8-27-2012

The relationship of multimodal executive function measurement and associated neuroanatomical factors in preschoolers born very low birth weight and full term

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THE RELATIONSHIP OF MULTIMODAL EXECUTIVE FUNCTION MEASUREMENT AND ASSOCIATED NEUROANATOMICAL FACTORS IN PRESCHOOLERS BORN VERY LOW BIRTH WEIGHT AND FULL TERM

by

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DISSERTATION

Submitted in Partial Fulfillment of the

Requirements for the Degree of
Doctor of Philosophy

Psychology

The University of New Mexico

Albuquerque, New Mexico

July, 2012

Dedication

This is dedicated to my family for the incredible amount of support, love and encouragement they have provided along the way.   To my husband, Andrew, my sister, Megan, my parents, Jack and Chris Woolsey, and Socrates, Busby, Zidane and Pele. For my grandparents, Roy & Dorothy Woolsey and Gerald & Ruth Reinert, especially the recently departed Ruth Reinert for her strength and patience and Roy Woolsey for always wanting to see my report cards.

ACKNOWLEDGMENTS

I gratefully acknowledge the contribution of several mentors, colleagues, and friends to the completion of this project. I would like to thank Dr. Sarah Erickson, Dr. Jean Lowe, Dr. Ron Yeo and Dr. Piyadasa Kodituwakku for their support, guidance, and encouragement throughout this process. Additionally, I would like to thank Dr. Tim Goldsmith for his statiscal guidance.

I would also like to acknowledge the research support provided by the Signature Program in Child Health Research and the Mind Research Network (MRN), particularly the principle investigators of the BRITE and BRITE Pilot Study, Robin Ohls, M.D., John Phillips, M.D., Arvind Caprihan, Ph.D., and Jean Lowe, Ph.D. Many thanks to Peggy MacLean Hoffman, Erica Montague, Lynette Silva, Joy VanMeter and Jessica Pommy for their assistance with data collection and data processing.   I also wish to express my gratitude to the families who have participated in this study. Without their participation, this study would not have been possible.

I would also like to thank my friends and family for all of their support. I would especially like to thank my father and mother, Jack and Christine Woolsey for always encouraging curiosity, creativity and perseverance. Finally, I thank my husband, Andrew Duvall, for his love and endless support through every part of this process.

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ABSTRACT

Objective: The current study investigated executive function (EF) in preschoolers born very low birth weight (VLBW) and full term by examining the dimensionality of EF and the relationship between multimodal measures of EF. Additionally, we investigated the neuroanatomical factors that may relate to EF in this population.

Participants and Methods: The sample included 101 preschoolers: 61 VLBW and 40 full term (mean=45.98 months (SD=5.05). EF measures included**:** Bear Dragon, Gift Touch, Gift Peek, Progressive Executive Categorization Battery, parent rated EF (BRIEF-P), and Child Compliance observational coding. Magnetic resonance imaging (MRI) data were analyzed through voxel-based morphometry (VBM) for a subset of preschoolers

Results: As expected, full term preschoolers were found to have higher EF scores than

VLBW preschoolers on all EF measures. When principal component analysis (PCA) was used for the combined group to assess the dimensionality of EF, only one factor emerged that included all four EF performance measures and excluded BRIEF-P scores and Compliance scores. In neuroanatomical analyses, preschoolers born full term had larger gray matter volumes in bilateral temporal, frontal paracentral, putamen, right inferior parietal, and right cerebellum anterior lobe. Preschoolers born VLBW had greater volumes for bilateral frontal, occipital, right cerebellum, right occipital, left frontal, left anterior cingulate, and left parahippocampal regions. In the combined sample, increased gray matter in the right occipital area was related to poorer EF. Additionally, increases in gray matter in the bilateral temporal, right temporal, right insula and right putamen were related to greater EF performance.

Conclusion: In this sample, EF performance measures loaded together onto a one-dimensional construct. EF and structural differences were found between VLBW and full term groups: EF was poorer, and structural volumes in the temporal and parietal areas were decreased and volumes in the frontal and occipital areas were increased in the VLBW group relative to the full term group. When examining the relationship between EF and structural volumes in the combined group, stronger EF performance was correlated with increased volume in temporal and deep gray matter as well as decreases in right occipital volume. The limitations in placing these results into the current literature are discussed.

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INTRODUCTION

Advancements in medical technology and practice have lead to increasing survival rates among premature infants. In fact, more premature infants are surviving at younger gestational ages and smaller birth weights than ever before, necessitating research on outcomes for these children. This advancement has resulted in populations of infants who are more medically fragile and at greater risk for developmental delays than their peers (Elgen, Johansson, Markestad, & Sommerfelt, 2005; Litt, Taylor, Klein, & Hack, 2005). Additionally, outcomes can be highly variable in this population; with some children born preterm demonstrating significant negative sequelae while others seem indistinguishable from their peers who were born full term. Thus, increasing our understanding of factors that relate to the variability in developmental outcomes among this population would be helpful in understanding risk and resilience factors in this population and in developing interventions to optimize these outcomes (Aylward, 2002; Kilbride, Thorstad, & Daily, 2004).

It has consistently been found that children who were born premature or low birth weight tend to have difficulties or delays in functioning (e.g. IQ, executive function, behavioral problems, learning difficulties, inattention, hyperactivity, few adaptive skills, social rejection) that persist over time (Anderson, Doyle, Callanan, & Victorian Infant Collaborative Study Group, 2003; Espy et al., 2002). Cognitive differences are widespread, as evidenced by lower intelligence quotient (IQ) scores in premature populations versus full term controls (Elgen, Johansson, Markestad, & Sommerfelt, 2005; Grunau, Whitfield, & Fay, 2004; Kilbride, Thorstad, & Daily, 2004; Lefebvre, Mazurier, & Tessier, 2005; Litt, Taylor, Klein, & Hack, 2005; Nadeau, Boivin, & Tessier, 2001; Rickards, Kelly, & Doyle, 2001; Schneider, Wolke,

Schlagmuller, & Meyer, 2004). Additionally, these lower scores are stable over time (Breslau, Paneth, & Lucia, 2004; Schneider, Wolke, Schlagmuller, & Meyer, 2004). It has also been found that children born low birth weight or premature have delays in motor skills that persist at least until age 5 (Kilbride, Thorstad, & Daily, 2004) and physical development delays (e.g. height, weight, and head circumference), which have been observed at adolescence (Elgen, Johansson, Markestad, & Sommerfelt, 2005; Kilbride, Thorstad, & Daily, 2004; Saigal, Stoskopf, Streiner, & Burrows, 2001). In brief, many outcome studies suggest long-term deficits across multiple developmental domains.

Children who are born preterm have varying levels of risk, often differentiated by birth weight and gestational age. Infants are considered preterm if they are born less than 37 weeks gestation, and they are considered low birth weight (LBW) if they are less than 2500 grams. Infants born less than 1500 grams are considered very low birth weight (VLBW), and very preterm if they are born at less than 32 weeks gestation. Infants classified as extremely low birth weight (ELBW) weigh less than 1000 grams at birth. The present study focused on children who were born VLBW and less than 1500 grams. However, since the delays and difficulties seen in the preterm population as a whole are similar in content but vary in degree, the relevant literature reviewed here includes LBW, VLBW and ELBW samples.

In characterizing the diversity of deficits observed in children born preterm, there is a tendency to look at broad measures of functioning such as intelligence. In fact, the most common outcome measure in children born premature is IQ (Alyward, 2002). Despite the fact that children born preterm have significantly lower IQ scores from term control subjects (Allen, 2002; Aylward, 2002), when children with major disabilities are excluded, most preterm children have IQ scores that fall within the average range (D'Agostino & Clifford, 1998; McGrath &

Sullivan, 2002; McGrath et al., 2005; Weindrich, Jennen-Steinmetz, Laucht, & Schmidt, 2003).

However, even after matching LBW children and full term children on age and IQ, it has been

found that children born LBW still have deficits in areas such as attention, visuospatial

processing, and spatial working memory (Vicari, Caravale, & Carlesimo, 2004). This suggests

that IQ may not adequately represent the various difficulties documented in Children born

VLBW (Alyward, 2002).

The organization of the central nervous system is at a particularly vulnerable stage in the

last trimester of development, which is when most preterm children are born. The organizational

process that occurs during this period has important implications for the development of

autonomic stability, state organization, attention, motor maturity, and self-regulation (Als, 1982).

There is also an increasing literature linking emotion regulation and cognition in the

developmental process (Bell & Wolfe, 2004; Posner & Rothbart, 2000). Beyond differences in

IQ, researchers have found that prematurely born children have difficulty regulating their arousal

and physiological states in infancy (Cichetti, Ganiban, & Barnett, 1991; Greenspan, 1992;

Porges, 1992).

The consequences associated with preterm birth can lead to important alterations in the

way in which children interact with their environments, and can have important ramifications for

psychosocial and later psychological functioning of preterm infants. For example, several

studies have found that adolescents who were born ELBW or VLBW have a variety of

psychosocial difficulties (Anderson et al., 2003; Grunau, Whitfield, & Fay, 2004; Nadeau,

Boivin, & Tessier, 2001; Rickards, Kelly, & Doyle 2001). These widespread difficulties include

lower scholastic and athletic achievement, lower job competence, lower romantic confidence,

reduced self-esteem, more internalizing and externalizing behavioral problems, increased social rejection, greater inattentiveness and hyperactivity, and fewer adaptive skills (Anderson et al., 2003; Grunau, Whitfield, & Fay, 2004; Nadeau, Boivin, & Tessier, 2001; Rickards, Kelly, & Doyle 2001). The psychosocial consequences demonstrated by these studies highlight the range of domains affected by premature birth.

Thus, it is important to study not only the substantiated differences in IQ test performance, but also children's real world abilities and degree of functional adaptation to daily life. For example, a child with a high IQ but poor adaptive functioning and self-regulation abilities may not be able to function in the world as well as a child with a lower IQ but excellent adaptive skills. Aylward (2002) discouraged the current trend of over interpreting IQ scores, and instead suggested relying on a broader approach to the follow-up of preterm children. It is important to look broadly at areas that affect adaptive functioning and quality of life. In fact, Hack et al. (2005) found poor predictive validity of subnormal scores on the Bayley Scales of Infant Development, Second Edition (BSID II, MDI scale) taken at 20 months corrected age, with cognitive function at school age (8 years old). Although predictive validity was relatively higher for the less impacted group (.37 for all ELBW infants and .20 for the neurosensory-intact subgroup), overall the relationship between measures of infant cognition and later cognitive function was substantial. Additionally, Harvey, O'Callaghan, and Mohay (1999) found limited and inconsistent correlations (ranging from Rho = -0.006 to .52) between ELBW 5-year-olds' planning, sequencing, and inhibition and previously obtained general quotient index scores using the McCarthy Scales of General Ability at 4 years of age. Even in full term control children, early IQ tests are inconsistent predictors of later outcome (Neyens & Aldenkamp, 1997). Thus there is a precedent for the questionable predictive utility of early IQ tests in general, and IQ tests

might even be poorer predictors of future abilities in preterm children than for full term children (Harvey, O'Callaghan, & Mohay, 1999; Neyens & Aldenkamp, 1997). The questionable predictive validity of early IQ tests to later cognitive function in premature infants is concerning and indicative of the need for more comprehensive measures.

Therefore, it is not enough to look primarily at IQ as an indicator of outcome or as a predictor of future outcome in this population. Another way to measure outcome is to consider children's executive function abilities. The plethora of deficits observed in children who are born preterm (IQ, behavioral problems, learning difficulties, inattentive, hyperactive, few adaptive skills, social rejection) is indicative of a broad and underlying cause. Poor executive function (EF) fits the pattern of difficulty that children born VLBW often encounter.

Executive Function

Executive function has been conceptualized as a unitary construct that includes an array of higher-level, inter-connected cognitive skills. Executive function includes many aspects of cognitive functioning, yet goes beyond the scope of traditional IQ testing to behaviorally anchor the building blocks of real world functional abilities (Norman & Shallice, 1986). There are myriad definitions of executive function, which range from functional to theoretical. In general, the term executive function (EF) commonly refers to cognitive processes that underlie flexible, goal-directed responses to novel situations.

Executive function is typically conceptualized as an umbrella term that encompasses three main areas: working memory, inhibition, and cognitive flexibility (Davidson, Amso, Anderson, & Diamond, 2006). Additionally, factor analytic studies have generally supported these three main EF factors (Lehto, Juujarvi, Kooistra, & Pulkkinen, 2003; Miyake, Friedman,

Emerson, Witzki, & Howerter, 2000). Working memory refers to the ability to hold information in mind, which can range from simple concrete memories to complex representations and symbols. Within the realm of EF, working memory is related to the manipulation of this information, as well as acting upon this information.

Inhibition is conceptualized as another central component of EF. Inhibition refers to acting by choice versus acting on impulse. This implies weighing factors to decide upon an appropriate response versus an automatic one. This usually involves self-regulation or self-control where an inappropriate response is resisted in favor of responding with an appropriate response (Davidson, Amso, Anderson, & Diamond, 2006). In EF tasks, inhibition can be measured by delay of gratification (where a desired item is presented as a temptation, but inhibition is required for future reward) or Stroop-like tasks, where stimuli have two relevant dimensions and participants are asked to inhibit the prepotent response and provide the less salient response (i.e., naming the color ink a word is printed in instead of reading the word) (Stroop, 1935).

Another component of EF is cognitive flexibility. Cognitive flexibility refers to the ability to quickly and accurately change behavior. This involves taking the situation into account when decisions are required. When cognitive flexibility is high, a person adapts their behavior to a particular situation and switches between behaviors as they became appropriate (Davidson, Amso, Anderson, & Diamond, 2006). In EF tasks, cognitive flexibility is measured through rule switching, where a certain rule is established and then reversed or changed. A common example is the Wisconsin Card Sorting Test (WCST), which is a neuropsychological test of set shifting that requires cards to be sorted by the 3 dimensions of color, shape, or number depending on the active rule (Heaton, 1981).

Planning is another aspect of EF that involves future orientation, selection or internalization of a goal, utilization of problem solving strategies, organization of time and resources, and formulation of the steps necessary to complete a task (Lezak, 1993; 1995). Common tasks used to measure this aspect of planning include the Tower of Hanoi and Tower of London tasks. Both of these tasks involve moving discs on pegs from a start state to an end state in as few moves as possible, in the face of increasing difficulty.

From a functional perspective, EF is conceptualized to be necessary in situations that involve purposeful and goal directed behavior. More broadly, EF can be observed in planning and decision-making, as well as error correction based on the incorporation of feedback, or troubleshooting. During these tasks the abilities of working memory, inhibition, and cognitive flexibility are challenged. EF is also activated during the initiation of a novel activity, or when danger or technical difficulty must be overcome (Norman & Shallice, 1986). EF processes are also engaged when overcoming a strong habitual response.

There are many cognitive processes that are associated with EF: anticipation, goal selection, planning and organization, initiation of a novel activity, self-regulation, mental flexibility, working memory, and utilization of feedback (Anderson, 2002). These processes are all interconnected and EF is believed to be the larger, overarching concept that weaves through them. EF is more than just a sum of the processes of which it is comprised, rather it is an underlying ability reflected through these measurable processes (Anderson, 2002; Duncan, 1986; Shallice & Burgess, 1991; Zelazo, Carter, Reznick, & Frye 1997).

When attempting to understand the current conceptualization of EF, another factor that must be considered is that there may be variability in how EF is functionally expressed. Some

researchers contend that EF is a consistent skill that varies in execution based upon different factors (Zelazo, Carter, Reznick, & Frye 1997). Thus, the same underlying EF skills may present differently depending upon a variety of contextual factors such as environmental context (inhibition may be better in a library or church than on a playground), culture (what is expressly taught in the home and or culture about expectations for behavior in children), social learning and role modeling (does a child have others to follow or are they acting independently) and temperament (general personality and tendencies). Thus, EF can simultaneously be an overarching ability and a context-dependent skill. This is often particularly salient in individuals who have generally high EF but who demonstrate variability in their EF skills across contexts.

In contrast, some researchers have contended that EF may have within itself different components (Carlson & Moses, 2001; Hongwanishkul, Happaney, Lee, & Zelazo, 2005). Thus, there is some support for the notion that EF may have cognitive components, context driven components, and behaviorally oriented components. For example, EF has been found to be related to intelligence and thus, overall cognitive ability may play a factor in problems solving, especially related to planning and organization around goal completion (Anderson, Bechara, Damasio, Tranel, & Demasio, 1999). Context may also be crucial in demonstrating EF skills. Novel situations are hypothesized to be the most valid way to assess EF skills and differentiate them from learned responses. Higher social or contextual demands may also result in better EF performance. Behavioral regulation has also been posited as a separate factor that influences one's ability to effectively demonstrate EF (Carlson & Moses, 2001). These components may reflect the impact of emotions on EF performance. Inhibitory control has been shown to be functionally distinct from intelligence and has been postulated to relate to emotionally salient decision-making (Friedman, et al., 2008; Hongwanishkul, Happaney, Lee, & Zelazo, 2005).

The intersection between emotions and EF is one contextual area that has been investigated. It has been hypothesized that there are two functional types of EF: 'Cool' and 'Hot' (Hongwanishkul, Happaney, Lee, & Zelazo, 2005). Cool EF is believed to be activated in situations that involve abstract reasoning and problem solving. For example, cool EF can be seen when a person is putting together pieces to solve a puzzle. Hot EF involves emotional activation in personally meaningful situations. For example, Hot EF would play a role in delaying gratification or gambling (Metcalfe & Mischel, 1999). Both Hot and Cool EF can involve decision-making, rule use, and memory.

The main difference between Hot and Cool EF is the amount of personal relevance as Hot EF situations are more emotionally charged, and can be seen as having higher personal stakes (Hongwanishkul, Happaney, Lee, & Zelazo, 2005). Hot EF can be conceptualized as emotional problem solving, while Cool EF can be understood as cognitive problem solving. The categorization of Hot EF and Cool EF is under debate. Some studies support the idea that these two types of EF are separate and have even demonstrated differential predictive utility and developmental trajectories (Brock, Rimm-Kaufman, Nathanson, & Grimm, 2009; Hongwanishkul, Happaney, Lee, & Zelazo, 2005). For example, Cool EF has been shown to have a stronger relationship to school readiness than Hot EF (Brock, Rimm-Kaufman, Nathanson, & Grimm, 2009). Additionally, age-related improvements in Cool EF were found to occur earlier than age-related improvements in Hot EF (Prencipe, et al., 2011). However, it has also been found that Hot EF and Cool EF are moderately related to each other and in exploratory factor analyses they have been found to load together into a single factor (Brock, Rimm-Kaufman, Nathanson, & Grimm, 2009, Prencipe, et al., 2011). Thus, the extent of overlap and differentiation in these two concepts is still unclear.

Development of Executive Function

As we grow older, our environment and our exposure to different experiences increase in both diversity and intricacy. These signals from our external and internal environments impact the connections that our brain establishes, reinforces and maintains. The hierarchical pattern of brain development, with frontal areas being the last to develop and mature, mirrors the overall patterns seen in the development of EF abilities over time (Volpe, 1995; 1997; 2001). There is much intraindividual and interindividual variability in the development of EF. Intraindividually, all EF domains do not develop evenly (Senn, Espy, & Kaufmann, 2004); for any individual, one EF domain can be more developed or less developed than any other EF domain at any given point in time. Interindividually, there is also great variation relative to chronological age: at the same age different individuals will naturally vary considerably in their level of development of various EF domains.

Despite this intraindividual and interindividual variability, the development of EF tends to follow a hierarchical pattern from simple to complex. Some aspects of EF are thought to be more foundational and to develop earlier than others. Studies have demonstrated that attentional control and working memory are the essential fundamental EF skills that are the building blocks for all executive tasks (Senn, Espy, & Kaufmann, 2004). Working memory and attentional control tend to develop first and are believed to be necessary, but not sufficient, for the successful completion of nearly all EF tasks. Working memory and attention set the stage for the development of more involved EF skills such as planning, flexible rule use, and organization in adolescence and early adulthood (DeLuca & Leventer, 2008; Smidts, Jacobs, & Anderson, 2004).

Executive Function Development and Brain Development

EF develops over time with periods of rapid growth that parallel brain development. From roughly 24 weeks gestation to birth, cortical organization occurs through the rearranging of neurons in the supporting structure of the cortex (Volpe, 1995; 1997; 2001). Additionally, structural differentiation in the central nervous system occurs (i.e., neuronal differentiation, glial cell growth, and axonal and dendritic growth); these neurons engage in synapse formation by sending out axons to connect with both nearby and distant areas of the brain. This early organizational process sets the foundation for circuitry connecting far reaching areas of the brain to the frontal lobes, which is essential for continued and normal development of the EF system (Volpe, 1995). From birth to age two, myelination and rapid synapse formation are the most active and important processes of cortical development. During this time rapid synapse formation is occurring throughout the brain, with peak synaptogenesis occurring relatively late in the prefrontal cortex (Huttenlocher & Dabhollkar, 1997). A similar pattern is seen in myelination, which occurs in a pattern from caudal to anterior and from dorsal to ventral regions (Kinney, Brody, Kloman, & Gilles, 1988). By age two the majority of brain myelination occurs, however, the prefrontal cortex is the last area in the brain to begin to myelinate, and myelination in the prefrontal cortex is not complete until the third decade of life (Klingberg et al., 1999).

In parallel to these increases in brain complexity and speed during the first 2 years of life, striking gains in EF abilities are also observable during this age range. The foundations of EF are present early in life and are first seen reliably between 7 and 8 months of age when the first signs of working memory and inhibitory control can be observed (Sun, Mohay & O'Callaghan, 2009). At this stage a child demonstrates object permanence and can find a toy after it has been hidden. By eight to nine months of age children can find a toy even when it changes locations.

Infants at this age can inhibit reaching to the previous spot and are able to search in a different location (the A-not-B task with a one second delay) (Diamond, 1985). By 12 months, children can respond appropriately to the A-not-B task with a 10 second delay (Diamond, 1985). Additionally, around one year of age successful performance on object search and measures of self-control can be seen (Welsh and Pennington, 1988). By age two, there emerges the ability to categorize and sort objects by a single rule (Carlson, 2005).

In preschool, notable gains in a child's EF abilities are observed; mirroring a continued increase in the frontal lobes due to steady increases in both gray and white matter (Sowell, Thompson, & Toga, 2004). Between 3 and 5-years-of-age, major gains in executive control (sustained attention and inhibition) have been documented. Posner, Rothbart, Sheese and Voelker (2012) have proposed that the interplay between orienting responses and emotional reactivity leads to the development of executive attention. Additionally, memory span, working memory capacity, and cognitive flexibility increase during the preschool age (Luciana & Nelson, 1998). Planning and goal directed behavior begin to emerge during this age, and are thought to be largely dependent upon the increases in inhibition, working memory and attention that precede them (Brocki & Bohlin, 2004). The use of two discriminating rules is mastered by age 3. The ability to switch dimensions, by attending to two disparate aspects of the same object, and sorting according to the requested dimension, is typically attained by age 5 (Davidson, Amso, Anderson, & Diamond, 2006; Zelazo, Carter, Reznick, & Frye, 1997). Errors in EF at this age are largely due to failure in applying knowledge effectively in the midst of changing rules and environments. For example, although children continue to perseverate in their errors during card sorting tasks, they can easily verbally state the correct rule. This EF error is thought to be caused by a failure in the inhibition of a prepotent response (Diamond, Kirkham, & Amso,

2002). During the preschool ages children are thought to possess EF abilities, but lack the awareness or metacognition to allow them to utilize these EF abilities effectively (Espy, 2004). Difficulties in integrating their disparate EF skills, and deploying them at the appropriate times in particular contexts, plague optimal EF performance at this age.

In late childhood and preadolescence a continued increase in cortical gray matter and white matter is observed, as well as continued myelination across the brain. This activity is especially pronounced in the frontal lobes (Rapoport et al., 1999). It has been documented that during this time period increases in processing speed occur, which facilitate EF performance. It is during this period that individuals are able to complete adult tasks of EF, which include complex stimuli and games that activate novel situations, and tax working memory (Golden, Hammeke, & Purisch, 1978; Heaton, Chelune, Talley, Kay, & Curtiss, 1993). Additionally, research shows that in late childhood and preadolescence some EF skills mature to levels commonly seen in the adult population. For example, by age 10, performance on the WCST reaches adult-like levels in categories achieved, trials, errors, and perseverative errors (Heaton, Chelune, Talley, Kay, & Curtiss, 1993).

Throughout adolescence, continued increases in white matter are found until white matter reaches mature levels around age 19 (Luna & Sweeney, 2001). This is paired with a decrease in gray matter, which is thought to result from the pruning of inefficient connections (Sowell, Thompson, & Toga, 2004). These brain developments are linked with increases in related EF abilities such as increased attentional control, processing speed, and mature levels of inhibitory control (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). Prefrontal cortex myelination continues well into the third decade of life, and peak EF skills are thought to occur between 20-29 years of age (DeLuca et al., 2003). Additionally, functional magnetic resonance

imaging (fMRI) studies have demonstrated that adults show less activation and more specific areas of activation, as measured by the volume of cortex engaged and the percent signal change, than children. Children are thought to have extra neuronal area recruitment and hyperactivation in response to EF tasks due to the immaturity of the primary brain areas that are utilized efficiently by adults when completing these tasks (Tamm, Menon, & Reiss, 2002). This level of efficiency and effectiveness appears to only last a few decades before these skills begin to deteriorate. In summary, EF develops continuously until late adolescence, peaking in early adulthood and declining with old age (Zelazo, Craik, & Booth, 2004). EF is thus conceptualized as an ability that grows and changes in sophistication over time.

Widespread Neural Bases of Executive Function

The developmental trajectory of increasing complexity in the disparate EF domains, as well as increasing facility in combining them into broader high-level EF, has been shown to correlate strongly with frontal lobe development (Anderson, 2008). Biological bases of EF are dispersed throughout the brain. Virtually every brain region and subcortical structure has been implicated in EF (Anderson, 2008). Although the prefrontal cortex was once synonymous with EF, it is now understood that EF depends on extensive reciprocal connections between the prefrontal cortex, brain stem, limbic system, cerebellum, subcortical regions, occipital, parietal, and temporal lobes of the brain (Fuster, 1993; Stuss & Benson, 1984).

Individuals can have profound EF deficits in the absence of a frontal lesion or other known frontal pathology, and damage to the frontal lobes does not necessarily translate to EF deficits (Roberts, Robbins, & Weiskrantz, 1998; Stuss & Benson, 1984). Additionally, diffuse brain injury (i.e. white matter damage) in the absence of frontal damage can lead to executive

dysfunction as well (Roberts, Robbins, & Weiskrantz, 1998; Stuss & Benson, 1984). Therefore, EF deficits are not just indicative of frontal lobe abnormalities, but in fact can result from disruption at any level of the aforementioned interrelated systems. Even if the frontal lobes are functioning optimally, damage or mis-wiring in the various subcortical, cerebellum, or limbic regions can result in EF impairments (Luna, et al., 2001). Thus, the executive dysfunction seen in both developmental and acquired disorders can result from impaired development, mis-wiring or disruption in any of the numerous pathways and feedback loops that connect the frontal lobe to other regions and structures in the brain.

The Importance of Studying EF

EF tasks tap areas that are closely related to real world adaptive functioning, and might speak more broadly and descriptively to outcome, in terms of constructs such as quality of life, than IQ tests alone. The development of EF skills is closely related to other milestones of childhood and many positive outcomes. For example, in healthy full term children, delay of gratification (a measure of impulse control) in preschoolers is predictive of cognitive, academic and social outcomes a decade later (including SAT scores) (Mischel, 1996; Mischel, Shoda, & Rodriguez, 1989; Shoda, Mischel, & Peake, 1990). The fact that EF is so predictive of positive outcomes, even after correcting for preschool intelligence, points to EF as a strong variable in the real world functioning, success, and adjustment of children. This long term predictive relationship has been seen in typically developing children, but has not yet been shown in children born preterm.

EF is relevant to study in preterm samples because it is a functional ability that taps into how well people solve everyday problems and interact with the world (Norman & Shallice,

1986). Additionally, it manifests in everyday situations, and is an applicable and generalized skill. For example, it has been shown that children with frontal lobe damage and executive dysfunction show impairments in social and moral functioning, as well as IQ (Price, Daffner, Stowe, & Mesulam, 1990). EF is also correlated with "fluid intelligence" or "g" (Anderson, Bechara, Damasio, Tranel, & Demasio, 1999). However, it has been found that three common EF abilities (response inhibition, working memory updating, and task-set switching) share a highly heritable common factor that can be distinguished from IQ or information processing speed (Friedman et al., 2008; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000). Friedman and colleagues (2006) found that IQ was significantly related to working memory updating, but was not associated with response inhibition or task-set switching. This demonstrates the potential unique contributions of EF above and beyond what IQ and processing speed measures can tell us.

There is a growing body of literature showing that EF is critically important for success in school and daily life. A number of studies have documented that EF in young children predicts school readiness better than IQ or entry-level academic knowledge (Blair & Diamond, 2008; McClelland, Morrison, & Holmes, 2000). There is also evidence that executive control dysfunction in children leads to a range of secondary disabilities such as drug and alcohol abuse, trouble with the law, incarceration, and deficient social skills (Streissguth et al., 2004, Schonfeld, Paley, Frankel, & O'Connor, 2006). Thus, typical EF function may be central to cognitive function, as well as social, emotional, and moral development.

Issues in the Measurement of EF in Children

Since EF is a developing ability, much research is now focused on the emergence of EF. The measurement of EF in children is a new area of interest and innovative measures are quickly being devised (Carlson, 2005; Jacques & Zelazo, 2001; Kochanska, Murray, & Harlan, 2000; Zelazo, Reznick, & Pinon, 1995). Many of these measures have been adapted from adult measures of EF and made more simple and child-friendly.

EF in children is challenging to measure and fraught with potential confounds and difficulties. One of the main problems with measuring EF is that automatic and controlled processes exist on a continuum. The processes underlying a controlled task will shift to more automatic processes over time (Carlson, 2005; Jacques & Zelazo, 2001; Kochanska, Murray, & Harlan, 2000; Zelazo, Reznick, & Pinon, 1995). A task will cease to be novel if it is repeated at length, and thus re-administration can never tap EF the same way the first administration did. This can result in poor test-retest reliability, and therefore has some serious limitations.

Additional challenges to measuring EF in children include task selection, summarizing overall functioning, the multifaceted nature of EF, and scoring concerns. The standard tasks that measure EF are complex and can vary greatly from study to study. Since there is no consensus on the operational definition of EF, it is probable that studies are not measuring the same construct. There is no "prototypical" task that is failed by all with dysexecutive problems (Burgess, 1997). In part, it seems that not all tasks tap into the same EF. Some tasks are designed to activate inhibition, others to tap working memory domains, while others focus more on flexible rule switching. Confusing the situation even more, many of the complex measures of EF contain multiple demands (i.e., working memory, inhibition, task switching and flexibility) so as to activate novel situations and tax working memory. In this case, the performance of an

individual on certain EF tasks actually reflects pooled outcomes of distinct processes, which can make it hard to parse (Hughes & Graham, 2002). Scoring is difficult in that many of the tasks given to children are scored as pass or fail, and the lack of many continuous variables makes relationships among various EF tasks difficult to ascertain.

Another concern in measuring EF in young children is that the ecological validity of lab based performance measures of EF is unclear and at times conflicting (Wodka, et al., 2008). Tarazi, Mahone, and Zabel (2007) argued that lab based tasks are inherently highly structured and the structure provided by the experimenter and the setting may serve to help organize and scaffold a child's EF performance. The highly structured setting may not place a strong enough demand on the child to truly tax EF abilities, and thus see enough variation in the test results. It has also been found that children with above average IQ might perform more highly on EF measures due to a lack of sensitivity in many performance based EF tasks (Mahone et al., 2002a). Since there are many concerns about EF performance based measures, clinicians have been encouraged to use performance based measures of EF in conjunction with other measures of EF, such as parent report of EF (Denckla, 2002). Thus, there are many discrete performance based tasks and parent report measures that are being developed for children, but it is unclear how to best summarize a child's EF into an overarching and coherent picture.

Executive Function in the Very Low Birth Weight Population

Thus far, several studies have shown EF deficits in children school-aged and older who were born prematurely (Anderson, et al., 2003; Anderson & Doyle, 2004; Böhm, Katz-Salamon, & Smedler, 2002; Curtis, Lindeke, & Georgieff, 2002; Hack et al, 2005; Harvey, O'Callaghan, & Mohay, 1999; Korkman, Liikanen, & Fellman, 1996; Luciana, Lindeke, & Georgieff, 1999;

Rickards, Kelly, & Doyle, 2001;Taylor, Klein, Minich, & Hack, 2000). Additionally, these differences in EF performance between VLBW and full term controls persist even after taking IQ differences into account (Bayless & Stevenson, 2007; Wolke & Meyer, 1999). In school age and adolescent populations, it has been demonstrated that compared to children born full term, preterm children appear to have EF deficits in sustained attention, working memory and planning. Mixed evidence exists for deficits in the areas of mental flexibility and inhibition (Anderson, et al., 2003; Anderson & Doyle, 2004; Bayless & Stevenson, 2007; Böhm, Katz-Salamon, & Smedler, 2002; Curtis, Lindeke, & Georgieff, 2002; Hack et al, 2005; Harvey, O'Callaghan, & Mohay, 1999; Korkman, Liikanen, & Fellman, 1996; Luciana, Lindeke, & Georgieff, 1999; Rickards, Kelly, & Doyle, 2001; Sun, Mohay, & O'Callaghan, 2009; Taylor, Klein, Minich, & Hack, 2000; Wolke & Meyer, 1999). Additionally, five year olds born VLBW were found to perform significantly more poorly on a composite of NEPSY II items measuring EF (auditory attention, visual attention, and inhibition) in comparison to full term controls (Lind et al., 2010).

Since EF deficits have been documented in school aged children born VLBW, studying these vulnerable populations at younger ages could result in clinically useful EF interventions. Measures have recently been developed which allow researchers to tap the foundations of EF in very young children, particularly in areas of working memory, impulse control, and rule use. Although these new measures for preschool children have been employed widely with typically developing populations (Carlson, 2005; Hongwanishkul, Happaney, Lee, & Zelazo, 2005), there are currently very few studies investigating EF in preschool children born prematurely.

Few studies have been conducted that examine EF in preschoolers born VLBW. The majority of these studies have found that preschoolers born VLBW have demonstrated EF deficits. However, some studies have not found EF deficits beyond the effect of global IQ differences. Specifically, preterm preschoolers were shown to have poorer performance on delayed-response type EF tasks compared to full term controls (Espy et al., 2002). Additionally, preschoolers born LBW without major neurological deficits may have specific difficulty in sustained attention, visuospatial processing, and spatial working memory when compared with full term children matched for chronological age and IQ (Vicari, Caravale, & Carlesimo, 2004). On measures of working memory and inhibition, 3-year-olds born ELBW performed more poorly on EF computer touch screen based tasks than full term children (Baron, Kerns, Müller, Ahronovich, & Litman, 2011). In contrast, Esbjorn, Hansen, Greisen and Mortensen (2006) found no effect of prematurity on EF beyond general cognitive deficits. The authors concluded that differences in EF performance between full term and preterm groups were due to general cognitive deficits, not specific EF deficits. However, this group of researchers excluded all of the ELBW children who did not complete the EF battery, which was a significantly greater proportion than for their full term control sample, which may have biased their results (Esbjorn, Hansen, Greisen, & Mortensen, 2006). In sum, it is currently unclear if the deficits seen at school age in children who were born VLBW can be detected as young as preschool; and whether these deficits are primarily due to more general cognitive deficits. A greater understanding of EF in preschoolers who were born VLBW would fill a glaring gap in the literature.

Understanding early EF differences in preschoolers born VLBW may benefit these populations by leading to the use of targeted interventions. Several intervention models have

been shown to improve EF and real world problem solving ability in at-risk children (Bierman, Nix, Greenberg, Blair, & Domitrovich, 2008; Blair & Diamond, 2008). If EF deficits were detectable before children began school, then there is the potential for early intervention designed to target these executive dysfunctions, which could improve EF abilities before school performance is affected.

Understanding the Dimensionality of the EF Construct in Children born VLBW

The construct of EF is poorly understood in the VLBW population, especially early EF that is emerging in the preschool age. In older children, there is some evidence that children born VLBW have EF deficits in all areas of EF (working memory, planning, sustained attention, mental flexibility and inhibition), which may suggest a one-dimensional EF construct in preschoolers born VLBW. Similarly, Anderson et al. (2010) examined early brain injury through varying etiologies (acquired in childhood, congenital and perinatal injury) to determine if age at injury was associated with different EF profiles. They found that congenital and perinatal brain injury before age 3 was associated with a global pattern of EF deficits. This would align with neuroimaging research that has demonstrated extensive diffuse white matter injury in preterm and VLBW children, and thus would predict global EF deficits and implicate a single underlying EF factor (Inder, Wells, Mongridge, Spencer, & Volpe, 2003; Luciana, 2003).

However, other studies show a more varied pattern of impairment in which children born VLBW have marked areas of deficit, with other areas of EF that are unimpaired. In school age and older populations, some studies report EF deficits in certain areas (working memory, planning, and sustained attention) and no deficits in the domains of inhibitory control and mental

flexibility. This may provide support for the idea that EF has multiple facets, some of which are impacted by preterm birth and others of which remain unaffected.

Not only is the dimensionality of EF in VLBW children poorly understood, there are also specific gaps in the current literature as to the dimensionality and nature of EF in typically developing preschool aged children. In typically developing populations some researchers argue that EF is a multidimensional concept like we see in adults (containing multiple facets) (Garon et al., 2008 for review), while other researchers have found evidence of a single dimension. Carlson (2005) conducted a principal components analysis (PCA) and found two unique factors related to delay (inhibition) and conflict (cognitive flexibility). Other studies have demonstrated that during the preschool period EF is an undifferentiated and unitary concept (Carlson, Mandell, & Williams, 2004; Hughes & Ensor, 2007; Wiebe, Espy, & Charak, 2008; Weibe et al., 2011). A main gap in the literature is that the construct of EF in VLBW populations has not been explored. An important question that has not been addressed to date in the literature is, when investigating performance based measures of EF, is EF a multidimensional or unitary construct in preschool aged children who were born VLBW?

Multimodal Measurement of EF

Performance Based Measures of EF

A variety of experimental behavioral EF measures designed for preschoolers have recently been developed. These have largely originated in the developmental literature as a way to examine typical developmental trajectories of EF. Many of these measures have been adapted from adult tasks of EF and made more simple and child-friendly (Carlson, 2005; Jacques &

Zelazo, 2001; Kochanska, Murray, & Harlan, 2000; Zelazo, Reznick, & Pinon, 1995). Common research paradigms include inhibitory control tasks (delaying of a desired outcome), inhibitory tasks (inhibit a prepotent response and provide an alternate response that is counterintuitive), and flexible rule use tasks (complete a task according to one rule then flexibly inhibiting the prior rule and switching to utilizing a new rule). In the current study we utilized a variety of performance based tasks designed to address these primary EF domains (detailed descriptions available in the measure section).

Inhibitory control was assessed through two delay of gratification tasks: Gift Peek and Gift Touch. In the Gift Peek task, the child has to inhibit peeking at a gift while it is noisily wrapped by the examiner (Carlson, 2005; Kochanska et al., 1996). In the Gift Touch task, the attractively wrapped gift is placed in front of the child who is told not to touch it (Espy, Kaufmann, Glisky, 1999; Vaughn, Kopp & Krakow, 1984).

To assess inhibition of prepotent responses, the Bear Dragon task was used (Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996; Reed, Pien, & Rothbart, 1984). In this task a bear hand puppet and a dragon hand puppet alternate giving commands (e.g., touch your nose). Children were told to comply with the bear's directions and to not move when the dragon gave a command.

To assess flexible rule use, a battery (Progressive Executive Categorization Battery (PECB)) was created from sequentially more difficult card sorting tasks. For these tasks the child was asked to first sort by one category (e.g., color) and then once a sorting set had been established through multiple trials, the sorting category was switched (e.g., shape). The PECB consisted of the following four tasks: Categorization and Reverse Categorization task (Carlson,

Mandell, & Williams, 2004), Dimensional Change Card Sort- Separated Dimensions task
(Diamond, Carlson, & Beck, 2005), and the original Dimensional Change Card Sort (DCCS task;
Frye, Zelazo, & Palfai, 1995).

Parent Report Measures of EF

In addition to experimental behavioral measures of EF, many studies of EF in children
born VLBW measure EF using parent report. No studies have examined the relationship between
parent report of EF and performance measures of EF in preschoolers born VLBW. The youngest
sample to address this question in children born VLBW was collected by Lind et al. (2010).
They examined 5 year old children who were born VLBW and found that some EF measures
(auditory attention, visual attention and inhibition) on the NEPSY-II were associated with parent
report of EF on the Five to Fifteen questionnaire (estimated regression coefficient = .183, p =
.002), while other NEPSY-II measures that had some EF demands (language abilities: speeded
naming, comprehension of instructions, phonological processing; memory: narrative memory,
memory for designs, word list interference) were not associated with parent report of EF.
Additionally, Carlson and Wang (2007) found that in typically developing preschoolers, parent
report of self-control was significantly correlated with children's performance on the measures of
inhibitory control (Gift delay, Simon says, and Forbidden gift). These correlations remained
significant even after controlling for age and verbal ability (Carlson & Wang, 2007).

The most commonly used standardized parent measure of EF is the BRIEF (6-18 years)
or the BRIEF-P (2-5 years). The relationship between the BRIEF-P and performance based
measures of EF have not been evaluated in preschoolers born VLBW. Poorer scores on the
BRIEF and BRIEF-P have been shown in groups with documented EF deficits. Additionally,

divergent validity has been shown between the BRIEF-P and other parent ratings of ADHD and other behavior problems (Gioia, Espy, & Isquith, 2003). However, the validity of parent-based measures of EF has been questioned (Denckla, 2002), and the relationship between lab based performance measures and parent report on the BRIEF-P has not been studied in preschoolers. The validity of the BRIEF-P in predicting EF performance in preschoolers has not been studied empirically. However, research with the BRIEF in older children with a variety of conditions and disorders has shown poor predictive utility and there are concerns that parent measures of EF (like the BRIEF and BRIEF-P) might be measuring more general behavioral difficulties seen at home (Denckla, 2002; Mahone & Hoffman 2007).

Some studies have examined the concurrent relationship between parent reported BRIEF-P and performance based EF tasks in typically developing preschoolers. Liebermann, Giesbrecht, and Mueller (2007) demonstrated that in a group of typically developing preschoolers (ages 3-6), BRIEF-P scores were not significantly correlated with children's performance on EF tasks (gift delay, backwards digit span, and intradimensional/ extradimensional shifts). Additionally, in a group of preschoolers with attention deficit hyperactivity disorder (ADHD) the BRIEF-P was not significantly correlated with performance-based measures of EF. Yet, the BRIEF-P was sensitive to symptoms of ADHD (Mahone & Hoffman, 2007). Thus, the parent report of EF on the BRIEF-P, in typically developing preschoolers and preschoolers with ADHD may not be tapping the same construct as performance based measures of EF. However, if parent report measures do tap EF, they may have more ecological validity than lab based performance tasks. This has yet to be explored in preschoolers born VLBW.

Much of the relevant outcome research has been conducted with the BRIEF in older school age samples. However, the relationship between the parent ratings of EF and

performance based EF at school age may still be informative in our understanding of the interrelationships between different types of measures of EF in preschoolers. In school aged children who are typically developing (Bodnar et al., 2007), children with brain disease (Anderson et al., 2002), children with traumatic brain injury (TBI) (Vriezen & Pigott, 2002), children with prodromal psychosis (Niendam et al., 2007), and children with ADHD (Mahone & Hoffman, 2007), the BRIEF has generally not been found to correlate well with performance based measures of EF. In fact, some have argued that the BRIEF seems to capture more disparate elements of the EF construct, such as general behavioral dysregulation and parental defiance, than is measured by performance based tests (Denckla, 2002; Mahone & Hoffman 2007).

A relationship between the BRIEF and measures of cognitive-executive function has not been consistently found. However, some significant correlations between the BRIEF and EF tasks have been demonstrated. In a sample of adolescents with ADHD, Toplack et al. (2009) found modest correlations between some scales of the BRIEF and EF performance measures of set shifting (correlation coefficients ranging from .23 to .39) and working memory (-.30 to -.41). They did not find significant correlations between the BRIEF and measures of inhibition (.09 to .21) or planning (-.22 to -.26). Additionally, in children with various types of brain disease, BRIEF domain scores were found to correlate with some cognitive EF measures including the Contingency Naming Test (CNT), Rey Complex Figure (RCF), Tower of London (TOL), and Controlled Oral Word Association Test (COWAT), in older children (Anderson, et al., 2002).

The relationship between performance based measures of EF and parent report measures of EF is unclear, and yet, some parent report measures of EF have shown considerable promise as predictors of symptomatology, adaptive skill development, and functional life skills (Mahone

et al., 2002b, Ries et al., 2003, Waber et al., 2006). Toplack et al. (2009) demonstrated the

clinical/ecological utility of the BRIEF over performance measures of EF in predicting ADHD

diagnosis. They also found no significant associations between the performance based EF tasks

and the number of inattentive and hyperactive/impulsive symptoms. However, parent report on

the BRIEF was significantly associated with the number of inattentive and hyperactive/impulsive

symptoms (Toplak, Bucciarelli, Jain, & Tannock, 2009). Thus, parent ratings of EF have the

potential to add to the predictive validity of performance based EF measures. However, the

authors of the BRIEF-P, as well as others, have provided the caveat that all behavioral report is

subject to rater bias and suggest that the BREIF-P be used as a complimentary assessment tool

alongside other developmentally appropriate performance based measures of EF (Denckla, 2002;

Isquith, et al, 2005).

Observational Coding of EF

Observationally coded measures of compliance have also been postulated to relate to EF.

No extant research has examined observational EF measurement in preschool children born

VLBW. However, some studies have been conducted with observationally coded compliance

and performance based EF measures in full term typically developing preschoolers. Vaugh,

Kopp, and Krakow (1984) found that inhibition of touching an attractive item in a lab based

performance task was related to a compliance task (picking up toys) in 18 and 30-month-olds,

but not in 24-month-olds. Hughes and Ensor (2006) used compliance from video coding of

parent child interactions as part of a behavioral problems measure in typically developing 2-year-

olds. EF and the behavior problems measure were highly correlated ($r = -.49$, $p < .01$): as non-

compliance increased, EF performance decreased. In fact, EF accounted for 24% of the variance in the behavior problems measure (Hughes & Ensor, 2006).

Additionally, there is some evidence that early compliance relates to later EF. One study found that typically developing toddlers' and preschoolers' compliance with an adult request requiring inhibition was predictive of EF at 14-years-old (Friedman, Miyake, Robinson & Hewitt, 2011). The relationship between observed compliance, EF tasks, and parent-reported EF has only been examined in one study to date. In typically developing toddlers, Morasch and Bell (2011) found that compliance was related to parent rated measures of temperament-based inhibitory control, but compliance was not related to EF performance based measures. Additionally, Kochanska, Murray and Coy (1997) found that parent report of inhibitory control was related to compliance with a mundane activity (e.g., cleaning up toys) in preschool children. Compliant children had higher ratings of parent-reported inhibitory control than children who refused to clean up the toys (Kochanska, Murray, & Coy, 1997). Combining observational coding, parent report and performance based measures of EF has infrequently occurred and may shed light on the interrelations between different methods of measuring EF. Additionally, observational coding of children's behavior in naturalistic situations may have more ecological validity than utilizing purely lab-based tasks.

Limited literature addresses the relationship between multimodal measurements of EF among preschoolers born VLBW. As stated earlier, the validity of the BRIEF-P in predicting EF performance in preschoolers has not been studied and the relationship between observationally coded compliance and EF performance has not been examined in preschoolers born VLBW. By triangulating the construct of EF through different assessment methods we can better understand the construct, and the construct validity of EF in children born VLBW

Some critical questions that remain unanswered include: in preschoolers born VLBW, do the various ways of measuring EF (parent report, behavioral coding and performance measures) relate to each other? More specifically, how does the parent report of EF relate to child EF performance and behavioral coding? Since the BRIEF-P is a parent report of children's everyday behavior, the naturalistic behavioral coding measure of EF (Compliance) might align with the BRIEF-P more than the performance-based measures of EF. Addressing these questions will give us a better understanding of EF in preschoolers born VLBW. Developing a better understanding of EF in preschoolers born VLBW would allow us to identify early EF differences and potential early predictors of later outcome.

Neuroanatomical Variables Related to EF

Exploring the relationship between EF and neuroanatomical structure can help us to better understand EF in children born VLBW. Heterogeneity and interindividual difference related to EF within the population is common; some individuals appear to experience no detectable EF impairment while others are severely impacted (Hack et al., 2000). Understanding this variability in outcome, and discovering the predictors of EF in children born VLBW would greatly increase our ability to tailor interventions for this population. Children born preterm are at greater risk for medical complications, including mortality, as well as acute and chronic disabilities. This vulnerability is believed to be due to the immaturity of multiple organ systems at birth, and thus smaller and more premature infants are at higher risk for increased medical complications (Hack & Fanaroff, 1999; Ward & Beachy, 2003). Perinatal brain injury is of particular concern in relation to executive function abilities. Three specific kinds of brain injury are associated with preterm birth: intraventricular hemorrhage (IVH), cystic periventricular

leukomalacia (PVL) and diffuse white matter abnormalities (Volpe, 2009). IVH and PVL have relatively low incidence rates (4% and 3% respectively). Diffuse white matter injury has the highest incidence, with 20% of infants born preterm displaying moderate to severe white matter abnormalities, and another 51% displaying mild abnormalities (Inder, Wells, Mongridge, Spencer, & Volpe, 2003).

Diffuse white matter injury, hypothesized to be caused by hypoxia/ischemia and cytokine attack early in life, can have far reaching consequences on brain development. Specifically, diffuse white matter injury can negatively impact subsequent myelination, development of subcortical structures such as the basal ganglia and thalamus (Inder, Wang, Volpe, & Warfield, 2003), cerebellar growth (Shah et al., 2006), maturation of gray matter structures (Inder et al., 1999), subsequent development of white matter fiber tracks (Huppi et al., 2001), and result in axonal damage and damage to immature oligodendrocytes (Volpe, 1997). White matter integrity is essential to prefrontal neural networks implicated in EF and attention processes, as well as efficient information processing and response speed (Filley, 2001). The extensive EF impairments seen in individuals who were born preterm are more consistent with diffuse white matter abnormalities rather than direct injury to the prefrontal cortex (Luciana, 2003). Elucidating the relationship between neuroanatomical factors and EF abilities can help provide relevant correlates to our EF measures and can help us to better understand EF in children born VLBW.

Neuroimaging Findings Related to EF

No studies to date have examined EF in preschoolers born VLBW in conjunction with neuroimaging. In fact, no neuroimaging studies have examined EF in healthy full term children

during the preschool age. Most neuroimaging studies of EF in the VLBW population have been

conducted during infancy at term (the equivalent of 40 weeks gestation) and these perinatal brain

images are then associated with EF abilities at later ages (Woodward, Edgin, Thompson, &

Inder, 2005). Other researchers have utilized adolescent or adult samples that were born VLBW

and examined their concurrent EF abilities and neuroimaging findings. Since concurrent

measures of EF and neuroimaging in preschool children have not been conducted, literature

examining the relationship between neuroimaging and EF in other ages (infant MRI predicting

EF in preschool children born VLBW, older children born VLBW, and adolescents born VLBW)

and other populations (typically developing and other special populations) will be summarized.

EF and Neuroimaging in Children, Adolescents and Adults Born VLBW

Infant Neuroimaging Predicts Toddler, Preschool and Childhood EF in VLBW

There is some support that MRI at term is related to neurodevelopmental outcomes in

toddlers who were born preterm. When examining regional brain volumes at term (the

equivalent of 40 week gestational age), Peterson et al. (2003) found that several areas were

significantly related to overall Bayley mental development scales at 18-20 months corrected age.

Specifically, neonatal MRI volumes at term in the following areas were related to developmental

outcome for the mental subscale of the Bayley: right and left white matter volumes in the

premotor regions, left and right white matter in the sensorimotor regions, left and right

midtemporal regions, the right subgenual region, gray matter in the left sensorimotor cortex, and

gray matter in the left midtemporal cortex. After correcting for gestational age, developmental

outcome still correlated with white matter volumes in the right midtemporal and right

sensorimotor regions (Peterson et al., 2003). Another study conducted by Woodward, Edgin,

Thompson, and Inder (2005) showed that MRI conducted at term was related to object working memory at age two. They found that working memory performance at age two was related to bilateral reductions in total tissue volumes in the dorsolateral prefrontal cortex, sensorimotor, parietooccipital, and premotor areas (Woodward, Edgin, Thompson, & Inder, 2005). Thus, there is some support for the idea that MRI volumes at term are related to overall mental ability and specific working memory skills in toddlerhood. The following areas have been implicated: midtemporal regions, dorsolateral prefrontal cortex, parietooccipital regions, and the right subgenual areas, with converging evidence existing for the importance of volumes in the premotor and sensorimotor areas.

Relationships have also been found in preterm children between MRI at term and neurodevelopmental outcomes at school age. Lind et al. (2010) compared term MRI volumes with NEPSY-II performance measures of EF and parent report of EF at age 5. They found no significant associations between the brain volumes and the NEPSY-II domains. For the parent report of EF in everyday situations (The Five to Fifteen (FTF) questionnaire) they found significant associations between a smaller total brain tissue volume, smaller cerebellar volume, and poorer parent report of EF. Even after controlling for total brain volume, the association between smaller cerebellar volume and poorer parent report of EF remained significant (Lind et al., 2010). Other more specific structural MRI measurements at term have also been found to be related to later school age outcome. Beauchamp et al. (2008) found that very preterm children, who had smaller hippocampal volumes as infants, were significantly more likely to perseverate on a working memory task. This remained true even after adjusting for relevant perinatal, sociodemographic, and developmental factors (Beauchamp et al., 2008). However, some studies have found limited relationships between MRI during infancy and school age outcomes.

One study found no relationship between white matter MRI abnormalities at age 1 and motor function, intellectual function, and perceptual function at six years of age in a group of children born VLBW without disabilities (Skranes et al., 1998). When concurrent cognitive function and MRI scans were conducted in 18-month-olds born VLBW, it was demonstrated that as orbital frontal volume decreased, the A-not-B scores of children born VLBW increased (Lowe, et al., 2011). In sum, mixed evidence exists for the relationship between infant MRI and school age developmental abilities in children born VLBW, with some studies finding no relationship between early MRI and later outcome, and other studies finding total brain volume, cerebellar volume, and hippocampal volume to be related to outcome in school age children. One possible explanation for the inconsistencies in this data is the heterogeneity of outcome variables utilized in these various studies.

Concurrent EF and Neuroimaging Findings in School Age Children Born VLBW

Although no studies to date have been published that examine whether concurrent EF and neuroanatomical variables are related in preschoolers born VLBW, studies have been conducted that investigate concurrent EF abilities and MRI structural findings in school age children, adolescents, and adults. White matter abnormalities, especially periventricular gliosis in the central occipital white matter and centrum semiovale, were related to lower scores on the WPPSI performance subtests of Block Design and Picture Completion in six year old children who were born preterm (Skranes et al., 1997). When examining structural volumes some correlations with IQ have been found in children born VLBW. In a sample of 8 to 10-year-old children who were born preterm and were at low risk (with limited medical complications), decreases in gray matter were found bilaterally in the temporal lobes and in the left parietal lobe (Soria-Pastor et al.,

2009). Additionally, specific gray matter in the middle temporal gyrus (BA 21) and postcentral parietal gyrus (BA 3) showed positive correlations with IQ (Soria-Pastor et al., 2009). In a group of 7-year-olds who were born preterm, IQ was correlated with right and left caudate volume and this association persisted (except for verbal IQ) even when total brain volume was taken into account (Abernathy, Cooke, & Foulder-Hughes, 2004). Decreased brain volumes in preterm children compared to full term children were found in the following areas: sensorimotor regions, premotor, midtemporal, parieto-occipital, and subgenual cortices, as well as smaller cerebellum, basal ganglia, amygdala, hippocampus, and corpus callosum volumes. Preterm children had larger ventricles (especially in the occipital and temporal horns) compared to full term children. Full-scale, performance, and verbal IQ were also positively associated with volumes in the sensorimotor and midtemporal cortices in eight-year-olds who were born preterm (Peterson et al., 2000). In school age children born preterm there appear to be white matter abnormalities and gray matter reductions in caudate volume, temporal, sensorimotor, and parietal areas that were related to lower IQ outcomes.

Concurrent EF and Neuroimaging Findings in Adolescents and Adults Born VLBW

Studies conducted with adolescents who were born VLBW show structural differences in brain volume and cortical thickness. Nagy et al. (2009) found that adolescents who were born preterm had 8.8% smaller overall gray matter volume and 9.4% smaller overall white matter volume than adolescents who were born full term. The gray matter reductions were found bilaterally in the temporal lobes, central, prefrontal, orbitofrontal, and parietal cortices, caudate nuclei, hippocampi, and thalami (Nagy et al., 2009). In a group of adolescents born VLBW, significant thinning was found in the middle temporal cortex and the posterior inferior parietal

cortex compared to adolescents who were born full term (Nagy, Lagercrantz, & Hutton, 2010). Areas where preterm adolescents had significantly thicker cortex were observed in the right anterior inferior temporal gyrus and the left ventrolateral prefrontal cortex. When this group was split by gestational age into greater than 28 weeks and less than 28 weeks groups, the greater than 28 weeks group showed significantly thinner cortex in the posterior regions of the parietal cortex and the prefrontal cortex, especially in the right dorsolateral prefrontal cortex, and also in right anterior temporal cortex. The group born less than 28 weeks showed pronounced thinning around the central sulcus and temporal lobes (Nagy, Lagercrantz, & Hutton, 2010). Martinussen et al. (2005) found reduced regional cortical thickness in the parietal, occipital, and temporal lobes, and increased thickness in the regional areas of the frontal and occipital lobes of adolescents who were born preterm.

Adolescents who were born VLBW show continued relationships between EF/cognitive abilities and regional brain volumes and cortical thickness. Martinussen et al. (2005) found that overall cortical thickness and surface area in the right and left hemispheres was positively associated with estimated IQ in adolescents born VLBW. Additionally, Martinussen et al. (2005) found that cognitive and perceptual function in adolescents born VLBW was predicted by cerebellar white matter volume. Allin et al. (2005) also found that poorer EF, visuospatial, and language functions were associated with decreased lateral cerebellum volume. When examining very preterm adolescents, Parker et al. (2008) found positive correlations between cerebellar volume and Full Scale IQ, Performance IQ and Verbal IQ. However, these relationships were not maintained after controlling for white matter volume. White matter was also implicated in the poor performance for adolescents born VLBW on the WCST (Skranes et al., 2008). Poor EF in this sample was related to larger ventricles, reductions in white matter, and thinning in the corpus

callosum (Skranes et al., 2008). Additionally, cerebral MRI pathology suggestive of perinatal white matter injury was related to disadvantages in performances in EF, but not to cognitive impairments in adolescents born VLBW (Skranes et al., 2008).

In adolescents who were born very preterm (less than 32 weeks), Nosarti et al. (2008) found that the very preterm group had increased volume in the white matter of the cingulate gyrus compared to full term adolescents, and that this was related to cognitive outcome. The very preterm group was found to have smaller volumes in the white matter of the brainstem, middle temporal gyrus, inferior temporal gyrus, and the occipital-frontal fasciculus, which predicted cognitive outcome (Nosarti, et al., 2008). Additionally, Nosarti et al. (2008) found that the very preterm group had smaller gray matter volume in the middle temporal gyrus, inferior temporal gyrus, and fusiform gyrus; all of which predicted cognitive outcome. Thus, in adolescents who were born preterm, relationships between cognitive outcome and neuroanatomical features were present for overall cortical thickness and surface area in the right and left hemispheres, overall cerebellar volume, cerebellar white matter volume, middle temporal gyrus, inferior temporal gyrus, corpus callosum, and overall white matter and ventricle size.

Studies have also examined the effects of very low birth weight on brain structure in adulthood. In adults born VLBW, Allin et al. (2004) found larger ventricles. They also found increases in ventricular dilation predicted decreased grey matter in subcortical nuclei and limbic cortical structures, as well as decreased periventricular white matter.

EF and Neuroimaging in Healthy Full Term Children

In healthy full term children the relationship between EF/cognitive outcomes and MRI has been examined. In a study of typically developing older school age children, structural brain findings were related to EF parent ratings. Specifically, parent rated working memory on the BRIEF and auditory working memory was correlated with total frontal gray matter volume (Mahone, Martin, Kates, Hay, & Horska, 2009). Wells et al. (2008) found that in healthy children, left and right temporal and frontal lobe volumes were significant predictors of Peabody Picture Vocabulary Test – 3rd Edition (PPVT-III) scores (D'Amato, Gray, & Dean, 1988). A longitudinal study examining cortical thickness changes within healthy children studied between 5 and 11-years-of-age over a 2-year span showed a significant relationship between gray matter thinning in the left lateral dorsal frontal and left lateral parietal areas and improved vocabulary scores. Performance on Block Design was also related to thickening in the left medial occipital region (Sowell et al., 2004). Additionally, in healthy children, orbitofrontal, medial temporal, and cerebellar volumes correlated with a task that measures shifting abilities (McAlonan et al., 2009), which implicates EF processes.

In another group of healthy children and adolescents, correlations were found between IQ and frontal white matter, temporal white matter and temporal gray matter (Lange, et al., 2010). The cerebellum has also been implicated in executive processes in healthy children. Dum and Strick (2003) hypothesized that the cerebellum white matter (especially the dentate nucleus) is involved in EF and has been specifically implicated in short term memory, rule based learning, and complex planning. Additionally, our understanding of complex reasoning might be furthered by the Parieto-Frontal Integration Theory (P-FIT). P-FIT hypothesizes that complex reasoning abilities in humans relies upon the interaction between parietal and frontal brain regions and the white matter structures that link them (i.e., arcuate fasciculus, superior

longitudinal fasciculus and Brodmann's areas (BA) (6, 9, 10, 45–47), anterior cingulate (BA 32), parietal gray matter (supramarginal (BA 40), superior parietal (BA 7), and angular gyri (BA 39)) (Jung & Haier, 2007).

EF and Neuroimaging in Other Special Populations

Examining other special populations with EF deficits may also help us to understand the relationship between neuroanatomical features and EF abilities in preschoolers born VLBW. ADHD is characterized by deficits in inhibition, attention, planning, and self-monitoring. In children with ADHD, anterior cingulate, striatal and medial temporal volumes were found to correlate highly with a response inhibition task (McAlonan et al., 2009). Additionally, McAlonan et al (2009) found that striatal and cerebellar volumes strongly correlated with a set-shifting task.

Several studies have also identified links between neuroanatomical markers in special populations and parent ratings of EF. In children with moderate to severe traumatic brain injury, a significant relationship existed between frontal white matter organization, measured by diffusion tensor imaging, and parent ratings on the BRIEF Emotional Control scale (Wozniak et al., 2007). Similarly, Anderson et al. (2002) reported that parent ratings on the BRIEF scales were elevated compared to controls, and were sensitive to differences between groups among children with hydrocephalus, effectively treated phenylketonuria (PKU), and frontal lesions. Additionally, in adults, as individuals progressed from concern about cognitive function to diagnosable Mild Cognitive Impairment, a commensurate increase in reported levels of executive dysfunction on an adult version of the BRIEF was found (Rabin et al., 2006).

Background Summary

Thus, children born preterm and VLBW weight are at increased risk for a variety of

neurocognitive and social-emotional difficulties compared to full term children (Anderson,

Doyle, Callanan, & Victorian Infant Collaborative Study Group, 2003). Although IQ is the most

common outcome measure in this population, researchers are discouraging the over

interpretation of IQ scores, and instead suggest relying on a broader approach to assessing

outcomes in preterm children (Aylward, 2002). EF, the ability to flexibly use rules, working

memory and inhibition, has the potential to tap important real world skills that have implications

for future outcome (Mischel, 1996; Mischel, Shoda, & Rodriguez, 1989; Shoda, Mischel, &

Peake, 1990) and recent tests have been developed that offer a window into EF abilities in

preschool children. Although impairments in EF have been documented in older children born

prematurely, little research has illuminated potential EF patterns and deficits in preschool

children born VLBW, and the dimensionality of EF in preschoolers born VLBW has not been

examined (Anderson, et al., 2003; Anderson, & Doyle, 2004; Böhm, Katz-Salamon, & Smedler,

2002; Curtis, Lindeke, & Georgieff, 2002; Hack et al, 2005; Harvey, O'Callaghan, & Mohay,

1999; Korkman, Liikanen, & Fellman, 1996; Luciana**,** Lindeke, & Georgieff, 1999; Rickards**,**

Kelly, & Doyle, 2001;Taylor, Klein, Minich, & Hack, 2000).

Exploring the relationship between EF and brain structural volumes can help us to better

understand EF in children born VLBW by placing the development of EF skills into a

neurodevelopmental context. Understanding the relationship between preschool EF and brain

development may help clarify the trajectories of brain specialization and EF skill development,

which may in turn yield a better understanding of how to intervene to benefit these children.

Further elucidating the relationship between different measures of EF and brain structure in

preschoolers born VLBW can help guide the development of interventions that can target EF

skills which have been shown to impact real world functioning. In this study we investigated EF abilities (both through direct performance based testing, child behavior coding, and parent report) and the relationship between neuroanatomical factors and EF skills in preschoolers born VLBW and full term.

Study Overview: Aims and Hypotheses

In order to further our understanding of executive function in preschool children born VLBW, and to build on the existing studies that have been reviewed in the previous sections, the current study examined EF in preschool children born VLBW and full term, and the neuroanatomical factors that may relate to EF in these samples. More specifically, the current study sought to (1) Better understand the construct of EF in preschoolers born VLBW through the examination of the dimensionality of EF in this sample by utilizing a variety of performance measures of EF (Bear Dragon, PECB, Gift Peek and Gift Touch), parent report of EF (BRIEF-P scales), and behavioral coding of EF (NICHD Cleanup Child Compliance); (2) Determine if EF abilities in preschoolers born VLBW align with structural brain differences gathered through MRI.

Aim One: Understanding the Construct of EF in Preschoolers Born VLBW

How does the theoretical construct of EF in preschoolers born VLBW map onto performance of EF tasks, parent report of child behavior, and naturalistic coding of child behavior? Many studies of EF in children born VLBW measure EF either by using parent report of EF or experimental performance measures of EF. Few studies have examined the relationship between parent report of EF, naturalistic child behaviors, and performance measures of EF. There are

concerns that parent measures of EF (like the BRIEF and BRIEF-P) might be measuring more general behavioral difficulties seen at home. In school aged children who are typically developing (Bodnar et al., 2007), children with brain disease (Anderson et al., 2002), children with TBI (Vriezen &Pigott, 2002), children with prodromal psychosis (Niendam et al., 2007), and children with ADHD (Mahone & Hoffman, 2007), parent measures of EF (i.e., the BRIEF) have not been found to correlate well with performance based measures of EF. In these groups, parent measures seem to capture disparate elements of the EF construct compared to those that are measured by performance based tests. Parent report is also limited by reading ability, parent-child relationship variables and overall child behavioral difficulties, leading to questioning of the validity of parent-based EF measures (Denckla, 2002, Mahone & Hoffman 2007). Therefore, it is likely that the BRIEF-P, which purportedly measures everyday EF abilities, is tapping into more general behavioral difficulties instead of EF as measured in EF performance based tasks in preschool aged children. However, this has not been studied, and if the BRIEF-P measures EF as it is purported to, then it would be expected to align with other EF measures.

Similarly, a relationship between observationally coded measures of compliance and EF has been postulated. If observational coding of children's behavior in naturalistic situations is related to EF then it would be expected to be related to other EF measures and may serve as a check for ecological validity of performance based measures. One study with typically developing toddlers found that compliance was related to parent rated measures of inhibitory control, but compliance was not related to EF performance based measures (Morasch & Bell, 2011). The convergent validity of the BRIEF-P, observational coding, and EF performance on lab-based measures of EF has not been studied in preschoolers born VLBW. Combining observational coding, parent report and performance based measures of EF may shed light on the

nature of EF and the interrelations between different methods of measuring EF in preschoolers born VLBW.

EF is an important outcome measure for children born VLBW, but few standardized measures of EF are currently available for preschool aged children. Most of the commonly used measures are theoretically derived but experimental in nature. It has been hypothesized that EF performance measures can be divided into Cool EF, tapped by rational and emotionless tasks such as card sorting and planning, and Hot EF, which is tapped by emotionally charged tasks such as delay of gratification or decision making about highly desired items. It is currently unclear how Hot and Cool EF tasks relate to each other in preschoolers born VLBW. In addition to measurement issues, the overall construct of EF is poorly understood in the VLBW population, especially early EF that is emerging in the preschool age. There are many studies that demonstrate that older children born VLBW have EF deficits in all areas of EF (working memory, planning, sustained attention, mental flexibility and inhibition). However, other studies show a more varied pattern of impairment in which children born VLBW have marked areas of deficit and other areas of EF that are unimpaired. Thus, although the majority of the literature supports the idea that children born VLBW have global EF deficits, which would suggest a single factor might account for EF performance, some studies have found specific areas of EF deficit in tandem with other areas of intact EF performance. Thus, it is unclear if EF performance in school aged children born VLBW loads onto a single factor or includes separate dimensions.

In typically developing populations, some researchers argue that EF in preschoolers is a multidimensional construct similar to what has been demonstrated with adults (containing the

facets of working memory, inhibition, and flexible rule use) (Garon et al., 2008 for review).

Others argue for unified and undifferentiated EF abilities during the preschool aged based upon

the patterns of brain development and specialization that occur over time.   A total of five studies

have been conducted to date that examine the dimensionality of EF performance based measures

in typically developing preschoolers. Four of these studies demonstrated that during the

preschool period EF is an undifferentiated and unitary concept (Carlson, Mandell, & Williams,

2004; Hughes & Ensor, 2007; Wiebe, Espy, & Charak, 2008; Weibe et al., 2011), while one

study found two unique factors related to delay (inhibition) and conflict (cognitive flexibility)

(Carlson, 2005). Thus, it is likely that EF as measured by performance based measures will load

onto a single factor. However, investigating how performance based measures of EF are related

to each other can help further our understanding of EF in the VLBW population.

In addition to a better understanding of the relationship between different measurements

of EF, this study also will add to the current literature about EF outcome during the preschool

age in children born VLBW. Although extensive research has documented the EF difficulties in

older VLBW children, fewer studies have explored EF in preschoolers born VLBW. Of the

limited literature that has examined this issue, most studies have found that EF deficits exist

within preschoolers born VLBW compared to their full term peers (Baron, Kerns, Müller,

Ahronovich, & Litman, 2011; Espy et al., 2002; Vicari, Caravale, & Carlesimo, 2004). However,

one study found EF differences were a result of global intelligence differences, not EF specific

deficits (Esbjorn, Hansen, Greisen, & Mortensen, 2006). In this study, preschoolers born VLBW

are expected to perform more poorly on measures of EF compared to preschoolers born full term

Thus, a main gap in the literature is that multiple methods of EF have largely not been studied in relation to each other in preschoolers born VLBW. Examining the relationship between the experimental performance measures of EF (Bear Dragon, Progressive Executive Categorization Battery (PECB), Gift Peek and Gift Touch), the parent report of EF (BRIEF-P scales), and the naturalistic behavior coding (NICHD Cleanup Child Compliance) will allow us to better understand the construct of EF. By triangulating the construct of EF through different assessment methods we can better understand the construct and the construct validity of EF in children born VLBW. Since the BRIEF-P is a parent report of children's everyday behavior, it might also be the case that the naturalistic behavioral coding measure of EF (NICHD Cleanup Child Compliance) might align with the BRIEF-P more than the performance-based measures of EF. Additionally, ascertaining whether the normed and standardized BRIEF-P scales map onto performance based measures of EF could inform test selection and utility. Thus, an important question to address is: How do the various ways of measuring EF (parent report, behavioral coding and performance measures) relate to each other? Addressing this question will give us a better understanding of how EF is functionally expressed in preschoolers born VLBW.

Yet another gap in the literature is that the construct of EF, as measured by lab based tasks, in VLBW populations has not been critically analyzed. This study will attempt to analyze how different performance measures of EF relate to each other in preschoolers born VLBW and full term by investigating whether EF is a multidimensional or unitary construct in this sample. Specifically, the current study will examine the dimensionality of EF in this sample by utilizing performance measures of EF (Bear/Dragon, PECB, gift delay peek, gift delay touch). The following hypotheses were used to examine the association between EF task based performance

measures in preschoolers born VLBW and full term. The following hypotheses examined the construct of EF in VLBW and full term preschoolers.

Hypothesis 1

When utilizing a principal components analysis (PCA) the multimodal EF variables will either offer a one-dimensional or two-dimensional construct of EF in VLBW and full term preschoolers in this sample. When including all measures of EF (Bear Dragon, PECB, Gift Peek, Gift Touch, BRIEF-P Global Executive Composite (GEC), and naturalistic behavioral coding (NICHD Cleanup Child Compliance score), either EF will be a unitary construct or a multidimensional construct for the preschoolers in this sample. Two specific rival hypotheses are presented. However, hypothesis 1a is predicted to be more likely if the BRIEF-P GEC and observational compliance coding are not truly tapping into EF, but rather more general behavioral difficulties, a conclusion that has more support from the literature:

> (1a) Based on results from similar studies in full term preschool children, when conducting principal component analyses, a single-factor solution is predicted with an eigenvalue greater than one, which will include all of the EF performance measures (Bear Dragon, PECB, Gift Peek and Gift Touch) and exclude the parent report of EF and the behavioral coding (BRIEF-P GEC and the NICHD Cleanup Child Compliance).

> (1b) Based on literature from typically developing preschoolers which showed observational coding and parent report to be more highly related to each other than EF performance measures, two components will emerge that will include: 1. The EF performance measures (Bear Dragon, PECB, Gift Peek and Gift Touch) and 2. The parent

report of EF and the behavioral coding (BRIEF-P GEC and the NICHD Cleanup Child

Compliance).

Hypothesis 2

When the VLBW and full term groups are combined, the EF performance-based measures will

either demonstrate a hypothesized one-dimensional construct of EF or a hypothesized two-

dimensional construct of EF in this group of preschoolers. Two rival hypotheses are presented

here. However, hypothesis 2a is assumed to be more likely since the limited number of similar

studies in full term preschool children have found that a single EF construct for performance

based measures has emerged more frequently than a two-dimensional factor structure.

(2a) Based on results from similar studies in full term preschool children, when

conducting principal component analyses, a single-factor solution is predicted with an

eigenvalue greater than one. Thus EF is predicted to be a unitary construct; with

performance measures of EF (Bear Dragon, PECB, Gift Peek and Gift Touch) being

different measures that tap into the same construct.

(2b) For the preschool children in this sample, EF will be a multidimensional construct

with a Hot component (Gift Peek and Gift Touch) and a Cool component (Bear Dragon,

and PECB).

Hypothesis 3

The VLBW group will perform more poorly on all derived PCA EF dimensions compared to the

full term group.

Aim Two: How Does EF Map Onto Brain Structure in MRI?

Perinatal brain injury is of particular concern with regard to EF abilities. Three specific kinds of brain injury are associated with preterm birth: intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL), and diffuse white matter abnormalities; of these, diffuse white matter injury has the highest incidence (Volpe, 2001, 2009). Diffuse white matter injury, hypothesized to be caused by hypoxia/ischemia and cytokine attack, early in life can have far reaching consequences on brain development. Specifically, diffuse white matter injury can negatively impact subsequent myelination, cerebellar growth (Shah et al., 2006), maturation of gray matter structures (Inder et al., 1999), and subsequent development of white matter fiber tracks (Huppi et al., 2001).

In healthy full term children, relationships between working memory and total frontal gray matter volume have been found (Mahone, Martin, Kates, Hay, & Horska, 2009). Reduced regional cortical thickness in the parietal, occipital, and temporal lobes, and increased thickness in the regional areas of the frontal and occipital lobes were found in adolescents born VLBW (Martinussen et al., 2005). Additionally, Dum and Strick (2003) hypothesized that the cerebellum white matter is involved in EF and has been specifically implicated in short term memory, rule based learning and complex planning. Parieto-Frontal Integration Theory, or P-FIT hypothesizes that complex reasoning abilities in humans relies upon the interaction between parietal and frontal brain regions and the white matter structures that link them (i.e., arcuate fasciculus, superior longitudinal fasciculus). The specific areas implicated in the P-FIT model include Brodmann's area (BA) 6, 9, 10, 45–47) and anterior cingulate (BA 32), parietal gray matter (supramarginal (BA 40), superior parietal (BA 7), and angular (BA 39)) (Jung & Haier, 2007). Previous studies show neuroanatomical differences in older children born VLBW with areas of gray matter reductions (temporal, frontal, parietal, cerebellum, caudate, and putamen)

and gray matter increases (parts of the frontal and temporal lobes, cingulate, fusiform gyri, and parts of cerebellum) relative to children born full term.

However, little research has examined brain volume differences in preschoolers, which could potentially illuminate the developmental trajectory of group differences. Additionally, no studies to date have examined the neuroanatomical correlates of EF in preschool aged children born VLBW. In the absence of prior literature to guide neuroanatomical hypotheses, voxel-based mophometry (VBM) will be used as a way to explore the entire cortex, while automatically adjusting for experiment wide error. VBM is a whole-brain unbiased objective technique that uses structural magnetic resonance images (structural MRI) to characterize brain differences between groups. Correlations between EF and whole brain voxel-wise comparisons will also be conducted. Due to the small sample size with neuroimaging, the relationship between EF and regional brain volumes will be explored in the combined sample of preschoolers born VLBW and full term while covarying for group. For the analyses with MRI data, all of the EF measures will be collapsed into EF summary scores based on the Principal Component Analysis findings in Aim 1. The following hypotheses were used to examine the neuroanatomical correlates of EF in preschool aged children born VLBW

Hypothesis 4

To identify structural differences between the groups, voxel-based mophometry (VBM) was utilized as an exploratory technique and voxel-wise comparisons were conducted between the VLBW and full term groups. Based upon literature in adult and adolescent neuroimaging studies, it is hypothesized that areas of regional difference will be found between groups. Based upon previous studies in older children and adolescents born VLBW, as well as developmental

patterns, in this sample the following areas are hypothesized to be areas of gray matter reductions (temporal, striatal, parietal and cerebellum) and gray matter increases (fusiform gyri) relative to the full term group. Both negative and positive analyses will be conducted to identify areas in which preschoolers born full term have larger volumes and areas where preschoolers born full term have smaller volumes compared to preschoolers born VLBW.

Hypothesis 5

Based upon previous studies with older children who were born VLBW, preschoolers with ADHD and typically developing preschoolers, the following areas are hypothesized to have a positive correlation with EF in this sample: temporal, orbitofrontal, cerebellar and striatal regions. Using voxel-based mophometry (VBM) as an exploratory technique, voxel-wise comparisons will be conducted with the EF summary score (based on the PCA results from Aim 1) in the combined group of VLBW and full term preschoolers. It is hypothesized that regional brain structures will be related to EF performance in the combined sample.

METHODS

Participants

The present study is part of a larger study that examined parent-child interactions and self-regulation in preschoolers born VLBW. A power analysis was conducted using pilot data. The minimum number of full term children deemed to be necessary to find a significant difference in EF measures was 25. Developmental data was collected for 61 preschoolers born VLBW and 40 preschoolers born full term between the ages of 3 and 4.5 years old, with a mean age of 45.96 months. Structural neuroimaging data was obtained during sleep for a subset of this larger study with a total of 33 subjects: 11 full term, and 22 preschoolers born VLBW (mean age = 43.9 months).

Children born VLBW were born with a gestational age less than 32 weeks, and/or had a birth weight of less than 1500 grams. Children born full term were healthy births with a gestational age between 37 and 42 weeks. All VLBW preterm children in this sample were singleton births, and were admitted to the Newborn Intensive Care Unit (NICU) at the Children's Hospital of New Mexico at birth. Children were excluded from the study if they had prenatal exposure to drugs, were part of a multiple birth, were unable to see or hear, and/or had a known genetic abnormality.

Study Procedure

Recruitment for children born VLBW was conducted through the University of New Mexico Hospital (UNMH) General Clinical Research Center's (GCRC) pediatric research nurses and a graduate student affiliated with the UNMH Special Baby Clinic. In order to recruit infants,

GCRC pediatric nurses received lists of infants admitted to the Children's Hospital of New Mexico's Newborn Intensive Care Unit (NICU) and determined which infants met eligibility criteria. The graduate student affiliated with the special baby clinic then called the parents of children who were in the age window and gave a brief description of the study and then asked if they would be interested in talking to someone in more detail about the study. If they agreed, the graduate student contacted them again to answer any questions they had concerning the study, asked them whether they wanted to participate, and then scheduled an appointment for the study.

For the recruitment of additional full term children, flyers were posted in public places (i.e., swimming pools and libraries) and on electronic list serves in accordance with the already approved HRRC procedures. Parents who called and expressed an interest in the study were given a brief description of the study, and a graduate student answered any questions they had concerning the study, and asked them whether they wanted to participate. At this point they were scheduled for an appointment for the study.

All parents completed consent forms prior to the start of the study. In order to ensure that participants understood the consenting process, the research coordinator read the consent form out loud, covered the most important aspects, and answered any questions they had about consent.

The study took place at the UNMH Pediatric Clinic, the Mind Research Network, or the participant's home and took approximately two hours to complete. The experimenter first briefly explained the study and what occurs during a visit. The parents then completed HRRC consent and HIPPA forms with the experimenter and received a gift card as compensation. Three different modalities were used to tap into the EF construct: performance based measures, parent-

report measures, and child behavioral coding. The parent was given a packet of questionnaires to complete. Then the experimenter conducted the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) with the child. After the developmental assessment was completed, the experimenter conducted the EF performance measures with the child (Bear Dragon, Gift Peek, Gift Touch, and Progressive Executive Categorization Battery).

Finally, a 15-minute mother-child interaction, consisting of a 10-minute semi-structured free play and a 5-minute clean-up task, was videotaped. During the mother-child free play, mothers were instructed to play with their children as they would normally do so at home. Mothers were provided a standard set of toys. At the end of the 10-minute free play, the research coordinator presented mothers with a card containing the clean-up instructions and a clean-up basket. The card communicated the following instructions, "Next, I would like you to get your child to clean up the toys. Please have (him or her) put the toys in the basket that I will bring you. You can manage the clean-up however you like, but we want your child to be involved. I will be out of the room during the clean-up and return in 5 minutes." The children and mothers were videotaped for 5 minutes or until all of the toys were placed in the clean-up basket, whichever came first. The purpose of presenting the clean-up instruction in card format was to prevent alerting the child to the clean-up instructions. After this, the questionnaires were collected from the parent and the visit was completed.

MRI

Scanning was performed at night during natural sleep (all children born full term) or with light chloral hydrate sedation (50 mg/kg orally), which was used for children born VLBW who did not fall asleep naturally. Parents remained with the children during the scanning. Once

children were asleep, scanning took 60 minutes to complete. Headphones were placed on children's ears for noise protection.

All MRI scans were performed on a Siemens 3 T Trio TIM scanner using the standard 12-channel phased array head coils provided with the system. Sagittal T1-weighted anatomical images were obtained with a multi-echo 3D MPRAGE sequence [TR/TE/TI=2530/1.64, 3.5, 5.36, 7.22, 9.08/1200 ms, flip angle=7°, field of view (FOV)=256 x 256mm, matrix=256 x 256, 1mm thick slice, 192 slices, GRAPPA acceleration factor=2].

In an analysis step that was required for children of this age, every scan was visually inspected for accuracy of regional segmentation. This occurred because we found that automatic segmentation of pediatric brains often missed areas of the anterior temporal and orbital frontal lobes. Thus all scans were evaluated for accuracy and manually corrected when necessary.

The current study used voxel-based morphometry (VBM) to elucidate potential differences in regional brain volume between preschoolers born full term and VLBW. VBM is a whole-brain, unbiased technique that utilizes structural magnetic resonance images and provides greater sensitivity for localizing small scale regional differences in gray or white matter (Mechelli, Price, Friston & Ashburner, 2005). Sagittal T1-weighted anatomical images were obtained with a multi-echo 3-dimensional Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence. The structural magnetic resonance images were normalized to a standard template in stereotactic space. VBM analyses used SPM8 with a matched-sex template for five year-olds, the youngest age cohort available, which was generated from the imaging data from the NIH study of normal brain development, which generates high-quality matched templates for any given group of subjects using the general linear model in the Template-o-matic

toolbox (http://dbm.neuro.uni-jena.de/software/tom/) for subsequent segmentation and normalization. These normalized images were then segmented into gray and white matter, and smoothed with a Gaussian kernel of 10. Using Random Field theory to correct for multiple comparisons, a series of voxel-wise comparisons of grey and white matter by group was conducted using a two-sample t-test analysis, with age and sex as covariates. Uncorrected threshold p values were set at 0.001, with a voxel extent threshold of 10 or greater. Locations were determined by Talairach coordinates in conjunction with the Atlas of the Human Brain, 3rd Edition (Mai, Paxinos, & Voss, 2008).

Measures

Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) (Wechsler, 2002)

The WPPSI-III is a structured developmental assessment, administered by a trained tester, for use with children aged 2:6 (2 years, 6 months old) to 7:3 with subtest batteries divided into two age groups: 2:6 to 3:11, and 4:0 to 7:3. Both batteries were used in the current study. The scales involve children pointing at pictures, naming pictures, answering questions about day to day information, building with blocks, and assembling puzzles. The WPPSI-III generates a Verbal IQ, Performance IQ, and Full Scale IQ. The alpha coefficients of the WPPSI-III subtests range from .83 to .95 and the alpha coefficients for the composite scales range from .89 to .96. Test re-test reliability of subtests range from .84-.93. The WPPSI-III FSIQ correlates highly with other composite scores of intelligence (.74-.90), which supports validity.

Bear Dragon (Reed, Pien, & Rothbart, 1984; Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996)

This is a simplified Go-No-Go or Simon Says task in which children are supposed to inhibit certain responses in response to commands. The experimenter introduced children to a "nice" bear puppet (using a soft, high-pitched voice) and a "grumpy" dragon puppet (using a gruff, low-pitched voice). It was explained that in this game "We will listen to the nice bear and do what he asks us to do" (e.g., touch your nose), but for the dragon "we will not listen to what the grumpy dragon tells us, so we will not do what he asks us to do." Practice trials were used where the bear gave a command in a nice voice ("touch your nose") and the dragon gave a command in a gruff voice ("touch your tummy"). The child practiced complying with the bear and remaining still during the command given by the dragon. Up to six practice trials were given, with verbal rule checks after each trial, or until the child passed one command by each puppet. Children who were unable to pass the practice trails were given a score of 0. After passing the practice trial, there were 10 test trials with the bear and dragon commands in alternating order. A rule reminder was given half way through regardless of performance. Children were seated at a table throughout the task. To score this task each response was assigned a score from 0 to 3, and the points were added to obtain a total score out of 30 possible points (3 points for each of the 10 test trials) (Carlson & Moses, 2001; Carlson, 2005). The Bear Dragon task has shown high inter-rater reliability and strong consistency with other measures of inhibition (Carlson & Moses, 2001; Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996).

Progressive Executive Categorization Battery (PECB)

This battery consists of the combination of four measures that tap into the executive domains of rule use, working memory, flexibility and inhibition. Because there is little current information on how preschool children born VLBW perform on EF tasks, several related tasks

that tap into the same EF domains were used to create a sliding progressive scale of four tasks

that typically developing children master between 2 and 5 years of age (Beck & Carlson, 2007)..

The PECB consisted of the following four tasks, Categorization and Reverse Categorization task

(Carlson, Mandell, & Williams, 2004), Dimensional Change Card Sort- Separated Dimensions

task (Diamond, Carlson, & Beck, 2005) and the original Dimensional Change Card Sort (DCCS

task; Frye, Zelazo, & Palfai, 1995).

      The Progressive Executive Categorization Battery was scored as the cumulative

percentage correct on all four EF card sorting tasks. For each of the four EF sorting tasks, a

percentage correct was calculated (e.g. 6/6 = 100% (1.0), 5/6 = 83.33% (0.833) or 2/6 = 33.33%

(0.33)) and the percentage correct on each task was added together to get a cumulative

percentage correct for the PECB score. Thus the best score was 400% correct (4.0), and the

worst possible score was 0% of trials correct (0.0). The test re-test reliability of each of the four

components of the Progressive Executive Categorization Battery has been shown to be between

.75-.80 (Beck & Carlson, 2007).

      The rationale for combining these four tasks is that these tasks all tap into the same EF

areas, and consist of sorting cards into boxes based on varying dimensions (e.g. category, shape,

color). The combination of these particular four measures into the Progressive Executive

Categorization Battery composite score is without precedent. However, we believe this

particular combination is justified because of the similarity between the measures in both their

form and the areas of EF they measure. Additionally, other studies have found that there appears

to be a gradient in difficulty level among these four tests progressing from Categorization to

Reverse Categorization, then Dimensional Change Card Sort- Separated Dimensions, and finally

the original Dimensional Change Card Sort (Carlson, 2005). This developmental gradient s also

supported by the increasing ages at which each task is usually passed in typically developing

populations (Carlson, Mandell, & Williams, 2004; Diamond, Carlson, & Beck, 2005; Frye,

Zelazo, & Palfai, 1995). In this sample, the VLBW, full term and combined groups showed a

similar gradient in difficulty (See Figures 1 & 2).Thus, there is a precedent for the gradation in

difficulty of these tasks, even if there is not a precedent for combining these tasks into a single

composite score (Beck & Carlson, 2007; Carlson, 2005).

By utilizing similar tasks that increase in difficulty, we anticipated that this measure

would account for the variability in EF performance often seen within the VLBW population.

In combining the four measures, each test is equally weighted. This is just one way to calculate a

combined measure and it includes an assumption that children who perform well on the more

advanced subtests will also perform well on the more simple subtests.

The details for the four tasks that comprise the PECB are presented below in order of

difficulty.

Categorization & Reverse Categorization (Carlson, Mandell, & Williams, 2004)

This is the most basic version of the card-sorting task. In this task children are presented

with cards containing line drawings of mommy animals and baby animals. Children were

introduced to two buckets and asked to help the experimenter sort mommy animals into a

"Mommy" bucket and baby animals into a "Baby" bucket (Categorization). After passing a

practice section, 6 Categorization trials were administered. Then the experimenter suggested that

they play a "silly game" and reverse the rules with baby animals going in the "Mommy" bucket

and mommy animals going in the "Baby" bucket (Reverse Categorization). Scores were the number of correct responses out of 6 trials for the Categorization task, and 10 trials on Reverse Categorization (Carlson, Mandell, & Williams, 2004). This has been shown to be a passable task by 24 months and almost mastered by 3 years in typically developing children (Carlson, 2005). Test-retest reliability was above the accepted level of 0.75-0.80 (Beck & Carlson, 2007). Percent correct was calculated as the number of correct responses out of the total number of responses.

Dimensional Change Card Sort- Separated Dimensions (Diamond, Carlson, & Beck, 2005)

This intermediate card-sorting task was been slightly modified from the original version. In the current version the target cards were a picture of a baby mounted on a blue background and a picture of a mommy mounted on a yellow background. After a practice trial was given to assure knowledge of the dimensions and colors used in the task, children were told that they should play the "color game" in which the blue cards go in the blue box (marked with blue baby) and the yellow cards go in the yellow box (marked with a yellow mommy). The children first passed a training phase in which the children sort plain yellow and blue cards. Then the children were given the sorting cards (e.g. yellow baby, blue mommy) and the experimenter labeled color, "Here is a blue one, where does it go?" The children were then told to match the sorting cards with the target cards (e.g. blue baby, yellow mommy) affixed to boxes in front of them. Each sorting card matches one target card on one dimension (color) and matches the other target card on the other dimension (shape). The child was first asked to sort six cards by color (this is referred to as the pre-switch phase), and then the child was asked to switch dimensions and sort six cards by shape (this is referred to as the post-switch phase). This required the child to inhibit the previous sorting rule (color) and only pay attention to the relevant dimension (shape).

Knowledge questions (e.g. "Where do the blue/baby ones go?") and rule reminders (e.g. "Remember, blue/baby ones go here (point) and yellow/mommy ones go here (point)") were given on alternating trials according to the procedure established by Diamond, Carlson, and Beck (2005). There are 10 total cards that were sorted. The percent correct score was the number of correctly sorted post-switch cards (out of 10). When the dimensions are physically separated into foreground and background, typically developing children as young as 2.5 years are able to successfully complete the task. Among 3-year-olds, the percentage of post switch responses that were correct was almost 2 ½ times greater when the dimensions were separated as when the dimensions were integrated (detailed explanation to follow) (Diamond, Carlson, &Beck, 2005). Test-retest reliability for this task falls in the 0.75-0.80 range (Beck & Carlson, 2007)

Dimensional Change Card Sort (DCCS, Frye, Zelazo, & Palfai, 1995)

This is the most difficult EF measure in the battery where the dimensions of color and shape are integrated into the same figure. The model and stimulus cards used in this study were identical to those used by Kirkham et al. (2003) and Diamond, Carlson, and Beck (2005) for their DCCS testing. The model cards consisted of a blue star and a red truck, each of these was on a white background while the stimulus cards consisted of a red star and blues truck, each on white backgrounds. After a practice trial was given to assure knowledge of the shapes and colors used in the task, the children were given the stimulus cards, and the experimenter labeled the relevant dimension. The children were told to match their sorting cards with the model cards, which were affixed to boxes in front of them. Each stimulus card matches one model card on one dimension (color) and matches the other model card on the other dimension (shape).   After passing the training phase, the child was asked to sort six cards by color (this is referred to as the pre-switch phase), and then the child was asked to switch dimensions and sort six cards by shape

(this is referred to as the post-switch phase). This required the child to inhibit the previous

sorting rule (color) and only pay attention to dimension asked for (shape). Knowledge questions

(e.g. "Where do the stars go?") and rule reminders (e.g. "Remember, stars go here (point) and

trucks go here (point)") were given on alternating trials according to the procedure established by

Diamond et al. (2005). There were 12 total cards that are to be sorted, 6 pre-switch and 6 post-

switch. The percentage correct score was the number of correctly sorted post-switch cards out of

6. Typically developing three year olds usually have no difficulty completing the pre-switch

phase, but often perseverate and make errors during the post-switch phase. Between 4 and 5

years old children are able to switch correctly to the new dimension (DCCS task; Frye, Zelazo, &

Palfai, 1995; Zelazo, Frye, & Rapus, 1996). Test-retest reliability has been shown to fall in the

0.75-0.80 range (Beck & Carlson, 2007).

For the overall Progressive Executive Categorization Battery (PECB) in this sample,

internal validity between Categorization, Reverse categorization, Dimensional Change Card

Sort-Separated, and Dimensional Change Card Sort-Original was relatively high (Chronbach's

alpha = .70).

Gift Peek (Gift Delay Peek, wrap; Kochanska et al., 1996, Carlson, 2005)

Children were told they were going to receive a prize, but the experimenter forgot to

wrap the child's present. The child was asked to turn around in their seat (facing away from the

experimenter) so it would be a surprise. Children were reminded not to peek. The experimenter

then wrapped a gift noisily for 60 seconds. Peeking was coded by latency to first peek in

seconds. Child behaviors were also recorded (e.g. gets up, cover eyes, talks to self). Test-retest

reliability on Hot EF delay tasks has been shown to be 0.80 (Beck & Carlson, 2007).

Gift Touch (Gift Delay Touch; Espy, Kaufmann, Glisky, 1999;Vaughn, Kopp & Krakow (1984)

  An attractively wrapped present was placed in front of the child, and then the child was told that the experimenter "forgot" to make them a card. They were then asked to wait and not touch the present while the experimenter made them a card. The experimenter then busied herself with the card while their back was partially turned away from the child and no attention was given to the child. Latency to touching the gift in seconds (max 120 seconds) was used as a measure of self-control and inhibition. Beck and Carlson (2007) found high test-retest reliability on Hot EF delay tasks (0.80) in preschoolers.

Behavior Rating Inventory of Executive Function- Preschool Version (BRIEF-P) (Gioia, Espy, & Isquith, 2003)

  The BRIEF-P is a 63-item parent report questionnaire that taps into child EF from 2:0 to 5:11. It contains questions that relate to 5 basic scales: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. These scales are also combined to yield the four summary scores of Inhibitory Self-Control (Inhibit and Emotional Control), Flexibility (Shift and Emotional Control), Emergent Metacognition (Working Memory and Plan/Organize), and a Global Executive Composite (Inhibit, Shift, Emotional Control, Working Memory and Plan/Organize). Additionally, the measure contains questions that help to assess Negativity and Inconsistency of the rater. Overall performance is judged according to age-standardized scores that have a mean of 50 and a standard deviation of 10. The BRIEF-P is an ecologically valid and efficient tool for screening, assessing, and monitoring a young child's EF and development (Gioia, Espy, & Isquith, 2003). The BRIEF-P has acceptable convergent and discriminant

validity with other parent-reported measures and has high internal consistency reliability (.80-.95), and high test-retest reliability (.78-.90) for parent report (Gioia, Espy, & Isquith, 2003). In this combined VLBW and full term sample the internal validity of this measure was high (Chronbach's alpha = .89).

Observational Compliance Coding

The Compliance scale of the mother-child coding system of the National Institute of Child Health and Human Development (NICHD) Early Child Care study (Whiteside-Mansell et al., 2003) was used to code child Compliance. The NICHD Early Child Care coding system has been used in numerous research projects including the National Early Head Start Evaluation Project (e.g., Tamis-LeMonda, Shannon, Cabrera, & Lamb, 2004) and a national evaluation study of cochlear implants for young children (e.g., Connor, Craig, Raudenbush, Heavner, & Zwolan, 2006). The Compliance scale was coded from the NICHD coding system during a cleanup task. This measure took place during the naturalistic activity of switching from playing with toys to cleaning up the toys, and was believed to tap into the areas of task switching, inhibition of a preferred activity, following rules, and flexibility. This rating captures the frequency of the toddler's compliance or noncompliance to maternal requests, how easy or difficult it is to get the child to cooperate with the adult's directions, requests, or demands.

Specific examples of noncompliance included: simple refusals to do what is requested, statements or explanations of the child's own preference or desire; excuses, delaying tactics, or attempts to negotiate/argue; ignoring the request, changing the subject or changing the activity to one not requested; opposition to the mother's requests for demands, doing exactly the opposite of what is requested, intensifying the behavior that is "off limits," and angry or aggressive

responses to requests, including yelling, throwing things, hitting and kicking, and having a

temper tantrum. Adequate reliability and test-retest reliability have been found with this coding

system (NICHD ECCRN, 2007). A single score was given ranging from 1 to 5, with higher

ratings indicating greater levels of noncompliance and lower ratings indicating immediate and

willing compliance. Two coders met regularly to code and maintain reliability. A single master

coder settled discrepancies. Inter-rater reliability, as determined from intraclass correlations

based on double coding of 20% of the videotapes, was .89.

Data Preparation

For all correlational analyses involving the EF measures, Spearman correlations were

used in order to guard against violations of the normal distribution and to avoid assumptions

about linearity and the nature of the variables. Due to the large number of EF measures present

in this study, we used principal component analysis (PCA) as a data reduction technique, and to

ascertain the relationship between EF measures at this age. We first ensured that the minimum

standard was passed for validity before a principal component analysis (PCA) was conducted on

this data. The Kaiser-Meyer-Olkin Measure of Sampling Adequacy and Bartlett's Test of

Sphericity were calculated for the sample. The Kaiser-Meyer-Olkin Measure of Sampling

Adequacy exceeded the suggested minimum value of .6 for all analyses. Additionally, Bartlett's

Test of Sphericity was utilized to test the null hypothesis that the correlation matrix is an identity

matrix. An identity matrix is a matrix in which all of the diagonal elements are 1 and all off

diagonal elements are 0, this null hypothesis must be rejected in order to conduct a principal

component analysis. Bartlett's Test of Sphericity exceeded the cutoffs necessary to conduct a

PCA analysis. Thus, all minimum validity standards were met prior to conducting PCA analyses

to address Aim 1. First, these analyses were performed on the entire sample (combined VLBW and full term) since the underlying factor structure for EF at this age is likely to be similar across groups. Follow-up confirmatory analyses were then conducted with each group separately to ensure this assumption was valid.

Bonferroni correction for multiple comparisons was not applied because of the a priori nature of the hypotheses to be tested (Perneger, 1998; Rothman, 1990). All hypothesis tests were two-sided and used a significance level of 0.05. All statistical analyses were conducted using either SPSS: Version 14, or SAS: Version 9 (SAS Institute Inc., Cary, NC). MRI neuroimaging analyses were completed with Statistical Paramentric Mapping (SPM8) for VBM analyses (Mechelli, Price, Friston, & Ashburner, 2005).

RESULTS

The results of this study are presented in three sections. The first section consists of the descriptive analyses. The second addresses the first aim of the study, which examines the relationship between different measures of EF in preschool aged VLBW and full term children. The third portion of the results section addresses the second aim of the study, which examines the neuroanatomical correlates of EF in preschool aged children born VLBW and full term.

Descriptive Statistics

See Table 1 for extended demographic information. In this study the VLBW and full term groups were well matched with no differences in age, ethnicity, or gender between groups. The mean age of all participants was 45.98 months. Through one-way analysis of variance (ANOVA), the VLBW group's age (mean = 46.70 months) was not significantly different from the full term group's age (mean = 44.78 months), $(F(99) = 3.219, p = .076)$. Similarly, gender across the VLBW and full term groups was not significantly different, $(\chi^2(1) = 1.915, p = .166)$. Distribution of child ethnicity was also not significantly different across groups $(\chi^2(3) = 3.158, p = .310)$. Although both groups scored within the average range on the FSIQ, in line with previous research, preschoolers born full term scored significantly higher (mean FSIQ = 105.45) than preschoolers born VLBW on overall IQ (mean FSIQ = 91.10), $(F(99) = 34.899, p \leq .001)$.

Within the subgroup of subjects who had MRI, 22 VLBW and 11 full term children, differences were also examined. Through one-way analysis of variance (ANOVA), the VLBW sample's age was not significantly different from the full term sample's age, $(F(32) = .257, p = .616)$. Similarly, gender across the VLBW and full term groups was not significantly different, $(\chi^2(1) = 1.704, p = .192)$. Distribution of child ethnicity was also not significantly different

across groups (χ^2 (3) = 2.584, p = .275). Preschoolers born full term scored significantly higher than preschoolers born VLBW on overall IQ (FSIQ, F(32)=13.97, p = .001).

As predicted, significant differences between the VLBW and full term groups were also evidenced in all EF measures. Preschoolers born full term had higher EF scores than preschoolers born VLBW on all four individual EF performance tasks, Progressive Executive Categorization Battery (F(99) = 22.67, p ≤ .001), Bear Dragon (F(99) = 33.43, p ≤ .001), Gift Peek (F(99) = 13.56, p ≥ .001), and Gift Touch (F(99) = 8.44, p= .005). Additionally, compared to preschoolers born full term, preschoolers born VLBW had higher rates of parent-reported executive dysfunction on the BRIEF-P in the following areas: Global Executive Composite (GEC) (F(99) = 10.097, p = .002), Inhibit (F(99) = 4.173, p = .044), Working Memory (F(99) = 10.82, p = .001), and Plan/Organize (F(99) = 13.418, p ≤ .001). Additionally, preschoolers born full term also showed greater levels of compliance with parent requests in a clean up task than preschoolers born VLBW (F(99) = 6.644, p = 0.011). See Table 1 for complete statistics.

In order to ensure that IQ and age did not unduly influence the relationships, we followed up with an ANCOVA that controlled for age and FSIQ. After controlling for age and FSIQ, preschoolers born full term still had higher scores than preschoolers born VLBW on all four individual EF performance tasks: Progressive Executive Categorization Battery (F(98) = 27.445, p ≤ .001), Bear Dragon (F(98) = 35.44, p ≤ .001), Gift Peek (F(98) = 13.296, p ≤ .001), Gift Touch (F(98) = 4.287, p = .007). Additionally, preschoolers born full term also had higher observational NICHD Child Cleanup Compliance scores (F(98) = 4.667, p = .004). Similarly, after controlling for age and FSIQ through ANCOVA, compared to preschoolers born full term, preschoolers born VLBW had higher rates of parent-reported executive dysfunction on the

BRIEF-P in the following areas: Global Executive Composite (GEC) (F(98) = 3.905, p = .011),

Working Memory (F(98) = 4.718, p = .004), and Plan/Organize (F(98) = 3.986, p = .010).

To further examine the group differences in EF performance based measures, we also

investigated the group differences between the EF performance measures when they were scored

on a pass or fail basis. In some early studies preschool EF measures such as the PECB, Bear

Dragon, Gift Peek and Gift Open were coded on a pass or fail basis, as that appears to mirror the

nature of typical children's performance on these types of tasks (Carlson, 2005). It is generally

found that typically developing children perform in three ways on these types of tasks: perfectly

or near perfectly, all or mostly incorrectly, or random responding. These three response patterns

are categorized in the following ways: pass (perfect or nearly perfect) or fail (all or mostly

incorrect and random responding). In this case, the cutoff for pass or fail scoring is determined

using binomial probabilities. Preliminary studies in special populations show that pass or fail

coding may under represent variability. As expected, even if these measures were coded in this

binomial manner, significant differences between the VLBW and full term groups were still

found on all of the EF measures (See Figure 1). A chi-squared test of independence was

performed to examine the relationship between group and passing the PECB, (χ^2 (4, N = 101) =

22.002, p ≤ .001), Bear Dragon (χ^2 (1, N = 101) = 24.125, p ≤ .001), Gift Peek (χ^2 (1, N = 101) =

4.396, p = .048), and Gift Open (χ^2 (1, N = 101) = 6.043, p = .014). Preschoolers born full term

were more likely to pass all of the EF measures than were preschoolers born VLBW.

Similar findings were noted in the subgroup that also completed an MRI. Preschoolers

born full term with a completed MRI scored better on all EF measures than preschoolers born

VLBW with an MRI. Specifically, the full term group outperformed the VLBW group on the

BRIEF-P GEC (F(32)= 6.58, p = .015), PECB (F(32) = 7.072, p = .012), Bear Dragon (F(32) = 13.39, p = .001), Gift Peek (F(32) = 14.03, p=.001), Gift Touch (F(32) = 7.148, p = .012), and observationally coded Compliance (F(32), = 5.493, p = .025).

Correlations Between EF Measures

Spearman correlations were used to investigate the relationship between the performance EF measures (Progressive Executive Categorization Battery, Bear Dragon, Gift Peek and Gift Touch) within the combined sample, full term and VLBW samples (See Tables 2-4). High significant correlations were found within the performance-based measures of EF across all of the groups. Within the combined sample and the VLBW sample, all of the EF performance measures were significantly correlated with each other (See Tables 2-3). In the full term group, all of the EF performance measures were significantly intercorrelated, except for PECB and Gift Touch (Rho = .267, p = .101) (See Table 4). As EF performance on one task increased so did scores on the other EF performance tasks. Following the inspection of the intercorrelations among the EF performance based tasks, we standardized all the scores and examined their internal consistency. The performance based tasks tapped a common capacity resulting in alpha = .843. Additionally, the average of the 15 inter-item correlations (inter-item total correlation) was .574.

Spearman correlations were also used to investigate the relationship between the performance EF measures (Progressive Executive Categorization Battery, Bear Dragon, Gift Peek and Gift Touch), the parent report EF measure (BRIEF-P GEC), and the NICHD Child Cleanup Compliance score within the combined, full term and VLBW samples (See Tables 2-4). When examining the relationship between parent-reported EF, observationally coded compliance

with parent directives, and performance based EF, differing patterns were found across groups. Within the combined sample significant correlations were found between the BRIEF-P GEC parent report measure of EF and the PECB (Rho = -.343, p ≤ .001), Bear Dragon (Rho = -.242, p = .015) and Gift Peek (Rho = -.329, p = .001). As the BRIEF-P Global Executive Composite increased (indicating greater problems with EF) PECB, Bear Dragon and Gift Peek scores decreased (See Table 2). In the combined sample NICHD Compliance scores were also found to correlate with performance on Bear Dragon (Rho = .226, p = .025), Gift Peek (Rho = .332, p = .001) and Gift Touch (Rho = .303, p = .002), with better compliance during a clean-up tasks associated with better performance on those EF tasks. Following the inspection of the intercorrelations among the multi-method EF measures, the scores were standardized using z-scores, and their internal consistency was examined. In the combined sample Compliance, BRIEF-P scales, Gift Touch, Gift Peek, PECB, and Bear Dragon scores were not as strongly related as when just examining the EF performance based measures (alpha = .772).

Within the VLBW sample significant correlations were found between the BRIEF-P GEC parent report measure of EF and the PECB (Rho = -.355, p = .005) and Gift Peek (Rho = -.387, p = .002). As the BRIEF-P Global Executive Composite increased (indicating greater problems with EF), PECB and Gift Peek scores decreased, (See Table 3). In the VLBW sample NICHD Compliance scores correlated with performance on Gift Peek (Rho = .404, p = .001) and Gift Touch (Rho = .357, p = .005), with better compliance during a clean-up tasks associated with better performance on those EF tasks. In contrast, in the full term sample the NICHD Compliance scores were only found to correlate with PECB performance (Rho = .311, p = .05). Additionally, in the full term sample BRIEF-P GEC scores were not found to correlate with any of the EF performance measures (PECB, Bear Dragon, Gift Peek or Gift Touch).

Post hoc exploratory analyses were employed to assess the seemingly different patterns of correlations between the VLBW and full term group. The five correlations with the largest differences across group were examined (correlation differences for these five sets ranged from .478 to .213). Fischer's r-to-z transformations were used to assess the significance of the difference between correlation coefficients in the VLBW and full term samples. The correlations between BRIEF-P GEC and Compliance were significantly different between the VLBW and full term groups (z = -2.32, p = .02). For the VLBW group, a negative correlational trend was found (r = -.27, p = .15): as compliance increased, parent reported executive dysfunction decreased. In contrast, for the full term group, the trend was positive (r = .20, p = .21): increased compliance was associated with increased parent reported executive dysfunction. The correlations between Gift Peek and Compliance were significantly different between the VLBW and full term groups (z = 2.11, p = .04). For the VLBW group, a significant positive correlation was found (r = .404, p = .001) where increased scores on Compliance were related to increased ability to delay on the Gift Peek task. No relationship was found between Compliance and Gift Peek in the full term group (r = -.02, ns). The contrasts between the other 3 sets of correlations, Gift Touch and Compliance (z = 1.7, p = .09), BRIEF-P GEC and Gift Peek (z = -1.71, p = .09) and Gift Touch and Bear Dragon (z = -1.4, p = .16), were not significantly different between the VLBW and full term groups.

Analyses for Aim One: Understanding the Nature of EF Utilizing a Variety of EF Measures (performance-based, parent report and observational) in Preschoolers Born VLBW and Full Term.

Hypothesis 1: Dimensionality of EF in Multimodal EF Measures

It was hypothesized that when including all measures of EF (Bear Dragon, PECB, Gift Peek, Gift Touch, BRIEF-P Global Executive Composite (GEC), and naturalistic behavioral coding (NICHD Cleanup Child Compliance score) into a principal components analysis (PCA) either EF would be a unitary construct or a multidimensional construct for the preschoolers in this sample. Two specific rival hypotheses were presented, however, hypothesis 1a predicted to be more likely if the BRIEF-P GEC is not truly tapping into EF, but rather more general behavioral difficulties, a conclusion that has more support from the literature:

> (1a) A single EF construct was predicted to include all of the EF performance measures (Bear Dragon, PECB, Gift Peek and Gift Touch).

> (1b) Two components were predicted: 1. The EF performance measures (Bear Dragon, PECB, Gift Peek and Gift Touch) and 2. The parent report of EF and the behavioral coding (BRIEF-P GEC and the NICHD Cleanup Child Compliance).

To assess these hypotheses a Principal Component Analysis (PCA) was conducted which included all of the proposed measures of EF (Bear Dragon, PECB, Gift Peek, Gift Touch, BRIEF-P GEC and the NICHD Cleanup Child Compliance measure) in the combined preschool group to examine dimensionality. All components with eigenvalues greater than 1 were maintained. Minimum validity statistics were surpassed with the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (MSA = .776), and the significant Bartlett's Test of Sphericity ($p \leq .001$). When all of these measures were placed into the PCA model, the extraction communalities for NICHD Compliance and BRIEF-P GEC were below the cutoff of 0.5 and were excluded from the PCA model (.227 and .295, respectively). Only one factor emerged in the combined group, which included all four EF performance measures (Bear Dragon, PECB, Gift Peek and Gift

Touch) and excluded both the BRIEF-P GEC and the NICHD Cleanup Child Compliance. This single factor comprising the four EF performance measures accounted for 68.24% of the variance in the combined group (eigenvalue of 2.73).

To determine if this unitary construct for EF was consistent across the groups, a PCA was attempted for each of the separate groups (VLBW and full term), which included all of the measures of EF (Bear Dragon, PECB, gift delay peek, gift delay touch, BRIEF-P GEC and the NICHD Cleanup Child Compliance measure) to examine dimensionality. All components with eigenvalues greater than 1 were maintained.

For the VLBW group, minimum validity statistics were surpassed with the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (MSA = .703) and the significant Bartlett's Test of Sphericity (p ≤ .001). When all of these measures were placed into the PCA model, the extraction communalities for NICHD Compliance and BRIEF-P GEC (.273 and .444, respectively) were below the cutoff of 0.5 and were excluded from the PCA model in sequential steps. Only one factor emerged in the VLBW group, which included all four EF performance measures (Bear Dragon, PECB, Gift Peek and Gift Touch) and excluded both the BRIEF-P GEC and the NICHD Cleanup Child Compliance. This single factor accounted for 63.81% of the variance in the VLBW group.

For the full term group, as noted earlier in the descriptive statistics sections, low correlations were found between NICHD Compliance, the BRIEF-P GEC, and the four EF performance based measures. Within the full term group the BRIEF-P GEC was not correlated with any EF performance measures, and only one significant correlation was found between a performance based measure (the PECB) and Compliance scores (Rho = -.320, p = .05). Thus a

PCA in the full term group could not validly be computed with all of the measures of EF (Bear

Dragon, PECB, gift delay peek, gift delay touch, BRIEF-P GEC and the NICHD Cleanup Child

Compliance measure) as minimum validity statistics were not surpassed with basic correlations.

Thus the findings in the combined group PCA are likely influenced by the correlations in

the VLBW group. In the VLBW group the BRIEF-P GEC was correlated with the Gift Peek

performance measure (Rho = -.387, p = .002) and the PECB (Rho = -.355, p = .005). The

Compliance score was also correlated with Gift Peek (Rho = .404, p = .001), and Gift Touch

(Rho = .357, p = .005), in the VLBW group. Thus, in the VLBW group inhibiting touching or

peeking at a gift was related to inhibition of playing with toys and starting to clean up. In

contrast, in the full term group only one significant correlation was found between a performance

based EF measure (the PECB) and Compliance scores, (Rho = -.320, p = .05). The fact that the

PCA could not be replicated in the VLBW and full term groups separately, when all proposed EF

measures were included, may indicate that the parent report of EF (BRIEF-P GEC) and the

Compliance coding have differential relationships to performance based EF measures across the

groups. However, since the PCA analyses for the combined group and the VLBW group

excluded the parent report and observational coding, these might be related but fundamentally

different constructs than the EF performance based measures, which were grouped together in a

single component. Thus parent report of EF and observational coding are thought to be related

to a different construct than the executive function performance tasks.

Hypothesis 2: Dimensionality of EF Performance Based Measures

To address the dimensionality of EF for the VLBW and full term children in this study,

Principal Component Analysis (PCA) was conducted on performance measures of EF (Bear

Dragon, PECB, Gift Peek and Gift Touch) in the combined preschool group. It was hypothesized that:

2a.) EF would most probably emerge as a unitary construct; with performance measures of EF (Bear Dragon, PECB, Gift Peek and Gift Touch) being different measures that tap into the same construct. Based on results from similar studies in full term preschool children, when conducting principal component analyses, a single-factor solution was predicted with an eigenvalue greater than one.

2b.) However, the rival hypothesis that EF would be a multidimensional construct with a hot component (Gift Peek and Gift Touch) and a cool component (Bear Dragon, and PECB) was also presented.

It was theorized that either one or two principal components would emerge but all components with eigenvalues greater than 1 were maintained.

To assess these hypotheses a Principal Component Analysis (PCA) was conducted which included the four EF performance measures (Bear Dragon, PECB, Gift Peek, Gift Touch) in the combined preschool group to examine dimensionality.   All components with eigenvalues greater than 1 were maintained. Minimum validity statistics were surpassed with the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (MSA = .771) and the significant Bartlett's Test of Sphericity ($p \leq .001$). When all of these measures were placed into the PCA model, all of the extraction communalities exceeded the cutoff of 0.5 and were included in the PCA model (See Table 5). Only one factor emerged in the combined group, which included all four EF performance measures (Bear Dragon, PECB, Gift Peek and Gift Touch). This single factor

comprising the four EF performance measures accounted for 69.769% of the variance in the combined group (eigenvalue of 2.89).

Thus, hypothesis 2a was supported: all of the EF performance measures comprised one factor in this combined VLBW and full term preschool sample. This is in line with prior research in typically developing preschoolers showing that EF is largely an undifferentiated component.   Strong performance on one EF lab based task is likely to be related to strong performance on other EF lab based tasks. Thus EF in this combined group can be conceptualized in a single framework and data reduction techniques such as PCA can be utilized to create a single EF component.

To determine if this unitary construct for EF was consistent across the groups, a PCA was attempted for each of the separate groups (VLBW and full term), which included all of the measures of EF (Bear Dragon, PECB, gift delay peek, gift delay touch) to examine dimensionality. Minimum standards were passed to validly conduct separate Principal Components Analyses in the VLBW and full term groups and separate follow-up PCA analyses were conducted for each group to confirm the similarity in constructs. All components with eigenvalues greater than 1 were maintained. Similar unitary constructs were found for the VLBW and full term groups when they were run separately.

For the VLBW group, minimum validity statistics were surpassed with the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (MSA = .731) and the significant Bartlett's Test of Sphericity (p ≤ .001). When the Bear Dragon, PECB, Gift Delay Peek and Gift Delay Touch were placed into the PCA model, the extraction communalities for all performance measures exceeded the cutoff of 0.5 and were included in the PCA model (See Table 5). Only one factor

emerged in the VLBW group, which included all four EF performance measures (Bear Dragon, PECB, Gift Peek and Gift Touch). This single factor accounted for 63.806% of the variance in the VLBW group (eigenvalue of 2.58).

For the full term group, minimum validity statistics were surpassed with the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (MSA = .703) and the significant Bartlett's Test of Sphericity ($p \leq .001$). When Bear Dragon, PECB, Gift Delay Peek and Gift Delay Touch were placed into the PCA model, the extraction communalities for all performance measures exceeded the cutoff of 0.5 and were included in the PCA model (See Table 5). Only one factor emerged in the full term group, which included all four EF performance measures (Bear Dragon, PECB, Gift Peek and Gift Touch). This single factor accounted for 62.191% of the variance in the full term group (eigenvalue of 2.48).

Since similar unitary constructs emerged from the VLBW and full term samples, this supports the idea that EF, as captured by performance on a variety of lab based tasks, is similar across these two groups at the preschool age. If a preschooler performed well on one EF performance based task then they were likely to perform well on other EF performance based tasks. Since a single component was able to explain a large amount of variance in this sample, and the grouping of EF performance based measures into a single factor was replicated in the VLBW and full term groups separately, the PCA combined analysis was used to generate a single EF component score for data reduction purposes. The internal consistency of the EF index was good for the combined sample (alpha = .843).

Hypothesis 3: Group Differences on EF Performance Between VLBW and Full Term Preschoolers

To test the hypothesis that the VLBW group would perform more poorly on all derived EF dimensions compared to full term children, a one-way ANOVA was computed with the group (VLBW or full term) as the between subjects factor and the single combined group PCA component as the dependent variable. A significant difference was found between the derived PCA EF component between the VLBW and full term groups, (F(99) = 28.049, p ≤ .001). Children born full term scored higher on the derived PCA EF component than the children born VLBW.

Analyses for Aim 2: Neuroanatomical Correlates of EF in Preschool Aged VLBW and Full Term Children

Hypothesis 4: Regional Structural Brain Volumes Will Differ in Preschoolers Born VLBW and Full Term

Based upon previous studies in older children and adolescents born VLBW as well as developmental patterns, in this sample the following areas were hypothesized to be areas of gray matter reductions (temporal, striatal, parietal and cerebellum) and gray matter increases (fusiform gyri) relative to the full term group. Using voxel-based mophometry (VBM) as an exploratory technique, voxel-wise comparisons were conducted between the VLBW and full term groups to identify structural differences between the groups. Based upon literature in adult and adolescent neuroimaging studies it was hypothesized that areas of regional difference will be found between groups. Both negative and positive analyses were conducted to identify areas in which full term children had larger volumes and areas where full term children had smaller volumes compared to preschoolers born VLBW.

As a preliminary step, regional brain differences between preschoolers born VLBW and full term preschoolers were examined with VBM analysis. Total gray matter volumes, white matter volumes, cerebral spinal fluid (CSF) volume, and intracranial volume (ICV: gray matter, white matter and CSF) were calculated for each group (See Table 6). Independent sample t-tests were utilized to assess differences across groups. No significant differences were found between groups in volume of gray matter (t (31) = 1.865, p = .072), CSF (t (31) = -.829, p = .413) or total ICV (t (31) = 1.585, p = .123). Significant differences were found between white matter volume across groups (t (31) = 2.383, p = .023). Larger volumes of white matter were found in the full term group compared to the VLBW group. In the VBM analyses, intracranial volume was not included as a covariate since differences in ICV were not found to be significant between the two groups and since ICV differences were already taken into account in the pre-processing of the images. In the process of segmenting and modulating for nonlinear effects only, adjustments for intracranial volume were already incorporated. With no covariate entered in the model, group differences were found in many areas, with the full term group showing larger volumes than the VLBW group in some areas, as well as areas where the VLBW group had larger volumes than the full term group. With no covariates in the model, gray matter volume was negatively correlated with group (full term > VLBW) for the following regions: Bilateral temporal (inferior, fusiform, superior, middle), left caudate head, left parahippocampal, right (frontal) paracentral, right inferior parietal, right putamen and right anterior cerebellum. With no covariates in the model gray matter, volume was positively correlated with group (VLBW> full term) for the following regions: Bilateral superior frontal gyrus, bilateral occipital ligual gyrus, right occipital (middle, fusiform), right cerebellum (posterior declive, anterior culmen), left middle frontal, left parahippocampal/fusiform and left anterior cingulate (See Table 7).

As the developing brain is changing over time, some studies covary for age when conducting VBM analyses. Additionally, it is also common to covary for sex since this can be an important factor. When correcting for age and sex with VBM, group structural brain differences were found between preschoolers born VLBW and full term. Gray matter was negatively correlated with group (full term > VLBW) for the following regions: Bilateral Temporal (middle, fusiform, superior), frontal paracentral, putamen (lentiform nucleus), right temporal (inferior) and right cerebellum anterior lobe. When correcting for age and sex, gray matter was positively correlated with group (VLBW > full term) for the following regions: Bilateral Frontal (superior), occipital (lingual), right cerebellum (posterior lobe declive and tonsil), right occipital (fusiform, middle), left frontal (middle), left anterior cingulated and left parahippocampal (See Table 8.)

Hypothesis 5: Brain Structural Volumes Will Relate to EF

Based upon previous studies with older children who were born VLBW, preschoolers with ADHD and typically developing preschoolers, the following areas were hypothesized to have a positive correlation with EF in this sample: temporal, orbitofrontal, cerebellar and striatal regions. Due to the small sample size with neuroimaging, the relationship between EF and regional brain volumes was explored in the combined sample of VLBW and full term preschoolers. For analyses with MRI data, all of the EF measures were collapsed into an EF summary score based on the Principal Component Analysis findings in Aim 1A. Using voxel-based mophometry (VBM) as an exploratory technique, voxel-wise comparisons were conducted with the EF summary score in the combined group of preschoolers born VLBW and full term

while covarying for group. It was hypothesized that regional brain structures would be related to EF performance in the combined sample.

In the combined sample, correlations were run through VBM and SPM to determine which brain regions were related to the derived PCA EF component. In the combined sample, gray matter was negatively correlated with EF for the following regions: Right occipital (inferior, fusiform and lingual). Thus increases in gray matter in these areas were related to poorer EF. In the combined sample, gray matter was positively correlated with EF for the following regions: bilateral temporal (middle, superior), right temporal (inferior, fusiform), right insula and right putamen. Thus, increases in gray matter in these areas were related to increases in EF (See Table 9). As a follow-up analysis, EF correlations were attempted in the VLBW and full term groups separately. In the separate VLBW and full term samples, no significant correlations with the EF index emerged. This is likely due to small sample sizes.

DISCUSSION

The development of executive function skills is closely related to other milestones of childhood and is related to many adaptive outcomes. For example, delay of gratification (a measure of impulse control) in preschoolers is predictive of cognitive, academic and social outcomes a decade later (including SAT scores) (Mischel, 1996; Mischel et al., 1989; Shoda, Mischel, & Peake, 1990). This predictive power makes executive functioning an especially powerful avenue for potential intervention. New EF measures from the developmental literature allow researchers to tap into the foundations of executive function, especially working memory, impulse control and rule use, in very young children. Although these new measures for younger children have been used with many special populations recently, there are currently limited studies looking at executive function in preschool children born prematurely. Understanding how executive functioning is related to a range of developmental outcomes in these children would have important implications for interventions.

Although EF in has been studied in typically developing preschool populations (Carlson, 2005; Hongwanishkul, Happaney, Lee, & Zelazo, 2005), there are currently very few studies investigating EF in preschool children born prematurely.   Few studies have examined EF in VLBW preschool aged children and they have found not found consistent results. Three studies have found that preschool children born prematurely have deficits in EF (sustained attention, inhibition, and working memory) when compared with full term children matched for chronological age and IQ (Baron, Kerns, Müller, Ahronovich, & Litman, 2011; Espy et al., 2002; Vicari, Caravale, & Carlesimo, 2004).   In contrast, one study found no effect of prematurity on EF beyond general cognitive deficits, and it was suggested that differences in performance

between control and preterm groups were due to general cognitive deficits, not specific EF

deficits (Esbjorn, Hansen, Greisen, & Mortensen, 2006).

Thus far, several studies have shown EF deficits in children school-aged and older who

were born prematurely. Compared to children born full-term, preterm school-aged children

appear to have EF deficits in sustained attention, working memory, and planning. Additionally,

mixed evidence exists for deficits in mental flexibility and inhibition (Anderson, et al., 2003;

Anderson & Doyle, 2004; Bayless & Stevenson, 2007; Böhm, Katz-Salamon, & Smedler, 2002;

Curtis, Lindeke, & Georgieff, 2002; Hack et al, 2005; Harvey, O'Callaghan, & Mohay, 1999;

Korkman, Liikanen, & Fellman, 1996; Luciana, Lindeke, & Georgieff, 1999; Rickards, Kelly, &

Doyle, 2001; Sun, Mohay, & O'Callaghan, 2009; Taylor, Klein, Minich, & Hack, 2000; Wolke

& Meyer, 1999). These differences in EF performance between VLBW and full term controls

persist even after taking IQ differences into account (Bayless & Stevenson, 2007; Wolke &

Meyer, 1999). As it is currently unclear if the deficits seen at school age in children who were

born very low birth weight can be detected as young as preschool, understanding the EF

performance of preschoolers born VLBW would fill a gap in the literature.

Differences in EF in Preschoolers Born VLBW Compared to Full Term

In the current study of diverse 3 to 4 ½ year olds, compared to preschoolers born full

term, preschoolers born VLBW were found to perform more poorly on all of the outcome

measures. Consistent with prior research, which typically finds a standard deviation difference

in IQ scores (Alyward, 2002), preschoolers born VLBW in this sample had significantly lower

overall cognitive function than preschooler born full term. Significant differences were found on

EF performance based measures (the PECB, Bear Dragon, Gift Peek and Gift Touch), parent

rated executive dysfunction (BRIEF-P) and behaviorally coded compliance during a naturalistic parent-child interaction (NICHD Compliance score). The VLBW group did more poorly on all EF measures than the full term group. These differences remained significant even after controlling for age and FSIQ. Thus, the results of this study add to the limited previous literature exploring EF in preschoolers born VLBW. These results align with prior research suggesting that EF differences can be seen in preschoolers born VLBW as young as age 3, and that these EF differences may be separate from general IQ differences (Baron, Kerns, Müller, Ahronovich, & Litman, 2011; Vicari, Caravale, & Carlesimo, 2004).

Correlations Between Multimodal EF Measurements in Preschoolers Born VLBW and Full Term

Although differences in EF were found between VLBW and full term groups in this sample, the dimensionality of EF is poorly understood. The relationship between different measures of EF is especially unclear for early EF that is emerging at the preschool age. Additionally, clinicians have been encouraged to use performance-based measures of EF in conjunction with other measures of EF, such as parent report of EF and behavior coding (Denckla, 2002).

No studies have examined the relationship between parent report of EF, behaviorally coded EF, and performance measures of EF in preschoolers born VLBW. Many studies with this population only utilize parent-reported EF, despite the fact that this measure has not been shown to correlate with EF abilities in preschoolers born VLBW. In fact, studies from the typically developing literature cast doubts about the validity of the BRIEF-P in regards to the relationship between this parent reported measure and EF abilities during the preschool age. In typically

developing preschoolers (ages 3-6), and preschoolers with attention deficit hyperactivity disorder (ADHD), BRIEF-P scores were not significantly correlated with children's performance on EF tasks (Liebermann, Giesbrecht, & Mueller, 2007; Mahone & Hoffman, 2007).. Due to this reported disconnect between parent report of EF and performance measures of EF, validity concerns have been raised that parent report of EF may not be measuring the same things as performance based measures of EF.

Similar validity concerns are present for observationally coded measures of EF, such as compliance.. In typically developing toddlers, Morasch and Bell (2011) found that compliance was related to parent rated measures of temperament-based inhibitory control, but compliance was not related to EF performance based measures. Additionally, Kochanska, Murray and Coy (1997) found that parent report of inhibitory control was related to compliance with a mundane activity (e.g., cleaning up toys) in preschool children. Compliant children had higher ratings of parent-reported inhibitory control than children who refused to clean up the toys (Kochanska, Murray, & Coy, 1997).

In sum, the relationships between multimodal measurements of EF have not been conducted in preschoolers born VLBW. By triangulating the construct of EF through different modalities (parent report, behavioral coding, and performance measures) we can better understand the relationship between different measures of EF during the preschool age. This may help in our understanding of the construct and the construct validity of EF in preschoolers born VLBW.

This study attempted to address this idea by examining the various ways of measuring EF (parent report, behavioral coding, and performance measures) and how they relate to each other

in VLBW, full term, and combined groups. Somewhat differing patterns were found across groups when examining the relationships between parent-reported EF, observationally coded compliance with parent directives, and performance based EF. Specifically, within the combined sample, significant correlations were found between the parent report and many of the performance measures of EF (PECB, Bear Dragon and Gift Peek). Similar significant correlations were seen in the VLBW group between parent report and performance on EF tasks (PECB and Gift Peek). In contrast, in the full term group the parent report of EF was not found to correlate with any of the EF performance measures. When examining observational coding, in the combined group, better behaviorally coded compliance during the clean-up task was associated with better scores on many of the EF performance tasks (Bear Dragon, Gift Peek and Gift Touch). Within the VLBW sample, better compliance during a clean-up task was also associated with better performance on EF tasks (Gift Peek and Gift Touch) tasks. In contrast, in the full term sample observationally coded compliance was only found to correlate with one EF measure (PECB. Compared to the full term group, parent-reported EF and observationally coded EF was more closely related to performance on EF tasks in the VLBW group. Additionally, in the combined, VLBW and full term samples, parent report of EF was not found to be related to behaviorally coded compliance.

Some significant differences were found between correlations for the two groups. A significant association between Gift Peek and Compliance was seen in the VLBW group but not in the full term group, and the difference between these two correlations was significant, indicating that this relationship may be specific to the VLBW group. Another significant difference between correlations was found between Compliance) and parent reported BRIEF-P GEC scores. In the VLBW group, better Compliance scores were associated with fewer EF

problems; whereas in the full term group, better Compliance scores were related to more difficulties with EF. Neither of these correlations was significant on their own, but the significance of the difference between groups may point to an important differential relationship that may exist across groups. Greater sample size might elucidate these relationships.

In general, significant relationships between multimodal EF measures were most commonly seen in the combined group, this was followed by many relationships within the VLBW group and the full term group showed the fewest significant relationships between various forms of EF measurement. These results can be interpreted in a variety of ways. For example, parent report and behavioral coding of EF may be more strongly related to general behavioral dysregulation versus EF specific ability. Additionally, parent reported behavior and observation of the child's compliance with parent directives may be colored by parent-child relationship variables. If the BRIEF-P and Clean-up Compliance are related to larger behavioral difficulties, then the lack of relationship between behaviorally coding of compliance and parent report of EF in any of the groups is also an interesting finding. One explanation may be that compliance within a new environment with new adults present (the lab) may also greatly vary from compliance and general behavior in the home setting. Compliance with parent directives may also be related to parenting styles. If a child has been specifically instructed to clean up toys when they are finished playing with them at home, then this expectation is likely to carry over into new environments as well. Thus, compliance may be impacted by direct parent instruction, exposure, and parent expectations at home.

It is also possible that the BRIEF-P GEC may be a poor measure of EF in preschoolers. The relationship between parent report of EF and EF performance in the VLBW and combined group is somewhat inconsistent with the literature on typically developing preschoolers and other

special populations, which generally does not find a strong relationship between parent report of EF on the BRIEF-P and EF performance at this age (Liebermann, Giesbrecht, & Mueller, 2007; Mahone & Hoffman, 2007). However, EF performance measures with a stronger influence on inhibition and attention have been shown to be related to other measures of parent report of EF in VLBW and full term preschoolers (Carlson & Wang, 2007; Lind et al., 2010). This may suggest that the BRIEF-P may not be especially sensitive to EF performance differences, while other measures of parent report of EF may be more strongly related to EF tasks.

Another consideration is that a summary score was utilized in the current study (the BRIEF-P Global Executive Composite (GEC)) as the parent report measure of EF. The BRIEF-P GEC incorporates information from five different subscales (Shift, Inhibit, Emotional Control, Planning/Organization and Working Memory). It is possible that utilizing the more specific scales of the BRIEF-P may have yielded additional relationships between parent report of EF, observational coding of EF and EF task performance.

Additionally, it is important to consider the issue of sample size. The largest amount of significant correlations were found in the group with the largest sample size (combined group, n=101), a moderate amount of correlations were found in the middle sized group (VLBW, n=61) and the fewest significant correlations were found in the smallest group (full term, n=40). This may suggest that sample size and power are important factors to consider in the interpretations of these results.

Underlying Components in the EF Construct

When examining EF in this sample through PCA analyses with performance, compliance, and parent report measures, only one factor emerged in the combined and VLBW groups. This single factor only included the performance measures. This suggests that EF in these combined

and VLBW preschool samples is a one-dimensional construct, which included all four EF

performance based measures and excluded observational coding and parent report. This is in

line with prior research in typically developing preschoolers that showed EF is largely an

undifferentiated component that does not relate strongly to parent report (Carlson, Mandell, &

Williams, 2004; Hughes & Ensor, 2007; Liebermann, Giesbrecht, & Mueller, 2007; Wiebe,

Espy, & Charak, 2008).

In the full term group, because the performance based EF measures did not have the

necessary minimum correlations with the parent report and observational EF measures, a PCA

could not be validly computed. This may be related to lower variability in EF measures within

the full term sample or it could be related to a smaller sample size in the full term group. Thus,

the findings from the combined group PCA are likely influenced by the correlations in the

VLBW group. The fact that the PCA could not be replicated in the full term group separately

may indicate that the parent report of EF (BRIEF-P GEC) and the NICHD Compliance coding

have differential relationships to performance based EF measures across the groups. In sum,

parent-reported EF and observational coding of compliance did not load with performance

measures of EF in this preschool sample. Additionally, consistent with previous research in

older children, parent-reported EF may not be highly associated with EF performance measures

at this age (Carlson, Mandell, & Williams, 2004; Hughes & Ensor, 2007; Wiebe, Espy, &

Charak, 2008).

When considering the PCA analyses, the parent report and observational coding were not

found to tap into the same construct as the performance based EF measures. Since the BRIEF-P

GEC and Compliance were eliminated from the PCA in both the combined and the VLBW

group, this might indicate that although some minimum correlations were present, the construct

underlying performance task based EF is not consistent with parent report or observational

coding. Instead of measuring performance based EF, parent report and observational coding

may relate to broader differences between children that are more associated with overall

behavioral difficulties, self-regulation differences, or parent-child interactional factors

(Liebermann, Giesbrecht, & Mueller, 2007). An additional factor that may impact parent

reported EF and observationally coded EF, and therefore may alter the relationship between

these measures and EF performance measures, is perceived child vulnerability. Research has

demonstrated that children born VLBW are often seen as more vulnerable than their full term

peers (De Ocampo, Marcias, Saylor & Katikaneni, 2003). This parental perception may persist

throughout childhood and may relate to differing expectations and parent-child interactions in

families with a child who is born VLBW compared to a child who was born full term.

Differences in child temperament may also be related to parent ratings of EF and observational

coding of parent-child interactions. These are just some possible factors that may confound or

obscure a relationship between performance based EF, parent report of EF and behaviorally

coded EF. Thus, performance based EF, parent report of EF, and observational coding may be

related domains (correlations may exist), but they may not be highly overlapping. The

relationship between multimodal measurements of EF should continue to be explored while

examining other important factors such as child temperament, parent-child interaction and

parenting strategies.

Relationship Between EF Performance Based Measures

Another area that has yet to be studied thoroughly in preschoolers born VLBW is the relationship between different lab based performance measures of EF. In older children born VLBW there is some evidence that children born VLBW have EF deficits in all areas of EF (working memory, planning, sustained attention, mental flexibility, and inhibition) (Anderson, et al., 2010). However, other studies show a more varied pattern of impairment in which children born VLBW have marked areas of deficit and other areas of EF that are unimpaired. Working memory, planning, and sustained attention are clearly implicated deficits in children born preterm and this finding is robust and tends to persist after controlling for cognitive skills (Taylor, Hack, & Klein, 1998; Taylor, Klein, Minich, & Hack, 2000; Taylor, Minich, Bangert, Filpek, & Hack, 2004; Vicari, Caravale, Carlesimo, Casadesi, & Allemand, 2004).

Even in typically developing preschoolers, demonstrating how different performance based measures of EF group together is poorly understood. With typically developing populations, some researchers have found that EF is a multidimensional concept, as has been demonstrated in adults (Carlson, 2005; Garon et al., 2008 for review), while other studies suggest that during the preschool period performance based EF is an undifferentiated and unitary concept (Carlson, Mandell, & Williams, 2004; Hughes & Ensor, 2007; Wiebe, Espy, & Charak, 2008, Wiebe et al., 2011). Although the nature of EF in typically developing preschool aged children is still under debate, of the dimensionality of EF in VLBW populations has yet to be critically analyzed.

In this study, high correlations were found between the performance based measures of EF across all of the groups. Within the combined and VLBW samples, all of the EF performance measures were significantly correlated with each other. In the full term group, all

of the EF performance measures were significantly intercorrelated, with the exception of the

PECB and Gift Touch. For all of the significant correlations, as EF performance on one task

increased so did scores on the other EF performance tasks.

When utilizing a PCA with only the performance based tasks, a single component

explained a large amount of variance across groups. Only one factor emerged, which included

all four EF performance measures (Bear Dragon, PECB, Gift Peek and Gift Touch). When only

examining the EF performance based measures, we were able to compare the components across

groups. This unitary EF construct emerged in the combined group, the VLBW group, and the

full term group. This supports the idea that performance on a variety of lab-based EF tasks

seemed to be related. If a VLBW or full term preschooler performed well on one EF

performance based task, then they were likely to perform well on other EF performance based

tasks. Similar to prior studies of typically developing children, the nature of EF in this sample of

preschoolers born VLBW was found to be undifferentiated and unitary (Carlson, Mandell, &

Williams, 2004; Hughes & Ensor, 2007; Wiebe, Espy, & Charak, 2008; Weibe et al., 2011).

It has also been postulated that EF as a larger overarching concept may have cognitive

components, behaviorally oriented components, and context driven components. The potential

division between cognitive and behavioral aspects of EF may be related to the idea of Hot and

Cool EF. The literature is currently divided about whether these ideas represent functionally

different components of EF. In this study, differential components of Hot and Cool EF were not

found in the VLBW or full term groups. The measures that are typically conceptualized as Hot

EF (Gift Touch and Gift Delay) were grouped into the same component as the Cool EF measures

(PECB and Bear Dragon). Additionally, EF has been touted as a larger construct that may have

broad relevance and relationships to many areas of real world functioning. Much like the

concept of *g* in the intelligence literature, EF may be highly related to functional performance in

many areas of life, with lab-based tasks representing a narrow and circumscribed view of EF as a

whole.

Regional Brain Differences Between VLBW and Full Term Groups

Structural differences are frequently seen in adult, adolescent, and older school age

VLBW individuals compared to individuals born full term. Studies conducted with adolescents

who were born very low birth weight show bilateral gray matter reductions in the temporal lobes,

central, prefrontal, orbitofrontal, and parietal cortices, caudate nuclei, hippocampi, and thalami

(Nagy et al., 2009). When examining cortical thickness, significantly thicker cortex in the right

anterior inferior temporal gyrus and left ventrolateral prefrontal cortex were observed in

adolescents born VLBW (Nagy, Lagercrantz, & Hutton, 2010). Martinussen et al. (2005) found

reduced regional cortical thickness in the parietal, occipital, and temporal lobes, and increased

thickness in the regional areas of the frontal and occipital lobes of adolescents who were born

preterm. In a sample of 8 to 10-year-old children who were born preterm and were at low risk,

decreases in gray matter were found bilaterally in the temporal lobes and in the left parietal lobe

(Soria-Pastor et al., 2009).

In the current study, regional brain differences between preschoolers born VLBW and

full term preschoolers were examined with VBM analysis. Global structural volumes were

found to be similar across groups for gray matter, cerebral spinal fluid, and total intracranial

volume. Significant differences were found between the VLBW and full term group in white

matter, with preschoolers born full term demonstrating larger white matter volumes compared to

preschoolers born VLBW. In the VBM analyses, intracranial volume (ICV) was not included as a covariate since significant differences were not found and since any differences in ICV were already taken into account in the pre-processing of the images. In the process of segmenting and modulating for nonlinear effects only, adjustments for intracranial volume were already incorporated. With no covariate entered in the model, group differences were found in many areas, with the full term group showing larger volumes than the VLBW group in some areas, as well as areas where the VLBW group had larger volumes than the full term group. Gray matter volume was negatively correlated with group (full term > VLBW) for the following regions: bilateral temporal (inferior, fusiform, superior, middle), left caudate head, left parahippocampal, right (frontal) paracentral, right inferior parietal, right putamen and right anterior cerebellum. Gray matter volume was positively correlated with group (VLBW> full term) for the following regions: bilateral superior frontal gyrus, bilateral occipital ligual gyrus, right occipital (middle, fusiform), right cerebellum (posterior declive, anterior culmen), left middle frontal, left parahippocampal/fusiform and left anterior cingulate.

As the developing brain is changing over time, many studies covary for age when conducting VBM analyses. Additionally, it is also common to control for sex since this can be an important factor (Mechelli, Price, Friston & Ashburner, 2005). Through VBM analyses, group structural brain differences were found between preschoolers born VLBW and full term when correcting for age and sex. Gray matter was negatively correlated with group (full term > VLBW) for the following regions: Bilateral Temporal (middle, fusiform, superior), frontal paracentral, putamen (lentiform nucleus), right temporal (inferior) and right cerebellum anterior lobe. When correcting for age and sex, gray matter was positively correlated with group (VLBW > full term) for the following regions: Bilateral Frontal (superior), occipital (lingual), right

cerebellum (posterior lobe declive and tonsil), right occipital (fusiform, middle), left frontal (middle), left anterior cingulated and left parahippocampal.

Thus, structural brain differences were found between VLBW and full term preschoolers in this sample. As hypothesized, temporal, striatal, parietal and cerebellar increases, as well as decreases in the fusiform areas were seen in full term preschoolers compared to preschoolers born VLBW. Overall, structural volumes in the temporal and parietal areas were decreased, and volumes in the frontal and occipital areas were increased in the VLBW group relative to the full term group. In addition to the hypothesized differences, preschoolers born VLBW also demonstrated larger frontal, occipital, anterior cingulate and parahippocampal volumes compared to the full term group. Although larger structural volumes may seem counter intuitive in the VLBW group, research has demonstrated that the typical growth and pruning cycles may be delayed in children born VLBW. Phillips et al. (2011) Showed that delayed cortical thinning was present in toddlers who were born preterm, and this delayed reduction directly correlated with degree of prematurity. This pattern of regional increases and decreases is consistent with the findings of prior studies in older children and may deepen our understanding of developmental trajectories in brain development among children born VLBW (Martinussen et al., 2005; Nagy, Lagercrantz, & Hutton, 2010; Soria-Pastor et al., 2009).

Structural Brain Volumes Relate to EF

No studies to date have examined EF in preschoolers born VLBW in conjunction with neuroimaging. In fact, no neuroimaging studies have examined EF in healthy full term children during the preschool age. Most neuroimaging studies of EF in the VLBW population have been conducted during infancy at term (the equivalent of 40 weeks gestation), and these perinatal

brain images are then associated with EF abilities at later ages (Woodward, Edgin, Thompson, & Inder, 2005). Other researchers have utilized adolescent or adult samples that were born VLBW and examined their concurrent EF abilities and neuroimaging findings.

There is some support for the idea that MRI volumes at term are related to overall mental ability and specific working memory skills in the following areas in toddlerhood: midtemporal regions, dorsolateral prefrontal cortex, parietooccipital regions, and the right subgenual areas, with converging evidence existing for the importance of volumes in the premotor and sensorimotor areas. (Peterson et al., 2003; Woodward, Edgin, Thompson, & Inder, 2005). Mixed evidence exists for the relationship between infant MRI and school age developmental abilities in children born VLBW, with some studies finding no relationship between early MRI and later outcome (Lind et al., 2010; Skranes et al., 1998), and other studies finding total brain volume, cerebellar volume, and hippocampal volume to be related to outcome in school age children. (Beauchamp et al., 2008).

When cognitive function was measured at the same time as MRI scans were conducted in 18-month-olds born VLBW, as orbital frontal volume decreased, the A-not-B scores of children born very low birth weight increased (Lowe, et al., 2011). Additionally, in school aged children born VLBW showed relationships between IQ and middle temporal gyrus, postcentral parietal gyrus, right and left caudate volumes, sensorimotor, and midtemporal cortices (Abernathy, Cooke, & Foulder-Hughes, 2004; Peterson et al., 2000; Soria-Pastor et al., 2009). In adolescents who were born preterm, relationships between cognitive outcome and neuroanatomical features were present for overall cortical thickness and surface area in the right and left hemispheres, overall cerebellar volume, cerebellar white matter volume, middle temporal gyrus, inferior

temporal gyrus, corpus callosum, and overall white matter and ventricle size (Nosarti, et al., 2008). However, a relationship between brain volume and EF was not found in a group of 12-year-old children born VLBW (Kesler, et al., 2008).

Additionally, in healthy school aged children, orbitofrontal, medial temporal, and cerebellar volumes correlated with a task that measures shifting abilities (McAlonan et al., 2009), which implicates EF processes. The cerebellum has also been implicated in executive processes in healthy children (Dum and Strick, 2003). In children with ADHD, anterior cingulate, striatal, cerebellum, and medial temporal volumes were found to correlate highly with EF task performance (McAlonan et al., 2009). However, no studies to date have examined the neuroanatomical correlates of EF in preschool aged children born VLBW.

Due to the small sample size with completed neuroimaging in the current sample, the relationship between EF and regional brain volumes was explored in the combined sample of VLBW and full term preschoolers. In the current study, the PCA combined group analysis was used to generate a single EF component score for neuroimaging analyses. This was supported by the results that a single PCA based EF component was able to explain a large amount of variance in this sample, and the four EF measures were related in the VLBW and full term groups separately. In the combined sample, correlations were run through VBM and SPM to determine what brain regions were related to the derived PCA EF component when covarying for group. The hypothesized positive correlations were found for the temporal and striatal regions. Contrary to the hypothesis, no relationships were found between orbitofrontal or cerebellar volume and EF in the combined sample and, occipital volume was negatively correlated with EF in the combined sample. In the combined sample, gray matter was positively correlated with EF

for the following regions: Bilateral temporal (middle, superior), right temporal (inferior, fusiform), right insula and right putamen. Thus, increases in gray matter in these areas were related to increases in EF. In the combined sample, gray matter was negatively correlated with EF for the following regions: Right occipital (inferior, fusiform and lingual), and increases in gray matter in these areas were related to poorer EF.

As noted above, these structural neuroimaging studies in relation to EF have never been examined in preschoolers born VLBW and full term. Thus, these findings are novel and may help provide insight into this little studied area, but they are difficult to place into the current neuroimaging literature. Most structural neuroimaging studies in premature populations have included adults or were conducted on the premature infants when they attained 40 weeks of age (at term). An astounding amount of brain growth and change occurs between 40 weeks gestational age and adulthood (Toga, Thompson, & Sowell, 2006). Additionally, few studies have shown replications of region specific findings, even within similar age ranges. The role that premature birth and associated medical complication might play on developmental trajectories is also poorly understood and adds an additional complication to the interpretation of these findings in the context of the literature.

However, the literature does suggest an empirical basis for the observed differences in parietal regions, anterior cingulate and insula volumes. These areas may be related to hypothesized developmental trajectories of executive attention. The development of executive attention (an initial component of executive function) is hypothesized to emerge from early orienting responses to sensory events in infants (Posner, Rothbart, Sheese, & Voelker, 2012). Responding to stimuli and orienting by choice versus by reflex is a critical development in attentional control that lays the foundation for later EF skill development. Executive attention in

adults has been demonstrated to rely on the anterior cingulate, insula and basal ganglia; in infancy orienting to sensory events is mediated by the parietal lobe and frontal eye fields, the amygdala is also involved ((Posner, Rothbart, Sheese, & Voelker, 2012). The developmental process underlying the shift from reaction to controlled process is linked to a specialization of brain networks and the development of control in these areas. Regional brain volume differences in the preschool period may reflect this emerging specialization.

Despite some context in the literature for specific relationships seen in the current study, the specific pattern of neuroanatomical findings demonstrated does not have a clear and parsimonious explanation. Known neurodevelopmental or brain maturational processes cannot offer a clear explanation for the particular patterns of regional volume increase and decreases seen across the VLBW and full term groups. Other complicating factors include the methodological difficulties of mapping areas of interest from adult studies onto the child brain. There is some evidence that the boundaries between regions may change developmentally (Karmiloff-Smith, 2010), which would have an impact on the regional structural determinations seen in this study.

Despite these considerations, the neuroimaging findings of this study, namely that increases in temporal and deep gray matter and decreases in occipital volumes were related to EF in the combined sample of preschoolers born VLBW, , has the potential to add to the literature. Although the frontal lobe was once synonymous with EF, it is now understood that EF depends on extensive reciprocal connections between the dorsal prefrontal cortex, sensorimotor, occipital, parietal, and temporal lobes of the brain (Volpe, 1995, 1997, 2001). Since the frontal lobe is the last area to fully develop and myelinate, it is possible that other diffuse brain regions are responsible for EF performance at this age. Additionally, a unitary construct of EF at this age

may speak to the recruitment of unspecialized, broad based brain regions in completing EF tasks. This relates to the idea that functional brain development does not revolve around the use of specific regions in isolation or the initiation of activity in specific regions. Brain activity and neural processes start as diffuse across many regions and in both hemispheres. With time, differential environmental experiences, and adaptation, brain activity becomes specialized within certain networks. What develops over time is likely a changing network of interregional and intraregional connections utilized in certain tasks (Karmiloff-Smith, 2010). These changes in functional coordination cannot be studied through structural MRI methods and must be explored through functional Magnetic Resonance Imaging (fMRI). The use of whole brain wide multivoxel activation may be especially useful in linking patterns of behavior to brain activation (Raizada, et al., 2010).

Another consideration is that the composition of the brain is changing rapidly during the preschool period as pruning occurs to streamline the efficiency of cognitive processes. The possibility that synaptogenesis and the elimination of cells and synapses could be impacting the relationship of structure and function in this age group should also be considered. The idea of plasticity and changes in plasticity over time may also be relevant to consider in this population. Recent research also suggests that plasticity may be region-specific (Karmiloff-Smith, 2010). This study provides a first glimpse into the structural differences between preschoolers born VLBW and full term, as well as some specific regions that may be related to EF in these groups. This study only provides a snapshot of this age and the developmental context and implications of these findings may need to be placed into a larger longitudinal development process in order to be fully understood.

Limitations

One limitation is that more performance-based measures of EF were utilized than parent report or observationally coded measures. This imbalance may have influenced the findings that performance based measures were the only ones that grouped together in a unitary construct. It is possible that method variance is influencing the results of this study in addition to true construct differences.

Additionally, there are potential limitations to the use of the PECB, as this was a novel combination of tasks to yield a cumulative percent correct. This way of combining these tasks is without precedent. However, there is a precedent for the gradation in difficulty of these tasks (Beck & Carlson, 2007). In this way of combining the four measures, each test is equally weighted. It should be noted that this is just one way that a combined measure could be calculated and it is assumed that children who perform well on the more advanced subtests will also perform well on the more simple subtests. Additionally, it is presumed that higher scores were due to strong performance on the more difficult tests. These assumptions were not examined in the course of this study. Additionally, the creation of new measures and the use of measures drawn from the developmental literature present a possible limitation in the interpretation of these results.

Another limitation is that parent report can often be a biased measure that depends upon a large variety of factors. Parent reading level, the quality of the parent-child relationship, parents' familiarity with "typical" child behaviors and varying parental expectations for preschoolers can all impact parent ratings of EF on the BRIEF-P. Additionally, child temperament may be a confounding factor in the interpretation of these results. Future studies may wish to include a child temperament measure to investigate this relationship. Possible biases in parent ratings

could have been addressed by obtaining information from multiple informants and this may be a valuable factor to consider in future studies. These factors were not systematically examined and the impact of these differences cannot be ruled out as possible reasons why parent reported EF did not relate strongly to performance measures of EF.

Although ethnic minorities can be underrepresented in research studies, the diversity in New Mexico allowed us to include a highly diverse sample. This diversity can be considered a strength of the current study as well as a possible limitation. Ethnically diverse samples are often not included in research and by having a highly diverse sample, which includes many children with Hispanic heritage, we may be better able to examine the impact of premature birth across sociodemographic lines. However, ethnicity (and associated parenting, nutritional and cultural practices) may be a factor that impacts outcomes in children born VLBW and may thus serve as a confounding factor. Additionally, the generalizability of our findings may be limited due to the very diverse nature of our VLBW and full term samples. Genetic variability may also account for some of the variance in EF outcomes and ethnicity may ultimately serve as an explanatory factor in outcome studies. Future studies are warranted to examine this possibility.

This study is also limited by a small sample size. A larger sample size would have afforded more power, which would have allowed separate VBM neuroimaging comparisons to be conducted for the relationship between EF and regional volumes in the VLBW and full term groups. Larger neuroimaging sample sizes may have revealed group specific EF correlations with brain volume. It is possible that differential relationships between brain structure and EF exist across the groups. Combining the groups for the VBM analyses may have clouded these relationships.

Additionally, there are limited published studies investigating concurrent brain structure and function in children born VLBW in this age group, as most previously published studies have conducted MRI at term and then correlated brain structure at term with developmental outcome several years later. This study is unique in that it examines concurrent volumetric and developmental outcome relationships in a group of preschoolers born VLBW, compared to those born full term. However, it was difficult to map our findings onto the body of research examining MRIs that were conducted at full term equivalence. This made the development of specific regional hypotheses difficult and led to a more exploratory neuroimaging analysis design. Though the VBM technique takes the large number of multiple comparisons into account when looking for differences, specific regional hypotheses might have resulted in a more focused statistical analysis with less room for error. As one of the first studies to compare brain structure with EF outcome in preschoolers born VLBW, this study offers significant hypothesis generating observations upon which to base future studies with a larger sample size. Small sample size may have also impacted non-neuroimaging results. Despite the fact that validity measures were appropriate for PCA analyses, PCA is a sample size impacted statistical test. It is possible that the PCAs may have yielded different or more numerous components if a larger sample size were collected.

Future Directions

Continued research with this population to build a broader base from which to learn about the EF abilities of preschoolers born VLBW is warranted. Furthering our understanding of the underlying relationship between EF and neuroanatomical correlates will help illuminate the developmental trajectory of this important construct. The observed differences in total white

matter structural volume between groups may be suggestive of important underlying neuroanatomical differences between preschoolers born VLBW and full term. White matter functional connectivity, as measured through diffusion tensor imaging, would be an informative future direction for research.

Additionally, it will be important to continue examining the relationship between EF and IQ and other real world variables. Although IQ and EF overlap to some extent, they tend to be predictive of different outcomes. Disentangling the shared and non-shared effects between EF ability and IQ will be crucial in creating interventions to better target EF skills. Conducting longitudinal studies that examine EF as a predictor of "real world" outcome (i.e. school success, emotional stability, broad independence) will also be important. If we can clarify the relationship of EF to functional outcomes in children born VLBW, we will be better able to design interventions that target these deficits.

The development of EF measurement tools for preschool aged children that have a strong normative base will be crucial in the continued pursuit of EF measurement in children born VLBW. Additionally, finding measures that are age appropriate and can capture a wide range of functional ability (without floor and ceiling effects) would allow for greater exploration of EF development in populations with expected delays.

Current EF performance based measures derived from the typically developing literature are based largely on stand-alone discrete tasks that cannot be given to broad age ranges. This limits the utility of EF performance based testing in preschoolers, as longitudinal measurement is not currently possible using a standard measure. Investigating EF through longitudinal study

would greatly improve our understanding of the developmental trajectory of EF across full term and preterm populations.

Further studies may also benefit from utilizing other behavioral coding to examine EF in preschoolers in ecologically valid environments. Some studies have examined inhibitory control by videotaping parents and children in a room with a prohibited object (something dangerous or something breakable or something belonging to someone else) (Kochanska, et al., 1996; 1997). These behavioral coding systems may be more strongly linked to a parent's daily experience of EF based inhibitory control. Additionally, conducting studies that look at the role that parents play in helping their children learn how to inhibit would contribute to the literature.

Another aspect that would be interesting to explore further would be parent report of EF. This study, consistent with other research, shows that parent report measures of EF often are not highly related to lab based EF measures. One reason could be that parents seldom see their preschool children acting completely independently without intervening, guiding, or scaffolding. Thus, their rating of their child's independent EF abilities may be inflated. It would be interesting to have parents predict how their children would do on lab based tasks prior to completion, and compare this to their actual performance. This may be a way to assess parent's insight into their preschooler's level of EF.

Another aspect that warrants future consideration is the wording of parent report EF measures. Changes in how instructions are worded across different parent report measures may be contributing to the variability in findings across studies. A greater focus on reducing subjectivity may lead to more accurate measurement. For example, on the BRIEF-P, the directions state that parents should rate "which of the following behaviors have been a problem

for your child in the last 6 months." Parental expectations of what typical preschool behaviors are may influence their likelihood of endorsing their child's behaviors as problematic. During data collection many parents questioned this instruction and indicated that their child had difficulty on the item in question but that it was not really "problematic" for them. As all preschoolers would be expected to have some difficulty with EF, perhaps having parents rate the level of intensity or the sheer presence of such behaviors would yield a less subjective or less variable report of excessive difficulties.

Another contribution of the current study is that previous samples of preschoolers born VLBW and full term that examined EF tended to be from less ethnically diverse samples. Many studies reported in the literature took place in Scandinavia, or involved large numbers of Caucasian and high socioeconomic status families (Baron et al., 2011; Lind et al., 2010). This study included a broad range of family income and a large percentage of the children were reported to be of Hispanic ethnic identity. This study showed that EF differences were found between ethnically and sociodemographically diverse VLBW and full term preschoolers. As ethnicity is a risk factor for premature birth in general, with Black non-Hispanic women having a two-fold increase in their risk of having their child born VLBW, studies that incorporate ethnically diverse samples would increase our understanding of outcomes in this population (Wise, 2003). Continued exploration of EF in diverse samples would facilitate our understanding on the impact of ethnicity and culture in EF development in children born prematurely. Socioeconomic differences would also be a critical area to examine in future studies. Socioeconomic differences may capture some of the variance in outcomes. It may also be interesting to covary for socioeconomic status in future studies in the neuroimaging analyses

Clinical Implications

The ability to discriminate children who have EF difficulties in the preschool period allows those children to be targeted for early intervention. Full term children were found to perform better on EF measures than preschoolers born VLBW in this sample. This may suggest that the EF deficits commonly seen in older children born VLBW may be present and identifiable even before these children enter school. EF difficulties in this population might be best addressed through early and targeted intervention. Several intervention models have been shown to improve EF and real world problem solving ability in full term children (Bierman, Nix, Greenberg, Blair, & Domitrovich, 2008; Blair & Diamond, 2008). Specifically, Tools of the Mind, which uses self-directed play and planning to increase self regulation through awareness, is a pre-kindergarten and kindergarten program that focuses on enhancing self regulation and has shown improvements in the EF abilities of children enrolled (Bodrova & Leong, 2007; Diamond, Barrett, Thomas, & Munro, 2007). Rueda, Checa, and Combita (2012) have also shown that ten sessions of computer training of attention (Attention Network Training) resulted in improvements in executive attention tasks, which were still present two months after discontinuing the training.

Applying interventions that have been shown to improve EF skills to children born VLBW might improve outcomes in this population. Interventions that target the specific areas of weakness identified in this and other studies (Emergent Metacognition, Inhibitory Self Control, Plan Organize, Working Memory and Inhibit) might be especially useful (Espy, 2002). The high risk of adverse outcome in NICU survivors necessitates long-term routine neurodevelopmental follow-up that includes EF assessment. This may be helpful in the clinical management and

early identification of those with problems (Johnson, Wolke, & Marlow, 2008). Infant developmental assessments are typically carried out up until 2 years of age for both clinical and research purposes, and they are crucial for outcome monitoring. However, this follow-up should continue at least through preschool age, and some argue through adolescence, to ensure that children with problems are being identified and are receiving appropriate services (van de Weijer-Bergsma, Wijnroks, & Jongmans, 2008).

Conclusion

In conclusion, relative to children born full term, EF deficits can be seen in preschool children born VLBW through a variety of measures, including performance based EF tasks, parent-reported EF and observational coding. Additionally, these deficits remain even when controlling for age and IQ. However, observational coding of preschooler's compliance with parental requests and parent-reported EF were not strongly related to performance based measures of EF, especially in the full term group. Although parents of preschoolers born VLBW reported that they had higher levels of dysexecutive behaviors compared to ratings of full term preschoolers, parent report of EF on the BRIEF-P did not fall onto the same factor as performance on the EF tasks. One possibility is that elevations on the BRIEF-P may represent broader behavioral difficulties that may be associated with poor EF (Denckla, 2002). The BRIEF-P is also a subjective parent report which may reflect different variables than performance based measures of EF. Observational coding of EF is also limited by the parent-child interactional factors that may be present. Thus, parent report of EF and observational coding of EF may not clearly reflect the extent, degree and nature of EF deficits that preschoolers born VLBW demonstrate on performance-based tasks.

The nature of EF in preschoolers born VLBW and full term seems to be a unitary construct with multiple performance based EF measures (Progressive Executive Categorization Battery, Bear Dragon, Gift Peek and Gift Delay) having high positive correlations. These EF performance measures were also found to load into a single component. One interpretation of this finding is that the four performance based EF measures used in this study are measuring a similar underlying construct.

Additionally, structural brain differences were discovered between preschoolers born full term and VLBW using exploratory voxel-based morphometry (VBM) analyses. Overall, structural volumes in the temporal and parietal areas were decreased while volumes in the frontal and occipital areas were increased in the VLBW group relative to the full term group. Associations were also found between brain structure and EF function in the combined sample., Increases in gray matter in the right occipital area (inferior, fusiform and lingual regions) were related to poorer EF. Increases in gray matter in bilateral temporal (middle, superior), right temporal (inferior, fusiform), right insula and right putamen were related to increases in EF.

In sum, this study identified differential relationships between multimodal methods of EF measurement. Parent report of EF may have questionable validity and utility at this age as a way to identify children who may be struggling with EF skills. However, various performance based EF measures were found to be highly related to each other and loaded into a single factor. In clinical contexts this may be useful in screening for EF deficits, as poor performance on one EF measure was highly related to poor performance on other EF measures. Practically, a single EF performance measure could be used to screen for EF difficulties during the preschool age. The relationship of EF performance to structural brain differences highlights the developmental

process implicated in EF acquisition. Furthering our understanding of the impact of premature

birth on brain development would help us to better predict which children may be at risk for

poorer EF outcomes. The range of EF deficits seen within this sample of preschoolers born

VLBW is indicative of a need for continued follow-up past toddlerhood. As we learn more

about the nature of EF within children born VLBW**,** we will be better able to adapt interventions

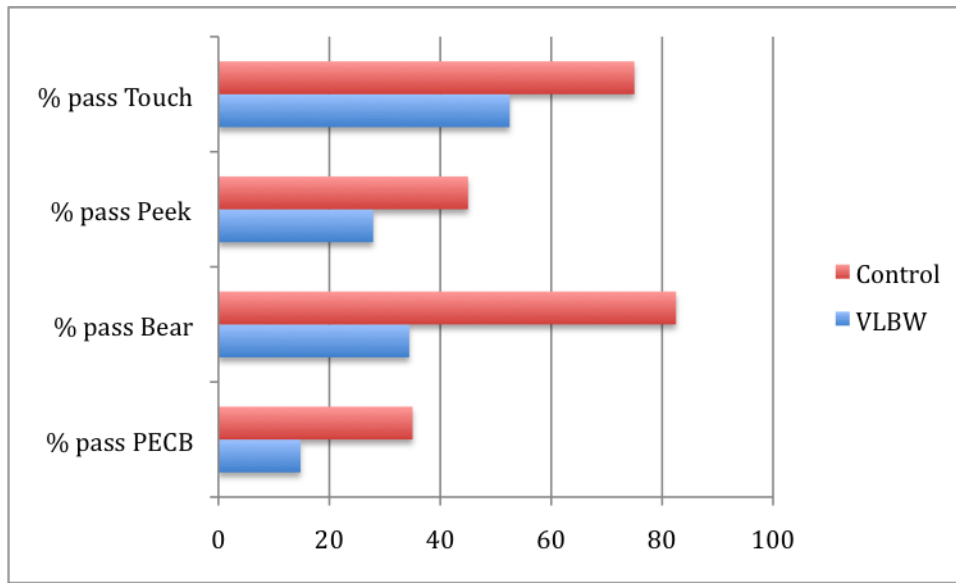that target EF abilities in this population.

Figure 1. Percentage Passing Each EF Performance Task by Group

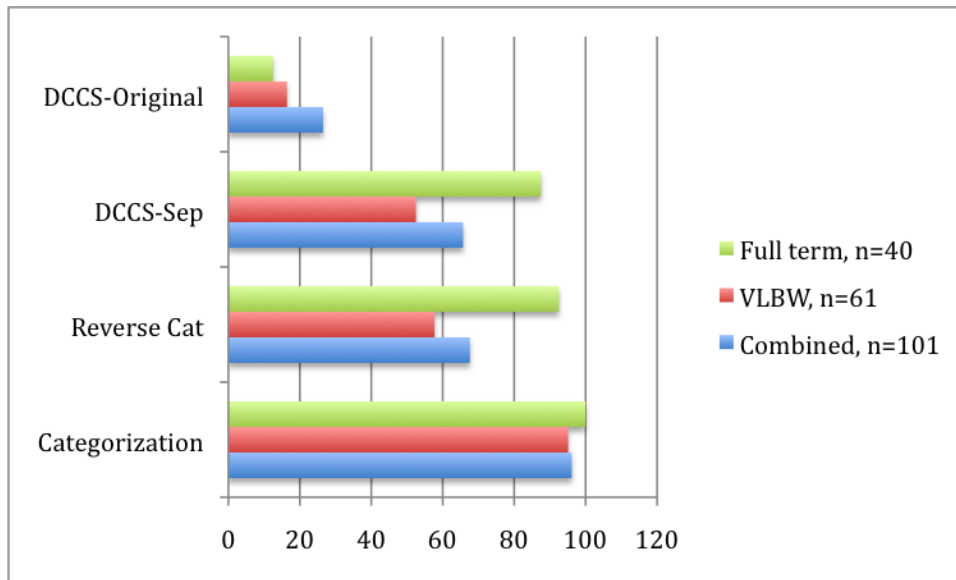*Figure 2. Percentage of the VLBW and Full Term Group Passing Each of the Four Components*

of the PECB

Figure 3. Glass Brain VBM SPM Analyses Where Gray Matter in Full Term > VLBW, No
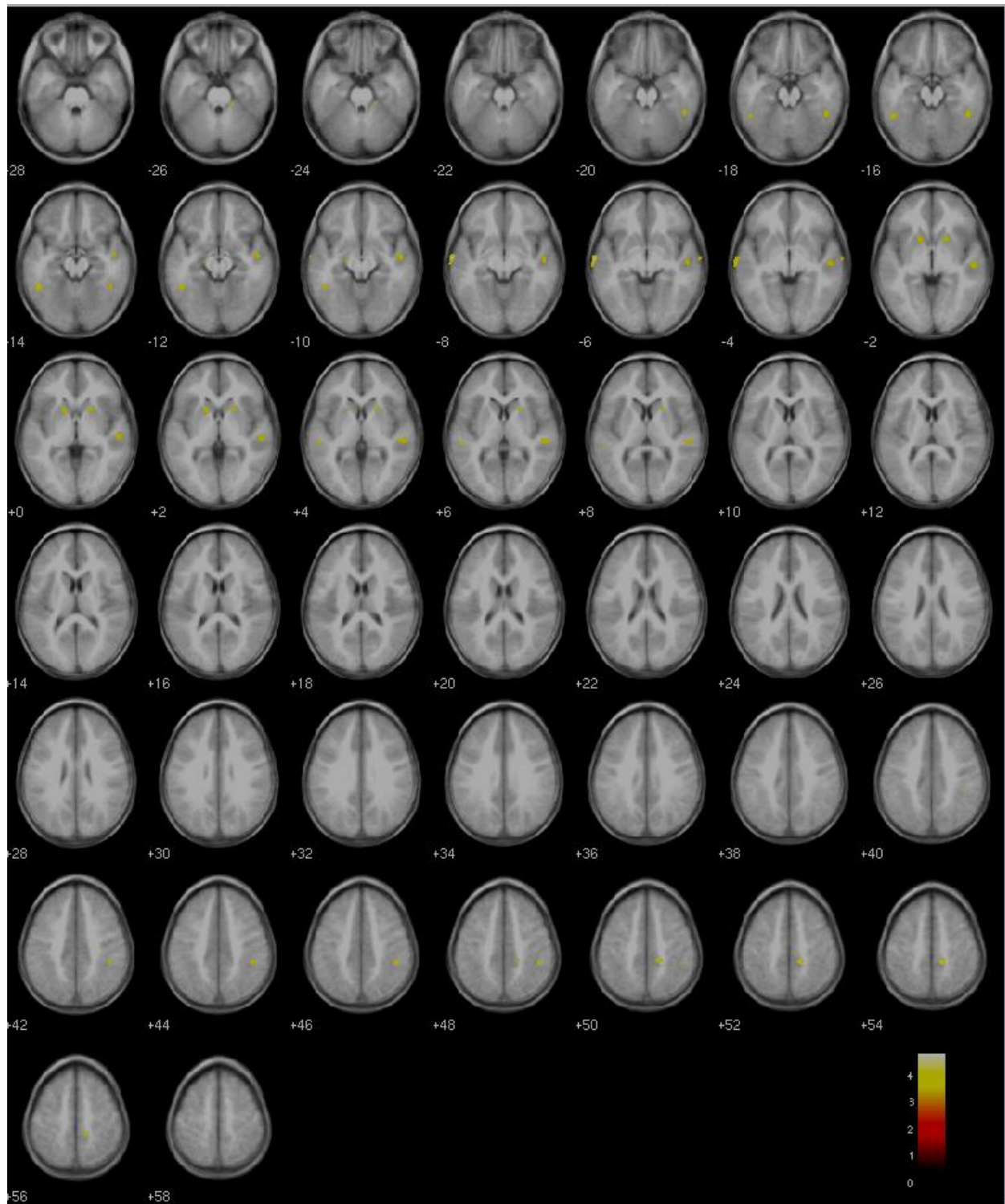
Covariates

Figure 4. Overlay on Template VBM SPM Analyses Where Gray Matter in Full Term > VLBW,
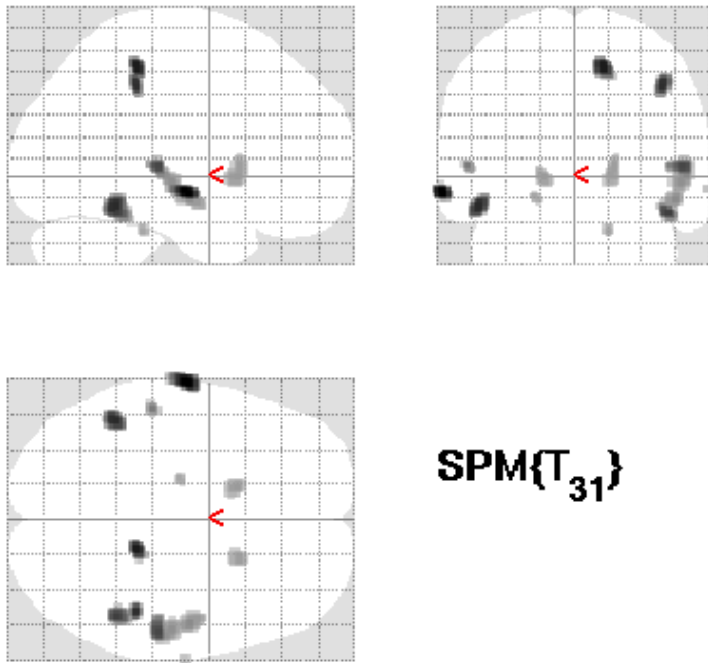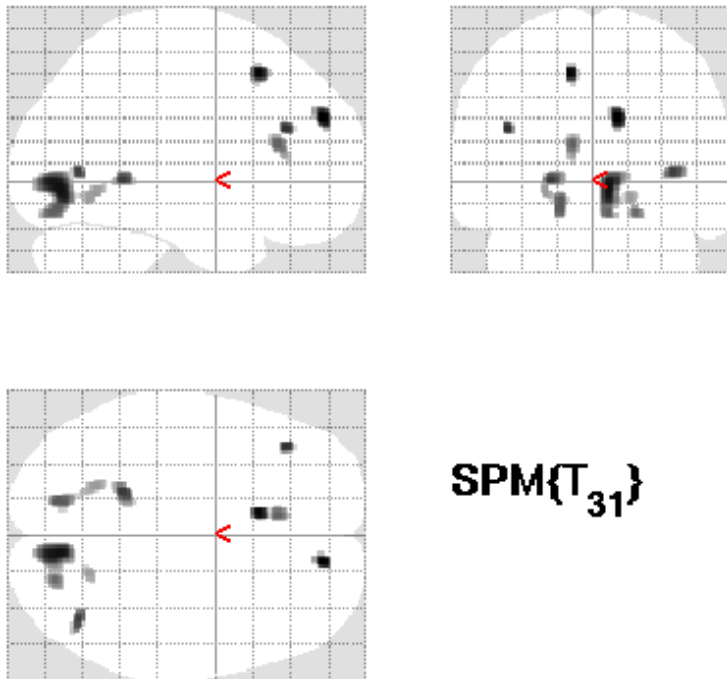
No Covariates

Figure 5. Glass Brain VBM SPM Analyses Where Gray Matter in VLBW > Full Term, No
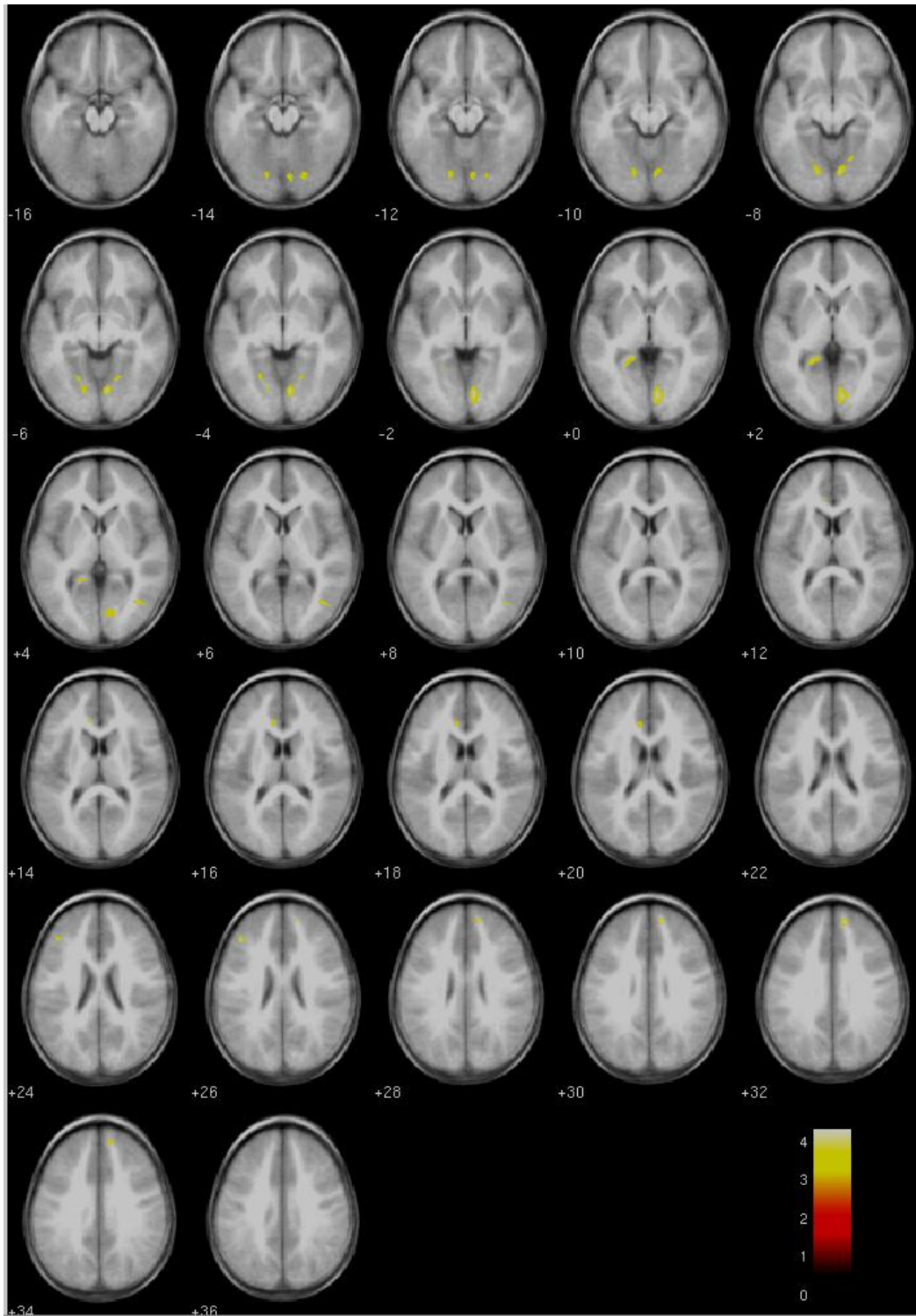
Covariates

Figure 6. Overlay on Template VBM SPM Analyses Where Gray Matter in VLBW > Full Term,

No Covariates
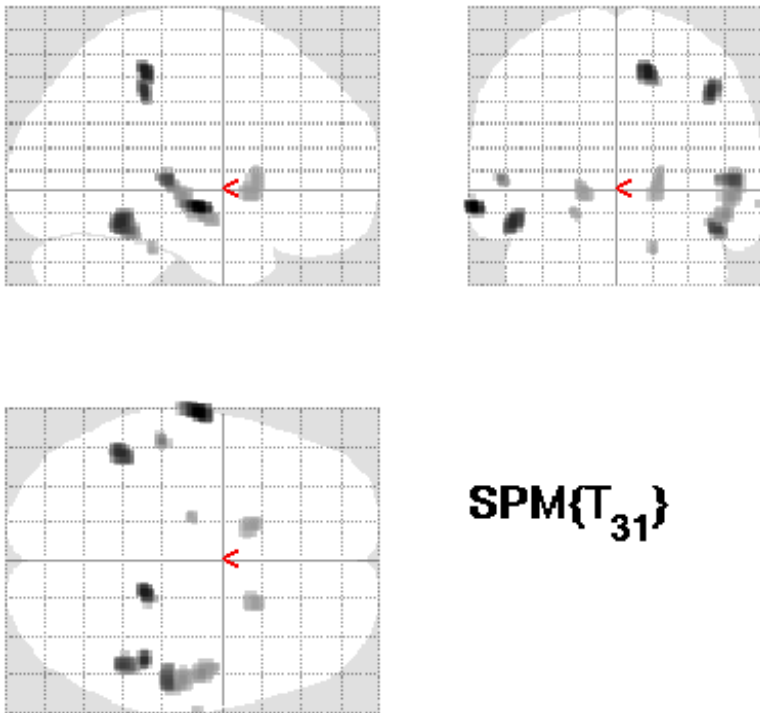
Figure 7. Glass Brain VBM SPM Analyses Where Gray Matter in Full Term > VLBW When Covarying for Age and Sex
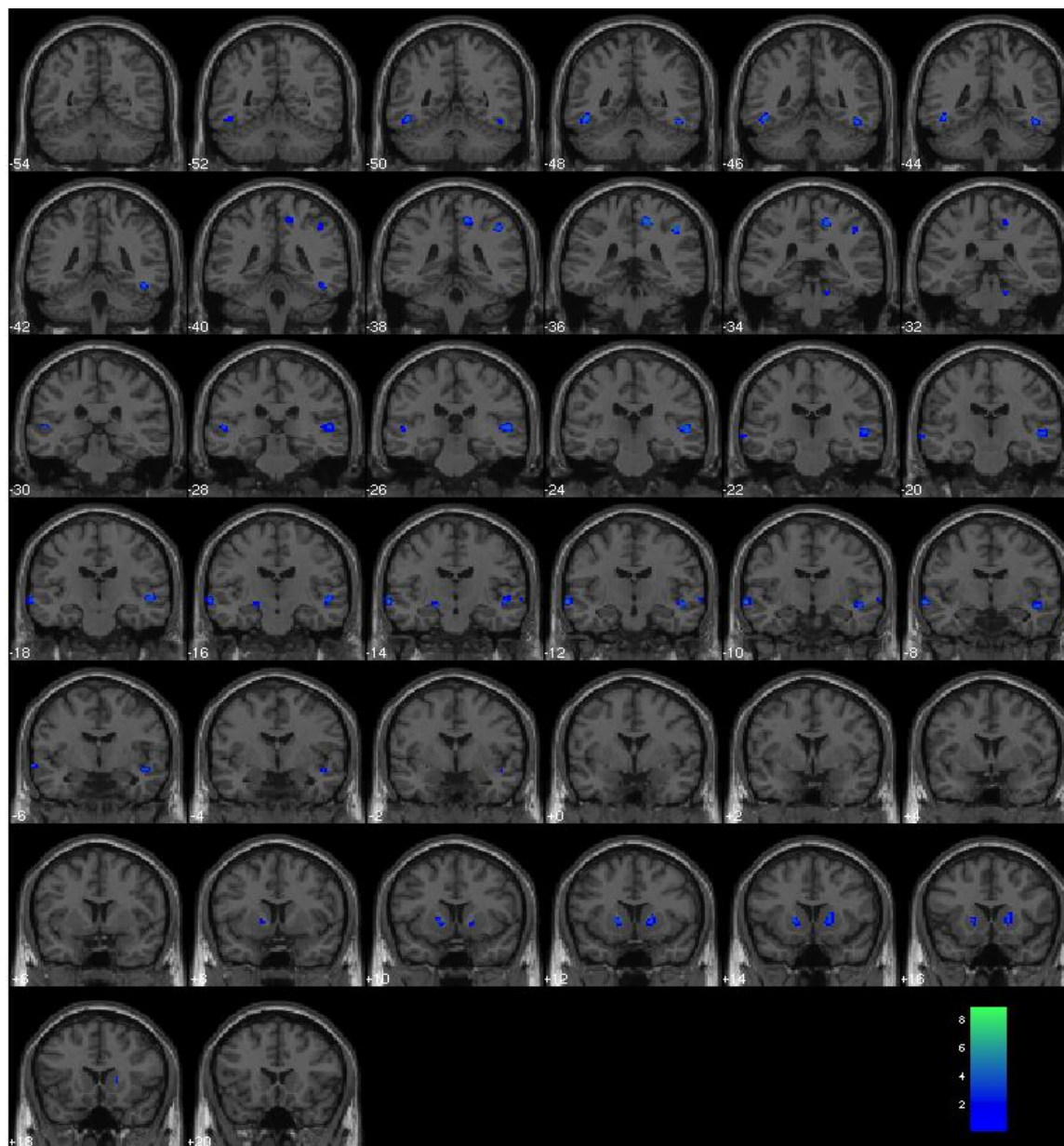
Figure 8. Overlay on Template VBM SPM Analyses Where Gray Matter in Full Term > VLBW

When Covarying for Age and Sex
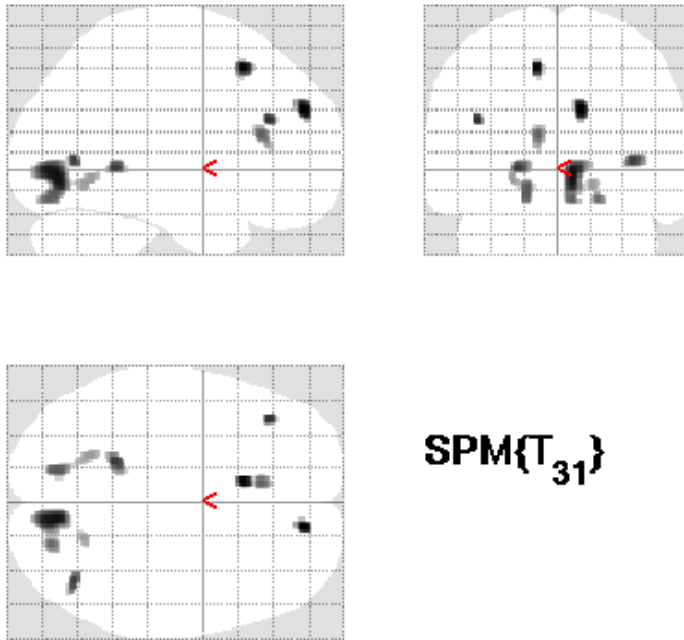
Figure 9. Glass Brain VBM SPM Analyses Where Gray Matter in VLBW > Full Term When Covarying for Age and Sex
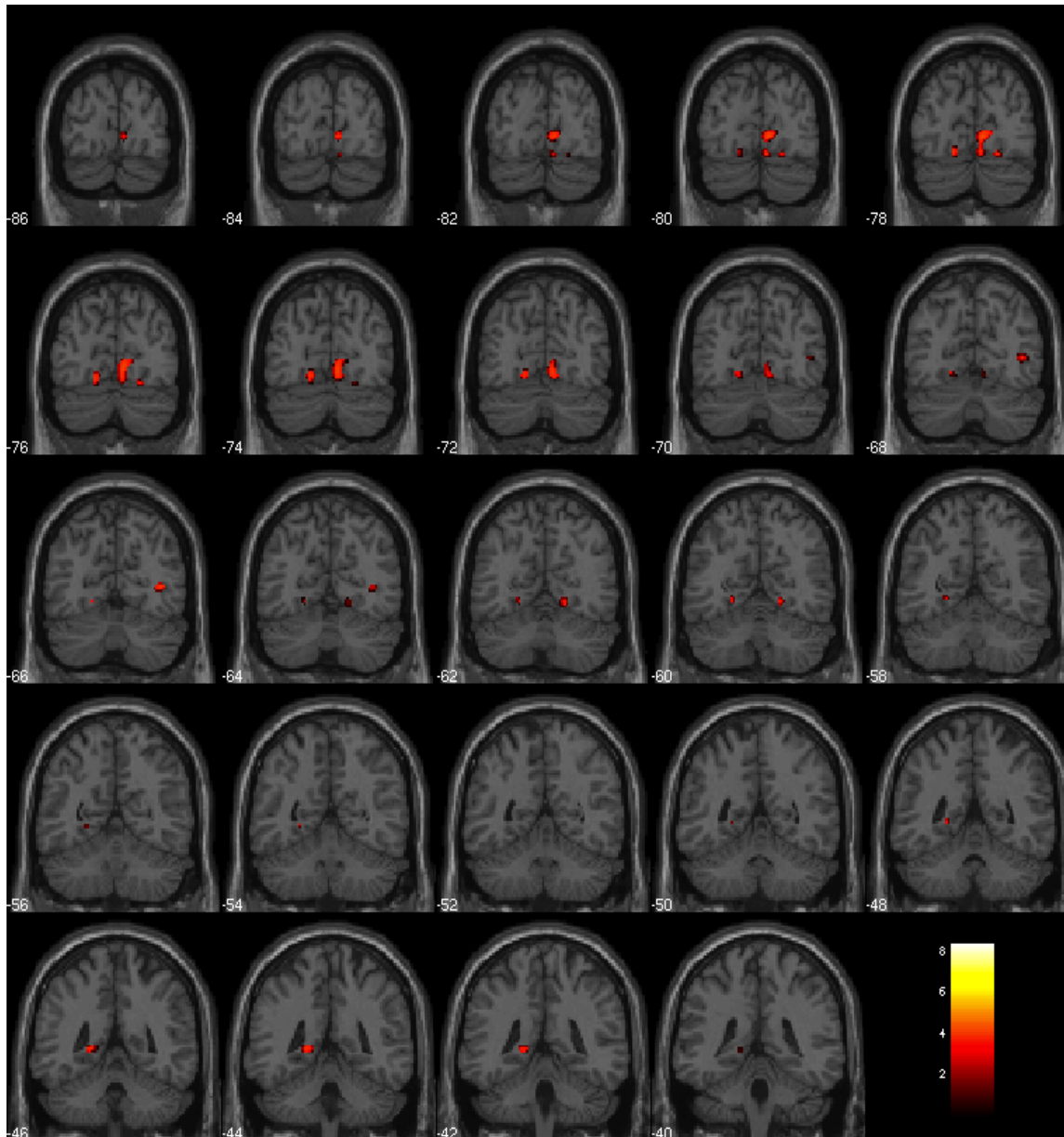
Figure 10. Overlay on Template VBM SPM Analyses Where Gray Matter in VLBW > Full Term When Covarying for Age and Sex

$$SPM\{T_{31}\}$$
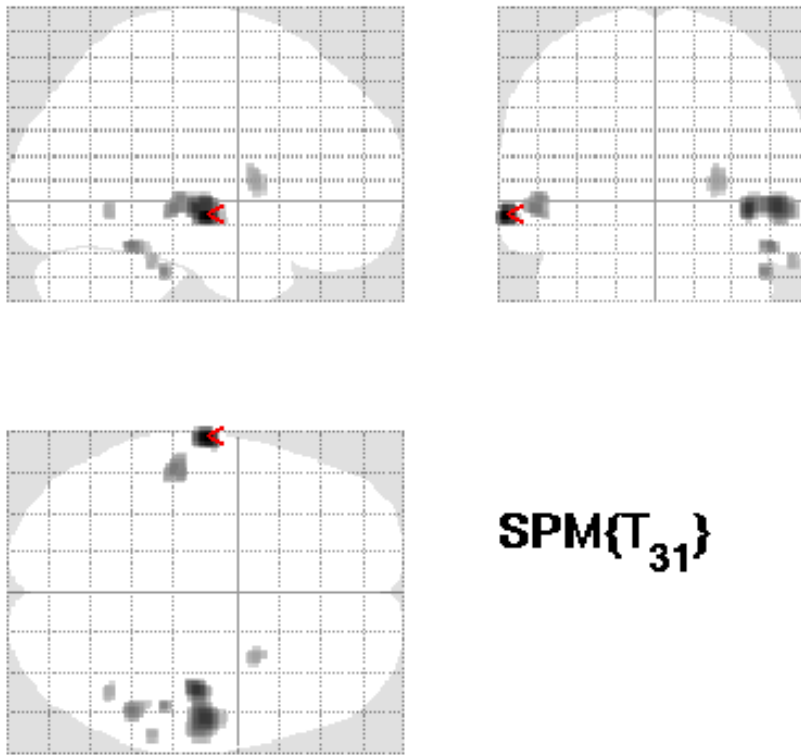
Figure 11. Glass Brain VBM SPM Analyses in Combined Sample Where Increases in Gray Matter Correlate with Increases in EF
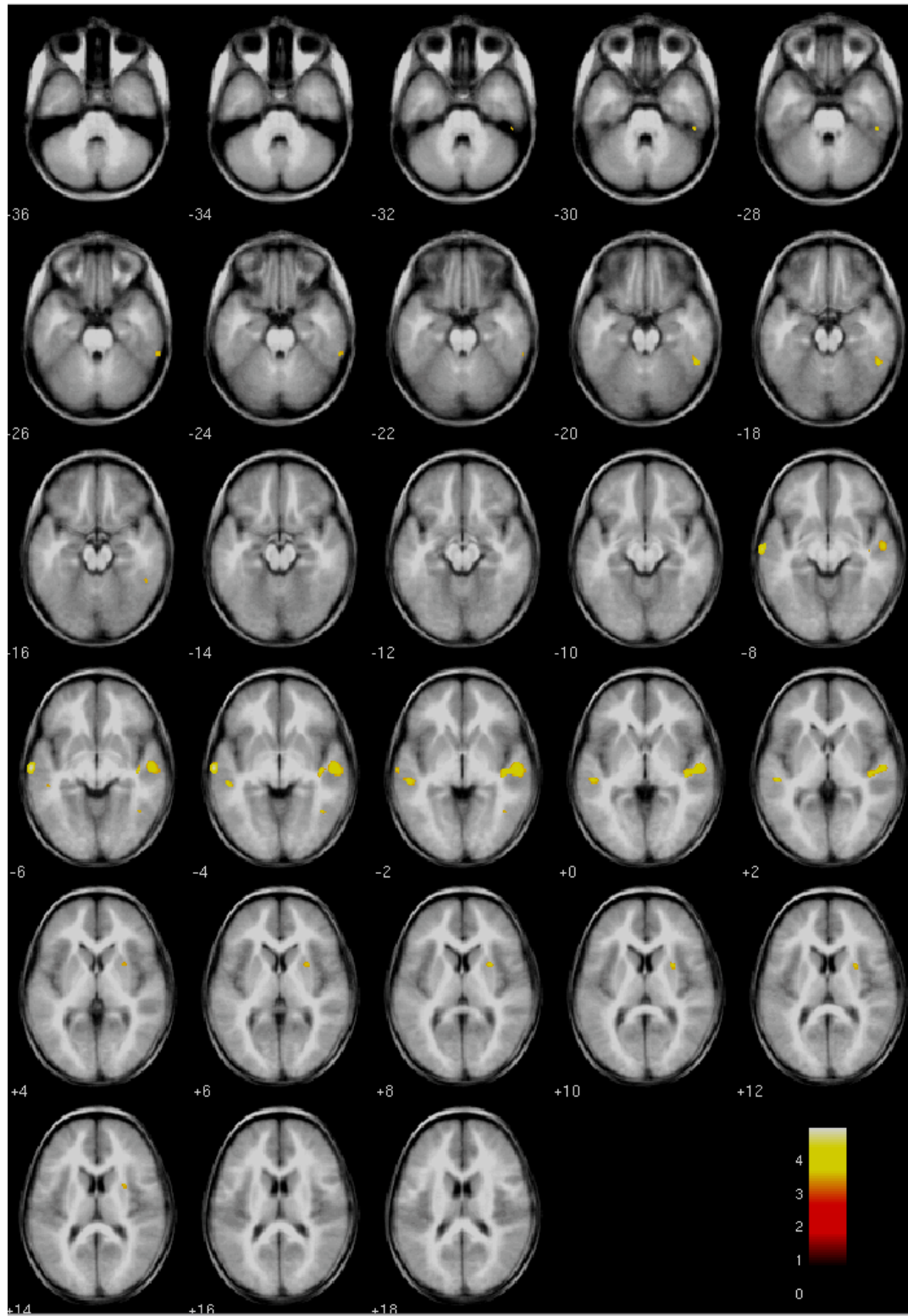
Figure 12. Overlay on Template VBM SPM Analyses in Combined Sample Where Increases in Gray Matter Correlate with Increases in EF
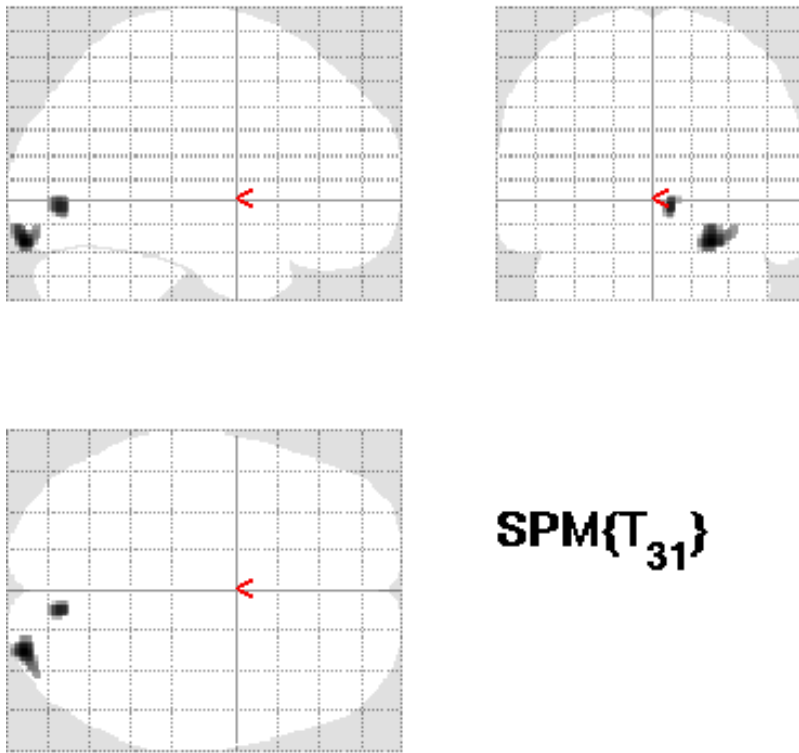
Figure 13. Glass Brain VBM SPM Analyses in Combined Sample Where Decreases in Gray Matter Correlate with Increases in EF
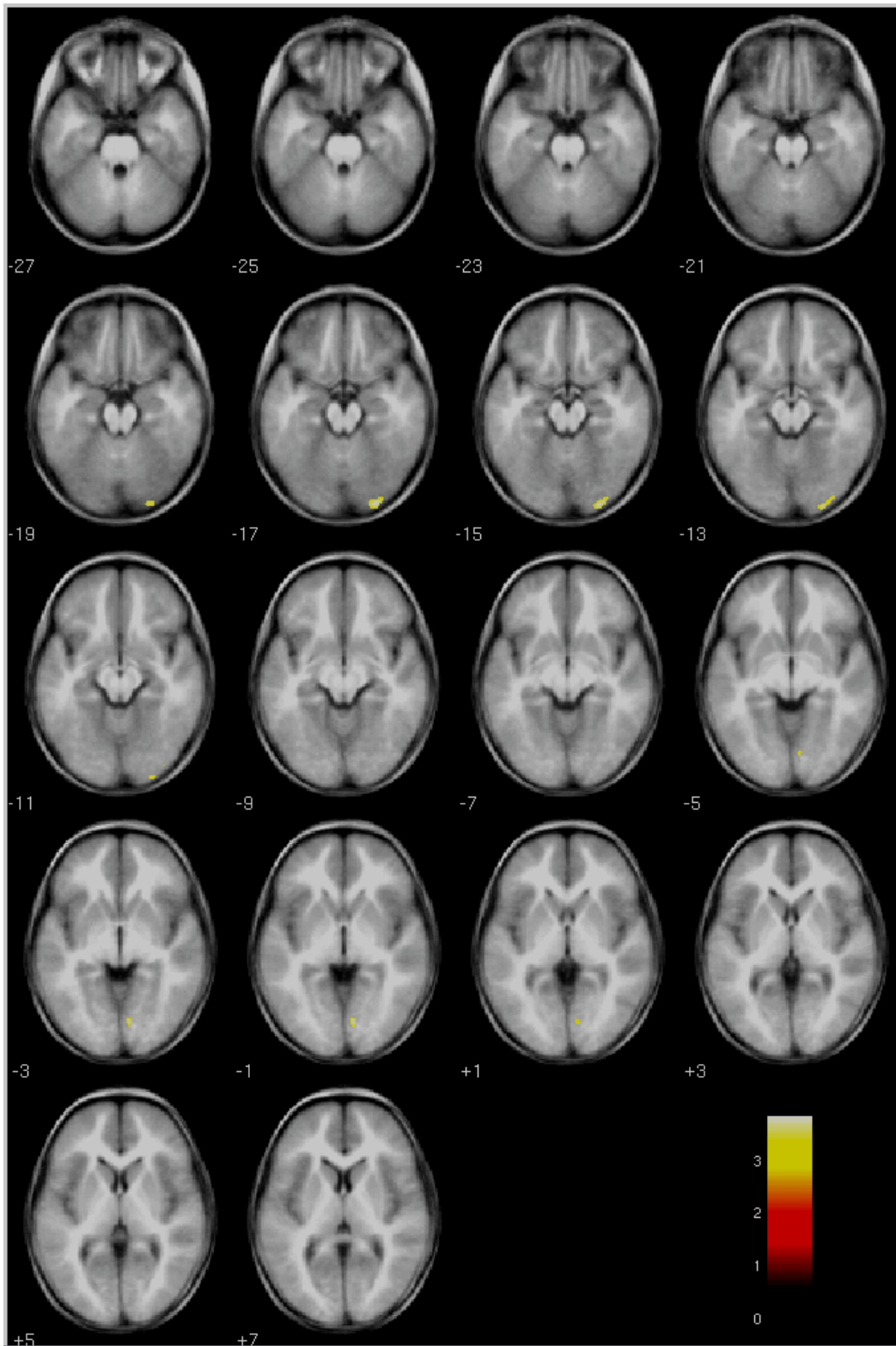
Figure 14. Overlay on Template VBM SPM Analyses in Combined Sample Where Decreases in Gray Matter Correlate with Increases in EF

Table 1.

Mean and Standard Deviations in Demographics, Cognitive and EF Measures in the VLBW, Full Term and Combined Groups

| Variable	Combined, n=101	VLBW, n=61	Full Term, n=40	ANOVA/Chi Square (sig)
Age in months	45.98 (5.05)	46.70 (5.19)	44.78 (4.74)	$F_{(99)}=3.219$ (.076)
Gender, male	62 (61.38%)	36 (59%)	26 (65%)	$\chi^2_{(1)} = 1.915$ (.166)
Ethnicity Hispanic White Native American Black	53 (52.48%) 29(28.71%) 13 (12.87%) 6 (5.94%)	32 (52.5%) 16 (26.2%) 9 (14.8%) 4 (6.6%)	21 (52.5%) 13 (32.5%) 4 (10%) 2 (5%)	$\chi^2_{(3)} = 3.158$ (.310)
WPPSI FSIQ	96.81 (13.89)	91.10 (12.27)	105.45 (11.61)	$F_{(99)}=34.899$ (.000)***
Executive Function Measures				
PECB sum	2.686 (.975)	2.35 (1.02)	3.242 (.594)	$F_{(99)}=22.67$ (.000)***
Bear Dragon	19.98 (12.91)	14.75 (12.77)	28.28 (8.121)	$F_{(99)}=33.43$ (.000)***
Gift Peek	36.62 (22.043)	30.46 (22.56)	46.18 (17.884)	$F_{(99)}=13.56$ (.000)***
Gift Touch	89.69 (42.62)	80.07 (47.58)	104.74 (28.721)	$F_{(99)}=8.44$ (.005)**
Compliance	3.364 (1.216)	3.117 (1.277)	3.744 (1.019)	$F_{(99)}=6.644$ (.011)*
BRIEF GEC	54.42 (12.348)	57.44 (12.88)	49.62 (10.04)	$F_{(99)}=10.097$ (.002)**
BRIEF Inhibit	55.06 (11.47)	56.92 (12.5)	52.08 (9.201)	$F_{(99)}=4.173$ (.044)*
BRIEF Shift	49.10 (9.44)	50.33 (9.68)	47.05 (8.888)	$F_{(99)}=2.655$ (.106)
BRIEF Emotional Control	49.61 (10.5)	50.56 (11.22)	48.05 (9.341)	$F_{(99)}=1.246$ (.267)
BRIEF Working Memory	56.38 (12.52)	59.54 (12.94)	51.46 (10.331)	$F_{(99)}=10.82$ (.001)***
BRIEF Plan Organize	55.07 (12.77)	58.62 (12.95)	49.44 (10.535)	$F_{(99)}=13.418$ (.000)***

Note: * = $p \le .05$, ** = $p \le .01$, *** = $p \le .001$

Table 2.

Spearman Correlations Between EF Measures in Combined VLBW and Full Term Sample

n=101

	PECB	Bear Dragon	Peek	Touch	BRIEF-GEC	Compliance
PECB	1	.744 (.000)***	.547 (.000)***	.399 (.000)***	-.343 (.000)***	.178 (.079)
Bear Dragon		1	.593 (.000)***	.521 (.000)***	-.242 (.015)*	.226 (.025)*
Peek			1	.490 (.000)***	-.329 (.001)***	.332 (.001)***
Touch				1	-.175 (.081)	.303 (.002)**
BRIEF-GEC					1	-.107 (.293)
Compliance						1

Note: * = p ≤ .05, ** = p ≤ .01, *** = p ≤ .001

Table 3.

Spearman Correlations Between EF Measures in VLBW Sample, n=61

	PECB	Bear Dragon	Peek	Touch	BRIEF-GEC	Compliance
PECB	1	.705 (.000)***	.570 (.000)***	.359 (.004)**	-.355 (.005)**	.161 (.220)
Bear Dragon		1	.461 (.000)***	.410 (.001)***	-.200 (.123)	.182 (.165)
Peek			1	.460 (.000)***	-.387 (.002)**	.404 (.001)***
Touch				1	-.174 (.180)	.357 (.005)**
BRIEF-GEC					1	-.274 (.150)
Compliance						1

Note: * = p ≤ .05, ** = p ≤ .01, *** = p ≤ .001

Table 4.

Spearman Correlations Between EF Measures in the Full Term Sample, n=40

	PECB	Bear Dragon	Peek	Touch	BRIEF-GEC	Compliance
PECB	1	.565 (.000)***	.378 (.018)*	.267 (.101)	-.226 (.161)	.311 (.05)*
Bear Dragon		1	.625 (.000)***	.623 (.000)***	-.016 (.921)	-.147 (.372)
Peek			1	.472 (.002)**	-.048 (.773)	-.015 (.929)
Touch				1	-.039 (.816)	.016 (.925)
BRIEF-GEC					1	.204 (.214)
Compliance						1

Note: * = p ≤ .05, ** = p ≤ .01, *** = p ≤ .001

Table 5.

PCA Extraction Communalities and Eigenvalues for Each Performance Based EF Measure by

Group

EF Performance Measure	Single Component Extraction Communalities for the combined group (N=101)	Single Component Extraction Communalities for the VLBW group (N=61)	Single Component Extraction Communalities for the full term group (N=40)
PECB	.864	.868	.681
Bear Dragon	.870	.817	.908
Gift Peek	.825	.801	.794
Gift Touch	.739	.699	.754
Eigenvalue	2.89	2.579	2.488

Table 6.

Global Brain Structural Volumes for Preschoolers Born VLBW and Full Term

Brain Tissue Type	VLBW Mean Volume (Standard deviation) mm^3 n=22	Full Term Mean Volume (Standard deviation) mm^3 n=11	T-test (significance)
Gray Matter	769,425.00 (41,402.15)	811,493.64 (89,285.06)	1.865 (.072)
White Matter	359,204.09 (33,816.23)	398,201.82 (60,712.33)	2.383 (.023)
Cerebral Spinal Fluid	168,312.27 (38,803.19)	157,826.36 (21,725.49)	-0.829 (.413)
Total Intracranial Volume	1,296,940.0 (95,019.66)	1,367,520.91 (161,652.10)	1.585 (.123)

Note: * = p ≤ .05, ** = p ≤ .01, *** = p ≤ .001

Table 7.

Significant VBM Group Differences in Gray Matter With No Covariates, All t-values Significant

at the 0.001 Level Uncorrected

Area (Brodmann's area)	T value
Gray matter volumes where full term > VLBW	
Left middle temporal gyrus (BA=21)	4.82
Right middle temporal gyrus (BA=21)	3.50
Right (frontal) paracentral lobule (BA=4)	4.56
Left inferior temporal gyrus/fusiform gyrus (BA=37)	4.42
Right inferior temporal gyrus/fusiform gyrus (BA=37)	4.26
Right inferior parietal (BA=40)	4.40
Right superior temporal gyrus (BA=41)	4.23
Right superior temporal gyrus (BA=38)	3.78
Right superior temporal gyrus (BA=22)	3.89
Left superior temporal gyrus (BA=22)	4.82
Left superior temporal gyrus (BA=22)	3.76
Left caudate head	3.71
Right putamen	3.69
Right anterior cerebellum	3.64
Left parahippocampal gyrus (BA=28)	3.63
Gray matter volumes where VLBW > full term	
Right superior frontal gyrus (BA=9)	4.32
Left superior frontal gyrus (BA=6)	4.29
Left middle frontal gyrus (BA=46)	4.03
Left parahippocampal gyrus (BA=30)	3.98
Right middle occipital gyrus (BA=37)	3.96
Left occipital lingual gyrus (BA=18)	3.85

Right occipital lingual gyrus (BA=18)	4.21
Left fusiform gyrus (BA=19)	3.59
Right fusiform gyrus (BA=19)	3.78
Left anterior cingulate (BA=24)	3.82
Right anterior cerebellum culmen	3.26
Right posterior cerebellum declive	3.81

Table 8.

Significant VBM Group Differences in Gray Matter After Correcting with Age and Sex as Covariates, All t-values Significant at the 0.001 Level Uncorrected

Area (Brodmann's area)		t-value
Gray matter volumes where full term > VLBW		
Right frontal paracentral (BA=5)	Left	t=5.09
frontal paracentral (BA=5)		t=3.69
Left middle temporal gyrus (BA=21)	Right	t=4.98
middle temporal gyrus (BA=21)		t=3.63
Left temporal fusiform gyrus (BA=37)		t=4.26
Right temporal fusiform gyrus (BA=37)		t=4.10
Right inferior parietal lobe (BA=40)		t=4.20
Right superior temporal gyrus (BA=22)	Left	t=4.06
superior temporal gyrus (BA=22)		t=3.92
Right cerebellum anterior lobe		t=3.87
Left putamen lentiform nucleus	Right	t=3.68
putamen lentiform nucleus		t=3.67
Gray matter volumes where VLBW > full term		
Right occipital lingual gyrus (BA=18)		t=4.56
Left occipital lingual gyrus (BA=18)		t=4.02
Right cerebellum posterior lobe		t=4.26
Right occipital fusiform gyrus (BA=19)		t=3.98
Left parahippocampal gyrus (BA=19)		t=3.72
Left parahippocampal gyrus (BA=30)		t=3.79
Left superior frontal gyrus (BA=6)		t=4.35
Right superior frontal gyrus (BA=9)		t=4.24
Left medial frontal gyrus (BA=6)		t=3.52
Right middle occipital gyrus (BA=37)		t=4.07
Left middle frontal gyrus (BA=46)		t= 4.01
Left anterior cingulate (BA=24)		t=3.80

Table 9.

Significant VBM Correlations Between Gray Matter and EF in the Combined Sample, All t-

values Significant at the 0.001 Level Uncorrected

Area (Brodmann's area)	t-value
Gray Matter Volumes Positively Correlated with EF	
Left middle temporal gyrus (BA=21)	4.95
Left middle temporal gyrus/superior temporal gyrus	3.93
(BA=21) Right superior temporal gyrus (BA= 21/22)	4.41
Right temporal, fusiform gyrus (BA=37)	3.96
Right middle temporal gyrus (BA=37)	3.64
Right inferior temporal gyrus (BA=20)	3.63
Right inferior temporal gyrus (BA=20)	3.85
Right insula (BA=13)	4.45
Right putamen	3.70
Gray Matter Volumes Negatively Correlated with EF	
Right occipital fusiform gyrus (BA=18)	3.85
Right occipital inferior gyrus (BA=18)	3.54
Right occipital lingual gyrus (BA=18)	3.74

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