

### NIH Public Access

**Author Manuscript**

Early Hum Dev. Author manuscript; available in PMC 2013 May 22.

#### Published in final edited form as:

Early Hum Dev. 2012 February ; 88(2): 111–118. doi:10.1016/j.earlhumdev.2011.07.018.

### **Executive Function Skills are Associated with Reading and Parent-Rated Child Function in Children Born Prematurely**

**Irene M. Loe, MD**\* , **Eliana S. Lee, BS**\* , **Beatriz Luna, PhD**#, and **Heidi M. Feldman, MD PhD**\* \*Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University

School of Medicine, Palo Alto, CA

#Department of Psychiatry and Psychology, Western Psychiatric Institute and Clinics, University of Pittsburgh, Pittsburgh, PA

#### **Abstract**

**Background—**Preterm children are at risk for executive function (EF) problems, which have been linked to behavior and learning problems in full term children. In this study, we examine the relationship between EF and functional outcomes in preterm children.

**Aims—**To evaluate (1) EF skills of 9- to 16-year-old children born across the spectrum of gestational age (GA), (2) relationship of degree of prematurity to EF skills, and (3) contributions of EF skills to two functional outcomes--reading scores and parent-rated child function.

**Method—**Preterm children <36 weeks gestation (n=72) were compared to full term children (n=42) of similar age, gender and SES, on measures of EF, reading, and parent-ratings of child function. Multiple regression models evaluated contributions to EF skills and functional outcomes.

**Results—**Compared to full term controls, preterm children had poorer EF performance on a complex planning and organization task and did not increase planning time as task difficulty increased. Their spatial memory capacity was not different. GA contributed to EF skills, but was mediated by IQ. EF contributed to the variance in reading skills but did not add to the variance in reading when IQ was considered. EF skills significantly contributed to the variance in parent-rated child function, but IQ did not.

**Conclusion—**EF skills contribute to measures of functional outcome in this high-risk population. The use of EF skills as an early marker for learning and functional problems and as a target for intervention in children born preterm warrants future study.

#### **Keywords**

preterm birth; prematurity; executive function; CANTAB; reading; function

**Conflict of Interest** The authors have no financial relationships or other conflict of interest relevant to this article to disclose.

<sup>© 2011</sup> Elsevier Ireland Ltd. All rights reserved

Corresponding author: Irene M. Loe, MD, Stanford University, 750 Welch Road, Suite 315, Palo Alto, CA, 94304; Phone (650) 723-5711; Fax (650) 725-8351; iloe@stanford.edu..

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

#### **1. Introduction**

Executive function (EF) refers to an interrelated set of abilities used to direct goal-oriented behavior. These abilities include response inhibition, spatial working memory, spatial capacity, cognitive flexibility, organization, and planning (1–3). EF skills have been linked in particular to prefrontal cortex, although other specific neural networks and brain regions, including parietal and temporal cortices, basal ganglia structures, and cerebellum, have been identified, depending on the specific EF skill measured on neuropsychological testing or on brain imaging (4–6). Deficits in EF skills have been implicated in some learning, psychiatric, and developmental disorders, such as attention-deficit/hyperactivity disorder (ADHD) and autism (7, 8).

Children born prematurely are at risk for executive function problems (9–11). A recent meta-analysis of very preterm ( $\overline{33}$  weeks' gestation) and or very low birth weight ( $\overline{1500g}$ ) children identified poor EF on measures of verbal fluency, working memory, and cognitive flexibility (9). Calculations of combined effect sizes for EF in the children born preterm showed decrements of 0.57 standard deviations (SD) for verbal fluency, 0.36 SD for working memory, and 0.49 SD for cognitive flexibility. Other studies also show deficits in attention and other EF skills (12–14), such as verbal, visuospatial, and visual working memory; and organization and planning (15, 16).

Children born prematurely are at risk for other adverse short- and long-term outcomes, including lower IQ, learning problems requiring special education or other therapeutic supports (17), poor academic achievement even in children who do not meet eligibility criteria for special education (18), behavior problems (9), and lower rates of high-school graduation and participation in post-secondary education (19). In many studies, preterm children have IQ scores on the order of 0.5 to 1 SD lower than term children matched for age, gender, and socioeconomic status (SES), even though IQ scores may be within the average range (20, 21). Meta-analysis of very preterm or very low birth weight children identified deficits in academic achievement, including math, reading, and spelling; as well as attention problems and internalizing behavior problems (9, 22, 23).

Studies of preterm children rarely relate EF problems to functional measures of outcome, even though children born prematurely are at high risk of longstanding functional impairment in social and academic domains (19). One study that examined parent ratings of attention, lab measures of attention, and functional outcomes focused on very low birth weight and extremely low birth weight children (ELBW) compared to full term children (24). Taylor and colleagues found that poorer performance on objective attention tests was associated with higher ratings of attention problems, lower ratings of social adjustment, and lower scores on math and written language tests; in addition, attention tests predicted achievement skills, indicating that such tests serve as meaningful predictors of outcome (24). Another study of ELBW children at eight years of age by Taylor and colleagues found that EF skills mediated the effects of neonatal risk on academic achievement and adaptive functioning  $(25)$ .

The pathogenesis of adverse EF and associated outcomes in preterm children may be due in part to brain injury, and in particular to white matter injury. Preterm children are highly susceptible to brain injury in periventricular regions due to the sensitivity of the germinal matrix (26). However, injury in preterm children may also be global, as documented by imaging studies showing decreased white matter volumes (25). White matter injury may also be characterized by focal, cystic lesions, diffuse injury, or both (27). Such injury may damage connections within neural networks or among prefrontal, parietal, and other brain regions that subserve EF skills.

Many biological, environmental, and child factors may contribute to the development of EF skills in children born preterm. Some studies have shown that neonatal complications do not confer additional risk on outcomes above that attributable to prematurity as indexed by birth weight or gestational age (28, 29). One study showed that family factors were stronger predictors of school outcomes than perinatal complications (30), while another study showed that both brain injury associated with preterm birth and low SES contributed to outcomes (16). Studies on the influence of gender on EF tasks are mixed (15), although a recent review suggests girls have better inhibitory control than boys between 3 months and 13 years of age (31). Poor EF skills have been associated with economic disadvantage in children (32–34). SES is also highly associated with cognitive and neurodevelopmental outcomes in children born prematurely (35). Age and IQ also affect performance of EF tasks. Although EF is associated with IQ, EF is considered a separate construct from IQ and cannot be used interchangeably with IQ. EF performance improves from childhood to adolescence and from lower to higher IQ (36, 37).

In this study, we had three aims: First, we sought to evaluate EF skills in a sample of 9-to 16-year-old children born across the spectrum of gestational age (24 to < 36 weeks) and birth weight (< 500 to 2500g). We hypothesized that preterm children would have poorer EF skills compared to full-term children. Second, we sought to examine factors that might contribute to the variation in EF skills. We considered the degree of prematurity, age, SES, and IQ. We hypothesized that prematurity would be a substantial contributor to poor EF skills. However, we recognized that IQ might partially mediate the effects of prematurity on EF skills. Finally, and most importantly, we were interested in whether EF skills would contribute to two functional outcomes relevant to school-aged children--reading scores and parent-rated child function. We sought to determine whether EF skills would contribute to these outcomes, after consideration of age, SES, and degree of prematurity. We hypothesized that EF skills would contribute to both reading and parent-rated child function, independent of other factors, including IQ.

#### **2. Methods**

#### **2.1. Participants**

Participants were part of a two-site study conducted in Pittsburgh, PA, and Palo Alto, CA. The larger study is a neuroimaging study of language, cognitive and executive function skills. Study subjects, age 9 to 16 years, had a history of preterm (PT) birth (< 36 weeks gestation) and birth weight (BW) < 2500 g (n = 72). Controls were born full term (FT) ( $\,$  37) weeks) and had BW  $\,$  2400 g (n = 42). Exclusion criteria for all participants included severe neurological disorders, receptive vocabulary standard score < 70; sensory impairments; and non-English speaker.

Recruitment of the study population began in 2006 and consisted of a convenience sample of children born between 1991 to 2001. Preterm subjects were recruited by flyers posted in early intervention newsletters distributed in Pittsburgh and surrounding areas and by letters sent to families of children who were evaluated at Infant Follow-up Services at Lucile Packard Children's Hospital in Palo Alto. Control children were recruited by local ads, school newsletters, and by word of mouth at both sites. Controls were group-matched to preterm children for age, gender, and race.

The study was approved by institutional review boards at the University of Pittsburgh and Stanford University. A parent or legal guardian provided informed consent, and children provided assent. Participants were compensated for participation.

#### **2.2. Measures and Variables**

**2.2.1. Participant characteristics—**Gestational age (GA), BW, and medical complications were gathered from parent report and confirmed with medical records. Demographic information included race, ethnicity, maternal education, and parent report of learning problems addressed with special education at school. Maternal education was used as the measure of SES; it was dichotomized as < 4-year college degree versus college degree or higher to capture low vs. high SES because this sample had relatively high SES. Due to the small numbers of individual ethnic/racial groups and the modest sample size, race was dichotomized as white versus non-white.

#### **2.2.2. Cambridge Neuropsychological Test Automated Battery (CANTAB)—**We

used the CANTAB (Cambridge Cognition, Ltd; Cambridge, England), a computerized battery of EF, that has been used in preterm children(15, 38), children with typical development, and children with neurodevelopmental disorders such as ADHD and autism. Advantages of the CANTAB include the use of nonverbal task stimuli and standard testing and scoring with the ability to capture precise reaction times through a touch screen. The two subtests used in this study include: (1) Stockings of Cambridge (SOC), a measure of frontal lobe function, requires the child to rearrange a set of 3 colored balls to match a specified pattern in the minimum number of moves. The task requires planning and execution of a sequence of moves to achieve a predetermined goal. Difficulty is manipulated by increasing the number of moves needed to match the pattern, and problems consist of 2-, 3-, 4- and 5- move problems. Easier problems require minimum planning, and harder problems require higher levels of planning, the development of sub-goals, and avoidance of incorrect moves. Completion requires multiple cognitive processes tapping EF skills such as response inhibition, working memory, spatial planning and organization. Children were presented 20 total problems, 8 practice and 12 scored. Outcome measures included problems solved in minimum moves; mean number of moves required to solve each problem; and initial thinking time, measured from the start of the problem to time of the first move as a measure of planning ability. (2) Spatial Span, a measure of working memory capacity, requires the child to observe a pattern of white squares which briefly change color in a variable sequence. The child must then touch the same boxes which changed color in the same order as displayed by the computer. The number of boxes increases from 2 to 9. Outcome measures include span length; total errors, the number of times an incorrect box is selected; and total usage errors, the number of times a box not in the sequence is selected.

**2.2.3. IQ—Full scale IO was estimated using the four subtest format of the Wechsler** Abbreviated Scale of Intelligence, a widely used, nationally standardized test of general intellectual ability that measures verbal and nonverbal cognitive ability (39). The four subtests include vocabulary, similarities, block design, and matrices.

**2.2.4. Reading Abilities—**The Woodcock-Johnson III Tests of Achievement (WJ-III) was used for assessment of reading abilities (40). The Broad Reading Cluster is comprised of two subtests: Letter-Word Identification, a measure of decoding, and Passage Comprehension, a measure of reading comprehension skills.

**2.2.5. Child Behavior Check List for Ages 6–18 (CBCL)—**Parents completed the CBCL, a well-validated behavior rating questionnaire (41). We previously reported on the behavior outcomes for this sample and described the measure in detail (42). For this study, we focus on the CBCL competence and adaptive function items, which provide concrete information about the child's functional strengths at home and school, with peers, and in recreational activities. The CBCL includes items about specific activities, ratings of the amount and quality of involvement in activities and relationships, and ratings of

performance in academic subjects. The items are grouped into scales designated as Activities (includes sports, recreational activities, jobs and chores, Social (includes group activities and social relationships), School (includes ratings of performance in academic subjects, remedial services, grade repetition and other school problems), and Total Competence. The Total Competence score is the sum of raw scale scores of the Activities, Social, and School Scales, and served as our measure of parent-rated child function. For Total Competence scores, higher T scores indicate more favorable functioning. The clinical range is  $T < 37$  (10<sup>th</sup> percentile); borderline range is  $T = 37-40$  (10<sup>th</sup> to 16<sup>th</sup> percentile); and normal range is  $T > 40$  ( $> 16<sup>th</sup>$  percentile). This measure is normed for age and gender.

#### **2.3. Statistical Analyses**

We used t-tests for univariate analyses of continuous variables and Pearson chi-square for dichotomous outcomes. Group differences for EF tasks were analyzed with group, preterm (PT) versus full term (FT), as the between-subjects factor for main EF outcome measures. Repeated-measures analysis of variance with task difficulty (2-, 3-, 4- and 5- move problems on the Stockings of Cambridge) as a repeated factor was applied to the data. Group was the between-subjects factor, and group by task difficulty interactions were analyzed for mean moves and initial thinking time on the Stockings of Cambridge task. Initial thinking time was natural log transformed due to nonparametric distribution. Univariate analyses for main EF outcome measures were repeated with group and gender as fixed factors to evaluate main effects of gender and group by gender interactions. We reasoned that if there were no effects of gender, then gender would not be included in the regression models predicting EF skills.

To investigate contributions of prematurity and other factors to EF outcomes, we used a similar mediation analysis method as Conrad et al. (43) and Baron et al. (44). Mediation analysis tests whether the effect of a given predictor variable on an outcome measure can be accounted for by its effect on an intermediate variable (mediator) which in turn affects the outcome measure. Mediation requires (1) a significant effect of the predictor (i.e., GA) on the outcome variable (EF), (2) a significant effect of the predictor (i.e., GA) on the mediator variable (i.e.,  $IQ$ ), (3) a significant effect of the mediator (i.e.,  $IQ$ ) on the outcome (EF) controlling for the predictor (GA), and (4) a significant decrease in the effect of the predictor on the outcome when controlling for the mediator.

Due to our interest in IQ as a mediator, we examined the contributions of GA and SES to IQ using hierarchical multiple regression. GA was entered in the first step, and SES was entered in the second step.

We then investigated IQ as a mediator between the predictors of age, SES, and GA and outcome of problems solved in minimum moves (PSMM) for the entire sample using hierarchical multiple regression. For each model, age and SES were entered in the first step. GA, a continuous variable used as an indicator of prematurity, was entered in the second step. IQ was entered in the third step. Analyses were repeated with BW; however, results using GA are shown given that GA and BW are highly correlated,  $r = .9$ ,  $p < .001$ . The model allows for determination of contributions of age, SES, and GA to PSMM. By adding IQ in the third step, any decrease in variance in PSMM due to GA after the addition of IQ suggests mediation.

A second set of hierarchical multiple regression models examined the contributions of PSMM to the functional outcomes of Broad Reading and Total Competence as a measure of parent-rated child function for the entire sample. For each model, SES was entered in the first step; GA, the second step; PSMM, the third step; and IQ in the final step.

We examined EF and IQ variables for multicollinearity, or strong correlations between the two predictors in the regression model. We found no violations of collinearity statistics, including variance inflation factors and tolerance factors. Significance level was set at  $p <$ . 05 for all analyses.

#### **3. Results**

#### **3.1. Participant Characteristics**

PT and FT participants did not significantly differ on mean age, gender, race (white vs. nonwhite), or maternal education (less than 4-year college degree versus college degree or higher) as a measure of SES. (Table 1) There were no differences between sites of testing for age, gender or race. SES was higher at the Palo Alto site than the Pittsburgh site,  $X^2(1)$  = 11.2,  $p = .001$ . PT children had a mean birth weight of 1226g and mean gestational age of 28.8 weeks. PT children had mean IQ scores in the normal range, but were approximately one SD lower than controls. PT children also had greater variability in IQ scores, ranging from below average to the superior range (scores of 67 to 136), compared to the low average to very superior range (scores of 86 to 142) for FT children. Medical complications in the PT group were as follows: 13 had abnormal findings on head ultrasounds or MRIs (at least grade 2 intraventricular hemorrhage, echodensities, or cystic lesions), 9 had mildly abnormal findings (defined as either grade 1 hemorrhage or choroid plexus cyst); 22 had respiratory distress syndrome and 7 developed chronic lung disease; and 4 were small for gestational age (defined as lying at or below the 3<sup>rd</sup>percentile in birth weight for gestational age).

Due to computer failure with data loss or inability to capture child responses, 2 PT children were missing part or all Stockings of Cambridge data and 5 PT children were missing spatial span data. Five PT and 3 FT children had incomplete data for the competence sections of the CBCL.

#### **3.2. Reading and Total Competence Scores**

PT children had lower broad reading scores than FT children, although the mean scores were in the average range. The reading and language outcomes for the sample have been reported previously (45). On parent-rated Total Competence scores from the CBCL, PT children had significantly lower scores, indicating poorer function, than FT children. (Table 1) PT children also had significantly lower scores on the School Scale, and there were trends for significantly lower scores on the Activities and Social Scales, compared to FT children. Chisquare analyses showed that there were significantly more PT than FT children with scores in the clinical and borderline clinical range for Total Competence, Social, and School Scales. Approximately 28% of the PT and none of the FT children were enrolled in special education.

#### **3.3. EF Tasks**

On the Stockings of Cambridge task, PT children completed significantly fewer total problems in minimum moves than FT children  $(6.9 \pm 2.2 \text{ vs. } 8.4 \pm 1.8)$ , F(1, 111) = 14.2, p  $< .001$ ; effect size of 0.73. There was a significant group by task difficulty interaction for mean moves,  $F(3, 107) = 4.04$ ,  $p = .009$  by Pillai's trace. (Figure 1) As task difficulty increased, the average number of moves to complete problems was higher for PT than FT children (Table 2). There was also a significant group by task difficulty interaction for initial thinking time,  $F(3, 90) = 4.4$ ,  $p = .006$  by Pillai's trace. As task difficulty increased, FT subjects increased the planning time to solve problems, but PT subjects did not. (Figure 2) There were no significant main effects of gender or group by gender interactions. On the spatial span task, there were no significant group differences for span length,  $F(1, 107) =$ 

2.5,  $p = .115$ , effect size of 0.32; total errors,  $F(1, 110) = 1.0$ ,  $p = .313$ ; or total usage errors,  $F(1, 110) = 2.3$ ,  $p = .132$  (Table 2).

#### **3.4. Contributions to EF skills on the Stockings of Cambridge task**

In examining contributions of various factors to EF skills using hierarchical multiple regression, we first evaluated the contributions of GA and SES to IQ due to our interest in IQ as a potential mediator. (Table 3) The first model was significant,  $F(1, 112) = 22.0$ ,  $p <$ . 001, showing that GA accounted for 16.4% of the variance. The second model was also significant,  $F(2, 111) = 13.5$ ,  $p < .001$ , accounting for 19.5% of the variance. SES was a significant predictor, contributing an additional 3.1% of the variance in IQ, F change<sub>1,111</sub> = 4.3,  $p = .04$ .

Age, SES, and GA showed significant contributions to EF skills (Table 4). The overall model predicting problems solved in minimum moves (PSMM) on the Stockings of Cambridge was significant,  $F(4, 107) = 13.8$ ,  $p < .001$ , and accounted for 33% of the variance. When IQ was added, the overall model was significant, accounting for 54% of the variance,  $F(5, 106) = 25.3$ ,  $p < .001$ . In the final model, age and IQ were significant contributors to the variance, but SES and GA were no longer significant due to mediation by IQ.

#### **3.5. Contributions to Functional Outcomes: Broad Reading and Total Competence Scores**

For Broad Reading and Total Competence scores, SES was not a significant contributor. (Table 5) In the second step, GA was a significant contributor to both outcomes. In the third step, addition of PSMM as the measure of EF skills showed significant contributions to both functional outcomes of reading and Total Competence. EF skills mediated the effects of GA on both reading and Total Competence. In the final step, after addition of IQ, PSMM was not a significant contributor to reading. In contrast, PSMM did contribute to Total Competence, and remained the only significant predictor of Total Competence after addition of IQ. IQ contributed a nonsignificant 2% of the variance in Total Competence, F change<sub>1, 99</sub> = 2.36, p = .128. Results were repeated for each component subtest of Broad Reading—Letter-Word Identification and Passage Comprehension; results were similar to those for Broad Reading.

#### **4. Discussion**

#### **4.1. Summary of findings**

We found that our first hypothesis was correct for the Stockings of Cambridge task, but not for the Spatial Span task. Compared to controls, PT children not only had poorer overall performance on the Stockings of Cambridge, but also showed increasingly poor performance and a lack of increased planning time as task demands increased. Our second hypothesis was correct—prematurity was a major contributor to EF skills, along with age and IQ. IQ significantly mediated the effects of prematurity on EF skills. We found that PT children had lower reading and Total Competence scores, despite having mean scores in the average range; a significantly greater number of PT children fell in the clinical and borderline clinical range for Total Competence, Social, and School Scales. For the third hypothesis, we found that EF skills contribute to functional outcomes of reading and Total Competence. EF skills, however, were not an independent contributor to reading when IQ was added to the model, but EF skills remained the only significant contributor to Total Competence after addition of IQ.

#### **4.2 EF**

Data from this population of PT children confirm EF problems on the Stockings of Cambridge, a complex task that requires response inhibition, working memory, spatial planning, sequencing, and organization. Many studies, including a recent meta-analysis (9), documenting behavior and EF problems have focused on children born with very low (< 1500 g, VLBW) or extremely low birth weight (< 1000 g, ELBW) or very early gestational age (≤ 33 weeks). A study of late PT preschool children with medical complications in the neonatal period found EF problems in the areas of visuospatial, visuomotor, and verbal fluency skills (46). Our study included children from a wide spectrum of GA and birth weight.

Using the same computerized EF battery, Luciana and colleagues found that compared to age-matched controls, 7- to 9-year-old children born prematurely demonstrated longer planning times on the Stockings of Cambridge and shorter spatial memory span (15). Our results differed in that PT children did not increase the planning time as task difficulty increased, which was associated with lower overall performance in terms of total problems solved. In addition, in our study spatial memory capacity was intact. These differences may reflect differences in the study populations, which differed in age and GA. The Stockings of Cambridge, a more complex task which taps multiple EF skills, was a better measure for capturing EF problems in this relatively high-SES, high-functioning group of PT children. Group by task difficulty interactions on a complex EF task indicate that PT children may need additional support and perhaps different cognitive strategies as task demands increase.

#### **4.3. Contributions to EF skills**

GA as an index of prematurity contributed to EF skills. Given our modest sample size, we were unable to assess relative contributions of various neonatal complications and chose to use GA as our summary measure of prematurity as our sample had a wide range of GA. Consistent with other literature, age and SES also contributed (32, 36, 47). In the final step of the regression model, the addition of IQ to the model predicting EF scores eliminated the significance of GA and SES, indicating that IQ mediates the effects of GA and SES on EF skills. A combination of factors may contribute to EF outcomes in preterm children. Studies using structural MRI have found associations between white matter injury and EF skills in preterm toddlers and preschoolers (48, 49). A recent study of preterm adolescents showed that severe brain injury on neonatal ultrasound and lower maternal education were the most consistent factors associated with poor EF outcomes (16). SES is highly associated with cognitive and neurodevelopmental outcomes in children born prematurely (35), and low maternal education is an independent risk factor for adverse outcomes (50). The effects of low SES have been found in all medical risk categories after premature delivery (47). SES is not usually considered to exert a direct influence on developmental outcomes, but rather to be a marker for various adverse psychosocial factors, including highly stressful environments, poor access to health and education services, limited verbal input and poor parenting skills. Although we found that SES did contribute to EF outcomes, the effect of SES was mediated by IQ in the final model. It is possible that the influence of SES on EF skills may not have been captured by a dichotomized measure of maternal education in this relatively high-SES sample. In addition, the influence of SES may have already been absorbed by IQ and PT status, as these variables are often correlated. Age, after IQ, made the largest contribution to EF outcomes in the final model. In our study, age likely reflects improvements in EF during this dynamic period from childhood to adolescence.

Preterm children often have lower IQ than full term children, although scores are often in the normal range (20, 21). Although some studies of EF skills control for IQ on finding differences between groups, there are sound theoretical reasons why IQ should not be used

as a covariate in cognitive studies of neurodevelopmental disorders (51). In our approach, we did not use IQ as a covariate in the ANOVAs analyzing the main EF outcome measures between groups; rather, we chose to investigate the role of IQ as a potential mediator of other factors that contribute to EF performance. We confirmed that IQ acts as a mediator of GA and SES on EF skills. In this sample, we previously reported that IQ mediated the effects of birth weight on attention, but not anxiety scores (42). These findings highlight the importance of considering the contributions of other neuropsychological factors, including IQ, to outcomes in PT children.

#### **4.4 EF and Functional Outcomes**

**4.4.1 Reading outcomes—**EF skills contributed significant variance to reading outcomes, although contributions of EF skills did not remain significant after addition of IQ to the model. Our results are similar to those of Frye and colleagues who found that better reading skills were associated with better EF skills (52). However, in their study, EF skills were also more strongly associated with reading skills than preterm birth status, as PT children were not significantly different from controls in reading (52). In the current study, hierarchical regression models showed that in the final model, IQ served as a better summary measure or predictor than EF skills. In a study of very PT children (< 31 weeks GA) at nine to ten years of age, Mulder and colleagues found that verbal processing speed, working memory, and group status were significant predictors of teacher-rated overall academic achievement, accounting for 57% of the variance in outcome (53); a comparison model with IQ showed that group status and IQ accounted for 65% of the variance in outcome. Although group differences in academic achievement were accounted for by processing speed, they also found that working memory was predictive of academic achievement independent of verbal processing speed. These results showed some similarities to ours in that EF skills and PT status were predictive of functional outcome, but they did not investigate EF skills and IQ in the model simultaneously.

**4.4.2 Total Competence Outcomes—**EF skills contributed to Total Competence and remained significant in the model after the addition of IQ. In contrast with reading outcomes, for Total Competence, EF served as a better measure of outcome than IQ. In a sample of ELBW children at eight years of age, Taylor and colleagues found that EF skills mediated the effects of neonatal risk on multiple measures of academic achievement and adaptive functioning (25). These findings again highlight the importance of considering the contributions of other neuropsychological factors to functional outcomes in PT children.

PT children often differ from FT children on IQ; however, measures of IQ are not considered stable until approximately seven or eight years of age. EF skills may be measured as early as infancy (54, 55) and may therefore be more reliable as an early marker of function than IQ. The association between better EF skills and Total Competence suggests that EF skills may serve not only as important early markers of function, but also as targets for intervention to improve outcomes.

#### **4.5 Limitations**

The sample was a relatively small convenience sample that may not be representative of all PT children, a weakness compared to geographic cohort studies. We are not able to assess baseline characteristics of nonparticipants as children were born over a decade in multiple hospitals at both study sites and possibly other areas for families that may have moved to the study site locations. The sample had a larger proportion of high-SES participants who likely have more access to resources and better outcomes. The findings of differences in EF between groups, despite being a higher SES sample, contributes to our understanding of EF across SES strata, as other studies often have higher proportions of low-SES participants.

The inclusion of PT children with brain injury may contribute to group differences and heterogeneity within the PT group in terms of EF outcomes. The study was cross-sectional and had a limited number of EF measures and functional outcomes. Longitudinal work would allow better understanding of how EF skills might predict later functional outcomes.

#### **4.6 Implications and Future Directions**

We found poorer EF and group by task difficulty interactions in PT children compared to FT children, indicating that PT children may need additional support and perhaps different cognitive strategies as task demands increase. IQ was an important predictor of reading outcomes. EF skills were associated with parent-rated child function. Longitudinal work is needed to determine if EF skills can serve as important early markers of function and possible targets for interventions. PT children are at risk for neural injury, including diffuse white matter injury that may be involved in functional connectivity between brain regions that subserve EF skills (56, 57). The results of our study also highlight the need for additional research to understand the neurobiological basis of EF and associated problems in PT children. We are currently using diffusion tensor imaging to evaluate the contributions of white matter injury to behavior and EF problems (58).

#### **Acknowledgments**

This study was supported by grant RO1-HD46500 from the National Institutes of Health (Dr. Heidi M. Feldman, principal investigator), NIH Pediatric Research Loan Repayment Program Award to the first author, and also supported in part by the Clinical and Translational Science Award 1UL1 RR025744 for the Stanford Center for Clinical and Translational Education and Research (Spectrum) from the National Center for Research Resources, National Institutes of Health. We thank the families and children who participated in the study.

#### **Abbreviations**



#### **References**

1. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. Cognitive Psychology. Aug; 2000 41(1):49–100. [PubMed: 10945922]

- 2. Anderson P. Assessment and development of executive function (EF) during childhood. Child Neuropsychol. 2002; 8(2):71–82. [PubMed: 12638061]
- 3. Barkley, RA. A handbook for diagnosis and treatment. 3rd ed. New York, NY; Guilford Press: 2006. Attention-deficit hyperactivity disorder.
- 4. Hwang K, Velanova K, Luna B. Strengthening of top-down frontal cognitive control networks underlying the development of inhibitory control: a functional magnetic resonance imaging effective connectivity study. Journal of Neuroscience. 2010; 30(46):15535–45. [PubMed: 21084608]
- 5. Luna B, Padmanabhan A, O'Hearn K. What has fMRI told us about the development of cognitive control through adolescence? Brain & Cognition. 2010; 72(1):101–13. [PubMed: 19765880]
- 6. Sheridan MA, Hinshaw S, D'Esposito M. Efficiency of the prefrontal cortex during working memory in attention-deficit/hyperactivity disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2007; 46(10):1357–66. [PubMed: 17885578]
- 7. Gathercole SE, Alloway TP. Practitioner review: short-term and working memory impairments in neurodevelopmental disorders: diagnosis and remedial support. J Child Psychol Psychiatry. Jan; 2006 47(1):4–15. [PubMed: 16405635]
- 8. Gioia GA, Isquith PK, Kenworthy L, Barton RM, Gioia GA, Isquith PK, et al. Profiles of everyday executive function in acquired and developmental disorders. Child Neuropsychol. Jun; 2002 8(2): 121–37. [PubMed: 12638065]
- 9. Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-Analysis of Neurobehavioral Outcomes in Very Preterm and/or Very Low Birth Weight Children. Pediatrics. Aug 1; 2009 124(2):717–28. 2009. [PubMed: 19651588]
- 10. Anderson PJ, Doyle LW. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. Pediatrics. Jul; 2004 114(1):50–7. [PubMed: 15231907]
- 11. Marlow N, Hennessy EM, Bracewell MA, Wolke D. Motor and executive function at 6 years of age after extremely preterm birth. Pediatrics. Oct; 2007 120(4):793–804. [PubMed: 17908767]
- 12. Mulder H, Pitchford NJ, Hagger MS, Marlow N. Development of Executive Function and Attention in Preterm Children: A Systematic Review. Developmental Neuropsychology. 2009; 34(4):393–421. [PubMed: 20183707]
- 13. Bayless S, Stevenson J. Executive functions in school-age children born very prematurely. Early Hum Dev. 2007; 83(4):247–54. doi: DOI: 10.1016/j.earlhumdev.2006.05.021. [PubMed: 16837146]
- 14. Ni T-L, Huang C-C, Guo N-W. Executive function deficit in preschool children born very low birth weight with normal early development. Early Hum Dev. 2011; 87(2):137–41. doi: DOI: 10.1016/j.earlhumdev.2010.11.013. [PubMed: 21194855]
- 15. Luciana M, Lindeke L, Georgieff M, Mills M, Nelson CA. Neurobehavioral evidence for workingmemory deficits in school-aged children with histories of prematurity. Developmental Medicine & Child Neurology. 1999; 41(8):521–33. [PubMed: 10479041]
- 16. Luu TM, Ment LR, Allan W, Schneider K, Vohr BR. Executive and Memory Function in Adolescents Born Very Preterm. Pediatrics. Mar.2011 127(3):e000.
- 17. Saigal S, den Ouden L, Wolke D, Hoult L, Paneth N, Streiner DL, et al. School-age outcomes in children who were extremely low birth weight from four international population-based cohorts. Pediatrics. Oct; 2003 112(4):943–50. [PubMed: 14523190]
- 18. Litt J, Taylor HG, Klein N, Hack M. Learning disabilities in children with very low birthweight: prevalence, neuropsychological correlates, and educational interventions. Journal of Learning Disabilities. 2005; 38(2):130–41. [PubMed: 15813595]
- 19. Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. New England Journal of Medicine. Jan; 2002 17346(3):149–57. [PubMed: 11796848]
- 20. Aylward GP. Neurodevelopmental Outcomes of Infants Born Prematurely. Journal of Developmental & Behavioral Pediatrics. Dec; 2005 26(6):427–40. [PubMed: 16344661]

- 21. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS. Cognitive and Behavioral Outcomes of School-Aged Children Who Were Born Preterm: A Meta-analysis. JAMA. Aug 14; 2002 288(6):728–37. 2002. [PubMed: 12169077]
- 22. Saigal S, Pinelli J, Hoult L, Kim MM, Boyle M, Saigal S, et al. Psychopathology and social competencies of adolescents who were extremely low birth weight. Pediatrics. May; 2003 111(5 Pt 1):969–75. [PubMed: 12728073]
- 23. Hack M, Youngstrom EA, Cartar L, Schluchter M, Taylor HG, Flannery D, et al. Behavioral Outcomes and Evidence of Psychopathology Among Very Low Birth Weight Infants at Age 20 Years. Pediatrics. Oct 1; 2004 114(4):932–40. 2004. [PubMed: 15466087]
- 24. Taylor H, Hack M, Klein NK. Attention deficits in children with <750 gm birth weight. Child Neuropsychol. Apr; 1998 4(1):21–34.
- 25. Taylor HG, Klein N, Drotar D, Schluchter M, Hack M. Consequences and risks of <1000-g birth weight for neuropsychological skills, achievement, and adaptive functioning. J Dev Behav Pediatr. Dec; 2006 27(6):459–69. [PubMed: 17164618]
- 26. Volpe JJ. Neurobiology of periventricular leukomalacia in the premature infant. Pediatric Research. 2001; 50(5):553–62. [PubMed: 11641446]
- 27. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurology. 2009; 8(1):110–24. [PubMed: 19081519]
- 28. Wagner AI, Schmidt NL, Lemery-Chalfant K, Leavitt LA, Goldsmith HH. The limited effects of obstetrical and neonatal complications on conduct and attention-deficit hyperactivity disorder symptoms in middle childhood. J Dev Behav Pediatr. Jun; 2009 30(3):217–25. [PubMed: 19433988]
- 29. Landry SH, Denson SE, Swank PR. Effects of medical risk and socioeconomic status on the rate of change in cognitive and social development for low birth weight children. J Clin Exp Neuropsychol. Apr; 1997 19(2):261–74. [PubMed: 9240485]
- 30. Gross SJ, Mettelman BB, Dye TD, Slagle TA. Impact of family structure and stability on academic outcome in preterm children at 10 years of age. J Pediatr. Feb; 2001 138(2):169–75. [PubMed: 11174612]
- 31. Else-Quest NM, Hyde JS, Goldsmith HH, Van Hulle CA. Gender differences in temperament: a meta-analysis. Psychological Bulletin. 2006; 132(1):33–72. [PubMed: 16435957]
- 32. Farah MJ, Shera DM, Savage JH, Betancourt L, Giannetta JM, Brodsky NL, et al. Childhood poverty: specific associations with neurocognitive development. Brain Research. 2006; 1:166–74. [PubMed: 16879809]
- 33. Noble KG, McCandliss BD, Farah MJ. Socioeconomic gradients predict individual differences in neurocognitive abilities. Developmental Science. 2007; 10(4):464–80. [PubMed: 17552936]
- 34. Noble KG, Norman MF, Farah MJ. Neurocognitive correlates of socioeconomic status in kindergarten children. Developmental Science. 2005; 8(1):74–87. [PubMed: 15647068]
- 35. Webster HH, Flenady V, Woodgate PG. Home-based post-discharge parental support to prevent morbidity in preterm infants. Cochrane Database of Systematic Reviews. 2002; (1)
- 36. Luna B, Garver KE, Urban TA, Lazar NA, Sweeney JA. Maturation of cognitive processes from late childhood to adulthood. Child Development. Sep-Oct;2004 75(5):1357–72. [PubMed: 15369519]
- 37. Asato MR, Sweeney JA, Luna B. Cognitive processes in the development of TOL performance. Neuropsychologia. 2006; 44(12):2259–69. [PubMed: 16797612]
- 38. Curtis WJ, Lindeke LL, Georgieff MK, Nelson CA. Neurobehavioural functioning in neonatal intensive care unit graduates in late childhood and early adolescence. Brain. Jul 1; 2002 125(7): 1646–59. 2002. [PubMed: 12077013]
- 39. Wechsler, Wechsler. Harcourt Assessment, Inc.; San Antonio, TX: 1999. Abbreviated Scale of Intelligence (WASI) Manual.
- 40. Woodcock, RW.; McGrew, KS.; Mather, N. Riverside Publishing; Itasca, IL: 2001. Woodcock-Johnson III Tests of Achievment.
- 41. Achenbach, TM.; Rescorla, LA. University of Vermont, Research Center for Children, Youth, & Families; Burlington, VT: 2001. Manual for the ASEBA School-Age Forms and Profiles.

- 42. Loe I, Lee E, Luna B, Feldman H. Behavior Problems of 9–16 Year Old Preterm Children: Biological, Sociodemograhic, and Intellectual Contributions. Early Hum Dev. Apr; 2011 87(4): 247–52. 2011. [PubMed: 21316875]
- 43. Conrad AL, Richman L, Lindgren S, Nopoulos P. Biological and Environmental Predictors of Behavioral Sequelae in Children Born Preterm. Pediatrics. Jan 1; 2010 125(1):e83–9. 2010. [PubMed: 20008432]
- 44. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. Journal of Personality and Social Psychology. 1986; 51(6)
- 45. Lee E, Yeatman J, Luna B, Feldman HM. Specific Language and Reading Skills in School-Aged Children and Adolescents are Associated with Prematurity after Controlling for IQ. Neuropsychologia. 2011
- 46. Baron IS, Erickson K, Ahronovich MD, Coulehan K, Baker R, Litman FR. Visuospatial and verbal fluency relative deficits in 'complicated' late-preterm preschool children. Early Hum Dev. Dec; 2009 85(12):751–4. [PubMed: 19879072]
- 47. Landry SH, Smith KE, Swank PR. Environmental effects on language development in normal and high-risk child populations. Semin Pediatr Neurol. Sep; 2002 9(3):192–200. [PubMed: 12350040]
- 48. Edgin JO, Inder TE, Anderson PJ, Hood KM, Clark CA, Woodward LJ. Executive functioning in preschool children born very preterm: relationship with early white matter pathology. J Int Neuropsychol Soc. Jan; 2008 14(1):90–101. [PubMed: 18078535]
- 49. Woodward LJ, Edgin JO, Thompson D, Inder TE. Object working memory deficits predicted by early brain injury and development in the preterm infant. Brain. Nov; 2005 128(Pt 11):2578–87. [PubMed: 16150850]
- 50. Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, et al. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. Pediatrics. 1999; 104(2 Pt 1):243–8. [PubMed: 10429002]
- 51. Dennis M, Francis DJ, Cirino PT, Schachar R, Barnes MA, Fletcher JM. Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. J Int Neuropsychol Soc. May; 2009 15(3): 331–43. [PubMed: 19402919]
- 52. Frye RE, Landry SH, Swank PR, Smith KE. Executive dysfunction in poor readers born prematurely at high risk. Developmental Neuropsychology. 2009; 34(3):254–71. [PubMed: 19437202]
- 53. Mulder H, Pitchford NJ, Marlow N. Processing speed and working memory underlie academic attainment in very preterm children. Arch Dis Child Fetal Neonatal Ed. 2010; 95(4)
- 54. Rose SA, Feldman JF, Jankowski JJ. Attention and recognition memory in the 1st year of life: a longitudinal study of preterm and full-term infants. Developmental Psychology. Jan; 2001 37(1): 135–51. [PubMed: 11206428]
- 55. Sun J, Mohay H, O'Callaghan M. A comparison of executive function in very preterm and term infants at 8†months corrected age. Early Hum Dev. 2009; 85(4):225–30. doi: DOI: 10.1016/ j.earlhumdev.2008.10.005. [PubMed: 19006652]
- 56. Christ SE, White DA, Brunstrom JE, Abrams RA. Inhibitory control following perinatal brain injury. Neuropsychology. Jan; 2003 17(1):171–8. [PubMed: 12597086]
- 57. Skranes J, Lohaugen GC, Martinussen M, Indredavik MS, Dale AM, Haraldseth O, et al. White matter abnormalities and executive function in children with very low birth weight. Neuroreport. 2009; 20(3):263–6. [PubMed: 19444947]
- 58. Lee E, Loe I, Yeatman J, Bammer R, Feldman H. White matter characteristics are associated with attention, anxiety, and executive function in preterm children. Neuroimage. 2011 Submitted.



**Figure 1.** Mean Moves for 2-, 3-, 4- and 5- move problems on the Stockings of Cambridge.





Participant Characteristics Participant Characteristics



\*

\*



පි $\vert$ 

NIH-PA Author Manuscript

Data analyzed by t-test

a b

'Data analyzed by chi-square (asymptotic or exact significance: 2-sided); categories of clinical and borderline clinical range vs normal range Data analyzed by chi-square (asymptotic or exact significance: 2-sided); categories of clinical and borderline clinical range vs normal range

Significance set at  $p < 0.05$ 

\*

 $+$  indicates trend for significance. indicates trend for significance.

#### Stockings of Cambridge and Spatial Span





 $p < .001$ , Significance set at  $p < .05$ 

 $\dot{\tau}$  indicates significant group by task difficulty interaction for mean moves, p = .009, and initial thinking time, p = .006. See Figures 1 and 2

Hierarchical Multiple Regression Models of the Contribution of Gestational Age (GA) and Socioeconomic Status (SES) to IQ Hierarchical Multiple Regression Models of the Contribution of Gestational Age (GA) and Socioeconomic Status (SES) to IQ



IES, higher SES was associated with higher IQ. Final model. Step 1, GA. For GA, higher GA was associated with higher IQ. Step 2, SES. For SES, higher SES was associated with higher IQ.

Significance set at  $p < .05$ .

\*

Hierarchical Multiple Regression Models of (1) the Contribution of Age, SES, and Gestational Age (GA) to Stockings of Cambridge Problems Solved in Hierarchical Multiple Regression Models of (1) the Contribution of Age, SES, and Gestational Age (GA) to Stockings of Cambridge Problems Solved in Minimum Moves (PSMM) and (2) Possible Mediation by IQ. Minimum Moves (PSMM) and (2) Possible Mediation by IQ.



Early Hum Dev. Author manuscript; available in PMC 2013 May 22.

<sup>2</sup>First Model. Step 1, age and SES. Increased age was associated with higher PSMM scores. First Model. Step 1, age and SES. Increased age was associated with higher PSMM scores.

Second Model. Step 1, age and SES. Step 2, GA. Age, SES, and GA were significant; higher age, SES, and GA were associated with higher PSMM scores. Second Model. Step 1, age and SES. Step 2, GA. Age, SES, and GA were significant; higher age, SES, and GA were associated with higher PSMM scores.

Final model. Step 1, age and SES; step 2, GA; step 3, IQ. Only age and IQ were significant; IQ mediated the effect of SES and GA on PSMM scores. Final model. Step 1, age and SES; step 2, GA; step 3, IQ. Only age and IQ were significant; IQ mediated the effect of SES and GA on PSMM scores.

Significance set at  $p < 0.05$ 

\*

Hierarchical Multiple Regression Models of Contributions of SES, GA, PSMM, and IQ to Broad Reading and Total Competence scores Hierarchical Multiple Regression Models of Contributions of SES, GA, PSMM, and IQ to Broad Reading and Total Competence scores





Outcomes are Broad Reading and Total Competence scores. B indicates unstandardized coefficient; SE B, standard error of B; B, standardized coefficient. Outcomes are Broad Reading and Total Competence scores. B indicates unstandardized coefficient; SE B, standard error of B; β, standardized coefficient.

 ${}^2\!F\!irst$  Model. Step 1, SES. SES was not significant First Model. Step 1, SES. SES was not significant

becond Model. Step 1, SES; step 2, GA (gestational age). Higher GA was associated with higher reading and competence scores. SES was not significant. Second Model. Step 1, SES; step 2, GA (gestational age). Higher GA was associated with higher reading and competence scores. SES was not significant.

Third model. Step 1, SES; step 2, GA; and step 3, PSMM. With PSMM in the model, GA is no longer significant. Higher PSMM was associated with higher reading and competence scores. Third model. Step 1, SES; step 2, GA; and step 3, PSMM. With PSMM in the model, GA is no longer significant. Higher PSMM was associated with higher reading and competence scores.

 $d_{\text{final model}}$  Step 1, SES; step 2, GA; step 3, PSMM; step 4, IQ. IQ is the only significant variable for reading scores. However, when IQ is in the model predicting competence scores, PSMM remains the Final model. Step 1, SES; step 2, GA; step 3, PSMM; step 4, IQ. IQ is the only significant variable for reading scores, However, when IQ is in the model predicting competence scores, PSMM remains the Final is the only significant predictor. only significant predictor.

 $*$ <br>Significance set at  $p < 0.05$ Significance set at  $p < 0.05$