October 29, 2009

Dr. Michael J. Meaney
Associate Director, Research
Douglas Hospital Research Centre
Perry Pavilion

Subject : **Protocol 03/45** *Maternal Adversity, Vulnerability and Neuro-development (MAVAN)*
Amendment

Dear Dr. Meaney,

Following the additional information and references provided, the REB re-examined your protocol amendment and found it satisfactory since the changes made were complete and met REB requirements. However, we would like to suggest that you add a paragraph or an addendum of the statistical power and sample size justification in your protocol to avoid further complications.

As Chairperson, I therefore give expedited approval to the proposed study.

Thank you for your cooperation.

Sincerely yours,

for:
J. Bruno Debruille, M.D., Ph.D.
Acting Chairperson
Douglas Hospital Research Ethics Board
/lmg

October 1st, 2009

J. Bruno Debruille, M.D., PhD
Chairperson
Douglas Hospital Research Ethics Board

Subject: Protocol 03/45 "*Maternal Adversity, Vulnerability and Neuro-development (MAVAN)*"

Thank you and the committee members for your time and comments on the submission of our Amendment – Addition of an evaluation at 72 months.

We have revised our amendment, and we submit this new protocol in strict accordance with the comments of the committee. Specifically,

• Sample Size and Power Considerations. The gene x environment analyses proposed here are innovative. However, these statistical analyses are directly comparable to those proposed in the CIHR grant awarded to Michael Meaney and James Kennedy. The section provided below is taken from this application, which was reviewed by the Behavioural Sciences B Committee. Likewise, Robert Levitan, of the MAVAN group, was awarded a grant by CIHR for gene x environment analyses focusing on birth weight by genotype interactions in defining individual differences in impulsivity and eating behaviour. Hence, statistical approaches comparable to those proposed in this application have been included in CIHR-funded proposals.

Studies reporting significant gene x environment interactions with measures of psychopathology typically range from 100-125 subjects (e.g., Hane & Fox et al., Psychol Sci 2006) to 500-600 subjects (e.g., Kendler et al., Arch Gen Psychiatry 2005). The MAVAN sample is in the range of the latter. Moreover, we have obtained significant gene (e.g., DRD1) x birth weight effects on attentional systems in 48 month-old children with a sample size of 85 subjects.

Finally, we have adopted an approach advocated by Wong et al. (International Journal of Epidemiology 2003;32:51-57) utilizing measures of continuous traits and continuous exposures (such as birth weight) provie a considerable strength in studies of gene x environment studies. Thus Wong et al. (please see attached) concluded that " that smaller studies with repeated and more precise

measurement of the exposure and outcome will be as powerful as studies even 20 times bigger, which necessarily employ less precise measures because of their size." We feel that out study represents such a case, an argument made in the CIHR applications.

• Sample size: Kennedy's previous publications with significant findings for child psychopathology, including ADHD phenotypes, have been done on sample sizes smaller than the MAVAN sample. For example, the G x E study (Müller et al. 2008) used a relatively small sample of less than 100 individuals, and had sufficient power to identify the modest effect of the serotonin transporter gene. In terms of power, for our MAVAN sample size of 500 individuals, assuming a population mean of 7 and standard deviation of 1.5 on the Intra/extra Dimensional Shift test, and an odds ratio of 1.2 for each of the G and E variables, under an additive model, with gene allele frequency of 0.1, we have greater than 90% power to detect a G x E odds ratio as low as 1.2. (Quanto program v 1.0; http://hydra.usc.edu/gxe). For multiple testing corrections our main strategy has been permutation analysis using for example the UNPHASED genetic data analysis software (version 3.03). The markers across a given gene are not independent tests, but rather have varying degrees of correlation, and this non-independence can be corrected using the Nyholt test (Nyholt et al. 2004), that incorporates the r-squared value between neighbouring pairs of markers. In this way the number of marker tests is reduced. We also have experience (Zai et al, in press) with genetics data reduction methods such as the Multi Dimensionality Reduction (MDR) technique (Moore et al. 2004) to reduce the effect of multiple testing.

• Consent forms:

-On page 2/9, the word "cohort" was replaced by "group".

- On page 4/9, we clarified the fact that the 50$ compensation is given at each visit.

-On page 6/9, we refer now to the Douglas Hospital Research Ethics Board instead of the Central Research Ethics Committee.

-We revised the grammar and orthographical mistakes (e.g. ANCOVA).

We thank you and the committee members for your time and consideration.

Sincerely

Michael J Meaney PhD, CQ, FRSC
James McGill Professor
Departments of Psychiatry and Neurology & Neurosurgery
McGill University
and
Associate Director
Research Centre
Douglas Mental Health University Institute

Summary

Our current research protocol investigates the influence of the early environment on infants' neuropsychological development. Our study is comprehensive and includes variety of psychological and physiological measures. Maternal adversity during **fetal life** including maternal stress (as well as depression), low social support, poor maternal nutrition, tobacco/alcohol consumption predict both preterm labor and intrauterine growth restriction. These birth outcomes, in turn, represent major epidemiological risk factors for neurodevelopmental impairments in children as well as heart disease, diabetes and depression in adulthood. **Postnatal** maternal adversity compromises maternal care/behaviour and infant development. It also predicts increased risk for obesity, heart disease, attention deficit disorders (ADD), drug abuse and depression. Despite the enormous potential for the interaction of prenatal and postnatal influences, research has largely been restricted to the effects of events occurring during only one period in development which, among other things, ignores the potential importance of 'protective' factors operating at later stages in development. Moreover, the underlying mechanisms by which perinatal adversity might directly affect neurocognitive development have been very poorly studied.

The original ethics approval supported the establishment of the MAVAN project as a longitudinal study of high-risk children until 60 month of age. In this project submission, we request the Douglas ERB to extend the project with children of 72 months of age. This approach will ultimately permit the prospective study of gene x environment interaction defining neurodevelopment in children with diagnosable ADD or anxiety disorders, allowing for the characterization of developmental trajectories that lead from high-risk condition to psychopathology. The additional procedures for the MAVAN study were developed with the experience gained with our first cohort, limiting the burden on participants as much as possible. Indeed, the 72-month protocol described here is less time consuming and requires fewer visits that those at earlier ages (e.g., 48 months). We maintain the same focus with the evaluation of the development of attentional processes and endophenotypes associated with anxiety. We introduce developmentally and age-appropriate instruments to identify in children early indicators and precursors of these outcomes. Children at 72 months can begin to explicitly report on their own strengths, perceptions and concerns, and thus we have included the DOMINIC-R in the current protocol (see below). These are powerful bearings for the early detection of emerging difficulties. Moreover, we have learned from MAVAN feedback questionnaires that mothers look forward to the visit of researchers interested in how they and their children are doing. Research assistants have developed a close relationship with mothers and both enjoy the opportunity to meet and follow the evolution of children's development.

Background and rationale

Adversity during the prenatal period is associated with emotional and behavioural difficulties in later life. Maternal stress, alcohol/tobacco intake and poor nutrition, all of which reflect a poor quality environment, predict fetal growth retardation. In turn,

impaired fetal growth, reflected in low birth weight for gestational age, predicts an increased risk for multiple disorders associated with emotional and cognitive function [1,2]. In the best studied case, that of Attentional Deficit Disorder, it is clear that the link lies between fetal growth and individual differences in attentional systems [3-5] and that the relationship cuts across the normal range of birth weights: the risk for inattention and ADD increases progressively as birth weight decreases, such that the effect of fetal development is not unique to a small population of very low birth weight children. Rather, cognitive development is related to the quality of fetal growth and development across the population. In studies with non-human primates, maternal stress results in attentional deficits in attentional deficits [6].

Although this issue has been less well clarified for other areas of psychopathology, there is emerging evidence for the association of birth weight with anxious and depressive symptomatology. Shyness, timidity, behavioural inhibition as well as negative and irritable temperament (greater frequency of negative emotional states) are positively related to the degree of growth restriction [7-9], while direct evidence of increased depressive symptoms have been found in children and adolescents with IUGR [1,9-11]. Likewise, maternal stress during gestation predicts both fetal growth restriction and negative temperament (irritability, negative emotionality) and anxiety in children [12,13]. Finally, prenatal glucocorticoid exposure, which directly produces in fetal growth retardation, is associated with an increased level of behavioural inhibition in humans [14,15].

What remain to be defined are the mechanisms that link developmental risk factors to the onset of symptomatology and to define developmental trajectories that reveal the expected effects on emotional and cognitive function, as well as potential protective factors. Not all children with prenatal adversity develop behavioural or cognitive disorders. We suggest that post-natal factors especially the quality of caregiver-child interactions are candidate mechanisms for the variation in psychopathological outcomes associated with prenatal factors. There is now a clear need to define developmental pathways by pre- and post-natal experience shapes vulnerability for psychopathology. Moreover, more vulnerable children, including those born at low birth weight, appear to be at increased sensitivity to the quality of the post-natal environment [16,17]. Thus, despite the link between fetal adversity and later psychopathology, there is good evidence for both continuities and discontinuities of psychopathology in the preschool age [18].

Evidence for this process comes from one of the few studies to examine the interaction between pre- and post-natal influences on neurodevelopment. One postulated mechanism includes decreased hippocampal volume [19] found in anxiety disorders and depression and one of the primary targets for both antidepressant and anti-anxiety medications. Interestingly, the effect of fetal growth on hippocampal volume is mediated by the perceived quality of maternal care [20]. In support of our proposed interaction between fetal growth and the quality of postnatal maternal care, we [20] reported evidence for an effect of birth weight on hippocampal volume in adult human subjects, that was moderated by the quality of perceived maternal (but not paternal) care. Thus, among individuals who reported a high quality of maternal care, there was no relation between birth weight and hippocampal volume. These findings are consistent with reports showing that the quality of the attachment relationship moderates

both the association between prenatal stress and fear reactivity and cognitive abilities [21]. Finally, this hypothesis is also consistent with the results of studies showing that interventions that target parenting have important outcomes for child development [17, 22].

We will examine the role of mother-child attachment in the development of early psychopathology in children with and without prenatal adversity, defined by birth weight (corrected for gestational age). We will also focus on early manifestations of psychopathology in order to study possible factors that might modify the risk of psychopathology before these pathologies become entrenched, and associated with disability later on. Such studies are consistent with the increased capacity for neuroplasticity over early childhood. This is a major advantage of the prospective, longitudinal approach of the MAVAN study.

An additional feature of the MAVAN studies is that of understanding the factors that influence the quality of mother – child interactions. Thus, we examine the quality of the maternal environment using measures that are known as the best predictors of individual differences in maternal care and infant attachment. The best environmental measures are those of 'marital' support and stress. Since both factors appear to operate through maternal mental health, we also include measures of maternal well-being. While we focus on those measures that are specific to the 72-month protocol, measures of mother – child interaction, maternal environment and maternal well being have been included in MAVAN since the prepartum period.

Hypothesis 1: The relation between birth weight and measures of childhood mental health will be moderated by the quality of post-natal maternal care. We will focus on two outcomes measures, the Connors questionnaire and the DOMINIC/QUE questionnaire.

Hypothesis 2: The quality of postnatal mother – infant interaction will be influenced by the quality of the maternal environment and maternal mental well being.

Measures

We focus our description on measures that are new to the MAVAN study. This list of measures is complete, and we note where measures have been previously approved. Also, in accordance with the comments on the previous submission, we emphasize new measures.

<u>Seventy-two month interview:</u> Home visit (150 minutes)

Mothers

Interview: Questionnaire on Maternal Well-Being (30 minutes)

This questionnaire has already been accepted by the Douglas Hospital Ethic Board with the original submission of the MAVAN project. This program of research examines the impact of maternal adversity on child development. Therefore, it is critical that we regularly monitor the level of maternal adversity. An extensive maternal interview protocol was administered at 6, 12, 24, 36, 48 and 60 months post-partum. At 72 months, we plan to administer the same version as used at 24 and 60 months.

The following questionnaires have already been accepted by the Douglas Hospital Ethic Board for different time points including in the initial submission: **Housing conditions** (10 minutes); **Health** of families (5 minutes); **Sleep patterns** (5 minutes) of children; the **Strength and Difficulties Questionnaire** (5 minutes) for screening psychopathology in children; and the **Beck Depression Inventory** (5 minutes) for assessing depressive symptoms in mothers.

Questionnaires (45 minutes)

Family Functioning (Family Assessment Device):
This questionnaire assesses family functioning on each dimension of the McMaster Model of Family Functioning (MMFF) according to individual family member's perception of their family's functioning. In addition to the six subscales of the MMFF (Problem solving, communication, roles, affective responsiveness, affective involvement, behaviour control) the FAD includes a General Functioning scale that measures the overall level of the family's functioning. Sixty statements, geared to an eighth-grade reading level, describe various aspects of family functioning. Each member of the family over the age of 12 completes the pen-and-paper questionnaire by rating how well the statement describes his or her family. There are four choices (strongly agree, agree, disagree, strongly disagree) per item for each dimension. Dimension items are purposely not listed in consecutive order. Each item matches only one dimension and may describe healthy or unhealthy functioning. The FAD takes approximately 20 minutes to complete.

Conner's questionnaire:
The measure has been previously approved for use in the MAVAN study. Developed by C. Keith Conners, Ph.D., the Conners' Rating Scales-Revised (CRS-R) are paper and pencil screening questionnaires designed to be completed by parents and teachers to assist in evaluating children (3-17 years) for **attention-deficit/hyperactivity disorder** (ADHD). The parents' short version contains 27 items and the teachers' short version has 28. The teacher version is similar but lacks the psychosomatic scale contained on the parent version. The Conner's is validated and the standard for informant-administered ADHD assessment both in clinical and research settings.

Family History Screen (FHS)
The FHS, a validated brief family psychiatric history instrument (Weissman et al, 2000) is administered to a parent, who reports on their child as well as on the proband's immediate biological relatives (biological parents, siblings). It takes 5 to 20 minutes to administer, depending on the size of the family and the presence of family illness. Information on 15 lifetime psychiatric disorders and suicide attempts is obtained. The

FHS begins with general questions about psychopathological features, treatment, and impairment, followed by more specific questions about psychopathological features during the course of the entire lifetime of all family members. If the informant answers affirmatively to any question, the interviewer determines specifically which family members had the symptom and records the name and identifying number. Probes are included for inquiring about family members and for helping the informant recall which relatives are involved. Periodically, the interviewer is instructed to remind the informant by naming the relatives. There is at least 1 question for each diagnosis (for major depressive disorder [MDD], there are 3; for mania, panic, conduct, and antisocial personality disorders, 2) that corresponds to the core symptom(s) of the disorder. Understanding the background of families is key to understanding the role of familial transmission.

Actiwatch

This measure has already been accepted by the Douglas Hospital Ethic Board for different time points included in the initial submission.

Children

THE DOMINIC=R QUESTIONNAIRE: (20 minutes)

The Dominic questionnaire (Valla et al., 1994) is a structured pictorial instrument assessing mental disorders in 6- to 11-year-old children. The Dominic assesses a child's perception of her/his own symptoms, which is critical to balance parents' and school professionals' perception. Ninety-nine drawings represent situations corresponding to DSM-III-R based ADHD, Conduct Disorder, Oppositional Defiant Disorder, Major Depressive Disorder, Separation Anxiety Disorder, Generalized Anxiety Disorder and Specific Phobia. The instrument takes 15-20 min to administer. The paper version of the Dominic questionnaire has been extensively validated (Valla et al. 1994, 1997b, 2000a). Intra-class correlation coefficients (ICCs) between test and retest ranged from 0.71 to 0.81 in a Montreal sample of 340 community children, and test-retest kappa values ranged from 0.44 to 0.69,with most kappa values around 0.60 (Valla et al. 1997b). Internalizing (53 items) and externalizing (42 items) disorder scales both yielded Cronbach's alphas of 0.89 (Cronbach 1951).Clinically referred (n=73) and non-referred (n=70) samples showed significant differences for every diagnosis ($p \leq 0.01$) using *t*-tests on mean scores. Kappa values ranged from 0.64 to 0.88 between *Dominic*-based diagnoses and DSM-III-R diagnoses based on clinical judgment in a sample of 117 general population children (Valla et al. 1994a).

Because of the lack of agreement between informants concerning the mental health of children, there is an obvious need to gather standardized information from children themselves on their own mental health.

By increasing young children's understanding of questions assessing mental health symptoms using a combination of visual and auditory signals, and by avoiding time-related components, the *Dominic-R* questionnaire allows reliable standardized assessment of children as young as 6 years. The DOMINIC-R is a structured, picture-based questionnaire (Valla, Bergeron, Berube, Gaudet, & St-George, 1994). With its original

format and robust psychometric properties, the *Dominic-R* questionnaire brings the structured interview of young child informants in line with standard clinical practice. The DOMINIC-R provides multiple symptom scales including attention deficit/hyperactivity disorder, conduct disorder, depression/dysthymia, overanxious disorder, oppositional defiant disorder, separation anxiety disorder and simple phobias.

The *Dominic-R* is appropriate for both clinical and epidemiologic purposes with strong test - re-test reliability with younger children (i.e., 6 – 11 years of age; Valla et al., 1997). Instead of being organized in diagnostic modules, symptoms have been randomly mixed to avoid the halo effect, and normal situations are intermixed with DSM-III-R abnormal behaviours. The Dominic character may be interpreted either as a boy or a girl to allow assessment of both genders. The pictorial format is in keeping with best clinical practice and with the cognitive abilities of young children, and at the same time complies with the epidemiological requirement for standardized assessment by lay interviewers.

We will analyze the results for each subscale independently. We predict a significant effect for birth weight (corrected for gestational age) on scores for the attention deficit/hyperactivity disorder, depression/dysthymia, overanxious disorder, separation anxiety disorder and simple phobias, reflecting the known relations between fetal growth and emotional function in childhood. We will also provide preliminary analyses on the scales for conduct disorder and oppositional defiant disorder for which there is to date very little data linking prenatal development to outcomes. We also predict that the effects of fetal growth will be moderated by the quality of postnatal mother – child relation such that the statistical relation between birth weight and clinical outcome will be non-significant in children with a high quality of maternal care and with a secure level of attachment. This finding will be represented as a significant statistical interaction (see below).

NEPSY: *A Developmental Neuropsychological Assessment* (15 minutes)
The NEPSY consists of a series of neuropsychological subtests offering a comprehensive assessment of neuropsychological development in children 3-12 years of age. These subtests enable the examiner to evaluate and explore the deficiencies that interfere with the child's learning. Some subscales (Sensory motor functions, Visuospatial processing) of the NEPSY have been accepted by the ERB for the 48 month assessment. But for the 72 month visits, we will focus on the language domain including the following subtests: Verbal Fluency (speeded naming), repetition of pseudowords, phonological processes.

The NEPSY is used as an age-appropriate measures for child general IQ for use as a potential covariate for effects on child emotional/cognitive functions.

Child Attribution Style Interview (24 items)
The Child Attributional Style Interview (CASI) is a measure of attributional style in children aged five years old and older. The interactive interview consists of sixteen events, which are presented to the child as 8 and ½" X 11" illustrations, in a storybook format. The events are centered on a main character; matched on gender to the child interviewed. The events are equally divided on two domains: valence (positive and

negative theme), and interpersonal (parents and peers) and achievement. This creates the possibility of four sub-categories for analysis (i.e. positive-achievement, negative-interpersonal etc.). After the presentation of each event, the child is asked three questions for their level of internal, stable and global attributions for each event. For example, to ask about how the child might internalize the cause of the event the research assistant asks the child, "How much is the event *because* of you?". To answer each question the child moves an arrow on a sliding scale, along an isosceles triangle. The larger side of the triangle represents in the example above, "*more because* of me" and the narrow side represents "less *because* of me". The CASI takes approximately 30 minutes to administer, which includes two practice sessions and administration of the sixteen CASI events.

The measure has been validated in a sample of five to seven year old by Conley, Haines, Hilt and Metalsky (2001) in a prospective, longitudinal study. The internal consistency for the measure was found to be between .73–.82 in children aged five and .77–.82 in children aged seven. In line with the reformulated learned helplessness theory, the children's answers on the CASI and self-esteem predicted changes in depression scores in times of increased stress. It should be noted that Conley et al. (2001) found that the younger children were more likely to pick extreme ends for each domain. However, the researchers found that the children had no bias for one extreme over another.

Seventy-two month interview: Laboratory visit (135 minutes)

Mother-child interaction (120 minutes)

Attachment protocol: The *Strange situation.* The primary purpose of this paradigm is to assess the establishment and quality of infant-mother attachment. This procedure has already been accepted the Douglas Hospital Ethic Board for the 18 and 36 month visits. At 72 month, we will use the procedure adopted by Main & Cassidy (1988) involving two long separations and two reunions. On arrival at the lab, mothers and children will ask to stay together in the Strange Situation room for 10 minutes (free play) followed by a separation (approximately 45 minutes) during which the child will complete problem-solving tasks with an experimenter while the mother complete questionnaires in another room. Just prior to the reunion, there will be a free-play session during which the experimenter was available to the child. Following the separation, mothers will be told to rejoin the child but will receive no specific instructions concerning the reunion. After the 5-minute reunion period, the mother and child remain in the room for a 10-minute snack time. A second 30-minute separation and 5-minute reunion period (structured like the first) will then take place. The child's attachment classification is given on the basis of behavior observed during both reunion periods. The predictive validity of this procedure for classifying attachment behavior in children of this age range with respect to socio-emotional and academic adaptation has been demonstrated in studies by Cassidy (1988), Cohn (1990), Easterbrooks, Davidson and Chazan (1993), Main et al. (1985), Moss et al. (1996; 1998), Moss and St-Laurent (2001), and Solomon et al. (1995). The scoring of this interaction is supervised by Professor Ellen Moss at UQAM, a noted expertise in the area of child attachment. Professor Moss is responsible for the

training of coders. The attachment classifications used in this study are secure versus insecure.

Mothers

Questionnaires (30 minutes)
The following questionnaires have already been accepted by the Douglas Hospital Ethic Board. The CEBQ (Child Eating Behaviour questionnaire examine eating behaviour and the Food Frequency questionnaire is a questionnaire on feeding patterns.

Sensitivity to Reward and Sensitivity to Punishment questionnaire (10 minutes)
This measure has already been accepted by the Douglas Hospital Ethic Board for the 60 month assessment. At 72 months, we will use the children version of this questionnaire.

BRIEF (Behavior Rating Inventory of Executive Function) (15 minutes)
The observations of parents and teachers provide a wealth of information about a child's behavior that is directly relevant to an understanding of that child's executive functioning. The BRIEF-P is the first standardized rating scale designed to specifically measure the range of behavioral manifestations of executive function in preschool-aged children--thus facilitating intervention at earlier stages of development. The BRIEF-P consists of a single Rating Form used by parents, teachers, and day care providers to rate a child's executive functions within the context of his/her everyday environments--home and preschool. The original Behavior Rating Inventory of Executive Function™ (BRIEF™) was the basis for the development of the BRIEF-P. Consequently, the BRIEF-P is an ecologically valid and efficient tool for screening, assessing, and monitoring a young child's executive functioning and development.

Children

Attention Tests: **CANTAB (60 minutes)**
This measure has already been accepted by the Douglas Hospital Ethic Board for the 60 month assessment. For the 72 mo assessment, we will use the same subtests as used in the 60 month protocol. The CANTAB battery will be performed during the 2 separation periods of the Strange Situation. During this separation, the mothers will be asked to fill in questionnaires in a separate room.

Nutritional status: Body weight and body fat percentage will be measured using the Tanita® BF 625 scale (foot to foot bioeletrical impedance) which functions as a portable regular scale. Height will be measured using a stadiometer. These measures have already been accepted by the Douglas Hospital Ethic Board for the 48-month assessment.

Analyses

In accordance with CIHR policy on identifying gender effects, analyses will be stratified by gender. Statistical significance will be corrected for multiple comparisons where appropriate. The sample size (currently ~600 children are enrolled in the MAVAN study) is well above the range of published interaction studies [e.g., 3,4,7-9,11], which typically include 100-150 subjects. As per the comments on the previous submission, we focus on the analyses of the new measures. Please note that the MAVAN Project has been funded by CIHR (2009-2014; Behavioural Sciences B) to examine birth weight x genotype interaction effects on cognitive development using the CANTAB measures described here as well as the Connors Rating Scale (Michael Meaney (PI) and James Kennedy (Co_PI).

Hypothesis 1: The relation between birth weight and measures of childhood mental health will be moderated by the quality of post-natal maternal care. We will focus on two outcomes measures, the Connors questionnaire and the DOMINIC-R questionnaire. We predict a significant interaction between birth weight corrected for gestational age x child attachment (secure versus insecure). Birth weight will be examined as a categorical variable using the following percentile groupings for birth weight for gestational age (0-20%, 21-40% and 41-70%). These percentiles are calculated using contemporary Canadian norms (Kramer, 2001). We have previously used these groupings to show significant effects of birth weight on tests of attention and impulse control. The results will be analyzed using a two way ANOVA (birth weight class) x attachment category, with a predicted interaction effect (post-hoc analyses) such that birth weight effects are apparent only amongst children showing insecure attachment. Subsequent ANCOVA's could be used to test the effects of possible moderators, including measures of sleep quality, which can affect mood as well as cognitive performance.

The same analysis will be applied to the results of the Connors Rating Scale, which is included as the current standard rating scale measure for symptoms associated with the Attentional Deficit Hyperactivity Disorder. The use of this measure also allows us to correlate a standard parent/teacher rating scale to the self-report measures of the child. Likewise, we predict a similar birth weight x child attachment interaction effect on the BRIEF (Behavior Rating Inventory of Executive Function) measure of executive function. A strength in this approach is that of the overlapping measures. While this implies greater number of statistical tests, this is the opportunity for the establishment of converging evidence should the predict interaction emerge in each of these analyses.

The inclusion of the CASI permits a direct measure of potential cognitive mechanisms for individual differences in the risk for psychopathology. The questionnaire measures the inclination for positive/negative self-attribution, which is considered linked to the risk for affective illness (Seligman et al., 1984). We will use the positive – negative subscale scores in a multivariate analysis. If indeed cognitive attributional style is a mediator for the vulnerability reflected in the DOMINIC-R scales, then the inclusion of this measure, especially the negative scale, should significantly reduce the predicted interaction effect between birth weight and child attachment.

Hypothesis 2: The quality of postnatal mother – infant interaction will be associated with differences in the quality of the maternal environment and maternal mental well-being. We will essentially use an analysis similar to that for case – control studies, splitting data according to child attachment category (secure vs insecure). We will use independent t-tests to compare the data for mothers of secure versus insecurely attached children on the McMaster Model of Family Functioning (MMFF) with separate analyses of the six subscales of the MMFF (Problem solving, communication, roles, affective responsiveness, affective involvement, behaviour control) as well as on the General Functioning scale that measures the overall level of the family's functioning. We predict significant differences across all scales. Subsequent analyses will explore the possibility that one subscale may be a better predictor of child attachment.

References

1. Costello EJ, Worthman C, Erkanli A, Angold A. 2007. Prediction From Low Birth Weight to Female Adolescent Depression: A Test of Competing Hypotheses. *Arch Gen Psychiatry.* 2007;64:338-344.
2. Rice F, Harold GT, Thapar A. (2006) The effect of birth-weight with genetic susceptibility on depressive symptoms in childhood and adolescence. *Eur Child Adolesc Psychiatry.* 15:383-391.
3. Breslau N, Chilcoat HD. (2000) Psychiatric sequelae of low birth weight at 11 years of age. Biol Psychiatry. 47, 1005-11.
4. Mick E, Biederman J, Prince J, Fischer MJ, Faraone SV. (2002) Impact of Low Birth Weight on Attention-Deficit Hyperactivity Disorder. Journal of Developmental and Behavioral Pediatrics. 23, 16-22.
5. Van der Reijden-Lakeman IE, de Sonneville LM, Swaab-Barneveld HJ, Slijper FM, Verhulst FC. (1997) Evaluation of attention before and after 2 years of growth hormone treatment in intrauterine growth retarded children. J Clin Exp Neuropsychol. 19, 101-18.
6. Schneider ML, Moore CF, Kraemer GW, Roberts AD, DeJesus OT. (2002) The impact of prenatal stress, fetal alcohol exposure, or both on development: perspectives from a primate model. Psychoneuroendocrinology. 27, 285-98.
7. Sykes DH, Hoy EA, Bill JM, et al. Behavioural adjustment in school of very-low-birth-weight children. *J Child Psychol Psychiatry* 1997;38:315-325.
8. Szatmari P, Saigal S, Rosenbaum P, Campbell D, King S. Psychiatric disorders at five years amongchildren with birthweights <1000g: a regional perspective. *Dev Med Child Neurol* 1990;32:954–62
9. Pharoah POD, Stevenson CJ, Cooke RWI, Stevenson RC. Prevalence of behaviour disorders in low birth weight infants. *Arch Dis Child* 1994;70:271–74.
10. Thompson C, Syddall H, Rodin I, Osmond C, Barker DJP. 2001. Birth weight and the risk of depressive disorder in later life. Br J Psychiatry 179:450-455.
11. Kelly YJ, Nazroo JY, McMunn A, Boreham R and Marmot M. Birthweight and behavioural problems in children: a modifiable effect? International Journal of Epidemiology 2001;30:88-94
12. Glover V. O'Connor TG. Effects of antenatal stress and anxiety: implications for development and psychiatry. British Journal of Psychiatry. 180:389-91, 2002 May.

13. O'Connor TG, Heron J, Glover V, Alspac Study Team. (2002). Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *J Am Acad Child Adolesc Psychiatry.* 41(12): 1470-7
14. Trautman, P.D. et al. (1995) Effects of early prenatal dexamethasone on the cognitive and behavioral development of young children: results of a pilot study. Psychoneuroendocrinology 20, 439–449
15. Meaney MJ, Szyf, M and Seckl JR. (2007) Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health. Trends in Molecular Medicine 13, 269-277.
16. Pluess, M and Belsky, J. Prenatal Programming of Postnatal Plasticity? In press
17. Belsky, J. (1997) Theory testing, effect-size evaluation, and differential susceptibility to rearing influence: the case of mothering and attachment. Child Dev 64, 598–600.
18. Rutter M, Kim-Cohen J, Maughan B. (2006) Continuities and discontinuities in psychopathology between childhood and adult life. *J Child Psychol Psychiatry.* 47: 277-295.
19. McEwen BS. Stress and hippocampal plasticity. Annual Review of Neuroscience. 22:105-22, 1999.
20. Buss C, Meaney MJ, Lupien S, Pruessner J. Maternal care modulates the relationship between prenatal risk and hippocampal volume. Journal of Neuroscience, 2007, 27, 2592-2595.
21. Fox, N., Nichols, K., Henderson, H., Rubin, K., Schmidt, C., Hamer, D., Ernst, M., & Pine, D. (2006). Evidence for a gene environment interaction in predicting behavioral inhibition in middle childhood. Psychological Science. 16, 921-6.
22. Olds DL, Sadler L, Kitzman H. Programs for parents of infants and toddlers: recent evidence from randomized trials. *J Child Psychol Psychiatry.* 2007;48:355-391.

Other References

Conley, C. S., Haines, B. A., Hilt, L. M., & Metalsky, G. I. (2001). The Children's Attributional Style Interview: Developmental tests of cognitive diathesis-stress theories of depression. *Journal of Abnormal Child Psychology, 29,* 445-463.

Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, Blondel B, Bréart G. (2001) A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics. 108, E35.

Seligman, M. E. P., Peterson, C., Kaslow, N. J., Tanenbaum, R. L., Alloy, L. B., & Abramson, L. Y. (1984). Attributional style and depressive symptoms among children. Journal of Abnormal Psychology, 93, 235-238.

Valla, J. P., Bergeron, L., Berube, H., Gaudet, N., & St-George, M. (1994). A structured pictorial questionnaire to assess DSM-lII-R-based diagnoses in children (6-11 years): Development, validity and reliability. *Journal of Abnormal Child Psychology, 22,* 403^23.

Valla, J. P., Bergeron, L., Smolla, N. (2000) The Dominic-R: A Pictorial Interview for 6- to 11-Year-Old Children. Journal of the American Academy of Child & Adolescent Psychiatry 39, 85-93.

Wong MY, Day NE, Luan JA, Chan KP and Wareham NJ (2003). The detection of gene–environment interaction for continuous traits: should we deal with measurement error by bigger studies or better measurement? *International Journal of Epidemiology* 2003;32:51–57.