plays a role in the causality of schizophrenia, that neurons are the major protagonist behind the manifestation of schizophrenia. The road ahead suggests that we, as a field, need to do some more trial blazing research that conceptualizes schizophrenia as not a "brain" disease and not as an "immune" disease, but as both.

Concurrent Symposia

16. DEVELOPMENTAL BIOMARKERS OF ENVIRONMENTAL ADVERSITY AND EPIGENETIC RISK FOR MAJOR PSYCHIATRIC DISORDERS: CLUES TO PATHOGENESIS

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Overall Abstract: Interaction between genetic risks and environmental adversities such as childhood trauma may underlie the etiology of psychiatric disorders. Mechanisms underpinning these interactions are poorly understood. This panel will present new data supporting a model in which epigenetic modifications and increased oxidative stress lead to altered trajectories and patients' stratification. Helen Fisher will introduce the field, how exposure to severe stress may have immediate as well as long-lasting damaging effects on learning, behaviour, and health, and has been implicated in the development of psychosis. She will present epigenome-wide analyses of poly-victimisation across childhood and adolescence, utilising data from the Environmental Risk (E-Risk) Longitudinal Twin Study, an epidemiological study of 2,232 children (1,116 twin pairs) born in 1994–1995 in England and Wales and followed to 18 years of age. Results related to associations with DNA methylation in peripheral blood at age 18 years, specific forms of victimization and candidate genes in the stress response will be discussed. Luis Alameda will show that childhood trauma (sexual, physical and emotional abuse) engages oxidative stress in a cohort of early psychosis patients (n=118). Patients with high peripheral oxidation status were found to have smaller hippocampal volumes and more severe clinical symptoms, while those with lower oxidation status evidenced a compensatory antioxidant regulation and better cognition. Linear discrimination analysis highlights blood oxidation status together with childhood trauma as markers for poorer psychopathological profile, allowing patients' stratification. Oussama Kebir will present the first longitudinal prospective study of genomic DNA methylation during psychotic transition in help-seeking young individuals (14 converters, 25 non converters). Alterations in gene promoters and pathways relevant for psychosis, including oxidative stress regulation, axon guidance and inflammatory pathways were observed. In particularly, antioxidant defense gene GTSTM5 is differentially methylated through time and two other genes of GST family might be differentially methylated after conversion to psychosis. These findings suggest that conversion to psychosis may depend on the specific control of oxidative metabolism and regulation between these genes. Darina Czamara will report on how cord blood methylation is affected by genetic and prenatal environment. Analysis on SNP (G) and environmental (E) effects as well as on GxE and G+E were performed using Illumina's Human Omni Express Exom as well as the 450k DNA methylation array in a cohort of 817 Finnish newborns. G and the combination of G and E explained DNA methylation best, environment alone was almost never the best predictor. Furthermore, epigenetic gestational age was associated with prenatal environment as well as with childhood psychiatric problem at age 3 indicating that it might be used as a potential biomarker.
Overall, these new results suggest new biomarkers of environmental and genetic adversity that are related to pathogenic mechanisms, including epigenetic, oxidative stress and structural abnormalities, in epidemiological studies and psychiatric disorders. These biomarkers offer the potential for individualized early intervention and preventive strategies.

16.1 EPIGENETIC SIGNATURES OF CHILDHOOD AND ADOLESCENT VICTIMISATION USING A GENETICALLY SENSITIVE LONGITUDINAL COHORT STUDY.

Helen Fisher*[,1], Sarah Marzi[2], Louise Arseneault[2], Chloe Wong[2], Radhika Kandaswamy[2], Terrie Moffitt[3], Susanna Roberts[2], Jonathan Mill[4], Avshalom Caspi[3]
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Background: Stress is a normal, adaptive response to stressors (e.g. events that make a person feel threatened or upset). However, healthy development can be derailed by excessive or prolonged exposure to stress especially during important developmental periods such as childhood and adolescence. Exposure to severe stress may have immediate as well as long-lasting damaging effects on learning, behaviour, and health, and has been implicated in the development of psychosis. One way these may occur is via changes to epigenetic processes (e.g. alterations in DNA methylation). Initial studies have shown that individuals exposed to severe psychosocial stress have different patterns of DNA methylation (epigenetic 'signatures') compared to individuals exposed to no/minimal stressful life events, but these studies are methodologically limited.
Methods: This paper describes our examination of the potential link between exposure to multiple forms of severe victimisation (poly-victimisation) during childhood adolescence and DNA methylation differences utilising data from the Environmental Risk (E-Risk) Longitudinal Twin Study, an epidemiological study of 2,232 children (1,116 twin pairs) born in 1994–1995 in England and Wales and followed to 18 years of age (with 93% retention). Multiple forms of victimisation were ascertained in childhood and adolescence (including physical, sexual and emotional abuse, neglect, exposure to intimate-partner violence, bullying, cyber- and crime victimization) by combining the best practices in survey research with comprehensive interview-based approaches. Whole blood samples were collected from participants at age 18, and the extracted DNA was used to quantify genome-wide patterns of DNA methylation.
Results: Epigenome-wide analyses of poly-victimisation across childhood and adolescence revealed several significant associations with DNA methylation in peripheral blood at age 18 years, but these were confounded by tobacco smoking and/or did not survive co-twin control tests. Secondary analyses of specific forms of victimisation revealed sparse associations with DNA methylation that did not replicate across different operationalisations of the same putative victimization experience. Hypothesis-driven analyses of six candidate genes in the stress response (NR3C1, FKBP5, BDNF, AVP, CRHR1, SLC6A4) did not reveal predicted associations with DNA methylation in probes annotated to these genes.
Discussion: Findings from this epidemiological analysis of the epigenetic effects of early-life stress do not support the hypothesis of robust changes in DNA methylation in victimised young people. It is possible that epigenetic epidemiology is not yet well matched to experimental, non-human models in uncovering the biological embedding of stress.

16.2 CHILDHOOD TRAUMA ENGAGES OXIDATIVE STRESS, HIPPOCAMPUS ALTERATIONS, AND POORER CLINICAL OUTCOME IN EARLY PSYCHOSIS PATIENTS

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Background: Exposure to childhood trauma (CT) is a global major public-health and social-welfare problem worldwide. CT increases the vulnerability to major psychiatric conditions including psychosis and is associated with poorer clinical outcome. CT affects the development of brain structures such as hippocampus, possibly through oxidative stress and neuroinflammation, two mechanisms linked to psychosis. We therefore hypothesized that there is an interplay between oxidative stress and CT in psychosis patients. We thus explored in early psychosis patients the relationships between CT and i) hippocampal volume, ii) antioxidant systems; and iii) clinical and cognitive outcomes.
Methods: We studied a cohort of 118 early psychosis patients, 36 were exposed to CT (experiences of physical, sexual, or emotional abuse/neglect before16 years old). In a subgroup of 48 patients (18 CT), hippocampal volume was determined by MRI. Antioxidant systems were quantified in blood for the whole cohort. Markers were: glutathione peroxidases (GPx) activity which appeared as a peripheral correlate of brain GSH levels (Xin &al, 2016); peroxiredoxine levels (Prx); Thioredoxine (Trx). Psychopathology (PANSS) and neuropsychology (MCCB) were assessed. The various groups were segregated by linear discriminant analysis.
Results: The previously observed decreased hippocampal volume in patients and association of small hippocampal volume with high blood GPx activity (reflecting high oxidative status) (Baumann &al, 2016) was due to the contribution of the traumatized group. Indeed, this association was absent in the no-trauma group, suggesting that the smaller hippocampus is linked to a redox dysregulation. To explore that point further, four groups were then formed, according to trauma and oxidative status: (i) noCT-lowGPx, (ii) noCT-highGPx, (iii) CT-lowGPx and (iv) CT-highGPx. Group CT-highGPx only had smaller hippocampi.
In CT patients, small hippocampal volume was associated with high GPx activity, while hippocampal volume was similar in CT patients with low GPx activity (CT-lowGPx) and in patients not exposed to CT. Interestingly, other antioxidant defense systems such as Trx and oxidized Prx levels correlated negatively with GPx in CT-lowGPx group, suggesting that the Trx/Prx system is able to compensate for changes/decreases in GPx activity. Moreover, CT-lowGPx patients perform better than the other patients on speed of processing, verbal memory and attention tests.
In contrast, hippocampal volume was decreased in CT patients with high GPx activity (CT-highGPx) compared with CT-lowGPx patients and patients not exposed to CT. There was no correlation between GPx and Trx/Prx system in this group. CT-highGPx patients had more severe positive, negative and disorganized symptoms than the other patients.
Discussion: We report that traumatized psychosis patients with high peripheral oxidation status (high GPx) had smaller hippocampal volumes and more severe clinical symptoms, while those with lower oxidation status (low GPx) had better cognition and appear to activate a compensatory antioxidant regulation by the Trx/Prx system.
These results suggest that, in early psychosis patients, traumatic experiences during childhood interact with different redox systems and have long term neuroanatomical and clinical impacts. Therefore, redox pathways such as GPx, Trx and Prx systems represent important translational biomarkers for patient selection and stratification in order to aid in diagnostics and treatment decision at early stages of the disease.

16.3 METHYLOMIC CHANGES OF OXIDATIVE STRESS REGULATION, AXON GUIDANCE AND INFLAMMATORY PATHWAYS DURING CONVERSION TO PSYCHOSIS

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Background: Epigenetics is hypothesized to mediate the interplay between genes and environment leading to the onset of psychosis
Methods: We performed a longitudinal prospective study of genomic DNA methylation during psychotic transition in help-seeking young individuals referred to a specialized outpatient unit for early detection of psychosis and enrolled in a 1-year follow-up (n=39). We used Infinium HumanMethylation450 BeadChip array after bisulfite conversion and analyzed longitudinal variations in methylation at 411 947 cytosine–phosphate–guanine (CpG) sites.
Results: We observed that conversion to psychosis was not associated with a global change in methylation and there was no individual CpG significantly associated with psychotic transition. By contrast, we found that conversion to psychosis was associated with specific methylation changes in genes involved in axon guidance, as well as genes of the IL-17 pathway and the glutathione-S-transferase family.
Discussion: Alterations in oxidative stress regulation, axon guidance and in inflammatory pathways could represent multiple theaters for the disruption in homeostasis that accompanies the emergence of full-blown psychosis.

16.4 EFFECT OF GENOTYPE AND EARLY ADVERSITY ENVIRONMENT ON DNA METHYLATION

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Background: Fetal or prenatal programming, i.e. the process in which environmental events during pregnancy are shaping and determining the development of the embryo, can be embedded by epigenetic changes including DNA methylation. Apart from environment, also the genome plays an important role and a variety of studies which identified meQTLs (methylation quantitative trait loci, i.e. SNPs which are associated with methylation levels) have been published.
Methods: Focusing on variably methylated regions (VMRs), we investigated if genotype (G), prenatal environment (E) or the combination of both (GxE, G+E) best explain cordblood DNA methylation in sample of 817 Finnish neonates. Furthermore, we used an epigenetic clock predictor to evaluate if accelerated or decelerated epigenetic age was associated with prenatal environment or with childhood psychiatric problems at age 3.
Results: We found that SNP genotype alone best explained methylation status in 44%, SNP x environment in 32% and SNP and prenatal environment in 24% of all VMRs. While functionally relevant meQTLs were located in close proximity to the specific CpG-site, functionally relevant SNPs involved in interaction models showed much broader peaks.
Concerning the epigenetic clock, lower gestational age was associated with maternal depression diagnosis and greater depressive symptoms throughout pregnancy. Epigenetic age deceleration was associated with pre-eclampsia. Furthermore, lower epigenetic gestational age was significantly associated with greater total and internalizing problems in boys.