A higher number of studies denotes greater publication bias. Trim and fill analyses also impute the missing studies and calculate adjusted meta-analytic effect sizes that account for bias.

Results

Cognitive Domains Across Age in SCD

Eight independent samples (14 studies) were used to calculate cognitive function effect sizes in infancy and preschool; 59 samples (89 studies) were used across effects for school-aged children; and 6 samples (7 studies) were used across effects in adulthood.

Results relative to the normative mean, described in Table I, show that infants and preschool-aged children with SCD display significant deficits in FSIQ, verbal reasoning, and executive function and attention with medium effects ($g = -.39$ to $-.63$). The effect for perceptual reasoning ($g = -.37$) and processing speed ($g = -.58$) were non-significant. School-aged children with SCD showed significantly large deficits across all cognitive domains ($g = -.83$ to -1.18). Adults showed significant medium-to-large deficits ($g = -.46$ to $-.86$) across all cognitive domains. Deficits in verbal reasoning had the greatest effect size in both preschool ($g = -.63$) and school-aged children ($g =$

Table I. *Effect sizes for cognitive function in SCD across age group*

Domain	Preschool-aged						School-aged						Adult					
	k'	*n*	Δ SS	*g*	95% CI	*Q*	*k'*	*n*	Δ SS	*g*	95% CI	*Q*	*k'*	*n*	Δ SS	*g*	95% CI	*Q*
Comparison: normative mean																		
FSIQ	7	399	−6.8	−.46***	[−0.70, −0.21]	46.52***	45	2341	−12.5	−.83***	[−0.94, −0.73]	361.01***	4	240	−9.5	−.63***	[−0.74, −0.53]	2.93***
Verbal reasoning	6	218	−9.4	−.63***	[−0.88, −0.37]	26.52***	37	1886	−17.6	−1.18***	[−1.51, −0.84]	2915.95***	5	273	−6.9	−.46***	[−0.57, −0.36]	2.91
Perceptual reasoning	3	86	−5.6	−.37	[−0.89, 0.15]	8.74*	38	2060	−17.2	−1.15***	[−1.49, −0.81]	2769.08***	6	250	−9.3	−.62***	[−0.72, −0.52]	3.82***
Executive function	4	121	−5.8	−.39***	[−0.53, −0.24]	2.21	29	1480	−13.1	−.88***	[−1.17, −0.59]	1020.54***	7	287	−9.3	−.62***	[−0.80, −0.44]	12.69
Processing speed	3	103	8.8	−.58	[−1.22, 0.05]	17.52***	17	938	−13.3	−.88***	[−1.05, −0.72]	109.04***	5	237	−12.9	−.86***	[−1.11, −0.61]	14.49
Comparison: sibling or healthy controls																		
FSIQ	–	–	–	–	–	–	16	829	−11.4	−.76***	[−0.97, −0.54]	60.28***	3	190	−6.4	−.43**	[−0.72, −0.13]	0.14
Verbal reasoning	–	–	–	–	–	–	17	776	−10.8	−.72***	[−0.92, −0.52]	59.62	4	187	−7.5	−.50*	[−0.89, −0.10]	9.75*
Perceptual reasoning	–	–	–	–	–	–	16	765	−9.1	−.60***	[−0.83, −0.38]	74.72***	4	200	−5.9	−.40***	[−0.60, −0.19]	0.90
Executive function	–	–	–	–	–	–	16	680	−8.0	−.53***	[−0.71, −0.36]	38.87**	5	237	−4.7	−.31**	[−0.51, −0.11]	1.13
Processing speed	–	–	–	–	–	–	13	495	−12.5	−.84***	[−1.05, −0.62]	36.16***	3	187	−10.4	−.70***	[−0.88, −0.51]	1.33

k' = number of independent samples; *n* = number of children, adolescents, or adults with SCD. Normative sample *n*'s range from 154 to 8,818 participants. Sibling or healthy control *n*'s range from 82 to 624 participants; Δ SS = difference in standard score based on a distribution of $M = 100$ and $SD = 15$, computed by multiplying Hedges' *g* by $SD = 15$; *g* = mean effect size (Hedges *g*); 95% CI = 95% confidence interval of Hedges' *g*; *Q* = *Q* statistic for total within heterogeneity.

*$p < .05$, **$p < .01$, ***$p < .001$.

−.1.18), and deficits in processing speed had the greatest magnitude of effects in adults ($g = -.86$). Categorical moderator analyses used to determine differences across groups (Table II) showed that school-aged children had significantly greater deficits relative to both preschool ($p_{Qb} < .05$) and adult samples ($p_{Qb} < .01$) in FSIQ, verbal reasoning, and perceptual reasoning. Adult samples only showed a significant difference in executive function relative to preschool-aged samples; all other comparisons were non-significant.

Effects across age group were also computed relative to sibling or healthy controls (see Table I). There was an insufficient number of independent samples available to compute mean effects in preschool samples. School-aged children with SCD showed significant medium-to-large deficits ($g = -.53$ to $-.84$) across each cognitive domain relative to sibling and healthy controls, with the largest magnitude effect in processing speed. Adults showed significant deficits across each domain, ranging from small to large effects ($g = -.31$ to $-.70$), with the largest deficit in processing speed. Categorical moderator analyses (Table II) showed that only deficits in verbal reasoning were significantly greater ($p_{Qb} < .01$) in school-aged children compared with adults; all other comparisons were non-significant or unable to be calculated.

Cognitive Domains Across Cerebral Infarct Status in SCA

Twenty-two independent samples (35 studies) were used to calculate effect sizes of cognitive function in samples without history of infarcts; 10 samples (23 studies) were used across effects for samples with a history of SCI; and 10 samples (19 studies) were used across effects for samples with a history of stroke.

Findings relative to the normative mean, summarized in Table III, show significant deficits in SCA across every cognitive domain and cerebral infarct status. Participants without a history of infarcts showed medium deficits across domains ($g = -.55$ to $-.65$), with the largest deficit in processing speed. The SCI group showed medium effect in executive function and attention ($g = -.52$) and large deficits across all other domains ($g = -.97$ to -1.03). Participants with a history of overt stroke showed the largest deficit across every domain ($g = -1.35$ to -1.82), with the largest deficit in verbal reasoning and processing speed. Categorical moderator analyses (Table IV) showed that samples of SCA with a history of stroke had significantly greater deficits across all domains ($p_{Qb} < .01$) relative to participants without infarcts and those with a history of SCI. Analyses also showed that samples of SCA with an SCI had significantly greater deficits ($p_{Qb} < .05$) in FSIQ, verbal reasoning, and perceptual reasoning compared with the no infarct group.

Table II. *Categorical moderator analyses for age group relative to the normative mean*

Domain	Preschool vs. school-aged		School-aged vs. adult		Adult vs. preschool	
	Q_b	Δ SS_b	Q_b	Δ SS_b	Q_b	Δ SS_b
Comparison: normative mean						
Full scale IQ	7.67*	5.7	6.82**	3.0	1.06	2.7
Verbal reasoning	7.23*	8.2	15.63***	10.7	1.39	2.5
Perceptual reasoning	14.10**	11.6	8.57**	7.9	0.88	3.7
Executive function	12.10**	7.3	2.12	3.8	3.96*	3.5
Processing speed	3.33	4.5	0.03	0.4	0.62	4.1
Comparison: sibling or healthy controls						
Full scale IQ	–	–	3.21+	5	–	–
Verbal reasoning	–	–	13.08**	3.3	–	–
Perceptual reasoning	–	–	1.81	3.2	–	–
Executive function	–	–	2.76+	3.3	–	–
Processing speed	–	–	0.94	2.1	–	–

Q_b = Q statistic for total between heterogeneity; *deltaSSb* = between group difference in standard score based on distribution of M = 100 and SD = 15.
$+p < .10$, $*p < .05$, $**p < .01$, $***p < .001$.

Effects across cerebral infarct status in SCA were also computed relative to sibling or healthy controls, described in Table III. Effects were not calculated for the SCI group due to the limited number of studies that assessed cognitive function in children with SCI relative to controls. Samples without infarcts showed medium to large deficits ($g = -.58$ to $-.76$) in each domain relative to healthy and sibling controls, with the largest deficit in FSIQ ($g = -.76$). Samples with a history of overt stroke showed a significant large deficit in verbal reasoning ($g = -1.28$), perceptual reasoning ($g = -1.10$), and executive function ($g = -.95$). Mean effects for FSIQ and processing speed were unable to be calculated due to the insufficient number of studies. Categorical moderator analyses (Table IV) showed that there was only a significant difference ($p_{Qb} < .05$) in perceptual reasoning between the stroke group and the no infarcts group; all other comparisons were non-significant or unable to be calculated.

Forest plots of all effects can be found in Supplementary Figures 2 through 5, and mean standard scores are presented in Supplementary Tables 4 and 5.

Publication Bias

Of the 22 significant effect sizes across age group, one effect (processing speed in adults relative to the normative mean) produced significant Egger's tests using two-tailed criterion at $p < .10$ (Egger et al., 1997). Of the 21 significant effect sizes across infarct status, two effects produced significant Egger's tests. Funnel plots for effects with significant Egger's are presented in Supplementary Figure 6. Trim and fill analyses were also conducted for all significant effects. Adjusted effect sizes for 18 effects are presented in Supplementary Tables 6 and 7.

Discussion

Deficits in cognitive function are one of the most pervasive adverse consequences of SCD. The present meta-analysis is the first comprehensive quantitative review of multiple domains of cognitive deficits in SCD across cerebral infarct status, and across the lifespan. The sample size of the articles included in this meta-analysis is substantially larger than previous reviews due to the inclusion of studies that assessed cognition in infants, pre school-aged children, and adults; the inclusion of non-Wechsler assessments; the inclusion of specific domains of cognitive function in addition to FSIQ; and the inclusion of participants across different infarct statuses. Main findings are: (a) significant cognitive deficits in functioning exist across all neurocognitive domains, age groups, and infarct status; (b) deficits in FSIQ, verbal reasoning, perceptual reasoning, and executive function increased from preschool to school-aged samples; (c) deficits in FSIQ, verbal reasoning, and perceptual reasoning decreased from school-aged to adult samples, likely due to sampling bias in adult samples; and (d) there were significant stepwise increases in deficits when comparing no infarct, to SCI, to overt stroke.

Findings in infants and preschool age children showed that significant deficits that are medium in magnitude in FSIQ, verbal reasoning, and executive function relative to the normative mean emerge early in the lifespan. Clinically, this emphasizes that early biological and environmental interventions to prevent deficits are necessary. Both verbal reasoning and executive function have been shown to be related to emotional function in pediatric SCD (Prussien et al., 2018), and both of these domains are important to develop prior to entering school in order to bolster academic performance (Rhoades, Warren, Domitrovich, Greenberg, 2011). Performance in perceptual reasoning and processing speed were non-significant; however these estimated effects also had the fewest number of studies. Further, few studies included healthy or sibling controls, so conclusions about

Table III. *Effect sizes for cognitive function in SCA across cerebral infarct status*

Domain	No infarcts							SCI				Stroke					
	k'	*n*	Δ SS	*g*	95% CI	*Q*	*k'*	*n*	Δ SS	*g*	95% CI	*Q*	*k'*	*n*	Δ SS	*g*	95% CI	*Q*
Comparison: normative mean																		
FSIQ	16	819	−8.2	−.55***	[−0.73, −0.37]	119.99***	9	397	−15.4	−1.03***	[−1.40, −0.65]	87.37***	5	67	−26.4	−1.76***	[−2.11, −1.41]	8.99***
Verbal reasoning	13	571	−9.4	−.63***	[−0.79, −0.47]	39.57***	7	280	−15.2	−1.02***	[−1.48, −0.55]	81.36***	8	126	−27.4	−1.82***	[−2.41, −1.23]	106.18***
Perceptual reasoning	11	490	−9.5	−.63***	[−0.78, −0.49]	25.83***	7	353	−15.4	−1.02***	[−1.37, −0.68]	43.22***	6	105	−23.2	−1.54***	[−1.78, −1.31]	7.79
Executive function	13	539	−8.1	−.54***	[−0.77, −0.30]	78.89***	4	74	−7.7	−.52*	[−1.02, −0.01]	9.52*	6	104	−20.2	−1.35***	[−1.63, −1.07]	9.02
Processing speed	9	455	−9.8	−.65***	[−0.89, −0.42]	43.71	3	94	−14.6	−.97***	[−1.18, −0.77]	1.42	4	53	−27.3	−1.82***	[−2.35, −1.29]	12.21**
Comparison: sibling or healthy controls																		
FSIQ	5	278	−11.4	−.76**	[−1.29, −0.23]	25.21***	–	–	–	–	–	–	–	–	–	–	–	–
Verbal reasoning	4	238	−8.7	−.58*	[−1.13, −0.03]	19.53***	–	–	–	–	–	–	5	72	−19.2	−1.28***	[−1.87, −0.69]	12.94**
Perceptual reasoning	3	212	−10.0	−.67**	[−1.07, −0.27]	6.33*	–	–	–	–	–	–	4	60	−16.4	−1.10***	[−1.63, −0.56]	5.98
Executive function	6	254	−7.2	−.48***	[−0.76, −0.20]	9.36	–	–	–	–	–	–	5	52	−14.3	−.95**	[−1.51, −0.33]	10.98*
Processing speed	7	272	−9.3	−.62***	[−0.89, −0.36]	4.29	–	–	–	–	–	–	–	–	–	–	–	–

k' = number of independent samples; *n* = number of children, adolescents, or adults with SCD. Normative sample *n*'s range from 357 to 8,818 participants. Sibling or healthy control *n*'s range from 106 to 192 participants; Δ SS = difference in standard score based on a distribution of $M = 100$ and $SD = 15$, computed by multiplying Hedges' *g* by $SD = 15$; *g* = mean effect size (Hedges *g*); 95% CI = 95% confidence interval of Hedges' *g*; *Q* = *Q* statistic for total within heterogeneity; SCI = silent cerebral infarct.

*$p < .05$, **$p < .01$, ***$p < .001$.

disease-specific contributions to deficits in these domains are limited. Future research should strengthen findings across domains in this age range, utilizing sibling or healthy controls.

Significant deficits were found across domains in school-aged children and adolescents. Although the emphasis of previous research has been on deficits in FSIQ and executive function, the largest deficits in school-aged children occurred in verbal reasoning relative to the normative mean and processing speed relative to controls. School achievement and academic functioning is strongly associated with these two domains (Deary, Strand, Smith, & Fernandes, 2007), underscoring their importance when assessing functioning and determining classroom accommodations and interventions in students with SCD. Analyses also showed that school-aged children had significantly greater deficits compared with preschoolers, which builds upon the moderator analyses across early adolescence described by Schatz et al. (2002), and replicating prior findings of the negative trend among age and FSIQ in this population.

Only a few studies have addressed cognitive function in adults with SCD. Although there were significant deficits across each domain of cognitive function, the magnitude of these effects was significantly lower than deficits in school-aged children; and, with the exception of executive function, deficits in adults were not significantly different from effects in preschool samples. At face value, this suggests that the trend of deficits across the lifespan may be curvilinear, increasing in magnitude from preschool to the school-aged years, and then decreasing again in adulthood. Cognitive recovery may be possible as prefrontal cognition generally improves in adulthood; however, given that over 50% of adults with SCD experience SCI in the prefrontal cortex or overt stroke in the brain (Kassim et al., 2016; Strouse, Jordan, Lanzkron, & Casella, 2009), sampling bias is the likely explanation. Possible explanations for sampling bias in adults with SCD include early death in adults with severe disease characteristics (Lanzkron, Carroll, & Haywood, 2013); the effect of cognition on medical adherence and attending clinic visits (Alosco et al., 2012; Insel, Morrow, Brewer, & Figueredo, 2006), during which research recruitment occurs; potential increases in depressive symptoms during the transition from pediatric to adult medical care (Jonassaint, Jones, Leong, & Frierson, 2016); reduced involvement of caregivers; and potential reduction of the perceived importance cognitive assessment after leaving the schooling system. Future studies need to make deliberate efforts to recruit patients during the transition period and older adults with SCD to better determine influences on sampling bias and the magnitude of cognitive deficits with increasing age.

Table IV. *Categorical moderator analyses for age group relative to the normative mean*

Domain	No infarcts vs. SCI		SCI vs. stroke		Stroke vs. no infarcts	
	Q_b	Δ SS_b	Q_b	Δ SS_b	Q_b	Δ SS_b
Comparison: normative mean						
Full scale IQ	6.13*	7.2	18.86***	11.0	48.02***	18.2
Verbal reasoning	4.69*	5.8	4.01*	12.2	10.86**	18.0
Perceptual reasoning	4.55*	5.9	10.92**	7.8	53.47***	13.7
Executive function	0.003	0.4	8.01**	12.5	21.25***	12.1
Processing speed	3.21^{+}	4.8	12.06**	12.7	20.11***	17.5
Comparison: sibling or healthy controls						
Full scale IQ	–	–	–	–	–	–
Verbal reasoning	–	–	–	–	5.38*	10.5
Perceptual reasoning	–	–	–	–	1.57	6.4
Executive function	–	–	–	–	1.98	7.1
Processing speed	–	–	–	–	–	–

Q_b = Q statistic for total between heterogeneity; ; *deltaSSb* = between group difference in standard score based on distribution of M = 100 and SD = 15; SCI = silent cerebral infarct.
$+p < .10$, $*p < .05$, $**p < .01$, $***p < .001$.

This quantitative review replicated and extended findings of cognitive function across infarct status described in Kawadler et al. (2016). Results showed that deficits in cognitive function are pervasive across domains, even in individuals without SCI or overt strokes, suggesting neurological impacts due to altered cerebral hemodynamics and anemia (Steen et al., 2003). Further, findings definitively demonstrate the gradient in cognitive loss when comparing patients with no cerebral infarcts, SCIs, and strokes. Fortunately, stroke incidence rates in children with SCA living in higher-income countries are decreasing because of primary stroke prevention strategies with transcranial Doppler screening coupled with either blood transfusion therapy, hydroxyurea therapy, or both in high risk children (Inati, 2009). Unfortunately, no primary prevention strategy exists for children with silent cerebral infarcts, which occur in up to 39% of the school-age children (DeBaun & King, 2016). Further research on medical interventions to reduce the incidence of infarcts and anemia on cognition is pertinent.

A unique and important component of this meta-analysis is the comparison of cognitive function to both the normative means and control samples. The magnitude of cognitive deficits, specifically in school-age children, relative to the normative mean was greater than deficits relative to sibling or healthy controls. The additional deficits relative to the normative mean in SCD are most likely due to environmental factors related to socioeconomic status and limited resources in the home and the community (Nisbett et al., 2012; Yarboi et al., 2017). For example, in a study of cognitive function in children with SCA, King et al. (2014) found that children of caregivers with high school education or less scored 6 FSIQ points lower than children of caregivers with some college education, whereas the presence of a SCI was associated with a 5 FSIQ point difference. Further, King et al. also showed that there was a 0.33 IQ point increase for every $1,000 of annual household income within the sample. Socioeconomic status is related to cognitive function in both African and European American samples primarily through social processes including decreased access to high quality schools and increased parent stress that is associated with impairments in responsive parenting (Barakat, Patterson, Tarazi, & Ely, 2007; Dexter, Wong, Stacks, Beeghly, & Barnett, 2013; Evans et al., 2010). Studies in pediatric SCD have shown that increased parent stress and lower responsive parenting skills are related to lower scores in FSIQ, working memory, and reading comprehension (Yarboi, 2017; Yarboi et al., 2017). It is necessary to examine both relative and absolute cognitive deficits in individuals with SCD in order to understand the true deficits with which they are faced and how these deficits can influence social adjustment, medical care, and medical adherence. Future interventions to improve cognitive function in children with SCD should consider these influences.

The findings of this meta-analysis definitively demonstrate that deficits in cognitive function are a hallmark of SCD occurring across the lifespan. Based on these findings, medical interventions to address a wide range of sequelae in this population will have limited impact if cognitive decline is not attenuated or ideally, halted. Similarly, cure of the disease with hematopoietic stem cell transplant or gene therapy with myeloablative preparative regimens may have unidentified negative consequences for cognitive function, and investigators should include assessment of cognition to evaluate for sequalae of treatment. With regards to psychosocial and environmental interventions, parenting interventions in families of preschool and young

school-aged children to reduce stress and improve responsive parenting styles could improve cognitive performance (King et al., 2014; Yarboi, 2017). Further, all interventions aimed to improve executive function in this population should consider the potential impact of deficits in verbal reasoning during intervention design and implementation.

Limitations and Future Research

While there are several strengths of the present meta-analysis, there are also limitations. First, findings across age range included a heterogeneous group of studies and sample characteristics, with a range of infarct status and treatments. Also, all age groups were included in findings across infarct status. Nevertheless, only four samples of infancy and preschool and one adult sample were included in the no infarct group; one adult sample was included in the SCI group; and the stroke group was composed entirely of school-aged children. Further, the current meta-analysis did not control for socioeconomic characteristics or other biological correlates throughout the lifespan that also have a significant influence on cognitive performance. Future reviews should assess environmental and other biological correlates of cognition in this population. Finally, although the current review was substantially more broad in age group, infarct status, domains, and reference groups; we were not able to compute mean effects across more specific domains of neurocognitive functioning (e.g., memory, visual-motor skills, academic functioning). The use of these broader domains of cognitive function, and the inclusion of multiple tests within each domain likely contributed to the significant heterogeneity within each effect. Future research and reviews should attempt to assess these specific domains in addition to academic achievement in this population.

Conclusions

In summary, the present comprehensive meta-analysis of preschool, school-age, and adults with SCD provides incontrovertible evidence of increased risk for cognitive deficits across multiple domains of cognitive functioning throughout the lifespan. Further, the significant increase in deficits in all domains from infancy and preschool to school-age samples emphasizes the importance for early intervention. Finally, more research is necessary to determine unbiased effects for cognitive function in adults with SCD, and future research on cognitive function in SCD should focus on the transition period from pediatric to adult medical care models.

Supplementary Data

Supplementary data can be found at: https://academic.oup.com/jpepsy.

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