

1. Critical periods in development

How Early Experience Shapes Human Development: The Case of Psychosocial Deprivation

Abstract - Experience plays an essential role in building brain architecture after birth. The question we address in this paper is what happens to brain and behaviour when a young child is deprived of key experiences during critical periods of brain development. We focus on the consequences of **institutional rearing**, with implication for the tens of millions of children around the world who from an early age experience profound psychosocial deprivation. Evidence is clear that deprivation can lead to a host of both short- and long-term consequences, including perturbations in brain structure and function, changes at cellular and molecular levels, and a plethora of psychological and behavioural impairments.

We summarize the findings from the **Bucharest Early Intervention Project**, the only project of its kind to examine the effects of early intervention in a **randomized control trial** with children who have been abandoned and are living in institutions. We specifically highlight findings that address the issue of critical periods in human development during which the influence of experience has a significant impact for particular domains.

Conceptual Framework: Critical vs. Sensitive Periods.

Animal Models of Psychosocial Deprivation and Inadequate Caregiving.

Caregiving Quality in Human Psychological Development – the stress response and attachment.

The Psychological and Biological Toll of Early Psychological Deprivation.

The Effects of Institutional Rearing on Development - Social-Emotional Disturbances, Psychiatric Disturbances, Neural Consequences, Biological Effects.

Recovery from Early Institutional Rearing.

Implications and Lessons Learned.

2. Gene environment and inhibition

Evidence for a Gene Environment Interaction in Predicting Behavioural Inhibition in Middle Childhood

Abstract - Gene-environment interactions are presumed to shape human behaviour during early development. However, no human research has demonstrated that such interactions lead to stable individual differences in fear responses. We tested this possibility by focusing on a polymorphism in the promoter region of the gene for the serotonin transporter (5-HTT). This polymorphism has been linked to many indices of serotonin activity. Specifically, we tested the hypothesis that an interaction between children's 5-HTT status and maternal reports of social support predicts inhibited behaviour with unfamiliar peers in middle childhood. Results were consistent with this hypothesis: Children with the combination of the short 5-HTT allele and low social support had increased risk for behavioural inhibition in middle childhood.

The 5-HTT gene consists of two alleles, the short and the long, with the short allele conveying diminished 5-HTT transcription, lower transporter levels, and reduced serotonin uptake, with functional effects on neural circuits regulated by serotonin (Hariri et al., 2002). The short allele has been associated with predispositions to anxiety and negative emotionality in adult humans (Munafo et al., 2003).

Studies relating presence of the short allele to the neural substrates of anxiety or fear include one that found the presence of the S allele to be associated with heightened amygdala activation to fear faces in adults (Hariri et al., 2002).

Caspi et al. found that adults who both had the short allele and reported high levels of stressful life events were more likely to exhibit major depressive disorder than individuals who had two long alleles. The only other study demonstrating a gene environment interaction in children involving this polymorphism is one by Kaufman et al. (2004). They examined 101 children, 57 of whom had been removed from their parents due to abuse or neglect. Kaufman et al. reported that the maltreated children with the short allele and no positive social supports had higher depression scores than children having all other combinations of social support and genotype.

The present study extends the research on 5-HTT gene-environment interactions by examining the developmental effects of such interactions on fear-related behaviours in young children.

In order to investigate environmental influences on children identified as having the temperament of behavioural inhibition, we focused on social support, as experienced by the mother, as an index of environmental stress. We used a longitudinal framework and direct observation of behaviour to examine the manner in which early gene-environment interactions shape development of behavioural inhibition.

We tested the hypothesis that behavioural inhibition in middle childhood is predicted by the combination of low social support reported by the mother and the short 5-HTT allele in the child.

Behavioural Inhibition at 14 Months - At age 14 months, infant behaviours were observed toward novel objects and an unfamiliar adult

The children were categorized by their scores from observations when they played in quartets at 48 months of age. For both the 48- and 84-month observations, the children were left alone in the playroom for 15 min with age-appropriate toys.

Predicting Shyness at 84 Months - The model predicting mothers' reports of shyness at 84 months showed a significant genotype-by-social-support interaction, paralleling the results for observed behavioural inhibition. Social support was related to shyness at 7 years differently for children who had the short 5-HTT allele and those who had the long allele. Controlling for behavioural inhibition at 14 months, 5-HTT genotype status exhibited increasingly strong association with the 84-months shyness score, at increasingly low levels of social support (see Fig. 1, bottom panel). Thus, we replicated the finding that for children in families with low levels of social support, having the short allele of the 5-HTT gene increased risk for behavioural inhibition, whereas for children in families with high levels of social support, the short allele did not convey increased risk for behavioural inhibition.

3. Gene environment and personality

Gene-environment interactions and their impact on the development of personality traits

Abstract - Although there is good reason to suspect that gene–environment interactions (GxE) contribute to the development of personality, there is relatively little research on this topic to date. This review examines available studies of GxE in personality, focusing specifically on the personality traits of negative emotionality (the propensity to experience aversive mood states) and impulsivity (difficulty inhibiting the expression of affect or impulse). Extant studies of impulsivity yield conflicting results, and thus do not allow for any clear conclusions. However, parenting does appear to hold promise as a moderator of genetic influences on negative emotionality. In particular, genetic influences appear to make important contributions to negative emotionality, but only in the absence of a negative parent–child relationship. By contrast, poor parenting appears to increase negative emotionality in offspring, regardless of the child’s genetic predispositions. Such findings represent an exciting, if somewhat unexpected, advance in the field, and highlight a clear need for additional research on this topic.

Introduction – negative emotionality (NEM) and high impulsivity (IMP) and the role of the serotonin transporter gene (5HTTLPR).

Gene environment interaction (GxE) - GxE are defined as the moderation of genetic predispositions by environmental experience, such that particular environmental experiences alter subsequent genetic expression. No matter what the manifestation of GxE, they are a logical contributor to personality. In particular, both NEM and IMP are approximately 50% heritable.

GxE studies: latent versus molecular - **Ignore this bit!**

Impact of GxE on negative emotionality (NEM) – an explanation of the table of studies

Impact of GxE on impulsivity (IMP) - an explanation of the table of studies

4. Holland et al and Anorexia

Anorexia nervosa: a study of 34 twin pairs and one set of triplets

Abstract - In a collaborative study between St George's and the Maudsley Hospitals, 34 pairs of twins and one set of triplets were identified in which the proband had anorexia nervosa. The diagnosis was based on standard criteria and zygosity was established by blood group analysis or by use of the physical resemblance questionnaire. In the 30 female twin pairs, 9/16 of the monozygotic (MZ) and 1/14 of the dizygotic (DZ) pairs were concordant for anorexia nervosa. Three of the non-anorexia co-twins had other psychiatric illnesses, and two had minor eating disorders. None of the male co-twins had anorexia nervosa.

Introduction - Dieting is widespread among adolescent women (Hueneman et al, 1966; Nylander, 1971; Crisp, 1983), but the relative contributions of specific life experiences and of constitutional factors in the development of the fully established anorexic syndrome remains uncertain.

The evidence for any genetic component has so far been inconclusive, but certain factors have been reported as being over-represented in anorexic families. These include obesity (Crisp, 1967a), depressive illness (Winokur et al, 1980), alcoholism, a concern over weight and middleclass attitudes' (Crisp, 1980).

Theander (1970) has reported a 6.6% sibling risk of anorexia nervosa in his series of 94 female anorexic patients. In a study of 102 anorexic patients, Crisp et al, (1980) found that 7% of the siblings, 14% of the mothers, and 9% of the fathers had a history consistent with a diagnosis of anorexia nervosa, and a further 10% of the mothers were obese.

In a study of 13 male anorexic patients, Crisp & Toms (1972) reported that anorexia nervosa was present in three siblings, and suggested that the siblings were taking turns in stabilising the family dynamics through their anorexic behaviour. A more recent study (Hudson et al, 1983), using DSM III (American Psychiatric Association, 1980) criteria, reported a 5.9% occurrence of eating disorders among the 70 first-degree relatives of 14 anorexic probands.

Aims - The aims of this study were: firstly, to investigate concordance rates for anorexia nervosa and other eating disorders in a relatively unselected and larger series of anorexic twins and secondly, to study the twins who were discordant for the disorder.

Method - The twin probands all had anorexia nervosa and were identified from three separate sources. Fourteen pairs (15 probands) and one of a set of male triplets were collected together over the period 1960 to 1982, having been referred to St George's Hospital.

Each twin and the parents were interviewed separately, using a semi-structured interview schedule. This was designed: (i) to explore the presence or absence of an eating disorder or other psychiatric illness in either of the twins; (ii) to obtain information on their birth order and weight, adverse perinatal factors, childhood neurotic traits, weight in childhood, age at menarche, and educational achievement; and (iii) to assess the dominance and other personality characteristics of each twin.

Results - Out of the total 30 pairs, nine out of 16 MZ and one out of 14 DZ pairs were concordant for anorexia nervosa. None of the three male/female DZ pairs, the male MZ pair, or the set of triplets were concordant.

Discussion - There is a genetic predisposition to anorexia nervosa, which could become manifest under adverse conditions such as inappropriate dieting or emotional stress. Such a genetic vulnerability might be a predisposition to a particular personality type, to psychiatric illness in general (and in particular affective disorder), to a disturbance of body image, or to a hypothalamic disorder.

Thus, MZ twins carrying one or more vulnerability factors would both have the potential for developing anorexia nervosa under conditions of stress. Other factors such as earlier life experiences or particular life events may be different in each of the twins, thus influencing the expression of the disorder.

The second possible explanation is that the equal environment' assumption made in twin research, is incorrect for anorexia nervosa, and that the MZ, compared to the DZ pairs, are treated in a more similar way, and are, therefore, more susceptible to the process of induction. At the time of adolescence, twins are exposed to the particular challenge of separation, and the development of anorexia nervosa may then reduce the individuals to an identical state, eliminating actual differences which may have emerged.

5. Maguire et al study

Navigation-related structural change in the hippocampi of taxi drivers

Abstract - Structural MRIs of the brains of humans with extensive navigation experience, licensed London taxi drivers, were analysed and compared with those of control subjects who did not drive taxis. The posterior hippocampi of taxi drivers were significantly larger relative to those of control subjects. A more anterior hippocampal region was larger in control subjects than in taxi drivers. Hippocampal volume correlated with the amount of time spent as a taxi driver (positively in the posterior and negatively in the anterior hippocampus). These data are in accordance with the idea that the posterior hippocampus stores a spatial representation of the environment and can expand regionally to accommodate elaboration of this representation in people with a high dependence on navigational skills. It seems that there is a capacity for local plastic change in the structure of the healthy adult human brain in response to environmental demands.

Introduction - One important role of the hippocampus is to facilitate spatial memory in the form of navigation. Increased hippocampal volume relative to brain and body size has been reported in small mammals and birds who engage in behaviour requiring spatial memory, such as food storing. In some species, hippocampal volumes enlarge specifically during seasons when demand for spatial ability is greatest. In the healthy human, structural brain differences between distinct groups of subjects (for example, males and females, or musicians and non-musicians, have been documented. From existing studies, it is impossible to know whether differences in brain anatomy are predetermined or whether the brain is susceptible to plastic change in response to environmental stimulation.

Method - Right-handed male licensed London taxi drivers participated. All had been licensed London taxi drivers for more than 1.5 years. The average time spent training to be a taxi driver before passing the licensing tests fully was 2 years. All of the taxi drivers had healthy general medical, neurological, and psychiatric profiles. The scans of control subjects were selected from the structural MRI scan database at the same unit where the taxi drivers were scanned.

Results - VBM. Significantly increased grey matter volume was found in the brains of taxi drivers compared with those of controls in only two brain regions, namely the right and the left hippocampi. No differences were observed elsewhere in the brain.

Changes with Navigation Experience - We examined the correlation between volume and amount of time spent as a taxi driver (including both training on The Knowledge and practicing as a qualified taxi driver). We found that length of time spent as a taxi driver correlated positively with volume in only one brain region, the right posterior hippocampus.

Discussion - The data presented in this report provide evidence of regionally specific structural differences between the hippocampi of licensed London taxi drivers compared with those of control subjects. Taxi drivers had a significantly greater volume in the posterior hippocampus, whereas control subjects showed greater volume in the anterior hippocampus. The converging results from these two independent analysis techniques indicate that the professional dependence on navigational skills in licensed London taxi drivers is associated with a relative redistribution of grey matter in the hippocampus.

6. Methyloomic analysis of twins

Methyloomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioural traits

Abstract - Autism spectrum disorder (ASD) defines a group of common, complex neurodevelopmental disorders. Although the aetiology of ASD has a strong genetic component, there is considerable monozygotic (MZ) twin discordance indicating a role for non-genetic factors. Because MZ twins share an identical DNA sequence, disease-discordant MZ twin pairs provide an ideal model for examining the contribution of environmentally driven epigenetic factors in disease. We performed a genome-wide analysis of DNA methylation in a sample of 50 MZ twin pairs (100 individuals) sampled from a representative population cohort that included twins discordant and concordant for ASD, ASD-associated traits and no autistic phenotype. Within-twin and between-group analyses identified numerous differentially methylated regions associated with ASD. In addition, we report significant correlations between DNA methylation and quantitatively measured autistic trait scores across our sample cohort. This study represents the first systematic epigenomic analyses of MZ twins discordant for ASD and implicates a role for altered DNA methylation in autism.

Introduction - Autism spectrum disorder (ASD) defines a collection of complex childhood neurodevelopmental disorders affecting 1% of the population and conferring severe lifelong disability. ASD is characterized by a triad of impairments: (1) deficits in social interactions and understanding, (2) non-social impairments, such as repetitive behaviour and interests, and (3) impairments in language and communication development. Quantitative genetic studies indicate that ASD has a strong heritable component.

Despite the high heritability estimates for ASD, there is notable discordance within monozygotic (MZ) twin pairs for diagnosed ASD, and often considerable symptom severity differences within ASD-concordant MZ twins, strongly implicating a role for non-genetic epigenetic factors in aetiology. Epigenetic mechanisms mediate reversible changes in gene expression independent of DNA sequence variation, principally through alterations in DNA methylation and chromatin structure.

The use of disease-discordant MZ twins represents a powerful strategy in epigenetic epidemiology because identical twins are matched for genotype, age, sex, maternal environment, population cohort effects and exposure to many shared environmental factors. Recent studies have uncovered considerable epigenetic variation between MZ twins, and DNA methylation differences have been associated with MZ twin discordance for several complex phenotypic traits, including psychosis and Type 1 diabetes.

Method - Participants were recruited from the Twins' Early Development Study (TEDS), a United Kingdom-based study of twins contacted from birth records. For this study, a total of 50 MZ twin pairs were identified within TEDS using the Childhood Autism Symptom Test (CAST), which assesses dimensional ASD traits, at age 8 years.

The analysis of DNA methylation – **ignore this, too complex to describe!**

Results - As expected, within-twin patterns of DNA methylation were highly correlated across all MZ twin pairs indicating that ASD and related traits are not associated with systemic changes in epigenetic programming.

Discussion - Our findings have several implications for our understanding about the aetiology of ASD. First, they document the presence of numerous DNA methylation differences in MZ twins discordant for ASD and ASD-related traits, as well as between autistic individuals and control samples.

Second, the observed DNA methylation differences in MZ twins discordant for ASD and ASD related traits, who are otherwise matched for genotype, shared environment, age, sex and other potential confounders, highlight the role of non-shared environmental factors in the aetiology of autism.

Third, our data suggest that although DNA methylation at some sites is consistently altered across the entire set of discordant twins, differences at other sites are specific to certain symptom groups, with considerable overall epigenetic heterogeneity between the three domains of autistic traits.

Fourth, the analysis of individual ASD-discordant twin pairs suggests that there is also considerable familial heterogeneity, with rare epigenetic alterations of large magnitude being potentially associated with ASD.

Fifth, the identification of significant correlations between DNA methylation and autism symptom scores across our sample cohort suggests that there is a quantitative relationship between the severity of the autistic phenotype and epigenetic variation at certain loci.

Finally, in addition to implicating a number of novel genes in the aetiology of ASD, we identified ASD-associated differential DNA methylation in the vicinity of multiple loci previously implicated in the pathogenesis of autism in genetic studies.

7. Pascual – Leoni 1995

Modulation of Muscle Responses Evoked by Transcranial Magnetic Stimulation During the Acquisition of New Fine Motor Skills

Summary – 1. Using TMS they mapped the cortical motor areas targeting the muscle and flexor areas of the right hand on a five finger piano exercise. Secondly, they studied the effects of mental and physical practice of the same five-finger exercise on the modulation of the cortical motor areas targeting muscles involved in the task.

2. Over 5 days of 2 hour practice, the cortical areas enlarged and the activation thresholds decreased.

3. They studied the effect of increased hand use for nonspecific skill (2 hours playing at will). Cortical effects were similar but not as great.

4. in the second experiment pp's were assigned randomly to either control, physical or mental practice group for 2 hours over 5 days. TMS measures were taken.

5. Mental practice led to same cortical changes as physical practice, and improvement in actual playing, but not as great as the impact of physical practice on playing

6. They concluded that the acquisition of motor skills is associated with modulation of the motor cortex.

7. They also concluded that mental practice promotes modulation of neural circuits involved in skill acquisition and gives pp's an advantage for further skill learning with minimal practice.

8. The critical period

This is just a short guide to aid your understanding!

9. Thinking positively

Thinking positively: The genetics of high intelligence

Abstract - High intelligence (general cognitive ability) is fundamental to the human capital that drives societies in the information age. Understanding the origins of this intellectual capital is important for government policy, for neuroscience, and for genetics. For genetics, a key question is whether the genetic causes of high intelligence are qualitatively or quantitatively different from the normal distribution of intelligence. We report results from a sibling and twin study of high intelligence and its links with the normal distribution. We identified 360,000 sibling pairs and 9000 twin pairs from 3 million 18-year-old males with cognitive assessments administered as part of conscription to military service in Sweden between 1968 and 2010. We found that high intelligence is familial, heritable, and caused by the same genetic and environmental factors responsible for the normal distribution of intelligence. High intelligence is a good candidate for “positive genetics” — going beyond the negative effects of DNA sequence variation on disease and disorders to consider the positive end of the distribution of genetic effects.

Introduction - A key question for genetic research is the extent to which the aetiology of high intelligence differs from the aetiology of the normal distribution of intelligence. More specifically, do the same genes affect both high intelligence and the rest of the distribution to the same extent? It cannot be assumed that the aetiology of high intelligence is the same. For example, very low intelligence (severe intellectual disability) differs aetiologically from the normal distribution. In recent molecular genetic studies, rare non-inherited mutations appear to be a major source of severe intellectual disability (Ellison, Rosenfeld, & Shaffer, 2013).

The Discontinuity Hypothesis - The Discontinuity Hypothesis posits different environmental and genetic aetiologies for high intelligence in contrast to the rest of the distribution.

Although the evidence showing substantial heritability for the normal distribution of intelligence is one of the most consistently documented findings in the behavioural sciences (Deary, Johnson, & Houlihan, 2009), researchers in the field of expert training have argued that “differences in early experiences, preferences, opportunities, habits, training, and practice are the real determinants of excellence”.

The Continuity Hypothesis - The Continuity Hypothesis posits that high performance is the quantitative extreme of the same environmental and genetic factors responsible for the rest of the normal distribution. From an environmental perspective, the prodigious practice and concentrated effort of high performers might be only quantitatively (e.g., number of hours of deliberate practice) but not qualitatively different from the factors responsible for the rest of the distribution.

Quantitative genetic analysis of high intelligence – how to measure it.

Previous studies of high intelligence –

The present study – Using a general factor from cognitive assessments of 3 million 18-year-old males administered as part of compulsory military service in Sweden between 1968 and 2010, we identified 370,000 sibling pairs and 9000 twin pairs. We selected the highest-scoring (top 5%) non-twin siblings and twins in order to investigate the familiarity and heritability of high intelligence and its links to the normal distribution.

Method - General cognitive ability was assessed with the Swedish Enlistment Battery (SEB).

Results - High intelligence, defined as the highest 5% of scores, is highly familial. In other words, almost half of the difference between high intelligence and the rest of the population is familial in origin. Familiality could be due to genetic or environmental influences. However, the twin data indicates that the familial effect is substantially genetic in origin. The mean for DZ twins of probands does not differ substantially from that of non-twin siblings. In contrast, MZ co-twins have a substantially higher mean score than that of DZs, suggesting a strong genetic association.

Discussion - These results provide strong support for the Continuity Hypothesis. Familial resemblance from non-twin sibling analyses and heritabilities from twin analyses were similar for high intelligence and for the rest of the distribution.

10. Twin studies and individual differences

The Importance of Twin Studies for Individual Differences Research

Abstract - Twin research designs and methods are valuable tools for examining genetic and environmental influences on behavioural and medical characteristics. A review of the biological bases of twinning and descriptions of 10 research designs are presented. Findings from a selected sampling of twin studies of learning disabilities, personality and temperament, attitudes, psychopathology, and social behaviour are summarized. The findings are discussed with special reference to the activities of mental health practitioners and counsellors.

Introduction – the biological basis of twinning.

Twin research design – 10 types of twin study designs.

Biases in twin research –

Summary of findings from twin research – learning disabilities, personality and temperament, attitudes, behavioural disorders, social behaviour.

Implications for mental health practice.
