Title Slide

Slide 1

Welcome to my Midway Evaluation. I hope to convey to you my interest in my PhD project which has held my attention these last two years -and for which I am still greatly enthused. I am working under the supervision of Stéphanie Le Hellard and Anne-Kristin Stavrum here in Bergen. I am also co-supervised by Tetyana Zayats at the Broad Institute and Ingrid Melle at NORMENT/UiO.

Slide 2

Plan for this talk

* Objectives
* Methods
* Status of project

Slide 3

The focus of my project is to identify epigenetic marks on the DNA that result from environmental contact or impact – within the context of psychiatric disorders such as schizophrenia, bipolar disorder and major depressive disorder.

1. Evaluate whether the association of SCZ versus controls on cell-type proportions is impacted by time-of-blood draw.
2. Identify differentially methylated regions (DMRs) associated with antipsychotic treatment for psychosis in SCZ, BPD, and MDD by investigating the common effects of antipsychotic polypharmacy and the specific effects of monotherapy with four AP drugs: Aripiprazole, Olanzapine, Quetiapine, and Risperidone.
3. Leverage results from aim 2 on Epigenome Wide Association Studies (EWAS) of psychosis and extract pharmacological treatment effects from disorder-specific differences in methylation.
4. Evaluate the role that developmental timing contributes to the etiology of SCZ and BPD.

Slide 4 - Show complex picture of epigenetic landscape

Definition of epigenetics

Epigenetic modifications such as DNAm, posttranslational histone modifications and non-coding RNA have an important role in the etiology of major psychosis (Gerscher et al., 2018)

We will be focusing on DNA methylation at cytosine positions – these are positions where a methyl group is covalently bound to a cytosine located immediately adjacent to a guanine. Methylation of cytosines is one area of epigenetics that has been actively studied for several reasons:

(Andrew E Teschendorff\* & Shijie C Zheng) Different functions – Jordana Bells’s paper

* DNAm is highly tissue and cell-type specific (ref) Jaffee? And plays an essential role in
* tissue differentiation (Reik)
* Key role in determining transcription factor binding and enhancer function during development (Ziller)
* DNAm is highly malleable, and is influenced by many environmental exposures, including diet, levels of *in utero*  nutrients and smoking (15-19)
* Over time the DNAm landscape changes as a function of age (20), cancer (20) and complex diseases (3)
* Severe mental disorders are complex and heterogeneous – and this aspect of development and the role of the environment is contributes to our understanding of these disorders.

Slide 4

First I´ll introduce SCZ

Slide 5

The classification of NDDs in *ICD‑11* does not diverge significantly from that in *DSM‑5* . Importantly, all NDDs in *DSM‑5* may include the specifier “associated with a known medical or genetic condition or environmental factor.”

Intro to Mental Disorders and their pharmacological treatment. What is known already about epigenetic findings of these drugs

Method

* EPIC
* Why we think blood is informative about what is happening in the brain

Aims –

To identify

Make a demographic table like Zong’s Table 1 but for SCZ, BPD and MDD

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Project 1 - Time of Blood Sampling

It is standard practice in EWA- studies to adjust for the heterogeneity of cell-type proportions. Cell-type proportions change during the course of the day and are influenced by many factors, including diet, exercise, smoking, ill-health and medication use. In this study, we looked at the association of schizophrenia versus healthy controls on cell-type proportions. It is well documented that patients with schizophrenia have higher neutrophil-to lymphocyte ratios than controls, suggestive of a low-grade inflammatory process. But recent studies report on the influence of time-of-day on DNA methylation levels. Here the natural process of methylation/demethylation in white blood cells is oscillating with circadian rhythms. Overlaps of these oscillating methylated cytosines with methylated sites associated with SCZ. The Function of the Circadian Clock Is Tissue Speciﬁc.Yeung and Feliz, 2018

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Project 1

Show the bimodal distribution

Slide 8

Project 1

Our findings

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Project 2

Common and Specific effects of antipsychotics on DNA methylation in Psychosis

Why we chose psychosis as a phenotype rather than diagnostic categories. Something about “trouble at the borders”. In this case, it is not about the treatment effect on the disorder, but the fact that the drug was prescribed for the symptoms of psychosis. And you can argue that there can be differences in the expression of the psychotic state, where individuals with scz may experience negative and frightful voices while individuals with psychosis in bipolar mania may experience voices of grandiosity. Tragically, in bipolar depression, voices in a psychotic state may seem clear and rational, and this is the danger in terms of suicide risk. In MDD, psychosis is …

Nevertheless,

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Project 2

To date there is evidence that antipsychotics ameliorate the symptoms of psychosis by … affecting neurotransmitter systems, like gaba and glutamate, as serotonin. Evidence from DNA methylation studies ….

Therefore we wish to see identify the common effects of antipsychotics in part one of the study, followed by the specific effects in part 2.

We can validate the risperidone.

Thefirst antipsychotic medication was introduced in the 1950s. Al-though this was thefirst medical treatment to reduce psychotic symp-toms, it was not until 20 years later that the underlying mechanism ofaction—blockade of the dopamine D2 receptor—was identified. Themost consistent and influential theory to date to explain the develop-ment of psychosis is that the disease is related to dopaminergic alter-ations. (Devi Treen)

Effects of AP on neutrotransmitter levels (Bojesen, 2020)

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Project 2

Slide 12

Project 3

Lithium (Li) is the cornerstone maintenance treatment for bipolar disorders (BD), but response rates are highly variable.

Effects of anticonvulsants on DNA methylation in Bipolar Disorder

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Project 3

Slide 14

Project 3

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End of public presentation

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Status of educational requirements

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Challenges - Technical

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Challenges – Scientific

Heterogeneity of disorders

Table

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