

COGNITIVE PROFILES OF MEDICAL MORBIDITIES
ASSOCIATED WITH PREMATURE BIRTH:
A STUDY OF CHILDREN WITH A HISTORY OF BPD, IVH, AND/OR PDA

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A DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy
in the Department of Psychology
in the Graduate School of
The University of Alabama

TUSCALOOSA, ALABAMA

2011

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ABSTRACT

Infants who are born prior to 37 weeks gestation are considered premature and are at high risk for medical and neuropsychological complications. Specifically, preterm infants are at risk for medical complications such as Intraventricular Hemorrhage, Patent Ductus Arteriosus, and Bronchopulmonary Dysplasia. While medical complications are often associated with cognitive difficulty, few studies have examined whether specific medical complications are related to specific cognitive difficulties. The purpose of the current study was to determine whether these medical complications differentially impact long-term cognitive outcomes of preterm infants. The current study assessed 55 preterm children born weighing less than 1500g at 9-12 years of age using a neuropsychological battery assessing intellectual, language, motor, attention, memory and executive function skills. The results of the current study indicated that each medical complication was associated with a different pattern of cognitive outcomes. Specifically, IVH was associated with impairments in Verbal IQ, executive function, and memory. However, these difficulties were no longer significant after controlling for SES and birthweight. BPD was associated with decreased gross motor and language skills, even after controlling for SES and birthweight. PDA was associated with improved outcomes in the areas of Performance IQ, executive function, language, memory, and fine motor skills. It is hypothesized that the medication often used to treat PDA (i.e., indomethacin) may be preventative with regards to long-term neuropsychological sequelae. Taken together, this study confirms that long-term outcomes associated with prematurity may be differentially predicted by the specific medical complications that occur following birth.

LIST OF ABBREVIATIONS AND SYMBOLS

IVH	Intraventricular Hemorrhage
BPD	Bronchopulmonary Dysplasia
PDA	Patent Ductus Arteriosus
LBW	Low Birthweight
VLBW	Very Low Birthweight
ELBW	Extremely Low Birthweight
α	Alpha: the probability that the null hypothesis will be incorrectly rejected
β	Beta coefficient: standardized coefficient in linear regression
η^2	Eta-squared: a ratio of the variance attributed to a specific effect
η_p^2	Partial eta-squared: a ratio of the variance attributed to a specific effect (partials out other factors in the model)
p	statistical indicator of a significant finding
F	value of test statistic in ANOVA
t	t test value
SD	Standard Deviation
R^2	percent of variance in dependent variable attributable to the independent variable

ACKNOWLEDGEMENTS

This research study would not have been possible without the assistance of many faculty, colleagues, family members, and friends. First and foremost, I would like to thank my dissertation chair, Laura Klinger, for her assistance and guidance over the course of my graduate training. This project would not have been possible without her training and experience. I would also like to thank Fred Biasini for sharing his expertise in the area of premature infant follow-up. It would not have been possible to run this extensive battery with this many subjects without the help of my research assistant, Desiree deJong. I would also like to thank Vivien Phillips and Ashley Evans for their assistance in identifying and recruiting subjects through their respective clinics. This study would not have been possible without the help of many personnel at the UAB Newborn Follow-up Clinic, the Pediatric Clinic at the University of Alabama, and the Civitan/Sparks Clinics. I would also like to express my gratitude to my committee members, Fred Biasini, John Lochman, Jim Hamilton, and Ed Merrill for their incredible patience, flexibility, and guidance throughout this process. Finally, I am so grateful to my family and friends for all of their support.

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Cognitive profiles of medical morbidities associated with premature birth: A study of children with a history of BPD, IVH, and/or PDA

While technological advances have greatly increased the survival of infants born prematurely (22-36 weeks gestation), the number of preterm births has increased over the past two decades (for review see Alexander & Slay, 2002). Moreover, these infants continue to suffer from medical complications such as Bronchopulmonary Dysplasia (BPD), Intraventricular Hemorrhage (IVH), and Patent Ductus Arteriosus (PDA) resulting in various associated cognitive, neurosensory, and neuromotor morbidities. Several studies have demonstrated that prematurity has detrimental effects on the cognitive outcome of children (Fawer, Besnier, Forcada, Buclin, & Calame, 1995; Saigal, Hoult, Streiner, Stoskopf, & Rosenbaum, 2000); however, very few have examined those outcomes as a function of the medical complications that are associated with prematurity. The goal of the current study was to examine the specific long-term neuropsychological effects of each of three medical complications, IVH, BPD, and PDA. Before discussing the specific medical complications, it is important to first discuss the definition of prematurity and then briefly review the existing research on neuropsychological, neurosensory, and neuromotor sequelae in prematurity.

Low birthweight infants fall into one of three categories based on weight. Infants born weighing less than 2500g are considered low birthweight (LBW). Those weighing less than 1500g are classified as very low birthweight (VLBW). Those weighing less than 1000g fall into the extremely low birthweight (ELBW) category. The physiological risks to the infant after birth

vary by birthweight, but include difficulty with the immature development of the heart, lungs, and brain. Later in life these infants may suffer from a variety of neurological, neurosensory, and neuropsychological impairments.

Studies have demonstrated that there are structural differences in the brain that can be attributed to preterm birth (Peterson, et al., 2000; Stewart et al., 1999). Peterson et al. (2000) found significant differences in the basal ganglia, corpus callosum, amygdala, and hippocampus of eight year-old children who were born preterm when compared to full term controls. These differences remained significant even after excluding children who had been diagnosed with brain bleeds that may have directly caused structural changes to the brain. Abnormalities in brain development can be seen on MRI scans as late as 14-15 years of age in the ventricles, corpus callosum, and white matter (Stewart, et al., 1999).

Given the demonstrated structural abnormalities in the brain that are associated with preterm birth, it is reasonable to expect premature infants to be at greater risk for neuropsychological difficulty in the areas of global cognitive skills, language development, executive function, behavioral regulation, working memory, academic achievement, visuospatial skills (Marlow, Hennessy, Bracewell & Wolke, 2007), and internalizing disorders. However, these deficits have been demonstrated in the absence of abnormal findings on brains scans, suggesting that these difficulties may not be explained solely by structural changes in the brain. Saigal and colleagues (2000) found that at least 28% of infants born weighing less than 1000g experienced neurosensory impairments including, cerebral palsy, hydrocephalus, blindness, autism, significant cognitive impairment, or deafness. Estimates indicate that the rates of mild neuropsychological deficits may be as high as 40-50% in preterm infants (for review see Howard, Anderson, & Taylor, 2008). Among preterm infants who display no evidence of

significant neurological impairments (e.g. no abnormal findings on neuro-imaging scans), 46.5% demonstrate some form of neuropsychological deficit, including neuromotor, visual, auditory, behavioral, or language difficulty at the age of 5 (Fawer, et. al., 1995). Preterm infants as a whole tend to score 10-15 points lower on tests of global intelligence (Saigal et al., 2000, Luu, Ment, Schneider, Katz, Allan & Vohr, 2009). Similar patterns of deficits have been found in young adults as well (Lohaugen, et al., 2010). As with most deficits, this effect on IQ tends to be correlated with birthweight (Boardman, Powers, Padilla & Hummer, 2002). A meta-analysis of studies conducted with preterm and/or VLBW infants indicated significant difficulty in the areas of attention, and executive function (cognitive flexibility, working memory, verbal fluency; Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009). Language difficulty has also been documented in preterm children when compared to term controls (Luu, Ment, Schneider, et al., 2009).

In addition to neuropsychological sequelae, premature infants are more likely to use special education services in the school systems (Luu, Ment, Schneider, et al., 2009) and demonstrate impairments on tests of academic achievement (Aarnoudse-Moens, et al., 2009; Resnick, et al., 1998). Special education usage varies by birthweight with approximately 5% of term children receiving special education assistance and 35% of ELBW children receiving these services (McGrath & Sullivan, 2002). There is a similar trend for other services in the school systems (e.g., speech/language services). In addition to birthweight, socioeconomic status has been shown to significantly impact outcomes for preterm infants in the areas of global cognitive ability, language skills, memory skills, and motor skills (Taylor, Klein, Minich & Hack, 2000). It should be noted that many of the previous studies have included all preterm infants without distinguishing among those with and without specific medical complications. Medical

complications may exacerbate the neuropsychological difficulties associated with premature birth. This is especially true for infants who are classified as ELBW as medical complications are more frequent and often more severe in this population (Hack, Klein, and Taylor, 1995).

Medical Complications

Three major medical complications associated with premature birth are Intraventricular Hemorrhage (IVH), Bronchopulmonary Dysplasia (BPD), and a Patent Ductus Arteriosus (PDA) which affect the brain, lungs, and heart, respectively. Because of the effects each of these has on oxygen availability, blood flow, and brain structures, they can often lead to later cognitive and neuropsychological sequelae. Infants may have one complication or they may have several of these complications in combination. Typically, the number and severity of the medical morbidities increase as the infant's birthweight decreases (Hack et al., 1995).

Intraventricular Hemorrhage.

Epidemiology and Etiology. Intraventricular hemorrhage (IVH) is a disorder that involves bleeding in the brain as a result of torn capillaries and vessels. In premature infants bleeding tends to originate in the germinal matrix, or the central point from which tissue migrates out during the formation of the brain (Paige & Carney, 2002). The germinal matrix is present from weeks 22-30 in the developing fetus and is still present in preterm infants born prior to 30 weeks gestation. The germinal matrix is only minimally protected from injury or trauma and is, therefore, subject to bleeding from still weakened capillaries. IVH typically occurs within the first few days of life with a trend toward earlier onset in lower birthweight infants (within 24 hours for infants weighing less than 750g; Perlman, 2002). Rates of IVH are approximately 15% in infants born weighing 501-1500g (Volpe, 2001) and do not appear to differ based on ethnicity or SES (Ross, Tessman, Auld, & Nass, 1992). The exact cause of IVH is likely a

combination of multiple factors including, gestational age, and additional antenatal factors; however, it can be triggered by a change in cerebral blood flow or blood pressure. This change in blood flow or blood pressure may be caused by respiratory factors, cardiovascular factors, metabolic or hematological factors, shock, pain, and/or stress (Paige, et al., 2002).

Diagnosis and Treatment. IVH is typically diagnosed using either ultrasonographic imaging of the head or CT scans of the brain. Bleeding is classified by severity from Grade I, indicating mild bleeding confined to the germinal matrix, to Grade IV, indicating that bleeding has expanded beyond the ventricles and into surrounding brain tissue (Paige, et al., 2002). The potential consequences of the IVH can be medically managed, but there is no treatment for the bleed itself. Most infants are monitored to ensure that blood oxygenation is within normal limits, pH is properly balanced, and seizure activity is minimal (Paige, et al., 2002). Some physicians have attempted to remove the blood from the brain; however, the benefit rarely outweighs the danger of the lumbar puncture procedure. Additionally, removing blood from the brain may increase bleeding by removing a source of pressure on the leaking capillaries and vessels. Approximately 65 -100% of infants who experience grade III or IV IVH will develop posthemorrhagic hydrocephalus, which results in the placement of a shunt in approximately 80-90% of those infants who develop the condition (Paige, et al., 2002).

Physical Sequelae. IVH has been associated with white matter injury in the brain, but not necessarily implicated as the cause of the injury (for review see Perlman, 1998; e.g., Perlman, Rollins, Burns, & Risser, 1993). In addition, research indicates that mild IVH is associated with damage to the head of the caudate nucleus and can affect cells that would have migrated to the thalamus and amygdala (Allan & Volpe, 1986; Pape & Wigglesworth, 1979).

Global Cognitive Impairment. Research with young children (Messinger, Dulcourt, King

Bodnar, and Beck, 1996; Wang, Wang, & Huang, 2008; Sherlock, Anderson, & Doyle, 2005; Boyce, Saylor, & Price, 2004, McGrath & Sullivan, 2002) indicates that the impact of IVH on global cognitive function seems to vary by severity of the bleeding, with greater severity resulting in the most significant deficits in global cognitive function. The most severe bleeds may result in a deficit of 10-15 points on measures of global cognitive function (Sherlock, et al., 2005; Boyce, et al., 2004). However, it should be noted that these studies found that only the most severe bleeds resulted in significant deficits. There was no difference between premature infants who experienced milder forms of IVH and premature infants who did not on global cognitive outcomes. McGrath and Sullivan (2002) found that this effect was true for Performance and Full Scale IQ; however, Verbal IQ was not significantly affected by IVH. Research specifically examining the effect of mild IVH on global cognitive outcomes is limited, inconsistent, and typically focused on younger populations (2-5 years of age). For example, Patra and colleagues (2006) found that a mild bleed can significantly impact developmental scores for young children. A limited number of studies conducted with young children have reported conflicting findings indicating that the presence of IVH does not significantly impact developmental outcomes at 2 years of age. (Sostek, Smith, Katz, & Grant, 1987; Stoelhurst et al., 2003). Overall, it appears that the presence of a severe IVH has a detrimental impact on Full Scale, and Performance IQ; however, the literature regarding the effect of milder IVH on global cognitive ability is somewhat limited.

Motor Impairment. Evidence tends to support the presence of motor impairments related IVH (Janssen, et al., 2009; Boyce, Smith, Casto, 1999; McGrath & Sullivan, 2002) in children who are 5 to 8 years of age. Janssen and colleagues (2009) found that IVH was significantly related to the presence of Cerebral Palsy. Moreover, when children with CP were excluded from

the analyses, mild IVH was still associated with mild impairments in motor function. Other research suggests a lack of impact on motor outcomes; however, all of these negative findings were found in studies of children under 3 years of age (Sostek, et al., 1987, Stoelhurst, et al., 2003, Ross, et al., 1992). Studies conducted with long term follow-up consistently have shown motor impairments associated with IVH, specifically in the form of diagnosed Cerebral Palsy. Little research has examined long-term fine motor versus gross motor impairment or mild vs. severe IVH.

Language Impairment. Very little research exists examining the effect of IVH on language outcomes; however, one study does suggest a possible link between mild IVH and language impairment (Vohr, et al., 2003). Specifically, this study found that receptive language as measured by the PPVT was lower in 8 year-old children who experienced IVH than those who did not. This study however, did not examine expressive language.

Attention Impairment/ADHD. Strong evidence exists linking attention difficulty and the presence of IVH (Boyce et al., 1999; Ross, et al., 1992, Indredavik, et al., 2010). This effect might be related to the damage caused in the caudate nucleus, hypothalamus, and amygdala of the developing brain (Isseroff, Rosvold, Galkin, & Goldman-Rakic, 1982). Boyce, et al., (1999) found elevated rates of attention problems in children ages 5-8 who had IVH as an infant. Ross et al., (1992) found that the presence of mild IVH resulted in impaired visual attention at 10 months of age. This study suggests that deficits in finer cognitive functions may exist in the infants who suffered less severe IVH.

Memory Impairment. Very few studies have specifically addressed memory in preterm infants with IVH. Based on the location of damage in the caudate nucleus, thalamus and amygdala, one would expect memory impairment in children who suffered from IVH (Isseroff,

et al., 1982). However, one study examined memory for localization and found no effect of IVH group membership when compared to preterm controls (Ross, et al., 1992). It should be noted that these infants were only 10 months old at the time of testing and no long-term follow-up study has been conducted.

Executive Function Impairment. No studies were found in the context of the current literature review that assessed executive function, specifically as it relates to IVH; however, based on frontal lobe connectivity with the previously mentioned damaged structures, one might expect executive function to be impaired.

Summary. Overall, findings regarding the long-term outcome of children with IVH have been contradictory or lacking. Research supports the presence of global cognitive impairments in children who experienced IVH, but only in the presence of the most severe forms of IVH. The limited research that exists with regard to motor and attention skills indicates that these areas are not directly affected by IVH. Based on what little research is available, as well as the potential damage to specific brain regions linked to IVH, there is potential for impairment in receptive language and executive function warranting further study. It should be noted that the majority of the studies that examined IVH as it relates to the various cognitive outcomes described above, focus on children who are 2-5 years of age. The longest follow-up study in the area was conducted with 8 year old children examining their global cognitive outcomes. Thus, there is a need for research examining the long-term sequelae of IVH.

Bronchopulmonary Dysplasia (BPD).

Epidemiology and Etiology. Infants who are born prematurely often lack the typical coating in the lungs (surfactant) that reduces surface tension among alveoli. Without surfactant, surface tension causes the alveoli to stick together when the lungs contract during exhalation and

reduces the ability for these cells to expand during inhalation. This condition is known as Respiratory Distress Syndrome. The treatment for Respiratory Distress Syndrome is positive pressure ventilation. However, this ventilation may result in damage to the lungs known as Bronchopulmonary Dysplasia (BPD). While Respiratory Distress Syndrome is one of the most common causes of BPD, other risk factors are also associated with the disorder (e.g., PDA, poor maternal nutrition, the degree of prematurity, a family history of asthma, antenatal or perinatal infection, etc.; Hagedorn, Gardner, & Abman, 2002).

Diagnosis and treatment. The National Institutes of Health define the severity of BPD by the length of time the infant requires supplemental oxygen and the amount of oxygen required (Ehrenkranz, et al., 2005). Mild BPD was defined as the need for supplemental oxygen at 28 days, but not by 36 weeks post menstrual age or discharge. Moderate BPD was defined as the need for no greater than 30% oxygen at 36 weeks gestation age equivalent. Infants who continued to require supplemental oxygen greater than 30% or positive pressure at 36 weeks gestation age equivalent were said to have severe BPD. There is a negative correlation between gestational age and rates of BPD; however, rates of BPD do not appear to vary by SES or ethnic group membership (Majnemer, et al., 2000; Singer, Siegel, Lewis, Hawkins, Yamashita, & Baley, 2001). Among infants born weighing 501-750g, 90% were diagnosed with BPD at 28 days of life. The rates in infants weighing 751 -1000g drop to 69%. The rates continue to drop in infants weighing 1001-1250g (37%) and 1251-1500g (18%; for review see Cole & Angert, 2002). The goal of treatment is to disrupt the cycle of re-injury by reducing those factors that cause injury to tissue. This is accomplished by maintaining proper ventilation, restricting fluids, administering steroids and other medications, and gradually weaning the infant from oxygen. Damage from BPD may take up to 2 years to fully resolve, during which time the infant is at risk

for additional complications (e.g., RSV). Treatment itself may have an adverse impact on cognitive and motor outcomes. Postnatal steroid administration has been linked to cognitive and motor impairment in school age children (Vohr, Wright, Poole, & McDonald, 2005; Yeh, et al., 2004). Specifically, postnatal steroid administration was found to impact the Full Scale and Performance IQ of children at 8 years of age.

Physical Sequelae. As a consequence of BPD, the lungs may fill with fluid, collapse, or produce excess amounts of mucous preventing proper oxygenation of the blood. BPD has been associated with longer need for supplemental oxygen and longer hospitalization when compared to preterm infants without BPD. In addition, BPD has been associated with periodic episodes of hypoxia in the infant. Hypoxia results from the reduced availability or consumption of oxygen in an organ or system in the body, in this case the brain. Hypoxia occurs periodically over the duration of mechanical ventilation and while supplemental oxygen is required. This hypoxia can cause damage in the basal ganglia and thalamic regions of the brain (for review see, Rutherford et al., 2006).

Global Cognitive Impairment. BPD has been associated with significant decreases in cognitive function due to the effect it has on oxygen availability in the brain and the increased need for supplemental oxygen (Stoelhurst, et al., 2003; McGrath & Sullivan, 2002; Hughes, et al., 1999; Gray, O'Callaghan, & Rogers, 2004). Stoelhurst et al., (2003) found that infants with BPD were on average 18-19 points below the standardized norm for mental and motor development at 2-3 years of age. Several studies have found that children with a history of BPD demonstrate significantly lower scores on measures of global cognitive function, especially within the performance domains (McGrath & Sullivan, 2002; Hughes, et al., 1999) Overall, research supports a link between BPD and impaired global cognitive function, most prominently

in the area of Performance IQ.

Motor Impairment. Motor deficits have also been consistently linked to a history of BPD (McGrath & Sullivan, 2002; Smith, et al., 1999, Taylor, Klein, Drotar, Schlucter, & Hack, 2006). McGrath and Sullivan (2002) found that BPD significantly predicted motor impairment in children at age 8. Smith et al., (1999) and also found that BPD predicted impairment in motor function and a much slower developmental progression of motor ability. Specific, impairments seem to be in the area of gross motor, upper extremity coordination, muscle reflexes, motor steadiness, and muscle tone (Smith et al., 1999, Majnemer, et al., 2000); however, some research exists implicating BPD in fine motor difficulty as well (Lewis, et al. 2002). These deficits may be related to the damage in the basal ganglia and thalamic regions of the brain (Rutherford et al., 2006).

Language Impairment. Research studies consistently show a link between BPD and language impairment in preterm children (Smith et al., 1999; Lewis, et al., 2002; Farel, Hooper, Teplin, Henry &, Kraybill, 1998). Smith et al., (1999) found that infants who suffered from BPD at birth had significantly lower language scores and tended to develop language at a slower pace than preterm controls. More specifically, Lewis et al., (2002) found that 8 year-old children who suffered from BPD at birth were impaired in the area of receptive language over and above the impairment seen in VLBW infants without BPD. Lewis and colleagues (2002) suggested that children who had experienced BPD had greater difficulty with spoken directions, specifically recalling them, interpreting them and then subsequently carrying them out.

Attention Impairment. Research regarding attention in children with a history of BPD is limited. Several studies have found that attention does not appear to be impaired in this population over and above that expected by prematurity alone (Short et al., 2003; Farel, et al.,

1998). In addition, Farel and colleagues found that children with severe BPD, as defined by 30 days on mechanical ventilation, experienced no significant impairment in attention. While, Short and colleagues (2003) did not find significant differences between children who had BPD and those who were VLBW, children who experienced BPD did experience significant impairments in attention when compared to full term controls. In addition, the rate of ADHD diagnosis in the children with a history of BPD was significantly higher than that of both the VLBW group and the full term control group

Memory and Executive Function. Very little research exists regarding memory or executive function in infants with BPD. However, given the research on hypoxia as it relates to BPD and damage to brain structures, as well as the possible connection between these subcortical structures and the frontal lobe, executive function could potentially be impaired. One study exists that indicates a potential association between BPD and memory impairment after controlling for severe IVH (Farel, et al., 1998). Farel and colleagues also (1998) found that children with a history of severe BPD scored lower on measures of short-term memory, verbal retrieval, and working memory than children who never experienced significant lung problems.

Summary. The current review of existing research in the area of BPD suggests that BPD may be associated more with global impairments in neuropsychological functions more so than specific impairments in individual domains (Sherlock, et al., 2005). Overall, research suggests that BPD has a detrimental impact on Full Scale, Performance and Verbal IQ. In addition, there is evidence to suggest that gross motor function is impaired in children who suffered from BPD as infants; however, findings regarding fine motor skills are equivocal. Little to no research exists regarding attention in this population; however, based on what does exist there does not appear to be any impairment in this area.

Patent Ductus Arteriosus (PDA).

Epidemiology and Etiology. Finally, one of the more common heart conditions associated with prematurity is a Patent Ductus Arteriosus (PDA). A PDA occurs when an artery that typically closes after birth fails to close in pre-term infants preventing adequate blood oxygenation. The artery, which is designed to bypass the non-functioning lungs while in utero, connects the aorta with the pulmonary artery. The aorta sends the oxygenated blood to the body, while the pulmonary artery returns the oxygen depleted blood to the heart and ultimately the lungs. While still in utero, the blood is oxygenated by the mother's blood supply, therefore eliminating the need to pass the blood through the lungs. Closure of the artery typically occurs within 96 hours of birth for full term infants and larger preterm infants weighing more than 1500g. However, in a few larger pre-term infants and many smaller pre-term infants the artery will fail to close, allowing oxygenated blood to flow back into the lungs instead of disseminating throughout the body, therefore causing too much blood to enter the lungs. In addition the blood can flow the other direction allowing the unoxygenated blood to mix with the oxygenated blood that is being pumped throughout the body. As a result, the heart must pump harder to force the blood out of the lungs or adequately oxygenate the organs and can become weakened and enlarged. Other complications that can result from a PDA include infections in the heart lining, inability to feed properly, shortness of breath, and possibly heart failure. PDA rates vary among studies of premature infants, ranging from 18% - 77%. Higher rates are associated with infants under 30 weeks and/or less than 1000g. Rates as high as 50% have been reported in infants born weighing less than 1000g and 70% of infants born before 28 week (for review see Bancalari, Claire, & Gonzalez, 2005; e.g. Fanaroff, Hack, & Walsh, 2003, Clyman, 2000).

Diagnosis and Treatment. PDA is diagnosed primarily based on physical findings and an

echocardiogram. Physically infants with PDA may experience abnormal pulses, a heart murmur, and signs of congestive heart failure. An echocardiogram will likely show evidence of shunting of blood in one or both directions through the ductus arteriosus (Montoya & Washington, 2002).

In some cases the PDA will close without treatment; however, the typical treatment for PDA includes either medication with Non-steroidal Anti-Inflammatory medications (e.g., Indomethacin) or surgical ligation (clipping or surgically closing the duct). Indomethacin is often the first line of treatment because of the risk of surgical procedures on small infants. A typical dose of indomethacin is between 0.1mg/kg, for those under 48 hours, and 0.2 mg/kg for slightly older infants (2-7 days), every 12-24 hours (for review see, Hammerman & Kaplan, 1999). Three doses is the standard care, with the initial dose being 0.2 mg/kg and two subsequent doses based on age, for a period of 2-3 days. This treatment is successful for 70-90% of infants. Prolonged administration of low dose indomethacin over the course of 5 days has been shown to reduce the rates of recurrence, which occurs in approximately 20-35% of infants. In these infants the duct is constricted, but not completely closed. Surgical ligation or a second round of indomethacin may be used to close the duct if the PDA recurs. For those who receive Indomethacin, there are additional risks in that Indomethacin has been shown to decrease cerebral blood flow and oxygenation (Patel, Roberts, Azzopari, Hamilton, & Edwards, 2000; Mosca, Bray, Lattanzio, Fumagalli, & Tosetto, 1997; Pezati, et al., 1999; Van Bel, Van de Bor, Stijnen, Baan, & Ruys, 1989). However, additional studies suggest that indomethacin may also reduce the risk and severity of IVH (Bada, et. al., 1989; Banstra, Montalvo, Goldberg, et la., 1988; Ment, Oh, Ehrenkranz, et al., 1994).

Neurological Sequelae. While the primary damage in both BPD and PDA is due to hypoxia, the hypoxia related to PDA occurs slightly earlier in brain development, within hours

after birth, while in BPD it really becomes evident over several days after damage to the lungs has occurred. In addition, PDA related hypoxia ends after the patent duct is closed, which occurs within days of treatment, whereas hypoxia may occur periodically for months or years in infants with BPD. MRI studies of children with PDA have found a significant decrease in cerebellar volume and pons diameter (Argyropoulou, et al., 2003).

Global Cognitive Impairment. PDA has demonstrated little to no effect on global cognitive function. Gray et al., (2004) found that PDA was associated with lower scores only on the performance domain of global cognitive function in children at 8 years of age.

Motor Impairment. Tran, Gray, and O’Callaghan (2005) found that while the presence of PDA did not significantly predict cerebral palsy (CP), the need for surgical ligation of PDA did predict CP at 2 years of age. No studies have examined motor impairments in children with a history of PDA beyond 2 years of age.

Language Impairment. Singer, et al., (2001) found that the presence of PDA and BPD together were associated with significant impairment in language function at age 3. PDA itself negatively affected language; however, PDA and BPD together resulted in the greatest language impairment. Singer and colleagues (2001) noted that it was unclear whether this impairment was caused by the PDA itself or to the Indomethacin used to treat the PDA. Individual aspects of language were not included in these analyses so it is difficult to determine what aspects of language are affected by PDA.

Executive Function, Attention, and Memory. Very little research exists examining the effects of PDA on memory, attention, or executive function. However, nothing in the literature on affected brain structures specific to PDA suggests that these areas would be impaired (Argyropoulou, et al., 2003).

Summary. Very little research has examined the cognitive effects of PDA; however, what does exist suggests that only Performance IQ and language would be impaired. Given the limited scope of the research regarding specific cognitive impairments and the focus on children under 5 years of age in the majority of the existing literature, the current study provides a unique contribution to the understanding of the long-term effects of PDA on cognitive outcomes.

Ethnicity and SES

Preterm birth is overrepresented in minority groups, for reasons that are yet unknown (for review see Behrman & Butler, 2007). Many potential explanations of the difference have been proposed including SES, maternal behaviors (e.g., smoking), stress, and infections. Data collected by the Institute of Medicine of the National Academies (Behrman & Butler, 2007) indicates that the rates of preterm birth to African American mothers ranges from 20% for those with less than 8 years of education to 13% for those with more than 16 years of education. The rates of preterm birth to Caucasian mothers ranges from 7 – 11%. This indicates that regardless of level of education there is still a racial disparity in rates of preterm birth. The same study found that the effect of maternal age on preterm birth is most extreme for African American mothers. Even when use of prenatal care was accounted for, African Americans still had higher rates of preterm birth. One possible explanation for the disparity was the disparity in daily stress between African American women and Caucasian women (James, 1993; Lu & Chen, 2004). Research also indicates that African American women are more likely to experience infections that would lead to preterm delivery (Fiscella, 1995; Meis, et al., 2000). However, the reasons for the elevated rate of infection are largely unknown.

In addition to racial/ethnic disparities, there are well-documented socioeconomic disparities in preterm birth as well. Again, the reason for this disparity is largely unknown;

however, several potential explanations have been proposed, including, physical activity, infection, maternal nutrition, and access to prenatal care (for review see Behrman & Butler, 2007).

Current Study

The previous literature review suggests that BPD and IVH might result in similar profiles of deficits, while PDA might result in fewer impairments when comparing across a sample of preterm infants. Specifically, IVH was hypothesized to be associated with impairments in overall cognitive ability and measures of performance IQ, receptive language, both fine and gross motor function, attention, memory, and executive function. It was predicted that BPD would be associated with impairments in global cognitive ability, receptive and expressive language, gross motor, memory, and executive function. PDA was hypothesized to be associated with deficits in language and the Performance IQ on global cognitive measures. Table 1 shows the areas of impairment for each medical complication that are supported by previous research or that are likely given the results of previous research. Table 1 also notes the distinction between impairments indicated by previous studies.

Table 1.

Summary of extant literature predicting outcomes for each medical complication.

	General Cognitive (FSIQ)	Language		Motor		Atten.	Mem	EF
		Rec.	Exp.	Fine	Gross			
IVH	YES	YES	No	YES *		YES	N/A	N/A
BPD	YES	YES	No	no	YES	no	yes	yes
PDA	NO	YES *		N/A	N/A	N/A	N/A	N/A

Note. All capital letters indicates that there is strong empirical evidence in support of or against impairment in an

area. All lower case letters indicates that the research is either limited or contradictory. N/A indicates that the area has not been studied. *Research did not differentiate the specific area of impairment.

The purpose of the current study was to examine the profile of cognitive deficits that were occurred with each of the following medical complications associated with prematurity: BPD, PDA, and IVH. To date there has been a lack of research regarding specific cognitive outcomes and how they are affected by each of these disorders. For example, executive function, memory, and attention have received little attention within the context of prematurity. Furthermore, the extant literature has primarily focused on children in preschool. Follow-up of children during school age and into adolescence is minimal and again focused on more global cognitive outcomes.

An additional goal of this study was to examine the unique impact of each medical condition in predicting outcomes across a sample of preterm infants. The evidence indicates that there is a significant overlap in medical complications such that some infants will experience two or more at once. In the case of BPD, PDA, and IVH the overlap ranges from 40 – 60% with estimates as low as 20% and as high as 65%. There is a 45-60% chance that an infant will experience both IVH and BPD (Vohr, et al., 2003; Lewis et al., 2002). Similarly, there is a 45-55% chance of having both BPD and PDA (Lewis, et al., 2002; Cunha, Mezzacappa-Filho, & Ribeiro, 2005). The odds ratio for an infant with PDA developing IVH is 2.4 in comparison to infants without PDA (Singer, Yamashita, Lilien, Collin, & Baley, 1997). To date very few studies have included all three of these conditions in order to control for the overlap when differentiating the outcome for each individual morbidity. The current study examined each condition individually to determine the cognitive outcome of that specific morbidity (e.g., IVH), while averaging over the effects of the other two conditions (e.g., BPD and PDA). The current study is unique not only in the consideration of overlap among conditions, but also the extension

of follow-up to children in the 9-12 year age range. As noted in previous section, the majority of follow-up studies have been conducted with young children below the age of 8.

Hypotheses. The goal of the current study was to examine the specific neuropsychological profile of impairments in school aged children with a history of three of the more common medical complications associated with prematurity, IVH, BPD, and PDA. Differences in comparison groups (e.g., other preterm infants vs. control), age at follow-up, and the measurement approaches used resulted in inconsistent findings in the literature. These contradictions and the lack of research in the area prevented the formation of specific hypotheses in the areas of verbal and performance IQ; however, these subscales were explored individually. Based on the extant literature on cognitive impairments and brain structures affected by IVH, BPD, and PDA, the following hypotheses were made (see Table 2):

H1: The presence of IVH, independent of BPD and PDA, will be associated with significantly lower scores on the following measures:

- a. Full Scale IQ
- b. Receptive Language and Expressive Language
- c. Gross and Fine Motor
- d. Attention
- e. Memory
- f. Executive Function

H2: The presence of BPD, independent of IVH and PDA, will be associated with significant impairments in the following areas:

- a. Full Scale IQ
- b. Receptive Language

- c. Gross Motor
- d. Memory
- e. Executive Function

H3: The presence of PDA, independent of IVH and BPD, will be associated with significant impairments in the following areas:

- a. Receptive and Expressive Language subtests

Table 2.

Hypothesized Cognitive Impairments for Each Medical Condition.

	General Cognitive (FSIQ)	Language		Motor		Attention	Memory	EF
		Rec.	Exp.	Fine	Gross			
IVH	X	X	X	X	X	X	X	X
BPD	X	X	X	-----	X	-----	X	X
PDA	-----	X	X	-----	-----	-----	-----	-----

Note. X indicates hypothesized impairment.

Additional research questions existed based on gaps in the literature. The following questions were addressed in secondary exploratory analyses.

R1: Did each medical condition offer any predictive ability above and beyond birthweight and SES for each of the outcome measures?

R2: Did the identified effects of each condition vary by severity of the condition for IVH and BPD?

R3: Did early intervention service usage affect the relationship between the medical conditions and the cognitive outcomes?

Method

Participants

The current study enrolled 55 children from two follow-up clinics in the Birmingham and Tuscaloosa areas. Specifically, 45 children were recruited from the University of Alabama, Birmingham's, Neonatal Newborn Follow-up Clinic, and 10 were recruited from the Pediatric clinic through University Medical Center at the University of Alabama, Tuscaloosa Children had to meet the following conditions in order to be included in the study 1) be 9 to 12 years of age at the time of testing, 2) have been born weighing less than 1500g, and 3) have been born before 37 weeks gestation. Mailing flyers were sent to the families of approximately 415 eligible children in various parts of the state. Multiple follow-up phone calls were made to the 320 children for whom there was a phone number available in the database. In total approximately 85 children (20%) were successfully located out of the original 415 potential participants. Approximately 25 families declined to participate, citing travel expenses, time off work, and distance to the testing center. Five children were excluded from the study due to multiple disabilities and significant developmental delays that prevented accurate assessment using the study battery. One child's data was excluded due to a consensus between the family and the evaluator that the results obtained were not an accurate assessment of the child's current functioning due to behavioral difficulty. The overall sample characteristics are presented in Table 3.

Table 3.

Demographic Characteristics of the Sample.

Child Characteristics		
Female gender, %		57
Race/Ethnicity, %		
	Caucasian	52
	African American	36
	Hispanic or Hispanic/Caucasian	11
Gestational Age, mean(range), wks		27 (22 - 35)
Birthweight, mean(range), g		826 (385 - 1384)
Length of time in NICU, mean(range), wks		12 (4 - 28)
Multiple Gestation, %		33
Age at assessment, mean(range), yrs		10.1 (9 - 12.92)
School-age IEP, %		33
Medical and Mental Health Diagnoses, %		
	Asthma	42
	Cerebral Palsy	4
	Seizures	4
	Intellectual Disorder	4
	Learning Disorder	18
	Autism Spectrum Disorder	8
	Attention-Deficit/Hyperactivity Disorder	23
	Anxiety/Mood Disorder	8
Medications, %		
	None	62
	Asthma	9
	Seizure	2
	ADHD	22
	Other	16
Family Characteristics		
Mother married to father, %		75
Mother Education, % ^a		
	Less than High School Graduate	13
	High School Graduate	17
	Some College	28
	College Graduate	22
	Graduate or professional training	20

^a Percentage may not total 100 due to rounding

Measures

Demographic Information. A demographic form developed by researchers at the Sparks Clinics at UAB was modified for use with this population (see Appendix B). This survey

included four forms, the verification of optimal testing conditions, special education services, parent/child demographics, and child's medical history. The first form, verification of optimal testing conditions, asked questions regarding the child's health at the time of testing, whether the child requires glasses/contacts or hearing devices, and whether the child had their glasses/contacts or hearing devices with them for testing.

The special education services form contained questions regarding the services the child received divided by time period, before and after five years of age. While the goal of this measure was to obtain information indicating the amount of services a child received, many families had difficulty recalling the specific length of time and frequency of services; therefore, this information was used in analyses to indicate only whether or not a child had received services before and/or after the age of five.

The two-factor form of the Hollingshead Index score (Hollingshead, 1965) was calculated based on the occupation and education of the employed adults supporting the household. Educational scores were coded using the following scale:

- 1 = < 7 years of school,
- 2 = 7-9 years of school,
- 3 = 10-11 years of school,
- 4 = high school graduate,
- 5 = 1-3 years of college,
- 6 = 4-year college degree, and
- 7 = professional degree.

Occupational scores were coded based on the following scale:

- 1 = farm or manual service workers (e.g., janitor, farm laborer, dishwasher),

- 2 = unskilled workers (e.g., waiter, garage worker, parking attendant),
- 3 = machine operators or semi-skilled workers (e.g., bus drivers, childcare workers, housekeepers),
- 4 = smaller business owners, craftspeople, and skilled workers (e.g., carpenter, mail carrier, plumber),
- 5 = clerical or sales workers, and small-business owners (e.g., bank teller, telephone operator),
- 6 = semi-professionals (e.g., air traffic controllers, construction inspectors, sheriffs,)
- 7 = managers and minor professionals (e.g., social worker, teacher, real estate, agent),
- 8 = administrators and owners of mid-sized businesses (e.g., pilot, nurse, clergy person),
- 9 = professionals and large business owners (e.g., lawyer, civil engineer, architect).

The following formula was used to calculate the Hollingshead Index: Occupation x 5 + Education x 3. This score was calculated for all employed individuals in the house and then averaged to obtain the score for the household.

Finally, parents were asked to complete the medical history form in order to obtain information about the child's birth history as well as the child's subsequent medical and mental health history.

Global Cognitive Ability Screening. The Wechsler Abbreviated Scale of Intelligence (WASI) was administered as a brief estimate of global intellectual functioning. The WASI consists of four core subtests that are taken from the longer versions of the Wechsler Adult Intelligence Scale and the Wechsler Intelligence Scale for Children. Administration time is approximately 30 – 40 minutes and yields three scores: Verbal IQ, Performance IQ, and Full Scale IQ. The Verbal IQ is composed of the Vocabulary and Similarities subtests which assess

the child's ability to define words/concepts and to describe the similarities between two concepts. The Performance IQ is composed of Block Design and Matrix Reasoning which require children to assemble patterns using blocks or complete patterns with missing components. Internal consistency for this test ranges from .81 -.97 for children (Psychological Corporation, 1999). The WASI is also correlated with its longer counterpart, the WISC (Psychological Corporation, 1999). The scale was chosen for its brevity and overall relationship to longer more in depth measures of intelligence (WISC-IV).

Language. The Clinical Evaluation of Language Function (3rd edition; CELF-3) was administered as a measure of language function. The CELF-3 contains three subtests assessing receptive language, and three subtests measuring expressive language requiring approximately 45 minutes to administer. Some of the tasks include identifying similar words from a list, following verbal directions, creating sentences based on pictures, and finishing verbal puzzles. The CELF-3 has a high coefficient alpha of .95 for children between the ages of 9 and 11 (Semel, Wiig, & Secord, 1995).

Attention. Attention was measured in both a task format and a caregiver rating format. Caregivers were given the Conners' Parent Rating Scale – Revised Long Form (CRS-RL). The scale consists of 80 items divided into 13 subscales, including DSM-IV: ADHD-Inattentive and ADHD-Combined scales. The report takes approximately 20 minutes to complete, and provides information across multiple domains, including inattention and impulsivity. Internal reliability for the DSM-IV: inattention subscale ranges from .92-.94 (Conners, 1997). This report was chosen because of its brevity, as well as its emphasis on inattention.

The Conners' Continuous Performance Test (CPT; Conners, 2000) was administered to children to assess attention and impulsivity. The CPT requires the child to attend to and react to

stimuli presented on a computer screen. This task required approximately 15 minutes to administer. While this measure was included as an objective rating of inattention and impulsivity, technical difficulty with one of the administration computers resulted in a number of missing data points. Additionally, the measure when administered to children who were medicated with stimulants, would not have accurately reflected their attention difficulty. Thus, this measure was not included in the final analyses.

Memory. Memory was assessed using four subscales of The Children's Memory Scale (CMS). For the purpose of this study only the immediate format was administered yielding an approximate administration time of 30 minutes. The immediate verbal memory scale includes the word pairs and stories subtests. In word pairs, participants are read a list of word pairs and are instructed to provide the second word in the pair when given the first word by the examiner. On the stories subtest, participants must remember a story that is read to them. The immediate visual memory scale consists of the faces and dot locations subtests, which require the child to remember either faces or positions of dots on a grid. Overall, the CMS exhibits internal consistency ranging from .73 -.92 for various subscales in standardization samples (Cohen, 1997).

Executive Function. Executive function was assessed in two different formats, a parent rating and an objective test of executive function. The parent or caregiver was given the Behavior Rating Inventory of Executive Function (BRIEF) Parent Form. The BRIEF provides information along eight domains of executive function, inhibit (e.g. interrupts others), shift (flexibility; e.g. becomes upset with new situations), emotional control (e.g. has explosive, angry outbursts), initiate (e.g. needs to be told to begin a task even when willing), working memory (e.g. when given three things to do, remembers only the first or last), plan (e.g. does not bring

home homework, assignment sheets, materials, and so on), organize (e.g. cannot find things in room or desk), and self-monitor (e.g. makes careless errors). Internal consistency for the BRIEF ranges from .80 -.98 (Gioia & Isquith, 2004).

Three subtests from the Delis-Kaplan Executive Function System (D-KEFS) were also administered as objective measures of executive function (Delis, Kaplan, & Kramer, 2001a). The Tower Task requires children to plan the steps to recreate a pattern using a set of discs on wooden pegs. The task is designed to measure spatial planning and impulse inhibition. Internal consistency for this task ranges from .56-.61 for children ranging in age from 8-12 (Delis, Kaplan & Kramer, 2001a & 2001b). The Sorting Task requires children to group a set of cards based on similarities in their physical appearance or the concepts listed on the cards. Internal consistency for this task ranges from .62-.80 (Delis, et al., 2001a & 2001b). The Trail-Making Task measures set-shifting ability by requiring individuals to connect dots by sequentially alternating between connecting numbers and letters. Several different trials are built in to serve as comparisons in which children sequence letters and numbers separately, scan a page for target numbers, and connect a series of dots. Internal consistency for this task ranges from .57-.78 (Delis, et al., 2001a & 2001b). Administration time for these three subtests of the D-KEFS was approximately 30 minutes.

Motor. Two subscales of the Bruininks-Oseretsky Test of Motor Proficiency – Second Edition were administered to measure fine and gross motor. These subscales are comprised of the following four subtests: Fine Manual Control (Fine Motor Precision, Fine Motor Integration) and Body Coordination (Bilateral Coordination, Balance). The fine motor subtests require participants to draw, cut, color or copy shapes and patterns. The gross motor subtests require a number of coordination and balance tasks such as walking a straight line, standing on one foot,

walking on a balance beam, and synchronized finger and foot tapping. Administration time for these four subtests was approximately 20-30 minutes. Overall internal consistency for this test is .87 (Bruininks, 1978).

Procedures

Researchers scheduled a three to four hour appointment at one of the two sites (UAB or UA). Families were contacted the week before the study to confirm the appointment and a reminder with directions was mailed to their home. Parents and children were consented for the study using the procedures approved by the UA and UAB IRB committees (see Appendix A for documentation of ongoing approval and consents). Parents provided their consent and signed a medical release to allow researchers to access the child's birth records, while children provided their assent. Parents were given the demographic form, the BRIEF and the CPRS. Children accompanied the evaluator to the testing room and completed the three to four hour assessment. Measures were counterbalanced to reduce the effects of fatigue on performance and breaks were taken as necessary in order to ensure the most accurate results possible. All three examiners were blind to the medical history of each child during administration of the battery. All reasonable efforts were made to maintain participant confidentiality. All information was kept in a locked file cabinet in the principal investigators office according to procedures approved by the IRB committees at both institutions. A randomly assigned six-digit identification number was used in place of identifying information on the study protocols.

Analyses

Data Preparation. For the purpose of the current analyses, participants were categorized into the following groups: (1) None of the three medical complications, (2) IVH only, (3) BPD only, (4) PDA only, (5) IVH and BPD, (6) IVH and PDA, (7) BPD and PDA, and (8) IVH, BPD,

and PDA (See Table 4).

Table 4.

Percentage of Children Represented In Each Combination of Medical Complications.

Group	# of participants (%)	Group	# of participants (%)
No complications	12 (21.8%)		
IVH Only	3 (5.5%)	Total IVH	19/55 (34.5%)
BPD Only	7 (12.7%)		
PDA Only	11 (20%)	Total BPD	23/55 (41.8%)
IVH & BPD	5 (9.1%)		
IVH & PDA	6 (10.9%)	Total PDA	28/55 (50.9%)
BPD & PDA	6 (10.9%)		
All 3 complications	5 (9.1%)		

The Verbal and Performance IQ Standard scores from the WASI, the Core Language Standard Score from the CELF-3, the Fine Manual Control and Body Coordination Scores from the BOT, and the ADHD-Inattentive T-score from the Conners Parent Rating Scale were all included in the analyses as individual dependent variables. Correlations among the three primary measures of executive function (Trails shifting condition, sorting, and tower) on the D-KEFS were analyzed before creating a composite score for executive function (see Table 5). The immediate visual and verbal memory standard scores on the CMS were also significantly correlated ($r=.373, p=.005$); therefore, a memory composite was created using the average of these two subscales.

Table 5.

Correlations Among Executive Function Scales on the D-KEFS.

	Trails	Sorting	Tower
Trails	-	.444*	.442*
Sorting		-	.527*
Tower			-

*p-value < .001

Primary Analyses. A 2x2x2 factorial ANOVA was performed with each medical complication treated as a separate factor. In this way, the main effect of each medical complication was considered in conjunction with the averages for each of the other medical complications. For these analyses the final sample size was 19 children with IVH, 23 children with BPD, and 28 children with PDA. The primary hypotheses were assessed by examining the main effects of each condition on the dependent variables. No interaction terms were included in the model. Follow-up analyses were conducted based on the results of the primary model as well as questions regarding potential confounding factors (e.g., SES, birthweight, and early intervention services).

Results

Sample Characteristics

Means and standard deviations for the overall sample across the various cognitive domains are presented in Table 6. Means for the sample were similar to those found in other samples of premature infants (Marlow, et al., 2007; Luu, Ment, Schneider, et al., 2009; Sherlock, et al., 2005; Short, et al., 2003); however, it should be noted that there are differences between these studies and the current study in the age of the sample and the focus on specific medical complications. Most previous studies used younger children (i.e., a shorter follow-up time) and did not examine outcomes as a function of specific medical complications associated with prematurity while accounting for the overlap among medical complications in preterm infants.

Table 6.

Overall sample means in each cognitive domain.

Scale	Mean	Std Dev
Verbal IQ (WASI)	97.36 ^a	17.87
Performance IQ (WASI)	86.95 ^a	13.58
Executive Composite (DKEFS)	6.88 ^b	2.82
Core Language (CELF-3)	83.69 ^a	20.17
Fine Manual Control (BOT-2)	39.14 ^c	9.96
Body Coordination (BOT-2)	38.48 ^c	10.69
Immediate Memory Composite (CMS)	93.21 ^a	15.10
ADHD-Inattentive (CPRS)	57.83 ^d	14.92

^a Standardized general population norms indicate a mean of 100 (SD=15),

^b Standardized general population norms indicate a mean of 10 (SD=3).

^c Standardized general population norms indicate a mean 50 (SD=10),

^d T-score above 70 is clinically significant, above 60 is borderline significant.

Overall, this sample of premature infants performed similarly to full term populations in the area of Verbal IQ. One sample t-tests indicated that means in seven of the eight cognitive

domains (except Verbal IQ) were significantly different from the standardized population norms. Children in the current sample were almost one standard deviation below the norm in the area of Performance IQ indicating a need to analyze the two domains within IQ separately. Additionally, they were at least one standard deviation below the mean in the areas of language skills, fine and gross motor, and executive function. The discrepancy between Verbal IQ and Performance IQ is consistent with other studies examining the long-term sequelae of prematurity that found that Verbal IQ was approximately average while Performance IQ was approximately 10-15 below the mean (Short, et al., 2003; Lewis, et al., 2002). Similar to the present results, Lewis and colleagues (2002) also noted fine and gross motor deficits in their study at 8 years of age. The current language measures are consistent with other studies that indicated language standard scores for preterm children were approximately one standard deviation below the mean (Luu, Vohr, Schneider, et al., 2009; Lewis et al., 2002). The executive function discrepancy between the current sample and the standardized norm are also consistent with Sherlock et al., (2007) who found that preterm children who did not experience severe IVH were 1 – 1 ½ SD below the mean on measures of executive function. Taken together, this appears to be a representative group of children born prematurely with similar complications to those reported in the literature; therefore, allowing for the examination of the differential effects of the three overlapping medical complications within a typical group of children born prematurely.

Primary Analyses

In order to address the primary hypotheses, a 2x2x2 factorial ANOVA was performed with IVH (presence or absence), BPD (presence or absence), and PDA (presence or absence) as the factors predicting each of the eight cognitive outcome measures. Tests of the assumptions of ANOVA (normality, linearity, and homoscedasticity) indicated that the Children's Memory Scale

score violated the assumption of homogeneity of variance. Therefore, a more conservative α of .01 was used to evaluate any relationships between memory and the three independent factors. Partial-eta squared and eta-squared were evaluated using the following guidelines to indicate small, medium, and large effect sizes, respectively: .0099, .0588, .1379 (for review see Richardson, 2011).

Hypothesis 1: IVH main effects. The ANOVA results indicated no significant main effect of IVH on any of the dependent cognitive outcome measures (see Table 7). Partial-eta squared values indicated medium effect sizes in the areas of Verbal IQ, executive function, and memory. An examination of estimated marginal means of Verbal IQ indicated that, while both groups are functioning in the average range, the group who experienced IVH at birth is over eight points below the group with no IVH (see Table 8). Similarly, children with a history of IVH scored seven points lower than children without IVH on the immediate memory tasks. The children with IVH are almost one standard deviation below the standardized mean for the immediate memory scale, whereas children who did not suffer from a brain bleed at birth are well within the average range. Finally, executive function for children with a history of IVH was one and a half standard deviations below the standardized mean. While both groups experienced difficulty in this area, the children in the IVH group were half a standard deviation below the children without IVH. Overall, IVH may be associated with moderate impairments in Verbal IQ, executive function, and memory skills.

Table 7

Main Effect of IVH on Cognitive Outcome Measures.

	F-statistic	<i>p</i> -value	η_p^2	Observed Power
Verbal IQ	<i>F</i>(1,50) = 3.37	.07	.063*	.436
Performance IQ	<i>F</i> (1,50) = 1.26	.27	.025	.196
Executive Function	<i>F</i>(1,51) = 3.56	.07	.065*	.457
Fine Motor	<i>F</i> (1,51) = 2.39	.13	.045	.329
Gross Motor	<i>F</i> (1,51) = 0.91	.35	.017	.154
Memory	<i>F</i>(1,51) = 3.17	.08	.058*	.415
Language	<i>F</i> (1,50) = 1.11	.30	.022	.179
Inattention	<i>F</i> (1,49) = 0.03	.86	.001	.054

* indicates a medium effect size

Table 8.

Estimated Marginal Means Associated With IVH.

	IVH	
	With	Without
Verbal IQ ^a	91.53	100.14
Performance IQ ^a	84.08	87.89
Executive function ^b	5.89	7.23
Fine motor ^c	36.27	40.28
Gross Motor ^c	36.10	38.84
Memory ^a	88.25	95.29
Core Language ^a	78.76	84.09
Inattention ^d	58.23	57.44

^a Standardized general population norms indicate a mean of 100 (SD=15),

^b Standardized general population norms indicate a mean of 10 (SD=3).

^c Standardized general population norms indicate a mean 50 (SD=10),

^d T-score above 70 is clinically significant, above 60 is borderline significant.

Hypothesis 2: BPD main effects. The results of the 2x2x2 ANOVA analyses indicated significant main effects of BPD on gross motor and core language standard scores (see Table 9). Both of these main effects were associated with medium effect sizes. Overall, children with a history of BPD scored approximately seven to eight points lower on the gross motor scale than did children without a history of BPD. Similarly, children with a history of BPD scored approximately 12 points (almost one standard deviation) lower than children without a history of

BPD on the Core Language Standard score (see Table 10). No significant main effects were indicated for the remaining six cognitive domains. Overall, BPD appears to be associated with moderate impairments in gross motor and language functioning.

Table 9.

Main Effect of BPD on Cognitive Outcome Measures.

	F-statistic	p-value	η_p^2	Observed Power
Verbal IQ	F(1,50) = 1.93	.17	.037	.276
Performance IQ	F(1,50) = 2.18	.15	.042	.304
Executive Function	F(1,51) = 2.03	.16	.038	.288
Fine Motor	F(1,51) = 1.25	.27	.024	.195
Gross Motor	F(1,51) = 7.27	.009	.125*	.754
Memory	F(1,51) = 0.81	.37	.016	.143
Language	F(1,50) = 5.82	.02	.104*	.657
Inattention	F(1,49) = 1.42	.24	.028	.215

* indicates a medium effect size

Table 10.

Estimated Marginal Means Associated With BPD

	BPD	
	With	Without
Verbal IQ ^a	92.70	98.97
Performance IQ ^a	83.58	88.39
Executive function ^b	6.07	7.04
Fine motor ^c	36.89	39.66
Gross Motor ^c	33.75	41.20
Memory ^a	90.06	93.48
Core Language ^a	75.53	87.33
Inattention ^d	60.31	55.35

^a Standardized general population norms indicate a mean of 100 (SD=15),

^b Standardized general population norms indicate a mean of 10 (SD=3).

^c Standardized general population norms indicate a mean 50 (SD=10),

^d T-score above 70 is clinically significant, above 60 is borderline significant.

Hypothesis 3: PDA main effects. The ANOVA results indicated significant main effects of PDA on Verbal IQ, Performance IQ, executive function, fine motor skills, memory skills, and language (see Table 11). Table 12 shows the estimated marginal means for each of the eight cognitive domains. Surprisingly, across all six domains, children with a history of PDA performed *better* than children without a history of PDA. These results indicated large effect sizes across all six domains. PDA was associated with a Verbal IQ that was 14 points higher than for children with a history of PDA. On the Performance IQ subscale, children with a history of PDA fell in the average range while children without a history of PDA averaged 14 points lower and fell outside of the average range. While both groups experienced difficulty in the area of executive function, children with a history of PDA were still within one standard deviation of the standardized mean, while children with no history of PDA fell outside of the average range. The same was true in the area of fine motor skills, in which children with a history of PDA outperformed children without a history of PDA by approximately one standard deviation. With regard to memory skills, scores for children with a history of PDA were comparable to those in typical standardized populations, while children without a history of PDA were one standard deviation below the mean. Finally, language skills for children without PDA were almost two standard deviations below the mean whereas children with a history of PDA fell at the low end of the average range. Overall, PDA was associated with differential effects in the areas of Verbal IQ, Performance IQ, executive function, fine motor, memory, and language skills indicating higher scores for children who experienced the defect.

Table 11.

Main Effect of PDA on Cognitive Outcome Measures

	F-statistic	p-value	η_p^2	Observed Power
Verbal IQ	<i>F(1,50) = 10.09</i>	<i>.003</i>	<i>.168**</i>	<i>.876</i>
Performance IQ	<i>F(1,50) = 18.94</i>	<i><.001</i>	<i>.275**</i>	<i>.989</i>
Executive Function	<i>F(1,51) = 15.57</i>	<i><.001</i>	<i>.234**</i>	<i>.972</i>
Fine Motor	<i>F(1,51) = 13.01</i>	<i>.001</i>	<i>.203**</i>	<i>.943</i>
Gross Motor	F(1,51) = 2.79	.10	.052	.374
Memory^a	<i>F(1,51) = 12.11</i>	<i>.001</i>	<i>.192**</i>	<i>.927</i>
Language	<i>F(1,50) = 14.77</i>	<i><.001</i>	<i>.228**</i>	<i>.965</i>
Inattention	F(1,49) = 0.02	.90	<.001	.052

^a α of .01 required to reject null hypothesis.

**indicates a large effect size

Table 12.

Estimated Marginal Means Associated With PDA

	PDA	
	With	Without
Verbal IQ ^a	102.88	88.79
Performance IQ ^a	92.98	78.99
Executive function ^b	7.87	5.24
Fine motor ^c	42.67	33.88
Gross Motor ^c	39.73	35.21
Memory ^a	98.24	85.30
Core Language ^a	90.56	72.30
Inattention ^d	57.58	58.08

^a Standardized general population norms indicate a mean of 100 (SD=15),

^b Standardized general population norms indicate a mean of 10 (SD=3).

^c Standardized general population norms indicate a mean 50 (SD=10),

^d T-score above 70 is clinically significant, above 60 is borderline significant.

Secondary Analyses

IVH follow-up. A one-way ANOVA was conducted to examine group differences among the 19 infants who experienced IVH based on the grade of the bleed (Grade I = 9 subjects, Grade II = 6 subjects, Grade III = 1 subject, Grade IV = 3 subjects). No comparisons can be made regarding those who experienced a Grade III bleed due to the limited number of

children in the group. Further, the one child in this category was an outlier among the children with IVH, and therefore, was not included in the ANOVA. No significant effect was detected for grade of IVH on any of the cognitive outcome measures (see Table 13). While there were no significant main effects detected, analyses indicated a large effect size of the grade of IVH on gross motor skills and medium effect sizes between grade of IVH and Verbal IQ, fine motor, language, and attention. The estimated marginal means for the eight cognitive domains are located in Table 14. Overall, the greatest decline in functioning occurred between Grade I and Grade II. In the area of Verbal IQ, children with a history of Grade I IVH obtained an average score, while children with a Grade II or higher scored at least 10 points lower. There was a similar trend with regard to fine motor skills, as children with a history of Grade I IVH were at the lower end of the average range, while children with a Grade II bleed or higher scored eight points lower and outside of the average range. Language trends were similar except that the decline from Grade II to Grade IV bleeds was more dramatic. Children who experienced a Grade I bleed scored seven points higher than children who experienced a Grade II bleed. Those who experienced a Grade II bleed scored eight points higher than those who experienced a Grade IV bleed. Finally, children who experienced Grade II and IV IVH obtained average parent ratings of inattention in the borderline significant range, whereas children with a history of a Grade I bleed obtained an average rating outside of the range of concern. Overall, there is evidence to suggest that the increasing severity of IVH may play an important role in determining outcomes within the Verbal IQ, motor, language, and attention domains; however, it should be noted that sample sizes across the three groups included in the analyses are low, and therefore, these results should be interpreted cautiously.

Table 13.

Main Effect of Grade of IVH on Cognitive Outcome Measures

	F-statistic	p-value	η^2
Verbal IQ	<i>F(2,15) = 0.75</i>	.49	.091*
Performance IQ	F(2,15) = 0.36	.70	.046
Executive Function	F(2,15) = 0.24	.79	.030
Fine Motor	<i>F(2,15) = 0.87</i>	.44	.104*
Gross Motor	<i>F(2,15) = 1.60</i>	.24	.175**
Memory	F(2,15) = 0.20	.83	.025
Language	<i>F(2,15) = 0.52</i>	.61	.064*
Inattention	<i>F(2,15) = 0.77</i>	.48	.093*

* indicates a medium effect size

**indicates a large effect size

Table 14.

Estimated Marginal Means Associated With Grade Of IVH

	IVH		
	Grade I	Grade II	Grade IV
Verbal IQ ^a	100.33	89.67	87.00
Performance IQ ^a	89.78	83.67	81.33
Executive Function ^b	6.89	6.00	5.44
Fine Motor ^c	41.44	34.00	33.67
Gross Motor ^c	42.11	31.83	31.67
Memory ^a	91.67	93.17	84.67
Language ^a	86.11	79.67	71.67
Attention ^d	54.67	61.33	67.67

^a Standardized general population norms indicate a mean of 100 (SD=15),^b Standardized general population norms indicate a mean of 10 (SD=3).^c Standardized general population norms indicate a mean 50 (SD=10),^d T-score above 70 is clinically significant, above 60 is borderline significant.

BPD follow-up. Two linear regressions were conducted to further explore the moderate effect of BPD on gross motor and core language skills in order to evaluate the relationship between these two variables and the severity of BPD as measured by the length of time on supplemental oxygen. The length of time on supplemental oxygen significantly predicted gross motor standard score, $\beta = -.433$, $t(53) = -3.50$, $p = .001$ and explained a significant portion of the

variance, $R^2=.19$, $F(1,53)=12.24$, $p <.01$ across the entire sample of preterm infants. In addition, the length of time on supplemental significantly predicted overall core language standard score, $\beta=-.324$, $t(52)=-2.466$, $p=.017$, and explained a significant proportion of the variance, $R^2=.105$, $F(1,52)=6.079$, $p=.017$. The longer supplemental oxygen was required the greater the difficulty with gross motor and language skills.

PDA follow-up. Due to the significant findings indicating a protective benefit rather than impairment associated with PDA, further analyses were conducted to evaluate the nature of this benefit in the presence and absence of additional medical complications, and to verify that this result was not an artifact of PDA being the least severe of the three conditions. Participants were categorized into the following four groups based on the presence or absence of PDA and the presence or absence of other medical complications: 1) None of the three medical complications (N=12), 2) PDA only (N=10), 3) IVH and/or BPD with no PDA (N=15), 4) PDA plus one or more additional complications (N=17). A one-way between subjects ANOVA was performed examining the predictive ability of group membership on the cognitive outcomes (see Table 15). There was a significant effect found for Verbal IQ, Performance IQ, executive function, fine motor, immediate memory, and core language. No significant effect was found with regard to group membership and gross motor or parent ratings of inattention; however, there was a medium effect size indicated for gross motor skills that is consistent with the pattern of children with PDA experiencing better long-term outcomes. Overall, scores across the six measures that were found to be significantly related to PDA (Verbal IQ, Performance IQ, executive function, fine motor skills, memory, and core language) were higher for children who experienced PDA regardless of the presence or absence of additional complications.

Table 15.

Main Effects for PDA Follow-Up Analyses

	F-statistic	p-value	η^2
Verbal IQ	<i>F(3,50) = 4.186</i>	.01	.201**
Performance IQ	<i>F(3,50) = 6.615</i>	.001	.284**
Executive Function	<i>F(3,51) = 5.099</i>	.004	.231**
Fine Motor	<i>F(3,51) = 3.972</i>	.01	.189**
Gross Motor	F(3,51) = 1.928	.14	.102
Memory	<i>F(3,51) = 4.437</i>	.008	.207**
Language	<i>F(3,50) = 5.886</i>	.002	.261**
Inattention	F(3,49) = 0.136	.94	.008

**indicates a large effect size

Table 16.

Post-Hoc Analyses Comparing Children With and Without PDA in the Presence or Absence of Other Complications

	Groups*		Mean Difference	p-value	
				Tukey's HSD	LSD
Verbal IQ	0	1	-5.95	.84	.41
	2	3	-19.19	.01	.009
Performance IQ	0	1	-9.42	.27	.07
	2	3	-17.04	.001	<.001
Executive Function	0	1	-2.53	.10	.02
	2	3	-2.65	.03	.005
Fine Motor	0	1	-7.37	.24	.06
	2	3	-9.48	.03	.006
Memory	0	1	-7.92	.53	.18
	2	3	-16.16	.01	.002
Core Language	0	1	-14.65	.22	.057
	2	3	-21.89	.008	.001

* Note. 0 = children with no BPD, IVH, or PDA, 1 = children with only PDA, 2 = children with BPD and/or IVH without PDA, 3 = children with BPD and/or IVH and PDA

^a Standardized general population norms indicate a mean of 100 (SD=15),

^b Standardized general population norms indicate a mean of 10 (SD=3).

^c Standardized general population norms indicate a mean 50 (SD=10),

^d T-score above 70 is clinically significant, above 60 is borderline significant.

LSD post-hoc analyses indicated that for children who experienced BPD and/or IVH, Verbal IQ, Performance IQ, executive function, fine motor, core language, and memory outcomes were significantly improved if they also experienced PDA (see Table). Comparisons of children who experienced none of the targeted medical complications and only PDA indicated that executive function outcomes were significantly improved if children experienced PDA as opposed to none of the three complications. Figures 1 through 3 show graphs of the means based on group membership for Performance IQ, executive function, and fine motor skills. The same patterns seen in Figures 1-3 were also evident in the graphs of Verbal IQ, memory, and language skills. Table 17 compares the means of children who experienced no additional complications (i.e. none of three medical complications vs. PDA only) and Table 18 compares the means for children who experienced BPD and or IVH with or without PDA (i.e., BPD/IVH in the absence of PDA, BPD/IVH in conjunction with PDA).

Table 17.

Means of Children With or Without PDA in the Absence of BPD or IVH.

	PDA	
	Without (n = 12)	With (n = 10)
Verbal IQ	97.75	103.70
Performance IQ	83.58	93.00
Executive Function *	6.11	8.64
Fine Motor	36.00	43.36
Gross Motor	38.50	44.36
Memory	91.58	99.50
Core Language	81.17	95.82
Inattention	56.45	58.73

* difference is statistically significant $p < .05$

^a Standardized general population norms indicate a mean of 100 (SD=15),

^b Standardized general population norms indicate a mean of 10 (SD=3),

^c Standardized general population norms indicate a mean 50 (SD=10),

^d T-score above 70 is clinically significant, above 60 is borderline significant.

Table 18.

Means of Children With or Without PDA in the Presence of BPD and/or IVH

	PDA	
	Without (n = 15)	With (n = 17)
Verbal IQ **	85.40	104.59
Performance IQ **	77.20	94.24
Executive Function **	5.13	7.78
Fine Motor **	33.93	43.41
Gross Motor	34.33	38.53
Memory **	83.20	99.26
Core Language **	68.29	90.18
Inattention	58.57	55.82

** difference is statistically significant $p < .01$

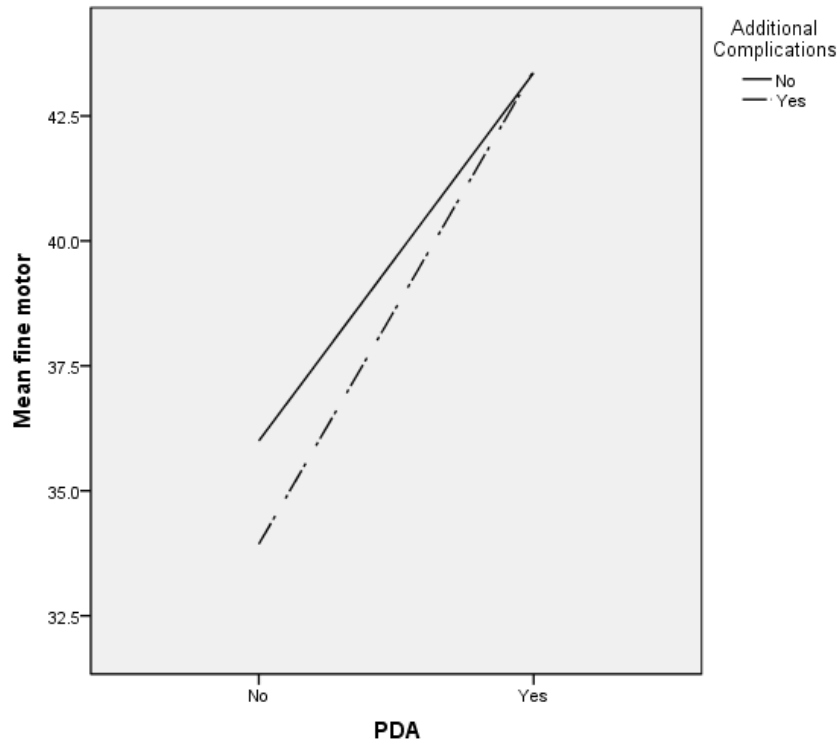


Figure 1. Means of Fine Motor Skills Based on the Presence or Absence of PDA and the Presence or Absence of the Other Two Complications

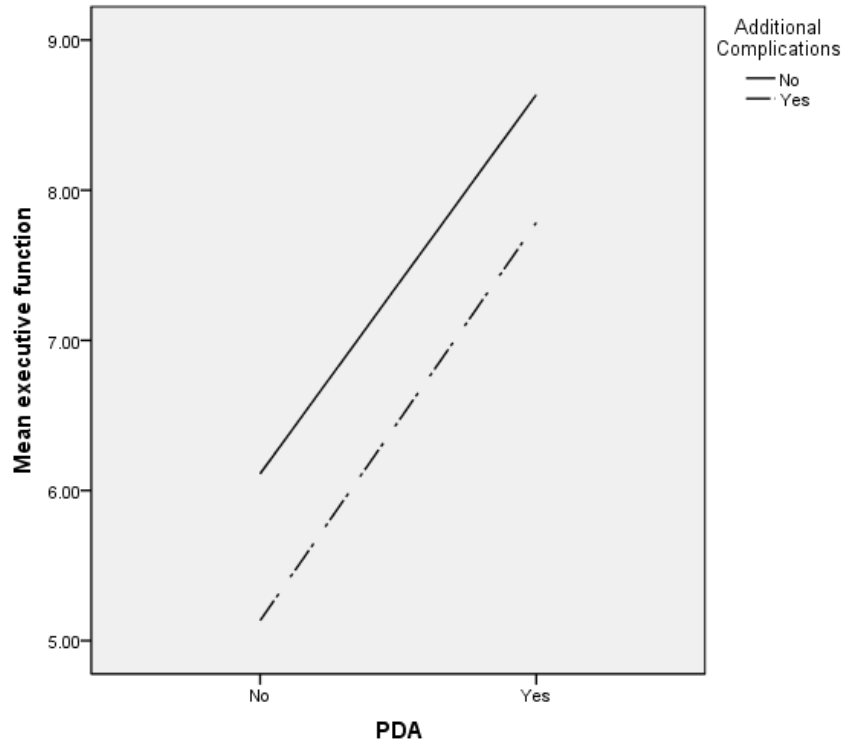


Figure 2. Means of Executive Function Based on the Presence or Absence of PDA and the Presence or Absence of the Other Two Complications.

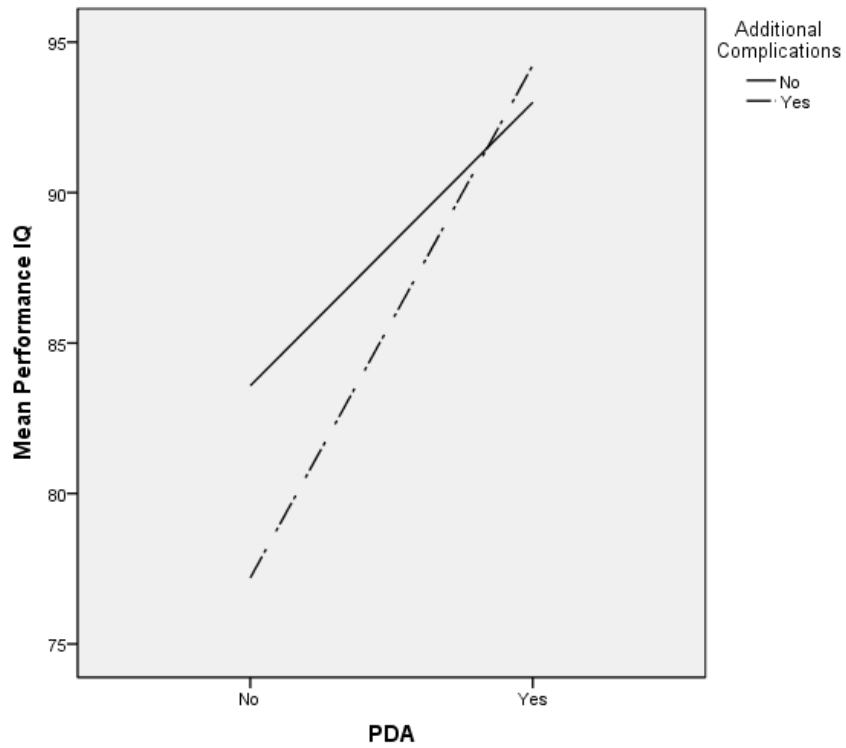


Figure 3. Means of Performance IQ Based on the Presence or Absence of PDA and the Presence or Absence of the Other Two Complications.

Birthweight and SES as covariates. Given the literature indicating that birthweight and SES are important predictors of outcome in premature infants, regression analyses were performed to examine the relationship between birthweight and each of the eight cognitive outcomes, as well as SES and each of the eight cognitive outcomes (see Table 19 and Table 20).

Table 19.

Regression Results Predicting Cognitive Outcomes from Birthweight

	β	<i>t</i> -statistic	R ²	F-statistic	<i>p</i> -value
Verbal IQ	.369	<i>t</i>(52)=2.86	.136	<i>F</i>(1,52)=8.19	.006
Performance IQ	.209	<i>t</i> (52)=1.54	.044	<i>F</i> (1,52)=2.37	.13
Executive Function	.251	<i>t</i> (53)=1.88	.063	<i>F</i> (1,53)=3.55	.07
Fine motor	.293	<i>t</i>(53)=2.23	.086	<i>F</i>(1,53)=4.99	.03
Gross Motor	.339	<i>t</i>(53)=2.62	.115	<i>F</i>(1,53)=6.88	.01
Memory	.264	<i>t</i>(53)=2.00	.070	<i>F</i>(1,53)=3.99	.05
Core language	.330	<i>t</i>(52)=2.52	.109	<i>F</i>(1,52)=6.33	.02
Inattention	-.083	<i>t</i> (51)=-.592	.007	<i>F</i> (1,52)=0.35	.56

Table 20.

Regression Results Predicting Cognitive Outcomes from SES

	β	<i>t</i> -statistic	R ²	F-statistic	<i>p</i> -value
Verbal IQ	.279	<i>t</i>(50)=2.06	.078	<i>F</i>(1,50)=1.24	.05
Performance IQ	.245	<i>t</i> (50)=1.79	.060	<i>F</i> (1,50)=3.20	.08
Executive Function	.335	<i>t</i>(51)=2.54	.112	<i>F</i>(1,51)=6.44	.01
Fine motor	.272	<i>t</i>(51)=2.02	.074	<i>F</i>(1,51)=4.06	.05
Gross Motor	.125	<i>t</i> (51)=0.90	.016	<i>F</i> (1,51)=0.81	.37
Memory	.294	<i>t</i>(51)=2.20	.087	<i>F</i>(1,51)=4.84	.03
Core language	.335	<i>t</i>(50)=2.51	.112	<i>F</i>(1,50)=6.30	.02
Inattention	-.114	<i>t</i> (49)=-0.80	.013	<i>F</i> (1,49)=0.64	.43

Overall, Verbal IQ, fine and gross motor skills, memory, and language were significantly

predicted by birthweight such that as birthweight increased, performance across domains increased. Birthweight accounted for 13.6% of the variance in Verbal IQ, 8.6% of the variance in fine motor skills, 11.5% of the variance in gross motor skills, 7% of the variance in memory, and 10.9% of the variance in core language skills. Additionally, SES significantly predicted outcomes in the domains of Verbal IQ, executive function, fine motor, memory, and language. As SES increases so does performance each of the aforementioned domains. Verbal IQ accounted for 7.8% of the variance in Verbal IQ, 11.2% of the variance in executive function, 7.4% of the variance in fine motor skills, 8.7% of the variance in memory skills, and 11.2% of the variance in language functioning. Given the significant predictive ability of SES and birthweight demonstrated in the previous regression analyses as well as the extant literature, the primary model was reevaluated including both predictors as covariates resulting in a 2x2x2 factorial ANCOVA. Given the low sample size and reduced power for this analysis, reports of the results will focus on primarily on effects sizes and trends.

IVH main effects. The inclusion of birthweight and SES significantly changed the pattern of results for IVH. The trends indicating a relationship between IVH and Verbal IQ, IVH and executive function, and IVH and memory no longer exist once birthweight and SES are included as covariates, indicating that the trends and medium effect sizes observed in the primary model may be more accurately attributed to some combination of birthweight and SES (see Table 21). The fact that there are no medium or large effects remaining, supports the interpretation that previous findings regarding IVH may have been a function of birthweight and/or SES.

Table 21

Main Effect of IVH on Cognitive Outcome Measures (Covariates = Birthweight and SES).

	F-statistic	<i>p</i> -value	η_p^2	Observed Power
Verbal IQ	F(1,46) = 0.92	.34	.020	.155
Performance IQ	F(1,46) = 0.28	.60	.006	.082
Executive Function	F(1,47) = 1.25	.27	.026	.195
Fine Motor	F(1,47) = 0.83	.37	.017	.145
Gross Motor	F(1,47) = 0.25	.62	.005	.078
Memory	F(1,47) = 0.93	.34	.019	.157
Language	F(1,46) = 0.03	.86	.001	.054
Inattention	F(1,45) = 0.01	.93	<.001	.051

BPD main effects. Including SES and birthweight as covariates accounted for some of the variance in the original model, but did not change the overall pattern of the results. BPD continued to negatively impact outcomes in the areas of gross motor and language function(see Table 22). The main effect of gross motor remained significant. Children with a history of BPD continue to score lower on measures of gross motor skills than children with no history of BPD even when controlling for SES and birthweight. While BPD was no longer significantly related to core language scores, the analyses continue to indicate a medium effect. Children with a history of BPD tended to score lower on measures of core language skills than those who did not experience BPD at birth. Overall, both language and gross motor outcomes appear to be negatively affected by BPD, even when controlling for birthweight and SES.

Table 22.

Main Effect of BPD on Cognitive Outcome Measures (Covariates = Birthweight and SES).

	F-statistic	<i>p</i> -value	η_p^2	Observed Power
Verbal IQ	F(1,46) = 0.34	.56	.007	.088
Performance IQ	F(1,46) = 1.55	.22	.033	.230
Executive Function	F(1,47) = 1.14	.29	.024	.182
Fine Motor	F(1,47) = 0.18	.68	.004	.069
Gross Motor	F(1,47) = 3.98	.05	.078*	.498
Memory	F(1,47) = 0.22	.64	.005	.075
Language	F(1,46) = 3.43	.07	.069*	.441
Inattention	F(1,45) = 0.67	.42	.015	.126

*indicates a medium effect size

PDA main effects. The inclusion of birthweight and SES did account for some of the variance attributed to PDA in the model, but did not change the pattern of the protective effects of PDA on cognitive outcomes. The main effect of PDA on Performance IQ, executive function, fine motor skills, and core language skills remained significant even after including the covariates (see Table 23). While the main effects of PDA on both Verbal IQ and memory were no longer significant after accounting for the variance associated with birthweight and SES, a trend indicating medium effect sizes remained for both. Overall, PDA appears to be related to better outcomes within a preterm infant sample in the areas of Verbal IQ, Performance IQ, executive function, fine motor, memory, and core language skills independent of the effects of birthweight and SES.

Table 23.

Main Effect of PDA on Cognitive Outcome Measures (Covariates = Birthweight and SES).

	F-statistic	p-value	η_p^2	Observed Power
Verbal IQ	F(1,46) = 2.90	.10	.059	.385
Performance IQ	F(1,46) = 9.61	.003	.173**	.859
Executive Function	F(1,47) = 6.06	.02	.114*	.674
Fine Motor	F(1,47) = 5.41	.02	.103*	.624
Gross Motor	F(1,47) = 0.57	.46	.012	.114
Memory	F(1,47) = 4.19	.05^a	.082*	.518
Language	F(1,46) = 5.26	.03	.103*	.613
Inattention	F(1,45) = 0.001	.98	<.001	.050

^a α of .01 required to reject null hypothesis.

*indicates a medium effect size

**indicates a large effect size

Services prior to 5. Within the current sample, 52.8% of children received early intervention services prior to the age of 5. Given that the goal of early intervention services is to improve later outcomes, the original primary 2x2x2x2 factorial ANOVA was repeated to include services prior to the age of 5 as well as interactions between services before 5 and the three medical complications. The only significant effect detected was the main effect of services prior to 5 years of age on fine motor skills, $F(1,46)=6.46$, $p=.01$, $\eta_p^2=.123$, Observed Power = .702. Children who participated in Early Intervention Services scored lower on measures of fine motor skill than did those who did not receive services prior to the age of 5 (43.17 vs. 36.26). None of the interactions were significant; however, there was a medium effect size indicated for the interaction between BPD and services under 5 on Verbal IQ, $F(1,45)= 3.27$, $p = .08$, $\eta_p^2=.068$, Observed Power = .425. Children with a history of BPD who participated in early intervention had lower scores than children who did not participate in early intervention (89.17 vs. 102.54), whereas in children without a history of BPD there was no difference in the scores of children who did and those who did not receive early intervention (102.75 vs. 97.54). Similarly, there was a medium effect size indicated in the interaction between participation in services prior to

the age of 5 and BPD with respect to fine motor skills, $F(1,45)=3.28$, $p=.08$, $\eta_p^2=.066$, Observed Power = .426. If children did not have a history of BPD there was very little difference between those who participated in early intervention and those who did not (38.52 vs. 40.60); however, for children with a history of BPD, early intervention services were associated with slightly lower scores (34.00 vs. 45.74). The results of the current analysis should be interpreted cautiously with regard to the interaction between IVH and services prior to the age of 5. While there were children who experienced IVH at each level of early intervention services, there were no children who only experienced IVH that did not also receive early intervention services.

Discussion

Previous studies have consistently demonstrated that preterm birth is associated with impairments in global IQ, executive function, language, fine and gross motor, memory, and attention skills (Fawer, et al., 1995; Saigal, et al., 2000); however, few studies have examined these deficits to determine if specific medical complications differentially effect the cognitive outcomes associated with preterm birth. Overall, the current study indicates that premature infants at 9-12 years of age are within the average range in the areas of Verbal IQ, Performance IQ, and immediate memory. This sample was slightly below average in the areas of fine and gross motor, core language, and executive function; however, these skills were still within 1 ½ SD of the mean. While there was no term comparison group, the current group was consistent with previous studies regarding the long-term outcomes of premature infants (Lewis et al., 2002, Short et al., 2003, Sherlock et al., 2007, Luu, Ment, Schneider, et al., 2009) suggesting that there are persistent effects of prematurity on neuropsychological functioning. The primary goal of the current study was to examine the independent effects of each of three common medical complications, IVH, BPD, and PDA, on the cognitive outcomes of preterm infants. The study was unique in the fact that it controlled for the overlap among these diagnoses while also controlling for other factors that have been associated with outcomes in preterm infants, specifically SES and birthweight. In addition, the targeted sample was older than those typically assessed in premature infant follow-up studies. The results of the current study confirmed that each of these three complications is associated with differential long-term outcomes in preterm infants.

Predicted impairments associated with the presence of IVH were not seen in the current study. Impairments were predicted in the areas of global IQ, language, motor skills, executive function, attention, and memory. In the initial model IVH was associated with moderate impairments in Verbal IQ, executive function, and memory; however, these effects did not remain after controlling for birthweight and SES. The differences in comparison groups (e.g., other preterm infants vs. full term infants) within the existing literature may partially explain the discrepancy between the hypothesized impairments and the current results. It should also be noted that the current sample is composed of relatively mild forms of IVH. Of the 19 children who experienced IVH, 15 of them fell in the mild category in which bleeding does not directly affect surrounding brain tissues. While the number of children who experienced severe bleeds in the current study was low, the percentages of children at each level was comparable to those found by Sherlock et al., (2005). The findings associated with IVH in the current study are also consistent with other studies that have indicated that mild IVH has very little long-term effect in preterm infants (Sherlock, et al., 2005; McGrath & Sullivan, 2002). It is possible that the children who experience IVH at birth are no more impaired than other preterm children at 9-12 years of age, which may indicate a better prognosis for this population than previously anticipated by studies conducted with younger children. Additional research is needed in this area to clarify whether impairments typically attributed to IVH, may be better explained by other perinatal (e.g., birthweight, severe IVH only), or environmental factors (e.g., SES). These studies should also examine whether the unique effect of IVH within a preterm infant sample may dissipate over time such that children with a history of mild IVH no longer demonstrate any greater cognitive difficulty than other preterm infants.

Findings associated with BPD confirmed a trend indicating that BPD is differentially

related to impairments in gross motor and language skills, even after controlling for SES and birthweight, confirming the link that has consistently been found in the research (Smith et al., 1999; Lewis, et al., 2002; Farel, et al., 1998, McGrath & Sullivan, 2002). The hypothesized effects of BPD on global IQ, memory, and executive function were not found in the current study. Research with regard to memory, attention and executive function has been limited; however, the current study would suggest that BPD does not uniquely impact these areas and that deficits in these areas may be attributed to more global factors such as SES and birthweight. A consistent link has been shown in previous studies between BPD and global cognitive functioning; however, one study suggested that BPD was no more predictive of IQ than low birthweight itself (Hughes, et al., 1999). This was supported in the current analysis as birthweight was the single best predictor of Verbal IQ. An additional explanation for the discrepancy between the hypothesized impairments and the current findings may be the definition of BPD used across the various studies (supplemental oxygen at 28 days of life vs. gestational age equivalent of 36 weeks). The definition of BPD chosen for the current study was based on the definition used by both collaborating clinics. However, more severe impairments would likely be associated with the more stringent definition of BPD. The current study demonstrated that increasing length of time on oxygen was associated with increased impairments in gross motor skills and language function. It is also possible that the remaining differences that were suggested in previous studies have already dissipated by the time children reach the age of the current study.

The most surprising results of the current study were the protective effects of PDA on Performance IQ, fine motor, executive function, and memory. Further analyses indicated that the pattern of the apparent benefit of PDA remained consistent regardless of the presence or absence

of the other two medical complications. In the case of performance IQ and fine motor skills, children who had PDA and one or both of the other medical complications outperformed children born prematurely without a history of any of the three complications examined in the current study. These analyses indicated that children with a history of PDA performed better than any other group examined in the current sample and were closer to the standardized population means (i.e., full-term infants) than the other children in the study.

One possible explanation for the differential protective effects for children with a history of PDA is the treatment administered to address the PDA. Non-steroidal anti-inflammatory drugs, specifically indomethacin and more recently ibuprofen, are the typical treatment for PDA. Recent research in newborn rat models indicates a possible protective benefit of indomethacin and other NSAIDS in that they may protect brain tissue from damage resulting from lack of oxygen (Taskin, Ozcan, Canacankatan, Satar, Yapicioglu, & Erdogan, 2009). Additional studies have been conducted with NSAIDS such as indomethacin that have shown that they may slow the cognitive decline associated with dementia (Rogers, et al., 1993; Stephan, Laroche & Davis 2003; Townsend & Pratico, 2005). Rogers et al., (1993) conducted a placebo-controlled, double blind study and found that indomethacin administration slowed the decline of patients with mild to moderate Alzheimer's Disease when compared to matched controls. Additional studies have suggested that administration prior to exposure may reduce after the negative effects of alcohol exposure (Elmer & George, 1995), and methamphetamine (Goncalves, et al., 2010). Specifically, Elmer and George (1995) found that rats who were administered indomethacin prior to being exposed to alcohol regained the reflex to right themselves faster than those who were not administered indomethacin.

Indomethacin studies specifically related to preterm infants have been limited to the

evaluation of the drug as a prophylactic measure to prevent IVH. Given that one potential trigger for IVH is an increase in cerebral blood flow or pressure, the administration of IVH, which reduces this flow has been hypothesized to result in a reduction of the incidence and severity of IVH. Ment and colleagues (2000) conducted one such randomized controlled trial of low-dose indomethacin as a prophylactic measure to prevent or reduce the severity of IVH in preterm infants. They found higher rates of intellectual disabilities in the placebo group when compared to those in the control. There was no significant difference at 4 ½ years of age between the rates of delays in Verbal IQ between then indomethacin and placebo groups; however, rates of delays among children in the indomethacin group tended to be lower than those in the placebo group on measures of Performance IQ. It should be noted that these effects were no longer present at subsequent follow-up at age 12 (Luu, Ment, Schneider, et al., 2009). There was also an initial benefit of indomethacin for males in the study, in that males who received indomethacin tended to score slightly higher than their preterm peers on measures of receptive language at 2 years of age; however, the rate of language development did not change (Luu, Vohr, Schneider, et al., 2009). It has recently become more common to administer Indomethacin or Ibuprofen as a prophylactic measure to preterm infants to reduce the risk for and severity of IVH. Luu, Ment, Schneider, et al., (2009) is the only study thus far to examine the long-term cognitive outcomes of children treated prophylactically with indomethacin. While no significant long-term benefits were identified, it should be noted that the study protocol focused on “low-dose” administration of indomethacin, which may be lower than the therapeutic dose required to treat PDA. The current study indicates that some aspect of PDA or its treatment is a protective factor across many cognitive outcomes. Further study will be required to determine if indomethacin might be that protective factor. If indomethacin does provide some protective benefit, the dosage

necessary to achieve the desired result will need to be carefully evaluated to minimize the risk of the more common gastrointestinal side effects of the indomethacin.

The current study also examined the relationship between early intervention services and medical complications as they relate to later cognitive outcomes. There was no difference in children who received services and those who did not in the areas of Verbal IQ, Performance IQ, executive function, language, memory, or gross motor skills. There was, however, a significant difference between children who participated in intervention services prior to five years of age and those who did not in the area of fine motor skills. Children who required these early services tended to score lower than children who did not. This is consistent with the requirements to qualify for Early Intervention services. Children identified for services would have presented with a greater than 25% delay in either speech/language skills or fine motor skills. The current findings indicate that children who receive services are improving to match their non-identified peers of similar birthweights and SES (with the exception of fine motor skills). The two moderate interaction effects between BPD and services indicate that damage resulting from BPD may be more difficult to rehabilitate than damage associated with other complications or with preterm birth alone. The results of the current study support this conclusion. Of the three medical complications studied, BPD was the only one to result in long-term deficits above the influence of SES and birthweight at 9-12 years of age.

Limitations and Future Directions

While the present sample size was large enough to detect medium and large differences associated with each medical complication, the sample size was not large enough to detect small to medium effect sizes while also including SES and birthweight as covariates. The sample size was limited due to the difficulty recruiting subjects following more than a six year gap since

children were released from their respective clinics. In addition, many children had attended the UAB clinic from different parts of the state and financial limitations prevented researchers from paying for travel (hotel, food, gas) in order to facilitate participation. The low sample size limited the scope of the current study in a number of ways.

First, while, the current study demonstrated that these three medical complications differentially affect cognitive outcomes when the variance attributable to overlap is minimized, the study is limited by the fact that only three medical conditions associated with prematurity were examined. The overlap of these conditions and the correlation between low birthweight and greater overall medical complications, make it difficult to recruit populations that have only one medical complication. A larger scale follow-up study is warranted to increase the numbers of participants with only one medical complication. In addition, this larger study would be able to expand the medical complications included to account for the presence of other common overlapping conditions (e.g. Necrotizing Enterocolitis [NEC], Retinopathy of Prematurity [ROP], Periventricular Leukomalacia [PVL]), as well as expanding the number of subjects with only one condition.

Second, the lower sample size resulted in very few children with a history of Grade III or IV IVH in the study. Therefore, the inferences that can be made with regard to the impact of severe brain bleeds on cognitive outcomes are also limited. Given the low rates of severe IVH in the general population, a larger study is required to obtain enough participants with severe IVH in order to draw conclusions about the relative impact of severe IVH as opposed to mild to moderate IVH. It should be noted that severe IVH has consistently been linked to greater impairments in cognitive functioning. The current study, while unable to make inferences with regard to severe IVH, does provide the opportunity to examine mild forms of IVH in an effort to

begin to clarify inconsistent findings across multiple studies.

In addition to expanding to include larger sample sizes and addition medical complications associated with prematurity, future studies will be needed to separate the effects of the treatments for specific complications with the direct effects of the complications themselves. Specifically, the current study noted an apparent benefit of PDA over the other medical complications and the absence of any of the three medical complications altogether. Research suggests that indomethacin, which is administered to treat PDA, may provide a protective benefit but studies examining the long-term effects of indomethacin are limited. Ideally, the present study could have examined the relation between indomethacin dose and outcome. However, the medical records for participants were not detailed enough to allow for this analysis to be conducted. This suggests that a prospective study may be necessary to specifically examine indomethacin and long term outcome.

Overall, the current study demonstrated that each of three common medical complications associated with prematurity has a differential effect on long-term cognitive outcomes that should be considered when providing intervention to premature children. Specifically, the current study demonstrated that the most significant long-term detrimental effects of premature birth are associated with BPD, both with regards to specific motor and language difficulties associated with BPD, but also the indications that the difficulties may be more difficult to ameliorate through early intervention services, especially within the motor domain. Given these findings, children with a history of BPD may require more intensive interventions in the areas of motor skills and language skills at an early age. In addition, the current study is unique in its follow-up of PDA. Historically, PDA is not studied in long-term follow-up studies due to the assumption that the complication is not as severe as others

associated with preterm birth. The current study adds to the extant literature by demonstrating a potential benefit of PDA itself, or the treatment of PDA, in preterm infants over and above children who did not experience BPD, IVH, or PDA. Finally, the breadth of the cognitive outcomes and age at assessment within this study are unique among the existing literature in the field. Many of the skills assessed in previous studies have not stabilized by the age of five when many studies cease follow-up (e.g., IQ, executive function). The current study extends the follow-up to 12 years of age in an effort to determine what deficits remain present over time.

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Appendices

Appendix A: IRB Approvals from UA and UAB IRB committees

Appendix B: Demographic Form

Appendix C: Description and protocol for the CELF

Appendix D: Description and protocol for the D-KEFS subtests

Appendix E: Description and protocol for the CMS immediate memory subtests

Appendix F: Description and protocol for the Bruininks-Oseretsky subtests

Appendix G: Directions for the CPT

Appendix H: Conners' Parent Rating Scale

Appendix I: Behavior Rating Inventory of Executive Function

Appendix J: Protocol for the WASI

Appendix A IRB Approvals

UA IRB Approved Renewal with consent forms – December 2010

UAB IRB Approved Renewal with consent forms – December 2010

Appendix B Demographic Survey

Appendix B includes the demographic survey form that each parent will complete. This form documents parental education and occupation, family structure, race/ethnicity, usage of special education services by the child, and medical issues the child currently experiences.

Parent Survey Form A
Verification of optimal testing conditions

Instructions: This is the first form to be completed. If the child is sick, or does not have his/her glasses or contact lenses, the appointment should be rescheduled.

Date: ___ ___ / ___ ___ / ___ ___

Study ID #: ___ ___ ___ ___

1. Is the child sick today? Y N
- a. If yes, with what? _____
- 1 = Cold/ear infection
- 2 = Diarrhea vomiting
- 3 = Fever
- 4 = Asthma
- 5 = Other, specify: _____
- _____
- _____

2. Does this child need any of the following?
- a. Eyeglasses or contacts Y N
- 1) If yes, did you bring the glasses/
is the child wearing the contacts? Y N
- b. Hearing Aid Y N
- 1) If yes, did you bring the hearing aid,
or is the child wearing it? Y N

STOP HERE if the child is sick today, or if the child needs glasses or contact lenses but did not bring them.

Parent Survey Form B
Educational Services

Date: ___ ___ / ___ ___ / ___ ___

Study ID #: ___ ___ ___ ___

History:

1. Prior to the age of 5 did child receive early intervention services? Y N
- a. If Yes, what type of services: _____
- (1) In home
 - (2) Center
 - (3) Clinic
 - (4) Other, Specify, _____
- b. If yes which of the following services:
- (i) Occupational Therapy (OT): Y N
 - Age started: _____
 - Age ended: _____
 - Frequency of services (sessions per month): _____
 - (ii) Physical Therapy (PT): Y N
 - Age started: _____
 - Age ended: _____
 - Frequency of services (sessions per month): _____
 - (iii) Speech Therapy: Y N
 - Age started: _____
 - Age ended: _____
 - Frequency of services (sessions per month): _____
 - (iv) Special Education: Y N
 - Age started: _____
 - Age ended: _____
 - Frequency of services (sessions per month): _____
 - (v) Counseling: Y N
 - Age started: _____
 - Age ended: _____
 - Frequency of services (sessions per month): _____
 - (i) Infant Stimulation Y N
 - Age started: _____
 - Age ended: _____
 - Frequency of services (sessions per month): _____

After the age of 5:

1. Grade your child is currently in or most recently completed: _____
2. Repeated grade(s)? Y N
If yes, what grade(s): _____

3. Current IEP? Y N

4. Type classroom child is in: _____

1 = Regular education classroom

2 = Combination of regular education and special education services

3 = Primarily self-contained special education classroom

5. Under what diagnosis does your child qualify for services through the school?

a. Please describe: _____

1 = Developmental Disability/ Mental Retardation

2 = Autism Spectrum Disorder

3 = LD (Learning Disabled)

4 = SBD (Severely Behaviorally Disordered)
or SED (Severely emotionally disordered)

5 = SLI (Speech/Language Impairment)

6 = OI (Orthopedically impaired)

7 = OHI (Other Health impairment)

8 = HI (Hearing Impaired)

9 = VI (Visually Impaired)

10 = MH (Multi-handicapped)

11 = Other, describe: _____

6. List any special service(s) the child receives through the school: _____

1 = Speech/Language Therapy

• Age started: _____

• Age ended: _____

• Frequency of services (sessions per month): _____

2 = Physical Therapy

• Age started: _____

• Age ended: _____

• Frequency of services (sessions per month): _____

3 = Vision Services

• Child receives special assistance in the
classroom on a regular basis.

Y N

4 = Adaptive PE

• Age started: _____

• Age ended: _____

• Frequency of services (sessions per month): _____

5 = Occupational Therapy

• Age started: _____

• Age ended: _____

• Frequency of services (sessions per month): _____

6 = Hearing Impaired services

- Child receives special assistance in the classroom on a regular basis. Y N

7 = Social Skills

- Age started: _____
- Age ended: _____
- Frequency of services (sessions per month): _____

and/or

- Child receives special assistance in the classroom on a regular basis. Y N

8 = Counseling

- Age started: _____
- Age ended: _____
- Frequency of services (sessions per month): _____

9 = Other, specify _____

7. Has your child ever been tested by the school for learning problems or placement purposes? Y N

Parent Survey Form C
Parent / Child Demographics

Date: ___ / ___ / ___

Study ID#: _____

1. What is the civil status of this child's mother / primary caretaker? _____
- 1 = Married and living with spouse (child's PARENT)
 - 2 = Married and living with spouse (NOT child's PARENT)
 - 3 = Married but living away from spouse
 - 4 = Separated due to marital conflict
 - 5 = Divorced
 - 6 = Widowed
 - 7 = Unmarried; living with boyfriend or mate (child's PARENT)
 - 8 = Unmarried; living with boyfriend or mate (NOT child's PARENT)
 - 9 = Unmarried; living alone (without mate)
 - 10 = Other: _____

2. If primary caretaker is divorced or separated, does he or she receive alimony or child support? Y N
- a. If yes, is this the primary means of financial support? Y N

3. Please Circle the highest grade of regular school this child's MOTHER has completed.

None	Grade School	High School	College	Graduate School
0	1 2 3 4 5 6 7 8	9 10 11 12	13 14 15 16	17 18

4. Please Circle the highest grade of regular school this child's FATHER has completed.

None	Grade School	High School	College	Graduate School
0	1 2 3 4 5 6 7 8	9 10 11 12	13 14 15 16	17 18

5. Is this child's MOTHER employed now? Y N

6. Besides her own housework, what kind of work does this child's MOTHER mainly do? (e.g., housekeeping, nursing, secretarial, salesperson, store manager, factory work, etc.)

Place of employment: _____

Job title: _____

7. Is this child's FATHER employed now? Y N

8. What kind of work does this child's father mainly do?

Place of employment: _____

Job title: _____

9. Is there another adult contributing to the financial income of the family (e.g., mother's spouse /mate who is NOT child's FATHER)? Y N

If YES, answer the following questions, If NO, skip to question 10:

a. What kind of work does this individual mainly do?

Place of employment: _____

Job title: _____

b. Please Circle the highest grade of regular school this individual has completed.

None	Grade School	High School	College	Graduate School
0	1 2 3 4 5 6 7 8	9 10 11 12	13 14 15 16	17 18

10. What race / ethnicity is this child? *List all that apply.* _____

- 1 = Caucasian
- 2 = African American
- 3 = Hispanic American
- 4 = Asian American
- 5 = Other: _____

Parent Survey Form D
Child Health Status

1. Has this child ever been diagnosed with any of the following medical conditions:

- | | | |
|---|---|---|
| a. Asthma | Y | N |
| b. Birth defect,
If YES, Specify _____ | Y | N |
| c. Lead Poisoning | Y | N |
| d. Cerebral Palsy | Y | N |
| e. Cancer | Y | N |
| f. Kidney Failure | Y | N |
| g. Meningitis | Y | N |
| h. Anemia | Y | N |
| i. Poisoning | Y | N |
| j. Congenital heart defect | Y | N |
| k. Seizures/fits/convulsions | Y | N |
| l. Frequent Ear infections (>6 per year) | Y | N |
| m. Sickle cell disease | Y | N |
| n. Head Injury /Concussion | Y | N |
| o. Poor growth | Y | N |
| p. Eye muscle problem (e.g. cross eye) | Y | N |
| q. Other, specify: _____ | | |

2. Has your child ever been diagnosed with any of the following psychological conditions:

- | | | |
|------------------------|---|---|
| a. Mental Retardation | Y | N |
| b. Learning Disability | Y | N |

Appendix C

Appendix C includes the description of the individual subtests of the Clinical Evaluation of Language Fundamentals-3rd Edition.

Clinical Evaluation of Language Fundamentals (Semel, Wiig, & Secord, 1995)

Receptive Subtests	Expressive Subtests
Concepts and Directions	Formulated Sentences
Word Classes	Recalling Sentences
Semantic Relationships	Sentence Assembly

Concepts and Directions: Testing begins with two familiarization items completed by the examiner and two trial items completed by the examinee. Testing then proceeds with the designated start point based on the examinee's age. In this subtest, participants are asked to point to a series of shapes based on the directions from the examinee. The examiner reads a set of instructions followed by the prompt "Go," indicating the directions are complete. For example, participants may be shown a series of three circles and three triangles and asked to, "Point to the second triangle and the third circle. Go." Each item is scored correct (1) or incorrect (0).

Formulated Sentences. Each examinee is given three trials in which he or she completes the task with the opportunity for teaching assistance from the examiner. Then each examinee begins testing with item 1. For each item the examinee is given a picture and a word from which to develop a sentence. Each sentence must be correctly formed, contain the target word, and be relevant to the associated picture. For example, the examinee may be shown a picture of a series of people in a checkout line at a grocery store. He or she will be given the word *before* and asked to tell the examiner a sentence relating to the picture using the word *before*. Each item is scored on a scale of 0-2 points based on the appropriate use of the target word, the relevance to the picture, and the structure of the sentence.

Word Classes. Each examinee is given three trials in which he or she completes the task with the opportunity to receive teaching assistance from the examiner. Each examinee then proceeds to the appropriate start point for his or her chronological age. For each item the examinee is given a set of three words and instructed to name the “two that go together best.” For example, the examinee is given the following words: *fast, wet, quick*, and expected to verbally select the words *fast* and *quick* as the two that go together. Each item is scored correct (1) or incorrect (0).

Recalling Sentences. Each examinee is given two trials during which he or she may receive instruction in the correct answers before proceeding to the appropriate start item for his or her age. Each item consists of a sentence that the examinee must repeat exactly to the examiner. Each response is scored 0-3 points based on the number of errors made.

Sentence Assembly. Each examinee watches a demonstration by the examiner and then completes two trials before proceeding to item 1 of the actual test items. Each examinee is shown a series of phrases that could be combined in at least two ways to form a sentence. The examinee must make two sentences out of the phrases provided. For example, if given the phrases *is, in the chair, the kitten*, the examinee should say the following two sentences: “The kitten is in the chair,” and “Is the kitten in the chair?” The examinee may use only the words provided to construct the sentences. Each response is scored as either correct (1) or incorrect (0).

Semantic Relationships. Each examinee receives two teaching trials before proceeding to the appropriate start point for his or her chronological age. Each item consists of a phrase, or question, that the examinee must complete, or answer, with two possible correct options. For

example, the examiner would show the examinee the following phrase and then read it and the subsequent word choices to the examinee:

Jan saw Pedro. Dwayne saw Francis. Who was seen?

- a) Jan
- b) Dwayne
- c) Pedro (correct)
- d) Francis (correct)

The examinee must provide both answers to receive 1 point for the item.

Appendix D

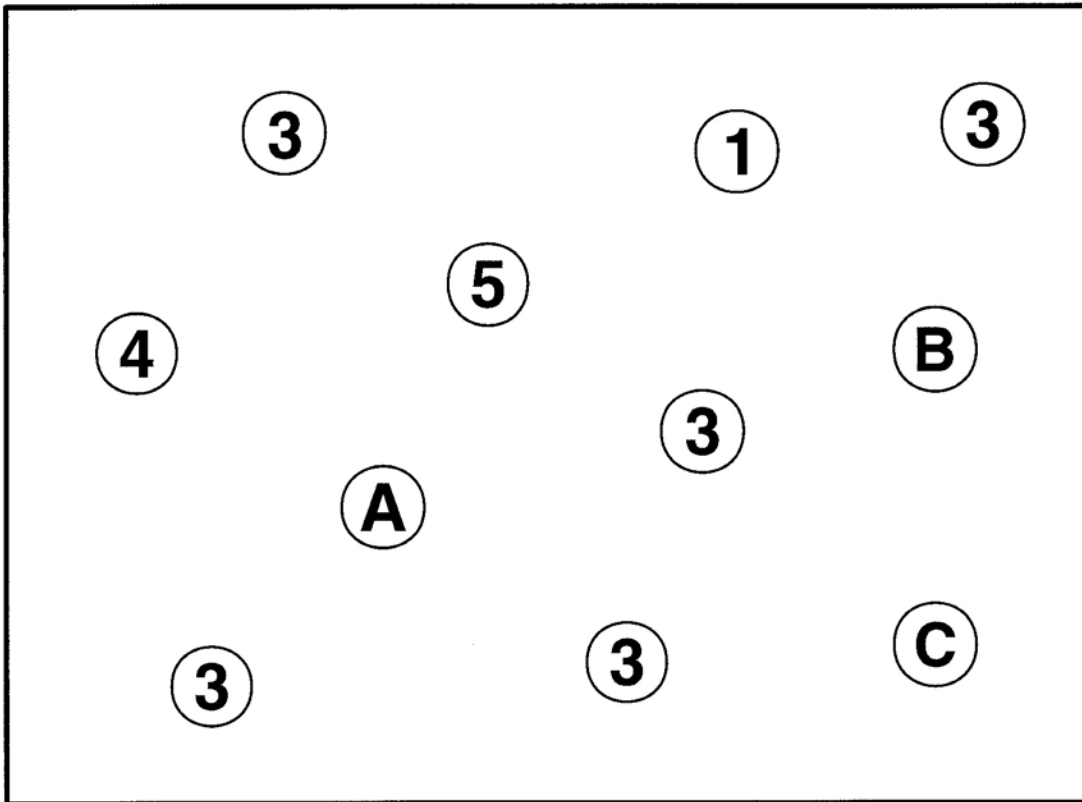
Appendix D contains the description of the three D-KEFS subtests.

Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001a)

Trail Making Test. The trail-making test measures flexibility of thinking. The primary condition assessing executive function in this task is condition 4; however, the other conditions provide baseline and normative data by which determinations can be made based on motor speed and sequencing ability. In this task there are four conditions presented.

Condition 1: A series of letters and numbers is presented to the examinee. The examinee is asked to cross out all of the “3’s”.

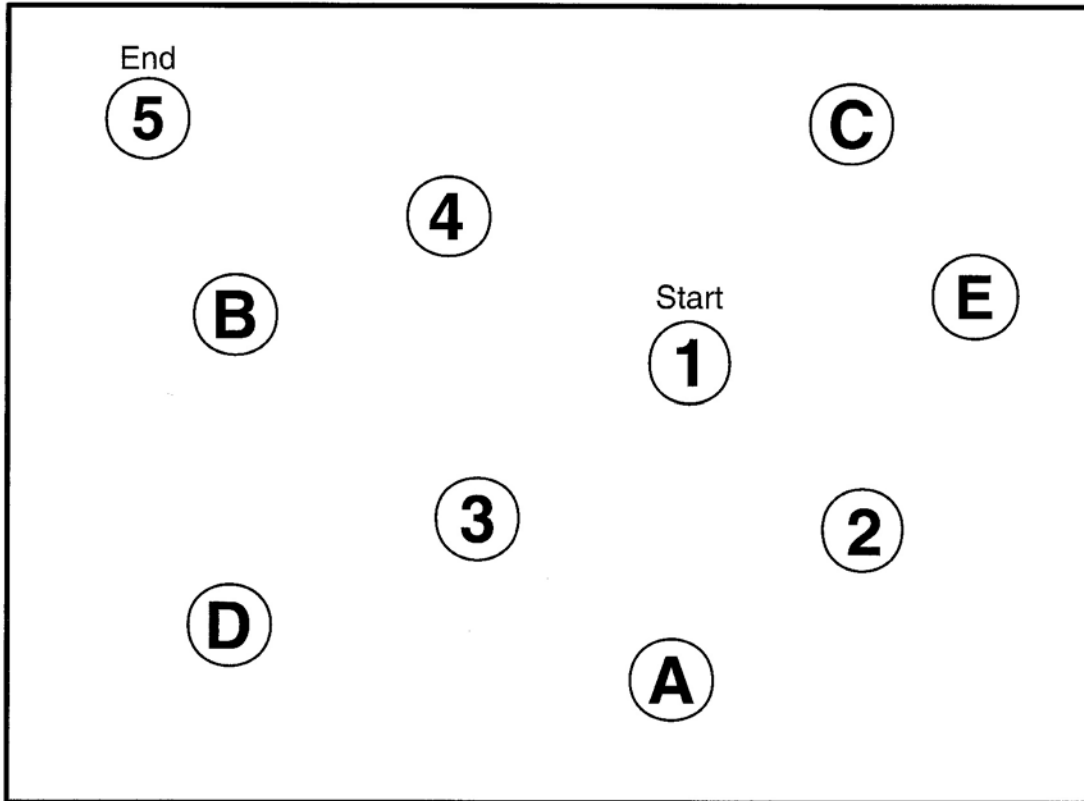
Practice



**Image taken from The Delis Kaplan Executive Function System (D-KEFS) Protocol © 2001 The Psychological Corporation*

Condition 2: A series of letters and numbers is presented to the examinee. The examinee is asked to connect the numbers in sequential order beginning with the number 1 and ending with the number 16.

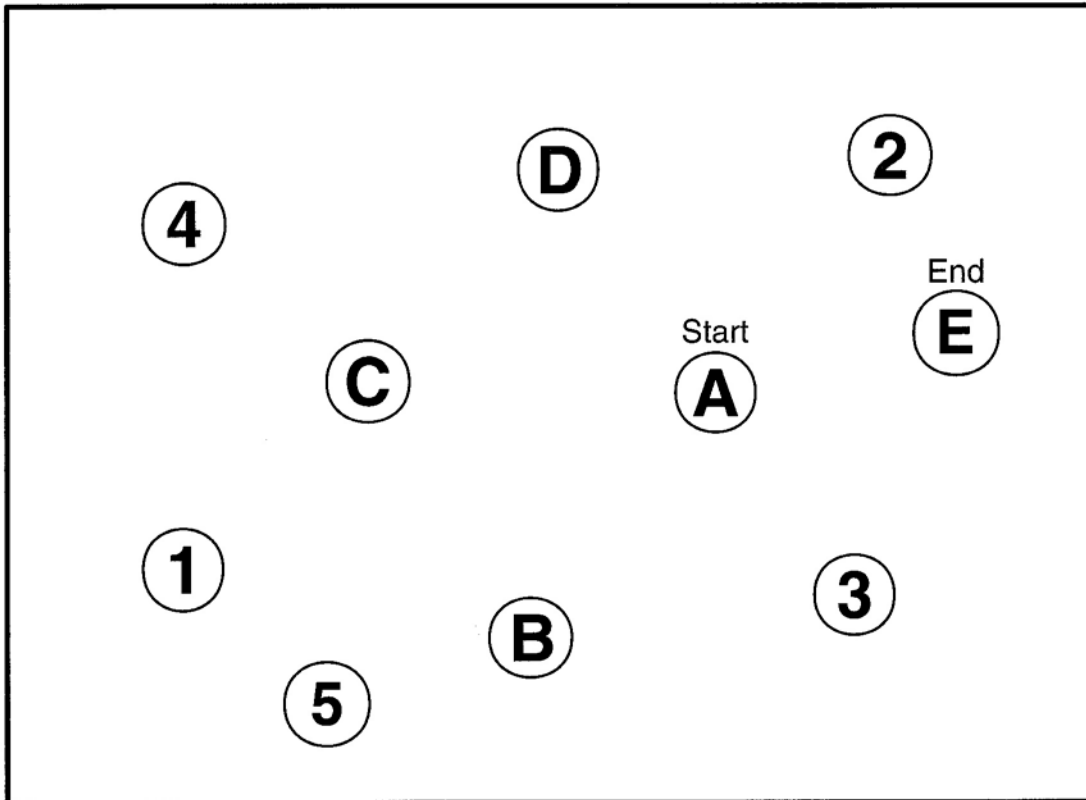
Practice



**Image taken from The Delis Kaplan Executive Function System (D-KEFS) Protocol © 2001 The Psychological Corporation*

Condition 3: A series of letters and numbers is presented to the examinee. The examinee is asked to connect the letters in alphabetical order beginning with the letter A and ending with the letter P.

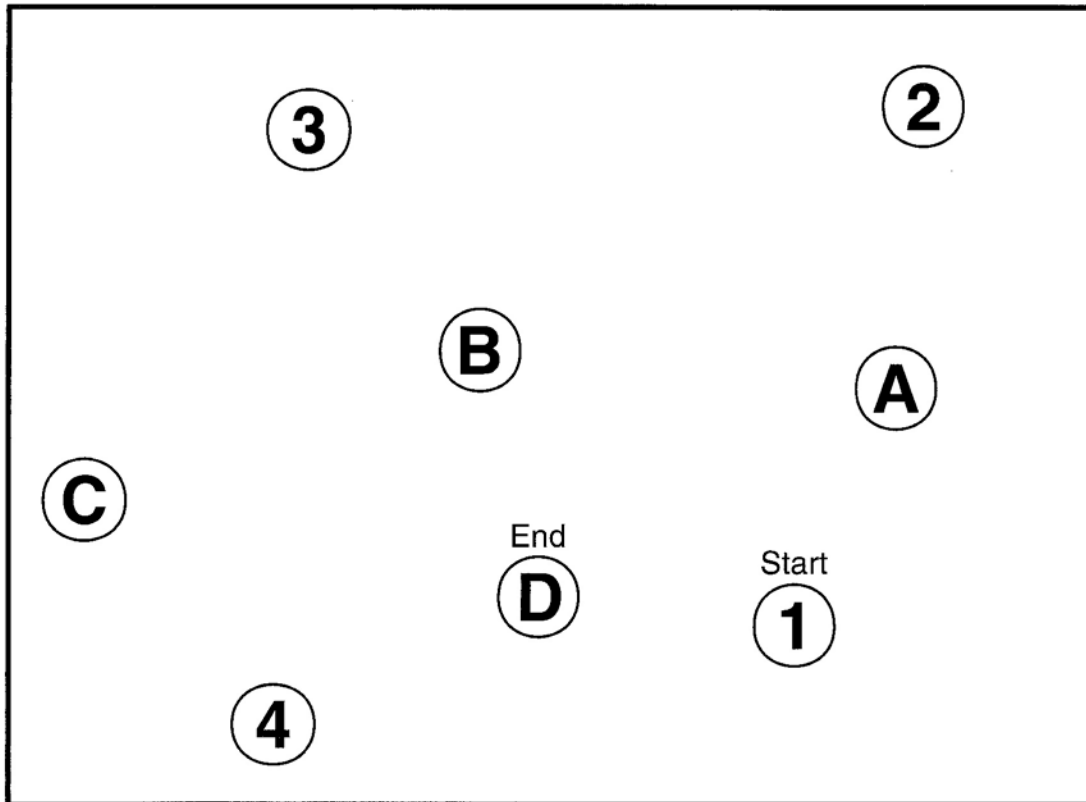
Practice



**Image taken from The Delis Kaplan Executive Function System (D-KEFS) Protocol © 2001 The Psychological Corporation*

Condition 4: A series of letters and numbers is presented to the examinee. The examinee is asked to alternate numbers and letters sequencing in alphabetical and sequential order. For example, the examinee would draw a line from 1 to A to 2 to B etc. until he or she has completed the task.

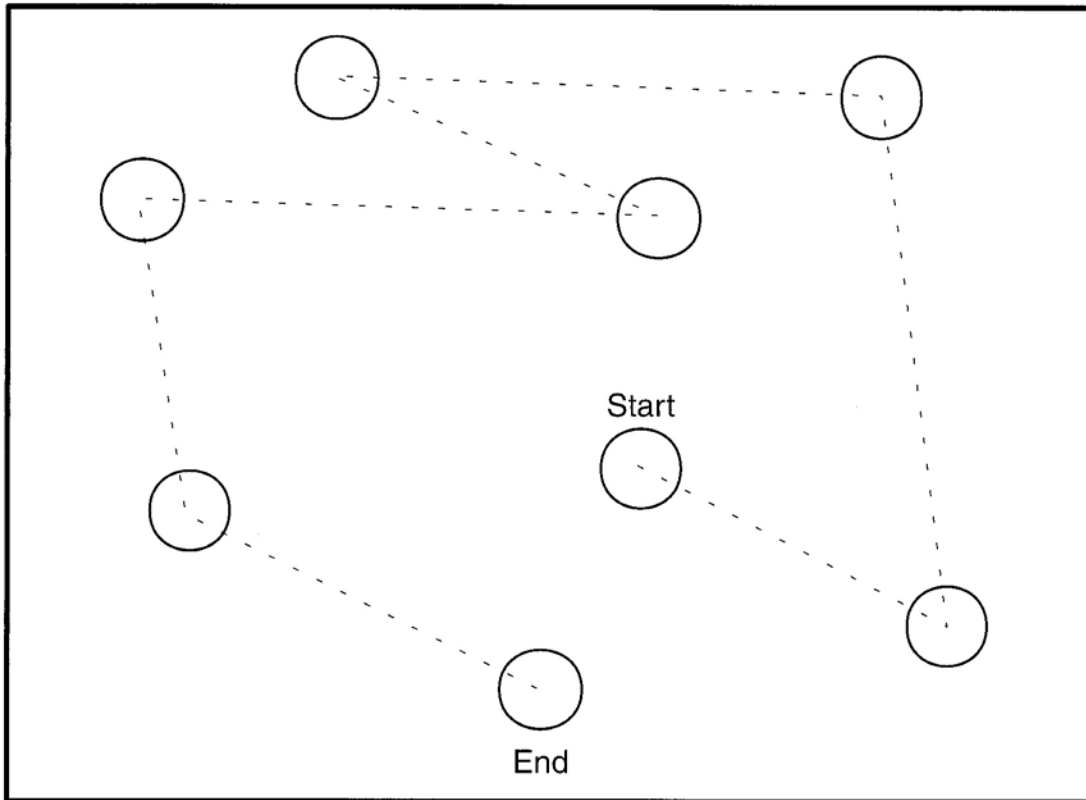
Practice



**Image taken from The Delis Kaplan Executive Function System (D-KEFS) Protocol © 2001 The Psychological Corporation*

Condition 5: The examinee is to trace a dotted line as fast as possible.

Practice



**Image taken from The Delis Kaplan Executive Function System (D-KEFS) Protocol © 2001 The Psychological Corporation*

Sorting Test. The sorting test is designed to measure concept formation and problem-solving ability, specifically the initiation of and modality of (verbal vs. nonverbal) problem-solving skills, the ability to explain abstract concepts, and the ability to inhibit responses from previous sorting sets. There are three sections to this test, a pretest and two testing conditions.

Pretest: In the pretest the list of words is presented and any words the examinee may not know are explained using the definitions provided in the manual.

Condition 1: In condition one the examinee is given six cards to sort in as many different ways as possible, each time explaining the rule he or she used to sort the cards. This is then repeated with a second card set. This condition is scored based on both the sorting response and the description of the rule used to sort the cards.

Condition 2: In condition two the examiner arranges the card sets in to groups and then asks the examinee to describe the rule the examiner used to sort the cards. This condition is scored only based on the description of the sorting rule.

Tower Test. This test assess spatial planning, rule learning, and inhibition of impulsive and perseveration. The goal of this test is to move a series of disks of different sizes from one peg to another on a 3 peg board in order to create a target tower. The examinee may only move one disk each time and may not place a larger disk on top of a smaller disk. For each item the starting position of the disks and the target tower to be built will vary. The goal is to move as quickly as possible with the fewest moves necessary to complete the task. Scoring is based on the number of moves required to achieve the correct tower.

Appendix E

Appendix E contains the description of the immediate memory subtests of the CMS.

Children's Memory Scale (Cohen, 1997)

Only four subtests of the Children's Memory Scale will be used in the current study and only in their immediate recall formats. These subtests are Dot Locations, Stories, Faces, and Word Pairs.

Dot Locations. The examinee is asked to remember the location of chips on a grid. They are given three chances with the same pattern in the learning phase and then an interference trial with a different pattern. The individual is then asked to remember the original pattern. This is the immediate recall score.

Stories. The examinee is asked to remember a story that is read to them by the examiner. For each aspect of the story recalled the examinee receives a point. This is repeated for a second story.

Faces. For this subtest the examinee is required to commit to memory a series of faces and then identify the faces that they saw.

Word Pairs. The examinee is given a list of word pairs to memorize. The examiner then gives the first word of the pair and the examinee must provide the second. Three different lists are completed in this manner before the examinee is asked to repeat the task with the first list without seeing the list again.

Appendix F

Appendix F contains the description of the Bruininks-Oseretsky Test of Motor Proficiency.

Bruininks-Oseretsky Test Of Motor Proficiency, (Bruininks, 1978)

The two subscales of the Bruininks (Fine Manual Control and Body coordination) in addition to one subscale will be used to calculate Fine motor, gross motor and dexterity for each participant.

Fine Manual Control. This subscale consists of 15 items. The examinee is required to fill in shapes (a circle and star), to draw lines through paths(crooked and curved), to connect dots, to fold paper, to cut out a circle, and to copy shapes (circle, square, overlapping circles, wavy line, triangle, diamond, star and overlapping pencils). Each item is scored based on specific criteria regarding the accuracy with which the individual completed the task (e.g. is the basic shape recognizable, is the shape closed, is the shape correctly oriented, etc.).

Body Coordination. This subscale consists of 16 items that assess a variety of gross motor movements. The examinee is asked to perform tasks such as jumping in place, touching the tip of their nose with their index finger while their eyes are closed, tapping their feet and fingers at the same time, either synchronizing the same sides of the body or the opposite sides of the body, walking a straight line, standing on one leg, and walking heel-to-toe on a line.

Appendix G

Appendix G contains the directions for the computerized version of the Conners' Continuous Performance Task.

Conners' Continuous Performance Task (Conners, 2000)

Examinees are instructed to sit at the computer and watch as letters are flashed across the screen. For each letter they are to press the space bar EXCEPT for the letter "X." The test lasts for approximately 10 minutes. The letters are presented at varying intervals of 1, 2 or 4 seconds between stimuli. The test provides information on the number of accurate responses, the number of errors of omission, and the number of errors of commission, which will be used in assessing inattention. It also provides a clinical likelihood of the individual having ADHD versus not having ADHD.

Appendix H

Appendix H contains the Conners' Parenting Rating Scale form assessing inattention, impulsivity, and hyperactivity.

Conners' Parent Rating Scale-Revised Long Form (CPRS; Conners, 1997)

The CPRS is a 201 question parent report form that assesses difficulty across a wide range of behavioral, emotional, and academic areas. It then uses the caregiver's responses to determine symptom severity and concerns based on the DSM-IV diagnostic categories (e.g., Learning Disorders, Mood/Anxiety Disorders, Developmental Disorders, Behavioral Disorders).

Appendix I

Appendix I contains the description of the BRIEF questionnaire assessing executive function.

Behavior Rating Inventory of Executive Function (BRIEF; Gioia & Isquith, 2004)

The BRIEF is an 86 question survey completed by the parent or caregiver of the participant. Symptoms are presented across a variety of executive domains and caregivers are asked to report how often each symptom is a problem for the child (Never, Sometimes, or Often). Symptoms are then tallied in the areas of inhibition, shifting attention, and emotional control, which provide a Behavioral Regulation Index score. Symptoms in the areas of initiation, working memory, planning and organizing, organization of materials, and self-monitoring are calculated to form a total Metacognition Index score. The sum of these two indices yields a Global Executive Composite Score. These three scores are compared to age and gender-based norms to determine standardized T-scores for comparison across samples.

Appendix J

Appendix J contains the description of the four subtests of the WASI.

Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999)

Performance Subtests	Verbal Subtests
Block Design	Vocabulary
Matrix Reasoning	Similarities

Vocabulary: Examinees are read a series of words and asked to define the word. Responses are scored on a scale of 0-2 points. The words gradually become more abstract and difficult to verbally define until the examinee can no longer correctly identify the words presented. Children who experience significant difficulty verbally defining words are given 4 pictures that they must identify.

Block Design: Examinees are presented with designs and asked to replicate those designs with blocks. Designs become increasingly complex, beginning with two block designs and progressing through 9 block designs. Responses are scored as correct or incorrect, but additional points are also earned based on the speed of completion.

Similarities: Examinees are given two words and are asked to explain how the two objects or ideas are alike. Responses are scored based on a scale of 0-2 points

Matrix Reasoning: Examinees are presented with a series of images arranged to form a pattern. The examinee must complete the pattern by selecting the appropriate image from five choices at the bottom of the page. Responses are scored as either correct or incorrect.