Selected reference list – Avshalom Caspi & Terrie Moffitt

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W. et al. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297,* 851-854.
Notes: Medical Research Council Social, Genetic, and Developmental Psychiatry Research Centre, Institute of Psychiatry, King's College, London SE5 8AF, UK
We studied a large sample of male children from birth to adulthood to determine why some children who are maltreated grow up to develop antisocial behavior, whereas others do not. A functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) was found to moderate the effect of maltreatment. Maltreated children with a genotype conferring high levels of MAOA expression were less likely to develop antisocial problems. These findings may partly explain why not all victims of maltreatment grow up to victimize others, and they provide epidemiological evidence that genotypes can moderate children's sensitivity to environmental insults

Kuntsi, J., Eley, T. C., Taylor, A., Hughes, C., Asherson, P., Caspi, A. et al. (2004). Co-occurrence of ADHD and low IQ has genetic origins. *American Journal of Medical Genetics, 124B,* 41-47.
Notes: Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, United Kingdom
Previous studies show that the symptoms of attention deficit hyperactivity disorder (ADHD) and lower intelligence quotient (IQ) covary in children. We investigated the aetiology of this association in a large population-based sample of 5-year-old twins. The twins were individually assessed on an IQ test, and data on ADHD symptoms were obtained from mother interviews and teacher ratings. Confirming previous studies, the phenotypic correlation between ADHD symptom scores and IQ was -0.3 and, in a categorical analysis, children with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) ADHD research diagnosis obtained IQ scores nine points lower, on average, than comparison children. We show here that the co-occurrence of ADHD and lower IQ has genetic origins: 86% of the association between ADHD symptom scores and IQ, and 100% of the association between ADHD diagnosis and IQ, was accounted for by genetic influences that are shared by ADHD and IQ. Some candidate genes for ADHD could also contribute to variation in IQ or vice versa. Copyright 2003 Wiley-Liss, Inc

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H. et al. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biological Psychiatry, 57,* 1117-1127.
Notes: Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, United Kingdom
BACKGROUND: Recent evidence documents that cannabis use by young people is a modest statistical risk factor for psychotic symptoms in adulthood, such as hallucinations and delusions, as well as clinically significant schizophrenia. The vast majority of cannabis users do not develop psychosis, however, prompting us to hypothesize that some people are genetically vulnerable to the deleterious effects of cannabis. METHODS: In a longitudinal study of a representative birth cohort followed to adulthood, we tested why cannabis use is associated with the emergence of psychosis in a minority of users, but not in others. RESULTS: A functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on developing adult psychosis. Carriers of the COMT valine158 allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they used cannabis. Cannabis

use had no such adverse influence on individuals with two copies of the methionine allele. CONCLUSIONS: These findings provide evidence of a gene x environment interaction and suggest that a role of some susceptibility genes is to influence vulnerability to environmental pathogens

Moffitt, T. E., Caspi, A., Harrington, H., Milne, B. J., Melchior, M., Goldberg, D. et al. (2007). Generalized anxiety disorder and depression: childhood risk factors in a birth cohort followed to age 32. *Psychological Medicine, 37,* 441-452.

Notes: BACKGROUND: The close association between generalized anxiety disorder (GAD) and major depressive disorder (MDD) prompts questions about how to characterize them in future diagnostic systems. We tested whether risk factors for MDD and GAD are similar or different. METHOD: The representative 1972-73 Dunedin birth cohort of 1037 males and females was followed to age 32 with 96% retention. Adult GAD and MDD were diagnosed at ages 18, 21, 26, and 32 years, and juvenile anxiety/depression were also taken into account. Thirteen prospective risk measures indexed domains of family history, adverse family environment, childhood behavior, and adolescent self-esteem and personality traits. RESULTS: Co-morbid MDD+GAD was antedated by highly elevated risk factors broadly across all domains. MDD+GAD was further characterized by the earliest onset, most recurrence, and greatest use of mental health services and medication. Pure GAD had levels of risk factors similar to the elevated levels for co-morbid MDD+GAD; generally, pure MDD did not. Pure GAD had risks during childhood not shared by pure MDD, in domains of adverse family environment (low SES, somewhat more maltreatment) and childhood behavior (internalizing problems, conduct problems, somewhat more inhibited temperament). Pure MDD had risks not shared by pure GAD, in domains of family history (of depression) and personality (low positive emotionality). CONCLUSIONS: Specific antecedent risk factors for pure adult MDD versus GAD may suggest partly different etiological pathways. That GAD and co-morbid MDD+GAD share many risk markers suggests that the presence of GAD may signal a pathway toward relatively more severe internalizing disorder

Institute of Psychiatry, King's College London, London, UK. t.moffitt@iop.kcl.ac.uk

Moffitt, T. E., Harrington, H., Caspi, A., Kim-Cohen, J., Goldberg, D., Gregory, A. M. et al. (2007). Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Archives of General Psychiatry, 64,* 651-660.

Notes: CONTEXT: The close association between generalized anxiety disorder (GAD) and major depressive disorder (MDD) prompts questions about how to characterize this association in future diagnostic systems. Most information about GAD-MDD comorbidity comes from patient samples and retrospective surveys. OBJECTIVE: To revisit the sequential and cumulative comorbidity between GAD and MDD using data from a prospective longitudinal cohort. DESIGN: Prospective longitudinal cohort study. SETTING: New Zealand. PARTICIPANTS: The representative 1972-1973 Dunedin birth cohort of 1037 members was followed up to age 32 years with 96% retention. MAIN OUTCOME MEASURES: Research diagnoses of anxiety and depression were made at ages 11, 13, 15, 18, 21, 26, and 32 years. Mental health services were reported on a life history calendar. RESULTS: Sequentially, anxiety began before or concurrently in 37% of depression cases, but depression began before or concurrently in 32% of anxiety cases. Cumulatively, 72% of lifetime anxiety cases had a history of depression, but 48% of lifetime depression cases had anxiety. During adulthood, 12% of the cohort had comorbid GAD + MDD, of whom 66% had recurrent MDD, 47% had recurrent GAD, 64% reported using mental health services, 47% took psychiatric medication, 8% were hospitalized, and 11% attempted suicide. In this comorbid group, depression onset occurred first in one third of the participants, anxiety onset

occurred first in one third, and depression and anxiety onset began concurrently in one third. CONCLUSIONS: Challenging the prevailing notion that generalized anxiety usually precedes depression and eventually develops into depression, these findings show that the reverse pattern occurs almost as often. The GAD-MDD relation is strong, suggesting that the disorders could be classified in 1 category of distress disorders. Their developmental relation seems more symmetrical than heretofore presumed, suggesting that MDD is not necessarily primary over GAD in diagnostic hierarchy. This prospective study suggests that the lifetime prevalence of GAD and MDD may be underestimated by retrospective surveys and that comorbid GAD + MDD constitutes a greater mental health burden than previously thought
Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK. t.moffitt@iop.kcl.ac.uk

Koenen, K. C., Moffitt, T. E., Caspi, A., Gregory, A., Harrington, H., & Poulton, R. (2008). The developmental mental-disorder histories of adults with posttraumatic stress disorder: a prospective longitudinal birth cohort study. *Journal of Abnormal Psychology, 117,* 460-466.
Notes: Clinical and epidemiologic studies have established that posttraumatic stress disorder (PTSD) is highly comorbid with other mental disorders. However, such studies have largely relied on adults' retrospective reports to ascertain comorbidity. The authors examined the developmental mental health histories of adults with PTSD using data on mental disorders assessed across the first 3 decades of life among members of the longitudinal Dunedin Multidisciplinary Health and Development Study; 100% of those diagnosed with past-year PTSD and 93.5% of those with lifetime PTSD at age 26 had met criteria for another mental disorder between ages 11 and 21. Most other mental disorders had first onsets by age 15. Of new cases of PTSD arising between ages 26 and 32, 96% had a prior mental disorder and 77% had been diagnosed by age 15. These data suggest PTSD almost always develops in the context of other mental disorders. Research on the etiology of PTSD may benefit from taking lifetime developmental patterns of comorbidity into consideration. Juvenile mental-disorder histories may help indicate which individuals are most likely to develop PTSD in populations at high risk of trauma exposure
Department of Society Human Development and Health, Harvard School of Public Health, Boston, MA 02115, USA. kkoenen@hsph.harvard.edu

Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. E. (2010). Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry, 167,* 509-527.
Notes: Evidence of marked variability in response among people exposed to the same environmental risk implies that individual differences in genetic susceptibility might be at work. The study of such Gene-by-Environment (GxE) interactions has gained momentum. In this article, the authors review research about one of the most extensive areas of inquiry: variation in the promoter region of the serotonin transporter gene (SLC6A4; also known as 5-HTT) and its contribution to stress sensitivity. Research in this area has both advanced basic science and generated broader lessons for studying complex diseases and traits. The authors evaluate four lines of evidence about the 5-HTT stress-sensitivity hypothesis: 1) observational studies about the serotonin transporter linked polymorphic region (5-HTTLPR), stress sensitivity, and depression in humans; 2) experimental neuroscience studies about the 5-HTTLPR and biological phenotypes relevant to the human stress response; 3) studies of 5-HTT variation and stress sensitivity in nonhuman primates; and 4) studies of stress sensitivity and genetically engineered 5-HTT mutations in rodents. The authors then dispel some misconceptions and offer recommendations for GxE research. The authors discuss how GxE interaction hypotheses can be tested with large and small samples, how GxE research can be carried out before as well as after replicated gene discovery, the uses of GxE research as a tool for gene discovery, the importance of construct

validation in evaluating GxE research, and the contribution of GxE research to the public understanding of genetic science
Department of Psychology, and Institute for Genome Sciences and Policy, Duke University, Durham, NC 27708, USA. ac115@duke.edu

Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R. S., Murray, R. M. et al. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. *American Journal of Psychiatry, 167*, 160-169.
Notes: OBJECTIVE: Premorbid cognitive deficits in schizophrenia are well documented and have been interpreted as supporting a neurodevelopmental etiological model. The authors investigated the following three unresolved questions about premorbid cognitive deficits: What is their developmental course? Do all premorbid cognitive deficits follow the same course? Are premorbid cognitive deficits specific to schizophrenia or shared by other psychiatric disorders? METHOD: Participants were members of a representative cohort of 1,037 males and females born between 1972 and 1973 in Dunedin, New Zealand. Cohort members underwent follow-up evaluations at specific intervals from age 3 to 32 years, with a 96% retention rate. Cognitive development was analyzed and compared in children who later developed schizophrenia or recurrent depression as well as in healthy comparison subjects. RESULTS: Children who developed adult schizophrenia exhibited developmental deficits (i.e., static cognitive impairments that emerge early and remain stable) on tests indexing verbal and visual knowledge acquisition, reasoning, and conceptualization. In addition, these children exhibited developmental lags (i.e., growth that is slower relative to healthy comparison subjects) on tests indexing processing speed, attention, visual-spatial problem solving ability, and working memory. These two premorbid cognitive patterns were not observed in children who later developed recurrent depression. CONCLUSIONS: These findings suggest that the origins of schizophrenia include two interrelated developmental processes evident from childhood to early adolescence (ages 7-13 years). Children who will grow up to develop adult schizophrenia enter primary school struggling with verbal reasoning and lag further behind their peers in working memory, attention, and processing speed as they get older
Department of Psychology, Duke University, Durham, NC 27708, USA

Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H. et al. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences of the United States of America, 108*, 2693-2698.
Notes: Policy-makers are considering large-scale programs aimed at self-control to improve citizens' health and wealth and reduce crime. Experimental and economic studies suggest such programs could reap benefits. Yet, is self-control important for the health, wealth, and public safety of the population? Following a cohort of 1,000 children from birth to the age of 32 y, we show that childhood self-control predicts physical health, substance dependence, personal finances, and criminal offending outcomes, following a gradient of self-control. Effects of children's self-control could be disentangled from their intelligence and social class as well as from mistakes they made as adolescents. In another cohort of 500 sibling-pairs, the sibling with lower self-control had poorer outcomes, despite shared family background. Interventions addressing self-control might reduce a panoply of societal costs, save taxpayers money, and promote prosperity
Department of Psychology, Duke University, Durham, NC 27705, USA