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THE IMPACT OF PAIN ON EXECUTIVE FUNCTIONING VIA ANXIETY IN YOUTHS
WITH SICKLE CELL DISEASE WITHOUT A HISTORY OF STROKE

by

DONALD J. BEARDEN

Under the Direction of Lindsey L. Cohen and Erin B. Tone

ABSTRACT

Research indicates that youths with SCD experience increased levels of pain-related anxiety and executive functioning impairments, even in the absence of stroke. Research also indicates that pain and anxiety predict executive functioning and that anxiety might mediate the relation between pain and executive functioning difficulties. The current study sought to evaluate the direct associations among pain, anxiety, and executive functioning, and to examine whether anxiety mediates the relation between pain and specific executive functioning impairments in a sample of youths (age 10 to 19 years) with SCD with no history of stroke. Findings did not support the hypothesis that pain-crisis frequency and anxiety predict executive functioning. Further, they did not indicate that anxiety mediated the relation between pain-crisis frequency and executive functioning.

INDEX WORDS: Sickle cell, Youths, Pain, Anxiety, Executive functioning

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DONALD J. BEARDEN

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

in the College of Arts and Sciences

Georgia State University

2014

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Donald Jay Bearden
2014

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1 INTRODUCTION

1.1 Epidemiology of Sickle Cell Disease (SCD)

Sickle cell disease (SCD) is a group of autosomal recessive genetic disorders that cause structural damage and functional impairment to red-blood cells. SCD is one of the most frequently occurring blood disorders, affecting between 90,000-100,000 people in the United States (Center for Disease Control and Prevention, 2012; CDC). Roughly one in 350-700 African Americans and one in 1,000-4,000 Hispanic Americans are born with the disorder annually (Smith & Baker, 2011; Wang, 2007). Individuals most likely to be diagnosed with SCD are those indigenous to regions where Malaria is or was prevalent, including sub-Saharan Africa, South America, the Caribbean, Central America, Saudi Arabia, India, and the Mediterranean (CDC, 2012). Prevalence of SCD in these areas is hypothesized to be due to the Malaria-resistant benefit of carrying one sickle cell gene (i.e., sickle cell trait; HbAS), which is typically asymptomatic (CDC, 2012). Although inheriting a single sickle cell gene may be adaptive, inheriting two (i.e., one from each parent) results in sickle cell anemia (i.e., HbSS; Ris & Grueneich, 2000), which is the most common form of SCD, accounting for approximately 65% of cases in the United States (Smith & Baker, 2011; Wang, 2007). Other subtypes of SCD exist, usually involving a sickle cell gene from one parent and another abnormal gene from the other parent (e.g., HbSC; HbSD, HbSE, HbSO, HbS- β thalassemia); these subtypes occur less frequently and typically result in fewer health-related problems than does the HbSS type (CDC; Gustafson et al., 2006; Platt et al., 1991; Ris & Grueneich, 2000; Smith & Baker, 2011; Wang, 2007).

1.2 Pathophysiology of SCD

Individuals with SCD, especially HbSS type, experience a number of health-related problems including fatigue, pain, and organ damage. These impairments may begin in the first few months of life and can range from mild to severe (CDC, 2012; Gustafson et al., 2006; Platt et al., 1991; Smith & Baker, 2011; Wang, 2007). Health complications stem from a mutation that impairs the processing of oxygen in red blood cells (Ris & Gruenich, 2000).

Specifically, healthy red blood cells contain oxygen-processing proteins called hemoglobin that allow cells to pick up, carry, and release oxygen throughout the body. Because healthy red blood cells are round, flexible, and disc-like, they can traverse the blood vessels of the body with ease. In contrast, in red blood cells damaged by SCD, hemoglobin proteins aggregate and adhere together in chains when oxygen is released, causing some red blood cells to take on a crescent or “sickle” shape (Smith & Baker, 2011; Wang, 2007). These distorted or sickled blood cells have a shortened lifespan, which often results in anemia—an abnormally low level of red blood cells. These cells also become sticky and rigid, which decreases their ability to travel through blood vessels.

Due to increased cell stickiness and distorted shape, clogged blood vessels are common among individuals with SCD. Clogging may cause tissue damage by preventing the supply of oxygen- and nutrient-rich blood from reaching areas of the body, including hands and feet, and organs such as the eyes, genitals (e.g., priapism), spleen (e.g., splenic sequestration), lungs (e.g., acute chest syndrome), and the central nervous system (CDC, 2012; Grueneich, 2004). Blood vessel clogging may also result in significant pain (Dampier, Ely, Brodecki, & O’Neal, 2002; Gustafson et al., 2006; Jacob, 2001).

1.3 Pain Crises in Youths with SCD

The most common symptom associated with SCD is recurrent acute pain episodes, often termed pain crises or vaso-occlusive crises (CDC, 2012; Dampier et al., 2002; Platt et al., 1991; Wang, 2007), which may begin as early as six months of age (Palermo, Schwartz, Drotar, & McGowan, 2002). Pain crises are the most common cause of emergency-room visits and hospitalizations among individuals with SCD and pain-crisis frequency has been linked to decreased life span in adults over 20 years old (Palermo et al., 2002; Platt et al., 1991). Pain crises are typically unpredictable, but can be triggered by a number of physiological (e.g., dehydration, fever, high hemoglobin levels) and environmental (e.g., extreme temperatures, high altitude; CDC, 2012) factors.

Severity and frequency of sickle cell pain crises vary widely. For example, in a study investigating pain quality among children and adolescents during pain crises, youths enrolled in the study described their pain in terms ranging from a “dull ache” to “stabbing” and “excruciating” (Beyer, Simmons, Woods, & Woods, 1999). In addition, research has suggested that pain-crisis frequency may range from zero to ten crises annually to as many as one every two weeks (Gil et al., 2000; Platt et al., 1991; Shapiro et al., 1995), and it is estimated that 10-20% of children with SCD experience frequent, impairing pain crises (Palermo et al., 2002; Walco & Dampier, 1990). Research has also indicated that pain crises occur more often and last longer as children become adolescents (Palermo et al., 2002; Powars, 1994; Ris & Grueneich, 2000; Walco & Dampier, 1990). Pain crises may last anywhere from minutes to weeks and may affect varied body areas, most commonly the chest, back, abdomen, and joints; pain may be widespread or confined to one area and may travel from one area to another (Jacob, 2001). In addition, following a severe pain crisis, an individual may experience mild achiness for several

days (Jacob, 2001; Searjent, 1992). Although individuals with SCD may also experience chronic pain (i.e., pain lasting for a minimum of 6 months; Thienhaus & Cole, 2002), this type of pain is typically related to bone-cell death (i.e., avascular necrosis) and occurs less frequently than acute pain crises (Okpala & Tawil, 2002).

Pain crises have been found to predict multiple areas of functioning in the lives of youths with SCD (Barakat, Patterson, Daniel, & Dampier, 2008). For example, frequent school absences, which are common among young people with SCD (Palermo, 2000; Palermo et al., 2002; Shapiro et al., 1995), have been found to relate significantly to their academic performance and attainment (Hurtig, Koepke, & Park, 1989; Schatz, 2004). Impaired social functioning has also been found to be associated with pain crises (Fuggle, Shand, Gil, & Davies, 1996; Palermo et al., 2002). Specifically, research has revealed reduced peer-related activity associated with pain crises in young people with SCD (Walco & Dampier, 1987; Fuggle et al., 1996). Parents of children and adolescents with SCD may be advised to restrict their children's activities (National Institute of Health, 2014), which might make it more difficult for them to interact with friends. Additionally, quality of sleep may be detrimentally impacted by pain crises (Dinges et al., 1990). In fact, research has indicated that pain-related sleep problems may lead to increased fatigue during waking hours and hinder academic performance.

Current treatments for pain crises include over-the-counter pain medication (e.g., ibuprofen; acetaminophen) for milder episodes and narcotic medications (e.g., opioids) for more severe episodes (Dampier et al., 2002). Frequently, long-lasting, severe pain crises that are unmanageable at home require hospitalization and intravenously administered analgesia. In addition to pain medication, patients with SCD may receive chronic treatment with hydroxyurea, which reduces sickling of red blood cells and has been found to reduce pain-crisis frequency

(Hankins et al., 2005); however, multiple side effects may occur, including neutropenia and thrombocytopenia. Chronic blood transfusions have also been found to alleviate pain crises (Davies and Brozovic, 1989; Keidan, Marway, Vaughan, Franklin, & Stuart, 1987), but may cause iron overload and alloimmunization (Makroo et al., 2013). Corticosteroids (Black & Smith, 2010) have been used to decrease pain-crisis duration, but may increase likelihood of pain-crisis rebound and return to the hospital.

Taken together, findings from these studies highlight the unpredictable nature of pain crises with regard to onset, frequency, duration, course, and severity of pain (e.g., Platt et al., 1991; Shapiro et al., 1995), as well as their adverse effect on the functioning (e.g., academic; social) of young people with SCD (e.g., Palermo et al., 2002). In addition, although numerous pain-reducing medical treatments are available, they are not always effective and many have detrimental side effects (e.g., Makroo et al., 2013).

1.4 Anxiety in Youths with SCD

Multiple studies have indicated that, in addition to pain, youths with SCD experience illness-related emotional distress, including anxiety (e.g., Alao & Cooley, 2001; Bennett, 1994; Benton, Boyd, Ifeagwu, Feldtmose, & Smith-Whitley, 2011; Benton, Ifeagwu, & Smith-Whitley, 2007; Key, Brown, Marsh, Spratt, & Recknor, 2001; Schoenherr, Brown, Baldwin, & Kaslow, 1992; Seigel, Golden, Gough, Lashley, & Sacker, 1990). For instance, research has revealed a higher prevalence of anxiety-related psychiatric disorders (e.g., generalized anxiety and separation anxiety disorders) in young people with SCD than in the normative population (Benton et al., 2011), as well as elevated rates of anxiety symptoms across the lifespan in comparison to healthy controls and normative data (for a review, see Benton et al., 2007). Other

research found that anxiety, along with emotional and psychological factors, was significantly related to somatic complaints in individuals with SCD (Wellington et al., 2010).

Despite compelling evidence that youths with SCD experience elevated levels of anxiety, many researchers have reported significant variability in their findings, with some studies indicating minimal or no emotional difficulties among affected children and adolescents (e.g., Helps, Fuggle, Udwin, & Dick, 2003; Noll et al., 1996; Simon, Barakat, Patterson, & Dampier, 2009; Treiber, Mabe, & Wilson, 1987; Kumar, Powars, Allen, & Haywood, 1976; Yang, Cepeda, Price, Shah, & Mankad, 1994). Multiple reviews of the literature examining emotional distress in youths with SCD, however, have found that although significant variability exists, increased anxiety is still prevalent in at least some subsets of this population (Benton, et al., 2007; Gustafson et al., 2006; Molock & Belgrave, 1994). In addition, other research has suggested that anxiety and other internalizing symptoms constitute the most common type of emotional distress manifested in individuals with SCD (e.g., Alao & Cooley, 2001; Barakat, Schwartz, Simon, & Radcliffe, 2007; Key, Brown, Marsh, Spratt, & Recknor, 2001).

Findings of increased anxiety among youths with SCD are not surprising given the many illness-related factors that may impact their emotional functioning (Alao & Cooley, 2001; Benton et al., 2007; Palermo et al., 2002). For example, young people with SCD may experience stress due to frequently missing school, physical-activity restrictions, medical treatments, and limited social support (Alao, Dewan, Jindal, & Effron, 2003; Brown, Doepke, & Kaslow, 1993; Fuggle et al., 1996; Harris, Parker, & Barker, 1998). In addition, individuals with SCD may experience increased anxiety related to recurrent pain (Helps et al., 2003). In summary, research has indicated that some children and adolescents with SCD experience increased levels of

emotional distress—including anxiety—compared to healthy peers, which may be associated with health-related issues.

1.5 The Relation of Pain to Anxiety in Youths with SCD

Although multiple factors appear to impair emotional functioning in youths with SCD, research has identified pain as one of the most significant contributors (Barakat et al., 2007; Gil et al., 2003; Gil et al., 2000; Graumlich et al., 2001; Hoff, Palermo, Schluther, Zebracki, & Drotar, 2006; Jacob, 2001; Jerrell, Tripathi, & McIntyre, 2011; Wagner et al., 2004). For example, researchers found that greater pain (i.e., frequency, intensity) among adolescents with SCD was related to increased negative mood, including anxiety and depression (Barakat et al., 2007; Gil et al., 2003). The link between pain and anxiety in youths with SCD is not surprising, given similar results from numerous studies examining this phenomenon in other chronic pain populations, including inflammatory bowel disease, recurrent abdominal pain, chronic musculoskeletal pain, chronic lower-back pain, juvenile rheumatoid arthritis, fibromyalgia, and migraines (e.g., Bennett, 1994; Cohen, Vowles, & Eccleston, 2010; Roy-Byrne et al., 2008; Thompson et al., 1999). Going a step further, multiple studies have found that pain-crisis frequency in youths with SCD is predictive of anxiety (Barbarin, Whitten, & Bonds, 1994; Barakat et al., 2007; Mahdi, Al-Ola, Khalek, & Almawi, 2010; Nater & Portadin, 1974; Unal, Toros, Kütük, & Uyaniker, 2011). For example, studies examining psychosocial functioning in children, adolescents, and young adults with SCD have revealed that emotional distress, including anxiety, was significantly related to pain-crisis frequency (Barbarin et al., 1994; Mahdi et al., 2010; Unal et al., 2011). Taken together, these findings indicate that pain is significantly related to emotional functioning in individuals with SCD and that pain-crisis frequency can predict anxiety in young people with SCD.

1.6 Executive Difficulties in Youths with SCD

In addition to pain and emotional distress, youths with SCD are at increased risk for a wide array of neurocognitive difficulties, including executive functioning problems (for a review, see Berkelhammer et al., 2007; Smith & Baker, 2011; Wang, 2007). Executive functioning includes a broad range of higher-order cognitive abilities that are necessary for the appropriate execution of other cognitive skills, including those within language, memory, and visual-motor domains. Although definitions of executive functions vary, they typically encompass a number of skills including attention, inhibition, planning, organization, sequential processing, response monitoring, decision making, judgment, reasoning, mental flexibility, problem solving, and working memory (Berkelhammer et al., 2007; Chan et al., 2008).

General neurocognitive difficulties observed in individuals with SCD typically result from neurological insults, including cerebrovascular accidents (CVAs) and silent strokes, which can occur as early as infancy and peak between two and five years of age. Epidemiological research has suggested that as many as 11% of youths diagnosed with SCD (HbSS) experience a CVA within their first 20 years of life and as many as 8-10% do so during childhood (Ohene-Frempong et al., 1998; Smith & Baker, 2011; Wang, 1998). Cerebrovascular accidents are typically highly debilitating, whereas “silent” strokes (i.e., involving minimal or no signs and symptoms, which may go unnoticed unless detected with MRI) are less impairing but much more common, affecting between 15-35% of youth with SCD (Berkelhammer et al., 2007; Bernaudin, 2000; Buchanan, DeBaun, Quinn, & Stenberg, 2004; Kirk et al., 2009; Pegelow et al., 2002; Smith & Baker, 2011; Steen et al., 2003; Switzer, Hess, Nichols, & Adams, 2006). In fact, some research has indicated that nearly 10% of children with SCD experience a silent stroke before age six (Smith & Baker, 2011; Wang et al., 2001).

Multiple studies have indicated poorer performance on executive functioning measures among children, adolescents, and young adults with SCD who have experienced a CVA than among individuals with SCD who have not had CVAs (Berkelhammer et al., 2007; Schatz & Buzan, 2006; Schatz et al., 1999; Smith & Baker). In addition, multiple studies have revealed impaired executive functioning (Berkelhammer et al., 2007; Craft et al., 1993; Schatz et al., 2001) and increased difficulty on tasks requiring working memory and processing speed (Craft et al., 1993; Schatz et al., 1999; Smith & Baker, 2011; Wang et al., 2001) in youths with SCD who have experienced silent strokes.

Even in the absence of CVA and silent stroke, research has indicated that youths with SCD may perform more poorly than healthy peers on measures of executive functioning (Brown et al., 1993; Fowler et al., 1988; Noll et al., 2001; Schatz et al., 2001; Schatz, Finke, Kellett, & Kramer, 2002; Sun et al., 2012; Swift et al., 1989); however, some of these studies did not include collection of neuroimaging data to assess for the presence of silent stroke (Noll et al., 2001), making it difficult to fully understand the source and nature of the observed impairments. Due to the prevalence of silent strokes among individuals with SCD, more recent studies examining neurocognitive functioning in youths with SCD without a history of stroke have gathered neuroimaging data to help rule out this confound (Steen et al., 2005; Sun et al., 2012). Resultant findings have revealed that despite being neurologically healthy, youths with SCD exhibited impaired performance compared to their healthy peers in areas of processing speed and auditory attention/working memory (Steen et al., 2005); performed significantly more poorly on measures of cognitive flexibility, speeded naming, and inhibition; and were significantly slower on a task of sustained attention (Sun et al., 2012).

Although some youths with SCD but no history of stroke appear free of cognitive difficulties (Craft et al., 1993; for a review, see Brown, Armstrong, & Eckman, 1993; Nabors and Freymuth, 2002), many exhibit executive functioning and other neurocognitive problems. To understand why such problems emerge in the absence of stroke, multiple researchers have investigated pathophysiological factors associated with SCD, including anemia, poor cell nutrition, chronic hypoxia, perfusion abnormalities, white- and gray-matter falsification, decreased oxygen saturation, elevated cerebral blood flow, cerebral vasoconstriction, and low birth weight (Aygün et al., 2011; Baldeweg et al., 2006; Bernaudin et al., 2000; Hogan, Haan, Datta, Kirkham, 2006; Hollocks et al., 2012; Kirk et al., 2009; Kral & Brown, 2004; Kral et al., 2003; Sanchez, Schatz, & Roberts, 2010; Scantlebury et al., 2011; Schatz, McClellan, Puffer, Johnson, & Roberts, 2008; Steen, Xiong, Mulhern, Langston, & Wang, 1999; Sun et al., 2012). Despite abundant research investigating potential explanations for neurocognitive dysfunction in youths with SCD with no history of stroke, a clear understanding of pathophysiological underpinnings does not yet exist (Kirk et al., 2009).

In sum, research suggests a higher prevalence of neurocognitive problems in youths with SCD than in healthy peers (Berkelhammer et al., 2007). Neurocognitive problems typically result from CVAs and silent strokes; however, even in the absence of observable neurological damage, youths with SCD may experience cognitive problems, including executive functioning difficulties. Although multiple SCD-related health problems have been put forth as potential causes for cognitive dysfunction in youths with SCD without stroke histories, no definitive etiology has been indicated. A potential explanation for neurocognitive problems among youths with SCD with no history of stroke is that recurrent pain crises and anxiety may be contributing factors.

1.7 The Relation of Pain to Executive Function

A rich literature suggests that pain predicts performance on measures of executive functioning (Dick & Rashiq, 2007; Eccleston & Crombez, 1999; Eccleston, Crombez, Aldrich, & Stannard, 1997; Moore, Keogh, & Eccleston, 2012; Oosterman et al., 2011; Sanchez, 2011). For instance, multiple studies examining cognitive ability in adults with chronic pain have revealed poorer than expected executive functioning in areas of attention and working memory (e.g., Dick & Rashiq, 2007; Oosterman et al., 2011); however, only one of these studies controlled for emotional factors, analgesic use, and sleep (Dick & Rashiq, 2007). Similarly, research on adults with recurrent pain (e.g., back, muscle, gastric, and headache pain) indicated that elevated pain was related to increased distractibility and poorer performance on a task of selective attention (Gijssen, Dijkstra, & van Boxtel, 2011), while controlling for age, sex, education level, and depressive symptoms.

Although there is currently limited research investigating cognitive deficits in children and adolescents with chronic pain, available findings appear to echo those from adult studies. In a comprehensive, systematic examination of the peer-reviewed literature over the past 20 years, Dick and Riddell (2010) found only nine studies that focused on cognitive skill in youths with chronic pain. Further, none of the reviewed studies conducted thorough neuropsychological examinations of participants. Despite this, findings from the review indicated that attention was vulnerable to impairment among youths with chronic pain. The authors discussed possible explanations for their findings, drawing in part from current research in the adult literature on chronic pain, which suggests that pain may draw attention away from other aspects of the individual's environment. In brief, multiple studies examining the relation between chronic/recurrent pain and cognitive ability in adults and young people have yielded evidence

that increases in pain are associated with poorer performance on executive functioning measures (e.g., working memory; attention) (e.g., Dick & Rashiq, 2007; Eccleston & Crombez, 1999).

1.8 The Relation of Anxiety to Executive Function

Anxiety, like pain, has been found to be associated with neurocognitive deficits. Specifically, research has indicated that anxiety is predictive of performance on executive functioning measures across the lifespan, with more anxious individuals earning lower scores (e.g., Boyer et al., 2006; Fisher, Allen, & Rose, 1996; Iezzi, Archibald, Barnett, Klinck, & Duckworth, 1999; Ikeda, Iwanaga, & Seiwa, 1996; Purcell et al., 1998; Richard, Richards, & McGeeney, 2000; Micco et al., 2009; Weissman, Chu, Reddy, & Mohlman, 2012). Research findings suggest that anxiety influences the way attention is allocated by diverting it away from goal-directed activities (e.g., cognitive tasks) and directing it to anxious internal (e.g., thoughts) or external experiences (e.g., perceived environmental danger) (Eysenck, Derakshan, Santos, Calvo, & Manuel, 2007; Corbetta & Shulman, 2002).

In adults, researchers have examined the relation between anxiety and performance on a variety of cognitive tasks, including those specific to executive functioning, such as task switching, inhibition, problem solving, spatial recognition and working memory, motor initiation, and task execution (Ansari & Derakshan, 2010; Derakshan, Ansari, Hansard, Shoker, & Eysenck, 2009; Derakshan, Smyth, & Eysenck, 2009; Purcell et al., 1998). Across these studies, findings revealed that anxiety was significantly predictive of poorer executive performance.

Although less research is available examining the association between anxiety and executive functioning in children, a study by Emerson, Mollet, and Harrison (2005) that compared visual attention, cognitive flexibility, and problem solving between a group of

anxious-depressed male children and a group of sex-matched, typical controls found that boys in the anxious-depressed group significantly underperformed their healthy peers in all areas except visual attention. Other researchers have focused specifically on the relation between anxiety and cognitive functioning. For example, multiple studies have examined cognitive performance in young people with anxiety-related psychiatric disorders (e.g., GAD, Panic Disorder, Post-Traumatic Stress Disorder), revealing difficulties with working memory, attention, inhibition, and visual problem solving (Beers & Bellis, 2002; Micco et al., 2009). In another study, researchers compared problem solving in learning disabled and non-learning disabled youths and found that across groups, anxiety was negatively related to performance on a task of verbal abstract reasoning and concept formation (Fisher et al., 1996). Additionally, a nonsignificant trend in the latter study suggested higher anxiety levels were related to poorer problem solving ability.

In short, results from numerous studies have found that anxiety is predictive of poorer performance on cognitive measures, including those that assess executive functioning (e.g., Ansari & Derakshan, 2010). To explain this phenomenon, other researchers have suggested the anxiety/executive functioning relation reflects the tendency to direct attention away from goal-focused tasks and toward anxiety-provoking stimuli (e.g., worrisome thoughts) when in an anxious state (Eysenck et al., 2007).

1.9 Pain, Anxiety, and Executive Function

Although many studies have examined associations between executive functioning and both pain and anxiety in isolation, other studies have suggested the possibility of a complex pattern of relations among pain, anxiety, and executive functioning. For example, in a study by Eccleston et al. (1997), adults experiencing chronic pain were asked to assess details of card

pairs flashing across a computer screen and to report their findings by pressing a computer key. Results revealed that self-reported pain and heightened somatic awareness were both related to difficulties with attention as indexed by accuracy on the computer task, and that increased negative emotion (e.g., anxiety) was related to heightened pain and somatic complaints. Research by Radanov, Dvorak, and Valach (1992) found that adults suffering from soft-tissue injury of the cervical spine who reported subjective feelings of nervousness prior to cognitive testing and exhibited more stress during testing endorsed more cognitive problems and performed more poorly on a divided-attention task compared to adults who did not report or exhibit nervousness and stress. In a later study, Radanov et al. (1999) examined relations among pain, anxiety, and executive functioning in a group of adults with late whiplash syndrome and found that both pain and anxiety were significantly related to performance on a divided-attention task.

Research with young people examining relations among pain, anxiety, and executive functioning has echoed adult research (Boyer et al., 2006; Compas & Boyer, 2001; Cruz, O'Reilly, Slomine, & Solorio, 2011). For instance, a study exploring anxiety and attention/working memory in children and adolescents experiencing disease-related pain found that a substantial percentage of participants in the study were experiencing anxiety (Cruz et al., 2011) and in another study, youths with a history of recent, recurrent abdominal pain were found to focus more on subliminally presented pain- and social threat-related words than neutral words (Boyer et al., 2006). The latter finding suggests that attention to stimuli perceived as painful or threatening in youths with pain histories may distract them from other information in their environment. Overall, findings from multiple studies examining the nuanced relations among pain, anxiety, and cognitive ability suggest that elevated anxiety levels along with other pain-

related factors in individuals with chronic or recurrent pain may be related to poorer executive functioning.

1.10 Anxiety as a Mediator of the Pain-Executive Function Association

Additional support for the idea that pain-related anxiety predicts impaired executive performance emerged from two reviews conducted by Hart and colleagues (Hart et al., 2000; Hart, Wade, & Martelli, 2003). In their reviews of the literature, Hart and colleagues highlighted research suggesting that executive functioning is more closely associated with pain-related emotional distress than with sensory aspects of pain and postulated that emotional distress may mediate the relation between pain and executive functioning. For example, numerous studies examining the relation between pain and executive functioning have found that once emotional distress (including anxiety) was controlled for, the relationship between pain and executive functioning was weakened significantly (Grace, Nielson, Hopkins, & Berg, 1999; Kewman, Vaishampayanm, Zald, & Hahn, 1991). Research exploring the anxiety—cognitive functioning association in individuals with chronic pain has revealed similar findings, indicating that increased levels of anxiety-related emotional distress were predictive of poorer performance on measures of executive functioning and nonverbal intellectual ability and that pain ratings were not significantly associated with cognitive performance (Iezzi et al., 1999). Another study took a different approach to examining whether performance on attention tasks was accounted for by emotional distress (Wade & Hart 2002) by classifying participants with chronic pain according to the intensity, immediate unpleasantness, and suffering associated with their pain (i.e., anxiety, frustration, fear, anger, depression, degree of lifestyle interference, level of control in reducing the pain, ability to endure the pain, and hope regarding a cure), as well as their pain-related behavior (e.g., extent of pain behavior at home, amount of solicitous feedback from others).

Findings from the latter study revealed that only stages of suffering and behavior were predictive of attention performance, with poorer attention performance among those with more severe suffering and higher engagement in pain behavior. In sum, results from these studies imply that emotional distress, including anxiety, may account for a portion of the relation between pain and executive functioning.

In addition to studies examining relations among pain, emotional distress, and executive functioning, the growing neuroimaging literature lends support to Hart and colleagues' argument that emotional distress may mediate the relation between pain and executive functioning. Specifically, research has revealed activation in the anterior cingulate cortex (ACC) during both pain-related emotional distress and when undertaking attention-demanding cognitive tasks (Buffington, Hanlon, & McKeown, 2005; Derbyshire, 1999; Hart et al., 2003; Peyron, Laurent, & Garcia-Larrea, 2000; Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Wade & Hart, 2002). The ACC is part of both limbic and frontal networks and is believed to play an executive role in allocating attention resources (Hart et al., 2003; Wade & Hart, 2002). Findings from neuroimaging studies have led to multiple hypotheses regarding ways in which emotional distress influences attention (Hart et al., 2003). First, research findings suggest that ACC involvement in pain processing and attention may result in a struggle for finite attention resources, which disrupts cognitive functioning (Hart et al., 2003; Peyron, 2000; Wade & Hart, 2002). Next, a meta-analysis of neuroimaging studies by Bush, Luu, & Posner (2003) revealed that ACC areas active during cognitively-rigorous tasks were suppressed during painful experiences, when anticipating pain, and when experiencing emotional distress. Taken together, findings from neuroimaging studies suggest that pain and related emotional distress may diminish performance on attention-demanding tasks and provide neuroanatomical support for

research identifying a negative relation between anxiety and executive functioning in the context of pain.

1.11 Summary and Study Purpose

In summary, many individuals with SCD experience pain associated with their illness. In addition, research indicates that youths with SCD experience increased levels of anxiety related to their pain crises. Although stroke is the leading cause of executive functioning impairment in youths with SCD, research has revealed that even without a history of stroke, youths with SCD exhibit executive functioning impairments. Research also indicates that both pain and anxiety predict executive functioning and that anxiety may mediate the relation between pain and executive functioning difficulties. Building upon these findings, the purpose of the current study was to evaluate direct associations among pain, anxiety, and executive functioning, and also to examine whether anxiety mediates the relation between pain and specific executive functioning impairments in youths diagnosed with SCD with no history of stroke. In the current study, I hypothesized that pain-crisis frequency would significantly predict anxiety and that pain-crisis frequency and anxiety would significantly predict executive function. In addition, I expected anxiety to significantly mediate the relation between pain-crisis frequency and executive functioning (Figure 1).

2 METHOD

2.1 Participants

The study used an intact archival database that comprises data from 34 African American participants diagnosed with SCD (HbSS), who ranged in age from 10 to 19 years ($M = 13.97$, $SD = 2.63$). All participants were referred to Children's Healthcare of Atlanta for an MRI scan of the brain as part of their standard care. Seventeen participants were male and 17 were female.

Although no official record was made of patients who did not attend their scheduled appointments during data collection, the researcher's informal observations indicated that most patients eventually completed the study; however, many families were noted to cancel and reschedule their appointments multiple times.

Regarding neuroimaging, no participants had a history of stroke as defined by a prior normal MRI or CT scan; however, nine participants had a history of gliosis, which has been found to predict cognitive functioning (e.g., Skranes et al., 1997). All participants had a history of abnormal cerebral blood flow volume (CBFV) as measured by transcranial Doppler (TCD); however, 20 had normal CBFV at the time of enrollment, 5 had abnormal CBFV, and 9 had no recent TCD results. In addition, seven participants had a history of chronic pain; two had been diagnosed with Attention Deficit/Hyperactivity disorder, for which one of the two was receiving pharmacological treatment; and two had a history of Major Depressive Disorder. At the time of enrollment, 20 participants were being treated for SCD with Hydroxyurea, nine were receiving chronic (monthly) erythrocyte transfusions, and five were receiving no treatment. As a measure of socioeconomic status, insurance information was collected. Twenty-three participants had private insurance, nine had Medicaid, and two had no insurance when enrolled in the study. Full-scale intelligence quotients ranged from a standard score of 75 to 125 ($M = 99.26$, $SD = 11.52$).

2.2 Measures

2.2.1 Demographic Information

Information regarding patients' age, sex, and race/ethnicity was collected by a study coordinator prior to the neuropsychological evaluation. Other health information, including history of chronic pain, gliosis, and insurance type, was collected from patients' medical records.

2.2.2 Intellectual Functioning

The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was used to estimate participants' intelligence. The WASI was developed for brief, individual administration to persons ranging from 6 to 89 years old. It is made up of four subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning) and was developed to assess verbal, nonverbal, and overall intellectual abilities. The WASI offers a briefer two-subtest version, which includes only Vocabulary and Matrix Reasoning and may be administered in 15 minutes; however, this version provides only an overall score of intellectual functioning. The two-subtest version was chosen for the current study due to its administration brevity. Information in the WASI manual indicated that the measure exhibited adequate content and construct validity. Average WASI subtest reliability coefficients ranged from .81 to .96 for youths (i.e., 6 to 19 years old) and reliability coefficients for youths' intelligence quotient on the two-subtest version ranged from .92 to .97 (The Psychological Corporation, 1999; Stano, 2004).

2.2.3 Pain

In line with previous research examining the impact of recurrent pain in youths with SCD (e.g., Barbarin et al., 1994; Unal et al., 2011), data regarding pain-crisis frequency in the current study included the number of pain crises that each participant experienced during the 12 months prior to enrollment in the study. Pain-related data were collected from participants' medical records. In the current study, pain crises were defined as acute pain caused by blood-vessel clogging and ischemia, which may be diffuse or localized and may occur in muscles, bone, joints, or organs (Mahdi et al., 2011; Stinson & Naser, 2003; Yale, Nagib, & Guthrie, 2000). Because healthcare clinicians used different terms to describe pain crises in the medical records, a physician and a nurse at Children's Healthcare of Atlanta corroborated terminology in the

charts. Terms counted as a pain crisis included “sickle cell related pain,” “sickle cell pain,” “sickle crisis,” “pain event,” “vaso-occlusive crisis,” “pain crisis,” “VOC,” and “crisis.”

2.2.4 Anxiety

Parent report on the Behavioral Assessment System for Children, Parent Rating Scales (BASC-2 PRS; Reynolds & Kamphaus, 2004) was used to assess participants’ adaptive and problem behaviors in community and home environments. The BASC-2 PRS is a widely used and well-established measure found to exhibit high internal consistency, good median test-retest reliabilities for children (.81) and adolescents (.84), and moderate median inter-rater reliabilities for children (.69) and adolescents (.77), as well as adequate construct validity. For the current study, only scores from the Anxiety subscale were analyzed (Reynolds & Kamphaus, 2004).

2.2.5 Executive Functioning

To investigate executive functioning, subtests from the Delis-Kaplan Executive Functioning System, including Trails Number-Letter Switching and Color-Word Interference/Inhibition (age range, 8 to 89 years old; DKEFS; Delis, Kaplan, & Kramer, 2001a-c) were administered. Subtests were chosen based on effect sizes calculated from previous research comparing cognitive functioning in youths with SCD without a history of stroke to their healthy peers, which indicated that of all areas of executive functioning measured, Trails Number-Letter Switching and Color-Word Interference/Inhibition yielded the largest effect sizes (-0.95 & -0.91, respectively; Brown et al., 1993; Sun et al., 2012; Steen et al., 2005). Trails Number-Letter Switching assesses simultaneous processing and divided attention, whereas Color-Word Interference/Inhibition assesses rapid naming skill and the ability to inhibit prepotent responses. Reliability (i.e., split-half; test-retest) in 8- to 19-year-olds was good for Color-Word Interference/Inhibition and poor for Trails-Switching (i.e., test-retest reliability =

.20; Delis et al., 2001c). Intercorrelation analyses and comparisons with other measures indicated adequate construct validity (Delis et al., 2001c; Homack, Lee, & Riccio, 2005).

2.3 Procedure

The current study is part of a larger project investigating the neurological impact of iron overload in youths with sickle cell disease. To recruit participants for the current study, fliers were posted in the Aflac clinic at Children's Healthcare of Atlanta (CHOA), Scottish Rite. Eligible individuals were offered \$150.00 for participation. Participants who responded to the recruitment request were scheduled for an appointment. At the appointment, Aflac Hematology medical staff at CHOA, Scottish Rite obtained informed consent and then collected background information and conducted physical assessments. Subsequently, neuropsychological assessment was conducted in the Neuropsychology Department at CHOA, Scottish Rite in a single session that lasted approximately two hours. Children underwent a series of tests, which were administered in the same order for each participant, and parents completed measures about their children's emotional and neuropsychological functioning. A check for \$150.00 was provided to participants or their parents immediately following testing.

3 RESULTS

3.1 Preliminary Analyses

Initial analyses were conducted to examine means and standard deviations of primary variables (pain-crisis frequency, anxiety, and executive functioning; Table 1). In addition, comparisons were made between mean anxiety and executive functioning (i.e., task switching and inhibiting) scores in the current study and previous research with youths with SCD and revealed similar scores (Simon et al., 2009; Sun et al., 2012). Regarding pain, a comparison of pain-crisis frequency proportions between the current study and a previous study (Unal et al.,

2011) revealed similar distribution patterns of pain crises, such that among participants who experienced one or more pain crises within the 12 months prior to data collection, the majority experienced between 1 – 4 crises (41.2%), followed by 5 – 10 crises (20.6%), with the smallest proportion reporting 10 or more crises (.03%). Unal et al. (2011) did not include patients reporting zero pain crises within the 12 months prior to data collection.

Next, analyses were conducted to evaluate relations among primary variables, between primary variables and demographic factors (i.e., child age and sex), and between primary variables and other factors (i.e., history of gliosis, history of chronic pain, treatment type, full scale intelligence, and insurance; Table 2). Pearson product moment correlations were used to test associations among primary variables and between primary variables and child age; *t*-tests were used to compare anxiety and executive functioning between male and female participants (Table 2).

Results of these analyses revealed significant positive relations between age and pain-crisis frequency, $r(34) = .58, p < .001$, history of chronic pain and pain-crisis frequency, $r(34) = 0.67, p < .001$, WASI Vocabulary performance and pain-crisis frequency, $r(34) = .51, p < .002$, and performances on Matrix Reasoning and DKEFS Trails Number-Letter Switching, $r(34) = .55, p < .001$. A significant negative relation was observed between BASC-2 Anxiety score and Matrix Reasoning performance, $r(34) = -0.45, p < .008$. No significant relations among insurance type, sex, history of gliosis, and type of treatment and any of the primary variables were found.

3.2 Primary Analyses

Primary analyses involved examining relations between pain-crisis frequency and anxiety, pain-crisis frequency and executive functioning (i.e., DKEFS Number-Letter Switching

and Color-Word Interference/Inhibition), and anxiety and executive functioning. Pain-crisis frequency was not significantly related to anxiety (Figure 2) or scores on either of the two DKEFS measures of executive functioning (see Figures 5 & 6). A large proportion of participants (35.3%; $n = 12$) had no history of pain crises in the 12 months prior to data collection; it was thus possible that the high number of crisis-free participants was obscuring true relations between pain-crisis frequency and anxiety and pain-crisis frequency and executive functioning performances. Therefore, pain data were dichotomized into zero (no pain crises in the 12 months prior to data collection) or one (one or more pain crises in the 12 months prior to data collection), and additional analyses were conducted examining the relations between these variables. Findings from these analyses were also nonsignificant. The analysis of the association between anxiety and executive functioning revealed a significant negative relation between BASC-2 Anxiety and DKEFS Trails Number-Letter Switching only, $r(34) = .48$, $p < .04$ (Figure 3); anxiety and Color-Word Interference/Inhibition were not related (Figure 4). Because no significant relation was found between pain-crisis frequency and anxiety, mediation analyses were not conducted.

4 CONCLUSIONS

In the current study, I hypothesized that pain-crisis frequency in youths with SCD without stroke histories would predict anxiety and executive functioning (i.e., task switching and inhibiting), that anxiety would predict executive functioning, and that anxiety would mediate the pain-executive functioning relation (Figure 1). The results partially supported the hypothesis that anxiety predicts executive functioning among youths with SCD, in that anxiety was negatively associated with scores on a measure of task switching. This finding is consistent with research built on Baddeley and Hitch's model of working memory (1974), which suggests the

existence of two attentional systems; one that allocates attention purposefully to the completion of current goals (e.g., cognitive tasks) and another that is automatic and directs attention to relevant environmental stimuli (Corbetta & Shulman, 2002; Eysenck et al., 2007). Eysenck et al. (2007) have suggested that anxiety influences the way attentional resources are allocated by diverting attention away from the goal-directed system, thereby negatively impacting performance efficiency. In addition, their research has revealed that task switching is particularly vulnerable to anxiety (Ansari, Derakshan, & Richards, 2008; Eysenck et al., 2007).

Neuroimaging studies lend support to an anxiety—task-switching relation. For example, research suggests that during task switching the anterior cingulate cortex (ACC), which is part of both limbic and frontal networks (Hart et al., 2003; Wade & Hart, 2002), increases activation (Luks et al., 2002) and oversees how attention will be directed when alternating between cognitive sets (Carter & Van Veen, 2007; Luks et al., 2002). The ACC also signals an increase in activation in the dorsolateral prefrontal cortex (Carter & Van Veen, 2007; Luks et al., 2002), which research has implicated in boosting cognitive control necessary for switching (Carter & Van Veen, 2007). Because of the ACC's dual limbic-frontal connections (Hart et al., 2003; Wade & Hart, 2002), its participation in processes associated with both attention and anxiety may result in a struggle for finite resources, which is believed to disrupt cognitive functioning (Hart et al., 2003; Peyron, 2000; Wade & Hart, 2002). In fact, research has found decreased activation in the ACC related to anxiety (Bishop, 2007).

The hypothesis that anxiety predicts inhibition was not supported in the current study. Lack of a significant association between anxiety and inhibition may be related to use of a small sample. In fact, a post-hoc power analysis using the correlation coefficient found between anxiety and inhibition in the current study (Table 2) indicated that a sample of 269 would have

been necessary to detect a significant relation between these variables ($\alpha = 0.05$, power = 0.8, two tailed; G*Power; Faul, Erdfelder, Lang, & Buchner, 2007).

Hypotheses that pain-crisis frequency predicts anxiety and executive functioning (i.e., task-switching or inhibition) and that anxiety mediates the relation between pain-crisis frequency and executive functioning were also not supported. Based on post-hoc power analyses using correlation coefficients from the current study (Table 2), non-significant findings may accurately reflect true associations among the three constructs of interest. For instance, despite previous research indicating medium to large effect sizes for associations between pain and anxiety and pain and executive functioning (e.g., Mahdi et al., 2010; Moore et al., 2012), post hoc analyses revealed that sample sizes ranging from 146 to more than 300,000 would have been necessary to detect significant relations among these variables ($\alpha = 0.05$, power = 0.8, two tailed; G*Power; Faul et al., 2007).

Another possible explanation for the lack of support for significant relations between pain-crisis frequency and other variables of interest (i.e., anxiety and executive functioning) was the use of participants' medical records as the only source of pain information. For instance, research suggests that pain is a subjective and internal experience (Jackson, 2002; von Baeyer, 2006), which are factors not accounted for in my study. In fact, compared to results from the current study, previous studies revealing significant relations among pain, anxiety, and executive functioning have used subjective pain information (e.g., Dick & Rashiq, 2007; Gil et al., 2003; Schierz, Nixdorf, Singer, & Reissmann, 2012), suggesting it may be a better detector of pain's association to anxiety and executive functioning than pain information collected from participants' medical records. Other studies that found pain was predictive of anxiety and/or executive functioning included participants experiencing pain at the time of assessment (e.g.,

Crombez et al., 1999; Dick & Rashiq, 2007; Grace et al., 1999; Iezzi et al., 1999), which when compared to the current study's results, suggests extant pain is more predictive of anxiety and executive functioning than merely a history of painful experiences.

An additional factor that may have contributed to the nonsignificant association between pain-crisis frequency and anxiety was the assessment of anxiety. Although the BASC-2 Parent Rating Scale (Reynolds & Kamphaus, 2004) has exhibited good validity and reliability in estimating children's emotional functioning, findings from prior research recommend gathering data from multiple sources (e.g., self, parent, teacher, and health-care professional) to gain the most accurate representation of children's anxiety (e.g., Achenbach, McConaughy, & Howell, 1987). Results from previous studies also reveal that emotional and behavioral symptoms differ by informant (e.g., parents, teachers, and peers) (Achenbach et al., 1987; Nauta et al., 2004) and behavior (e.g., externalizing versus internalizing). Relatedly, previous studies identifying significant relations between pain and anxiety in clinical populations have relied on measures of pain-related anxiety (e.g., McCracken, Zayfert, & Gross, 1992) as opposed to measures of general anxiety. Thus, lack of support for a significant relation between anxiety and pain-crisis frequency in the current study may have been due to use of parent report on the BASC-2 as the only measure of participants' anxiety.

Furthermore, the average number of reported pain-crises in the 12 months prior to enrollment among participants in the current study was low. Participants experienced an average of approximately three pain crises ($M = 2.68$, $SD = 3.49$) and only 23.5% ($n = 8$) of participants reported more than four pain crises. The modest number of reported pain-crises among participants in this study was likely associated with SCD-related treatments that participants were receiving during the study. Specifically, over half of the participants were being treated

with hydroxyurea (58.8 %) and over a quarter of the sample was undergoing chronic blood transfusions (26.4%), both of which have been found to reduce pain-crisis frequency (Charache et al., 1995; Keidan et al., 1987). The low number of pain crises may help explain the lack of significant relations among variables of interest in the current study.

Significant findings from the current study that were not specified in hypotheses included a negative association between anxiety and performance on a matrix-reasoning task (i.e., WASI Matrix Reasoning; Wechsler, 1999). Research suggests that matrix reasoning relies on working memory (e.g., Salthouse, 1993). Thus, similar to the hypothesized finding that anxiety predicts task-switching performance, the finding that increased anxiety was related to poorer performance on a task relying on working memory can be interpreted based on prior findings that anxiety diminishes working memory capacity (e.g., Darke, 1988; Eysenck & Calvo, 1992; Eysenck, Derakshan, Santos, & Calvo, 2007; Eysenck, Payne, & Derakshan, 2005; Hayes, Hirsch, & Matthews, 2008). Another unpredicted finding was a positive relation between youth age and pain-crisis frequency, which is consistent with results from previous research suggesting that as children age, pain-crisis frequency increases (e.g., Powars, 1994; Ris & Grueneich, 2000; Smith & Scherer, 2010). The positive relation between age and pain-crisis frequency may be explained by research suggesting that as children with SCD reach puberty, their red blood cell levels increase, including those deformed due to SCD (Naets & Wittek, 1968; Smith & Scherer, 2010). The data also yielded evidence of a positive association between pain-crisis frequency and history of chronic pain, which is supported by research indicating that frequent, acute pain crises may lead to unmanageable chronic pain, especially if crises are inadequately treated over a long span of time (Ballas, 2007; Benjamin, 2008).

Future research investigating associations among pain, anxiety, and executive functioning in youths with SCD will benefit from addressing limitations in the current study, such as inclusion of a larger sample size and detailed pain information (e.g., frequency, severity, and duration) from multiple informants, as well as information regarding pain's impact on daily activities. In addition, health-related quality of life (Palermo et al., 2002) and school attendance (Schwartz, Radcliffe, & Barakat, 2009) in youths with SCD have been found to relate to their psychosocial functioning and are important factors to consider when examining relations among pain, anxiety, and executive functioning. Subsequent studies investigating pain-anxiety-executive functioning relations might also benefit from using anxiety measures specific to pain, and conducting cognitive and emotional assessments during pain crises.

Additional limitations of the current study included use of a convenience sample and use of multiple cognitive measures that were not normed together. Specifically, because participants included only those patients visiting the Aflac clinic at Children's Healthcare of Atlanta (CHOA) who chose to respond to the recruitment request, individuals unable to travel to CHOA may have been inadequately represented (e.g., financially strained families with no transportation). In fact, according to the measure of socioeconomic status used in this study, only two participants had no insurance at the time of data collection, whereas 18 had private insurance and 14 had Medicaid. Next, normative data for cognitive and emotional measures employed in the current study (i.e., BASC-2; Reynolds & Kamphaus, 2004; DKEFS; Delis, Kaplan, & Kramer, 2001) were collected from different population samples, using different norming and standardizing procedures, which may have been confounding factors in analyses of anxiety-executive functioning relations.

In summary, the current study examined relations among pain, anxiety, and executive functioning, and whether anxiety mediates the relation between pain and specific executive

functioning skills (i.e., task switching and inhibition) in youths diagnosed with SCD with no history of stroke. Findings were consistent with the extant literature in that participants' anxiety was related to task-switching performance; however, results did not support the hypotheses that pain crises predict anxiety or performance on executive functioning tasks, or that anxiety predicts inhibition performance. Given that anxiety was predictive of task switching in the current study, taken together with prior research revealing executive functioning difficulties and pain-related emotional distress in youths with SCD both with and without histories of stroke (e.g., Benton, et al., 2007; Gustafson et al., 2006; Smith & Baker, 2011; Steen et al., 2005), it is important that future research continue to examine how anxiety in pediatric patients with SCD might interfere with cognitive functioning. Future studies of youths with SCD may benefit from including large samples and fine-grained measures to determine relations among pain, anxiety, and executive functioning. Greater understanding of how these variables influence one another might lead to new avenues for intervention to improve the functioning and quality of life of youths with SCD.

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APPENDICES

Appendix A

Appendix A.1

Table 1.

Means and Standard Deviations of Pain-crisis Frequency, Anxiety, and Executive Functioning

	<u>M</u>	<u>SD</u>	<u>Range</u>
Pain-crisis frequency ($n = 34$)	2.68	3.488	0 – 16
BASC-2 Anxiety ($n = 34$)*	98.18	21.023	46 – 156
DKEFS Trails Number-Letter Switching ($n = 34$)*	89.853	18.524	55 – 115
DKEFS Color-Word Interference/Inhibition ($n = 34$)*	91.618	14.073	55 – 115

*Note: Standard scores

Appendix A.2

Table 2.

Intercorrelations for age, pain-crisis frequency, history of chronic pain, anxiety, executive function, and intellectual ability

	1.	2.	3.	4.	5.	6.	7.
1. Age ($n = 34$)	-						
2. Pain-crisis frequency ($n = 34$)	.58*	-					
3. History of chronic pain ($n = 34$)	-.43*	-.67**	-				
4. Anxiety ($n = 34$)	.16	-.005	.13	-			
5. DKEFS Trails Number-Letter Switching ($n = 34$)	-.04	.23	-.18	-.48**	-		
6. DKEFS Color-Word Interference/Inhibition ($n = 34$)	-.21	.10	.11	-.17	.40*	-	
7. WASI Vocabulary ($n = 34$)	.21	.51**	-.27	-.19	.33	.64**	-
8. WASI Matrix Reasoning ($n = 34$)	.08	.02	.03	-.45*	.55**	.31	.20

** $p \leq 0.01$

* $p \leq 0.05$

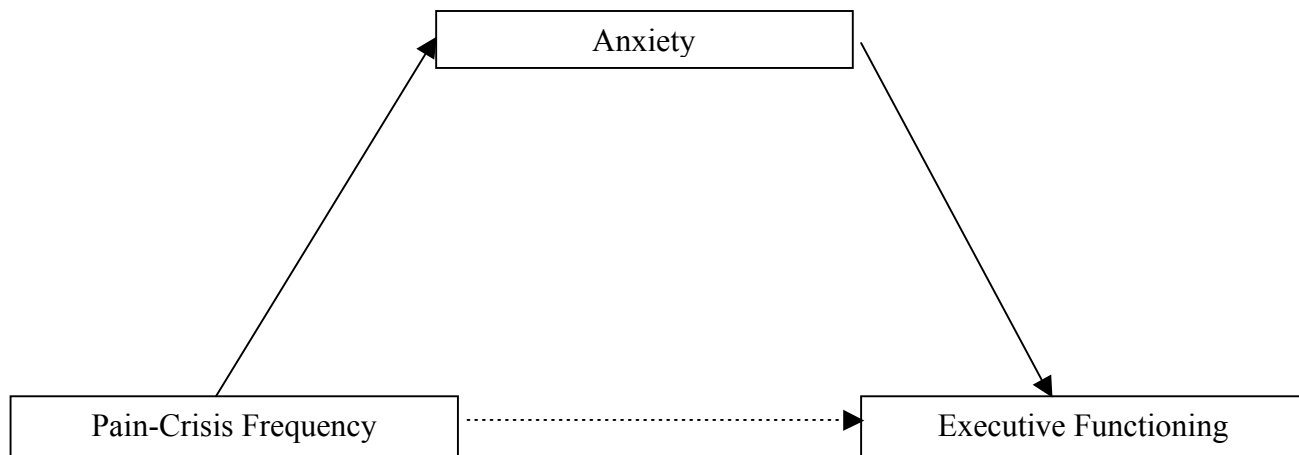
Appendix B*Appendix B.1*

Figure 1. *Model of anxiety mediating the relation between pain-crisis frequency and executive functioning*

Appendix C

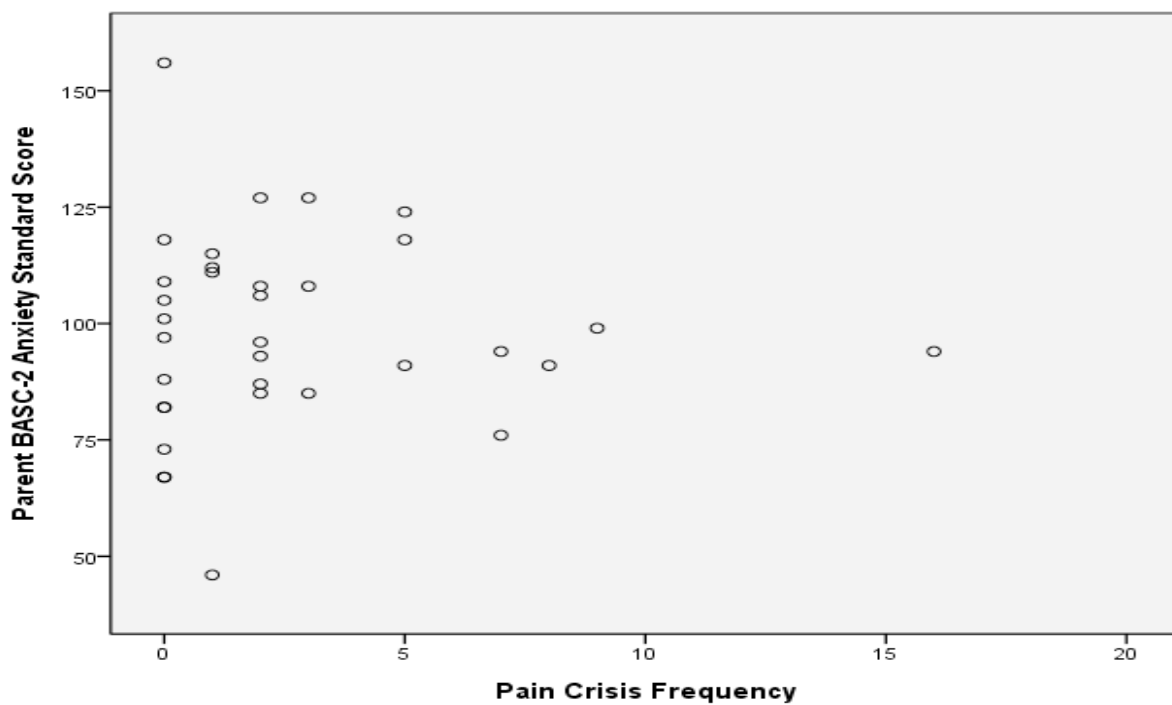
Appendix C.1

Figure 2. *Scatter plot of the relation between anxiety and pain-crisis frequency*

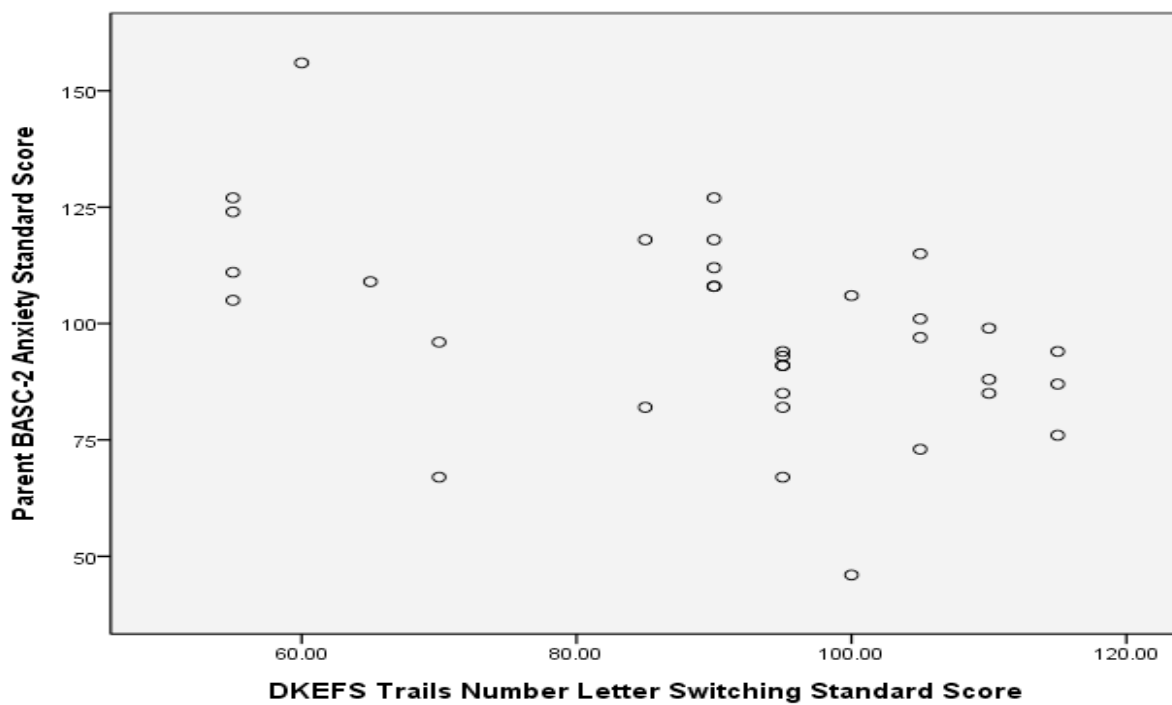
Appendix C.2

Figure 3. Scatter plot of the relation between anxiety and task switching

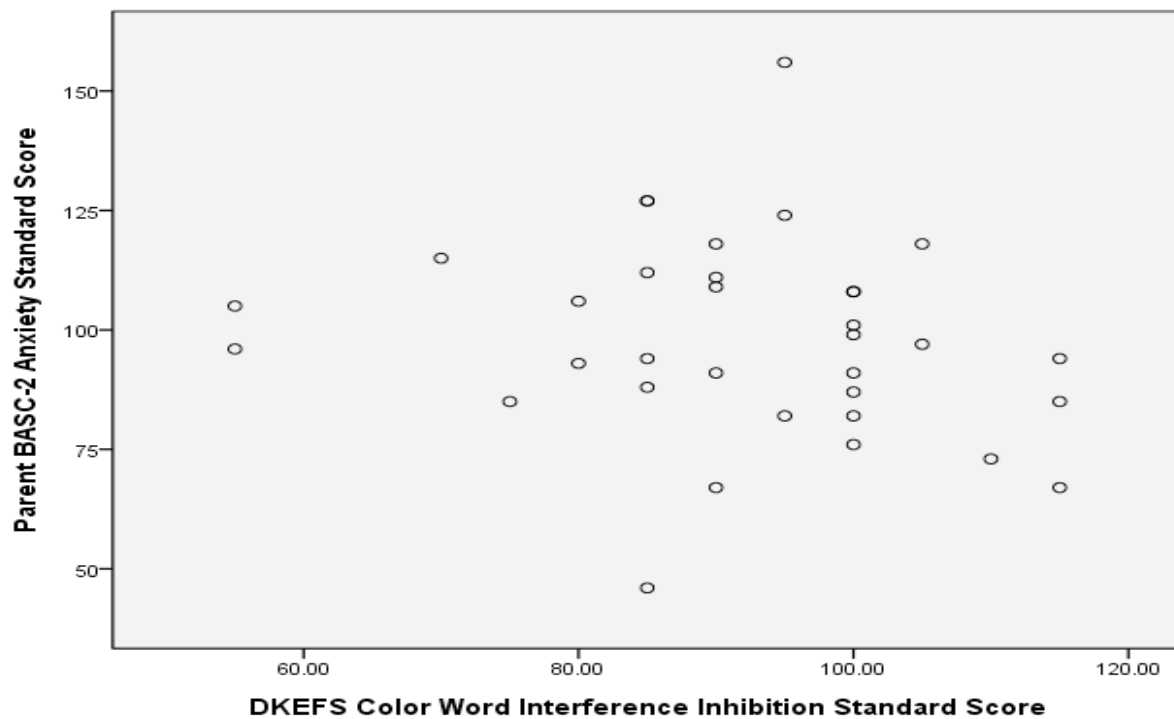
Appendix C.3

Figure 4. *Scatter plot of the relation between anxiety and inhibition performance*

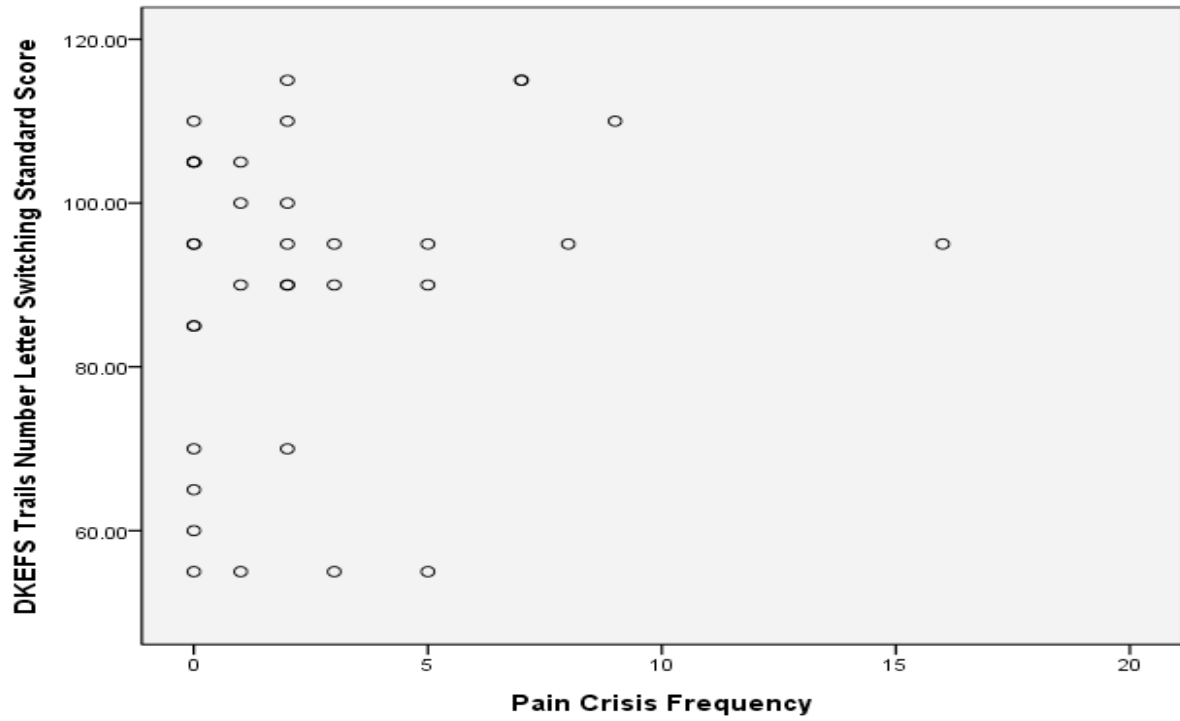
Appendix C.4

Figure 5. Scatter plot of the relation between task switching and pain-crisis frequency

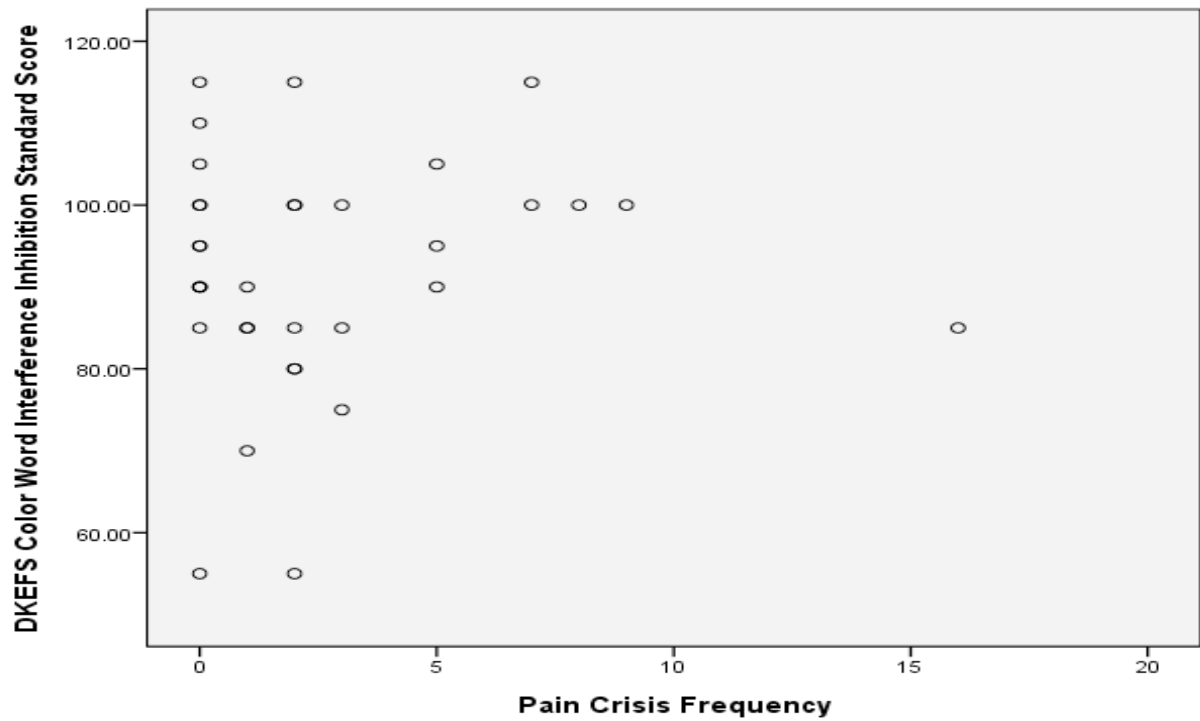
Appendix C.5

Figure 6. *Scatter plot of the relation between inhibition performance and pain-crisis frequency*