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.

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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 exposure – within the context of psychiatric disorders such as schizophrenia, bipolar disorder and major depressive disorder. These disorders are characterized by abnormalities of thought, behavior, cognition and mood. They are thought to have similar etiologies and affect over 2 % of the world´s population (Steardo, 2019, Yu, 2019)

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 (jordana bells paper?) (ref from Gurel)

Definition of epigenetics epigenetics refers to the patterns of gene transcription changes that occur without alterations in the DNA sequence (check Grealy). What is interesting is that epigenetic is a dynamic process and epigenetic modiﬁcations are reversible as opposed to genetic changes (Föcking et al., 2019; Wróblewski et al., 2019). DNAm is the first described and most studied epigenetic mechanism.

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.

DNAm is a highly dynamic process and it is thought that disruption of the methylation-demethylation balance is what contributes to pathogenesis of many neurological and psychiatric disorders (Greenberg and Bourc’his, 2019; Ovenden et al., 2018).

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CpG dinucleotides in which the methyl group is transferred, are not randomly distributed in the human genome and are predominantly concentrated in "CpG islands" located at gene promoters. Hypermethylation of CpG islands which are normally hypo or unmethylated leads to transcriptional inactivation of associated gene. The second type of DNA methylation (cytosine methylation; 5mC) is observed at the gene body and gene-body DNA methylation is associated with the activation of genes in contrast to the methylation observed in CpG islands (Greenberg and Bourc’his, 2019). In the past, DNA methylation was believed to be an irreversible and static epigenetic event related to gene repression, which could only be alleviated by DNA replication (Rasmussen and Helin, 2016). Today, however, it is known that DNA methylation is a highly dynamic process. Indeed, studies have shown that ten eleven translocation (TET) proteins (TET1, TET2, TET3) can modify 5mC and potentially erase DNA methylation.

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The initial studies investigating the relationship between DNA methylation alterations and major psychosis were focused on disease-related genes such as DRD2, MB−COMT, RELN, GAD1, and SOX10 (Grayson and Guidotti, 2013; Zhao et al., 2015). Among these genes, RELN and GAD1 have been most associated with abnormal methylation in major psychosis.

Among these genes, RELN and GAD1 have been most associated with abnormal methylation in major psychosis. The RELN gene expresses an extracellular matrix glycoprotein reelin, an important function in directing neurons and radial glial cells to their correct position in the developing brain (Lee and D’Arcangelo, 2016). GAD1 expresses the glutamic acid decarboxylase 67 (GAD67) which catalyzes the conversion of L-glutamate to the inhibitor neurotransmitter γ-amino butyric acid (GABA) (Magri et al., 2018).

Another gene shown to contribute to the etiopathology of the major psychosis of the methylation change pattern is the membrane encoding catechol-O methyl transferase (MB−COMT) that is responsible for the dissimilation of neurotransmitters such as dopamine and noradrenaline. The evidence that the MB−COMT gene promoter methylation is more common in the postmortem brains of patients with SZ and BD compared to controls shows that this may increase the risk of major psychosis (Abdolmaleky et al., 2006

But we are interested in the AP

BP patients using mood stabilizers have a higher 5mC level compared to patients using atypical antipsychotics (Burghardt et al., 2019).

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

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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

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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

Pai, et al, 2019, reported that significant hypomethylation of an enhancer in the insulin-like growth factor 2 (IGF2) gene was observed in major psychosis neurons. This enhancer targets the tyrosine hydroxylase (TH) gene which is responsible for dopamine synthesis (Ibid). Read what Sudderman found about adolescents – is this an indicator of a gene that points to development?

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Project 3

Peripheral blood DNAm of SZ and BPD compared to controls has shown that the promoter methylation of the serotonin receptor type-1 (HTR1A) gene is significantly increased (Carrard et al, 2011). Recently, Sugawara et al. suggested that gene hypermethylation of FAM63B and intergenic region on chromosome 16 may be a common epigenetic risk factor in the pathogenesis of these diseases (Sugawara et al., 2018).

Point out the difference between SCZ and BPD findings – are any associated with development.

Check Hannon papers – and Mill

Recently, another study on the blood and brain tissues of SZ patients emphasized that DDR1 hypermethylation in leukocytes and brain tissue could be associated with psychosis, physiological stress and inﬂammation (Garcia-Ruiz et al., 2020).

The most important questions likely to be addressed by new studies in this context are whether epigenetic changes can be used to diagnose subtypes of major psychosis

Promisingly, studies on abnormal gene expression in the postmortem brain and peripheral blood sample have revealed that epigenetic mechanisms may be viable tools for early diagnosis for some cases of SZ ve BD (Akbarian and Huang, 2009; Fachim et al., 2019; Liu et al., 2017). However, there is limited research data to examine the eﬀects of DNMT and HDAC inhibitors in reducing cognitive deﬁcits and the role of antipsychotic drugs on epigenetic changes in the brain (Abel and Zukin, 2008; Bowden, 2007; Deutsch et al., 2008; Dong et al., 2008).

Table

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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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