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Developmental origins of child mental health disorders

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This special issue on pre and perinatal processes in child mental health and disease is timely because there has been a revival of theory and hypothesis of persistent effects of adverse early environments on mental as well as physical health. The articles included here offer interesting contributions and generate intriguing questions about the complexity inherent in this area that makes research very challenging to conduct. Our commentary is intended to provide a critical appraisal of the area of research as well as of the individual articles in this special section.

As a framework for our commentary, we used background articles in the literature that formed the basis for a meeting of 20 eminent geneticists (Swanson, Wadhwa, & Sing, 2006) convened to address genes, environments, and human development, health, and disease (GEHDHD) (see <https://webfiles.uci.edu/xythoswfs/webui/jmswanso/GEHDHD%20Irvine%20Meeting>), and two selected articles from the literature that discuss the concept of biological programming (Rutter, O'Connor, and the English and Romanian Adoptees Study Team, 2004 and Gluckman, Hanson, & Spencer, 2007b).

Rutter et al. (2004) provide historical context about the waxing and waning of the hypothesis about adverse effects of the early environment, with initial claims made that were later discounted by the continuity hypothesis (i.e., that early disadvantage was usually followed by later disadvantage, but could be overcome if the pattern was interrupted due to priority of effects of the current environment on outcome), which was followed by a relatively recent revival based on the biological programming hypothesis (i.e., that early disadvantage produces adaptations in structure and function of the brain with enduring effects). Gluckman et al. (2007b) describes one variant of this approach, the Developmental Origins of Health and Disease (DOHaD), which has become so popular that an international society has been formed and is actively promoting research and collaboration in this area (see <http://www.mrc.soton.ac.uk/dohad/>). One section of the GEHDHD meeting focused on epigenetic processes, the molecular mechanisms presumed to underlie some forms of biological programming (see Swanson et al., 2006).

The DOHaD approach evolved from observations of enduring effects of the fetal environment on adult physical health and disease. Barker, Osmond, Winter, Margetts, and Simmonds (1989) noted that low birth weight was associated with adverse adult outcomes, such as coronary heart disease, stroke, high blood pressure, and type 2 diabetes. This stimulated detailed animal and human studies and sophisticated accounts of what is now called predictive adaptive programming (see Gluckman et al., 2007b). The basic premise of the DOHaD approach is that early phenotypes such as low birth weight are correlated with prenatal conditions that may elicit biological programming, which operates to shape the structure and function of organs for optimal performance in the fetal environment. For example, one predictive adaptive programming response to energy-poor fetal conditions (i.e., fetal malnutrition) may be to develop resistance to the effects of insulin that moves glucose out of the blood stream into tissues (Phillips, 1996). This may produce a 'thrifty' phenotype (Hales

& Barker, 1992) characterized by small size and insulin resistance, which for a fetus receiving inadequate amounts of glucose may be adaptive (beneficial). One benefit that has been hypothesized is that this thrifty phenotype may protect the glucose supply to the brain (Bateson et al., 2004). However, the thriftiness conferred by the predictive adaptive response may lead to adverse effects manifested in subsequent stages of life if the experienced fetal environment does not match the predicted future environment of the child. That is, it may confer continued advantage in a postnatal environment that is energy-poor but may have adverse consequences (e.g., increased risk for obesity) in a nutritionally enriched postnatal environment.

Gluckman, Hanson, and Beedle (2007a) outline several reasons why the DOHaD phenomenon represents physiological plasticity not pathology. Rather than disrupt normal development, this form of biological programming appears to modulate development and permit a range of phenotypes to be expressed from a given genotype. This allows for more rapid adaptation to changing environmental conditions (i.e., within a lifetime by sculpting thrifty phenotypes) than by classical genetic mechanisms (i.e., across many lifetimes by shaping of the species by survival of the fittest in stable environments that produces thrifty genotypes by Darwinian natural selection).

Another account of biological programming is presented by Rutter et al. (2004). In the formulation of hypotheses about the long-term effects of severe deprivation of Romanian orphans after adoption, two classes of theory were contrasted: one was based on the notion of physiological plasticity due to biological programming that modulates normal development, and the other on the notion of pathology that may also result from some environmental exposures and disrupt normal development. Environmental risk factors during pregnancy, such as maternal smoking, alcohol consumption, or exposure to toxins (e.g., lead, pesticides, etc.), have been associated with brain pathology and adverse behavioral consequences (see Linnet et al., 2005; Jacobson & Jacobson, 2005; Braun, Kahn, Froehlich, Aulinger, & Lanphear, 2006; Nigg, 2006). One label attached to subtle brain pathology is minimal brain dysfunction (MBD), which has a long history (see Bax & MacKeith, 1962; Wender, 1971; Nichols & Chen, 1981). The initial use of this label was dismissed in part due to lack of specificity for any particular disorder, but a revival of the MBD approach has been proposed by Lou (1996) to specifically address attention-deficit/hyperactivity disorder (ADHD). This approach is based on the hypothesis that repeated bouts of prenatal hypoxia may damage developing dopamine neurons before the formation of dopamine-rich structures in the brain such as the striatum. In this model, the neurological basis for MBD is characterized by smaller brain structures (e.g., caudate) rather than differences in brain morphology. Some evidence from brain imaging studies using positron emission tomography (Neto, Lou, Cumming, Pryds, & Gjedde (2002) and magnetic resonance spectroscopy (Jin, Zang, Zeng, Zhang, & Wang, 2001) support the revival of the MBD theory to account for an etiologic subtype of ADHD (see Swanson et al., 2007 for a review).

We consider both approaches – the DOHaD approach based on plasticity and the MBD approach based on pathology – to be relevant to the discussion of the 9 empirical studies and 2 reviews articles in this special issue on ‘Pre- and Perinatal Processes in Child Mental Health and Disorder’. All of these articles face the very difficult task of addressing complexity inherent in the outcomes related to child mental health and disorder that are likely have multi-factorial etiology. To make matters more complex, some of the articles address the nature of combined effects of multiple etiological factors –whether they have additive or interactive effects on outcomes.

Furthermore, outcome-specificity and predictor-specificity introduce more complexity: for any given outcome it is possible to get there from different starting points, and for any given risk factor (condition) it is possible to get to different outcomes. The two example reviews and

theoretical accounts of biological programming make this point. For example, Rutter et al. (2004) formulated a hypothesis about enduring effects of severe postnatal deprivation on psychological outcome, and when considering contrasts of biological programming and neural damage, they noted that 'we saw no clear way of differentiating between these two alternatives with the measures available to us' (p. 84). Also, Gluckman et al. (2007) noted that even within one of these alternatives – predictive adaptive programming and plasticity – 'a relatively similar phenotype can be induced by a variety of nutritional or hormonal manipulations acting either early or late in development' (p. 7).

What can be done in the face of such complexity? The empirical studies in the special issue attempt to address this in a variety of ways – some by utilizing large samples, some with moderate samples but designs to limit complexity based on timing of exposure to adversity, and some with fine-grained evaluation of exposures and outcomes with small but well-characterized samples. Here we will try to integrate these articles in a common framework based on some generic critical issues that are covered across the studies but not all by any of them separately. First, we will organize the eclectic set of articles and briefly summarize the primary conclusion of each one. In addition, we will illustrate a critical issue by presenting a question that is not meant to provide an additional review of the article but instead was meant to identify issues that might direct the next round of studies. Second, we will integrate the diverse studies based on a few organizing principles. Third, we will offer an appraisal and recommendations for the emerging area that this special section identifies and addresses.

Brief summaries of conclusions and questions

1. Long-term follow-up from established longitudinal studies

Four of the articles make efficient and innovative use of data from large longitudinal studies initiated in the distant past. Ramchandani et al. (this issue) used the sample ($n = 7,601$) of the Avon Longitudinal Study of Parents and Children (ALAPAC) (see Golding, Pembrey, & Jones, 2001) that was initiated in the UK in 1991 and 1992; Nomura, Rajendran, and Newcorn (this issue) used long-term follow-up of the sample ($n = 1,686$) from one site of the National Collaborative Perinatal Project (NCPP) (see Hardy et al., 1997) that was initiated in the USA between 1959 and 1965; Robinson et al. (this issue) used the sample ($n = 1,707$) from the Western Australia Pregnancy Cohort Study (see Newnham et al., 1993) initiated between 1989 and 1991 in Perth.

Ramchandani et al. (this issue) evaluated the adverse effects of the psychosocial environment created by a depressed parent on behavior problems in childhood, using a novel natural experiment of depression in fathers that occurred during the prenatal or postnatal period, or both. Starting with the relatively large ALSPAC cohort, three subgroups were identified that differed on pattern of bouts of paternal depression: $n = 175$ with pre-only, $n = 166$ with post-only, $n = 89$ with both, and a large subgroup with neither. This natural experiment generates an elegant 2×2 factorial design, with the opportunity to perform 3 orthogonal (independent) tests of prenatal and postnatal main effects and their interaction. These subgroups were used to evaluate whether direct effects (postnatal depression that the child experiences) add to the latent genetic effects and exposure to paternal depression before birth. The primary conclusion was that latent factors appeared to account for risk of general psychopathology, supporting the continuity hypothesis, but a direct effect appeared to increase risk specifically for conduct problems. However, the analytic methods suggest a question about multiple comparisons. Since the analytic approach used a large number of multiple comparisons (i.e., the product of the factorial combination of 4 tests that were not independent, a complex 6-step procedure, and 5 outcome measures at 2 time points), was adjustment for multiple comparisons necessary?

Nomura et al. (this issue) evaluated links between antisocial behavior in adolescence and neurological abnormalities (age 1), language (age 3) and cognitive (age 4) development, and academic performance (age 7) in childhood in a large sample of cases born near-term (i.e., with premature births excluded). The primary conclusion was based on structural equation modeling that suggested a sequence of associations with each dependent on the prior one, starting with neurological abnormalities associated with early cognitive deficits, then with IQ academic performance deficits, and eventually with antisocial behavior in adolescence. The description of the sample presents a two-part question about selection. First, the sample was from the NCPP study initiated a half-century ago when the MBD hypothesis was in vogue (see Nichols & Chen, 1981), and by choice the cases with preterm births were excluded. Could this subsample be used to address the old MBD question in a new light, by relating the findings to the old (Nichols & Chen, 1981) or new (Lou, 1996) MBD approach? Even though the sample was described as a 'randomly selected, population-based sample', it consisted of predominately one ethnic group (African-American), one economic group (poor), and one level of education (low). Would the discussion of findings be improved with more of an emphasis of the lack of a representative sample of the population of the USA than a scant mention in one line in the limitations section?

Robinson et al. (this issue) evaluated a comprehensive set of antenatal, perinatal, and postnatal risk factors for behavior problems in children at 2 and 5 years of age. The primary conclusion was based on multinomial logistic regression, which suggested that prenatal (stress and smoking during pregnancy), postnatal (maternal depression and breastfeeding), and demographic factors (maternal ethnicity and sex of child) all were significant predictors of mental health problems in preschool children. The method of assessment of mental health problems in a population-based study suggests a question. The instrument used, the Child Behavior Checklist, was described as a 'dimensional measure of child behavior', but it is based on rating categories that assess presence or absence of psychopathology. Since this produces a highly skewed distribution in the population distributions of its subscales, does this make the use of T-scores (that by definition assume normality) inappropriate?

2. Long-term follow-up of small samples from clinics

Three of the articles made efficient and innovative use of data from long-term follow-up studies with relatively small samples. Gale et al. (this issue) provides information from a long-term follow-up of a subset of pregnant women ($n = 217$ of 559) who attended a clinic in Southampton in 1991 and 1992 and were entered into a study of nutrition during pregnancy (Godfrey, Robinson, Barker, Osmond, & Cox, 1996). Hay, Pawlby, Waters, and Sharp (this issue) used long-term follow-up into adolescence ($n = 121$) of the offspring of a random sample of 150 pregnant women from general medical practices in the South London Child Development Study initiated in 2001 to 2002. Bergman, Sarkar, Glover, and O'Connor (this issue) use a sample of pregnant women ($n = 123$) recruited from patients who attended an amniocentesis clinic in South London between 2001 and 2005.

Gale et al. (this issue) evaluated the controversial hypothesis that maternal consumption of fish during pregnancy may have a beneficial effect on behavior and IQ on offspring at 9 years of age. A plausible biochemical hypothesis was proposed related to omega-3 fatty acids, dopamine, brain development and ADHD, and some positive findings in the literature. The primary conclusion was that children of mothers who ate no fish during early pregnancy (compared to those who did) had a greater risk for high ratings of hyperactivity but not other domains of behavior. The self-selection of cases suggests a question. Since the description of the participating cases described censoring for low levels of education, age, and social class, which was also present for mothers who ate oily fish in late pregnancy, should the possible impact of this double selection (which resulted in a residual sample with a triad of

characteristics – mothers with higher education, older at birth, and from non-manual social classes) be considered to generate competing or alternative explanations for the reported effects of fish intake on IQ?

Hay et al. (this issue) evaluated effects of postpartum depression on two domains of long-term outcome (IQ and psychopathology in adolescents). The primary aim was to test the hypothesis that effects of infant exposure to maternal postpartum depression are independent of, or in addition to, effects of antenatal or later (3 months or more postpartum) lifelong exposure to depression. The primary conclusion based on logistic regression analyses suggested that after controlling for antenatal depression, postpartum depression did not have a significant effect on diagnoses of emotional and behavioral problems in adolescents. The acceptance of the null hypothesis suggests a question. Since the hypotheses of the study were tested by sequential tests (whether effects of postpartum depression could be explained by antenatal depression, then whether effects of both could be explained by later maternal depression), and the primary conclusion drawn was based on the absence of significant main or interaction effects, should the small sample size for the cell sizes for the 2×2 interaction (which appeared to vary from $n = 3$ to $n = 12$) be presented explicitly and discussed before (perhaps prematurely) dismissing effects of these pre- and perinatal processes on child mental health and disorder?

Bergman et al. (this issue) evaluated the impact of postnatal parenting on overcoming effect of antenatal stress. Three models were proposed (stress-buffering, exacerbation, and cumulative risk). Laboratory assessment of child–parent attachment and child fearfulness were obtained when the children were 1.6 years of age. The primary conclusion was that parental attachment appeared to affect the correlation between maternal stress and fearfulness and the pattern suggested that poor early caregiving may exacerbate the adverse effects of antenatal stress. The definition of the control condition suggests a question. Since the main effect of attachment was due primarily to a large difference in insecure subgroups (2.24 for disorganized vs. .75 for ambivalent) that fell on either side of the secure subgroup (1.21), and the large correlation of the fear composite (from the laboratory temperament assessment battery) and antenatal stress was reported to be high ($r = .78$) only for the resistant (ambivalent) attachment, and was based on a very small subgroup ($n = 14$) that had very low scores for attachment and increases the possibility of a false positive findings, was it justified to designate the insecure-ambivalent subgroup as the ‘control’ condition in hierarchical regression analysis?

3. Short-term evaluation of clinical samples

Two of the articles used detailed evaluation of new births recruited from medical clinics in the USA. Brennan et al. (this issue) used a sample ($n = 189$) recruited from the Emory Women’s Mental Health Center in Atlanta. Swain et al. (this issue) evaluated a small sample ($n = 12$) of new mothers recruited from the Yale New Haven Hospital postpartum wards and selected on the basis of mode of delivery of the child ($n = 6$ by Caesarean delivery and $n = 6$ by vaginal delivery).

Brennan et al. (this issue) evaluated the effects of effects of maternal depression on infant cortisol measured multiple times under controlled settings for estimating baseline level and reactivity. Fetal and infant exposure to depression was evaluated based on the pattern of maternal depression in subgroups ($n = 32$ prenatal only, $n = 36$ postnatal only, and $n = 36$ both). The primary conclusions were that lifetime diagnosis of depression predicted baseline infant cortisol but not cortisol reactivity, with no difference across the subgroups, and that depressed women who were not treated with anti-depressants during pregnancy had children with the highest cortisol levels in infancy, suggesting that maternal medication treatment during pregnancy may offset effects of maternal depression on infant cortisol levels. Comorbid anxiety in combination with depression predicted cortisol reactivity, but this finding suggests a question. Since the measure of cortisol reactivity was expressed as change from baseline and

further adjustments were made based on the observation of a large negative correlation of change scores with the baseline score ($r = -.47$), is this relationship different than expectation by chance due to the principle of regression to the mean when the same score is included on both sides of the equation for the correlation coefficient?

Swain et al. (this issue) evaluated effects of the auditory stimulation (the sounds of babies crying) on the mothers' brain activation by use of fMRI. Regions of brain activation were defined by whole-brain, voxel-based cluster threshold analysis. Analyses of variance with pair-wise comparisons was used to contrast effects of recorded cries of the mothers' own or others' babies to control sounds (matched white noise bursts) on activation of brain circuits. The primary conclusion was that large effects of mode of delivery were present, with greater brain activation for own-baby cry vs. control sound and for the own-baby vs. other-baby cry for the vaginal than Caesarean delivery subgroup. If true, this is an extraordinary and very important finding. The large and consistent differences reported are based on a very small sample, and this demands a follow-up attempt to replicate with a larger sample. Other explanations deserve consideration, and a difference in average age for the subgroups suggests a question. If the mothers in the two groups also differed substantially in age (by 7 years) as well as by mode of delivery, would an adjustment for age moderate the reported effect?

4. Cross-sectional study

One of the articles was a cross-sectional study of genetic factors related to ADHD. Altink et al. (in press) used a subset of the International Multi-center ADHD Genetics (IMAGE) sample ($n = 946$) recruited from academic clinics in Ireland, the UK, and the Netherlands. The aim was to evaluate well-documented associations with ADHD with a genetic factor (polymorphism of the DRD4 gene) and an environmental (maternal smoking during pregnancy) and their gene-environment (G×E) interaction. The outcomes measures were symptom-severity ratings from multiple sources (parents and teachers) and of domains (hyperactivity, inattention, opposition) of behavior. The primary conclusion which suggested complex patterns of significance that depended on diagnostic status. In ADHD cases there were significant and clear genetic main effects for parent ratings, but the 'risk' allele was associated with lower not higher parent ratings of symptom-severity and non-significant G×E interactions. In non-ADHD participants, there was a significant genetic main effect but for a different source and in the opposite direction compared to the ADHD cases – the 'risk allele' was associated with higher teacher ratings of symptom-severity. Also, in the non-ADHD participants, there was a significant G×E interaction. The basic rules for evaluating interactions suggest a question. Since the 3-way interaction of Diagnosis (ADHD vs. Unaffected) × DRD4 status (7-repeat carrier or not) × Maternal Smoking status (Yes or No) was not significant, was the simple effect analyses of the two separate two-way interactions of DRD4 status × Maternal Smoking a post hoc test, and if so would adjustment for multiple comparisons be necessary?

Integration of empirical studies

1. Timing and interaction of exposures to parental depression

The timing and possible interactions of exposure to parental depression was the focus of 4 of the 9 empirical articles in this special section. Two of the 4 articles address the possible interaction of timing of exposure to depression on outcomes defined by child mental health and disorder, and the primary findings seem to support the continuity hypothesis. Hay et al. (this issue) and Ramchandani et al. (this issue) used natural experiments to contrast 3 patterns of exposure to parental depression (prenatal only, postnatal only, or both) using very different methods. Hay et al. (this issue) suggested that cumulative exposure to maternal depression rather than exposure at specific times in development mediated child mental health and disorder assessed by structured psychiatric interviews at 11 and 16 years of age. Ramchandani et al.

(this issue) used the same 3 pre-post patterns but for paternal depression, and based on assessment of child outcomes on behavioral and emotional problems at 3.5 and 7 years of age, suggested that prenatal and postnatal exposure had similar and cumulative effects on emotional problems, with weak evidence that postnatal exposure alone may increase risk for one type of behavior problem (conduct disorder). The study by Robinson et al. (this issue) focused on multiple antenatal, perinatal, and postnatal risk factors, but used very subjective and ill-defined definition of depression (e.g., maternal depression immediately postpartum was defined by response on a questionnaire about 'baby blues'). Exposure to mothers with 'baby blues' postpartum contributed to increased risk for internalizing problems at 2 and 5 years of age. The fourth article in this subset (Brennan et al., this issue) suggested that exposure to peripartum depression had effects on infant cortisol reactivity above and beyond the cumulative effect of lifetime maternal depression.

What can be gleaned from these articles that address timing of exposure to parental depression? The complexities of multiple factors that may interact make it difficult to draw firm conclusions, but across the first 3 studies outlined above the findings seem to support the continuity hypothesis rather than the biological programming hypothesis. However, the fourth used a very different outcome measure – cortisol level and reactivity – and in contrast to the other 3 articles that focused on behavioral, these measures appear to provide support for the biological programming hypothesis.

2. Pathology, plasticity, and outcome specificity

As discussed earlier, the DOHaD approach is based on plasticity and the MBD approach is based on pathology. Four of the articles focused on one of these approaches, which were discussed in the two relevant articles cited above that present reviews of the literature on biological programming. As discussed earlier in his commentary, Gluckman et al. (2007a) reviewed and discussed the DOHaD approach and offer examples related to physical development and disorder, and Rutter et al. (2004) reviewed and discussed the biological programming approach and the pathology approach and offered examples related to mental development and disorder.

The two review articles in this special section amplify the approaches addressed by these two example reviews of existing literatures. Geva and Feldman (this issue) specifically addresses the pathology approach and Mill and Petronis (this issue) specifically addresses the plasticity approaches. Geva and Feldman (this issue) presents a framework that originates with pathology (damage to the brainstem) that may be propagated during development to disrupt neural function at progressively higher levels. This pathology approach is comprehensive, and plausible links are proposed about how this pathology may affect later regulation of emotions, cognition, and behavior during multiple stages of development.

In contrast, Mill and Petronis (this issue) present a framework based on plasticity – the developmental origins of health and disease (DOHaD) approach – and applied it to one child mental health disorder – ADHD. As discussed in the introduction, the DOHaD approach has been used to evaluate aspects of physical development, and they propose to extend this to psychosocial development. The primary content of the article is a thorough review and discussion of emerging area of epigenetics, which may offer an account for the underlying basis of neural plasticity (*in utero* environment altering patterns of gene expression) that affect development of brain circuits that in turn affect behavior.

Two of the empirical articles also emphasized these two approaches. One provides an example of the pathology approach (Nomura et al., in press) and the other (Gale et al., in press) provides an example of the plasticity approach. Nomura et al. (in press) used the archived database from the NCPP that was initiated about a half-century ago. The NCPP database was reviewed and

summarized by Nichols and Chen (1981) over 25 years ago in a monograph entitled 'Minimal Brain Dysfunction: A Prospective Study'. Nomura et al. (this issue) extended the use of this database with additional follow-up that provided measures of long-term outcome, and integrated the findings from perinatal observations at birth, neurological exams in infancy at 1 year of age, early development of hearing, speech, and language at 3 years of age, early measures of IQ at 4 years of age, and early academic performance in school at 7 years of age, on a broad outcome related to antisocial behavior in adolescence based on recall in adulthood. They claim confirmation of their hypothesis that perinatal problems progress to antisocial behavior, and proposed that this progression is mediated by cognitive and academic problems in childhood.

In contrast, Gale et al. (this issue) other of the empirical articles used the plasticity approach, which is exemplified by Gale et al. (this issue), who used the database from a parent study described by Godfrey et al. (1996) and provided follow-up to assess child development, mental health and disorder. The parent study, initiated almost 2 decades ago, was designed to evaluate the effects of maternal diet on behavioral and cognitive outcomes in childhood at 9 years of age, and thus was a test of the DOHaD hypothesis based on a sound theory of brain development. The assessment was with state-of-the-art instruments, the Strengths and Difficulties Questionnaire (SDQ) and Wechsler Abbreviated Scale of Intelligence (IQ). They claim confirmation of their hypothesis of effects of consumption of fish during pregnancy, but qualified these findings due to complex results that depended how reports of fish consumption were analyzed – as qualitative (yes or no) or quantitative (number of times a week), and by type of fish (oily or not), with differences based on consumption associated with childhood behavioral outcomes (hyperactivity) and timing of consumption (late in pregnancy) associated with intelligence (verbal IQ).

What can be gleaned from these articles? The Nomura et al. (this issue) article could benefit from reference to the old MBD approach used by Nichols and Chen (1981), which provided an account of the early outcomes of this sample that was part of the NCPP, or from reference to the new MBD approach offered by Lou (1996), which was based on both early outcomes (Lou et al., 1996) and long-term follow-up (Neto et al., 2002) of a sample presumed to be at risk for early pathology. Gale et al. (this issue) deserves special attention because it serves as an extension and partial replication of findings from the ALSPAC study (Hibbeln et al., 2007) about effects of fish consumption during pregnancy on later behavioral outcomes in childhood.

It is surprising that none of the 4 articles – neither the 2 empirical nor the 2 review articles – addressed both of these approaches in terms of how they may apply either sequentially or in combination. Each of the 4 articles addressed just one approach – either the pathology approach or the plasticity approach –but not both. However, as others have pointed out, these distinctly different pathways may produce similar outcomes, so it may be difficult to distinguish one from each other and both possible etiologies might be considered (see Swanson et al, 2007). For example, Rutter et al. (2004) formulated a hypothesis about enduring effects of severe postnatal deprivation on psychological outcome depending on biological programming or neural damage and noted that 'we saw no clear way of differentiating between these two alternatives with the measures available to us' (p. 84). If both approaches had been considered and discussed in these articles, the interpretations of findings may have been different and improved. It would be of interest to consider pathology the extreme of plasticity, with predictive adaptive programming operating to prevent pathology (see Hales & Barker, 1992) but only up to a point.

Tests of the biological programming principle

In their review, Gluckman et al. (2007) suggested that the underpinnings of predictive adaptive responses are epigenetic processes. However, from the review by Mill and Petronis (this issue), one might conclude that at this time this hypothesis is based mostly on speculation, at least when applied to the topic of this special section. Changes on the early environment in humans has not yet progressed to the point of documenting changes at the molecular level (e.g., changes in methylation of DNA or chromatin structure that produce altered gene expression in the face of specific fetal environments), which is the mechanism hypothesized to produce enduring effects of specific early environmental cues.

Two of the prime example animal models were described in the GEHDHD meeting by Randy Jirtle (see Waterland & Jirtle, 2004) and Michael Meaney (see Meaney & Szyf, 2005), and background on epigenetic processes and analyses were described by Andrew Feinberg (Callinan & Feinberg, 2006 and Bjornsson, Fallin, & Feinberg, 2004). Waterland and Jirtle (2004) describes the use of the yellow agouti mouse model, which shows that methyl supplementation of the diet of mothers during pregnancy produces increases in CpG methylation, which alters imprinting of the agouti gene, shifts the distribution of coat color toward brown in offspring and of body weight toward obesity. Meaney and Szyf (2005) describes how variations in parent-offspring interactions influence development and have effects at the molecular level of analysis, using as an example work with rats that shows that maternal care (licking and grooming) increases DNA methylation in the rat hippocampal GR gene (in exon 1 γ , a brain-specific promoter). This underlies hippocampal expression of the glucocorticoid receptor mRNA and protein, which results in decreased hypothalamic corticotrophin release factor and reduced hypothalamic-pituitary-adrenal response to stress. This proof-of-principle research documents how variation in maternal care can alter the stress response in offspring via maternal programming. A recent example of adaptive programming was provided by Aagaard et al (2008), who used a primate model to show that a high-fat maternal diet during pregnancy (which was associated with increased fetal liver triglycerides and evidence of fatty liver disease) epigenetically altered fetal chromatin structure and gene expression in fetal liver tissue. This provided additional evidence of a molecular basis for the DOHaD hypothesis. Callinan and Feinberg (2006) outlines epigenetic modifications to the genome, including chemical changes (methylation) and shape changes (histone modification), describes imprinting (silencing of one parental copy of a gene) and the role of methylation in this process, and also describes the loss of imprinting as a factor in some diseases, using as an example the insulin-like growth factor II gene (IGF2). Differential methylation results in differential expression and contributes to cancer and Beckwith-Wiedemann syndrome. Bjornsson, Fallin, and Feinberg (2004) presents an analysis approach for common disease genetic epidemiology that includes estimating direct effects epigenotype as well as indirect effects that modulate the expression of disease-causing variants of a gene to mask or unmask the disease phenotype.

While these and other animal models (see Gluckman et al., 2007) have been used to provide strong proof-of-principle studies that these epigenetic mechanisms operate, studies with humans to test this underlying principle of the DOHaD hypothesis and the molecular basis for predictive adaptive programming are just emerging in the literature. Epigenetic changes are not necessarily pervasive and may be tissue-specific. Recently, new methods for evaluating epigenetic processes in human fetal development have focused on tissue from the placenta, which is crucial for fetal growth and development. These have included methods for evaluating loss of imprinting (Lambertini et al, 2008) and allele-specific methylation and expression (Kerkel et al, 2008). These new methods and human studies, as well as the animal models and proof-of-principle studies, appear to be directly related to human studies in this special issue

on maternal diet during pregnancy (see Gale et al., in press) and maternal nurturing (see Swain et al., in press) in this special section.

What can be gleaned from these 2 articles? Since the Gale et al. (this issue) article provides a replication of a specific effect of diet on behavior (see above), it seems to support targeting maternal diet during pregnancy as a trigger for the molecular basis (i.e., epigenetic effects) of predictive adaptive programming in fetal development that may have enduring effects on behavior later in life. If the effects reported by Swain et al. (this issue) with a very small sample are found to be reliable, this might be a remarkable and important documentation of effects to maternal nurturing.

Methodological concerns

It seems critical to point out some obvious weaknesses that seem pervasive across the methods used in this set of articles – the lack of statistical power, the failure of any study to adjust for multiple comparisons, and the tendency to use non-significance to accept the null hypothesis despite warnings of statisticians that ‘the absence of evidence is not evidence of absence’ (see Kraemer & Kupfer, 2005).

To highlight this pervasive limitation, consider the range of sample sizes across the empirical articles in this special section. Ramchandani ($n = 7,601$), Robinson ($n = 1,707$), Nomura ($n = 1,686$), Atlink ($n = 946$), Gale ($n = 217$), Bergman ($n = 123$), Hay ($n = 121$), Brennan ($n = 104$), and Swain ($n = 12$). For the large sample sizes (e.g., $n > 1,500$), it might appear that ample statistical power would be achieved to address adequately the topic of this special issue (i.e., pre and perinatal processes in child mental health and disorder).

However, since subgroups from the designated samples sizes were used in the analyses, those are more relevant than the overall sample size. A cursory review documents the range of subgroup sizes: Ramchandani ($n = 22$ to 28), Robinson ($n = 57$ to 113), Nomura ($n = 20$ to 934), Atlink ($n = 29$ to 92), Gale ($n = 15$ to 18), Bergman ($n = 14$ to 62), Hay ($n = 3$ to 80), Brennan ($n = 32$ to 36), and Swain ($n = 6$). In most of the articles in the special section, analyses were used that compared subgroups across multiple outcome variables. The cursory review suggests that the number of comparisons in these studies varied from 12 to 72 . We estimate that if the Bonferroni correction for multiple comparisons were applied, the significance levels to maintain an overall level of $p < .05$ would be from $.00417$ to $.00069$. This suggests a question for the set of articles: how many of the reported statistically significant effects would have survived this adjustment?

As usual for any area that addresses complex disorders, the necessary limitations on number of comparisons and number of outcome measures should be respected, in order to minimize false positive and false negative conclusions. Some of the crucial findings reported in this special section may be attributed to false positive effects, and none of the excluded hypotheses should be rejected based on non-significant tests of hypotheses. Based on these statistical limitations, perhaps the findings from the articles in this special section should be considered as exploratory rather than offered as scientific evidence in support of hypotheses. This does not diminish the value but may alter the interpretation of the reported findings.

Future studies

Due to the complexity inherent in the investigation of the topic of child mental health and disorder, we propose that the next phase of research to address the topic of the special issue – pre- and perinatal processes in child mental health and disorder – would benefit substantially from large cohort studies with prospective measures of broad domains of exposures and outcomes.

There is a debate about the best way to obtain data from such a study. The recent debate by Willett et al. (2007) and Collins and Manolio (2007) addressed two approaches. Willett et al. (2007: 'Merging and Emerging Cohorts') suggest that the use of a combination of existing cohort compared to establishing new cohorts would provide data '... more rapidly and more cheaply, and with similar scientific validity', while Collins and Manolio (2007: 'Necessary but Not Sufficient') favor establishing a new cohort representing the age spectrum in the population from childhood to adulthood, with cross-sectional evaluation of development over a short time period (e.g., 4 years). They point out that the use of existing cohorts '... may ultimately jeopardize our ability to address these evolving health risks in an epidemiologically rigorous manner'. Both commentaries mention strengths of the birth cohort design. Willett et al. (2007) note that 'Ultimately, cohorts established during childhood will be more informative' and Collins and Manolio (2007) note that 'If we wish to address complex disease risk across the lifespan, we need to study diseases developing in adolescence and young adulthood'.

As we have mentioned earlier, it is likely that many complex common disorders in adults have their origins in fetal development and in early childhood (see Barker et al., 1989; Gluckman et al., 2007a). Neither extending existing cohorts nor establishing a new cohort mainly of adults takes into account the concept of the developmental origins of health and disease. The birth cohort design may be necessary to identify the critical developmental processes that underlie complex physical disorders that have unacceptably high prevalence and are increasing at alarming rates, such as premature birth, asthma, obesity, and diabetes, as well as for child mental health disorders that are the focus of the special issue on child mental health and disorders.

There are current examples of birth cohorts studies, such as the Danish National Birth Cohort of 100,000 (see Olsen et al., 2001; Olsen, 2005) and the Southampton Women's Survey (see Inskip et al., 2006). Also, a prospective birth cohort is now under way in the USA. The National Children's Study (NCS) was authorized by the Child Health Act of 2000 and has been under development since that time. The NCS sample will be recruited at 105 sites over a 4-year period beginning in 2010, with approximately 1,000 children entered from each site. The recruitment will start with randomly designated neighborhoods and a survey of households within them to identify 750,000 women between the ages of 18 and 40 years who are not pregnant or within the first trimester of pregnancy. These women will be evaluated and followed until approximately 105,000 become pregnant and give birth. Broad exposure and outcome domains will be assessed up to 16 times across stages of development (before conception; 3 times during pregnancy; at birth; at 1, 6, 12, and 18 months of age in early childhood; at 3, 5, 7, 9, and 12 years of age in childhood; at 16 and 20 years of age in adolescence). Thus, the NCS will provide a prospective evaluation of a large birth cohort with early and frequent direct observation of the same individuals over time.

In the GEHDHD meeting (see Swanson et al., 2006), three critical issues were identified that highlight the extraordinary value of the birth cohort design: (a) If the nature of the combined effect of multiple genetic and environmental risk factors is non-additive, then the only way to elucidate these interactive effects is to assess the various risk factors simultaneously in *the same cohort rather than in separate cohorts*; (b) if vulnerability to a particular risk factor or disease phenotype is determined not only by the genome acquired at conception but by the nature of its interplay with the environment during critical periods of early development, then *a longitudinal assessment of the environment* from before conception through pregnancy, fetal life, birth, and infancy (as opposed to assessment of the environment in adult life) is crucial to better understand disease susceptibility; (c) if the interplay between genes and environment is characterized by dynamic modifications to the genome, then not only the stable DNA sequence but also *the epigenetic modifications to nuclear DNA and chromatin structure* must be

investigated during critical periods in early development and over time and under various environmental conditions to adequately assess gene–environment interactions.

In addition, two remarkable characteristics of the NCS birth cohort are worth noting. The sample of 100,000 is large enough to provide adequate statistical power to address some of the issues related to pre and perinatal processes in child mental health and disease. For example, if the percentages reported by Ramchandani et al. (in press) for the ALSPAC study hold for the NCD, then the subgroups related to timing of paternal depression could increase by a factor of 13, and thus might be all over 1,000 (i.e., $n = 2,275$ for pre-only, 2,158 for post-only, and $n = 1,157$ with both). In addition, the NCS sample will be representative of the US population, so the disorders that emerge over time should be free from the typical referral biases that are likely to be present on clinically referred samples of child mental health diseases.

We must acknowledge that our strong personal bias favoring the birth cohort design may be due to our participation in the NCS and our intent to make use of the extraordinary data that will be generated by this extraordinary project. We must also acknowledge a strong personal bias toward the use of the DOHaD approach (we are members of the society). We believe that the prospective birth cohort design of the NCS, with repeated observations in the same individuals over time, along with hypotheses and analyses directed by the DOHaD approach (perhaps in combination with the MBD approach), will provide giant steps forward and help identify relevant exposure and outcome domains related to the developmental course of health and disease in childhood.

As we discuss in our commentary, the 9 empirical studies and the 2 reviews provide a set of interesting conclusions and unanswered questions that point the way for the next steps in the investigation of pre-and perinatal processes in child mental health and disorder.

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