Cerebral Hemodynamic and Psychosocial Correlates of Executive Function in Sickle Cell Anemia

By

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Psychology

June 30, 2021

Nashville, Tennessee

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For my mother, Simone Louis Prussien

ACKNOWLEDGEMENTS

Everything that I have achieved has been a product of hard work and opportunity, and I would like to thank every person that I've met along my path that gave me the opportunity to work hard. From my first grade teacher, to my high school summer research mentor, my undergraduate advisors, and several mentors throughout my graduate education—I have been surrounded by people who believed in me, my dream, my ambition, and my ability to do the work. Of course, I would like to particularly thank my graduate advisor, Dr. Bruce E. Compas, for his support and guidance over the last 5 years.

This population is immensely important to me, and I am honored to have had the opportunity to work hard for them.[1]

[1] This research as supported by a Ruth L. Kirschstein National Research Service Award for Individual Predoctoral Fellowship (F31HD095592) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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CHAPTER I

BACKGROUND

Sickle cell disease (SCD) is a genetic disorder that results in the production of abnormal hemoglobin. SCD affects approximately 1 in every 400 African-Americans, and it also severely affects individuals in the Caribbean islands and West African countries such as Nigeria and Ghana (Hassell, 2010; WHO, 2006). Sickle cell anemia (SCA) is the most common and severe phenotype of SCD, and it often results in serious health complications including hypoxia, low hemoglobin levels, and chronic anemia. Due to the clinically indistinguishable phenotypic expressions and clinical risks associated with HbSS and HbSβ^0 Thalaseemia (Escourt et al., 2017), randomized controlled trials for SCA include both genotypes (e.g., DeBaun et al., 2014; Lee et al., 2006); therefore, this classification will be used in the current studies.

Chronic anemia in SCA has downstream effects on multiple aspects of health. Individuals with SCA suffer from chronic pain and fatigue and commonly experience additional conditions, including acute chest syndrome, splenic sequestration, and silent and overt cerebral infarcts. Although the medical complications of the disease are associated with shortened lifespan (Lanzkron, Carroll, & Haywood, 2013; Platt et al., 1994), recent treatments such as hydroxyurea, a chemotherapy drug used to increase levels of fetal hemoglobin and prevent the red blood cells from sickling, and chronic transfusions, used to decrease the percentage of HbS in the blood stream, have been shown to improve medical symptoms, increase quality of life, and reduce rates of mortality in individuals with SCD (Stegenga, Ward-Smith, Hinds, Routhieaux, & Woods, 2004; Steinberg et al., 2003; Thornburg, Calatroni, & Panepinto, 2011).

As a result of biological and environmental factors, children and adults with SCD

experience significant deficits in cognitive function (Prussien, Jordan, DeBaun, & Compas, 2019a; Prussien et al., 2020b). In a recent comprehensive meta-analysis of cognitive function in SCD, Prussien et al. (2019a) found significant deficits in several domains of cognitive function in across the lifespan. Findings for samples of infants and preschool-aged children showed that significant deficits in Full Scale Intelligence Quotient (FSIQ), verbal reasoning, and executive function emerge early in the lifespan. School-aged samples with SCD showed large deficits in FSIQ, verbal reasoning, perceptual reasoning, executive function, and processing speed relative to the normative mean (g = -.83 to g = -1.18) and medium to large effects compared with sibling or healthy controls (g = -.53 to g = -.84). Further, school-aged children showed significantly greater deficits in FSIQ, verbal reasoning, and perceptual reasoning relative to preschool-aged samples; supporting the hypothesis that cognitive deficits increase with age in SCD (King et al., 2014; Schatz et al., 2002).

Adults with SCD also showed deficits across every domain of cognitive function relative to both normative means (g = -.46 to -.86) and control groups (g = -.31 to -.50); however, these effects were significantly lower than deficits in school-age samples (Prussien et al., 2019a). At face value, this suggests that the trend of deficits across the lifespan may be curvilinear, increasing 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 may be a more likely explanation for this finding. That is, few studies assessed cognitive function in adults with SCD, and there may also be a bias for higher functioning adults with SCD to participate in research, leading to higher scores on measures of cognitive function

relative to younger samples. Prussien et al. (2019a) concluded that more data is needed on adults with SCD, particularly young adults before and after the transition from pediatric to adult medical care to further assess the developmental trajectory of cognitive function in this population.

Cerebral infarction is the most-common cause of central nervous system injury in children with SCD (DeBaun & Kirkham, 2016; Ohene-Frempong et al., 1998), and infarcts are associated with significantly lower scores in general intelligence and in specific areas of cognitive functioning (Kawadler, Clayden, Clark, & Kirkham, 2016; King et al., 2014; Prussien et al., 2019a). Prussien et al. (2019a) found that individuals with SCA and history of silent infarcts showed large deficits across domains of cognitive function (g = -.63 to g = -1.03), and those with a history of overt stroke had significantly larger deficits than individuals with SCI (g = -1.28 to g = -1.82). Similar findings have been presented in prior meta-analyses that only included only children with SCD (Kawadler et al., 2016; King et al., 2014).

Hemodynamic Correlates of Cognitive Deficits in SCD

While cerebral infarcts increase the risk and severity of cognitive impairment, significant cognitive deficits still occur in those without a history of stroke. The meta-analysis reported by Prussien et al. (2019a) also found that although SCA samples without a history of infarcts were less impaired than those with SCI or stroke, samples with no stroke history showed large deficits relative to the normative mean (g = -.55 to -.74). This suggests that chronic disease-related hemodynamic characteristics may also contribute to cognitive impairment in patients without an acute insult to the brain. Disease characteristics, such chronic anemia, have been found to be significantly associated with Verbal IQ, Performance IQ, and FSIQ (Bernaudin et al., 2000;

Hijmans et al., 2011). For example, Steen et al. (2003) found that the degree of chronic anemia explained 23% of the variance in predicting FSIQ in children with SCD without a history of stroke; and a recent meta-analysis of correlates of cognitive function in SCD suggests that hematocrit percentage and hemoglobin level were significantly associated with higher scores in FSIQ, verbal reasoning, and executive function with small to medium effects (Prussien et al., 2020b).

It is hypothesized that the relation between anemia and deficits in cognitive functioning may be due to chronic hypoxia in the brain even after compensatory hemodynamic consequences of chronic anemia. For example, several studies have found that cerebral blood flow velocity measured with transcranial doppler ultrasound (TCD), is significantly related to measures of cognitive function in a sample of children with SCA, such that higher TCD velocity is related to lower cognitive scores (Bakker et al., 2014; Prussien et al., 2019b). A meta-analysis of correlates of cognitive function in SCD (Prussien et al., 2020b) suggests that TCD velocity has a significant negative association with perceptual reasoning, but there was not a main effect for FSIQ, verbal reasoning, or executive function. More research is necessary to understand more specific cerebral hemodynamic characteristics associated with cognitive function in this population.

Psychosocial Correlates of Cognitive Deficits in SCD

SCD poses significant sources of stress related to recurrent pain, disruptions in daily role functioning, uncertainty about the future and challenges with social and peer stress, and these stressors can lead to increased risk for emotional distress (Hildenbrand, Barakat, Alderfer, & Marsac, 2013; Prussien et al., 2016). Further, deficits in cognitive function may lead to greater difficulty in coping with these stressors (Compas et al., 2017; Prussien et al., 2018), which can

then lead to increased risk for internalizing symptoms (e.g., symptoms of anxiety and depression; Compas et al., 2012).

Specific deficits associated with increased risk for emotional problems include difficulty initiating cognitive strategies (Hertel & Gerstle, 2003), slowed processing speed (den Hartog, Derix, Van Bemmel, Kremer, & Jolles, 2003), and overall depleted cognitive resources (Matthews & MacLeod, 1994). Executive function, in particular, has been shown to be most-consistently associated with anxiety (Moran, 2016) and major depressive disorder (MDD; Snyder, 2013). A meta-analysis assessing 177 samples showed that self-reports of anxiety symptoms were significant associated with deficits in working memory (Moran, 2016). A separate meta-analysis conducted by Snyder (2013) assessed the association between multiple components of executive function and MDD across 113 studies. There was a reliable association between executive function and MDD such that participants with lower scores on executive function measures had more severe symptoms of depression, with effect sizes ranging from d = 0.32 to 0.97. Patients with MDD also demonstrated lower scores on processing speed (d = 0.33), impairments in inhibition (d = 0.58), shifting (d = 0.47), updating (d = 0.57), verbal working memory (d = 0.45), and a small effect for verbal fluency (d = 0.14). It is noteworthy, however, that the direction of the association between EF and depression is still unknown. That is, executive function is theorized to be a causal link for a variety of different psychopathologies (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Olley, Malhi, & Sachdev, 2007; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), but psychopathology may lead to deficits in executive function, or executive function and psychopathology may both be a result of neurobiological differences or structural differences in the brain caused by stress (Holmes & Wellman, 2009; Nugent, Tyrka, Carpenter, & Price, 2011; Tsunoka et al., 2009).

A recent meta-analysis of correlates of cognitive function examined psychosocial corelates of cognitive function in SCD, in addition to hemodynamic and environmental associations (Prussien et al., 2020b). However, findings of this systematic review identified only six studies that assessed the association between cognitive function and emotional/behavioral problems in this population, with only two studies specifically assessing internalizing problems. Nevertheless, authors were able to estimate an effect size for the association of FSIQ with Total Problems, measured by the CBCL/YSR Total Problems Scale (Achenbach & Rescorla, 2001) and reverse effects for the Pediatric Quality of Life measure (Panepinto et al., 2013). Findings suggest a significant negative association among FSIQ and Total Problems (r = -.13), suggesting that individuals with SCD with lower cognitive function may have higher emotional/behavioral problems and lower quality of life. More research on specific domains of emotional and behavioral functioning, including internalizing problems, in relation to specific domains of cognitive function is necessary within this population.

The Current Studies

The field is faced with at least two primary questions related to cognitive function in individuals with SCA. First, what biological and environmental characteristics are associated with deficits in cognitive function? And second, how do these deficits in cognitive function affect individuals' everyday wellbeing and psychosocial adjustment?

The following two studies focus specifically on executive function, and they aimed to examine hemodynamic and psychosocial correlates of executive function in a sample of children, adolescents and young adults with SCA (see Figure 1 for a heuristic model of these hypothesized processes). Specifically, Study 1 assessed the associations between a novel measures of a

cerebral hemodynamic characteristic, CBF and oxygen extraction fraction (OEF), with executive function (see Figure 2). Study 2 assessed how executive function is associated with both coping and depressive symptoms, along with the moderating effects of age and perceived control (see Figure 3).

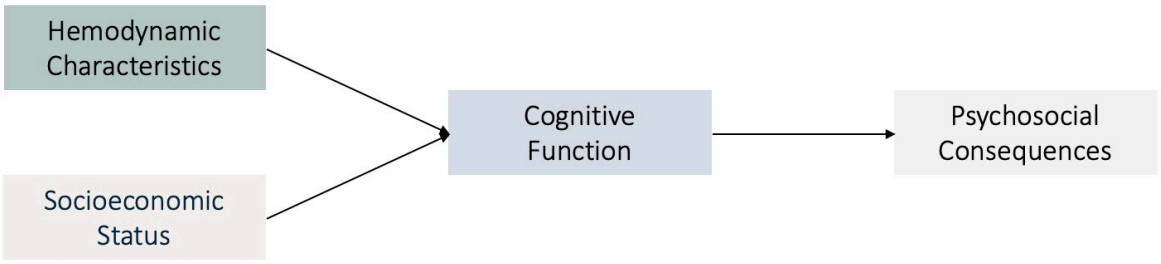


Figure 1. Heuristic model of correlates of cognitive function in SCA from Prussien et al. (2020b).

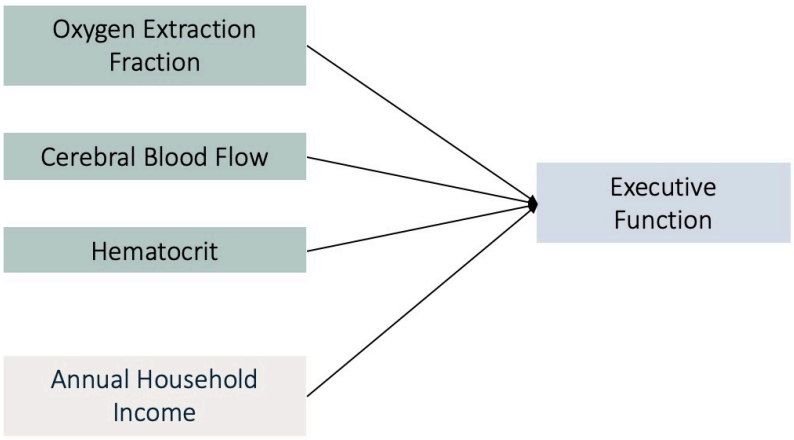
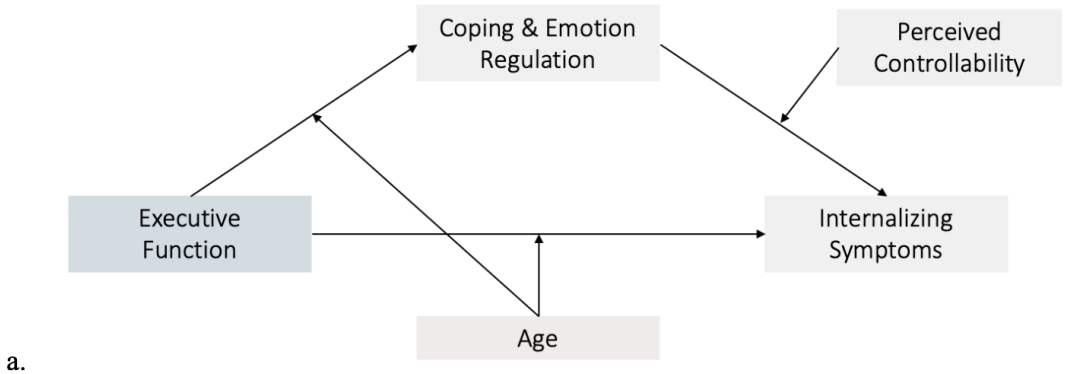


Figure 2. Conceptual model of hemodynamic and socioeconomic predictors of cognitive function.



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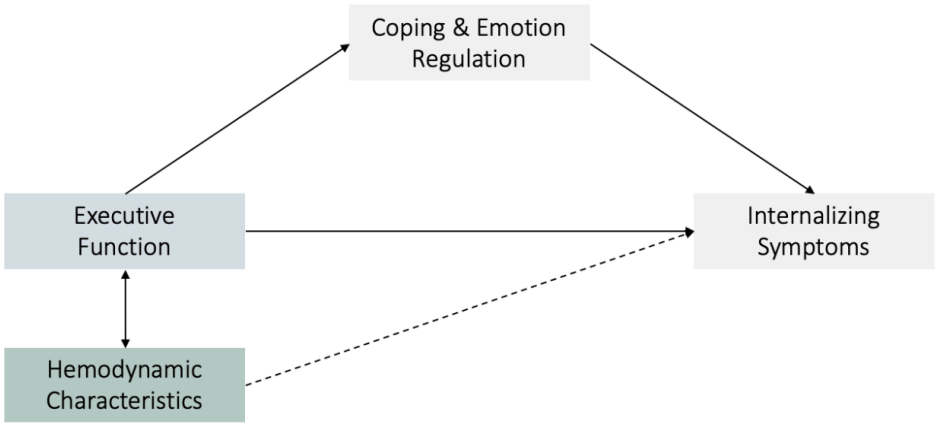


b.

Figure 3. Conceptual models of psychosocial consequences of cognitive function. (a) Assesses moderated mediation of participant age and perceived control of stress on the effect of cognitive function on anxiety/depression through coping and emotion regulation. (c) Contingent supplementary analysis assesses hemodynamic characteristics that are significantly associated with cognitive function (see Study 1) as a distal predictor of symptoms through both cognitive function on anxiety/depression and coping and emotion regulation.

CHAPTER II

CEREBRAL HEMODYNAMICS AND EXECUTIVE FUNCTION IN SICKLE CELL ANEMIA

Introduction

Sickle cell anemia (SCA) is a genetic hemoglobin disorder characterized by abnormal hemoglobin that result in chronic anemia throughout the body and the brain, and cerebral infarction and deficits in cognitive function are the hallmarks of the disease. Although several studies have investigated hemodynamic predictors of cognitive function in SCA, only proxies of cerebral metabolism have been used (Bakker et al., 2014). The current study will provide the first test of the association of novel MRI measurement of oxygen extraction fraction (OEF) with measures of cognitive function and the first study to assess the influence of OEF on cognition in individuals with SCA.

Cerebral hemodynamics in individuals with SCA can be quantified by four measures: the volume of blood being delivered to brain tissue (i.e., cerebral blood volume; CBV; ml blood/100g tissue); the rate of blood delivery to brain tissue brain (i.e., cerebral blood flow; CBF; ml blood/100g tissue/min); the metabolic rate of oxygen consumption ($CMRO_2$; ml O_2/100ml brain/min); and the percentage of oxygen extracted from the blood by the tissue relative to the volume of oxygen delivered (i.e., OEF). Due to lower levels of oxygen throughout the brain in this population, there is a compensatory effect for blood flow such that the rate of blood delivery is increased to compensate for the hypoxic conditions. Low oxygen, compensatory increases in CBF, and the presence of a prior infarct all increase the risk of cerebral infarcts in children with SCD (DeBaun & Kirkham, 2016). Recent clinical practice has

introduced the use of transcranial Doppler ultrasound (TCD) velocity measurements for primary stroke prevention in children without a history of cerebral infarction. TCD velocity is a gross proxy of CBF that assesses the blood flow velocity in left and right major cerebral arteries to determine oxygen delivery to the brain. Nevertheless, TCD has not been shown to be an indicator of stroke after the first occurrence (Adams, 2005). Further, although both CBF and CBV are used as measures of cerebral oxygenation, they do not provide information about the amount of oxygen that is absorbed by brain tissue. Finally, although $CMRO_2$ describes the amount of oxygen utilized, it is fairly stable and does not account for how much oxygen is delivered. Hypothesized relations amongst hemodynamic characteristics across impairment are shown in Figure 4.

OEF is hypothesized to be a better indicator of neurological failure compared to the other cerebral hemodynamic measures. When arterial oxygen content decreases, CBF and CBV may also increase in order to sustain oxygen delivery (Vorstrup et al., 1992). Under these conditions, OEF will also increase if the total oxygen delivery is inadequate and $CMRO_2$ is preserved (Derdeyn et al., 2002). The primary method of measuring OEF has been positron emission tomography (PET; Xu, Ge, & Lu, 2009), but recent studies have explored and validated the use of magnetic resonance imaging (MRI; e.g., Ge et al. 2012; Liu et al. 2014; Lu et al., 2011). Findings from Jordan et al. (2016) show that adults with SCA have higher OEF than healthy controls, and a similar pattern has been shown in children and adolescents with SCA (Fields et al., 2018). Further, findings show that CBF and OEF levels decrease after red blood cell exchange transfusion (Guilliams et al., 2018; Juttukonda et al., 2018), showing that these cerebral hemodynamic measures are sensitive to biological interventions for stroke prevention, which could also reduce risk for deficits in neurocognitive functioning.

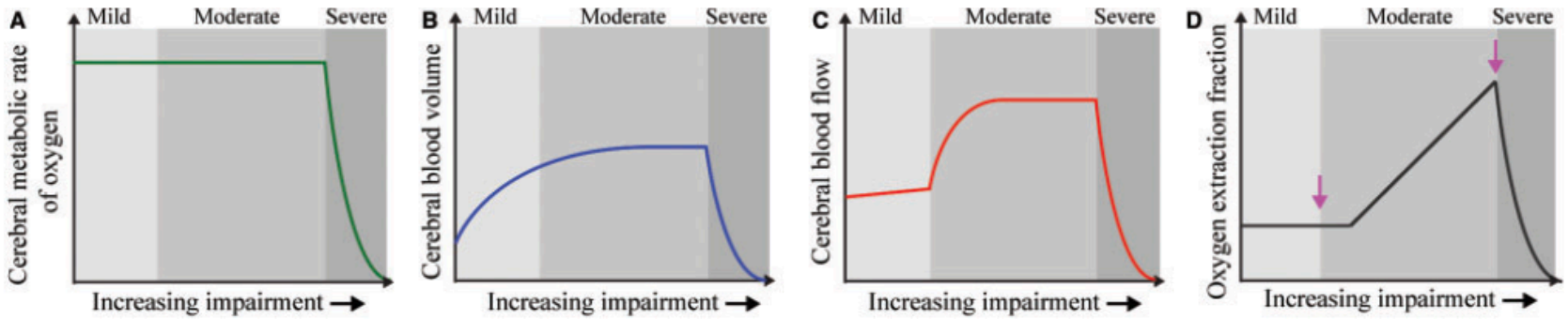


Figure 4. Mechanistic models for increasing stages of hemo-metabolic impairment in SCA from Jordan et al. (2016). (A) Cerebral metabolic rate of oxygen consumption remains constant until severe impairment. (B) Large arteriole CBV may increase on average in moderate stages via vasodilation to maintain CBF. (C) CBF increases sharply in moderate stages to maintain adequate delivery of oxygen to tissue. (D) Once autoregulatory capacity is reached, or vasculopathy becomes severe, CBF plateaus or declines and OEF increases. When oxygen can no longer be supplied by these mechanisms, a stroke occurs. We postulate that in adults with SCA, elevated oxygen extraction fraction (D) can be used to identify those at increased risk of having new ischemic event.

In the most comprehensive meta-analysis of cognitive function in SCD across the lifespan, Prussien et al. (2019a) found that there are significant deficits in several domains of cognitive function in children and adults with SCD relative to both the normative means and healthy controls. Cerebral infarction is the most-common cause of neurological damage in children with SCD (Ohene-Frempong et al., 1998), and infarcts are associated with significantly lower scores on measures of general intelligence and in specific areas of cognitive functioning (Kawadler et al., 2016; King et al., 2014). Prussien et al. (2019a) found that individuals with SCA and history of silent infarcts showed large deficits across domains of cognitive function that were significantly greater than in samples without a history of SCI, and those with a history of overt stroke had significantly larger deficits than samples of SCI.

While cerebral infarcts increase the risk and severity of impairment, significant cognitive deficits still occur in those without a history of stroke. The meta-analysis by Prussien et al. (2019a) found that although scores on assessments of cognitive function in samples without a history of infarcts were significantly higher than those with SCI or stroke, these samples also showed medium to large deficits, suggesting that chronic disease-related hemodynamic characteristics may also contribute to cognitive impairment in patients without an acute insult to the brain. It is hypothesized that the relation between anemia and deficits in cognitive functioning may be due to chronic deoxygenation of the brain. Several studies have found that cerebral blood flow velocity measured with TCD is significantly related to measures of cognitive function in a sample of children with SCA, such that higher cerebral blood flow velocity is related to lower scores (Bakker et al., 2014; Prussien et al., 2019b Sanchez et al., 2010); however, meta-analytic findings suggest that more research is needed to determine if this relation is reliable (Prussien et al., 2020b). More studies on the effect of the more direct measurement of

oxygen delivery to the brain (i.e., CBF) are needed.

A small number of studies have assessed the relation between OEF (measured with PET) and cognitive function. In a sample of older adults with hemodynamic cerebral ischemia, Sasoh et al. (2003) found that increased OEF and CBF were related to lower FSIQ scores before and after extracranial-intracranial bypass surgery. Further, after surgery, OEF and CBF decreased to normal levels and FSIQ increased. Neural activation during cognitive tasks requires increased metabolic demand and CBF, and Sasoh et al. (2003) concluded that OEF may be associated with cognitive performance because when baseline OEF and CBF are high, the brain may not be able to meet the additional cognitive demand. Decreased OEF and CBF levels post-intervention might provide additional room for change in blood flow velocity during the cognitive tasks. Similar findings on the association between OEF and neurocognitive function were also shown in a sample of patients with carotid artery occlusion (Marshall et al., 2012), suggesting that high baseline OEF is related to lower scores on tasks of cognitive function.

A study by Jordan et al. (2016) of adults with SCA found that OEF and CBF are correlated at low-to-moderate OEF levels; however, they are not correlated at high OEF levels (see Figure 4). This suggests that OEF in children with SCA could be uniquely associated with cognitive impairments above and beyond CBF and CBV due to the lack of shared variance at high OEF levels. However, no published study has assessed how OEF is related to measures of cognitive function in a sample of children with SCD or using MRI methods. A primary goal of the current research is to test OEF as a key mechanism through which SCD leads to deficits in cognitive function; i.e., inadequate oxygen absorption leads to damage in brain tissue that in turn results in cognitive impairment.

In addition to biological risks, environmental factors are also significantly associated with

intelligence and executive function in children with SCD. Children with SCD often grow up in low socioeconomic status (SES) households, and this environment also poses significant risk for cognitive development. King et al. (2014) found that children living with a parent with no college education scored 6.2 IQ points lower than those living with a parent who had some college education. This finding remained significant even when controlling for history of SCI, such that there was a main effect for parent education relative to stroke in predicting child cognitive functioning. Further, a meta-analysis of correlates of cognitive function in SCD (Prussien et al., 2020b) showed that measures of SES were significantly associated with multiple domains of cognitive function, with small-to-medium effects. Thus, it is important to account for social-environmental factors in tests of the association of biological characteristics of SCA and cognitive function.

The Current Study

The current study aimed to address specific gaps in the literature by examining OEF as a novel MRI-derived measure of biological risk for deficits in cognitive function in children and young adults with and without SCA while controlling for other hemodynamic characteristics (Figure 2). Due to the extensive evidence in the literature across pediatric populations, and SCA in particular, of the association between biological characteristics and executive function (Prussien et al., 2020b), analyses are focused specifically on how hemodynamic characteristics are related to multiple measures of executive function. If high OEF is associated with lower executive functioning, this would suggest that one mechanism for these deficits would be related to compensatory mechanisms to maintain nourishment in an undernourished brain (He et al., 2008). The primary study hypothesis was that OEF would be inversely related to executive

function deficits, even after controlling for other measures of pathophysiology (i.e., history of infarcts) and environmental factors (household income).

Method

Participants

Children, adolescents, and young adults with SCA, and healthy controls were recruited from an existing study assessing OEF as an indicator of stroke risk (Jordan et al., 2016) to participate in a follow-up study of neurocognitive function. Children, adolescents, and young adults with SCA (hemoglobin (Hb) SS or HbSβ^0 Thalassemia) and age 6 to 35 years at follow-up assessment were prospectively enrolled. This age range was chosen to assess and control for the potential effects of age on executive function. Healthy control participants were matched based on age within three years for participants with SCA, race, and socioeconomic status. Patients with SCA and healthy individuals were not recruited if they were unable to tolerate MRI without sedation, have a metallic implant in body that precludes MRI or makes MRI difficult to interpret (e.g., braces), pregnancy, history of bone marrow transplant, disorder other than SCA that is associated with stroke or vasculopathy, or any other significant neurological disorders.

Fifty-four participants with SCA (HbSS or HbSβ^0) were enrolled in the study, 29 of whom were children and adolescents, and 25 were young adults. Participants with SCA were between 6 to 35 years old (M = 17.2, SD = 8.12), and 55.6% were female. SCA participants came from a range of annual household income levels (25.9% earned $10,000 or under; 11.1% earned $10,001 - $20,000; 14.8% earned $20,001 - $30,000; 13% earned $30,001 - $40,000; 5.6% earned $40,001 - $50,000; 5.6% earned $50,001 - $60,000; 1.9% earned $70,001 –

$80,000; and 11.1% earned $80,001 or more). Participants with SCA had an average hemoglobin level of 9.24 (*SD* = 2.40) and hematocrit percentage of 25.48 (*SD* = 4.41) at the time of their MRI. Patient MRI from parent study indicated that 40.7% had a healthy MRI, 42.6% had a silent infarct, and 9.3% had an overt stroke. Forty-two participants (77.8%) were treated with hydroxyurea and 17 (31.5%) received regular blood transfusions. The average time between MRI and neurocognitive assessment for the SCA cohort was 19.02 months (*SD* = 10.87). Children and adolescents with SCA had significantly lower CBF ($d = 1.05$, $p < .001$) and the time between MRI and neurocognitive assessment ($d = 1.34$, $p < .001$) relative to young adults. All other demographic, disease, and hemodynamic characteristics were not significantly different across age groups.

Ten healthy controls, all of whom were children and adolescents, were also enrolled in the study. Healthy controls were between 8 and 15 years old (*M* = 10.73, *SD* = 3.04), and 40% were female. Healthy controls came from a range of annual household income levels (10% earned $10,000 or under; 10% earned $10,001 – $20,000; 10% earned $20,001 – $30,000; 10% earned $30,001 – $40,000; 30% earned $40,001 – $50,000; 10% earned $70,001 – $80,000; and 20% earned $80,000 or more). Healthy controls had an average hemoglobin level of 12.94 (*SD* = 0.93) and hematocrit percentage of 40.20 (*SD* = 2.39) at the time of their MRI. No healthy control participant had a history of either silent infarct or overt stroke, and the average time between their MRI and neurocognitive assessment was 8.34 months (*SD* = 10.50). Healthy controls had significantly lower mean age ($d = 1.06$, $p = .020$), CBF ($d = 2.22$, $p < .001$), OEF HbF calibration model ($d = 1.59$, $p = .001$), and time between MRI and neurocognitive assessments ($d = 1.00$, $p = .016$) compared to the SCA sample. The control sample also had significantly greater mean hemoglobin level ($d = 2.03$, $p < .001$) and hematocrit percentage ($d =$

4.15, $p < .001$) than the SCA cohort, and samples did not significantly differ in term of sex ($p = .365$), annual household income ($p = .363$). Due to the large difference in sample size relative to the SCA sample, the healthy controls were only included in preliminary group comparisons in FLAIR and CBF imaging data (Figure 5).

Procedure

Recruitment occurred at the Monroe Carrell Jr. Children's Hospital at Vanderbilt and Vanderbilt University Medical Center, where participants received their care between January 2018 and December 2019. Families of individuals with SCA were approached by a member of the research team during a routine clinic visit or transfusion appointment. To reduce sampling bias, participants who were less likely to attend clinic visits were also contacted by phone and email. Age and race matched healthy controls were also recruited from the parent study, and all healthy control families were contacted by phone or email.

Participants completed an MRI of the brain with standard structural sequences and hemodynamic sequences; cognitive assessments were completed during a separate office-based study visit. Families were compensated at the conclusion of each visit. The current study was approved by the Vanderbilt University Institutional Review Board. Written informed consent was obtained from all adults and caregivers of children and adolescents, and informed assent was obtained from all children and adolescents.

Measures

Anatomical Imaging and Analysis. Each participant received a 3-Tesla (Philips Healthcare, Best, The Netherlands) MRI of the brain, magnetic resonance angiography of the

head without contrast, and a neurologic examination by the study neurologist. Two board-certified neuroradiologists independently recorded neuroimaging findings including presence of existing cerebral infarcts (lesion at least 3 mm in 1 dimension and visible in 2 planes on T2-weighted fluid-attenuated inversion recovery images) and intracerebral hemorrhage according to prior established MRI criteria (DeBaun et al., 2014). If detailed neurologic examination was normal or an abnormality on neurologic examination could not be explained based on location of the infarct-like lesion, infarcts were judged to be silent (DeBaun et al. (2014). Due to the small number of participants with overt strokes (n = 5) relative to silent infarcts (n = 20), the data was dichotomized into participants with and without infarcts in study analyses.

Hematocrit Percentage. Hematocrit values were obtained from venipuncture at the time of MRI.

Cerebral Blood Flow. Pseudo-continuous ASL (pCASL) MRI was performed for the measurement of CBF. Labeling of arterial blood water was achieved using a train of Hanning-windowed block pulses in a 13-mm thick plane placed 93 mm inferior to the center of the corpus callosum and approximately 10 mm inferior to the confluence of the vertebral arteries. As blood velocity is expected to be slightly higher in children relative to adults, a shorter post-labeling delay (1600 ms) was used in children relative to adults (1900 ms). Other common scan parameters were multi-slice 2D single-shot echo planar gradient-echo readout, TR/TE = 3675/13 ms, spatial resolution = 3.0 × 3.0 × 7.0 mm^3. An identical readout scheme was used for images with no labeling of blood water. Equilibrium magnetization (M_0) images were acquired following the ASL scan using a similar readout technique, without spin labeling and with TR = 15,000 ms.

Oxygen Extraction Fraction. T_2-relaxation-under-spin-tagging (TRUST; Lu & Ge, 2008;

Lu, Xu, Grgac, Liu, Qin, & van Zijl, 2012) data were acquired twice per session (spatial resolution = 3.4 × 3.4 × 5 mm3, τ_{CPMG} = 10 msec, eTE = 0, 40, 80, and 160 msec, TR/TE = 1978/3.6 msec, averages = 3; Jordan et al., 2016; Lu et al., 2012). Control and venous-labeled (transfer-insensitive labeling technique; TILT) TRUST images were acquired from a slice containing the superior sagittal sinus, approximately 20 mm superior to the confluence of the sinuses; the image slices were positioned parallel to the anterior commissure / posterior commissure line.

TRUST data were pairwise subtracted , and venous blood water T_2 was quantified in the superior sagittal sinus; venous blood water T_2 values were then converted to venous oxygen saturation (Y_v) using two previously characterized calibration curves generated with HbF blood (Bush et al., 2017) and HbA blood (Liu et al., 2016). Y_v was then utilized along with arterial oxygenation saturation (Y_a), which was acquired from two-wavelength pulse oximetry, to calculate OEF = $(Y_a-Y_v)/Y_a$. Finally, the OEF values from both TRUST measurements were averaged to obtain the OEF value for each participant. The observable from this analysis was a global measure of cerebral OEF.

Executive Function. Participants were either administered either the Working Memory Index (WMI) from the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-5; Wechsler, 2014), or the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; Wechsler, 2008). The WMI, composed of the Digit Span and Picture Span subtests in the WISC-5, and Digit Span and Arithmetic subtests in the WAIS-IV, is a valid and reliable measure of the ability to sustain attention and exert mental control with auditory and visual stimuli. Participants also completed the NIH Toolbox Cognitive Battery (NIHTB-CB; Weintraub et al., 2013; Zelazo et al., 2013) to assess other domains of executive function using the following modules: Dimensional Change

Card Sort, Flanker Inhibitory Control and Attention Test, and the List Sorting Working Memory, Pattern Comparison Processing Speed, and Picture Sequence Memory, all of which are combined to yield the Fluid Reasoning Composite.

*Demographic characteristics***.** Participants and/or their caregivers completed questionnaires at the time of the neurocognitive assessment, which included questions on annual household income.

Data Analytic Strategy[2]

Summary statistics for continuous variables are reported using mean and standard deviation, and categorical variables are reported using proportion of sample size and percentage. All statistical tests used a two-tailed $p < 0.05$ for significance. Independent samples t-tests were used to compare demographic, biological, and neurocognitive characteristics with continuous variables across control and SCA cohorts and across SCA age groups. Categorical participant characteristics were compared across groups using Pearson chi-square tests. Further, Pearson correlations were used to determine bivariate association among hemodynamic characteristics and measures of executive function. To correct for possible Type I error in the bivariate correlation analyses, supplemental analyses were conducted using the False Discovery Rate (Benjamini & Hochberg, 2000). Finally, a series of linear regression analyses were used to determine the unique variance of hematocrit percentage, CBF, and two calibration models of OEF on executive function. Each regression model controlled for participant age, annual household income, history of either silent or overt infarct, and time between MRI and neurocognitive assessment. All statistical analyses were performed using SPSS, version 26.

[2] Supplemental analyses related to Study 1 are presented in Appendix A

Results

Executive Function Descriptive Statistics

Descriptive statistics on participant demographics are available in Table 1. The standardized mean for all tests of executive function was 100, with a standard deviation of 15. Participants with SCA scored significantly lower than the normative mean on the majority of neurocognitive assessments, including Wechsler WMI ($M = 94.06$, $d = .39$, $p = .007$), NIHTB-CB Dimensional Change ($M = 89.57$, $d = .63$, $p < .001$), NIHTB-CB Inhibitory Control ($M = 79.53$, $d = 1.42$, $p < .001$), NIHTB-CB Working Memory ($M = 92.81$, $d = .50$, $p = .001$), NIHTB-CB Processing Speed ($M = 86.22$, $d = .83$, $p < .001$), and NIHTB-CB Fluid Cognition ($M = 83.06$, $d = 1.05$, $p < .001$). The mean score on NIHTB-CB Memory ($M = 97.06$) for the total SCA sample was not significantly different from the normative mean. Children and adolescents with SCA scored significantly higher than young adults with SCA on Wechsler WMI ($M_{children} = 99.79$, $M_{adults} = 87.40$, $d = .86$, $p = .003$) and NIHTB-CB Inhibitory Control ($M_{children} = 85.24$, $M_{adults} = 73.58$, $d = .92$, $p = .002$), and all other executive function scores were not significantly different across age groups.

Bivariate Correlations

Bivariate correlations among study variables in the total SCA sample are shown in Table 2. Mean hematocrit percentage was positively related to NIHTB-CB Fluid Cognition ($r = .34$, $p = .020$). Results also showed that CBF was negatively related to Wechsler WMI ($r = -.35$, $p = .009$) and NIHTB-CB Inhibitory Control ($r = -.33$, $p = .026$). Figure 5 shows scatterplots of the association among CBF with Wechsler WMI and NIHTB-CB Inhibitory Control in participants

Table 1. Demographic characteristics of study subjects

	Healthy Controls [a]	SCA	*p* Value	Children w/ SCA	Young Adults w/ SCA	*p* Value
Age at assessment, *M* (*SD*)	10.73 (3.04)	17.2 (8.12)	.020[b]	10.59 (2.77)	24.88 (4.73)	< .001[b]
Sex, *n* (*%*)			.365[c]			.625[c]
Male	6 (60.0)	24 (44.4)		12 (41.4)	12 (48.0)	
Female	4 (40.0)	30 (55.6)		17 (58.6)	13 (52.0)	
Household income, *n* (*%*)			.363[c]			.245[c]
$10,000 or under	1 (10.0)	14 (25.9)		9 (31.0)	5 (20.0)	
$10,001 - $20,000	1 (10.0)	6 (11.1)		2 (6.9)	4 (16.0)	
$20,001 - $30,000	1 (10.0)	8 (14.8)		4 (13.8)	4 (16.0)	
$30,001 - $40,000	1 (10.0)	7 (13.0)		6 (20.7)	1 (4.0)	
$40,001 - $50,000	3 (30.0)	3 (5.6)		1 (3.4)	2 (8.0)	
$50,001 - $60,000	0 (0.0)	3 (5.6)		1 (3.4)	2 (8.0)	
$60,001 - $70,000	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
$70,001 - $80,000	1 (10.0)	1 (1.9)		0 (0.0)	1 (4.0)	
$80,001 or more	2 (20.0)	6 (11.1)		4 (13.8)	2 (8.0)	
Medical characteristics						
SCD phenotype, *n* (*%*)			-			.113[c]
HbSS	-	49 (90.7)		28 (96.6)	21 (84.0)	
$HbSB^0$	-	5 (9.3)		1 (3.4)	4 (16.0)	
Hemoglobin, *M* (*SD*)	12.94 (0.93)	9.24 (2.40)	< .001[b]	9.34 (3.09)	9.13 (1.24)	.752[b]
Hematocrit %, *M* (*SD*)	40.20 (2.39)	25.48 (4.41)	< .001[b]	24.89 (4.96)	26.16 (3.66)	.296[b]
Hydroxyurea, *n* (%)	-	42 (77.8)		22 (75.9)	20 (80.0)	.715[c]
Transfusions, *n* (%)	-	17 (31.5)		10 (34.5)	7 (28.0)	.609[c]
CBF, *M* (*SD*)	48.07 (10.04)	80.49 (18.10)	< .001[b]	72.34 (15.16)	89.30 (17.08)	< .001[b]

Table 1 (*cont.*)

	Healthy Controls [a]	SCA	*p* Value	Children w/ SCA	Young Adults w/ SCA	*p* Value
OEF (HbF), *M* (*SD*)	31.88 (1.55)	39.86 (6.94)	.001[b]	39.07 (8.30)	40.74 (5.05)	.390[b]
OEF (HbAA), *M* (*SD*)	31.94 (1.48)	34.52 (5.91)	.177[b]	33.43 (6.65)	35.74 (4.78)	.156[b]
History of either silent infarct or stroke, *n* (%)	0 (0.00)	25 (46.30)	.006[c]	11 (37.9)	14 (56.0)	.184[c]
Neurocognitive Function, *M* (*SD*)						
Wechsler VCI	98.90 (10.21)	91.33 (13.29)	-	91.21 (14.60)	91.48 (11.89)	.924[b]
Wechsler WMI	89.80 (14.91)	94.06 (15.68)	-	99.79 (16.09)	87.40 (12.44)	.003[b]
Digit Span	8.20 (2.66)	8.78 (2.96)	-	9.10 (3.10)	8.40 (2.80)	.388[b]
Wechsler PRI	93.15 (9.87)	91.98 (13.30)	-	92.48 (12.99)	91.40 (13.90)	.769[b]
WISC-V VSI	90.70 (9.39)	-	-	89.59 (13.05)	-	-
WISC-V FRI	95.60 (12.07)	-	-	95.38 (14.72)	-	-
Wechsler PSI	91.00 (11.58)	88.81 (12.73)	-	89.41 (15.37)	88.12 (9.02)	.713[b]
Wechsler FSIQ	92.80 (10.82)	88.81 (13.13)	-	89.72 (14.95)	87.76 (10.84)	.588[b]
NIHTB-CB						
Dimensional Change	93.30 (10.44)	89.57 (18.16)	-	91.52 (18.61)	87.54 (17.85)	.449[b]
Inhibitory Control	84.60 (13.57)	79.53 (13.84)	-	85.24 (11.46)	73.58 (13.81)	.002[b]
Working Memory	90.60 (9.72)	92.81 (13.45)	-	90.36 (10.75)	95.48 (15.69)	.191[b]
Processing Speed	97.40 (25.83)	86.22 (18.07)	-	85.40 (19.04)	87.08 (17.37)	.748[b]
Memory	91.33 (11.75)	97.06 (15.45)	-	97.40 (15.84)	96.71 (15.36)	.877[b]
Fluid Cognition	87.44 (17.25)	83.06 (17.20)	-	83.36 (17.49)	82.74 (17.27)	.902[b]
Months between MRI and assessment, *M* (*SD*)	8.34 (10.50)	19.02 (10.87)	.016[b]	13.24 (6.44)	25.69 (11.43)	< .001[b]

CBF = cerebral blood flow; OEF = oxygen extraction fraction; VCI = verbal comprehension index; WMI = working memory index; PRI = WAIS-IV perceptual reasoning index and mean WISC-V visual spatial index and fluid reasoning index; PSI = processing speed index; FSIQ = full scale IQ; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery
[a]All healthy control participants were children and adolescents. [b]*p* value of independent samples t test with equal variances assumed. [c]*p* value of Fisher's exact test; Healthy Controls N = 10; Children & Adolescents N = 29; Young Adults N = 25

Table 2. Correlation of Hct, CBF, and OEF with executive function in participants with SCA

	Hct	CBF	OEF (HbF)	OEF (HbAA)
Hct	-			
CBF	-.27*	-		
OEF (HbF)	-.47***	-.05	-	
OEF (HbAA)	-.15	-.19	.92***	-
Executive Function				
Wechsler WMI	-.08	-.35**	-.02	.03
Wechsler Digit Span	-.07	-.16	.01	.08
NIHTB-CB Dimensional Change	.24+	-.20	-.17	-.08
NIHTB-CB Inhibitory Control	.16	-.33*	-.12	-.08
NIHTB-CB Working Memory	.26+	-.01	-.18	-.07
NIHTB-CB Processing Speed	.28+	-.08	-.29*	-.22
NIHTB-CB Memory	.23	-.11	-.09	.02
NIHTB-CB Fluid Cognition	.34*	-.14	-.25+	-.13

WMI = working memory index; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery; Hct = hematocrit percentage; CBF = cerebral blood flow; OEF = oxygen extraction fraction.
Wechsler N = 54
NIHTB-CB N = 49
$^{+}p < .10$, $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

with and without infarcts, in addition to FLAIR and CBF images. Finally, the OEF HbF calibration model was negatively related with NIHTB-CB Processing Speed (r = -.29, p = .044) with a medium effect. These associations were no longer significant after using False Discovery Rate to control for multiple comparisons. OEF HbAA calibration model was not related to any measure of executive function. Hemodynamic characteristics were not significantly related to any other domain of cognitive function assessed.

Multivariate Linear Regressions

Multivariate regression analyses were conducted to determine the unique relation between hemodynamic characteristics with tests of executive function in SCA, described in

Table 3. When controlling for participant age, annual household income, history of either silent or overt stroke, and time between MRI and assessment, both OEF calibration models were significant negative predictors of NIHTB-CB Processing Speed, such that higher OEF was associated with lower scores in processing speed (HbF calibration model: β = -.35, p = .020; HbAA calibration model: β = -.36, p = .021). Hematocrit and CBF were not related any test of executive function across the multivariate models.

Participant age was a significant negative predictor of Inhibitory Control across three equations (β_{range} = -.37 to -.41, ps < .05), and history of silent or overt infarct was a significant negative predictor of NIHTB-CB Inhibitory Control (β_{range} = -.36 to -.41, ps < .05) and Fluid Cognition (β_{range} = -.35 to -.39, ps < .05) across all equations. Annual household income did not predict any measure of executive function in the multivariate analyses.

Discussion

The current study tests the association of novel MRI measurement of OEF with measures of cognitive function in SCA, and results suggest that cerebral hemodynamic stress is related to reduced cognitive performance in children and adults with SCA. Elevated hematocrit percentage is related to greater fluid cognition scores, elevated CBF is correlated with reduced working memory and inhibitory control, and elevated OEF (HbF calibration model) was correlated with reduced processing speed. Most importantly, in adjusted multivariate analyses, both OEF calibration models were unique predictors of processing speed, a specific aspect of executive function.

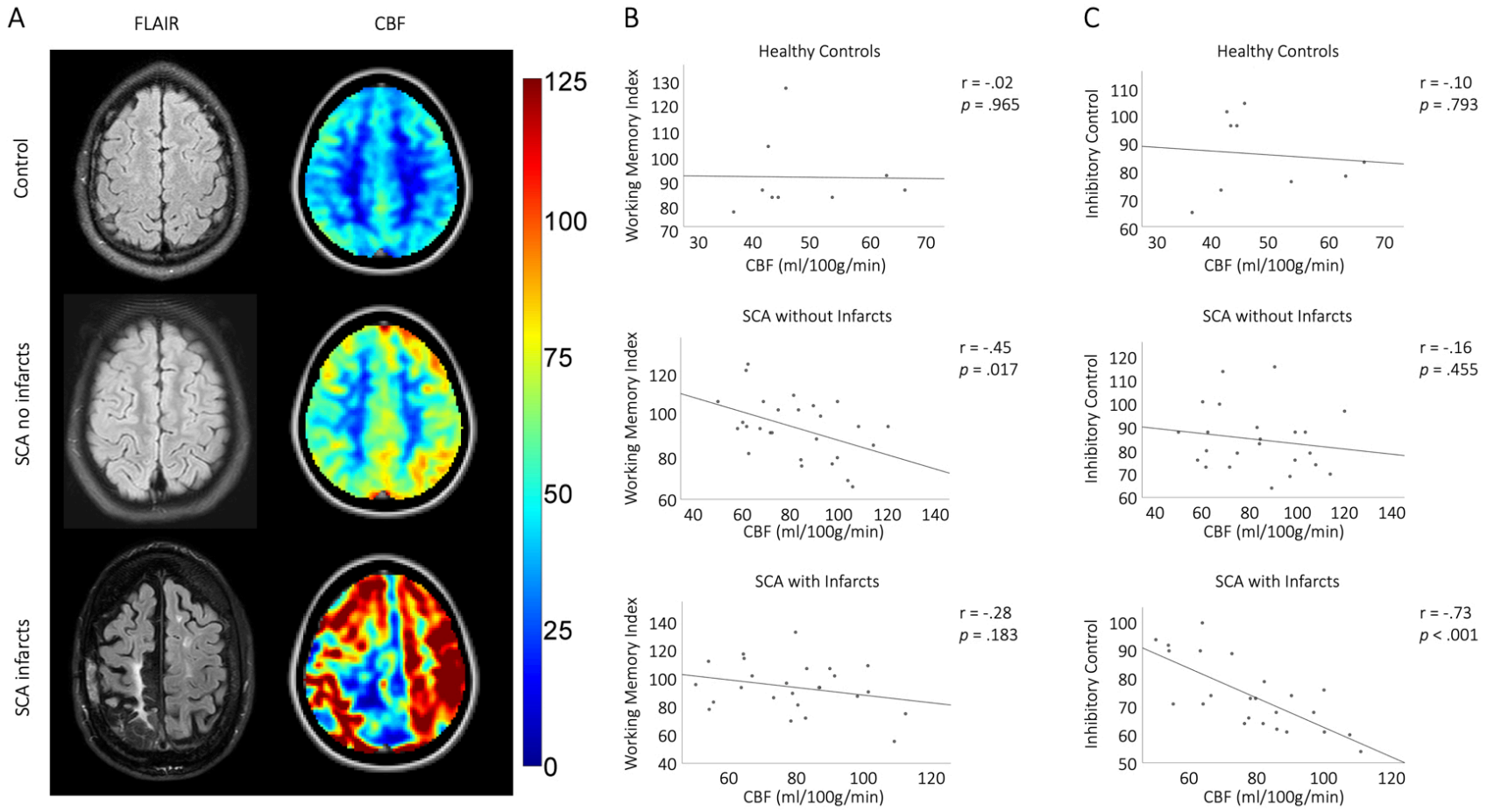


Figure 5. (A) An example of a healthy control, a child with SCA and no infarcts, and a child with SCD and large and small infarcts on FLAIR images. Cerebral blood flow (CBF) as measured by MRI arterial spin labelling is in the normal range in the control, elevated in the child with SCA and no infarcts and further elevated in the child with SCA and large infarct. Color bar is CBF in units of ml blood / 100g tissue / minute. (B) Scatter plot of the association among CBF and Wechsler Working Memory Index in healthy controls, SCA without infarcts, and SCA with infarcts. (C) Scatter plot of the association among CBF and NIHTB-CB Inhibitory Control in healthy controls, SCA without infarcts, and SCA with infarct.

Table 3. Summary of multivariate linear regressions predicting measures of executive function in participants with SCA

	Wechsler WMI			NIHTB-CB Inhibitory Control			NIHTB-CB Processing Speed			NIHTB-CB Fluid Cognition		
Predictors:	B	β	R^2	B	β	R^2	B	β	R^2	B	β	R^2
Equation 1			.13			.32			.18			.30
Hct	-.09	-.02		.77	.21		1.10	.22		1.22	.26^{+}	
Age	-.61	-.31^{+}		-.63	-.37*		.12	.05		-.21	-.10	
SES	.98	.19		.03	-.01		-.59	-.10		.20	.04	
History of infarct	-2.85	-.09		-10.21	-.38**		-10.02	-.28^{+}		-13.05	-.39**	
Time	.00	.05		.01	.16		.01	.23		.02	.35*	
Equation 2			.19			.32			.14			.26
CBF	-.26	-.30^{+}		-.17	-.23		-.09	-.10		-.10	-.11	
Age	-.39	-.21		-.53	-.31		.12	.05		-.24	-.12	
SES	1.17	.24		.24	.05		-.49	-.08		.45	.08	
History of infarct	-3.56	-.12		-11.00	-.41**		-9.13	-.26		-.12.32	-.37*	
Time	.00	.05		.01	.22		.02	.31^{+}		.02	.50**	
Equation 3a			.12			.28			.24			.29
OEF (HbF)	.04	.02		-.11	.05		-.92	-.35*		-.60	-.24^{+}	
Age	-.60	-.31^{+}		-.66	-.39*		.27	.12		-.16	-.07	
SES	1.01	.20		.04	.01		-.50	-.09		.28	.05	
History of infarct	-2.54	-.08		-9.60	-.36*		-8.61	-.24^{+}		-11.60	-.35*	
Time	.00	.04		.01	.22		.01	.26		.02	.40*	
Equation 3b			.13			.28			.24			.27
OEF (HbAA)	.24	.09		.03	.01		-1.01	-.36*		-.53	-.18	
Age	-.64	-.33^{+}		-.70	-.41*		.28	.12		-.19	-.09	
SES	.98	.20		.04	.01		-.38	-.07		.35	.06	
History of infarct	-2.75	-.09		-9.71	-.36*		-8.14	-.23		-11.52	-.35*	
Time	.00	.04		.01	.22		.02	.29^{+}		.02	.42*	

WMI = working memory index; NIHTB-CB = National Institutes of Health Toolbox; Hct = hematocrit percentage; CBF = cerebral blood flow; OEF = oxygen extraction fraction; Age = participant age at neurocognitive assessment; Time = days between MRI and neurocognitive assessment

Wechsler N = 54; NIHTB-CB N = 49

$^{+}p < .10$, $^{*}p < .05$, $^{**}p < .01$

Analyses focused specifically on executive function in SCA, with comparisons relative to the normative mean and across age groups. Findings showed that adults with SCA had significantly greater deficits in several tasks of executive function relative to children and adolescents, and age was negatively related to inhibitory control in multivariate analyses controlling for hemodynamic characteristics, history of infarcts, and annual household income. Although meta-analyses in school-aged children with SCD found that deficits in cognitive function increase with age (Schatz et al., 2002), a recent meta-analysis comparing domains of cognition in school-aged children with adults with SCD found that adults scored significantly higher than children and adolescents (Prussien et al., 2019a). This meta-analysis concluded that this finding was likely due to the small number of studies assessing cognition in adults with SCD and potential sample bias that occurs during recruitment, as adults with greater impairment might be less likely to attend clinic or transfusion appointments. The current study attempted to address these biases in participant recruitment by contacting participants by phone and email in addition to approaching them in clinic, which could have resulted in a more representative sample of adult patients. Findings provide new evidence on the association of age with executive function from childhood and adolescence into young adulthood in SCD, supporting the hypothesis that deficits increase with age.

Prior research has shown that indicators of chronic anemia are related to deficits in cognitive function (Prussien et al. 2020b), and results from the current study replicates these findings. Hematocrit percentage had a positive medium association with a broad composite of executive function, such that participants with higher hematocrit had higher scores in fluid cognition. Individuals with SCA and history of silent infarcts show large deficits across domains of cognitive function that are significantly greater than in samples without a history of SCI, and

those with a history of overt stroke have significantly larger deficits than samples with SCI (Kawadler et al., 2016; Prussien et al., 2019a). While cerebral infarcts increase the risk and severity of impairment, significant medium-to-large cognitive deficits still occur in those without a history of stroke (Prussien et al., 2019a). Taken together, findings from the current study and prior meta-analyses suggest that chronic disease-related hemodynamic characteristics may also independently contribute to cognitive impairment in patients.

Results of the current study showed that CBF is correlated with reduced working memory and inhibitory control, and these findings extend the literature on the relation between CBF with cognition in SCA. Prior research on cerebral hemodynamic predictors of cognitive function in SCD has focused primarily on TCD velocity. Several studies have found that TCD velocity is significantly related to measures of cognitive function in a sample of children with SCA, such that higher cerebral blood flow velocity was related to lower scores (Bakker et al., 2014; Prussien et al., 2019b); however, meta-analytic findings suggest that more research is needed to determine if this association is relation is reliable (Prussien et al., 2020b). TCD velocity is a proxy for blood flow to the brain, whereas CBF (ml blood/100 g tissue/min) assesses the actual rate of blood that is delivered to brain tissue. Nevertheless, few studies have assessed this more precise measure in SCD samples. Only one prior study to date assessed the association between MRI-measured CBF and cognitive function in SCD, and findings in a small sample of children suggested that left, right, anterior, and global CBF was significantly related to Performance IQ (Strouse et al., 2006).

In addition to extending findings for the measurement of CBF, the current study also provides the first evidence of the association of OEF with a measure of executive function in SCA. Both the compensatory increased rate of oxygen delivery and increased proportion of

oxygen intake were related to greater deficits in tests of executive function. Further, OEF was the only significant hemodynamic predictor of executive function after controlling for psychosocial characteristics and history of infarcts, suggesting that OEF could play a uniquely important role in cognitive function in individuals with SCA above and beyond the effect of cerebral infarcts.

Although elevated CBF and OEF are adaptive compensatory mechanisms in the brain to accommodate for hypoxic and anemic conditions, elevations are indicators for risk of stroke and deficits in executive function. Increased baseline CBF and OEF suggest that the brain is exerting significant effort to maintain minimum oxygen consumption, and this might make it difficult to meet additional demands during cognitive tasks. Lower OEF and CBF baseline levels could provide additional room for change during the cognitive tasks. Elevations in OEF and CBF could be used as early predictors of deficits in executive function, and these elevations may validate the use of more aggressive treatment due to potential downstream effects on executive function. Prior research has shown that whole-brain OEF and CBF have improved (i.e., decreased) after transfusion therapy (Juttukonda et al. 2018) and bone marrow transplant (Jordan et al., 2019), and separate research have also shown that these therapies also improve executive function (Hood et al. 2019) and processing speed (Prussien et al. 2020a). Changes in cerebral hemodynamics could be important mediating factors in the association between SCA treatments and changes in executive function.

Limitations

Several limitations should be considered when interpreting the findings of the current study. First, the modest sample size of 54 SCA participants and 10 controls limited power and clinical interpretation. As a result, bivariate correlations were no longer significant after

accounting for false discovery rate to control for multiple comparisons. Therefore, the novel findings presented here require replication with a larger sample in order to clarify hemodynamic association with executive function. Further, the current study used whole-brain assessments of CBF and OEF, and future research should assess cerebral hemodynamics in specific brain regions related to different domains of cognitive function. Finally, the current study assessed a prospective association among cerebral hemodynamics and executive function, with wide variance across participants in the time between the MRI and neurocognitive assessment. It will be important for future research to implement a truly longitudinal design, measuring executive function at the time of the MRI measuring cerebral hemodynamics with a heterogenous time lag between baseline and prospective measures.

Conclusion

Findings provide preliminary evidence that elevated CBF and OEF are related to specific tasks of executive function, and OEF is a unique predictor of processing speed after rigorously controlling for environmental factors and history of cerebral infarcts.

CHAPTER III

EXECUTIVE FUNCTION, COPING, AND DEPRESSION IN SICKLE CELL ANEMIA: EXAMINING THE MODERATING EFFECTS OF AGE AND PERCEIVED CONTROL

Introduction

As a result of disease and environmental characteristics, individuals with SCD are at an increased risk for deficits in cognitive function (Prussien et al., 2019a). Findings in SCD and other pediatric populations have found that deficits in cognitive function may also be related psychosocial consequences (Hocking et al., 2011; Prussien et al., 2020b; Robinson et al., 2015). The primary aim of this second study is to assess how cognitive deficits are related to coping and emotional distress in a sample of children, adolescents, and young adults with SCD, and to assess the potential moderating role of participant age and perceived control over stress.

In a recent comprehensive meta-analysis of cognitive function in SCD, Prussien et al. (2019a) found that there are significant deficits in several domains of cognitive function in across the lifespan. Findings in school-aged samples with SCD showed significant large deficits in Full Scale IQ, verbal reasoning, perceptual reasoning, executive function, and processing speed relative to the normative mean and sibling or healthy controls. Adults with SCD also showed significant deficits across every domain of cognitive function relative to both the normative mean and control groups. Previous meta-analyses in studies of school-aged children with SCD have found a significant negative relation between cognitive function and age (King et al., 2014; Prussien et al., 2018; Schatz et al., 2002). However, the meta-analysis by Prussien et al. (2019a) found that school aged children and adolescents performed significantly lower than pre-school aged children, and they also scored significantly higher than adults across domains. More

research on the association of age within a sample of adolescents and adults rather than group comparisons are important in understanding this association.

Deficits in cognitive function have far reaching effects, including impairment in coping with stress. Recent research has provided support for a control-based model of coping in pediatric, high risk, and healthy child and adolescent populations (Compas et al., 2012, 2017). The model is based on the theory that the actual and perceived controllability of a stressor is important in in understanding the adaptive skills that children and adolescents need to use in order to cope (Compas et al., 2012). The control-based model of coping organizes coping into three distinct groups: primary control coping, secondary control coping, and disengagement (Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001; Connor-Smith, Compas, Wadsworth, Thomsen, & Saltzman, 2000). Primary control coping describes behaviors and cognitive strategies that act directly to change the stressor (i.e., problem-solving) or the emotional response to the stressor (e.g., emotional expression and emotional modulation). Secondary control coping involves adapting to the stressor, and this sub-factor includes cognitive reappraisal, positive thinking, acceptance, and distraction. Finally, disengagement describes a direct attempt to orient oneself away from the stressor (e.g., avoidance, wishful thinking, denial). Within pediatric illnesses, the majority of the stressors experienced are highly uncontrollable; however, there are circumstances where uncontrollable situations have controllable components. Therefore, secondary control coping, for uncontrollable stressors, and primary control coping, for controllable stressors are hypothesized to be the most adaptive when it comes to reducing the risk of emotional distress (Compas et al., 2012). Nevertheless, the specific impact of perceived control on coping has not been extensively investigated.

Previous research across pediatric populations has shown that cognitive function is

significantly related to the ability to generate adaptive coping responses in children with chronic health conditions (e.g., Campbell et al., 2009; Hocking et al., 2011; Robinson et al., 2015). Cognitive reappraisal relies on executive function skills that emphasize the ability to hold information, manipulate it, and view it from an alternative perspective. Campbell et al. (2009) investigated the relation between coping and cognitive function in children with acute lymphocytic leukemia. Results indicated that working memory and self-monitoring were positively associated with cognitive reappraisal and other forms of adaptive coping and negatively associated with disengagement coping (e.g., avoidance, denial). Further, using fMRI methods in a sample of childhood brain tumor survivors, Robinson et al. (2015) found that increased activation in the prefrontal cortex during a working memory task was significantly related to the use of primary and secondary control coping when coping with stress related to survivorship. Activation in the prefrontal cortex was also related to better psychosocial functioning in this study.

Cognitive function has also been shown to be directly related to depression and anxiety in typically developing children and pediatric populations. Specific deficits associated with increased risk for emotional problems include difficulty initiating cognitive strategies (Hertel & Gerstle, 2003), slowed processing speed (den Hartog et al., 2003), and overall depleted cognitive resources (Matthews & MacLeod, 1994). Meta-analyses utilizing over 100 studies have found significant associations between deficits domains of executive function with both anxiety and depression (Moran, 2016; Snyder, 2013), such that participants with lower scores on executive function measures had more severe symptoms of anxiety and depression. It must be noted, however, that the direction of the association between EF with depression and anxiety is still not clear. That is, executive function is theorized to be a causal link for a variety of different

psychopathologies (Fioravanti et al., 2005; Olley et al., 2007; Willcutt et al., 2005), but executive function and psychopathology may be a result of neurobiological differences or structural differences in the brain caused by stress (Holmes & Wellman, 2009; Nugent et al., 2011; Tsunoka et al., 2009). Therefore, because cognitive deficits likely increase with age in SCD (Prussien et al., 2019a; Schatz et al., 2002), and the risk for internalizing symptoms also increase across adolescence, an important aim of the current study is to assess whether participant age is a significant moderator of the association between cognitive function and internalizing symptoms in this population.

In a meta-analysis of correlates of cognitive function in SCD, Prussien et al. (2020b) found that Full Scale IQ was significantly related to greater emotional and behavioral problems across five samples, and there were not enough studies to assess aggregate associations among domains of cognition and specific symptoms of internalizing disorders. Prussien et al. (2018) were the first to investigate associations among cognitive function, coping, and depressive symptoms in children with SCD. Using standardized cognitive tests and parent-reports of children's coping and distress, findings showed that deficits in working memory and verbal comprehension were associated with how children cope with the stress of their illness as well as their depressive symptoms. Working memory also had a direct association with depressive symptoms. Verbal comprehension, however, was significantly associated with secondary control coping (cognitive reappraisal, acceptance, distraction), such that lower verbal ability was related to less use of secondary control coping with stress related to SCD. Further, verbal comprehension had a significant indirect association with depressive symptoms such that coping accounted for a significant portion of the variance in this association. While Prussien et al. (2018) found that secondary control coping with SCD-related stressors was related to depressive

symptoms, perceived control of the stressor was not assessed.

The Current Study

The current study aims to build on prior findings in Prussien et al. (2018) by examining two psychosocial correlates (coping/emotion regulation and symptoms of anxiety and depression) of cognitive function in SCA. Prussien et al. (2018) assessed how children and adolescents cope with disease-related stress using the control-based model of coping; however, the present study assessed how individuals with SCA cope with peer stress, given that previous studies have shown that deficits in cognitive function is related to fewer social skills in pediatric SCD (Hensler et al., 2014). Although there is evidence of the association between FSIQ and verbal reasoning with psychosocial functioning in SCD, there is a broad and extensive amount of research on the association of executive function with coping and depressive symptoms across various pediatric and healthy populations. Therefore, working memory was assessed as the primary index of cognition.[3] The hypotheses are as follows:

- Secondary control coping will account for a significant portion of the association between cognitive function and depressive symptoms.
- Due to the hypothesized increased deficits in executive function and increased depression symptoms across age, it is hypothesized that the association between working memory and depressive symptoms will be moderated by age.
- Perceived control of stress will moderate the association between secondary coping and depressive symptoms.

[3] Supplemental analyses related to Study 2 are presented in Appendix B

Method

Participants

Participants included 54 children, adolescents, and young adults with SCA (HbSS or HbSβ^0 Thalaseemia) ages 6 to 35 years (M = 17.2, SD = 8.12), and 46.3% were female. Participants came from a range of annual household income levels (25.9% earned $10,000 or under; 13% earned $10,001 - $20,000; 13% earned $20,001 - $30,000; 13% earned $30,001 - $40,000; 5.6% earned $40,001 - $50,000; 5.6% earned $50,001 - $60,000; 1.9% earned $70,001 – $80,000; and 11.1% earned $80,001 or more). Participants with SCA had an average hemoglobin level of 9.24 (SD = 2.40) and hematocrit percentage of 25.48 (SD = 4.41) at the time of their MRI. Patient MRI from parent study indicated that 40.7% had a healthy MRI, 42.6% had a silent infarct, and 9.3% had an overt stroke. Forty-two participants (77.8%) were treated with hydroxyurea and 17 (31.5%) received regular blood transfusions.

Procedure

The current study has been approved by the Vanderbilt University Institutional Review Board (IRB #171725). All participants were recruited from an existing study assessing OEF as an indicator of stroke prevention. Participants were excluded from the parent study if they were unable to tolerate MRI without sedation, had a metallic implant in body that precludes MRI or makes MRI difficult to interpret (e.g., braces), pregnancy, history of bone marrow transplant, disorder other than SCA that is associated with stroke or vasculopathy, or any other neurological disorders (such as neurofibromatosis, lead poisoning, or tuberous sclerosis). Participants were further excluded from the current study if they recently underwent bone marrow transplantation.

Recruitment occurred at the Monroe Carrell Jr. Children's Hospital at Vanderbilt and Vanderbilt University Medical Center, where participants receive their care, between January 2018 and December 2019. Families were approached by a member of the research team during a routine clinic visit or transfusion appointment, and they were recruited for participation if interested. In order to reduce sampling bias, participants who were less likely to attend clinic visits and consented to be contacted for research opportunities were also contacted by phone and email. During an office-based laboratory visit, participants completed cognitive assessments and psychosocial questionnaires. Caregivers, adolescents, and young adult participants (ages 10 to 25 years old) were also asked to complete questionnaires on psychosocial functioning and demographic information. Total visit time was 2 hours, and families were compensated for their time.

Measures

Demographic Characteristics. Caregivers and young adults provided demographic information on the participant, including age, education level, race, household income, and marital status.

Working Memory. Children and adults were administered the Working Memory Index (WMI) from the WISC-5 (Wechsler, 2014) and WAIS-IV (Wechsler, 2008), respectively. The WMI from the WISC-5, composed of the Digit Span and Picture Span subtests, and the WAIS-IV, composed of the Digit Span and Arithmetic subtests, are measures of the ability to sustain attention and exert mental control with auditory and visual stimuli.

Coping and Emotion Regulation. Responses to Stress Questionnaire–Peer Stress (RSQ-PS, self-report and parent-report; Compas et al., 2017; Connor-Smith et al., 2000) was used to

assess children's coping with peer-related stressors. The RSQ-Peer Stress version includes a list of 9 peer-related stressors (e.g., being around kids/people who are rude, not having as many friends as you want, being teased or hassled by kids/people, feeling pressured to do something), and 57 items reflecting voluntary (coping) and involuntary (automatic) stress responses of children/adolescents in response to peer-related stressors. The coping factors include primary control coping (i.e., problem-solving, emotional modulation, emotional expression), secondary control coping (i.e., acceptance, cognitive restructuring, positive thinking, distraction), and disengagement coping (i.e., avoidance, denial, wishful thinking). Internal consistencies for parent-reports of coping are as follows: primary control, $\alpha = .87$; secondary control, $\alpha = .90$; and disengagement, $\alpha = .84$.

Perceived Control. Adolescents, young adults, and caregivers completed a questionnaire asking how much control they believe the participant has over each stressor items from the RSQ-Peer Stress using a 4-point Likert scale. Caregivers completed reports on children and adolescents (ages 6 to 17 years), and adolescents and young adults (ages 11 to 35 years) completed self-reported measures. Internal consistency for this scale was $\alpha = .95$.

Depressive Symptoms. Child and adolescent symptoms of depression was assessed using parent-reports of the Affective Problems DSM-oriented scales on the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001), adolescent and adult self-reports on the Youth Self Report (YSR), and young adult reports from the Adult Self Report (ASR). Reliability and validity are established for the CBCL, YSR, and ASR, and normative *T* scores are derived from a nationally representative sample of children, adolescents, and young adults (6 to 17 years old; 18 to 25 years old.

Data Analytic Strategy

Summary statistics for continuous variables are reported using mean and standard deviation. Hypothesis 1 was tested using identical analytical procedures conducted in Prussien et al. (2018). PROCESS macro (Hayes, 2013)[4] model 4 was used to determine direct and indirect associations between working memory and depressive symptoms through coping. Path a assesses the association between working memory and coping; path b assesses the association between coping and depressive symptoms; path c assessed the association between working memory and depressive symptoms; path c' assesses the association between working and depressive symptoms while controlling for the effect of coping on symptoms; and finally, path ab assesses the indirect effect of working memory on depressive symptoms through coping. Hypothesis 2 was tested using PROCESS macro model 8 to assess participant age as a moderator of path a and path c. Hypothesis 3 was tested using PROCESS macro model 14 to assess perceived controllability of peer stress as a moderator of path b. Finally, PROCESS macro model 22 was used to assess the moderating effect of age and perceived control on the direct and indirect association of working memory on depressive symptoms in one model. Parent-reported and adolescent/young adult self-reported measures were used in separate analyses to determine if multi-informant and developmental relations exist.

Supplemental Analyses. Supplemental analyses were conducted to assess if CBF (assessed in Study 1) is also a distal predictor of depressive symptoms through both working memory and coping using PROCESS macro model 6 (see Figure 3b).

[4] See Appendix C for conceptual and statistical diagrams for PROCESS macro models

Results

Descriptive Statistics

Participant demographic characteristics and cognitive function scores are presented in Table 1, and they are described in detail in Study 1. Means and standard deviations of parent-reported and self-reported psychosocial variables are reported in Table 4.

Table 4. Means and standard deviations for measures of participant peer stress, perceived controllability, coping, and emotional distress in participants with SCA

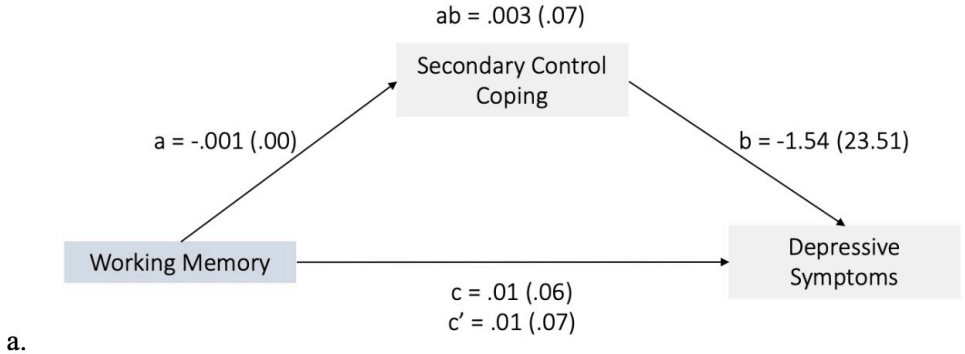
	Parent-Reported	Self-Reported
Variables	M (SD)	M (SD)
Peer Stress	1.51 (0.67)	1.87 (0.82)
Perceived Controllability	2.45 (1.06)	2.31 (0.84)
Coping		
Primary control	0.19 (0.05)	0.19 (0.04)
Secondary control	0.26 (0.05)	0.26 (0.06)
Disengagement	0.15 (0.03)	0.15 (0.03)
Emotional Distress		
Depressive symptoms	55.97 (6.16)	55.19 (6.88)
Anxious-Depressed	51.84 (3.14)	54.59 (7.91)
Internalizing Problems	50.50 (9.06)	50.68 (12.05)

Scores for coping are ratio scores, and scores for the CBCL are standardize T-scores (M = 50, SD = 10). Self-Report N = 37. Parent- Report N = 32

Path Analyses

The direct and indirect paths for the association between working memory and depressive symptoms through secondary control coping are shown in Figure 6. There was no association between working memory and parent-reported secondary control coping (path a = -.001, p =.198) or depressive symptoms (path c = .01, p = .877; path c' = .01, p = .895) in children and adolescents, and there were also no significant effects for model 4 in the self-reported variables

in adolescents and young adults (path a = -.00, p = .492; path c = .08, p = .277; path c' = .05, p = .405). Further, working memory was not indirectly related to depressive symptoms through secondary control coping for either parent-reported (path ab = .003, Boot SE = .07, 95% CI = -.11 to .16) or self-reported (path ab = .06, Boot SE = .08, 95% CI = -.10 to .24) coping and symptoms. Nevertheless, self-reported secondary control coping was significantly and negatively related to depressive symptoms, such that greater use of reappraisal, positive thinking, acceptance, and distraction was associated with fewer symptoms of depression (path b = -.69.08, p < .001) in adolescents and young adults.



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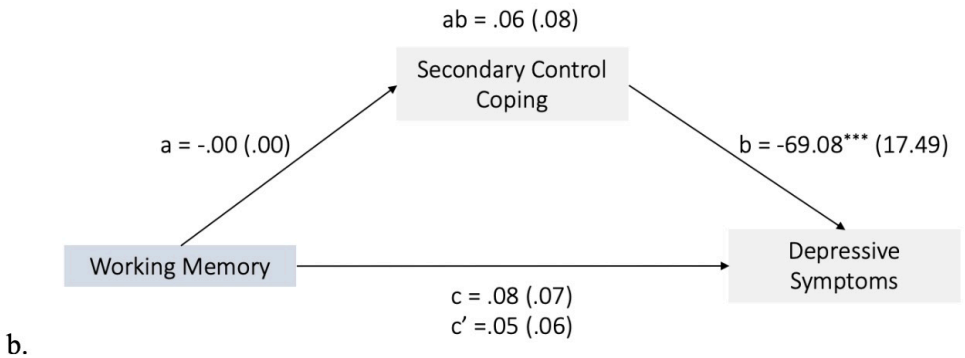


b.

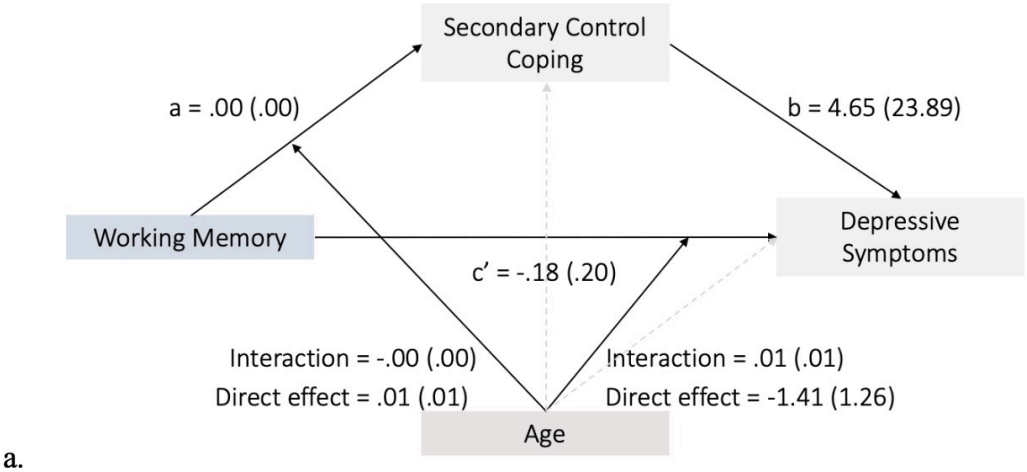
Figure 6. PROCESS Model 4. (a) Parent-reported control, coping, and depressive symptoms in children and adolescents with SCA. (b) Self-reported perceived control, coping, and depressive symptoms in adolescents and young adults with SCA. The PROCESS macro program only produces unstandardized regression coefficients. Owing to the difference in scaling between

predictors and the ratio scores from the Responses to Stress Questionnaire, the unstandardized path coefficient is small. $^{***}p < .001$

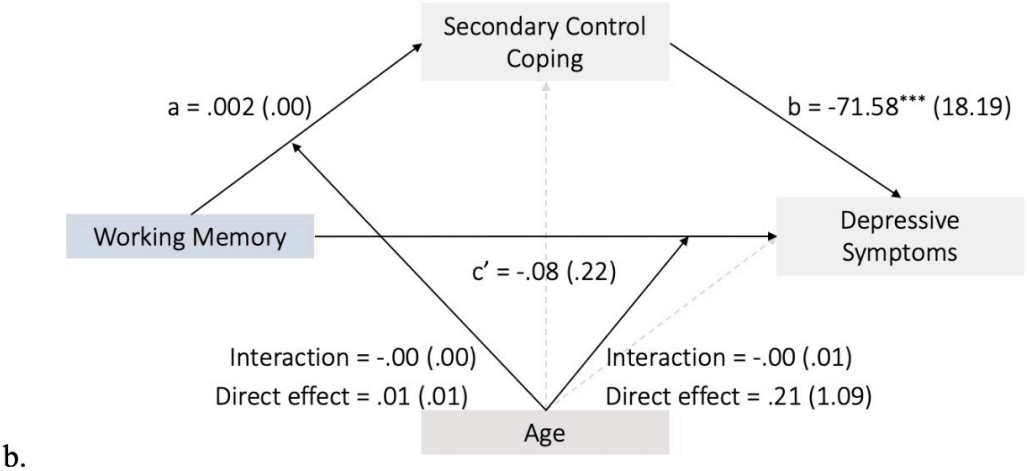
The moderating effect of participant age on the association between working memory with secondary control coping and depressive symptoms are presented in Figure 7. Age was not a significant moderator of either the association of working memory with secondary control coping or depressive symptoms in both parent-reported (age*WMI predicting coping: -.00, p = .210; age*WMI predicting depressive symptoms = .01, p = .442) and self-reported models (age*WMI predicting coping: -.00, p = .329; age*WMI predicting depressive symptoms = -.00, p = .950). Age also did not directly predict secondary control coping (parent-reported main effect = .01, p = .201; self-reported main effect = .01, p = .285) or depressive symptoms (parent-reported main effect = -1.41, p = .273; self-reported main effect = .21, p = .849).

The moderating effect of perceived control on the association between secondary control coping and depressive symptoms are presented in Figure 8. Parent-reported perceived control of stress was a significant moderator of the association between secondary control coping and depressive symptoms in children and adolescents (control*coping predicting depressive symptoms = 69.91, p = .025), such that there was a significant negative association of secondary control coping with depressive symptoms only for low perceived control. A graph of the interaction effect is shown in Figure 9. Perceived control of stressors was also a significant positive predictor of depressive symptoms (main effect = -.20.01, p = .021). These effects were not found in the self-reported model in adolescents and young adults.

Findings of including the moderating effects of age and perceived control in one model are presented in Figure 10. There were no significant paths or moderating effects across both parent- and self-reported models.



a.



b.

Figure 7. PROCESS Model 8. (a) Parent reported control, coping, and depressive symptoms in children and adolescents with SCA. (b) Self-reported perceived control, coping, and depressive symptoms in adolescents and young adults with SCA. The PROCESS macro program only produces unstandardized regression coefficients. Owing to the difference in scaling between predictors and the ratio scores from the Responses to Stress Questionnaire, the unstandardized path coefficient is small. $^{***}p < .001$

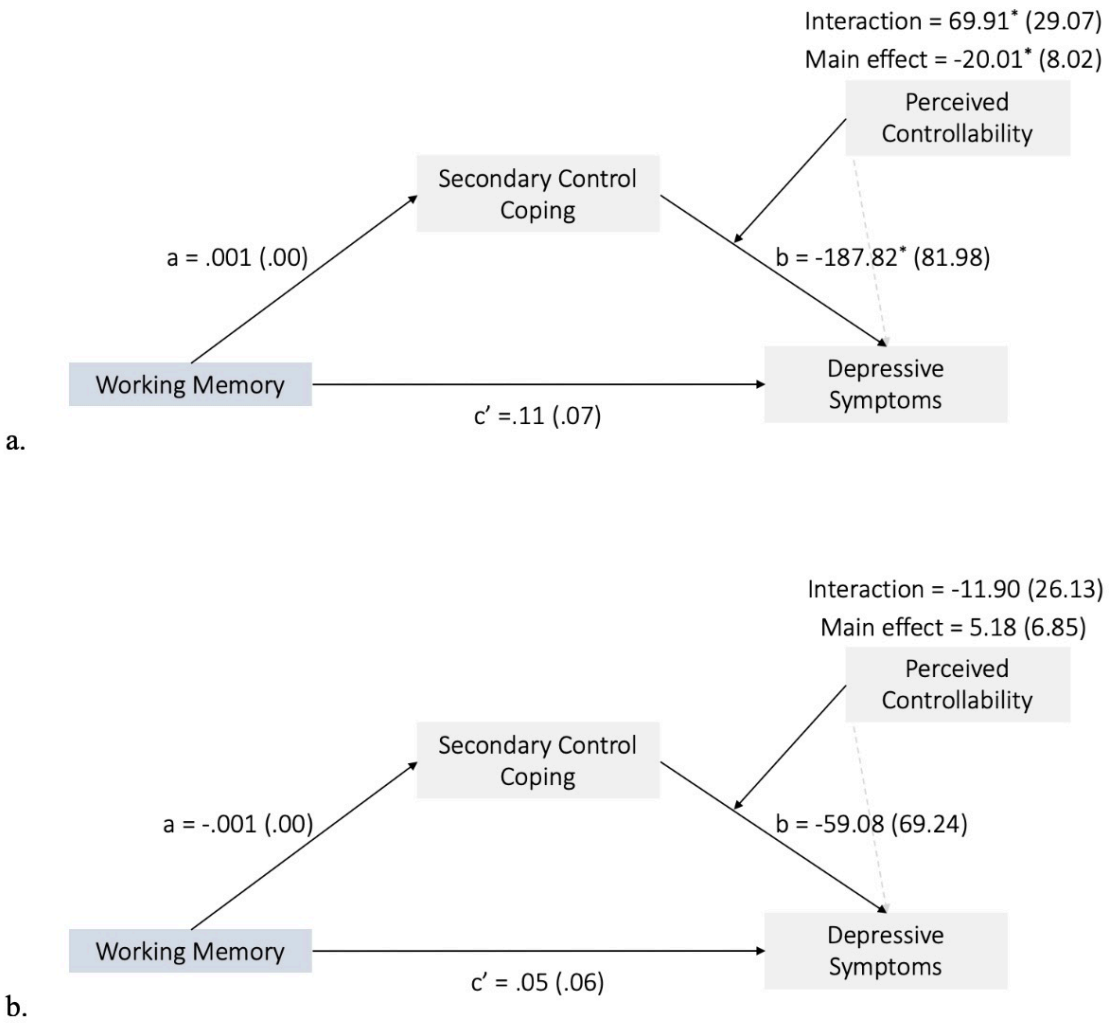


Figure 8. PROCESS Model 14. (a) Parent reported control, coping, and depressive symptoms in children and adolescents with SCA. (b) Self-reported perceived control, coping, and depressive symptoms in adolescents and young adults with SCA. The PROCESS macro program only produces unstandardized regression coefficients. Owing to the difference in scaling between predictors and the ratio scores from the Responses to Stress Questionnaire, the unstandardized path coefficient is small. $^{*}p < .05$

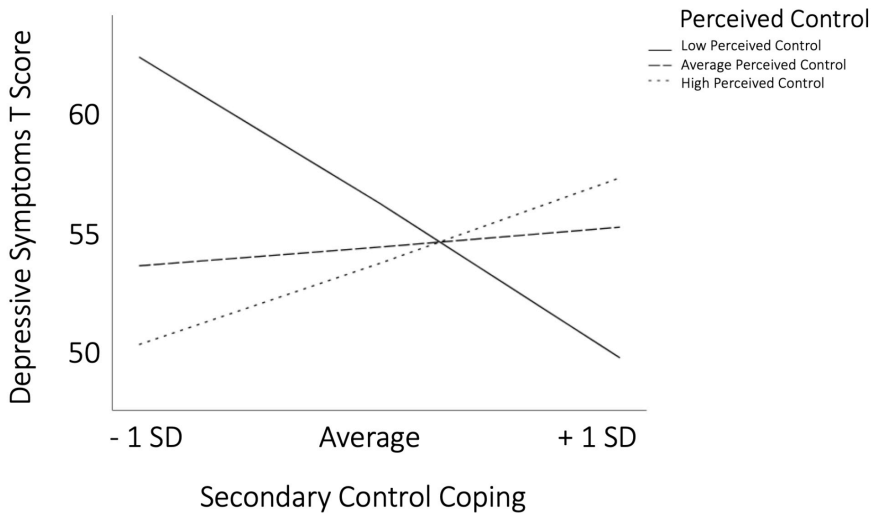
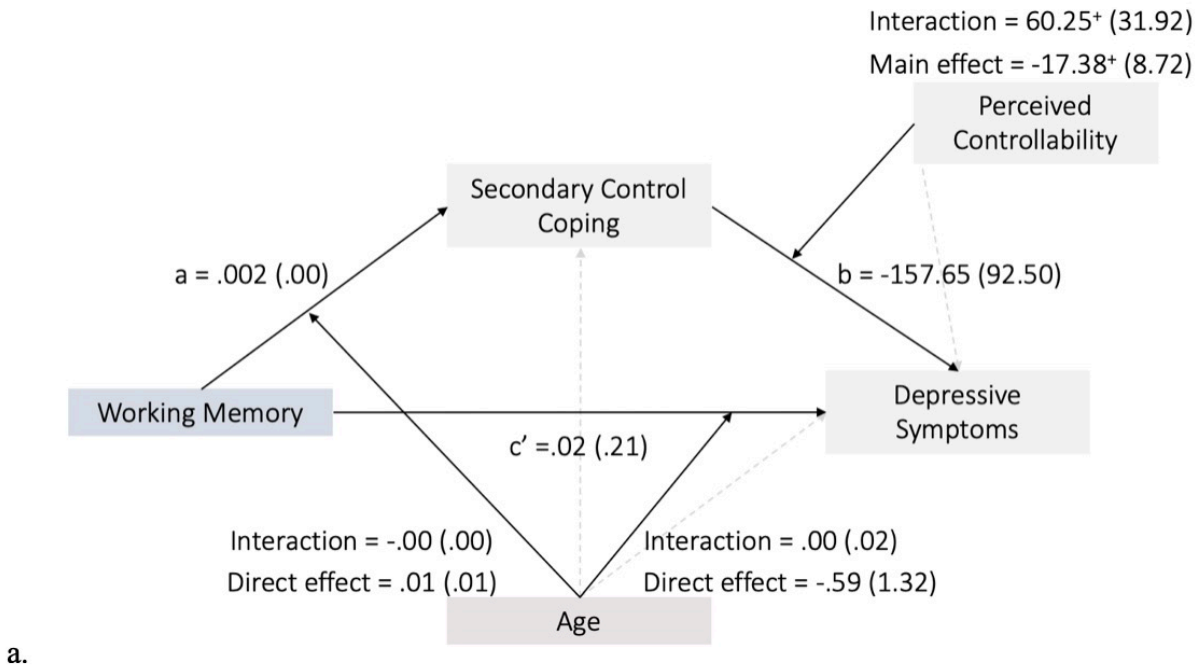


Figure 9. Interaction of parent-reported secondary control coping and perceived control of stress as predictors of depressive symptoms, such that there was a significant negative effect of secondary control coping on depressive symptoms only for low perceived control.

Supplemental analyses assessing CBF as a distal predictor of depressive symptoms are shown in Figure 11. Results showed that CBF did not have a direct or indirect association with depressive symptoms through either working memory or secondary control coping in both parent- and self-reported models.

Discussion

Children, adolescents, and young adults with SCD are faced with peer-related stress, and although there are other disease and environmental stressors that could influence depressive symptoms, this study provides preliminary evidence that how individuals with SCD cope with peer stress, and their perception of the controllability of these stressors, are related to depressive symptoms. Although results were unable to replicate the association among working memory with coping and internalizing symptoms, findings were able to replicate and extend previous research on the control-based model of coping in SCD.



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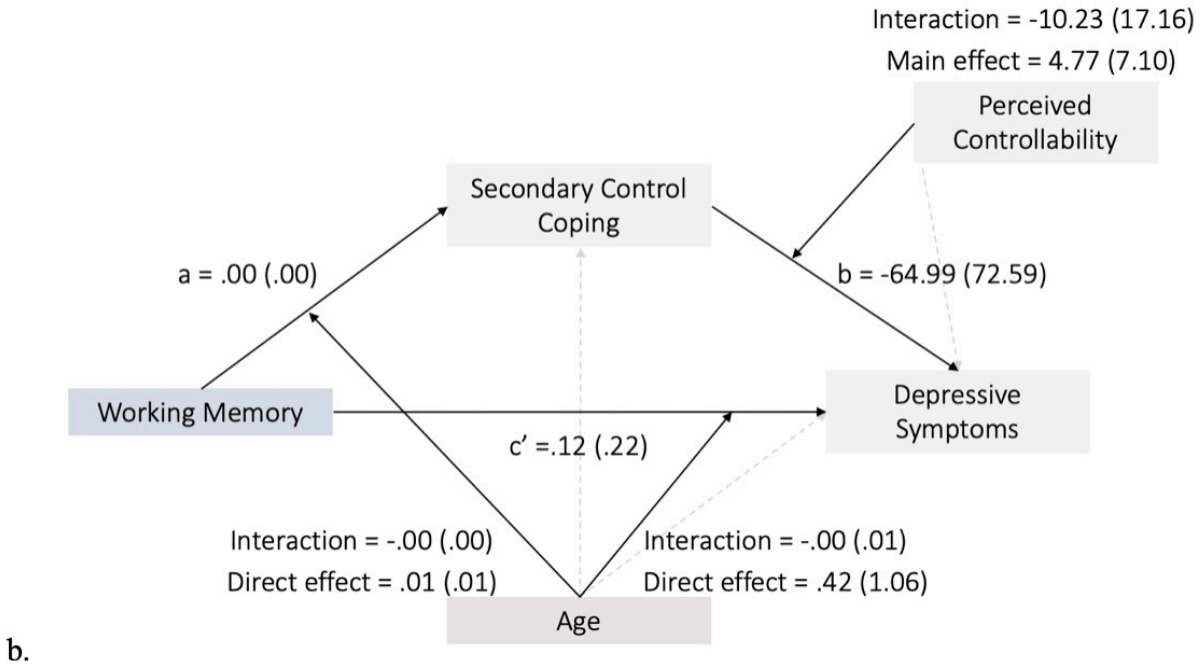

b.

Figure 10. PROCESS Model 22. (a) Parent reported control, coping, and depressive symptoms in children and adolescents with SCA. (b) Self-reported perceived control, coping, and distress in adolescents and young adults with SCA. The PROCESS macro program only produces unstandardized regression coefficients. Owing to the difference in scaling between predictors and the ratio scores from the Responses to Stress Questionnaire, the unstandardized path coefficient is small. $^{+}p < .10$

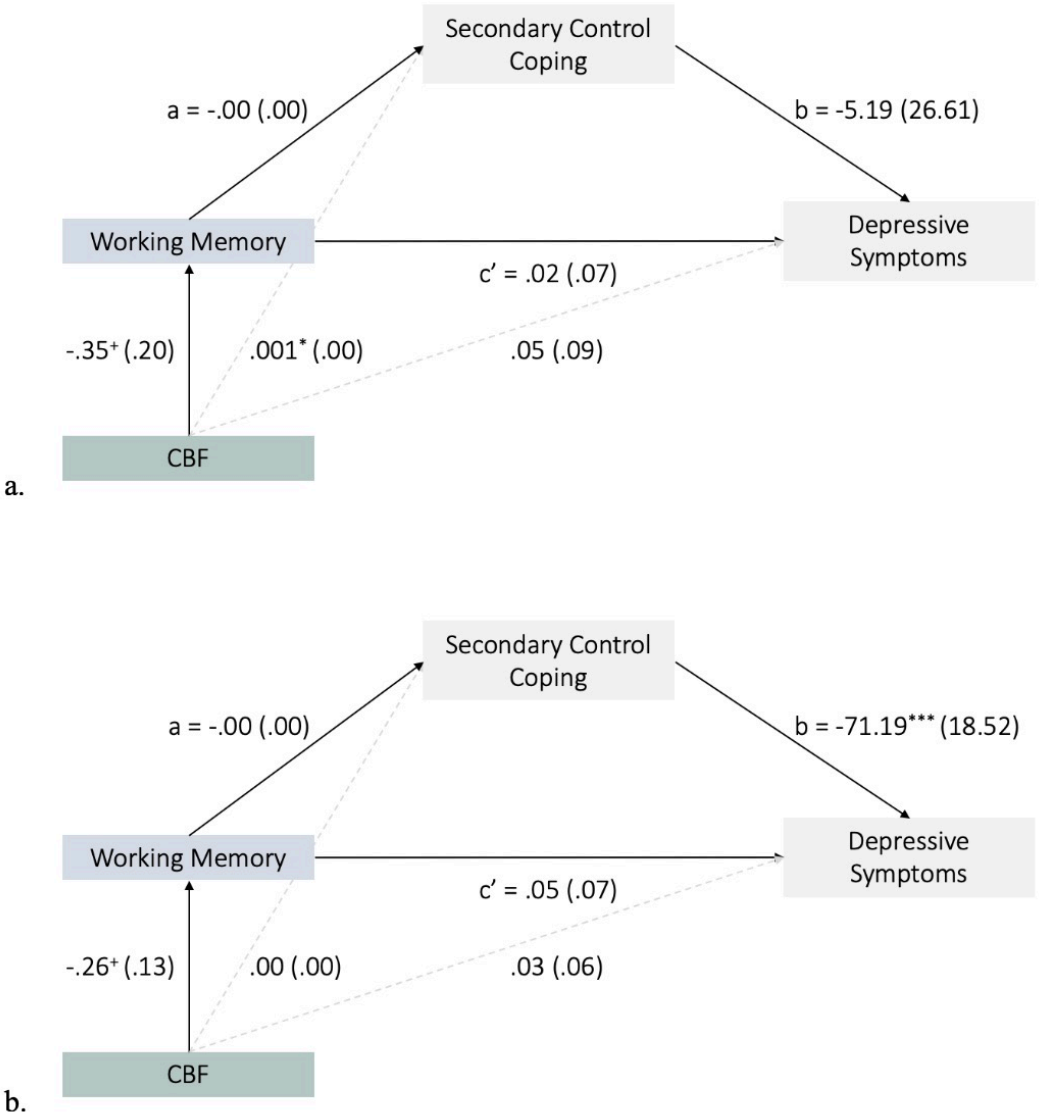

Figure 11. PROCESS Model 6. (a) Parent reported control, coping, and depressive symptoms in children and adolescents with SCA. (b) Self-reported perceived control, coping, and depressive symptoms in adolescents and young adults with SCA. The PROCESS macro program only produces unstandardized regression coefficients. Owing to the difference in scaling between predictors and the ratio scores from the Responses to Stress Questionnaire, the unstandardized path coefficient is small. $^{+}p < .10$, $^{***}p < .001$

The results did not support the first hypothesis that secondary control coping will account for a significant portion of the association between cognitive function and depressive symptoms. Prior research on the association among executive function, coping, and depression focused

specifically on how children and adolescents with SCD cope with disease-related stress, and findings indicated that working memory was negatively related to depressive symptoms (Prussien et al. 2018). In the current study, working memory was not related to either secondary control coping or depressive symptoms. Further, findings from Prussien et al. (2018) indicated that there was a significant indirect association between verbal reasoning and depressive symptoms through secondary control coping. Findings for verbal reasoning in the current study are presented in the appendix, and there were no significant direct or indirect effects through coping. In the current study, coping was assessed specifically related to how children, adolescents, and young adults coped with peer stress. Taken together, findings could suggest that verbal reasoning is specifically related to how children and adolescents are able to cope with disease-related stress rather than peer-related stress. Nevertheless, results here should be cautiously interpreted, as the modest sample size and lack of power limits clinical interpretation.

Support was not found for the second hypothesis. Due to prior research on increased deficits in executive function and increased depressive symptoms across age, it was hypothesized that the association between working memory and depressive symptoms would be moderated by age. The current study found participant age was not a significant moderator of the association between working memory with secondary control coping or the association between working memory with depressive symptoms. These relations have not been investigated in prior research on cognitive function and coping in pediatric populations; however, future research with larger samples and more statistical power should continue to assess the influence of age on these psychosocial processes.

The primary finding from the current study was that perceived control of stressors moderated the association between secondary coping and depressive symptoms, providing partial

support for the final study hypothesis. Using parent reports of coping and depressive symptoms in children and adolescents, results showed that greater use of secondary control coping was related to significantly lower depressive symptoms only for children and adolescents who perceived their peer-stressors as uncontrollable. Although researchers have hypothesized that secondary control coping measured by the RSQ is most adaptive due to the uncontrollable nature of many stressors (Compas et al., 2018; Prussien et al., 2018), this is among the first studies using the control-based model of coping to support the theory that the use of cognitive reappraisal, positive thinking, and distraction are more effective in reducing the downstream effect of stress on depressive symptoms when the stressors are uncontrollable in SCD.

Perceived control in the current study was assessed an aspect of personal competence (i.e., "Can I control this?") rather than outcome contingency (i.e., "Can kids in general control this?"), an important distinction described by Weisz (1986). Future research on the control-based model should assess how the relative impact of personal competence and outcome contingency on internalizing problems, and how the difference between the two domains of perceived control might also be related to psychological adjustment. Further, although perceived control was a significant moderator in parent-reports of their child or adolescent's coping, perceived control, and symptoms of depression, findings did not show significant moderating effect of perceived control on this relation in the self-reported data in adolescents and young adults. This discrepancy could either explained by the limited sample size across groups, differences informant perspective, or differences in age and developmental status. Future research should continue to assess these associations using multi-informant data, and investigate how perceived control of stressors may change as children and adolescents develop into young adults. Finally, although findings showed that perceived control moderated the association between secondary

control coping and depressive symptoms, similar findings were not shown for primary control coping. The control-based model of coping also poses that primary control coping (i.e., problem-solving, social-support seeking) is most adaptive for controllable stressors. Theoretically, primary control coping should only be related to depressive symptoms for stressors that are controllable. Future research should continue to assess all aspects of the control-based model of coping.

Limitations

The current study had several strengths, including the use of a multimethod approach including direct assessment of performance-based executive function, nationally normed measures of depressive symptoms, and multi-informant questionnaires in a sample of children, adolescents, and young adults with SCA receiving the most up-to-date medical treatments. However, it is important to address the limitations of this study in future research. Although the overall sample of enrolled participants was larger than prior research, samples for parent- and self-reports in the analyses were small. Future research should continue to assess the association among cognitive function, coping, and depression, and the moderating effects of age and perceived control using multi-informant data in a larger sample of SCD.

Conclusion

Although executive function was not related to psychosocial outcomes and age was not a significant moderator of associations, perceived control was a significant moderator of the association between secondary control coping and depressive symptoms in children and adolescents with SCD.

CHAPTER IV

GENERAL DISCUSSION

Two primary questions related to cognitive function in children, adolescents, and young adults with SCA were posed. First, what biological and environmental characteristics are associated with deficits in executive function in SCA? And second, how do deficits in cognitive function affect an individual's everyday wellbeing and psychosocial adjustment?

Findings provide new evidence on biological factors related to deficits in executive function. Specifically, lower hematocrit percentage and high CBF and OEF are related to greater deficits in executive function. Annual household income was the only environmental characteristic investigated, and although it was not a significant predictor of executive function in multivariate analyses presented in Study 1, supplemental bivariate analyses suggest that income was associated with broader domains of cognitive function (Appendix A, Table 6). More research is necessary to assess the integration of these two important domains relevant to risks for deficits in cognitive and executive function in SCA.

Psychosocial consequences of these deficits are less clear. The primary finding for Study 2 suggested that perceived control was a significant moderator of the association between secondary control coping and depressive symptoms in children and adolescents with SCD, and there were no significant associations among executive function with psychosocial variables. Results were significantly limited by the limited sample size across both parent- and self-reports, and future research should continue to assess how deficits in cognitive and executive function affect wellbeing and psychosocial adjustment in SCA.

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Appendix A. Supplemental Analyses for Study 1

Table 5. Correlations among cognitive function measures in participants with SCA

	1	2	3	4	5	6	7	8	9	10	11	12
1. Wechsler VCI	-											
2. Wechsler WMI	.36**	-										
3. Wechsler PRI	.36**	.59***	-									
4. WISC-V VSI	.33	.52**	.93***	-								
5. WISC-V FRI	.41*	.60**	.94***	.75***	-							
6. Wechsler PSI	.30*	.42**	.39**	.31	.37*	-						
7. Wechsler FSIQ	.71***	.71***	.82***	.68***	.84***	.62***	-					
8. NIHTB-CB Dimensional Change	.52***	.42**	.52***	.35+	.34+	.42**	.65***	-				
9. NIHTB-CB Inhibitory Control	.39**	.31*	.20	.22	.04	.28+	.36*	.59***	-			
10. NIHTB-CB Working Memory	.38**	.34*	.42**	-.17	-.00	.19	.48**	.43**	.14	-		
11. NIHTB-CB Processing Speed	.32*	.15	.21	-.04	.03	.14	.32*	.56***	.32*	.34*	-	
12. NIHTB-CB Memory	.26+	.37**	.49***	.37+	.54**	.47**	.58***	.45**	.19	.48**	.30*	-
13. NIHTB-CB Fluid Cognition	.55***	.40**	.49***	.22	.29	.43**	.66***	.86**	.60***	.64***	.73***	.68***

VCI = verbal comprehension index; WMI = working memory index; PRI = perceptual reasoning index; VSI = visual spatial index; FRI = fluid reasoning index; PSI = processing speed index; FSIQ = full scale intelligence quotient; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery

Wechsler N = 54

NIHTB-CB N = 49

$^{+}p < .10$, $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

Table 6. Correlations among age, income, CBF, and OEF with cognitive function in participants with SCA

	Age	Income	Hct	CBF	OEF (HbF)	OEF (HbAA)
Age	-					
Income	.08	-				
Hct	.16	-.09				
CBF	.37**	.16	-.27*	-		
OEF (HbF)	.25+	.06	-.47***	-.05	-	
OEF (HbAA)	.36**	.13	-.15	-.19	.92***	-
Cognitive Function						
Wechsler VCI	-.00	.25+	.03	-.16	-.17	-.10
Wechsler PRI	.01	.31*	-.04	-.06	-.06	-.01
Wechsler PSI	-.09	.19	.10	-.20	-.01	.09
Wechsler FSIQ	-.05	.37**	-.04	-.15	-.12	-.04
Executive Function						
Wechsler WMI	-.31*	.17				
NIHTB-CB Dimensional Change	-.10	.11				
NIHTB-CB Inhibitory Control	-.40**	-.04				
NIHTB-CB Working Memory	.08	.09				
NIHTB-CB Processing Speed	.10	-.01				
NIHTB-CB Memory	.01	.10				
NIHTB-CB Fluid Cognition	-.02	.09				

Age = participant age at neurocognitive assessment; Income = annual household income; Hct = hematocrit percentage; CBF = cerebral blood flow; OEF = oxygen extraction fraction; VCI = verbal comprehension index; PRI = perceptual reasoning index; PSI = processing speed index; FSIQ = full scale intelligence quotient; WMI = working memory index; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery
Wechsler N = 54
NIHTB-CB N = 49
$^{+}p < .10$, $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

Table 7. Correlation of cognitive function with CBF and OEF across infarct status

	Healthy Controls			SCA No Infarcts			SCA Infarcts		
	CBF	OEF (HbF)	OEF (HbAA)	CBF	OEF (HbF)	OEF (HbAA)	CBF	OEF (HbF)	OEF (HbAA)
Wechsler WMI	-.02	-.18	-.17	-.45*	.07	.14	-.28	-.07	-.06
NIHTB-CB Inhibitory Control	-.10	-.31	-.23	-.16	-.16	-.14	-.73***	-.01	.12
NIHTB-CB Processing Speed	.64^{+}	-.05	.04	-.01	-.36*	-.27	-.23	-.19	-.12
NIHTB-CB Fluid Cognition	-.09	-.34	-.22	-.06	-.19	-.04	-.29	-.24	-.11

WMI = working memory index; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery; CBF = cerebral blood flow; OEF = oxygen extraction fraction
Healthy Controls N = 8 to 10
SCA No Infarcts N = 22 to 27
SCA Infarcts N = 24 to 25
$^{+}p < .10$, $^{*}p < .05$, $^{***}p < .001$

Table 8. Multivariate linear regressions predicting NIHTB-CB Fluid Cognition in participants with SCA

	No Infarcts			Infarcts		
	B	β	R^2	B	β	R^2
			.23			.26
Hct	.81	.19		1.56	.35	
Age	-.37	-.20		-.01	-.00	
Income	.14	.03		.22	.04	
Time	.02	$.45^{+}$		.02	.29	

NIHTB-CB = National Institutes of Health Toolbox Cognition Battery; Hct = hematocrit percentage; Age = participant age at neurocognitive assessment; Time = days between MRI and neurocognitive assessment.
No Infarcts N = 22
Infarcts N = 20
$^{+}p < .10$

Table 9. Multivariate linear regressions predicting Wechsler Working Memory Index in participants with SCA

	No Infarcts			Infarcts		
	B	β	R^2	B	β	R^2
			.33			.15
CBF	-.39	-.52*		-.02	-.02	
Age	-.42	-.25		-.54	-.25	
Income	1.42	.27		1.07	.22	
Time	.01	.22		-.01	.12	

NIHTB-CB = National Institutes of Health Toolbox Cognition Battery; CBF = cerebral blood flow; Age = participant age at neurocognitive assessment; Time = days between MRI and neurocognitive assessment.
No Infarcts N = 25
Infarcts N = 21
*$p < .05$

Table 10. Multivariate linear regressions predicting NIHTB-CB Inhibitory Control in participants with SCA

	No Infarcts			Infarcts		
	B	β	R^2	B	β	R^2
			.20			.45
CBF	.01	.02		-.45	-.62*	
Age	-.80	-.49+		-.13	-.09	
Income	-.66	-.13		.39	.11	
Time	.01	.37		.00	.08	

NIHTB-CB = National Institutes of Health Toolbox Cognition Battery; CBF = cerebral blood flow; Age = participant age at neurocognitive assessment; Time = days between MRI and neurocognitive assessment.
No Infarcts N = 21
Infarcts N = 20
$^{+}p < .10$, $^{*}p < .05$

Table 11. Multivariate linear regressions predicting NIHTB-CB Processing Speed in participants with SCA

	No Infarcts			Infarcts		
	B	β	R^2	B	β	R^2
			.21			.29
OEF (HbF)	-1.26	-.44^{+}		-.57	-.25	
Age	.35	.16		.18	.08	
Income	-.88	-.14		-.29	-.06	
Time	.01	.18		.03	.42^{+}	

NIHTB-CB = National Institutes of Health Toolbox Cognition Battery; OEF = oxygen extraction fraction; Age = participant age at neurocognitive assessment; Time = days between MRI and neurocognitive assessment.
No Infarcts N = 23
Infarcts N = 20
$^{+}p < .10$

Table 12. Multivariate linear regressions predicting NIHTB-CB Processing Speed in participants with SCA

	No Infarcts			Infarcts		
	B	β	R^2	B	β	R^2
			.23			.27
OEF (HbAA)	-1.46	-.47*		-.63	-.22	
Age	.26	.16		.17	.08	
Income	-.84	-.13		.18	-.04	
Time	.01	.23		.03	.44+	

NIHTB-CB = National Institutes of Health Toolbox Cognition Battery; OEF = oxygen extraction fraction; Age = participant age at neurocognitive assessment; Time = days between MRI and neurocognitive assessment.
No Infarcts N = 23
Infarcts N = 20
$^{+}p < .10$, $^{*}p < .05$

Appendix B. Supplemental Analyses for Study 2

Table 13. Correlations among psychosocial variables in participants with SCA

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Parent-Reported															
1. Peer stress	-														
2. Perceived controllability	.44*	-													
3. Primary control coping	-.16	.13	-												
4. Secondary control coping	-.07	.13	-.02	-											
5. Disengagement coping	.22	-.08	-.56**	-.30+	-										
6. Anxiety symptoms	.47**	-.02	-.22	-.39*	.34+	-									
7. Depressive symptoms	.08	-.15	-.09	-.02	.13	.36*	-								
8. Anxious-depressed	.26	-.07	-.15	-.53**	.23	.84***	.30+	-							
Self-Reported															
9. Peer stress	.06	-.02	-.03	-.03	.05	.31	.27	.27	-						
10. Perceived controllability	.16	.20	-.05	.49	-.14	.02	-.20	.07	.39*	-					
11. Primary control coping	-.30	-.00	.19	.08	-.20	-.52*	-.29	-.41	-.32+	.19	-				
12. Secondary control coping	-.15	-.17	.00	.15	-.47+	-.46+	-.48+	-.45+	-.35*	.36*	.45**	-			
13. Disengagement coping	.56*	.14	-.14	-.01	.56*	.47+	.45+	.48+	.40*	.02	-.44**	-.58***	-		
14. Anxiety symptoms	-.20	.13	.05	.36	-.19	.31	.21	.21	.43**	.14	-.46**	-.39*	.19	-	
15. Depressive symptoms	.40	.24	-.15	.05	.18	.62**	.64**	.57*	.45**	.01	-.52**	-.57***	.36*	.79***	-
16. Anxious-depressed	-.04	-.10	-.15	.10	-.01	.60*	.41	.51*	.41*	.02	-.49**	-.48**	.23	.83***	.87***

Parent-report N = 28 to 32
Self-report N = 36 to 37
Cross-reports N = 16 to 17
$^{+}p < .10$, $^{*}p < .05$, $^{**}p < .01$

Table 14. Correlations among cognitive function and parent-reported stress, perceived control, and coping in children and adolescents with SCA

	Peer Stress	Perceived Control	Primary Control Coping	Secondary Control Coping	Disengagement Coping
Wechsler VCI	.23	.24	-.13	.10	-.31^{+}
Wechsler WMI	.26	.34^{+}	-.22	-.24	.17
Wechsler PRI	.16	.23	-.02	-.04	-.14
Wechsler PSI	.23	.24	-14	-.21	.04
Wechsler FSIQ	.27	.21	-.15	-.10	-.10
NIHTB-CB Dimensional Change	.02	.38^{+}	.16	.15	-.36^{+}
NIHTB-CB Inhibitory Control	.26	.46*	-.04	-.02	-.18
NIHTB-CB Working Memory	-.01	.11	-.24	.01	-.04
NIHTB-CB Processing Speed	-.09	-.06	-.16	.17	.05
NIHTB-CB Memory	.38^{+}	.38^{+}	-.37+	.04	.11
NIHTB-CB Fluid Cognition	.11	.31	-.16	.15	-.15

VCI = verbal comprehension index; WMI = working memory index; PRI = perceptual reasoning index; PSI = processing speed index; FSIQ = full scale intelligence quotient; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery
$^{+}p < .10$, $^{*}p < .05$

Table 15. Correlations among cognitive function and parent-reported emotional distress in children and adolescents with SCA

	Anxiety Symptoms	Depressive Symptoms	Anxious - Depressed
Wechsler VCI	-.06	-.10	-.16
Wechsler WMI	-.16	-.03	-.11
Wechsler PRI	-.10	-.03	-.08
Wechsler PSI	-.09	-.08	-.25
Wechsler FSIQ	-.10	-.06	-.18
NIHTB-CB Dimensional Change	-.16	-.33^{+}	-.20
NIHTB-CB Inhibitory Control	.11	.05	.05
NIHTB-CB Working Memory	-.07	-.20	-.22
NIHTB-CB Processing Speed	-.17	-.03	-.18
NIHTB-CB Memory	.26	-.10	.04
NIHTB-CB Fluid Cognition	-.06	-.23	-.18

VCI = verbal comprehension index; WMI = working memory index; PRI = perceptual reasoning index; PSI = processing speed index; FSIQ = full scale intelligence quotient; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery

$^{+}p < .10$

Table 16. Correlations among cognitive function and self-reported stress, perceived control, and coping in adolescents and young adults with SCA

	Peer Stress	Perceived Control	Primary Control Coping	Secondary Control Coping	Disengagement Coping
Wechsler VCI	-.04	-.04	.06	.14	-.29^{+}
Wechsler WMI	.04	-.00	-.11	-.12	.15
Wechsler PRI	.13	.10	-.03	.04	.05
Wechsler PSI	-.04	-.09	.13	.20	-.27
Wechsler FSIQ	.08	.04	-.05	.09	-.08
NIHTB-CB Dimensional Change	.04	-.00	-.13	-.14	-.02
NIHTB-CB Inhibitory Control	.22	.01	-.13	-.22	.04
NIHTB-CB Working Memory	-.04	-.01	-.05	.06	-.15
NIHTB-CB Processing Speed	.02	-.00	-.21	-.21	-.11
NIHTB-CB Memory	-.11	.13	-.09	.06	-.13
NIHTB-CB Fluid Cognition	-.01	.06	-.15	-.07	-.16

VCI = verbal comprehension index; WMI = working memory index; PRI = perceptual reasoning index; PSI = processing speed index; FSIQ = full scale intelligence quotient; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery

$^{+}p < .10$

Table 17. Correlations among cognitive function and self-reported emotional distress in adolescents and young adults with SCA

	Anxiety Symptoms	Depressive Symptoms	Anxious - Depressed
Wechsler VCI	.08	.17	.21
Wechsler WMI	.06	.18	.05
Wechsler PRI	.00	.09	.04
Wechsler PSI	-.06	-.18	-.14
Wechsler FSIQ	.04	.15	.10
NIHTB-CB Dimensional Change	.28	$.30^{+}$	$.33^{+}$
NIHTB-CB Inhibitory Control	.26	$.41^{*}$	$.50^{**}$
NIHTB-CB Working Memory	.19	.20	.18
NIHTB-CB Processing Speed	.11	.16	.25
NIHTB-CB Memory	.06	.06	.02
NIHTB-CB Fluid Cognition	.24	$.30^{+}$	$.34^{+}$

VCI = verbal comprehension index; WMI = working memory index; PRI = perceptual reasoning index; PSI = processing speed index; FSIQ = full scale intelligence quotient; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery

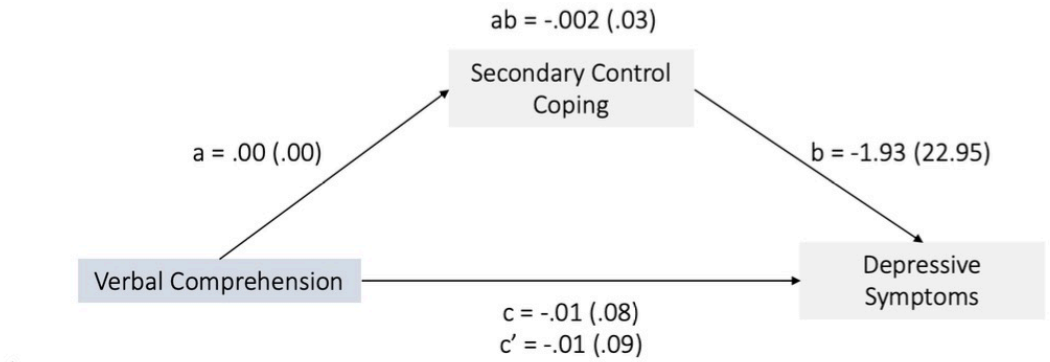
$^{+}p < .10$, $^{*}p < .05$, $^{**}p < .01$

Table 18. Correlations among psychosocial variables, Hct, CBF, and OEF in SCA

	Hct	CBF	OEF (HbF)	OEF (HbAA)
Parent-Reported				
Peer stress	.20	-.15	-.10	-.02
Perceived controllability	.08	-.08	.11	.10
Primary control coping	-.11	.08	.13	.02
Secondary control coping	-.13	.43*	-.08	-.16
Disengagement coping	.28	-.26	.01	.19
Anxiety symptoms	.19	-.17	-.07	.00
Depressive symptoms	-.37*	.11	.24	.09
Anxious-depressed	.03	-.21	.07	.10
Self-Reported				
Peer stress	.20	-.10	-.04	.07
Perceived controllability	-.03	.24	.21	.24
Primary control coping	-.17	.08	.37*	.34*
Secondary control coping	-.10	.19	.07	.01
Disengagement coping	.12	-.21	.07	.14
Anxiety symptoms	.10	-.01	-.06	.01
Depressive symptoms	.05	-.07	.05	.10
Anxious-depressed	.18	-.03	-.06	.03

VCI = verbal comprehension index; WMI = working memory index; PRI = perceptual reasoning index; PSI = processing speed index; FSIQ = full scale intelligence quotient; NIHTB-CB = National Institutes of Health Toolbox Cognition Battery

$^{+}p < .10$, $^{*}p < .05$



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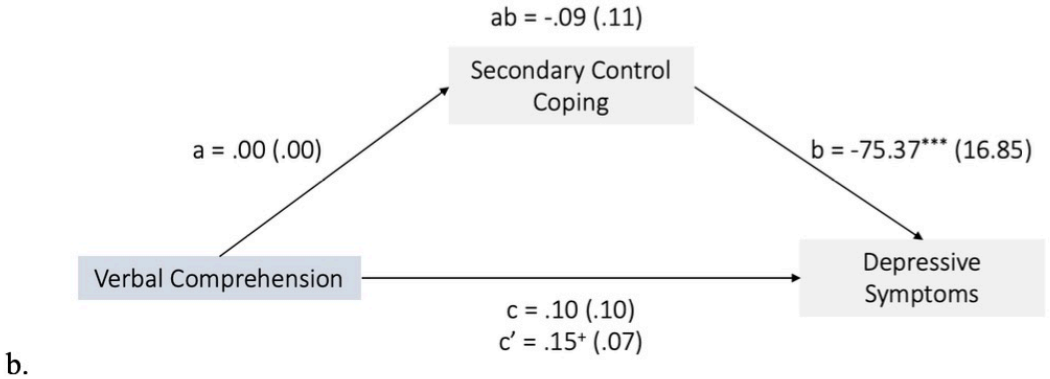
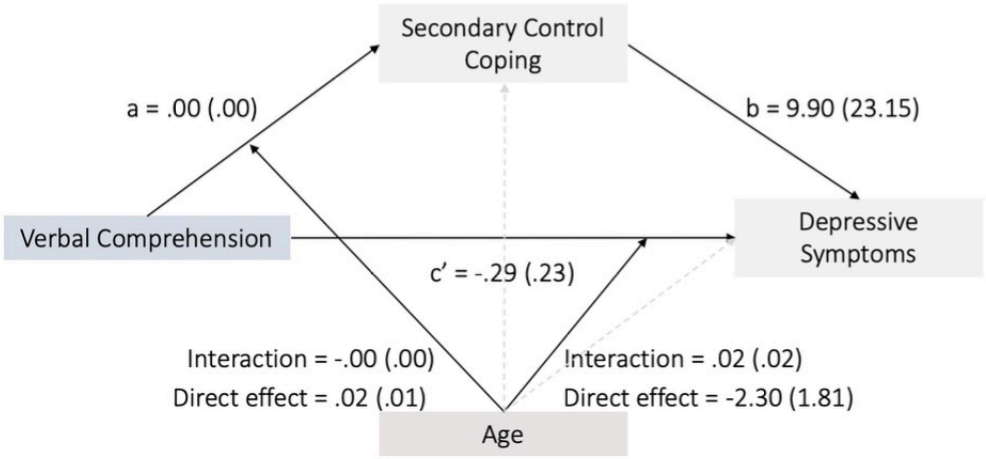


b.

Figure 12. PROCESS Model 4. (a) Parent-reported control, coping, and depressive symptoms in children and adolescents with SCA. (b) Self-reported perceived control, coping, and depressive symptoms in adolescents and young adults with SCA. The PROCESS macro program only produces unstandardized regression coefficients. Owing to the difference in scaling between predictors and the ratio scores from the Responses to Stress Questionnaire, the unstandardized path coefficient is small.
$^{+}p < .10$, $^{***}p < .001$



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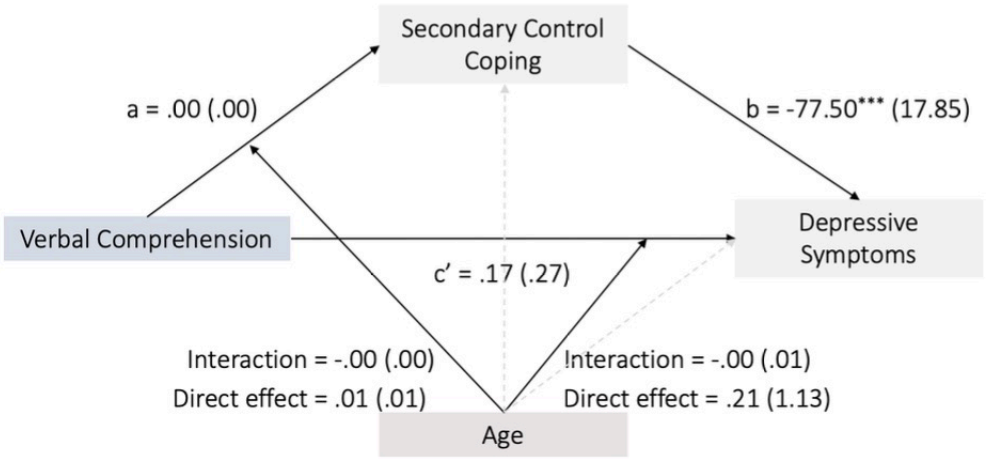


b.

Figure 13. PROCESS Model 8. (a) Parent reported control, coping, and depressive symptoms in children and adolescents with SCA. (b) Self-reported perceived control, coping, and depressive symptoms in adolescents and young adults with SCA. The PROCESS macro program only produces unstandardized regression coefficients. Owing to the difference in scaling between predictors and the ratio scores from the Responses to Stress Questionnaire, the unstandardized path coefficient is small.
$^{***}p < .001$

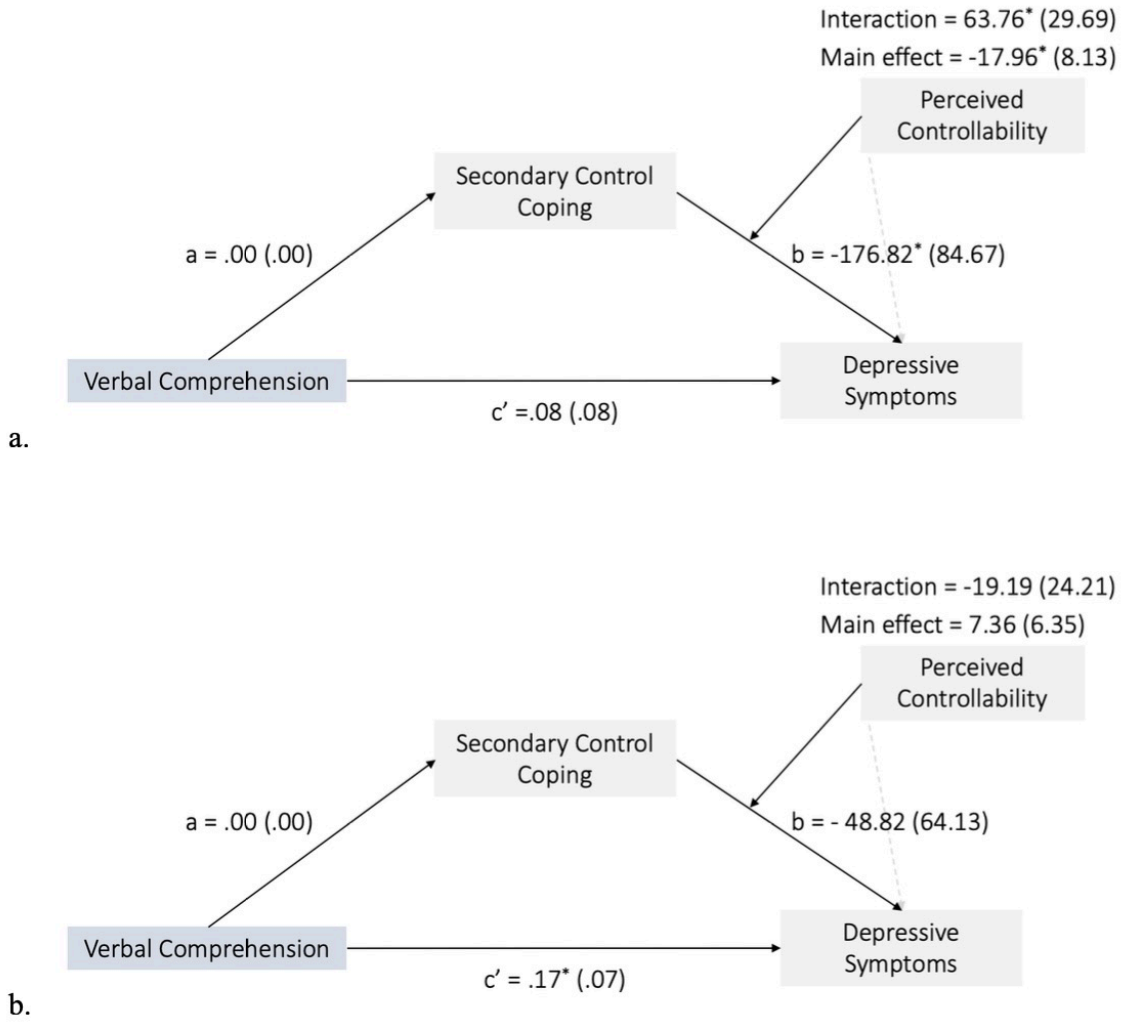
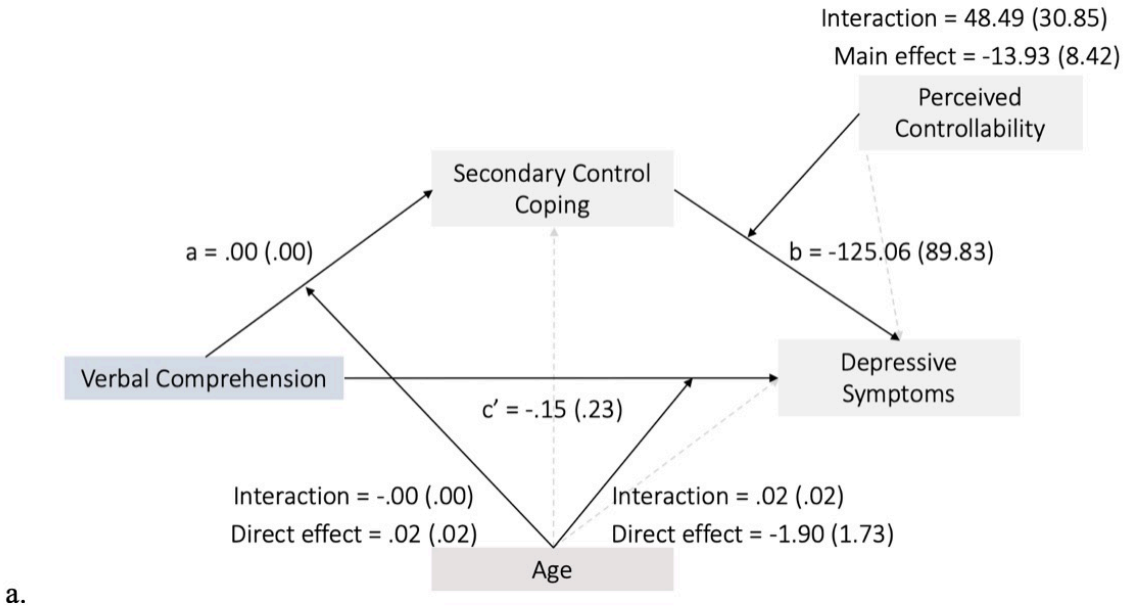


Figure 14. PROCESS Model 14. (a) Parent reported control, coping, and depressive symptoms in children and adolescents with SCA. (b) Self-reported perceived control, coping, and depressive symptoms in adolescents and young adults with SCA. The PROCESS macro program only produces unstandardized regression coefficients. Owing to the difference in scaling between predictors and the ratio scores from the Responses to Stress Questionnaire, the unstandardized path coefficient is small.
*$p < .05$



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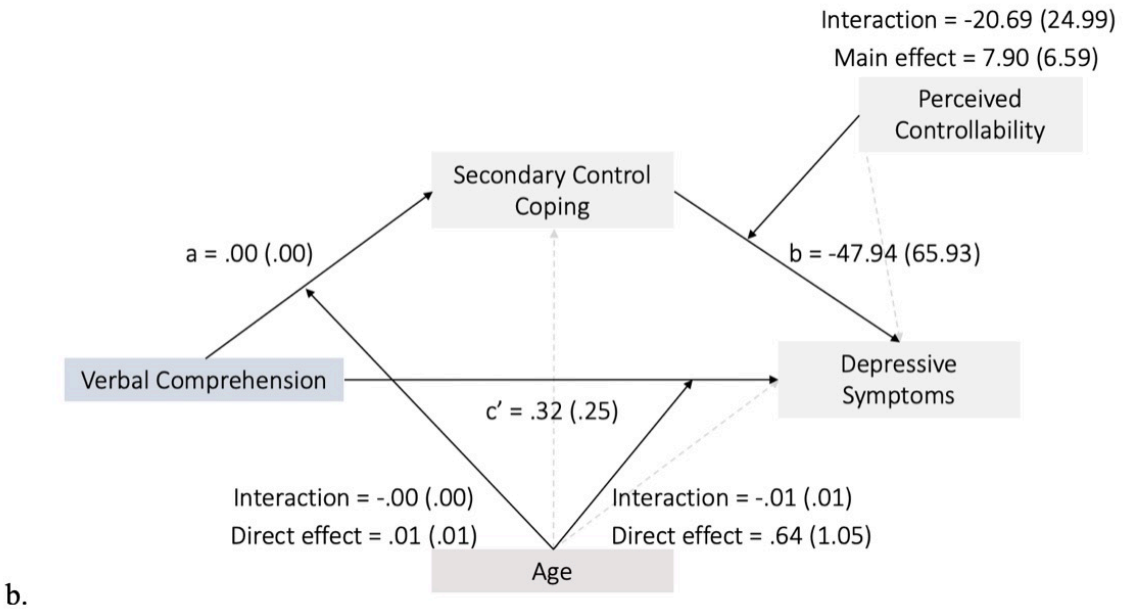
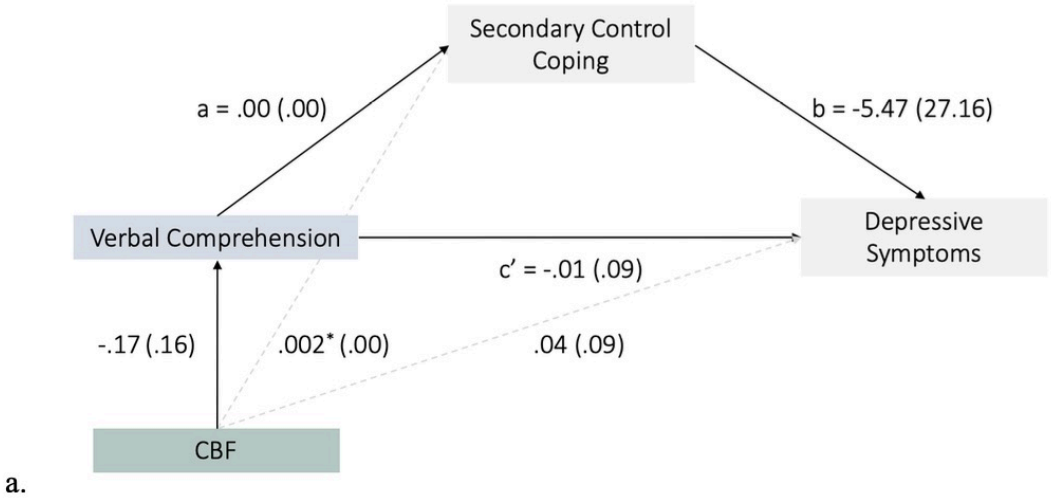


b.

Figure 15. PROCESS Model 22. (a) Parent reported control, coping, and depressive symptoms in children and adolescents with SCA. (b) Self-reported perceived control, coping, and distress in adolescents and young adults with SCA. The PROCESS macro program only produces unstandardized regression coefficients. Owing to the difference in scaling between predictors and the ratio scores from the Responses to Stress Questionnaire, the unstandardized path coefficient is small.



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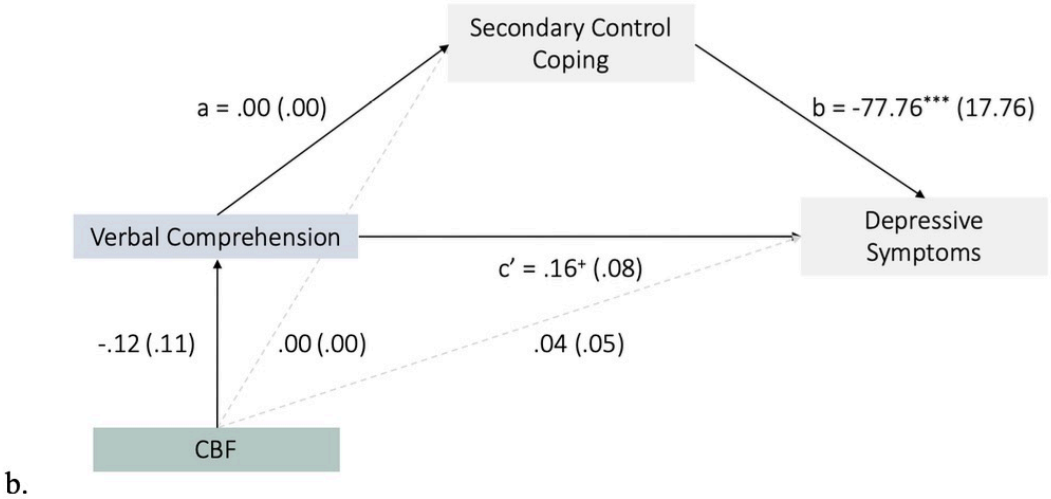


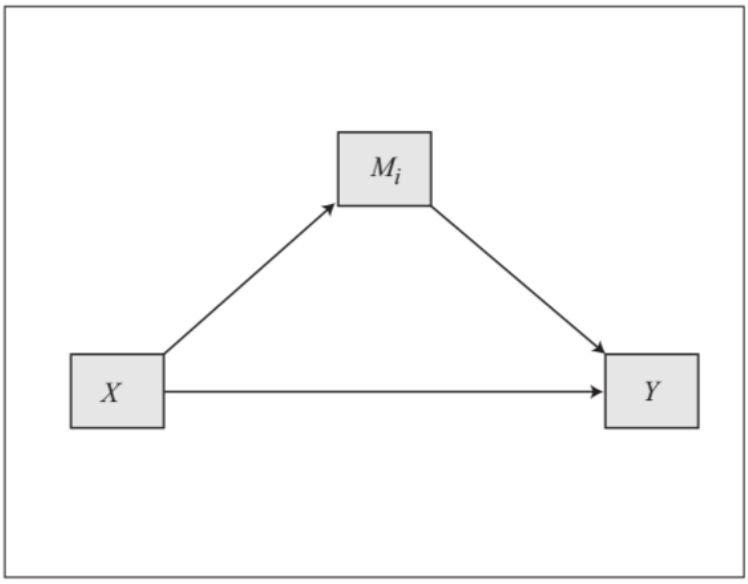
b.

Figure 16. PROCESS Model 6. (a) Parent reported control, coping, and depressive symptoms in children and adolescents with SCA. (b) Self-reported perceived control, coping, and depressive symptoms in adolescents and young adults with SCA. The PROCESS macro program only produces unstandardized regression coefficients. Owing to the difference in scaling between predictors and the ratio scores from the Responses to Stress Questionnaire, the unstandardized path coefficient is small.
$^{+}p < .10$, $^{*}p < .05$, $^{***}p < .001$

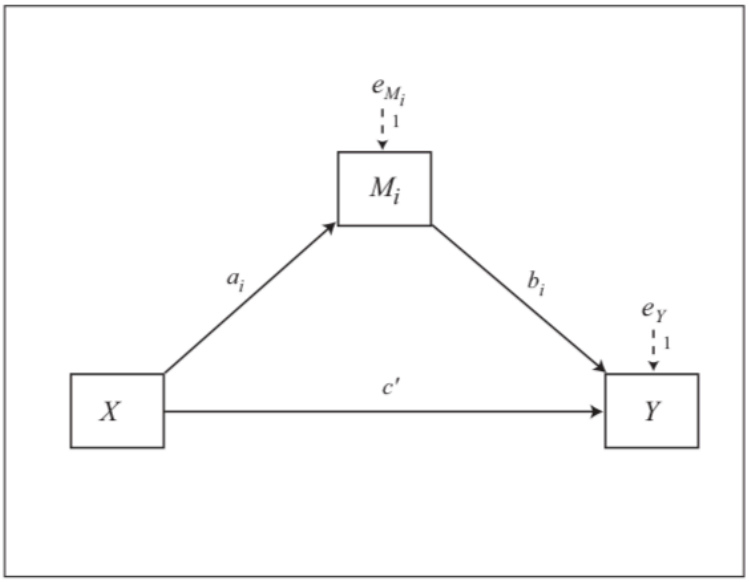
Appendix C. PROCESS Macro Conceptual and Statistical Diagrams

Model 4

Conceptual Diagram



Statistical Diagram



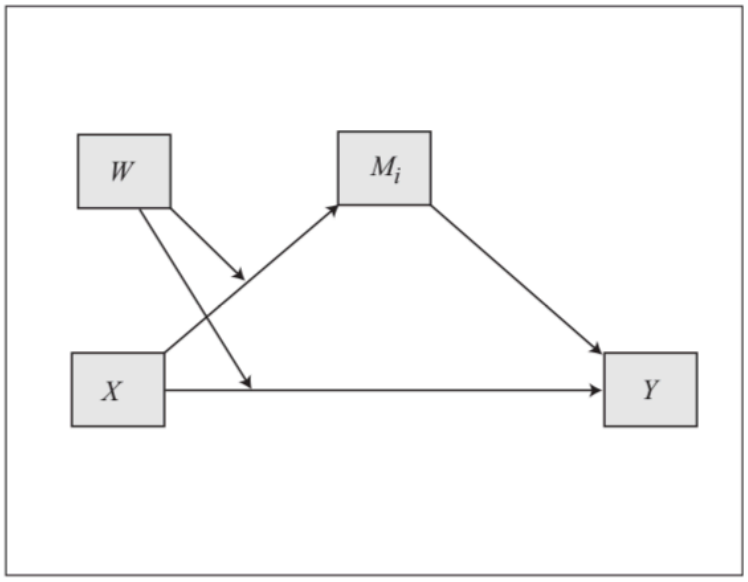
Indirect effect of X on Y through $M_i = a_i\, b_i$

Direct effect of X on $Y = c'$

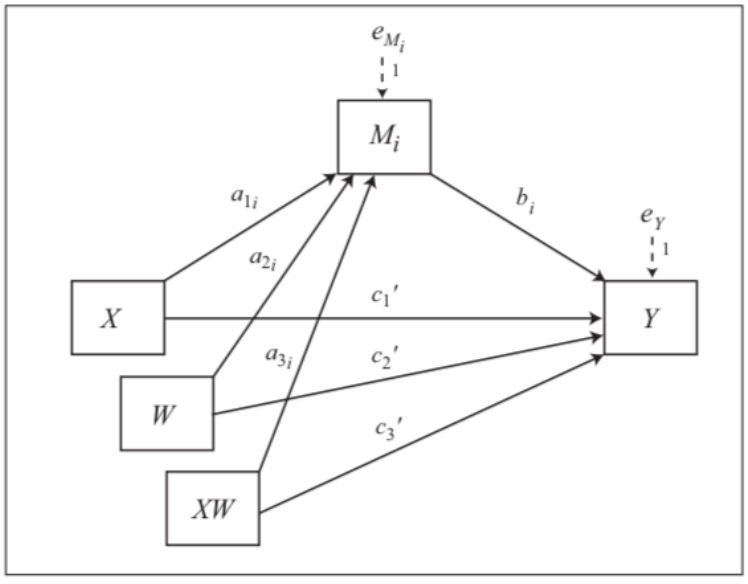
*Model 4 allows up to 10 mediators operating in parallel

Model 8

Conceptual Diagram



Statistical Diagram



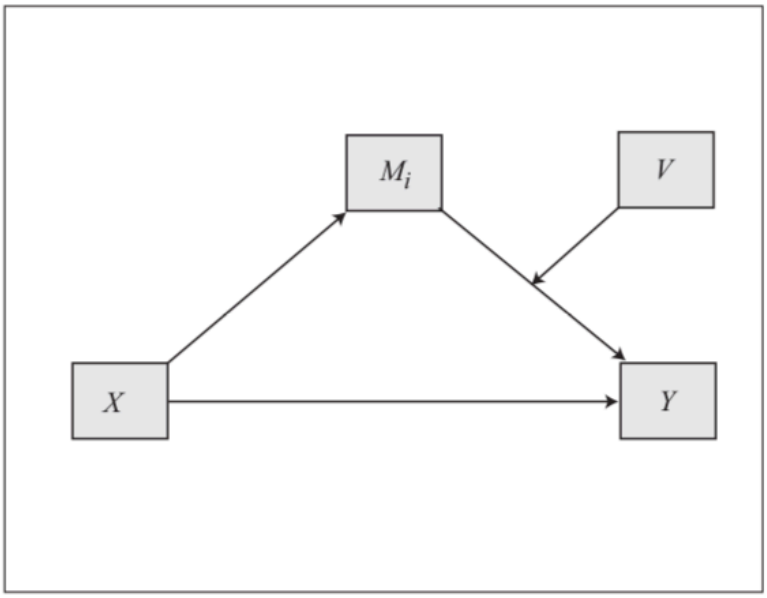
Conditional indirect effect of X on Y through $M_i = (a_{1i} + a_{3i}W)b_i$

Conditional direct effect of X on $Y = c_1' + c_3'W$

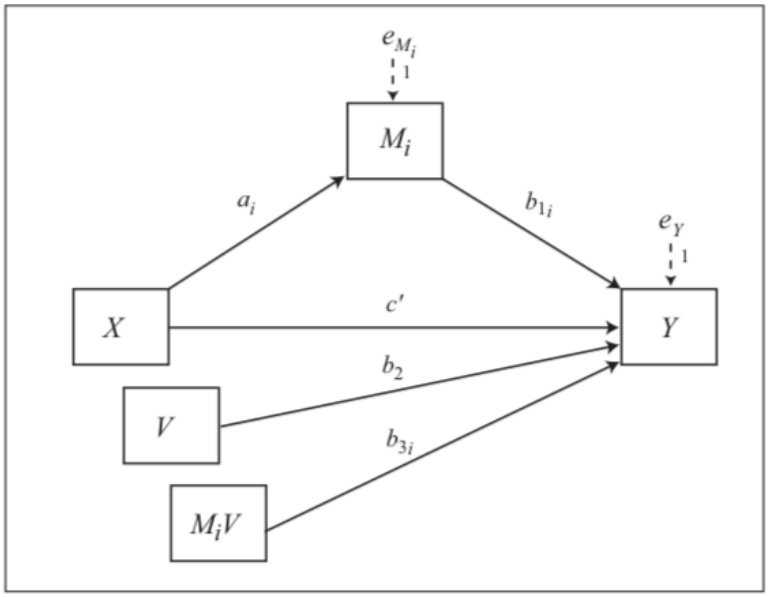
*Model 8 allows up to 10 mediators operating in parallel

Model 14

Conceptual Diagram



Statistical Diagram



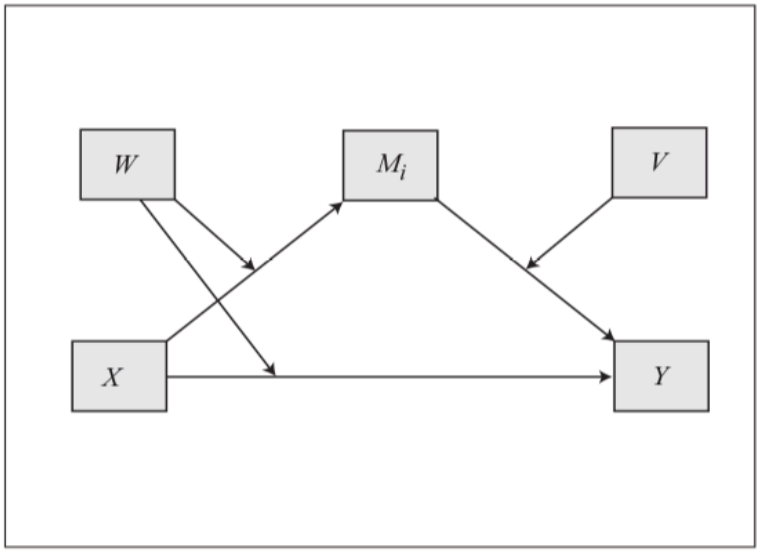
Conditional indirect effect of X on Y through $M_i = a_i\,(b_{1i} + b_{3i}V)$

Direct effect of X on $Y = c'$

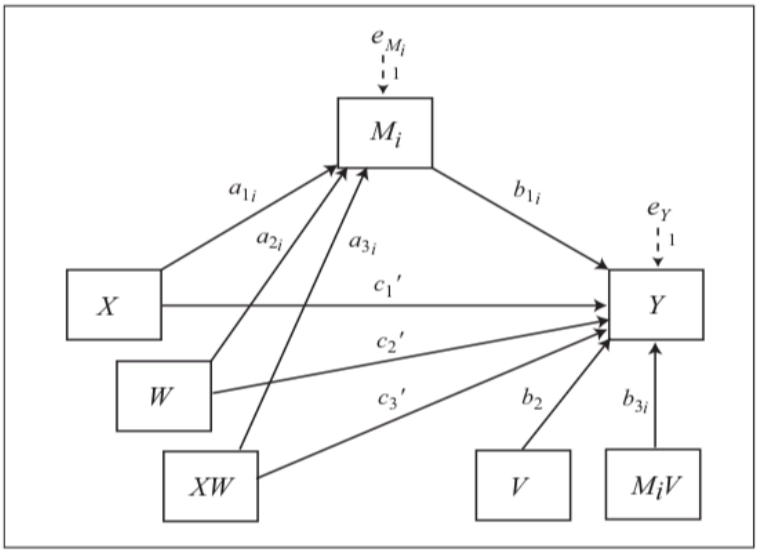
*Model 14 allows up to 10 mediators operating in parallel

Model 22

Conceptual Diagram



Statistical Diagram



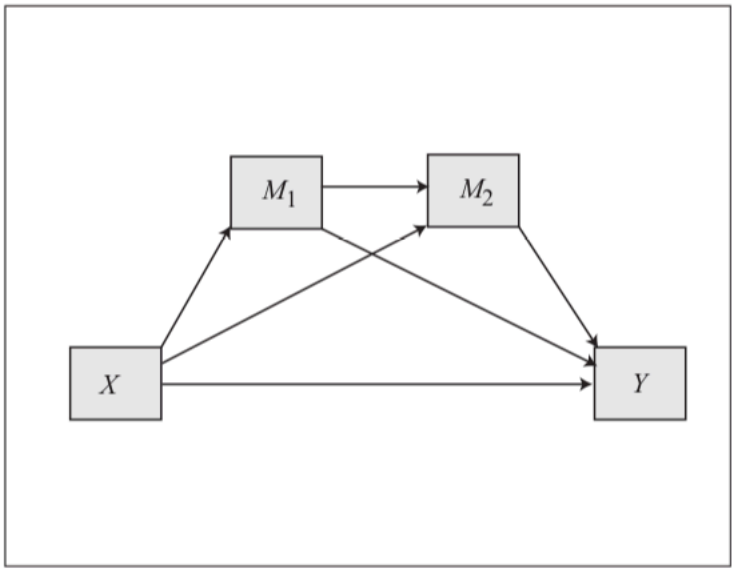
Conditional indirect effect of X on Y through $M_i = (a_{1i} + a_{3i}W)(b_{1i} + b_{3i}V)$

Conditional direct effect of X on $Y = c_1' + c_3'W$

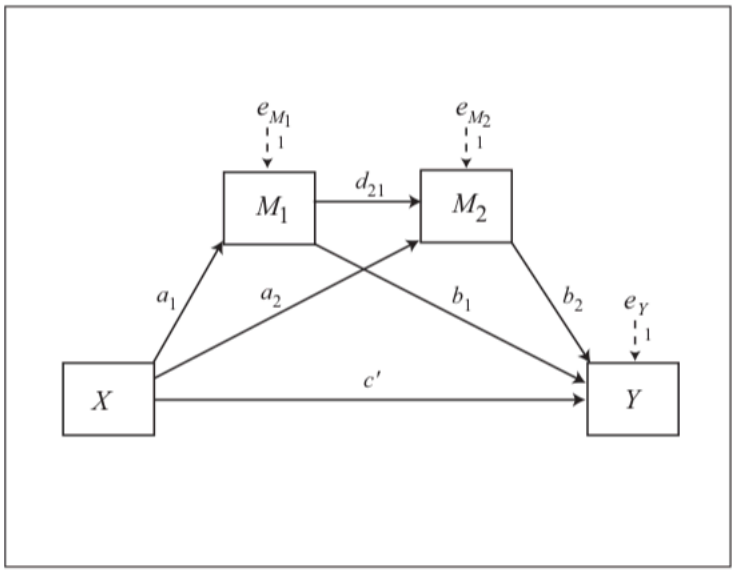
*Model 22 allows up to 10 mediators operating in parallel

Model 6
(2 mediators)

Conceptual Diagram



Statistical Diagram



Indirect effect of X on Y through M_i only = $a_i b_i$
Indirect effect of X on Y through M_1 and M_2 in serial = $a_1 d_{21} b_2$
Direct effect of X on Y = c'