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Research report

# Impact of preeclampsia on cognitive function in the offspring

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## HIGHLIGHTS

- We assessed children of preeclamptic pregnancies by psychometrics and eye-tracking.
- Psychometric testing revealed impairment in working memory.
- Eye-tracking revealed impairment in oculomotor control.

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## ABSTRACT

Preeclampsia (PE) is a significant clinical disorder occurring in 3–5% of all human pregnancies. Offspring of PE pregnancies (PE-F1s) are reported to exhibit greater cognitive impairment than offspring from uncomplicated pregnancies. Previous studies of PE-F1 cognitive ability used tests with bias that do not assess specific cognitive domains. To improve cognitive impairment classification in PE-F1s we used standardized clinical psychometric testing and eye tracking studies of saccadic eye movements. PE-F1s ($n = 10$) and sex/age matched control participants ($n = 41$ for psychometrics; $n = 59$ for eye-tracking) were recruited from the PE-NET study or extracted from the NeuroDevNet study databases. Participants completed a selected array of psychometric tests which assessed executive function, working memory, attention, inhibition, visuospatial processing, reading, and math skills. Eye-tracking studies included the prosaccade, antisaccade, and memory-guided tasks. Psychometric testing revealed an impairment in working memory among PE-F1s. Eye-tracking studies revealed numerous impairments among PE-F1s including additional saccades required to reach the target, poor endpoint accuracy, and slower reaction time. However, PE-F1s made faster saccades than controls, and fewer sequence errors in the memory-guided task. Our study provides a comprehensive assessment of cognitive function among PE-F1s. The development of PE may be seen as an early predictor of reduced cognitive function in children, specifically in working memory and oculomotor control. Future studies should extended to a larger study populations, and may be valuable for early studies of children born to pregnancies complicated by other disorders, such as gestational diabetes or intrauterine growth restriction.



## 1. Introduction

Preeclampsia (PE) is a significant clinical disorder that occurs in 3–5% of all human pregnancies [1]. PE is clinically diagnosed by new-onset hypertension (>140/90 mmHg) and at least one of proteinuria (>300 mg/day), thrombocytopenia (platelets <$10^5$/μl), renal insufficiency (serum creatinine >1.1 mg/dl), impaired liver function (blood liver transaminases 2× normal), pulmonary edema, or cerebral or visual disturbances occurring after the 20th week of gestation [2]. Although several biomarkers predictive of PE are known, precise causes and pathogenic mechanisms for this syndrome are not fully understood. Options for effective treatment are sparse, such that prompt delivery of the placenta and fetus are normally required to alleviate maternal signs and symptoms. This frequently means premature birth with its associated complications.

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PE-related complications do not end at delivery. Numerous studies have shown that mothers who experience a PE pregnancy have significantly elevated lifetime risks for cardiovascular disease, hypertension, metabolic syndrome, diabetes, and stroke [3–6]. The offspring of PE pregnancies (PE-F1) also exhibit elevated lifetime risks for cardiovascular disease and stroke [7,8], but are additionally reported to show cognitive impairments [9–12]. Specifically, as children PE-F1s exhibit deficits in verbal reasoning [13], total intelligence quotient (IQ) score [11,14], and mental development index (MDI) [15,16]. As adolescents and young adults, PE-F1s continue to exhibit deficits in verbal reasoning [17], and total IQ score [17,18], while additionally exhibiting deficits in arithmetic reasoning [17]. As adults, and into old age, PE-F1s exhibit greater rate of decline in cognitive function and greater cognitive impairment overall [19,20], while also exhibiting increased depressive symptoms [21]. While some studies of cognitive function in PE-F1s used large sample populations [13,18,22–24] or very long follow-up [9,25], most studies have relied on general or superficial measures of cognitive ability such as IQ tests. IQ tests provide estimates of cognitive ability that may be biased by the participant's ethnicity [26,27], socioeconomic status [27,28], the person administering the test [29], or individual cognitive strategies [30].

A superior approach to assess cognitive function in children is through the use of standardized psychometric tests, such as the Neuropsychological Assessment (NEPSY). These tests, designed specifically for children, assess specific domains of cognitive function through simple tasks, without relying on learned abilities. Through this approach, these psychometric tests are better able to identify cognitive deficits, which might be masked during IQ testing in higher functioning forms of specific disorders, such as autism [31]. To complement psychometric testing, a further unbiased approach to cognitive assessment is through eye-tracking [32,33]. Eye-tracking is a simple, non-invasive, computer-regulated test which measures eye movements or saccades. It does not rely on language, motor coordination, or any other learned ability to assess sensory-motor and cognitive function. Additionally, because the neural circuitries controlling voluntary and automatic eye movements are very well understood, defects in the function of specific brain structures can be identified, even in very young children [32,34]. We previously used eye-tracking to identify specific neural deficits in children and adolescents associated with fetal alcohol spectrum disorder (FASD) [35,36]. In the current study we hypothesized that standardized psychometric tests and eye movement control tasks, that assess specific domains of cognitive function, would identify overlapping, specific brain regions altered during brain development in PE-F1s compared to sex and age matched typically developing control children.

## 2. Materials and methods

### 2.1. Participants

All experimental procedures were reviewed and approved by the Human Research Ethics Board at Queen's University and Kingston General Hospital. Participants were recruited from the Pre-eclampsia New Emerging Team (PE-NET) study database [37]. Briefly, pregnant women were recruited to the PE-NET study at Kingston General Hospital between September 2003 and October 2009. Women were diagnosed with PE if blood pressure was >140/90 mmHg and proteinuria >300 mg/24 h or ≥2+ on a repeat dipstick. Control women, with uncomplicated pregnancies, were enrolled and matched to test subjects for age, race and parity. Women with a history of chronic hypertension, diabetes (including gestational diabetes), or renal disease were excluded. For this pilot study, women from the PE-NET database were contacted between July 2014 and February 2015 to request participation of their child. PE-F1s aged 7–10 y ($n = 10$) were matched as closely as possible for age and sex to a child born to an uncomplicated pregnancy ($n = 10$). Data for additional 7–10 y control children were extracted from the NeuroDevNet study database ($n = 31$ for psychometric measures; $n = 49$ for eye-tracking measures) who had previously undertaken the identical study protocol [38]. Following parental consent and participant assent, children underwent psychometric and eye-tracking studies as described below during a single 2 h session. During the same session, the child's parent or guardian completed a questionnaire encompassing demographic variables. Socioeconomic status (SES) was calculated according to Hollingshead's four factor index of social status [39]. Participants received a $25 gift card upon completion of the testing session. Biostatistical information on pregnancy, birth and current parameters for participants recruited through the PE-NET database is included in our recent publication that established neuroanatomical differences between the child groups in this pilot study using magnetic resonance imaging [40].

### 2.2. Psychometric measures

#### 2.2.1. Neuropsychological Assessment, 2nd edition (NEPSY-II)

The NEPSY-II tool is used to assess multiple cognitive domains in children aged 3–16 y [41]. The tool consists of 32 subtests, of which 5 were chosen for this study to minimize the duration of testing of each participant. Each subtest included a teaching example and practice round. All subtests have an age-corrected standard score of 10 with standard deviation of 3. The 5 subtests used in this study were:

i) Memory for names which assesses the participant's ability to retain names in short- and long-term memory. The child is shown 8 cards with drawings of children on them while being read the name of the imaged child. Immediately thereafter, the cards are randomized and the participant is asked to remember each name. This is repeated three times. Following a delay of 25–35 min, the child is shown the cards again and asked to recall as many names as possible.
ii) Animal sorting which assesses the participant's ability to formulate basic concepts and successfully use those concepts to shift between categories. The child is shown 8 cards with drawings of different animals in various scenes. The child is asked to sort the cards into 2 groups of 4 cards using various self-initiated sorting criteria.
iii) Auditory attention and response set assesses selective attention, shifting, and vigilance. The child listens to a series of words and touches variously colored circles on a placard upon hearing a target word.
iv) Inhibition which assesses the participant's ability to inhibit automatic responses and switch between response types. The child looks at a series of black and white shapes or arrows and is instructed to name the correct shape/direction, the opposite shape/direction, or a combination of the two depending on the color of the shape/arrow.
v) Arrows assesses visuospatial processing of line orientation. The child looks at an array of arrows arranged around a target, and indicates the arrow(s) that points to the center of the target.

#### 2.2.2. Working Memory Test Battery for Children (WMTB-C)

The WMTB-C is a standardized test battery for children aged 5–15 y, which assesses working memory through 9 subtests [42]. For this study, 2 subtests were chosen: