**Outline of ideas to report to Stephanie**

**In mammals the master circadian pacemaker resides in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The SCN is primarily responsible for the generation of circadian rhythms (Dibner et al., 2010).**

1. Evolution: Methyl cycle and circadian rhythms tightly coupled (Fustin et al., 2020)
2. Disruption of circadian rhythms in mental disorders –
3. Sleep disorders, evening profile – therapeutic drug txt helps with these symptoms
4. Circadian rhythms dysregulated in SCZ (Pritchett, 2012), BPD (Lall et al, 2012), and ADHD (Coogan et al., 2016)(Kooij & Bijlenga, 2013)
5. Circadian rhythms and AP
6. DNAm and AP

SCZ - Disrupted-in-schizophrenia 1 enhances the quality of circadian rhythm by stabilizing BMAL1 (DISC1 appeared to be not methylated at all.

1. Circadian rhythms and Lithium –

Lithium effects the circadian clock shifting patients towards morningness. (Ni Xu et al, 2021). Chronobiological effects of lithium might be an inherent component of its therapeutic effect. (Moreira, 2016)

DNAm and Lithium

1. ADHD-alterations in CR and strongly associated with sleep disturbances
2. Circadian rhythms and Methylphenidate

Diagram

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CORTISOL

The adrenal [glucocorticoid](https://www-sciencedirect-com.pva.uib.no/topics/pharmacology-toxicology-and-pharmaceutical-science/glucocorticoid) stress hormone [cortisol](https://www-sciencedirect-com.pva.uib.no/topics/pharmacology-toxicology-and-pharmaceutical-science/hydrocortisone) plays a key role in the hypothalamic–pituitary–adrenal (HPA) axis, but is also an important output of the master circadian pacemaker, and its secretion is regulated by output pathways of the SCN involving [arginine vasopressin](https://www-sciencedirect-com.pva.uib.no/topics/neuroscience/argipressin) and [corticotropin-releasing hormone](https://www-sciencedirect-com.pva.uib.no/topics/neuroscience/corticotropin-releasing-hormone) ([Keller et al., 2006](https://www-sciencedirect-com.pva.uib.no/science/article/pii/S0278584616300082" \l "bb0275)). Cortisol displays a circadian rhythm in its secretion consisting of an increase just before waking up in the morning, a peak within an hour of waking and then a decline over the rest of the 24-hour day, and environmental light exposure directly after awakening increases the amplitude of the morning peak ([Van Someren and Riemersma-Van Der Lek, 2007](https://www-sciencedirect-com.pva.uib.no/science/article/pii/S0278584616300082" \l "bb0535)). Cortisol is thought to be involved in the regulation of circadian rhythms in particular the entrainment of the peripheral oscillators ([Keller et al., 2006](https://www-sciencedirect-com.pva.uib.no/science/article/pii/S0278584616300082#bb0275), [Van Someren and Riemersma-Van Der Lek, 2007](https://www-sciencedirect-com.pva.uib.no/science/article/pii/S0278584616300082#bb0535)).

MELATONIN

Another important output of the circadian system is the [pineal hormone](https://www-sciencedirect-com.pva.uib.no/topics/pharmacology-toxicology-and-pharmaceutical-science/pineal-body-hormone)[melatonin](https://www-sciencedirect-com.pva.uib.no/topics/neuroscience/melatonin), which is synthesised in the [pinealocytes](https://www-sciencedirect-com.pva.uib.no/topics/neuroscience/pinealocyte) from the precursor [tryptophan](https://www-sciencedirect-com.pva.uib.no/topics/neuroscience/tryptophan). The secretion of melatonin exhibits a clear circadian rhythm, with peak plasma levels usually between 02:00 and 03:00 am and sympathetic input from the [cervical ganglion](https://www-sciencedirect-com.pva.uib.no/topics/neuroscience/cervical-ganglia) under influence from the SCN via GABAergic mechanisms is thought to regulate pineal melatonin synthesis ([Arendt, 2005a](https://www-sciencedirect-com.pva.uib.no/science/article/pii/S0278584616300082" \l "bb0035)). Furthermore input from the master pacemaker is essential for the synchronisation of the circadian rhythm of melatonin to the light–dark cycle and the persistence of the rhythm ([Arendt, 2005b](https://www-sciencedirect-com.pva.uib.no/science/article/pii/S0278584616300082" \l "bb0040)). Melatonin also plays a role in mediating various circadian activities throughout the body including the regulation of reproductive capacity, hormone secretion, immune responsiveness, daily rhythms of activity and entrainment of [sleep/wake cycles](https://www-sciencedirect-com.pva.uib.no/topics/neuroscience/sleep-waking-cycle). The circadian rhythm of melatonin synthesis is closely linked to the sleep rhythm as demonstrated by the nocturnal onset of melatonin secretion, which usually occurs 2 h in advance of the individual's habitual bedtime, and correlates with evening sleepiness and the sleep promoting effect of exogenous melatonin ([Arendt, 2005b](https://www-sciencedirect-com.pva.uib.no/science/article/pii/S0278584616300082#bb0040)). Melatonin is believed to have a strong entraining influence on the master circadian clock through its ability to directly feed back to the SCN ([Pevet and Challet, 2011](https://www-sciencedirect-com.pva.uib.no/science/article/pii/S0278584616300082" \l "bb0430)).

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