Project Notes:

Project Title: Using a Machine Learning Model to Prevent Misdiagnosis of Narcolepsy
Name: Daniel Shi

Contents:

Knowledge Gaps:

This list provides a brief overview of the major knowledge gaps for this project, how they were resolved and where to find the information.

Knowledge Gap	Resolved By	Information is located	Date resolved
How is melatonin administered and what are the recommended/optimal doses?	Finding an article that explained different ways to use melatonin and described what it may be used to treat	Article 6	9/3/2023
Can differences in certain circadian parameters lead to increased risk for different conditions and diseases?	Read an article about evening chronotype being linked to increased risk for stomach cancers	Article 7	9/4/2023
How do you determine if someone is an “early bird” or “night owl” in an accurate way?	Found the methodology to determine chronotype in a journal article	Article 8	9/13/2023
What are the most reliable ways to accurately gauge subjective sleep quality of a person?	Read an article that used subjective sleep surveys as part of their procedure, talked to Peter who used the PSQI and used his website (Stem I)	Article 8 https://users.wpi.edu/~pliang/	8/27/2023
What are devices/methods that can be used to measure different stages of sleep?	Read an article that brought up different ways to track sleep	Article 8	9/13/2023
Is there a link between sleep and neurodegenerative disorders?	Read an article that linked a certain stage of sleep to increased levels of a biomarker of neurodegenerative diseases	Article 13	10/12/2023

Literature Search Parameters:

These searches were performed between 07/12/2023 and XX/XX/XXXX.
List of keywords and databases used during this project.

Database/search engine	Keywords	Summary of search
Quanta	Biology, morphology, genetics	Found articles regarding the science behind certain morphological mechanisms in different animals, some including how they evolved
Live Science	Neurons, brain	Found a variety of articles regarding studies about neurons, neurotransmitters, neurological diseases, and new discoveries in the field of neuroscience
Live Science	Dreams, REM, sleep, phases	Found articles related to the different phases of sleep, particularly REM and its involvement in dreams; also found some articles about sleep and sleep phases in animals
Science	Behavior, model organism	Found articles about studies on different behaviors exhibited in various model organisms
Science	Sleep, genes, insomnia	Found some journal articles about genes and gene mapping for variations and disorders in sleep
Science Direct	Melatonin, sleep, dosage, signals	Found many articles about the use of melatonin in clinical practices in addition to information about dosages and ways to administer it
Google Scholar	Chronotype	Found various articles about studies regarding the genetics of chronotype and its effect on other conditions

Google Scholar	Chronotype AND sleep quality	Found article “Effect of Chronotype on Sleep Quality in a Laboratory Setting”
Nature	Multiple sclerosis	Found various articles about the misdiagnosis
Nature	Multiple sclerosis AND EBV	Found many articles that explained the link of EBV and MS
Nature	Multiple sclerosis AND AI	Found articles regarding the use of AI in diagnosing MS and other autoimmune and neuroinflammatory diseases

Tags:

Tag Name	
#background	#introduction
#methodology	#technology
#sleep	#ms
#effects	#disorders

Article #1: Biologists Home In on Turing Patterns - 7/12/2023

Source Title	Biologists Home In on Turing Patterns
Source citation (APA Format)	Ouellette, J. (2013). Biologists Home In on Turing Patterns. *Quanta Magazine.* https://www.quantamagazine.org/biologists-home-in-on-turing-patterns-20130325/
Original URL	https://www.quantamagazine.org/biologists-home-in-on-turing-patterns-20130325/
Source type	Website
Keywords	Genetics, biology, patterns
#Tags	#introduction
Summary of key points + notes (include methodology)	Proposed by Alan Turing, Turing patterns suggested that two morphogens that diffused at different rates. With one being an activator and one being an inhibitor, they could explain the natural patterns on animals; it is just one of the factors that can determine the workings of a biological system. - Called “Turing mechanisms” - His idea has been mostly theoretical up until recently - Challenging to identify specific molecules involved - May not account for scaling - Analogy of grasshoppers in a dry field and setting fire - grasshoppers would sweat and dampen some areas to leave uncharred
Research Question/Problem/ Need	How do the patterns that Alan Turing suggested help to determine morphological patterns found in nature?
Important Figures	n/a
VOCAB: (w/definition)	Morphogens: chemicals that diffuse at different rates, including both an activator and an inhibitor to express unique patterns.
Cited references to follow up on	https://www.science.org/doi/10.1126/science.1226804 for a more specific example
Follow up Questions	What are other mechanisms that interact with Turing mechanisms to determine

	the morphology of something and how do they work? I.e. the one for controlling the scaling. How would changing the levels/efficiency of the activator or inhibitor change the visual outcome of the patterns?

Article #2: Scientist Find a Strange New Cell in Human Brains: The ‘RoseHip Neuron’ - 7/19/2023

Source Title	Scientists Find a Strange New Cell in Human Brains: The 'Rosehip Neuron'
Source citation (APA Format)	Saplakoglu, Y. (2018). Scientists find a strange new cell in human brains: the “Rosehip neuron.” *LiveScience.* https://www.livescience.com/63441-new-brain-cell-rosehip-neuron.html
Original URL	https://www.livescience.com/63441-new-brain-cell-rosehip-neuron.html
Source type	Website
Keywords	Brain, neuron
#Tags	#introduction
Summary of key points + notes (include methodology)	Scientists discovered a new type of neuron and named it the rosehip neuron according to its appearance. It acts as an inhibitory neuron, so it restrains the activity of other excitatory neurons. The rosehip neuron is not found in mice. - Dendrites are compact with many branch points and large bulbs - lead to naming - Rare in the brain - Difficult to obtain brain tissue for study - could explain why it hasn’t been found before - Exact role still not understood despite being inhibitory - Highlights importance of using human brain tissue for research, as it isn’t present in mice - Since human brain tissue is hard to obtain and the neuron isn’t present in mice, it may be hard to further research about this neuron
Research Question/Problem/ Need	How does the discovery of the rosehip neuron lead to new possibilities in thinking about how certain functions are carried out within the brain?
Important Figures	n/a
VOCAB: (w/definition)	Neocortex: the most recently evolved part of the cortex, involved in sight and hearing Pyramidal cells: a type of excitatory neuron

Cited references to follow up on	https://www.livescience.com/62971-daily-aspirin-alzheimers-disease.html to study some similarities between mice and human brains
Follow up Questions	Why might it not be found in mice, and what does this suggest? Have any new discoveries about this neuron been made since the time of the article? What other types of neurons have a similar function to the rosehip neuron?

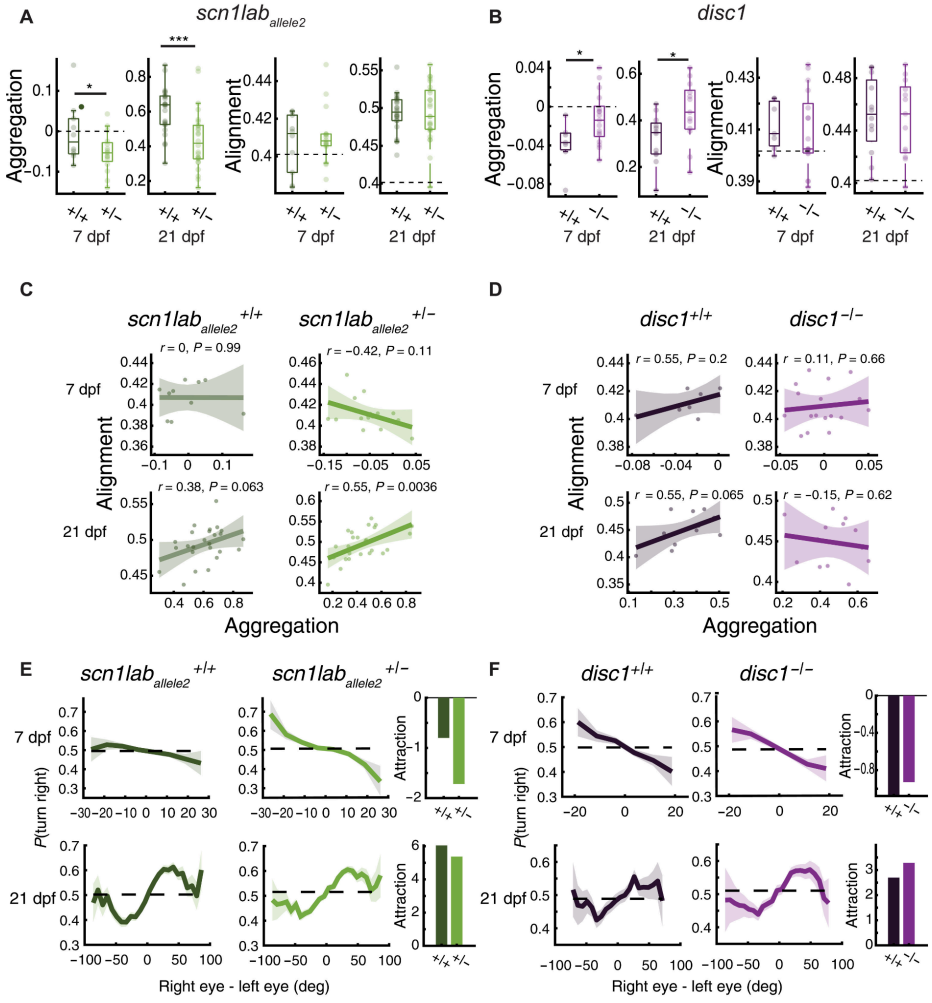
Article #3: Sweet dreams, spidey: Arachnids experience REM sleep, and may even dream - 7/30/2023

Source Title	Sweet dreams, spidey: Arachnids experience REM sleep, and may even dream
Source citation (APA Format)	Nalewicki, J. (2022, August 12). Sweet dreams, spidey: Arachnids experience REM sleep, and may even dream. *livescience.com*. https://www.livescience.com/jumping-spider-rem-sleep-dream
Original URL	https://www.livescience.com/jumping-spider-rem-sleep-dream
Source type	Website
Keywords	Dreams, REM, sleep
#Tags	#introduction
Summary of key points + notes (include methodology)	By examining the jumping spiders while they slept, scientists noticed twitching and retinal movements in the spiders. These movements indicate a REM phase of sleep, and point to the possibility of dreaming in spiders. - The sleep patterns of invertebrates has not been as studied as that of mammals or birds - Research suggests that jumping spiders exhibit REM-like phases of sleep - Noticed eye-tube movements during sleep in addition to leg curling and twitching - Can suggest dreams in invertebrates - However, too early to say for sure - Brain scans can help identify this REM-like state and provide further evidence - There are challenges with this, since their brains are small and easily crushed - Can show the functions and patterns of sleep in different species
Research Question/Problem/ Need	How do sleep patterns and movements in spiders lead to the possibility of dreams?
Important Figures	n/a
VOCAB: (w/definition)	REM: rapid-eye-movement, the phase in sleep at which dreaming can occur

Cited references to follow up on	https://www.pnas.org/doi/10.1073/pnas.2204754119 for a journal report
Follow up Questions	Can further studying of the possibility of dreams in non-mammals result in more connections to our dreams?

Article #4: Collective behavior emerges from genetically controlled simple behavior behavioral motifs in zebrafish - 8/20/2023

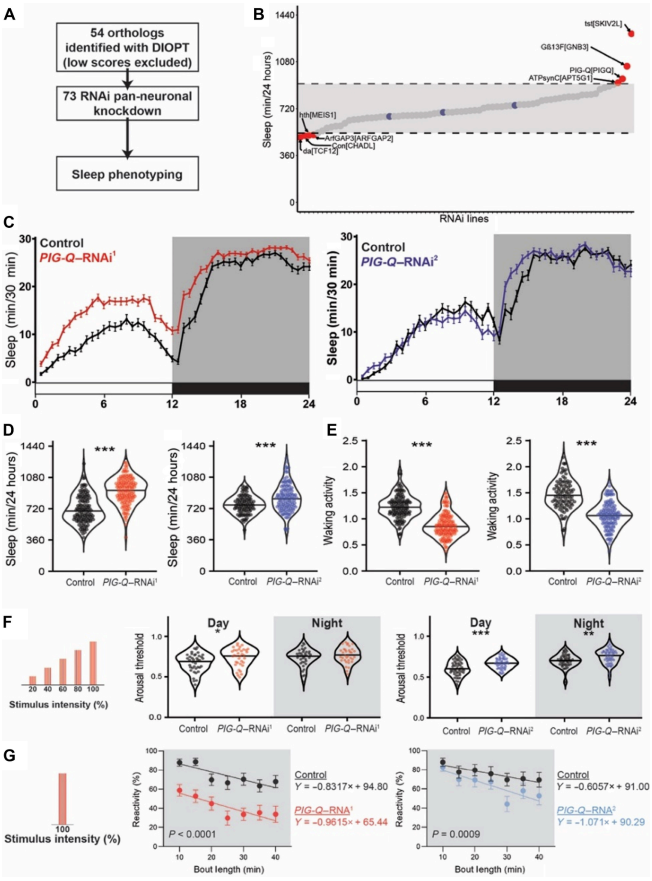
Source Title	Collective behavior emerges from genetically controlled simple behavior behavioral motifs in zebrafish
Source citation (APA Format)	Harpaz, R., Aspiras, A. C., Chambule, S., Tseng, S., Bind, M.-A., Engert, F., Fishman, M. C., & Bahl, A. (2021). Collective behavior emerges from genetically controlled simple behavioral motifs in zebrafish. *Science Advances*, *7*(41) https://doi.org/10.1126/sciadv.abi7460
Original URL	https://www.science.org/doi/10.1126/sciadv.abi7460
Source type	Journal
Keywords	Genetics, behavior
#Tags	#introduction
Summary of key points + notes (include methodology)	To study the behavior of zebrafish as they aged, scientists observed how they interacted at different intervals after they were born. Larvae at seven days post-fertilization (dpf) tend to repel each other, and as they get older, they start to aggregate together. Mutations of different genes associated with Dravet's syndrome and schizophrenia can cause fish to swim further apart and more close to each other respectively. - Collective moments of animals are adaptive so that they can react to their situation and surrounding (like predators(- Zebrafish need to assess movements of their peers to achieve successful shoaling and schooling - Young larvae are repelled by high visual clutter - Reverses and they become attracted as they grow - Can predict behaviors that emerge in groups of fish

	- Mutations associated with disorders like schizophrenia were also tested to see how they could affect the behavior of groups - Used drift-diffusion model (DDM) to model and predict behavior - Also focus on alignment reflex of fish in response to motion cues - Dravet's syndrome + autism associated gene mutations caused fish to move more apart - Schizophrenia associated genes mutations cause fish to move more closely - Alignment gets stronger as fish age - better reflex to motion cues - Ventral hindbrain is involved in response for both visual clutter and motion - Could help in understanding more complex disorders - study simplifies them down into things like reflexive patterns
Research Question/Problem/ Need	How does the genetic makeup of zebrafish affect the patterns of collective behavior like schooling and shoaling?
Important Figures	Fig 2 for measuring aggregation and alignment at different dpf  Higher aggregation 21 dpf for A and B

	Downward trend for C +/- group at 7dpf Similar attraction 7 and 21 dpf for both groups as shown in F
VOCAB: (w/definition)	Dpf: days-post-fertilization Shoaling: where individuals swim in proximity Schooling: where individuals of the group swim in the same direction Visuomotor - relating to movement coordination and visual perception from the brain
Cited references to follow up on	C. J. Torney, A. Berdahl, I. D. Couzin, Signalling and the evolution of cooperative foraging in dynamic environments. *PLoS Comput. Biol.* **7**, e1002194 (2011). C. C. Ioannou, L. J. Morrell, G. D. Ruxton, J. Krause, D. I. Bolnick, M. A. Geber, The effect of prey density on predators: Conspicuousness and attack success are sensitive to spatial scale. *Am. Nat.* **173**, 499–506 (2009). To learn more about signaling and group behaviors
Follow up Questions	How do the fish know that they will be swimming longer distances as they get older? How are fish able to distinguish between retinal clutter and determine whether it's one of them or something else completely? How would factors like pollution and acidification affect the genetic makeup and possibly behavior?

Article #5: Variant-to-gene mapping followed by cross-species genetic screening identifies GPI-anchor biosynthesis as a regulator of sleep - 8/20/2023

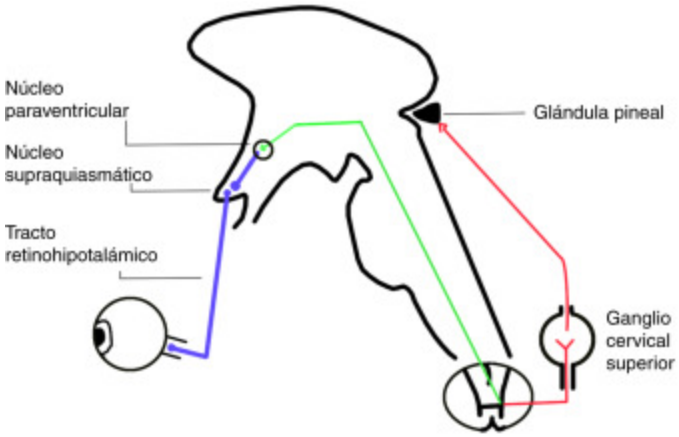
Source Title	Variant-to-gene mapping followed by cross-species genetic screening identifies GPI-anchor biosynthesis as a regulator of sleep
Source citation (APA Format)	Palermo, J., Chesi, A., Zimmerman, A., Sonti, S., Pahl, M. C., Lasconi, C., Brown, E. B., Pippin, J. A., Wells, A. D., Doldur-Balli, F., Mazzotti, D. R., Pack, A. I., Gehrman, P. R., Grant, S. F. A., & Keene, A. C. (2023). Variant-to-gene mapping followed by cross-species genetic screening identifies GPI-anchor biosynthesis as a regulator of sleep. *Science Advances*, *9*(1) https://doi.org/10.1126/sciadv.abq0844
Original URL	https://www.science.org/doi/10.1126/sciadv.abq0844
Source type	Journal
Keywords	Genetics, protein, mapping, biosynthesis
#Tags	#introduction #sleep
Summary of key points + notes (include methodology)	Scientists have studied organisms like roundworms, fruit flies, zebrafish, and mice to identify genetic sleep regulators. The PIG family proteins were found to be regulators, namely the PIG-Q gene, which is involved in GPI-anchor biosynthesis. Located on the cell membrane and having a multitude of functions, the synthesis of GPI-anchored proteins can explain variation in sleep. - Many physiologic processes, if not all, are affected by sleep - Previous GWAS have identified gene loci associated with sleep traits - Mapped genetic variants associated with sleep - Looking for candidate genes involved with sleep regulation - Found 88 possible candidates - Used RNAI in fruit flies and zebrafish to identify genes that affect sleep quality and duration - Identified PIG-Q gene through knockdown - led to increased sleep duration and depth in both model organisms

	- The role of PIG-Q in sleep regulation is consistent throughout different species - Genetic variations in genes like PIG-Q may lead to differences in sleep duration - Can further be used in research for psychiatric disorders due to link between mental health and sleep - Further research can also include specific variants and their effects
Research Question/Problem/ Need	How can gene mapping lead to identifying proteins as sleep regulators?
Important Figures	Figure 2 for sleep duration + depth, PIG-Q gene  Figure D shows that knockdown of the PIG-Q gene increases total time in sleep, while figure E shows that knockdown of the same gene decreases waking activity Figure G shows that the knockdown reduces nighttime reactivity
VOCAB: (w/definition)	Knockdown: expression of gene is reduced GWAS - genome-wide association study, research approach used to identify certain parts of genes that could lead to disease or risk for disease Dysregulation - abnormality/impairment in a process SNP - specific genetic variant

	RNAI - RNA interference - mechanism that turns a gene off by using its own DNA sequence
Cited references to follow up on	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1978335/ Behavioral and physiological consequences of sleep restriction https://www.nature.com/articles/s41467-018-08259-7 Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. More insight on genes and the role they play in circadian rhythms
Follow up Questions	How would a mutation in PIG-Q affect someone's sleep? What other factors (age, pre existing conditions, etc.) can affect PIG and GPI-anchor biosynthesis? How could differences in zebrafish and fruit flies affect the outcome of identifying sleep regulators?

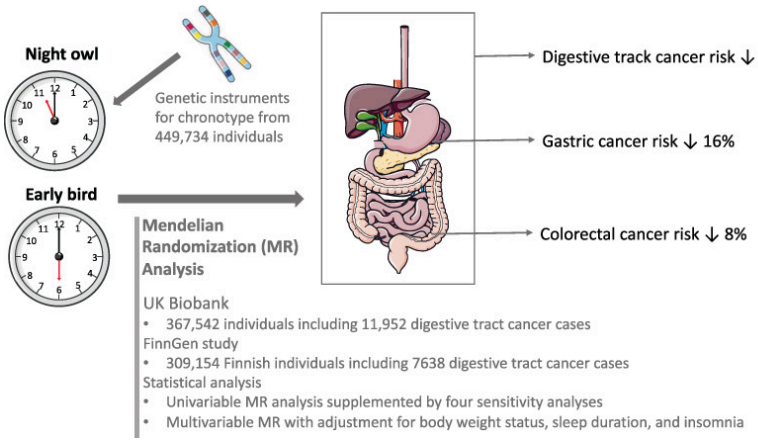
Article #6 Notes: Melatonin in sleep disorders - 9/3/2023

Source Title	Melatonin in sleep disorders
Source citation (APA Format)	Poza, J. J., Pujol, M., Ortega-Albás, J. J., & Romero, O. (2022). Melatonin in sleep disorders. *Neurología (English Edition)*, *37*(7), 575–585. https://doi.org/10.1016/j.nrleng.2018.08.004
Original URL	https://www.sciencedirect.com/science/article/pii/S217358082030184X?via%3Dihub
Source type	Review article
Keywords	Melatonin, Circadian rhythm, Primary insomnia, Comorbid insomnia, Circadian rhythm sleep disorders
#Tags	#introduction, #background #sleep
Summary of key points + notes (include methodology)	Melatonin, which is involved in regulating the sleep-wake cycle, is often used as an over-the-counter pharmacological treatment for sleep disorders like insomnia, after cognitive behavioral therapy. Though the body naturally secretes it, melatonin production peaks before puberty and declines as one gets older. - Melatonin is made in many organs/tissues - pineal gland, retina, GI tract - Secretion and synthesis regulated by SCN - Synthesis occurs in response to darkness and his inhibited by light - Secretion follows circadian rhythm - Melatonin production declines throughout puberty and further aging - SCN coordinates circadian rhythms - Melatonin has antioxidant and anti-inflammatory effects, could potentially inhibit tumor growth, and can enhance the immune system as an immunostimulator Pharmacokinetics - taking melatonin - Melatonin reaches peak concentration in 40 minutes after taking it, which is delayed by food intake - Over 90% of it is metabolized in the liver - Metabolized with half-life of 45-65 minutes with immediate-released - Half life of 3.5-4 hours with prolonged-released - Binds to two main receptors, MT1 and MT2 - There is an MT3 but function is not yet clear - MT1 linked to hypnotic effects - MT2 associated with circadian system regulation

	- Can be used to treat sleep disorders like insomnia - Low doses preferred in children and adolescents - CBT takes priority in treatment in adults, but melatonin can also be useful - Prolonged-release can mimic the gradual secretion of melatonin, which can help in regulating and maintaining sleep - Effectiveness and dosage can still vary among individuals
Research Question/Problem/ Need	How is melatonin used to treat sleep-related disorders like insomnia and circadian rhythm disorders in different age groups?
Important Figures	 This figure shows how the pineal gland, and subsequently production of melatonin in the body is regulated by light stimuli (in Spanish).
VOCAB: (w/definition)	Suprachiasmatic nucleus (SCN) - regulates melatonin synthesis and secretion Ganglion cells - neurons, relay information from the retina to the brain GABA - an inhibitory neurotransmitter in the brain Metabotropic receptors - transmitter acts indirectly by triggering a chemical reaction/series of reactions for a slower mode of action, MT1 and MT2 are metabotropic receptors Cognitive behavioral therapy (CBT) - treatment for mental health conditions, which aims to change behaviors Somnolence - a strong desire to fall asleep
Cited references to follow up on	https://www.tandfonline.com/doi/epdf/10.1080/01616412.2017.1315864?src=getftr A review of sleep disorders and melatonin https://faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fj.10-154450 Melatonin signaling and cell protection function
Follow up Questions	What is the most suitable dose range for melatonin? Melatonin binds to three receptors, of which MT1 and MT2 have a theorized function; what is the function of MT3? What scenarios might prolonged-release melatonin be better than immediate-release and vice versa?

Article #7: Morning chronotype and digestive tract cancers: Mendelian randomization study - 9/4/2023

Source Title	Morning chronotype and digestive tract cancers: Mendelian randomization study.
Source citation (APA Format)	Yuan, S., Mason, A. M., Titova, O. E., Vithayathil, M., Kar, S., Chen, J., Li, X., Burgess, S., & Larsson, S. C. (2023). Morning chronotype and digestive tract cancers: Mendelian randomization study. *International Journal of Cancer*, *152*(4), 697–704. https://doi.org/10.1002/ijc.34284
Original URL	https://onlinelibrary.wiley.com/doi/10.1002/ijc.34284
Source type	Journal article
Keywords	Chronotype, digestive tract, genetics
#Tags	#background #sleep
Summary of key points + notes (include methodology)	To look for a possible connection between chronotype and digestive tract cancers, scientists conducted a Mendelian randomization study, observing over 300 variants of genes associated with chronotype. They found that the morning chronotype was less susceptible to up to six digestive tract cancers. - Digestive tract cancers cause 3.4 million premature deaths in the US in 2018 - Previous risk factors include obesity, smoking, alcohol - Evening chronotype - Investigated chronotype and its effect on cancers - Esophageal, stomach, liver, biliary tract, pancreatic, colorectal - Obtained from UK Biobank - Accounted for other factors that could affect the study like sleep duration, insomnia, BMI, etc. - The association between morning chronotype and reduced risk for these cancers remained constant - Influence of gut micro bacteria, DNA methylation, metabolic factors - Further exploration is needed for more details about these influences - Essentially, “morning people” have lower risk - Provides insight into risk factors for cancer

Research Question/Problem/ Need	Can a person's chronotype affect their risk for developing digestive tract cancers?
Important Figures	 Graphical abstract showing chronotypes and the risk of different cancers
VOCAB: (w/definition)	MR study - Mendelian randomization - uses measured variation in genes to examine causes and effects of certain characteristics in individuals Chronotype - the body's preferences for sleep and wake times; i.e. whether you're a night owl or an early bird Colorectal - relating to the colon/rectum
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/35955020/ chronotype, physical activity, and sedentary behavior (which can increase risk for cancer) https://pubmed.ncbi.nlm.nih.gov/34695305/ gut microbiota and its relation to chronotypes
Follow up Questions	What do the gut bacteria *Alistipes* and *Lachnospira* do, and how could they play a role in the development of GI tract cancers? Are there any advantages of evening-type chronotypes?

Article #8: Effect of Chronotype on Sleep Quality in a Laboratory Setting - 9/13/2023

Source Title	Effect of Chronotype on Sleep Quality in a Laboratory Setting
Source citation (APA Format)	Harfmann, B. D., Swalve, N., Mitrzyk, J., & Montoye, A. H. K. (2020). Effect of Chronotype on Sleep Quality in a Laboratory Setting. *International Journal of Exercise Science*, *13*(3), 1283–1294. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7523902/
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7523902/
Source type	Journal article
Keywords	Circadian rhythms, social jet lag, electroencephalography
#Tags	#background #sleep
Summary of key points + notes (include methodology)	Because most studies on sleep quality have only been conducted through surveys, scientists studied the possible impact of circadian parameters like chronotype on sleep quality in a laboratory setting. They used the MCTQ to determine chronotype, an EEG to track certain parts of sleep and then had patients report about their sleep. Differences were found in certain parts of sleep like sleep-onset latency, number of awakenings, and percentage of REM sleep between those with different chronotypes. Additionally, those who had more social jet lag tended to be happier with their sleep. The findings of this experiment show that circadian parameters can play a role in predicting sleep quality. - Circadian parameters including chronotype can influence sleep quality - Lab setting allows for EEG and qualitative data instead of only using surveys - Participants completed surveys for chronotype, social jet lag, and sleep quality - More social jet lag = more satisfied with sleep, probably because they're so sleep deprived - Over two-thirds of the population experience 1+ hour of SJL - Munich Chronotype Questionnaire for determine chronotype - there are seven of them, simplified down to three (early, normal, late) due to a small sample size

	- Evening chronotype - greater nightmare prevalence - does that play a role in sleep quality? - Most common chronotype was slight late - Participants allowed to do different activities before bed, as well as the optional use of an alarm clock - possible factors that can affect the data? - Less than one hour of sleep discrepancy or social jet lag -> low SD/SJL - More than one hour of sleep discrepancy or social jet lag -> high SD/SJL - Later chronotypes - higher SOL (harder time falling asleep), higher WASO (more awakenings) and greater percent of sleep in REM (less deep sleep) - Less sleep discrepancy - lower sleep duration - Circadian parameters can be predictors of sleep quality - Limitations: small sample size, narrow age range (early 18-31 y/o), done over one night of sleep, no familiarization with sleep lab, lack of access to polysomnography (PSG, considered gold standard - heart, eye, muscle movement)
Research Question/Problem/ Need	How can a person's chronotype affect the social jet lag and the sleep quality that people experience?
Important Figures	Table 5 shows the chronotype as well as sleep discrepancy and social jet lag.
VOCAB: (w/definition)	Social jet lag - the discrepancy between our internal clock and when we actually sleep/wake up due to society (school, work, etc) Electroencephalography (EEG) - involves attaching probes to someone's head and measuring their brain's electrical activity Sleep onset latency (SOL) - the time it takes for a person to fall asleep; normally 10-20 minutes Wake after sleep onset (WASO) - the amount of time someone is awake after they've initially fallen asleep Endogenous - having an internal cause Exogenous - external factors; exogenous factors like work shifts can affect endogenous rhythms that people may have when it comes to sleep Sleep discrepancy - the difference between what the patient reports about their SOL and WASO compared to what the objective means of measuring report
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/27339174/ genetic + environmental influences in teens that affect sleep https://pubmed.ncbi.nlm.nih.gov/8621064/ about how lack of sleep leads to reduced immune responses, not super related but I found it there and it could make for some interesting project ideas https://pubmed.ncbi.nlm.nih.gov/23606613/ chronotype and more about the social jet lag - lives of shift-workers who have to adhere to a certain schedule no matter their circadian preferences https://pubmed.ncbi.nlm.nih.gov/23606612/ more about the MCTQ for determine chronotypes
Follow up Questions	What kinds of activities were done before sleep, and could this have affected

	quality? What about the individual sleep cycles between deep sleep and REM? Were those tracked? As they only measured sleep for one night, how could taking multiple nights affect the data? How could the results of the study be different for an older or younger group? (like ages 65+ or 18-) As participants were allowed to sleep with or without an alarm clock, how might the alarm clock have played a role in social jet lag for certain individuals?

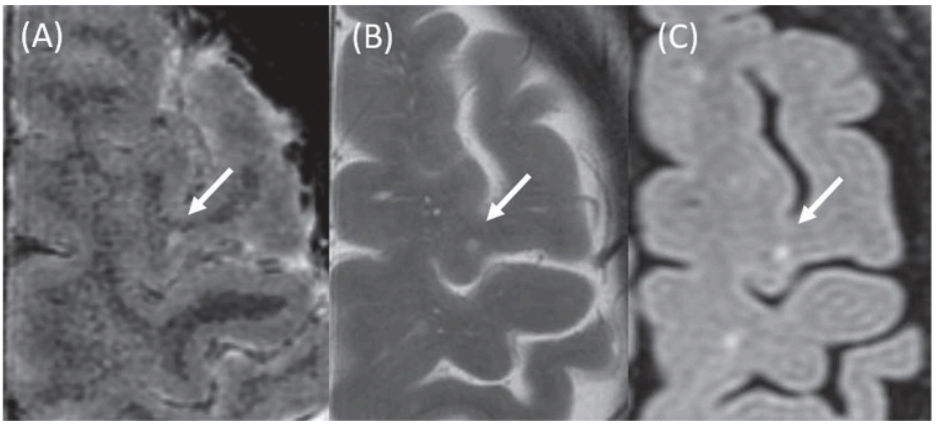
Article #9: Misdiagnosis of multiple sclerosis - 9/17/2023

Source Title	Misdiagnosis of multiple sclerosis
Source citation (APA Format)	Solomon, A. J., Naismith, R. T., & Cross, A. H. (2019). Misdiagnosis of multiple sclerosis. *Neurology*, *92*(1), 26–33. https://doi.org/10.1212/WNL.0000000000006583
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6336166/
Source type	Review article (for background knowledge)
Keywords	Multiple sclerosis, diagnosis, demyelination
#Tags	#background #ms
Summary of key points + notes (include methodology)	Multiple sclerosis (MS) is a disease that affects over 900,000 people in the United States, yet the cause is still unknown and misdiagnoses are common. The McDonald Criteria for the diagnosis of MS is widely used and has been changed throughout the years in an attempt to increase the accuracy of diagnoses. Especially in patients with conditions that don't fit the typical expectations for signs and symptoms of MS, it's extremely hard to apply the McDonald Criteria. Misinterpretations of scans like MRIs can also lead to misdiagnosis. - Misdiagnosis of MS is a severe issue in clinical settings - Unnecessary therapies due to misdiagnosis - McDonald Criteria used to help diagnose - Objective neurologic findings like MRIs are necessary - can't rely on prior history alone - Misinterpretation of MRI findings can lead to misdiagnosis - Lesion size, location, and morphology are important - Importance of cautiously applying McDonald Criteria to diagnose patients - CSF-restricted OCBs can help to diagnose - However, many of these bands are not specific to just MS, despite it being a characteristic of the disease - Challenges with diagnosing PPMS - McDonald Criteria is mostly for patients with typical symptoms, so other recommendations are used for diagnosis of patients with atypical symptoms - This is all based off of 2017 McDonald Criteria
Research Question/Problem/	What are factors that play into the misdiagnosis of multiple sclerosis?

Need	
Important Figures	**Table 1** Clinical syndromes typical and atypical for multiple sclerosis (MS)–related demyelination **Typical for MS** / **Atypical for MS** **Unilateral optic neuritis, mild and with partial or full recovery** / Bilateral optic neuritis; severe optic neuritis; poor recovery from optic neuritis **Diplopia due to internuclear ophthalmoplegia** / Headache, with or without diplopia or visual obscuration **Facial sensory loss or trigeminal neuralgia in young patient** / Acute or subacute cognitive impairment **Cerebellar syndromes that include ataxia and nystagmus** / Dizziness or vertigo without brainstem or cerebellar findings **Sensory impairment or motor weakness localizing to the spinal cord, with partial or full recovery** / Sensory loss in extremities without a clear CNS pattern Complete transverse myelopathy
VOCAB: (w/definition)	Multiple sclerosis (MS) - a disease in which the immune system attacks the myelin sheaths that cover nerve fibers Periventricular - the area around the ventricles in the brain where nerves carry messages to muscles in the body Juxtacortical - near cortex Primary-progressive multiple sclerosis (PPMS) - a steady progression of signs and symptoms for MS without relapses Dissemination in space (DIS) - different places within the brain/spinal cord that have been damaged, part of the McDonald Criteria Dissemination in time (DIT) - new attacks/lesions/relapses over time, part of the McDonald Criteria OCB - oligoclonal band
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/18805839/ Differential diagnosis of suspected multiple sclerosis: a consensus approach https://pubmed.ncbi.nlm.nih.gov/29196574/ Clinical biomarkers differentiate myelitis from vascular and other causes of myelopathy (possibly using biomarkers in my project in a similar way to differentiate MS?) https://pubmed.ncbi.nlm.nih.gov/21849338/ Using atypical symptoms and red flags to identify non-demyelinating disease https://pubmed.ncbi.nlm.nih.gov/29082586/ Use (and misuse) of the McDonald criteria to diagnose multiple sclerosis (if I want to look more into the criteria and possibly seeing if there are other viable methods)
Follow up Questions	What are some of the most common conditions that are confused with MS? Could there be any specific indicators in methods such as MRI scans that could come close to guaranteeing a diagnosis of MS? Aside from McDonald Criteria, have there been other significant ways of diagnosing MS? Has the McDonald Criteria changed after this article was written? If so, what has it included to increase accuracy?

Article #10: Juxtacortical Lesions in Multiple Sclerosis: Assessment of Gray Matter Involvement Using Phase Difference-enhanced Imaging (PADRE) - 9/17/2023

Source Title	Juxtacortical Lesions in Multiple Sclerosis: Assessment of Gray Matter Involvement Using Phase Difference-enhanced Imaging (PADRE)
Source citation (APA Format)	Futasuya, K., Kakeda, S., Yoneda, T., Ueda, I., Watanabe, K., Moriya, J., Murakami, Y., Ide, S., Ogasawara, A., Ohnari, N., Okada, K., Adachi, H., & Korogi, Y. (2016). Juxtacortical Lesions in Multiple Sclerosis: Assessment of Gray Matter Involvement Using Phase Difference-enhanced Imaging (PADRE). *Magnetic Resonance in Medical Sciences*, *15*(4), 349–354. https://doi.org/10.2463/mrms.mp.2015-0099
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5608108/
Source type	Journal article
Keywords	multiple sclerosis, phase difference enhanced imaging, juxtacortical lesion, gray matter involvement
#Tags	#methodology #technology #ms
Summary of key points + notes (include methodology)	Juxtacortical lesions at the border between gray matter (GM) and white matter (WM) occur in multiple sclerosis (MS). Phase difference enhanced imaging (PADRE) is a recently developed technique that researchers wanted to assess the usefulness of in detecting GM involvement in lesions. They took scans of healthy patients and patients with MS, and PADRE was able to show a lesion with GM involvement. Overall, the research can provide a better understanding on the pathologic processes that cause MS lesions. - Conventional MRI techniques are used for MS diagnosis - Lack of knowledge surrounding GM involvement in lesions - PADRE enhances tissue contrast, highlights differences in myelin concentration - Examined PADRE images in healthy subjects and 13 patients with MS

	- PADRE provided better contrast between GM and WM - Classification of lesions changed when they went from using conventional MRI to PADRE - Ended up with 75% of lesions involving GM when using PADRE - Could help in better understanding the pathology behind MS - Could enhance MS accuracy diagnosis, though further research is needed to both confirm results and implement it into a clinical setting
Research Question/Problem/ Need	Can phase difference enhanced imaging (PADRE) be useful in the detection of gray matter involvement of juxtacortical MS lesions?
Important Figures	 This shows different imaging methods, with PADRE being A; this shows a lesion involving both the gray matter and U-fibers, compared to the other two just showing U-fibers.
VOCAB: (w/definition)	Subcortical - below cortex White matter - network of axons in the brain to allow communication of information throughout the brain Gray matter - high concentration of neuronal bodies, plays a role in day-to-day functions U-fibers - show connections between neighboring areas of the cerebral cortex, located in white matter Phase difference enhanced imaging (PADRE) - imaging technique that yields high tissue contrast Artifact - in the context of a brain scan, something that isn't present in the original object but shows up in the image
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/14016083/ The distribution of plaques in the cerebrum in multiple sclerosis https://pubmed.ncbi.nlm.nih.gov/15987979/ Intracortical lesions in multiple sclerosis: improved detection with 3D double inversion-recovery MR imaging https://pubmed.ncbi.nlm.nih.gov/19641168/ In vivo imaging of cortical pathology in multiple sclerosis using ultra-high field MRI https://pubmed.ncbi.nlm.nih.gov/18952832/ 3D MPRAGE improves classification of cortical lesions in multiple sclerosis

Follow up Questions	How can these lesions show different symptoms and severities of MS? How could less contrasted WM and GM areas in a lesion affect the quality of the results? How accessible is PADRE right now? Could these lesions be indicative of any other diseases and conditions?

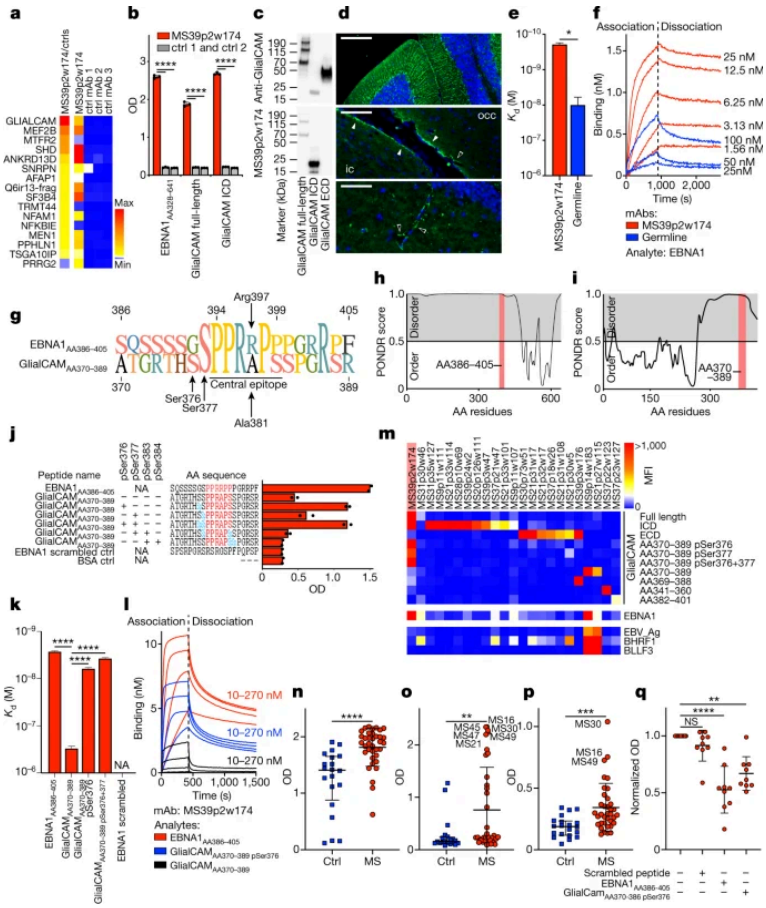
Article #11: Study identifies how Epstein-Barr virus triggers multiple sclerosis - 9/23/2023

Source Title	Study identifies how Epstein-Barr virus triggers multiple sclerosis
Source citation (APA Format)	Leggett, H. (2019, August 7). *Study identifies how Epstein-Barr virus triggers multiple sclerosis*. News Center. http://med.stanford.edu/news/all-news/2022/01/epstein-barr-virus-multiple-sclerosis.html
Original URL	https://med.stanford.edu/news/all-news/2022/01/epstein-barr-virus-multiple-sclerosis.html
Source type	News
Keywords	Multiple sclerosis, Epstein-Barr virus, autoimmune diseases, antibodies
#Tags	#background
Summary of key points + notes (include methodology)	There has been a suspected link between EBV and MS for a long time, but scientists did not prove these connections. This article shows some of the findings of a study that found a link - a protein of EBV called EBNA1 that mimics a protein named GlialCAM. When antibodies target EBV, they also end up targeting GlialCAM as well, which can damage the myelin. When they tested on mice with a model of MS, they also exhibited more symptoms of demyelination. Overall, it provides evidence that EBV is a major trigger for MS, and it could possibly pave the way for future MS treatments.
Research Question/Problem/ Need	What is the link between multiple sclerosis (MS) and Epstein-Barr virus (EBV)?
Important Figures	N/A
VOCAB: (w/definition)	EBNA1 - protein from EBV GlialCAM - glial cell adhesion molecule, found in the brain and spinal cord Oligoclonal bands - patterns of certain antibodies produced by MS patients
Cited references to follow up on	https://www.nature.com/articles/s41586-022-04432-7 Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM - this is the study that the news article was based off of

Follow up Questions	Could there be links between EBV and other autoimmune diseases? As suggested by the article, how would a reverse vaccine involving DNA plasmids for EBV work?

Article #12: Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM - 9/24/2023

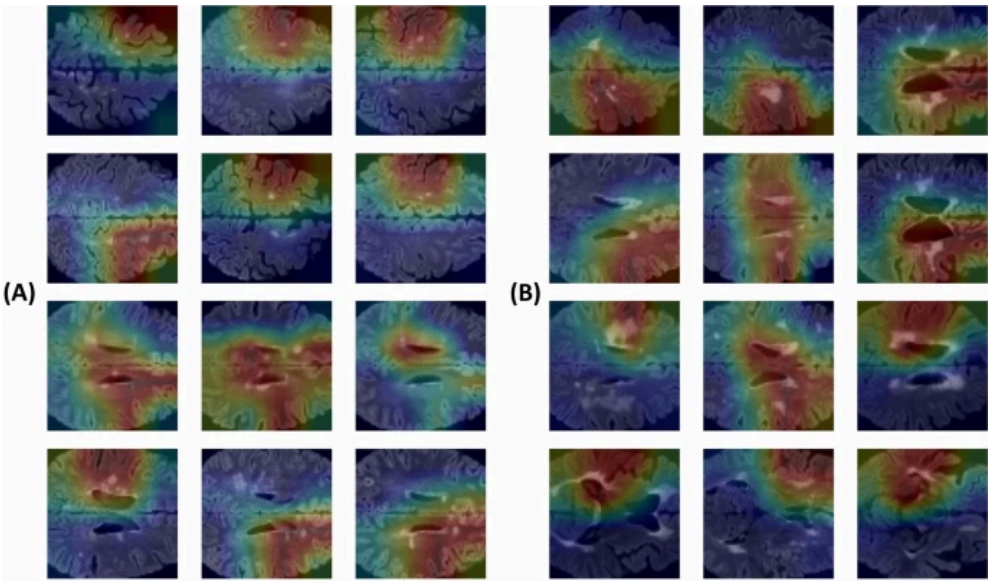
Source Title	Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM
Source citation (APA Format)	Lanz, T. V., Brewer, R. C., Ho, P. P., Moon, J.-S., Jude, K. M., Fernandez, D., Fernandes, R. A., Gomez, A. M., Nadj, G.-S., Bartley, C. M., Schubert, R. D., Hawes, I. A., Vazquez, S. E., Iyer, M., Zuchero, J. B., Teegen, B., Dunn, J. E., Lock, C. B., Kipp, L. B., … Robinson, W. H. (2022). Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM. *Nature*, *603*(7900), 321–327. https://doi.org/10.1038/s41586-022-04432-7
Original URL	https://www.nature.com/articles/s41586-022-04432-7
Source type	Journal article
Keywords	Multiple sclerosis, oligoclonal bands, pathobiology, molecular mimicry, EBV
#Tags	#ms #methodology
Summary of key points + notes (include methodology)	To investigate the connection between multiple sclerosis (MS) and Epstein-Barr Virus (EBV), scientists looked at the molecular mimicry between EBV nuclear antigen 1 (EBNA1) and the central nervous system protein glial cell adhesion molecule (GlialCAM). Through identifying a cross-reactive antibody to both EBNA1 and GlialCAM, they were able to demonstrate molecular mimicry between the two molecules. Further testing was done in mice, and immunization with EBNA1 was shown to exacerbate an MS-like disease in the mice. These findings provide a mechanistic link between MS and EBV and suggest new therapies that could work in treating and diagnosing MS. Notes: https://docs.google.com/document/d/1cRtzVhBZyHUCeH0jD7bl3n4WNJVmr_da9yNPPFP4hVU/edit
Research Question/Problem/ Need	What is the role of Epstein-Barr virus and its protein EBNA1 in the pathobiology of multiple sclerosis?

Important Figures	 Figure 3: molecular mimicry between EBNA1 and GlialCAM - Protein microarray (a) showed higher reactivity in the antibody to EBNA1 and GlialCAM - Western blotting + immunofluorescence to confirm MS antibodies in mice (c, d) - Peptide analysis - Modifying GlialCAM influenced interaction between MS antibodies and regions of EBNA1 and GlialCAM
VOCAB: (w/definition)	Lymphocyte - type of white blood cell Glial - type of cell that helps to maintain neurons OCB - oligoclonal bands - bands of immunoglobulins that aid in helping to diagnose diseases like MS Mononucleosis - an infection caused by EBV Flow cytometry - used to analyze properties of cells Plasmablast - part of the antibody response SMH - somatic hypermutation - immune system adapting to new elements Intrathecal - injection into spinal canal Polyreactivity - ability of an antibody to bind to molecularly distinct antigens Lysate - containing the products of lysed cells Germline - sex cells Astrocytes - subtype of glial cells involved in the CNS

	Oligodendrocytes - generate myelin Western blot - method used to separate proteins Linear epitope - binding site on an antigen - recognized by antibodies Multimerization - mechanism for the activation of protein kinases
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/31862243/ Epstein-Barr Virus in Multiple Sclerosis: Theory and Emerging Immunotherapies https://pubmed.ncbi.nlm.nih.gov/32808238/ Antibodies from Multiple Sclerosis Brain Identified Epstein-Barr Virus Nuclear Antigen 1 & 2 Epitopes which Are Recognized by Oligoclonal Bands https://pubmed.ncbi.nlm.nih.gov/24162037/ Immune cell subtyping in the cerebrospinal fluid of patients with neurological diseases
Follow up Questions	What kinds of new therapies could be explored? What are the challenges of taking the findings of this study and applying them into clinical practice? Are there other potential cross-reactivities with other proteins and the antibodies mentioned that could affect the findings?

Article #13: Differentiation between multiple sclerosis and neuromyelitis optica spectrum disorder using a deep learning model - 10/4/2023

Source Title	Differentiation between multiple sclerosis and neuromyelitis optica spectrum disorder using a deep learning model
Source citation (APA Format)	Seok, J. M., Cho, W., Chung, Y. H., Ju, H., Kim, S. T., Seong, J.-K., & Min, J.-H. (2023). Differentiation between multiple sclerosis and neuromyelitis optica spectrum disorder using a deep learning model. *Scientific Reports*, *13*(1), 11625. https://doi.org/10.1038/s41598-023-38271-x
Original URL	https://www.nature.com/articles/s41598-023-38271-x
Source type	Journal article
Keywords	Multiple sclerosis, autoimmune disorders, deep learning, central nervous system, MRI, demyelinating disorders, diagnostic imaging, myelooptic neuropathy, nuclear magnetic resonance imaging, pathology
#Tags	#background #ai #ms
Summary of key points + notes (include methodology)	Misdiagnosis of MS is common and potentially dangerous, and it shares many characteristics with neuromyelitis optica spectrum disorder (NMOSD). Proper diagnosis is vital, especially in the early stages so that the right therapies can be implemented. Machine learning models have been used before, but they were not completely automated and still required the attention and evaluation of experts. To address this, Seok et al. developed a deep learning model using ResNet18 that could differentiate between MS and NMOSD. (76.1% accuracy) By further exploring the model, they found that it focused on white matter lesions to classify. This model could aid in the diagnosis of MS and help to prevent misdiagnosis in clinical practice. - MS gets misdiagnosed often - dangerous in early stages for therapies - An autoantibody that targets an aquaporin has been discovered in NMOSD, but it can prove false-negative results. - Likewise, machine learning models not completely automated and still need expert evaluation to be effective

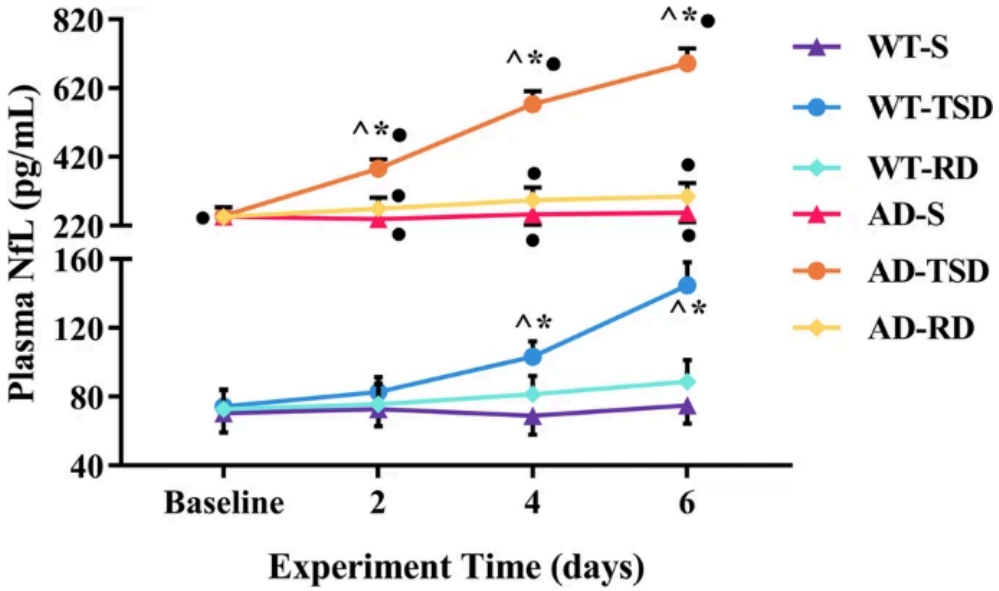
	- Seok et al developed a deep learning model using ResNet18 convolution neural network and training it with axial MRI scans - 76.1% accuracy of the model - Further exploration of model - found that white matter lesions in brain were used to classify disorders - Could aid in diagnosis of MS. prevent misdiagnosis in clinical setting - Further research required to develop fully automated model for CNS demyelinating diseases - 68.8% of scans were taken in chronic remission - Trained binary classification so no healthy brain scans were used
Research Question/Problem/ Need	How can deep learning be used to help differentiate multiple sclerosis from neuromyelitis optica spectrum disorder?
Important Figures	 A is the Grad-CAM results for MS and B is the Grad-CAM results for MSNOD - Shows white matter lesions, which is what the AI identified to make its differentiations
VOCAB: (w/definition)	Aquaporins - water channels for the cell membrane Seronegative - absence of a certain antibody Axial - section that passes horizontally through the brain Epoch - period of time Remission - no sign of the condition in your body (mostly applicable to cancer) - not representative of a cure Periependymal - surrounding the ependyma - lining of the ventricular system of the brain and central canal of spinal cord Cervicomedullary - region where brainstem continues as spinal cord Acute stage - inflammatory stage, severe in onset
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/31451912/ Artificial intelligence as an emerging technology in the current care of neurological disorders - this could help with the

	possible implementation of AI into a project regarding MS https://pubmed.ncbi.nlm.nih.gov/33329357/ Deep Learning-Based Method to Differentiate Neuromyelitis Optica Spectrum From Multiple Sclerosis https://pubmed.ncbi.nlm.nih.gov/29521337/ The current role of MRI in differentiating multiple sclerosis from its imaging mimics - could provide some other conditions that could be differentiated?
Follow up Questions	How would the MRI scans of the brains of healthy subjects be used to compare with the scans of patients with MS or NMOSD? How could a deep learning model be used to differentiate MS from other neuroinflammatory and autoimmune diseases? - Would white matter still be an important thing to look at to classify them? Could this model detect any signs of gray matter? What are the difficulties in incorporating this into clinical practice?

Article #14: NREM sleep loss increases neurofilament light chain levels in APP/PS1 and C57BL/6 J mice - 10/10/2023

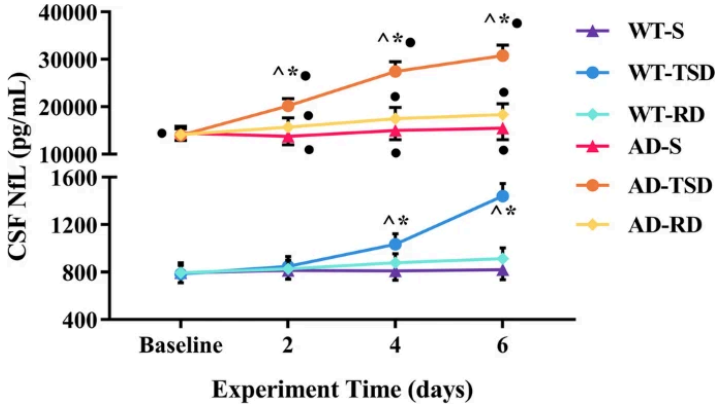
Source Title	NREM sleep loss increases neurofilament light chain levels in APP/PS1 and C57BL/6 J mice
Source citation (APA Format)	Liu, S., Zhang, Z., Shi, S., Meng, Y., Zhang, X., Lei, Q., & Li, Z. (2023). NREM sleep loss increases neurofilament light chain levels in APP/PS1 and C57BL/6 J mice. *Sleep and Breathing*, *27*(4), 1495–1504. https://doi.org/10.1007/s11325-022-02719-7
Original URL	https://link.springer.com/article/10.1007/s11325-022-02719-7
Source type	Journal article
Keywords	Neurofilament light chain, non-rapid eye movement sleep, sleep deprivation
#Tags	#background #effects #sleep
Summary of key points + notes (include methodology)	Neurofilament light chain (NfL) proteins in the CSF and plasma can indicate the severity of neuronal apoptosis, which is present in neurodegenerative diseases like Alzheimer's. By sleep depriving groups of both wild-type mice and a model with Alzheimer's in different ways and then measuring their NfL levels, scientists aimed to find a connection between NREM sleep and the survival of neurons. They found that NfL levels in the CSF and plasma were significantly increased when the mice were deprived of their NREM phase of sleep, signifying the importance of NREM sleep in neuronal survival. Additionally, they measured spatial cognitive function, which was shown to have decreased with sleep deprivation. Notes: https://docs.google.com/document/d/1xethWz2B8y0Dno3MeY-w-6hbR-yKK9f-azXWgpbvUiU/edit?usp=sharing
Research Question/Problem/ Need	What is the role of NREM in neuronal survival?
Important Figures	This visual outlines the procedures that they used - when they took CSF and plasma samples, when they tested the cognitive ability via MWM, and the

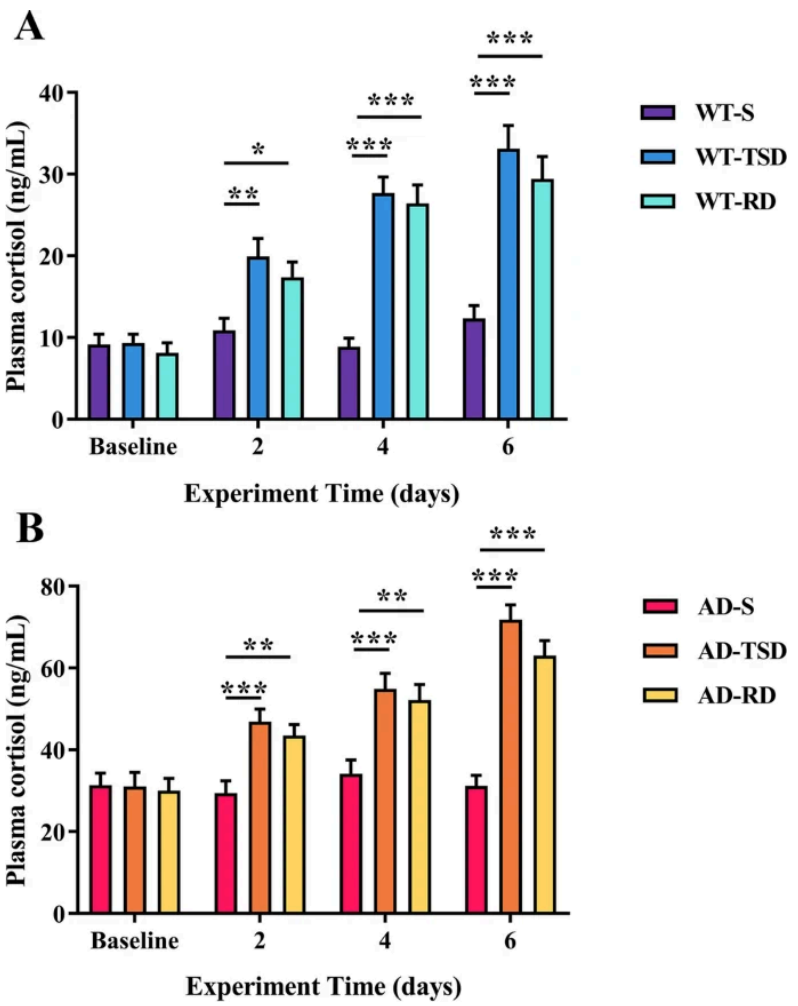
different groups and treatments that they used



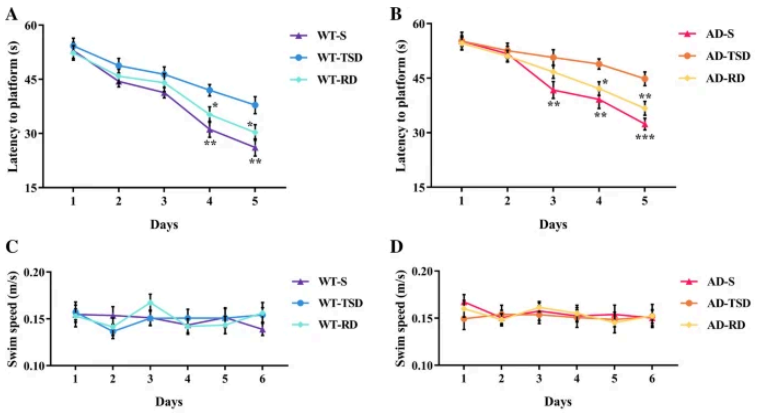
This graph shows plasma NfL levels in both groups after 2, 4, and 6 days. While the S and RD groups for both WT and AD mice were relatively unchanged, the TSD group experienced a significant increase in plasma NfL. All the AD groups were higher in NfL level at all points in time compared to their WT counterparts.

This graph shows the CSF NfL levels in both groups after 2, 4, and 6 days. They follow similar trends compared to the plasma NfL levels





This shows the cortisol levels in the plasma after the samples were collected. In both of the graphs, the S group had lower levels of cortisol compared to both the TSD and RD groups



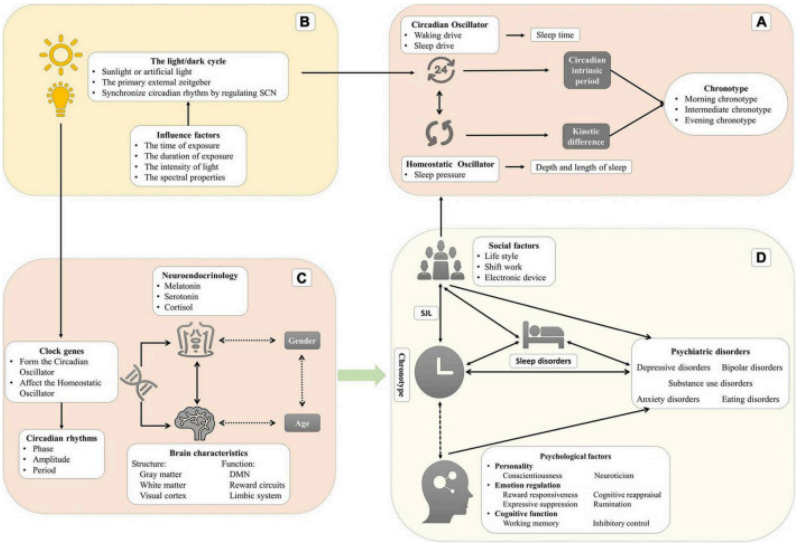
Latency was longer in the TSD group compared to the RD group, which was longer than the S group. Swim speeds had no big difference - normal motor ability

VOCAB: (w/definition)	NfL - neurofilament light chain, released into CSF and then plasma when neurons die WT - wild-type AD - Alzheimer's MWM - Morris water maze, the test used for spatial memory TSD - total sleep deprivation, including both REM and NREM RD - REM deprivation Cortisol - stress hormone
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/22811426/ Control of sleep and wakefulness https://pubmed.ncbi.nlm.nih.gov/25945148/ Sleep deprivation and oxidative stress in animal models: a systematic review
Follow up Questions	What other types of cognitive function (excluding spatial) can be tested and implemented? How translatable are the findings in mice compared to humans? What differences in sleep patterns are there in mice compared to humans? How does NfL as a biomarker compare to other biomarkers for neurodegeneration? Could circadian differences such as chronotype influence NREM and REM sleep, and subsequently NfL levels as a result of sleep deprivation? How could an EEG be used to obtain quantitative data?

Article #15: Chronotype, circadian rhythm, and psychiatric disorders: Recent evidence and potential mechanisms

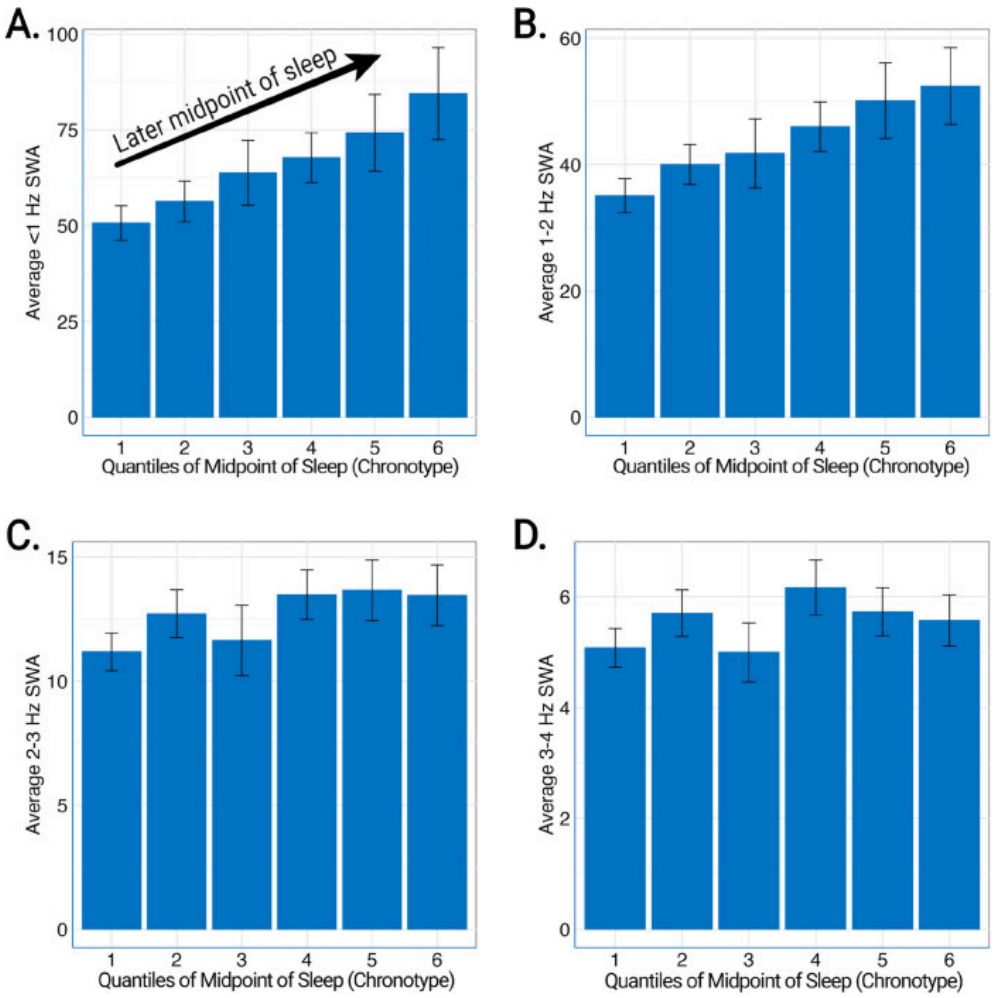
Source Title	Chronotype, circadian rhythm, and psychiatric disorders: Recent evidence and potential mechanisms
Source citation (APA Format)	Zou, H., Zhou, H., Yan, R., Yao, Z., & Lu, Q. (2022). Chronotype, circadian rhythm, and psychiatric disorders: Recent evidence and potential mechanisms. *Frontiers in Neuroscience*, *16*, 811771. https://doi.org/10.3389/fnins.2022.811771
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9399511/
Source type	Review article
Keywords	Chronotype, circadian rhythm, psychiatric disorders, depression, sleep disorder
#Tags	#disorders #background #sleep
Summary of key points + notes (include methodology)	This article provides a review of chronotype and how it affects the brain structure, and subsequently provides insight into its association with psychiatric disorders. It also brings up zeitgebers, environmental factors that can affect the development of chronotype; these can be both nature-related (e.g. solar) or societal (e.g. work shift schedules). - Circadian oscillator - process C - regulates sleep timing - Homeostatic oscillator - process S - regulates sleep duration - Morning chronotypes are advanced forward 2-3 hours compared to evening - Sleep duration not always affected but greater sleep debt for evening and variable sleep-wake habits - MDD, BD, SAD have been associated with evening chronotype - SJL calculated as the absolute value of the difference in midpoint sleep time between weekdays and weekends using MCTQ - Social zeitgebers have become more significant influences on chronotype - Polymorphisms in clock genes are associated with chronotype and psychiatric disorders Brain structure - Morning - lower regional gray matter density in the precuneus, left posterior parietal cortex and surrounding regions - Evening - greater volume of left anterior occipital sulcus

	- Evening - associated with impaired emotional regulation circuitry - Difference between chronotypes can affect the level of structure in the brain and function - differences in psychological performance - Evening - later melatonin rhythms, decreased mean levels and peaks Age - babies are more often morning, young adults are more often evening, and the elderly tend to wake up in the morning - Cortisol, melatonin and body temp vary at different ages The light/dark cycle is the primary external zeitgeber - Next to that is the plethora of social factors like shift work Differences emotional regulation can lead to differences in personality between chronotypes and risk for psychiatric disorders Chronotype is a strong predictor of sleep disorders - Poor sleep quality/sleep disorders mediate the association between evening chronotype and depressive symptoms in patients with mood disorders - Overall, evening chronotype is an independent risk factor for psychiatric–especially depressive–disorders, sleep disorders can show a partially or fully mediating effect Chronotype has an association with - Depressive disorders (MDD in particular) - evening chronotype is a risk factor, morning chronotype is a protector - Bipolar disorders - Anxiety, but other sleep factors may be more closely linked than chronotype - Schizophrenia - evening is more at risk as a result or recent studies - Substance use disorders (?) - Eating disorders Chronotype can change with different environments Causal relationship between chronotype and psychiatric disorders still not identified
Research Question/Problem/ Need	How can chronotype affect psychiatric disorders?

Important Figures	 Figure 1 - A shows the two oscillators that lead to chronotype - B shows the light/dark cycle and its influence factors - C shows the differences in the brain that are associated with differences in chronotypes - D shows the effect on psychiatric disorders, while including other contributing factors such as social
VOCAB: (w/definition)	Zeitgebers - environmental cues that affect the timing of circadian rhythms Oscillators - produce continuous waves/signals MDD - major depressive disorder BD - bipolar disorder SAD - seasonal affective disorder
Cited references to follow up on	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6338075/ Rhythms of life: circadian disruption and brain disorders across the lifespan https://pubmed.ncbi.nlm.nih.gov/24958244/ The independence relationships between insomnia, depression, subtypes of anxiety, and chronotype during adolescence (if I want to use EEG with adolescents this could help) https://pubmed.ncbi.nlm.nih.gov/18271906/ Chronotype distribution in bipolar I disorder and schizophrenia in a Korean sample https://pubmed.ncbi.nlm.nih.gov/32019630/ Influence of chronotype on daily mood fluctuations: pilot study in patients with depression
Follow up Questions	In the studies that provide links between personality and factors like stress, were there any other factors that could have affected the results? What similarities are there in schizophrenia with other diseases that affect the brain that could be affected by chronotype? Are there major biomarkers for the aforementioned psychiatric disorders that could be influenced by chronotype?

Article #16: Chronotype is Associated with Sleep Quality in Older Adults - 11/8/2023

Source Title	Chronotype is Associated with Sleep Quality in Older Adults
Source citation (APA Format)	Sauers, S. C., Toedebusch, C. D., Richardson, R., Spira, A. P., Morris, J. C., Holtzman, D. M., & Lucey, B. P. (2023). Chronotype is Associated with Sleep Quality in Older Adults. *MedRxiv*, 2023.09.04.23294997. https://doi.org/10.1101/2023.09.04.23294997
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10508806/
Source type	Journal
Keywords	Chronotype, Alzheimer's disease, dementia, circadian rhythm, sleep quality, actigraphy
#Tags	#disorders #sleep
Summary of key points + notes (include methodology)	Many sleep measures associated with increase risk for AD - Self-reported sleep quality - Shorter or longer sleep durations - Fragmentation of sleep - Decreased sleep efficiency - Increased WASO - Increased SOL - Time spent in different stages - AD can disrupt circadian system - unpredictable rhythm, fragmented sleep - Study can support chronotype as a possibly modifiable AD risk factor Methods - Single-channel EEG - measured time in N2 and N3, time in REM, sleep efficiency, and slow wave activity in NREM - Actigraphy - way of defining chronotype - Sleep logs - Took CSF samples from patients after overnight fasting - Statistical analysis - Used MCTQ - Later chronotypes - lower REM time, longer REM onset latency, greater N2 and N3, higher slow-wave activity - Later chronotypes may also have more restless sleep due to the number of

	nighttime awakenings - Results indicate that midpoint of sleep or chronotype is associated with measures that indicate poorer sleep quality - Chronotype can be modified by light exposure To address how chronotype affects the midpoint of sleep and other parameters in adults, scientists measured time in different phases and found the midpoint of sleep for each individual after determining chronotype. Late chronotypes were found to have lower time spent in REM sleep as well as more disruptions like nighttime awakenings. This study provides evidence for the impact of chronotype on factors that would affect sleep quality; future studies could investigate other treatments that could alter chronotype and improve sleep quality.
Research Question/Problem/ Need	What is the relationship between different factors of sleep and chronotype?
Important Figures	 Figure 3: relationship of midpoint of sleep and NREM slow wave activity - higher bars indicate a later midpoint, slow wave activity (SWA) increased with midpoint of sleep, which later chronotypes have

VOCAB: (w/definition)	AD - Alzheimer's WASO - wake after sleep onset SOL - sleep onset latency SWA - slow wave activity
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/23814339/ Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons https://pubmed.ncbi.nlm.nih.gov/29862086/ Association between the Munich Chronotype Questionnaire and Wrist Actigraphy https://pubmed.ncbi.nlm.nih.gov/25392279/ The midpoint of sleep on working days: a measure for chronodisruption and its association to individuals' well-being
Follow up Questions	How could interventions like light exposure, exercise, and diet affect the midpoint of sleep? From this study, how would a link between chronotype/midpoint of sleep and Alzheimer's be investigated? What factors that contribute to sleep disorders result from a change in chronotype?

Article #17: Quantitative Evaluation of EEG-Biomarkers for Prediction of Sleep Stages - 11/19/2023

Source Title	Quantitative Evaluation of EEG-Biomarkers for Prediction of Sleep Stages
Source citation (APA Format)	Hussain, I., Hossai, M. A., Jany, R., Bari, M. A., Uddin, M., Kamal, A. M., Ku, Y., Kim, J. "Quantitative Evaluation of EEG-Biomarkers for Prediction of Sleep Stages." *Sensors (Basel, Switzerland)*, vol. 22, no. 8, Apr. 2022, p. 3079, https://doi.org/10.3390/s22083079.
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9028257/
Source type	Journal article
Keywords	Electroencephalogram, sleep stages, physiological biomarker, neuroscience, polysomnography, machine-learning, sleep monitoring
#Tags	#sleep #EEG #methodology
Summary of key points + notes (include methodology)	- N2 - ocular movements, heart rate, body temperature, brain activity start to decrease - N3 - deep sleep/slow-wave sleep - no eye or muscular movement, muscles and tissues healed - Tracking brain waves is essential for assessing cognitive load - PSG requires human expert to score a whole night of sleep data manually - EEG signals can be more helpful during sleep scoring than other PSG signals - can directly track brain activity and differentiate sleep patterns - Study seeks to automate sleep scoring process - uses data from three EEG channels from F4, C4 and O2 - frontal lobe, central lobe, occipital lobe - Sleep-stage dependent responses of the CNS would be immediately sensed by EEG - Identified EEG biomarkers consisting of frequency spectral measures for sleep stages - ML models were developed to classify the neurological states in different sleep stages EEG data pre-processing - Separated eye and muscle movements using EOG and EMG recordings from EEG signal Feature extraction

	- EEG defined in terms of frequency and power within different frequency bands - delta band from 0.5-4.0 Hz - Theta from 4.0 to 8.0 - Alpha from 8.0 to 13.0 - Beta from 13.0 to 30.0 - Gamma from 30.0 to 44.0 - EEG features extracted from signals using Fast Fourier transforms Feature selection - Reduces time and memory required for data processing ML classification approach - ML algorithms used to classify neurological features during each phase - EEG data from 80% of selected features used for training - 20% of data was used for testing the algorithms - Used Neural Network, CHAID and C5.0 models to distinguish Statistical analysis of features - DAR - ratio of delta to alpha band power - DTR - ratio of delta to theta band power - DTABR - relative sum of slow wave (first two) power to fast-oscillating wave (latter two) power Sleep is an important process, yet the gold-standard for tracking different movements during sleep (PSG) is very time-consuming. To address this, scientists used brain wave data from EEG signals to show the power of each type of wave during different phases of sleep. They also trained three different machine-learning algorithms to classify the different stages of sleep, which was shown to be more accurate in two of the models compared to previous studies. The results of this study could help to predict sleep stages, and this study also identified biomarkers for each stage of sleep in the form of wave power ratios.
Research Question/Problem/ Need	How can physiological biomarkers for an EEG be identified and implemented in a machine-learning algorithm to help score sleep?

Important Figures

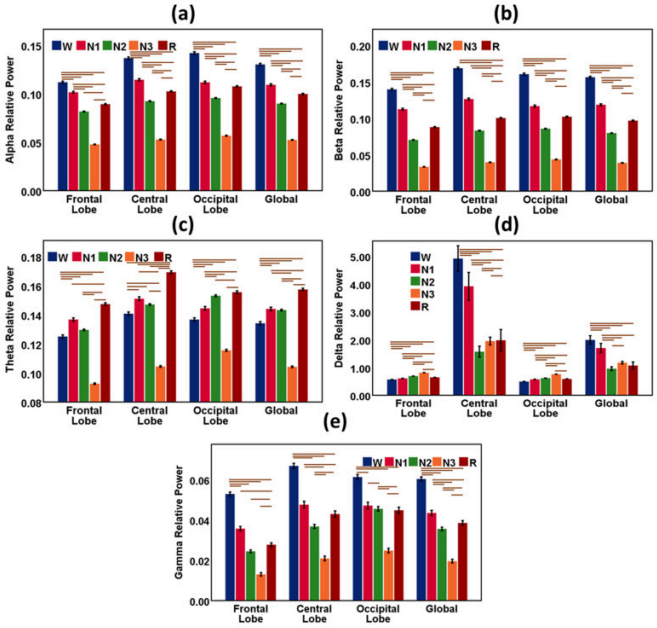


Figure 2: shows bar charts with error bars (95% confidence interval) of EEG features and frequency bands

- Global data indicates average measures of the features of each lobe
- Horizontal bars (brown) are outcomes of hypothesis tests - indicate significant differences if $p < 5\%$ in EEG features among sleep stages
- Alpha is highest in wake stage, lowest in N3, weakens as sleep gets deeper - gains strength in REM
- Beta also more prevalent in wake stage, similar to alpha
- Theta highest in REM stage, lowest in N3 - increases in light sleep
- Delta highest in N3 - highest in wake stage in central lobe
- Gamma highest in wake stage, lowest in N3 - weakens as sleep deepens - still comes back in REM

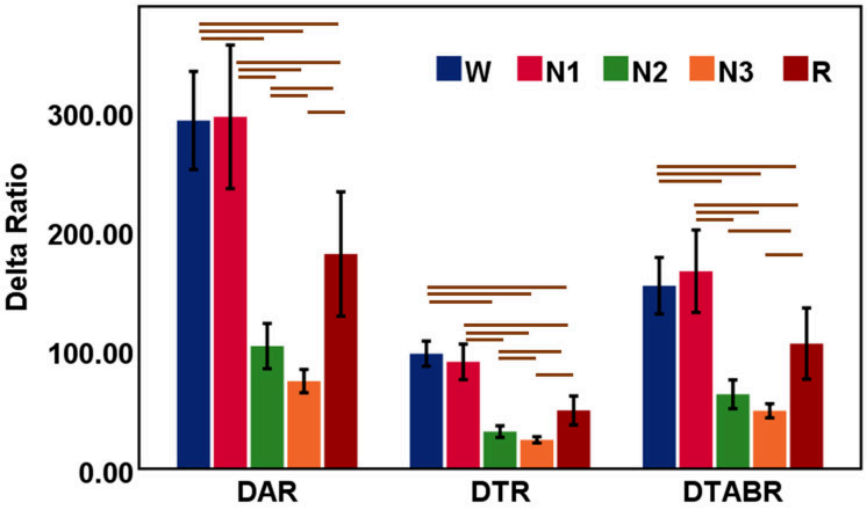
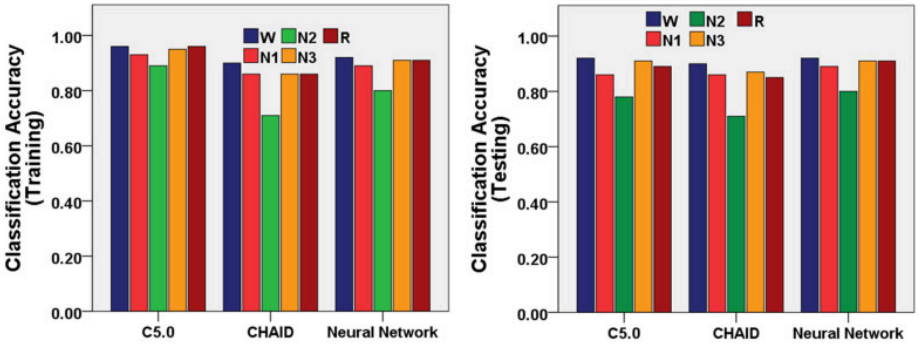


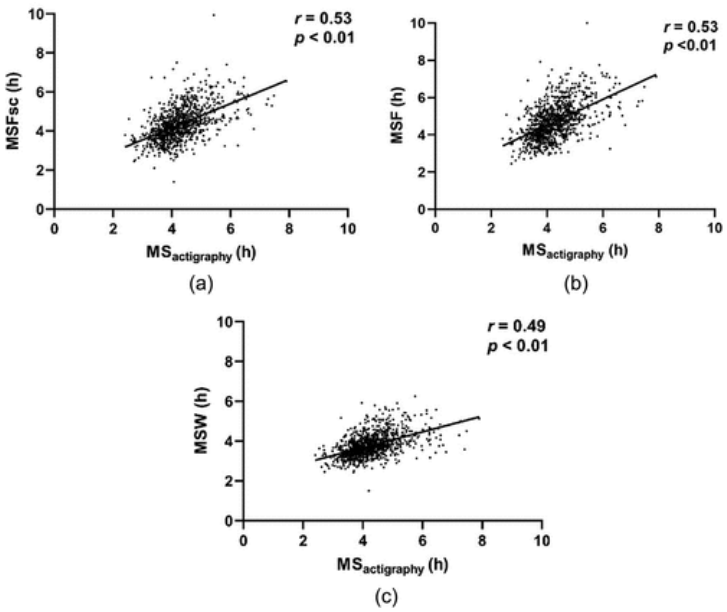
Figure 3: results from each of the ratios during the sleep stages

- Bar chart describes relative mean power of the EEG waves

	- Vertical error bar - black - 95% CI - Global is average measures - Horizontal bars are outcomes of hypothesis tests, indicate significant differences in EEG features  Figure 4: showing performance of the three ML models to classify sleep stages with both training and testing - N2 was the least accurate possibly because it is also a light sleep stage and may get mislabeled as N1 Table 10 compares the proposed work with other previous models, and both the C5.0 and Neural Network models have the highest accuracies at 91% and 92% respectively
VOCAB: (w/definition)	W - wake phase of sleep N1 - NREM-1 phase of sleep N2 - NREM-2 phase of sleep N3 - NREM-3 phase of sleep Attenuate - weaken Frontal lobe - important for voluntary movement, language and other functions Occipital lobe - visual perception, depth perception, recognition CNS - central nervous system CHAID - chi-square automatic interaction detector DAR - delta-alpha ratio DTR - delta-theta ratio DTABR - delta + theta over alpha + beta ratio
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/11915486/ Human alpha oscillations in wakefulness, drowsiness period, and REM sleep: different electroencephalographic phenomena within the alpha band https://mdpi.com/2079-9292/9/3/512 Automatic Sleep Disorders Classification Using Ensemble of Bagged Tree Based on Sleep Quality Features
Follow up Questions	How could the different types of waves be influenced by chronotype? Why did they pick three different algorithms to test? What clinical implications do the results have in the context of predicting or treating sleep disorders? Are there any other factors that could have affected the sample data?

Article #18: Validation of the Munich Chronotype Questionnaire (MCTQ) in Chinese College Freshmen Based on Questionnaires and Actigraphy - 11/24/2023

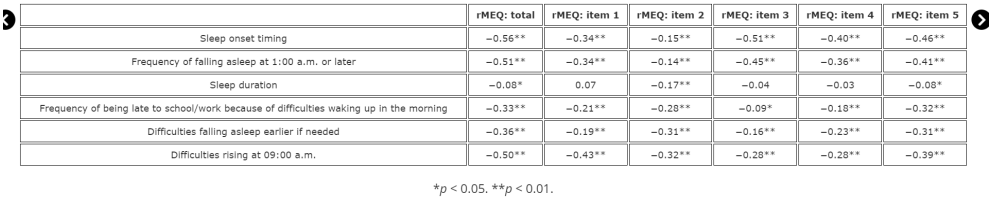
Source Title	Validation of the Munich Chronotype Questionnaire (MCTQ) in Chinese College Freshmen Based on Questionnaires and Actigraphy
Source citation (APA Format)	Wang, S., Wang, H., Deng, X., Lei, X. "Validation of the Munich Chronotype Questionnaire (MCTQ) in Chinese College Freshmen Based on Questionnaires and Actigraphy." *Chronobiology International*, vol. 40, no. 5, May 2023, pp. 661–72, https://doi.org/10.1080/07420528.2023.2202246.
Original URL	https://www.tandfonline.com/doi/full/10.1080/07420528.2023.2202246
Source type	Journal
Keywords	Chronotypes, sleep midpoint, sleep debt, circadian, alarm clock
#Tags	#methodology #sleep
Summary of key points + notes (include methodology)	The Munich Chronotype Questionnaire (MCTQ) was developed to assess an individual's chronotype through user input. However, it has not been effectively verified for a large sample and compared to various other questionnaires and actigraphy measures. This study used a large sample of 1066 people and compared their results from the MCTQ with other questionnaires, most notably the Morningness-Eveningness Questionnaire (MEQ and its reduced version (rMEQ)), which have been previously used to determine chronotype. Additionally, they were compared with actigraphy results for more objective methods of assessing sleep. Being consistent with many reliable measures and offering other insights into sleep times and parameters, the MCTQ was verified to be an effective assessment of an individual's chronotype. - Previous issues with MEQ - too subjective and ignores differences on weekends - Dim light melatonin onset can measure circadian phases but is super expensive and impractical - Self-reported questionnaires have become widely used to determine chronotype - Hypothesized that MCTQ would have good validity when tested against both subjective and objective parameters

	- Looking at different parameters and seeing possibly which one is most effective for measuring chronotype - Translated the MCTQ to Chinese to be understandable by all the college freshmen - Original MEQ has 19 items, so they used the shortened version - Used sleep diary and actigraph for subjective/objective - Sleep diary was filled out immediately after waking for the best subjective recount of sleep - Limit - college freshmen from a specific place - Used violin plot - Good test-retest reliability of MCTQ - Activities involving blue light from phones before bed can lead to later sleep - MCTQ is consistent with actigraphy
Research Question/Problem/ Need	How can the MCTQ be validated for a large sample using both subjective and objective means?
Important Figures	 Figure 2: The correlation of MSactigraphy with MCTQ parameters - shows how consistent the MCTQ was with actigraphy by using different parameters - pval being less than .01 indicates that there is significant evidence that the parameters of the MCTQ are consistent with actigraphy results
VOCAB: (w/definition)	Actigraphy - non-invasive method of monitoring cycles, commonly used for assessing sleep
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/30614272/ The reduced Morningness-Eveningness Questionnaire: Psychometric properties and related factors in a young Swedish population https://pubmed.ncbi.nlm.nih.gov/32654545/ Comparison of Munich Chronotype

	Questionnaire (MCTQ) and Morningness-Eveningness Questionnaire (MEQ) Czech version https://pubmed.ncbi.nlm.nih.gov/24156294/ The association between use of electronic media in bed before going to sleep and insomnia symptoms, daytime sleepiness, morningness, and chronotype
Follow up Questions	How can the use of alarm clocks and how they can affect chronotype further be investigated? How does collecting data over a long time period affect results, considering that students can have different stressors and other factors at different points in the school year? How could this knowledge be applied to other populations?

Article #19: The reduced Morningness–Eveningness Questionnaire: Psychometric properties and related factors in a young Swedish population - 12/6/2023

Source Title	The reduced Morningness–Eveningness Questionnaire: Psychometric properties and related factors in a young Swedish population
Source citation (APA Format)	Danielsson, K., Sakarya, A., & Jansson-Fröjmark, M. (2019). The reduced Morningness–Eveningness Questionnaire: Psychometric properties and related factors in a young Swedish population. *Chronobiology International*, *36*(4), 530–540. https://doi.org/10.1080/07420528.2018.1564322
Original URL	https://www.tandfonline.com/doi/full/10.1080/07420528.2018.1564322
Source type	Journal
Keywords	Reduced Morningness-Eveningness Questionnaire, chronotype, adolescents
#Tags	#methodology
Summary of key points + notes (include methodology)	This study assessed the reliability and validity of the reduced Morningness–Eveningness Questionnaire (rMEQ) in young Swedish individuals and explored factors correlated with rMEQ scores. They showed fair validity, correlating well with sleep-related questions. However, there are concerns about consistency and there needs to be caution taken when interpreting the results of this questionnaire. This suggests a need for further research to enhance the reliability of the questionnaire. - Chronotype can play a role in diseases such as insomnia in adolescents - rMEQ only includes items 1, 7, 10, 18, and 19 of the original MEQ, making it easier for participants to fill out - Has been used and evaluated in many countries - Wanted to test it when translated to Swedish - ISI is a 7-item scale to measure sleep disturbance - ESS is an 8-item scale to help measure daytime sleepiness - Looked at age, sex, alcohol intake, drugs, and occupation - Mean rMEQ score was 13.1 - Scores ranged from 4 to 24 - Age had a positive correlation to rMEQ - rMEQ score negatively correlated with ISI score

	- Lower rMEQ scores associated with higher severity of sleep difficulties and depressive system - Limitation might be that it was too reliant on self-reported - One-factor structure - Usefulness of the rMEQ questioned - Could be used for if a short questionnaire is needed - Overall satisfactory but not optimal reliability
Research Question/Problem/ Need	How reliable is the reduced version of the Morningness-Eveningness Questionnaire and how can it effectively be applied?
Important Figures	 *p < 0.05. **p < 0.01. Table 3: correlations between rMEQ scores and questions assessing sleep onset, sleep duration, and rising in the morning - Negative correlation between rMEQ score and sleep variables - Evening-oriented people had later sleep onset timing
VOCAB: (w/definition)	MEQ - Morningness-Eveningness Questionnaire - a method previously developed to determine chronotype rMEQ - Reduced MEQ CT - chronotype ISI - insomnia severity index
Cited references to follow up on	https://www.sciencedirect.com/science/article/pii/S0165032716319176?casa_token=oYBT4dSZAEYAAAAA:KN723Puj0skqzaTLaTXJ-RIpFkSEA9fyhacvv1uq1MokwxV1UWCGtogyVFazyk8vmEv50Eew The relationship between chronotype and depressive symptoms: A meta-analysis https://pubmed.ncbi.nlm.nih.gov/21422657/ Distribution of chronotypes in a large sample of young adult Saudis https://www.tandfonline.com/doi/full/10.1080/09291016.2014.939442 Exploration of transcultural properties of the reduced version of the Morningness–Eveningness Questionnaire (rMEQ) using adaptive neuro-fuzzy inference system
Follow up Questions	How could an objective measure be paired with a questionnaire to obtain better results? What aspects could make it less reliable compared to other questionnaires? How can other external factors that affect sleep onset be investigated and accounted for?

	rMEQ: total	rMEQ: item 1	rMEQ: item 2	rMEQ: item 3	rMEQ: item 4	rMEQ: item 5
Sleep onset timing	−0.56**	−0.34**	−0.15**	−0.51**	−0.40**	−0.46**
Frequency of falling asleep at 1:00 a.m. or later	−0.51**	−0.34**	−0.14**	−0.45**	−0.36**	−0.41**
Sleep duration	−0.08*	0.07	−0.17**	−0.04	−0.03	−0.08*
Frequency of being late to school/work because of difficulties waking up in the morning	−0.33**	−0.21**	−0.28**	−0.09*	−0.18**	−0.32**
Difficulties falling asleep earlier if needed	−0.36**	−0.19**	−0.31**	−0.16**	−0.23**	−0.31**
Difficulties rising at 09:00 a.m.	−0.50**	−0.43**	−0.32**	−0.28**	−0.28**	−0.39**

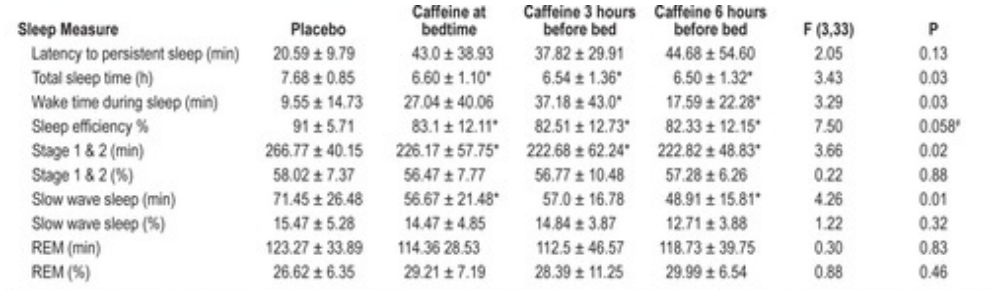
Article #20: The Role of EEG in the Diagnosis and Management of Patients with Sleep Disorders - 12/9/2023

Source Title	The Role of EEG in the Diagnosis and Management of Patients with Sleep Disorders
Source citation (APA Format)	Behzad, R., & Behzad, A. (2021). The Role of EEG in the Diagnosis and Management of Patients with Sleep Disorders. *Journal of Behavioral and Brain Science*, *11*(10), 257–266. https://doi.org/10.4236/jbbs.2021.1110021
Original URL	https://www.scirp.org/journal/paperinformation?paperid=112539
Source type	Review article
Keywords	Sleep disorders, electroencephalogram, brain activities, EEG electrodes system
#Tags	#methodology #technology
Summary of key points + notes (include methodology)	Sleep disorders are a common problem for many individuals in the US, and can pose a significant health and safety concern. An electroencephalogram (EEG) can be used to help diagnose such disorders, and this article describes the different types of waves and stages of sleep. It is shown that the thalamus and cerebral cortex are vital for obtaining good EEG signals, and that the normalized power for different types of waves is different in healthy patients and insomniacs. This shows that the EEG is an effective tool for diagnosing sleep disorders. - Perfect EEG signal comes from cerebral cortex - Hypothalamus, brain stem, thalamus, pineal gland, basal forebrain are involved in sleep - Sleep scoring can be very tedious manually, so there are auto-classification methods for it - Electrical activity recorded reflects the the activity of excitatory and inhibitory postsynaptic potentials in pyramidal neurons - Tests subjects should only wear EEG after being awake for at least 12 hours and having a day of normal activity - EEG signals can be contaminated with other signals from the brain - Sleep disorders are very common - Wake has high frequency and low amplitude - N1 starts to have occasional bursts of slow waves - Stage 2 has theta activity - N3 has high-amplitude delta

	- Methods to remove artifacts - removing them helps to improve the interpretation of EEG signals - BSS or Wavelet methods to remove artifacts - Could possibly use MATLAB for signal processing - Insomnia patients had high delta normalized power and lower alpha, beta, and theta signals - Need thalamus and cerebral cortex for the most significant signal - EEG is functionally safe and non-invasive
Research Question/Problem/ Need	How can an electroencephalogram be used to help diagnose sleep disorders?
Important Figures	N/A
VOCAB: (w/definition)	Parasomnia - disorder occurring in a state between sleep and wakefulness Artifacts - other electrical signals from the brain that interfere with getting the desired data
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/22110467/ Functional Anatomy of Non-REM Sleep https://www.sciencedirect.com/science/article/pii/S1984006316300487 Diagnosis of Insomnia Sleep Disorder Using Short Time Frequency Analysis of PSD Approach Applied on EEG Signal Using Channel ROC-LOC https://pubmed.ncbi.nlm.nih.gov/18002055/ Sleep-Stage and Event Dependency of Brain Asynchrony as Manifested through Surface EEG
Follow up Questions	What are other methods for diagnosing sleep disorders? How does using an EEG compare to other methods in diagnosing sleep disorders? How can EEG track periods of wake after sleep onset?

Article #21: Caffeine Effects on Sleep Taken 0, 3, or 6 Hours Before Going to Bed - 12/12/2023

Source Title	Caffeine Effects on Sleep Taken 0, 3, or 6 Hours Before Going to Bed
Source citation (APA Format)	Drake, C., Roehrs, T., Shambroom, J., & Roth, T. (2013). Caffeine Effects on Sleep Taken 0, 3, or 6 Hours before Going to Bed. *Journal of Clinical Sleep Medicine*, *09*(11), 1195–1200. https://doi.org/10.5664/jcsm.3170
Original URL	https://jcsm.aasm.org/doi/10.5664/jcsm.3170
Source type	Journal
Keywords	Caffeine, insomnia, sleep disruption, sleep quality
#Tags	#background
Summary of key points + notes (include methodology)	To investigate how caffeine consumption can affect and disrupt sleep, scientists administered caffeine at different times before bedtime. They used a placebo group and a caffeine group, and measured objective measures with EEG and PSG. They found that taking caffeine (400mg) even at six hours before bedtime can reduce sleep by an hour, showing the caffeine can be a disruptor of sleep if it is taken too late in the day. - Caffeine taken 30 min before can disrupt sleep and cardiovascular effects during sleep - Aims to see if caffeine administered at different times can affect sleep - Caffeine content in drinks and foods is increasing over time - From a study, it was estimated that 90% of individuals consume caffeine in the afternoon (12-18:00) - Caffeine administration has been used as a model of insomnia - Increasing doses of caffeine administered near bedtime are associated with significant sleep disturbances - Habitual caffeine consumption calculated from asking how much caffeine the participant consumes on an average day - Excluded subjects who consumed >5 caffeinated beverages per day - Participants retained normal sleep schedules - No napping - Sleep diary data was collected in the morning for all nights - Measured sleep disturbance with in-home sleep monitor - headband with

	single-channel EEG - Data analyzed using repeated-measures ANOVA - Caffeine significantly reduced minutes of stage 1 and 2 sleep compared to placebo - Caffeine had no effect on REM sleep - Mostly used young/middle-age participants so hard to generalize study - Results show that high doses of caffeine can negatively affect sleep even when used in the early evening
Research Question/Problem/ Need	How does taking caffeine at different times before bed affect sleep duration?
Important Figures	 Table 3: Objective sleep measures for each condition - Mean +- SD - Caffeine resulted in lower minutes in stage 1 and 2 sleep - Reductions in duration of slow wave sleep observed for all three times of administration - No effect on REM - No significant differences in % of sleep stage distributions between caffeine conditions
VOCAB: (w/definition)	TST - total sleep time SE - sleep efficiency LPS - latency to persistent sleep WTDS - wake time during sleep - similar to WASO (wake after sleep onset)
Cited references to follow up on	https://academic.oup.com/sleep/article/27/3/374/2707947 Low-Dose Repeated Caffeine Administration for Circadian-Phase-Dependent Performance Degradation During Extended Wakefulness https://link.springer.com/article/10.1007/BF02244139 Effect of caffeine on physiological sleep tendency and ability to sustain wakefulness at night https://journals.sagepub.com/doi/abs/10.1177/1090198109341783?casa_token=qvrbokoSCJ4AAAAA:a7nuW7xf5HFU9ZCV63JrKGYri7OYV4oKgsIxjZlWgVakGcIIg91oAaBMWHQeXk7cZ2N3o2N7ERCn Understanding Adolescent Caffeine Use: Connecting Use Patterns With Expectancies, Reasons, and Sleep
Follow up Questions	How could there be major discrepancies from the habitual caffeine consumption that the participants recorded and the actual amount?

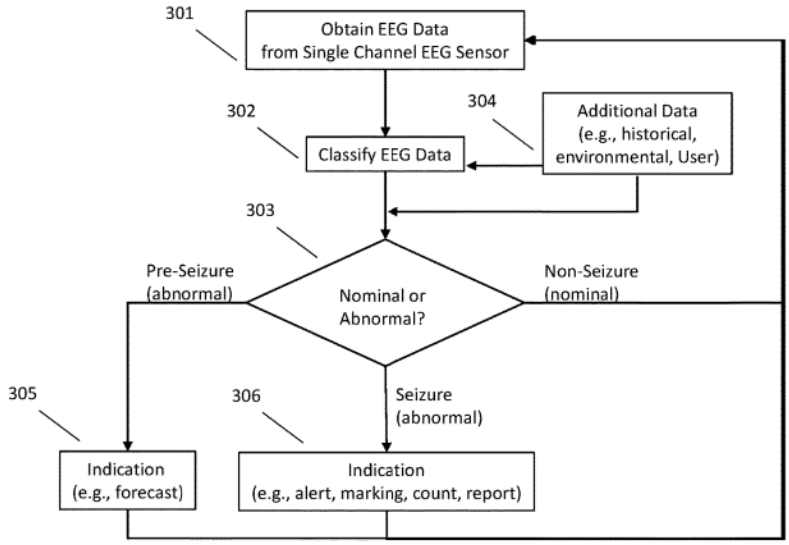
Sleep Measure	Placebo	Caffeine at bedtime	Caffeine 3 hours before bed	Caffeine 6 hours before bed	F (3,33)	P
Latency to persistent sleep (min)	20.59 ± 9.79	43.0 ± 38.93	37.82 ± 29.91	44.68 ± 54.60	2.05	0.13
Total sleep time (h)	7.68 ± 0.85	6.60 ± 1.10*	6.54 ± 1.36*	6.50 ± 1.32*	3.43	0.03
Wake time during sleep (min)	9.55 ± 14.73	27.04 ± 40.06	37.18 ± 43.0*	17.59 ± 22.28*	3.29	0.03
Sleep efficiency %	91 ± 5.71	83.1 ± 12.11*	82.51 ± 12.73*	82.33 ± 12.15*	7.50	0.058#
Stage 1 & 2 (min)	266.77 ± 40.15	226.17 ± 57.75*	222.68 ± 62.24*	222.82 ± 48.83*	3.66	0.02
Stage 1 & 2 (%)	58.02 ± 7.37	56.47 ± 7.77	56.77 ± 10.48	57.28 ± 6.26	0.22	0.88
Slow wave sleep (min)	71.45 ± 26.48	56.67 ± 21.48*	57.0 ± 16.78	48.91 ± 15.81*	4.26	0.01
Slow wave sleep (%)	15.47 ± 5.28	14.47 ± 4.85	14.84 ± 3.87	12.71 ± 3.88	1.22	0.32
REM (min)	123.27 ± 33.89	114.36 28.53	112.5 ± 46.57	118.73 ± 39.75	0.30	0.83
REM (%)	26.62 ± 6.35	29.21 ± 7.19	28.39 ± 11.25	29.99 ± 6.54	0.88	0.46

*p < 0.05 pairwise comparisons vs. placebo; #Nonparametric related samples test of Friedman two-way analysis of variance by ranks was performed as data was not normally disturbed following transformation.

	How could caffeine consumption affect an older age group differently? How were electronic activity and other factors that could affect sleep time limited in all patients?

Patent #1: EEG recording and analysis - 12/13/2023

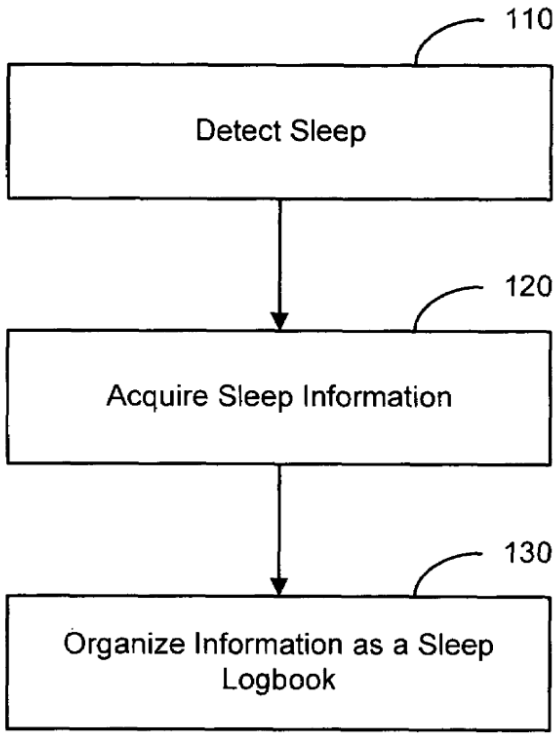
Source Title	EEG recording and analysis
Source citation (APA Format)	Elwood, M. K., Frankel, M. A., Lehmkuhle, M. J., Wheeler, J. M., Lingstuyl, R., West, E. M., Mcgrath, T. D. (2022). *EEG recording and analysis*. 11638551. Epitel, Inc. https://www.freepatentsonline.com/11638551.html
Original URL	https://www.freepatentsonline.com/11638551.html
Source type	Patent
Keywords	EEG, classification
#Tags	#technology
Summary of key points + notes (include methodology)	Scientists developed a method that includes obtaining EEG data from sensors worn by a user, classifying the data, and providing an indication associated with a classification of the data. Additionally, they have the ability to transmit the EEG data to a remote device. This will help in areas that do not have easy access to EEG monitoring, as many hospitals rely on making arrangements with larger hospitals. - Ideal results would entail high quality and long term EEG studies with 19+ channels - Such conditions are difficult to perform and very expensive - Small sensor can sense single-channel EEG data - Senses voltage differentials between two electrode contacts - Has a single-channel transmitter and data logger - EEG data can be analyzed via an analysis by local/remote device or ML model - Sensor can be worn on scalp - forehead or bi-parietal region of the user to capture data over a long period of time - Works even when user goes about their daily activities - Allows for event markers to quickly determine areas within the EEG data that can be indicative of seizure - EEG data of two or more sensors can be displayed - Training data for an ML approach to classify EEG data can use both single-channel EEG data and data from multiple sensors or multi-channel wired EEG - Product involves a computer that can connect to other remote computers or databases - PAN, LAN, or WAN but can also include other networks - Computer can execute program instructions configured to store and analyze EEG data

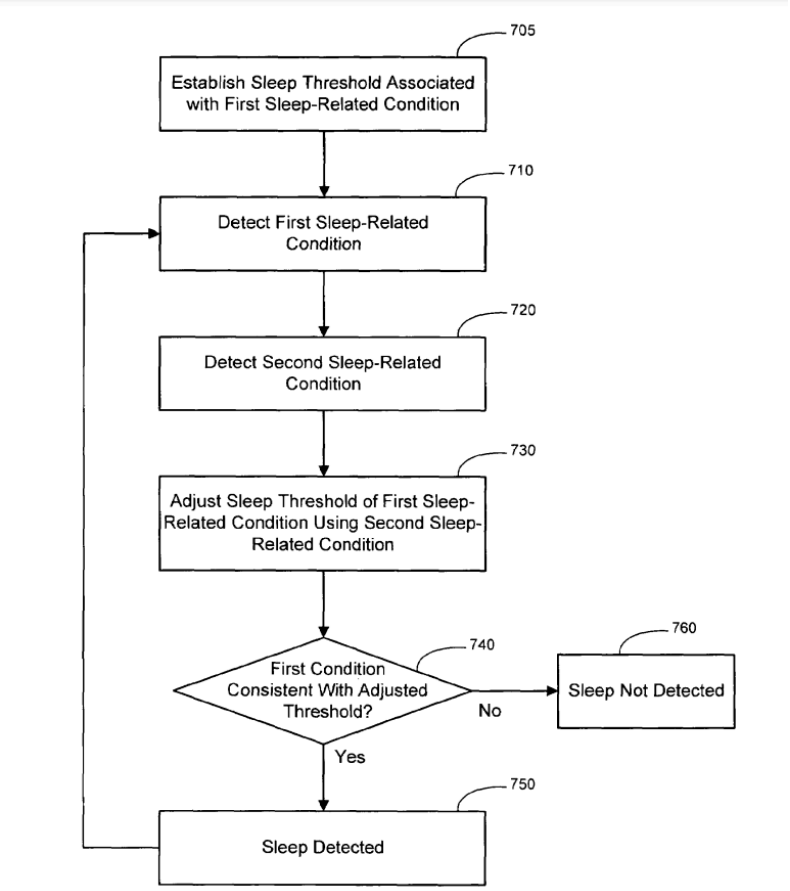
Research Question/Problem/ Need	How can EEG data be obtained and analyzed in an easily transferable and effective manner?
Important Figures	 FIG. 3 Figure 3 shows the process of how the EEG data is processed - Obtained from sensor - Input additional data about the user - Classify data
VOCAB: (w/definition)	Convulsive - clinical Non-convulsive - subclinical PAN - personal area network LAN - local area network WAN wide area network
Cited references to follow up on	https://iopscience.iop.org/article/10.1088/1742-6596/1201/1/012065 Seizure Type Classification on EEG Signal using Support Vector Machine
Follow up Questions	How does this method of classification differ from other current methods? How could this product be used in a clinical setting?

Patent #2: Sleep logbook - 12/14/2023

Source Title	Sleep logbook
Source citation (APA Format)	Stahmann, J. E., Hartley, J. W., Ni, Q., Lee, K., Haltestad, J. D. (2009). *Sleep logbook*. 7572225. Cardiac Pacemakers, Inc. https://www.freepatentsonline.com/7572225.html
Original URL	https://www.freepatentsonline.com/7572225.html
Source type	Patent
Keywords	Sleep, logging, wakefulness
#Tags	#methodology #sleep

Summary of key points + notes (include methodology)	Sleep is an important part of our lives, and yet many people suffer from sleep disorders, which have a number of health and safety risks. Scientists invented an automated sleep logbook to track activity when an individual sleeps. Through organized entries of when an individual sleeps and the activities associated with that period of rest, tracking features associated with different sleep disorders is made easier. While the logbook collects data on patients, physicians can use the results from the logbook to help with diagnosing and managing sleep disorders.
	- Lack of sleep/decreased sleep quality has many causal factors
	  - Nerve/muscle disorders, respiratory disturbances, emotional conditions
	- Chronic sleep disorders such as chronic insomnia, sleep-disordered breathing, sleep movement disorders can significantly affect sleep quality and quality of life in general
	- Movement disorders are common especially among older patients
	- Sleep logbook involves automated method for collecting and organizing information associated with sleep
	- Logbook also includes sleep detector
	- Variety of conditions associated with assessing sleep quality
	  - Cardiovascular system
	  - Respiratory system
	  - Nervous system
	  - Blood chemistry
	  - Muscle system
	  - Environmental
	  - Body-related

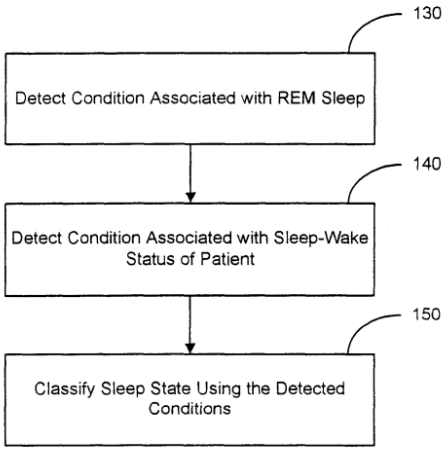
	- Historical - Can be used with a physician who remotely monitors cardiac and respiratory functions - Contains many entries, each corresponding to a separate period - Many ways to organize and access the logbook entries, such as chronologically or by types of events identified - User interface of the sleep logbook can provide access to medical information - Information collected can be stored in memory - Sleep periods can be displayed in menu and selected according to different criteria - Can help in tracking sleep disorder events
Research Question/Problem/ Need	How can sleep be tracked on a regular basis to assist with the management of sleep disorders?
Important Figures	 Figure 1 - Outlines the process of how the sleep logbook collects data on an individual's night of sleep - First needs to detect sleep - Then can record information - Then organizes information according with other dates of sleep

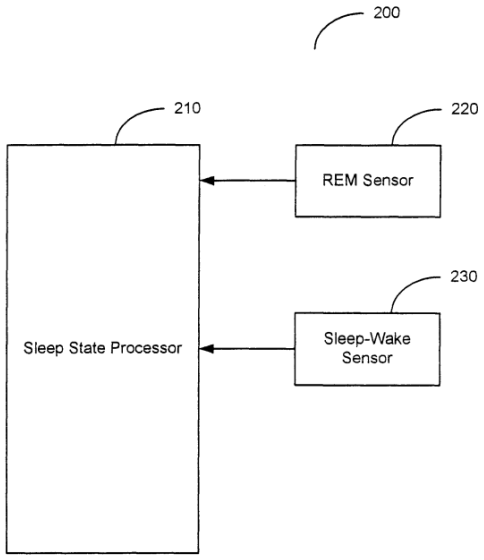
	 Figure 7 Figure 7 shows sleep-detection process - Detects a series of sleep-related conditions to see if the individual is sleeping - Once sleep is detected, it can start collecting information
VOCAB: (w/definition)	SNA - sympathetic nerve activity BNP - brain natriuretic peptide Atonia - muscle paralysis during REM sleep
Cited references to follow up on	https://onlinelibrary.wiley.com/doi/10.1111/j.1542-474X.1997.tb00323.x Sleep Related Cardiovascular Risk: New Home-Based Monitoring Technology for Improved Diagnosis and Therapy https://pubmed.ncbi.nlm.nih.gov/8730394/ Sleep, dreams, and sudden death: the case for sleep as an autonomic stress test for the heart
Follow up Questions	How comfortable is the device for the wearer? Can methods of artifact rejection and feature extraction be applied to the data collected? How easy is it for physicians to use compared to previous products?

Patent #3: Sleep state classification - 12/14/2023

Source Title	Sleep state classification
Source citation (APA Format)	Lovett, E. G., Sweeney, R. J., Keknight, B. H. (2013). *Sleep state classification*. 8600502. Cardiac Pacemakers, Inc. https://www.freepatentsonline.com/8600502.html
Original URL	https://www.freepatentsonline.com/8600502.html
Source type	Patent
Keywords	Sleep stages, classification, rapid eye movement
#Tags	#sleep #methodology #technology

Summary of key points + notes (include methodology)	As the name suggests, sleep disorders occur during sleep; however, there are a plethora of other diseases that can show symptoms during sleep, such as respiratory and cardiovascular conditions. Tracking and classifying sleep stages can help scientists to better understand the physiological processes that occur during each phase, so this sleep state classification was created. This approach involves sensing sleep-related conditions to obtain a condition that will help to discriminate between different periods of sleep and wakefulness. This classification can help to inform individuals about proper therapy and treatments for various disorders.
	- Sleep happens in 90-minute intervals
	- In patients with respiratory or heart disease, the brain can facilitate breathing disturbances, myocardial ischemia, or arrhythmia during sleep
	- Invention aims to classify sleep stages
	- Senses sleep-related conditions and uses signals to classify
	- Includes an REM-modulated condition and a condition associated with a sleep-wake status of patient
	- Can also use the REM-modulated condition to classify one or more sleep stages
	- People experiencing an apnea event stop breathing for a period of time
	  - Can happen hundreds of times a night and in varying intervals
	  - Associated with excessive daytime sleepiness, systemic hypertension, increased risk of stroke, angina, and myocardial infarction
	- Classifying sleep state can be used to provide more effective therapy for cardiac and respiratory disorders
	- Tracking physiological changes during sleep states can help with diagnosing sleep-related disorders

	- Diagnostic testing can be performed during sleep states - Determines a patient to be a asleep if the patient's activity level is below a certain threshold/relatively low - Detected with accelerometer, heart rate sensor, respiratory minute ventilation sensor - Cardiac therapy may be triggered during particular sleep stages to help with cardiovascular conditions during certain sleep periods - Invention includes an REM sensor - Some components have wireless communication
Research Question/Problem/ Need	How can different sleep stages be easily classified?
Important Figures	 Figure 1B Figure 1B - Shows how the product classifies sleep state - First detects a condition associated with REM sleep - Then documents the activity of the patient - Uses these conditions to classify sleep state

	 Figure 2 Figure 2 - Uses an REM and sleep-wake sensor on the patient - Inputs into a processor to help classify sleep state
VOCAB: (w/definition)	SWS - slow wave sleep Myocardial ischemia - when blood flow to the heart muscle is obstructed by a blockage of a coronary artery Arrhythmia - irregular heartbeat Myocardial infarction - heart attack
Cited references to follow up on	https://www.semanticscholar.org/paper/Detection-of-apnea-using-a-short-window-FFT-and-an-Waldemark-Agehed/abc38dd80b36c0e04adb6e19066ba68db5c4a80b Detection of apnea using a short-window FFT tecnhique and an artificial neural network https://pubmed.ncbi.nlm.nih.gov/12668504/ Sleep apnea and heart failure: Part I: obstructive sleep apnea https://pubmed.ncbi.nlm.nih.gov/10498490/ A mechanism of central sleep apnea in patients with heart failure
Follow up Questions	How does this compare to current ML models in accuracy and efficiency? How could this system be integrated with existing sleep monitoring devices? What specific software and hardware limitations are there with this system?