2018

The Effects of Preexisting Disease or Illness on Circadian Rhythm

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The Effects of Preexisting Disease or Illness on Circadian Rhythm

An Honors Program Thesis

by

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Fall, 2018

Health Sciences

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Dec. 10, 2018

Abstract

This thesis will investigate the effect that Alzheimer's disease, blindness, cancer, and Parkinson's disease have on natural circadian rhythms. Circadian rhythms are the biological cycles within our bodies that repeat themselves which can be observed in correspondence to a relative time frame of 24 hours. These cycles can be influenced by a wide variety of factors, both internal and external, such as the daily transitions between daylight and nightfall, an individual's diet or hunger tendencies, and the daily number of hours of sleep that a person gets. Should any of these cycles become disrupted, the result may be a deterioration of an array of physiological processes. In conjunction with pre-existing or pre-diagnosed diseases or conditions, one's quality of life generally becomes worsened when paired with disrupted circadian rhythms. This thesis will further investigate and explain the relationship between the various diseases and their effects on natural circadian rhythms.

Table of Contents

Abstract ……. 1

Introduction …….. 3

Alzheimer's Disease ……. 8

Parkinson's Disease ……... 20

Cancer ……. 31

Blindness ……. 44

Findings of Huntington's Disease ……..... 51

Comparison and Conclusion ……. 52

Glossary …….. 53

Works Cited ……..... 55

Introduction

Since the beginning of time, all living organisms on planet Earth were faced with the need to change and adapt over time and varying conditions in order to survive. Many of these organisms were able to progress and evolve to their modern forms due to their beneficial traits or natural genetic advantages. Although unaware then of what we know now, scientists would come to learn that some of the most important adaptive behaviors surrounded circadian cycles. For instance, the ability of sustaining a properly synchronized circadian cycle would allow an organism the ability and knowledge to anticipate different shifts that would occur for certainty with the passage of each day. These shifts could be as simple as recognition of fluctuations between periods of daylight and nightfall, or as complex as developing an understanding of seasonal and weather-related modifications. Ultimately, the thread that ties this together was the intuitive ability to both process and interpret natural surroundings, and to store these findings in one's memory to properly prepare for the future.

Without the scientific discoveries and experiments of the past, we wouldn't have nearly the same understanding or developed technology that, in present day, have allowed us to learn more about our world and surroundings. This statement also holds true in regards to the field of chronobiology, a subdivision of general biology with a greater emphasis placed on inspecting and analyzing cyclical patterns and phenomena. For instance, some of the origins of studying biological rhythms date all the way back to the early 1700's. Specifically, in 1729, French scientist Jean-Jacques d'Ortous de Mairan published a monograph in which he explained his examinations of the *Mimosa pudica* plant. He observed that even during periods which were completely absent of light, the plants leaves would continue to move and proceed to unfold in

their typical fashion. From these observations, de Mairan suggested that the movement acted as a result of some internal mechanism and not as a response to the amount of sunlight that the plant was receiving. Just a few hundred years later, this phenomenon would become better identified and formally referred to as an "internal clock", the driving force of actions among all living organisms (Vitaterna et al., 2001).

Towards the end of the 19th century and into the start of the 20th century, Austrian neurologist Constantin Von Economo made an important discovery which played a pivotal role in identifying relevant anatomical regions responsible for patterns of sleep and wakefulness. While conducting research and investigating the pathology of *encephalitis lethargica*, Von Economo ultimately proposed the idea that a sleep center existed within the brain, in the anterior hypothalamus, with a comparable wake center existing as well, within the posterior hypothalamus. Although these were simply Von Economo's theories based off of observed correlations, these ideas were subsequently proven to be true following a study conducted by researcher and neuroanatomist Walle Nauta. Utilizing a population of rats as his experimental subjects, Nauta was able to prove patterns of prolonged wakefulness as a result of a lesion to the anterior hypothalamus, as well as similar patterns of extended sleep in the presence of a lesion to the posterior hypothalamus. These crucial discoveries not only provided proof of Von Economo's theories, but also allowed us to pinpoint that both sleep and wakefulness were somehow driven by or related to the hypothalamic region of the brain (Moore, 2007).

Another crucial scientific discovery was made by biologist Curt Richter while conducting his Ph.D. thesis which studied biological clocks within the body and their impact on behavior. Conducting a lesion study on a population of lab rats, Richter was able to conclude that the rats

with hypothalamic lesions experienced a loss of rhythms related to both rest and activity. The evidence collected from this study supported the inference that the hypothalamus in general contained the "master clock" among rats, as well as other organisms with similar anatomy (Moore, 2007; Schulkin et al., 1994).

Additionally, throughout the 1950's and 1960's, continued experimentation and research related to the brain stimulated the development of more sophisticated and refined technology. For example, the creation and use of the encephalogram (EEG) allowed researchers to measure and record electrical activity conducted within the brain by attaching electrodes to the scalp. Likewise, there was the development of an anatomical method of tracing neurological pathways of the brain which provided scientists with the ability to study the networks of neuroactive peptides and various chemicals produced by the brain including GABA, glutamate, and monoamine neurotransmitters (Moore, 2007). On the research front, biologist Colin Pittendrigh and fellow biologist and physician Jürgen Aschoff conducted studies on fruit flies and humans, respectively, which led to the identification of circadian rhythmicity, leading to Pittendrigh and Aschoff commonly being recognized as the co-founders of the field of chronobiology (Vitaterna et al., 2001).

Before examining the effects that the various diseases previously mentioned had on circadian rhythms, it is important to have a fundamental understanding of exactly what circadian rhythms are, and the impact that they have on the internal framework of living organisms. Following that, we will examine the crucial main components and primary biological pathway for conducting these signals. Circadian rhythms can be mental, behavioral, or physical shifts, and are an organism's primary responses to fluctuation periods between daylight and darkness in

one's own environment. Circadian rhythms are endogenous in nature, meaning that they are developed internally within an organism. Any factor impacting circadian rhythms which originates outside of the organism's body is exogenous, or known as a zeitgeber, and can include various environmental cues like light, temperature, and even the seasons. While their origins are still unclear, many scientists hypothesize that organisms developed these rhythms as products of one main regulatory internal clock, constantly evolving to provide protection or advantages. The main regulatory clock of the human body, also commonly referred to as the "master clock" is the suprachiasmatic nucleus (SCN) which is located within the hypothalamus, the area of the brain that forms a connection between the nervous and endocrine systems. It consists of approximately 20,000 neurons and is responsible for overseeing all mechanisms and rhythms for all cells of the human body. The SCN itself is connected to the optic nerve, allowing for its ability to detect the amount of visual brightness perceived. Additionally, it allows for active responses to shifts between periods of both brightness and darkness from the environment ("Circadian Rhythms", 2017).

All of these components play a significant role in the transmission of perceived stimuli from an organism's surroundings to be processed and expressed as rhythmic patterns. One of the main factors impacting circadian rhythms is light, and whether or not it is present in the environment and surroundings. This is where the pathway of transmission is essentially initiated. When light is present, the organism's eyes receive the light initially through the lens, which is channeled through thick vitreous humor and directed towards the back of the eye known as the retina. Beyond the rows of rods and cones which process the color and definition of what we view, another row of crucial cells exists within the retina. These cells are called

photosensitive retinal ganglion cells, a specific kind of neuron, and their function is to detect the level of brightness of what we are seeing. These cells are connected to and feed the input to the optic nerve, acting as a conduit between the eyes and the brain. The information is then delivered directly to the SCN, the body's master clock. From this point, the SCN decides based on the received information how to delegate and what to transmit to the other miniature clocks controlling the other cells of the body. In this particular example, the presence of light acted as the stimuli to engage the pathway, indicating the body needs to be in an alert state in order to function. For this scenario, the SCN will communicate to the other cells to increase blood pressure and simultaneously decrease the production of the chemical melatonin. Melatonin is a hormone commonly associated with inducing the sensation of sleep. Contrastingly, at the end of a day when light starts to fade from one's surroundings, the body needs to prepare for rest, and the SCN reacts appropriately, instructing for increased production of melatonin. This cycle, being dependent on the fluctuation periods of lightness and darkness and having an approximate span of one full day, make it truly a circadian cycle (What Makes You Tick: Circadian Rhythms, 2015).

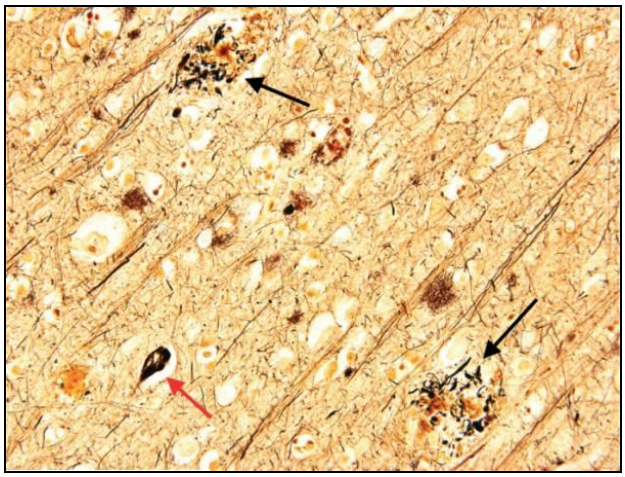
Alzheimer's Disease (AD)

Alzheimer's is a very common form of dementia and accounts for approximately 60-80 percent of all dementia cases. This particular disease impacts and hinders one's mind and behaviors. The majority of the affected population are typically of age 65 or older, however younger adults may also suffer from early-onset Alzheimer's and are typically diagnosed in their 40's or 50's. AD is a progressive disease, meaning that the amount of overall physiological deterioration increases over time. With respect to other diseases and illnesses, AD is the sixth leading cause of death within the United States alone. Depending on the individual, in combination with both age and lifestyle, an affected person can survive anywhere between 4 and 20 years with the disease. Currently, there is no cure that exists, but researchers continue to study the disease in hopes of one day providing a true remedy.

Due to its progressive nature, AD is generally recognized as a sequence of three general stages: mild AD/ early stage, moderate AD/ middle stage, and severe AD/ late stage. During the mild AD phase, the affected individual is still likely able to function mostly independently. The symptoms of the disease may not yet be apparent to those other than close friends or family members. Typical difficulties around this stage include trouble recalling recently learned information, misplacing valuable objects, struggles when searching for a proper word or name, and increased difficulty in planning or organizing. Next, the moderate AD phase, usually the longest stage of the three, can last for several years. An individual at this stage can still participate in some activities of daily living but with assistance. Typical symptoms at this phase may include increased mood swings, greater tendencies to wander or get lost, shifts in sleeping patterns, difficulty controlling one's bladder, and forgetfulness of personal history or events. In

the final stage, also known as late stage AD, an individual requires round-the-clock supervision and aid with both daily and personal tasks. These individuals may also have increased difficulty in verbal communication, swallowing, physical ability, and unsubstantiated feelings or suspicions towards friends and family. In typical fashion of many different diseases, the range or severity of symptoms may differ from individual to individual, and theoretically no two individuals will suffer from exactly the same set or intensity of symptoms. Although no cure exists to save an individual from this disease, some treatments do exist that can reduce the severity of some of the previously listed symptoms. This could possibly provide the individual with less discomfort, as well as an improved quality of life.

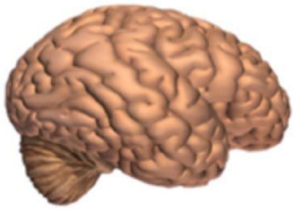
AD impacts the brain by making microscopic changes before any signs of the characteristic memory loss are even apparent. This specific period of time is referred to as 'preclinical Alzheimer's disease' and can last for several years. As a typical sign of aging, most individuals will develop small structures known as plaques and tangles. Plaques are composed of beta-amyloid protein fragment deposits which accumulate between nerve cells, and typically appear as round, dark disc shapes. Tangles are made up of twisted tau protein fibers which also



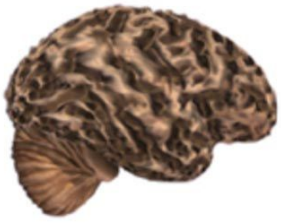
Temporal cortex of a patient with AD, 100x magnification (Perl, 2010)
Plaques are identified by the black arrows, a tangle identified by the red arrow.

gather within cells, and appear as dark, teardrop-like shapes. Although these two different structures can be commonly found in majority of the aging population, those with Alzheimer's develop them in more predictable patterns, with emphasis placed on their location near the memory centers of the brain ("What Is Alzheimer's?", 2018).

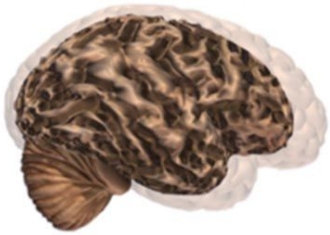
When looking at the brain's morphology as impacted by the disease over time, it is important to note a gradual shrinking. As the disease progresses within the body, the main cells targeted are the neurons of the brain. The neurons gradually become damaged and defective, and start to die. The deterioration specifically starts in the hippocampus, the brain center responsible for learning and memory. As the cells continue to degenerate, the brain's mass also shrinks as a result of general substantial tissue loss. The figures below depict a comparison of a healthy brain with one affected by AD.



A brain without AD



A brain in advanced stage AD



How the two brains compare

("Brain Tour Part 2: Alzheimer's Effect", 2018)

The first study pertaining to AD also highlights a unique characteristic and symptom of the disease, sundowning. Sundowning is a phenomenon generally describing heightened intervals of active behavioral symptoms, especially during afternoon and evening periods in a day. In addition to exploring the impact of sundowning, the goal of this study was to establish

what modifications are made on circadian cycles when paired with the presence of AD. In the first study the researchers explain that circadian rhythmicity generally can be observed by impacting body temperature, heart rate, secretion of certain hormones, red blood cell production, and others. They then proceed to state that when compared to their healthy counterparts, the affected elderly population typically experienced the greatest amount of total daily activity during the evening, likely attributed to the effects of sundowning syndrome.

The study consisted of a total of 25 male patients from a dementia study unit at one of the Department of Veteran Affairs' hospitals. These men had a collective mean age of 71 years old, with a range from 60-88, and a mean diagnosis period of 11 years. All of these men were noted as having some degree of neurological deterioration, with some cases more severe than others. Some of the patients with more severe cases were non ambulatory, and the remainder able to walk. None of these subjects received either sedatives nor antipyretic medications within 24 hours prior to recording any results. Additionally, there were nine healthy adult males that were observed as controls. These men had a mean age of 73.4 years, ranging from 67-83, with no history of neurological disorders and no medications. Both the patients and the healthy control individuals were studied at the same time in order to prevent any external seasonal impact on behavior. In order to keep other factors consistent and prevent any bias, all participants of the study had fixed scheduled mealtimes and regulated periods of when the lights were kept on, from 6:00 in the morning until 10:00 in the evening for the duration of the study. The healthy individuals were housed in a research ward of the hospital and were allowed to rest and sleep as they normally would. The participants were instructed to wear portable activity monitors, worn in a vest pocket positioned at waist level, in order to record pertinent data. Relative activity

levels and core body temperatures were tracked by a combination of the monitors and other methods, which reported data back to researchers every 5 minutes over the course of a 72 hour period. In conjunction with the quantitative recorded data, staff members of the hospital were asked to evaluate the degree of sundowning behavior they observed in the subjects, as well as the frequency of sleep-wake disturbances.

After comparing the results of the affected individuals and the control subjects, the researchers were able to draw a few conclusions. One of the important conclusions was that patients with AD generally displayed greater nocturnal activity, as well as decreased daily motor activity when compared to control subjects. From the actual recorded results, in terms of locomotor activity relative to a 24 hour clock, patients with AD averaged an acrophase time of 16.92. Specifically, the average among the ambulatory patients was 16.38 and nonambulatory 17.46. This means that the peak point of their activity occurred at approximately 5:00 in the afternoon, while the control subjects averaged an acrophase of activity at approximately 1:00 in the afternoon. This was an important discovery because it supported the idea that individuals affected by AD may also exhibit signs of sundowning syndrome, and further explained why these individuals had increased nocturnal tendencies in terms of activity. It is also important to note that these findings may suggest that as the disease progresses, the greater the impact on the acrophase of activity. Additionally, the researchers concluded that patients with AD generally had slightly higher average core body temperatures (37.2 degrees celsius) compared to control subjects (36.9 degrees celsius). The core body temperature would likely be higher in patients with AD because the interaction of the disease pathology with the brain disrupts the hypothalamus which acts as the body's thermostat. Additionally, it is also typical of patients

with AD to secrete lower quantities of melatonin, which could also be related to the slightly raised temperatures. With the presence of melatonin as the body prepares to sleep, the hypothalamus typically responds by cooling the body down, and therefore reducing the temperature slightly lower than standard.

Substantial observations were made from this study to support the idea that as AD progresses within the body, it is able to disrupt more of the natural processes typically regulated by the hypothalamus. The important functions mentioned in this particular study were the amount of daily activity and acrophases suggesting possible sundowning, as well as the regulation of core body temperature. It was concluded that on account of both of these processes, affected patients with AD displayed increased activity during late hours and higher body temperatures when compared to control subjects (Volicer et al., 2001). While this specific study was very thorough in its experimentation and attempt to reduce as much bias as possible, one necessary critique would be that of the environment it which it was conducted. It is possible that the hospital routines and environment may have had some impact on the circadian cycles observed, however this cannot necessarily be proven. For instance, the AD patients, being residents of the hospital, may have already developed modified internal patterns in order to acclimate to hospital cycles and procedures on a permanent basis. This would not be the case for the control subjects who live normal lives outside of the study, with standard and unaltered internal cycles. Despite this, the hospital as an environment was a necessary component for this study so that the patients with AD could receive necessary care and supervision that comes with progressed stages of the disease.

The second study focuses more on the general impact of AD on sleep-wake cycles. The subjects for this study consisted of 28 male patients from a dementia study unit of a Department of Veteran Affairs' hospital. These men had a collective mean age of 71 years old, with a range from 61-82, and a mean duration of 10 years of being diagnosed with AD. These subjects were described as being quite cognitively impaired, unable to walk, communicate, or conduct activities of daily living without assistance from hospital staff. Other than AD, the hospitalized study individuals did not suffer from any other forms of illness, and did not receive antipyretic medications within a 24 hour period before recording results. For comparison, the study also included ten control subjects, specifically eight males and two females, with an average age of 73, ranging from 67-80. These individuals also did not have any illnesses, nor mental deficits, and were not taking any medications prior to the study being conducted. The two groups were studied at the same time to prevent any external environmental bias, were regulated by the same amount of time in artificial lighting, and were fed on identical schedules. Beyond these parameters, AD patients received nursing care twice a day, while control subjects were allowed to live normal lives within the confines of the research wing. To record data, participants were asked to wear an activity monitor strapped to their ankle. The device would record counts of activity at five minute intervals over the span of the 72 hour study. The researchers also used rectal thermometers paired with an ambulatory recorder in order to take core body temperatures of the participants.

When analyzing the data, in order to compensate for the two groups which varied in size, the researchers took the relevant mean values from each independent population and conducted an unpaired *t* test to better compare the values between the affected participants and controls.

The researchers were able to reach several informative conclusions. No correlation was recorded between the ages of the participants with AD and the duration of the illness within the body. This means that one of the relatively younger AD participants may have more abnormally shifted cycles and acrophases than an older patient from the study who might have been affected by the disease for a longer period of time. Additionally, when compared to the controls, the AD patients displayed overall lower mean daily locomotor activity and increased nocturnal activity, characteristics consistent in individuals affected by the disease. The AD patients were overall less active than the controls, and had recorded acrophases lagging approximately 4.5 hours after the mean acrophase among the controls, as displayed by the figure below.

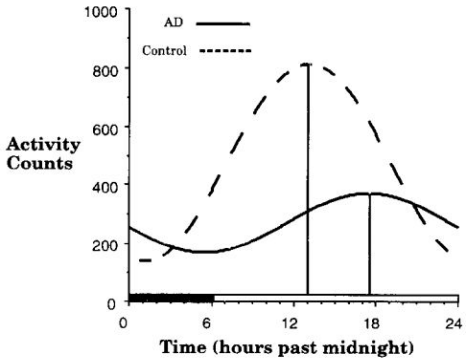


Fig. 2 displays lower amounts of activity overall in AD patients, with a delayed acrophase of 4.5 hours compared to controls (Satlin et al., 1995)

Another important detail to mention was that the researchers noticed that the AD patient population displayed frequent periods of small nocturnal activity, further supporting the idea of fragmented and disrupted sleep cycles. The main differences were observed when comparing locomotor activity levels. However, there were minimal differences when analyzing core body temperature (CBT) rhythms, with a mean average higher in patients with AD than the controls. One encapsulating statement made towards the end of the journal article explains that the

combination of atypical temperature and locomotor activity levels, supplemented with fragmented sleep patterns, provides substantial evidence of loss of pacemaker function, and therefore disrupted circadian rhythms as well.

One critique I would make on this article was actually brought to light by the researchers themselves. They noted that there may have been environmental differences in the control patients that weren't adapted to the hospital as a residence like the AD patients were. These differences may have altered some results and findings of this particular experiment. However, the researchers mention that for future related studies, they would take this information into account and plan an acclimation period for the control subjects prior to the start of a new study to eliminate as many differences between the two groups (Satlin et al., 1995).

The third and final study pertaining to AD tests the impact of imposing bright light as a possible viable treatment for patients with the disease. Specifically, this research article focuses on whether or not circadian cycles and rhythms could be shifted or corrected in patients with AD by imposing artificial external light. Initial research into AD revealed that disordered circadian cycles may be attributed to loss of cells composing the SCN, thus diminishing its overall ability to function properly. These deficits and abnormalities are believed to be responsible for causing interrupted sleep cycles and sundowning behavior. The research team hypothesized that bright light 'pulses' during evening hours prior to sleep would improve circadian rhythms as well as lessen agitation in those also displaying behaviors associated with sundowning.

The study consisted of ten patients with AD, nine males and one female, with a mean average age of 70 years. These patients were studied in the dementia unit of a veterans' hospital for a period of three weeks. All of the participants were deemed either moderately or severely

demented, with an average duration of AD illness of approximately 9 years. All of the patients were under full time supervision of nurses. The nurses analyzed the overall behavior of their patients at the end of each shift, three total times per day, and scored them on their level of agitation, ranging from zero to three. A score of zero indicated none or minimal agitation, whereas a three indicated a severe level. They also recorded the amount of restraint required to control the patients, and how frequently they needed to administer prescription medications to each patient. Like the other two studies, locomotor activity was measured via a portable activity monitor worn in the pocket of a vest at about waist level. All ten of the subjects were monitored and observed over a total period of three weeks. The first week was to establish baseline measurements of the patients, the second week to test the hypothesized bright light treatment, and the third and final week for post-treatment observations. During the second week in which treatment was provided, the subjects were exposed to two hours of bright light bursts from 7:00-9:00 pm each evening of that week. The light was delivered in the form of a light box which contained three U-shaped fluorescent bulbs.

The researchers found that generally the light therapy helped improve sleep-wake cycles in eight out of the ten total participants, based on clinical ratings provided by the nursing staff. In the initial week intended for establishing baseline values, the mean score of the cycles among participants was rated 6.2/10. After the second week in which treatment was provided, the scores dropped down to 3.0, and reaching lowest scores, averaging 2.3 at the end of the third week (post treatment values). Generally, it was concluded that the bright light pulses resulted in improved sleep-wake behaviors in evening hours, decreased severity of the symptoms associated with sundowning, and reduced amounts of locomotor activity during evening. The researchers

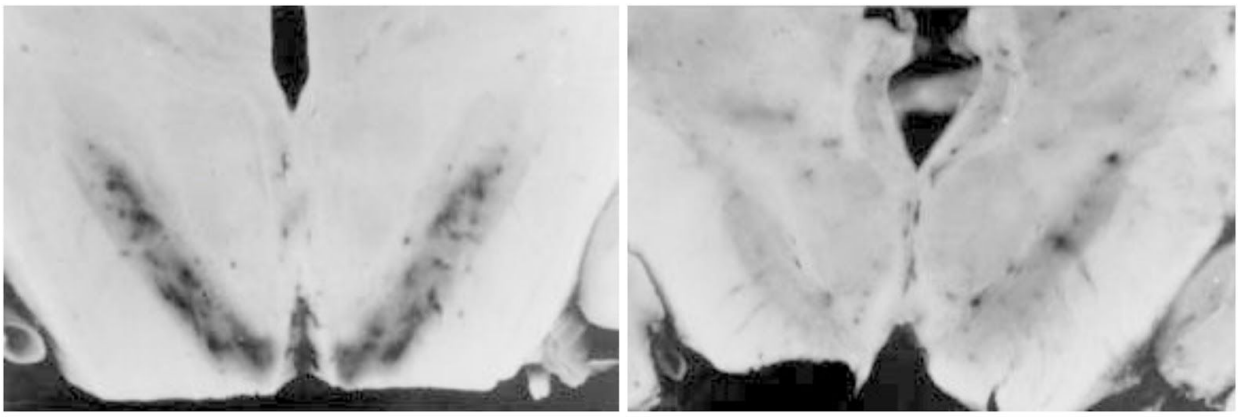
also mentioned that the locomotor activity acrophase was shifted approximately one full hour earlier at the end of the second and third weeks when compared with the baseline values. Although these results were not significant enough to make a conclusion for this particular study, further extensive testing over a longer period of time may prove to be a successful treatment option for AD patients (Satlin et al., 1992). One major critique and concern I have regarding this study is related to the selected sample of participants. It appears unusual that of the ten total selected participants, nine out of the ten were in fact men, with only a single woman participating. This lack of a balanced or diverse sample may have sad some sort of impact on the recorded results of this study.

Alzheimer's disease is a complex progressive degenerative disease of the mind which has proven relationship with circadian cycles and functioning of the brain. Generally, it was observed that patients with AD experience reduced amounts of daily activity and heightened amounts of nocturnal activity, a component of the disease which may be attributed to sundowning. Specifically, when compared to healthy control subjects, the AD patients of the studies cited consistently expressed shifted cycles away from the norm, with later acrophases. Additionally, as the disease progressed in severity, patients displayed increasingly shifted cycles and later acrophases. Findings were also consistent in suggesting that the impact of the disease is stronger in those who have been diagnosed with the disease for longer periods of time, with no correlation attributed to age. One other noticeable trait of AD is a slightly elevated core body temperature when compared to healthy individuals. These findings make sense when understanding the degree of neurodegeneration of the brain, specifically of the SCN and hypothalamus in general, the centers responsible for regulating homeostatic levels within the

body. One encouraging discovery made was the possible future development of technology incorporating bright light as a form of treatment for patients with AD. The artificially imposed bright light may be able to alter rhythms in such a way to reintroduce a sense of normalcy back to those impacted by the disease. In turn, this form of therapy could also help reduce the severity of associated symptoms of sundowning.

Parkinson's Disease (PD)

Parkinson's Disease is a neurodegenerative disease, specifically impacting the substantia nigra of the brain. The substantia nigra is located within the brainstem of the brain, specifically in the midbrain section. It is primarily responsible for the production of the neurotransmitter dopamine via dopaminergic neurons. In a healthy brain, the substantia nigra is described as a crescent-shaped cluster of darkly-pigmented cells. As PD begins to take its course on the brain, these cells are gradually destroyed, resulting in lack of pigment upon visual examination in more severe and developed cases. Dopamine is responsible for the control of movement and emotional responses of the human body, and in the presence of PD, the dopaminergic neurons are impaired, thus impacting movement.



Substantia nigra of a healthy brain (left), and depigmentation of substantia nigra in PD brain (right) at 0.7 x magnification (Triarhou, "Dopamine and Parkinson's Disease").

This disease is progressive and worsens in severity with time. PD affects approximately one million individuals in the United States alone, and approximately ten million internationally. The majority of the affected population are typically of age 50 or older, however younger adults may also suffer from young-onset Parkinson's disease (YOPD) and account for a total of

between two and ten percent of all cases within the U.S. alone. Statistically, according to the CDC, complications associated with PD constitute the 14th leading cause of death in the United States. The general cause of the disease is unknown, making it idiopathic in nature, and currently no cure exists. However, there are treatment options available such as medications and surgery that can help treat certain associated symptoms ("What is Parkinson's", 2018).

This disease in particular has a specific set of characteristic signs and symptoms, including but not limited to tremors, stiffness of the limbs, issues with gait or balance, and several others. Additionally, in terms of non-motor symptoms, examples include cognitive changes, early satiety, excessive sweating, fatigue, hallucinations and delusions, mood disorders, sleep disorders, urinary frequency and incontinence, and vision loss. While symptoms tend to develop slowly over years of being affected, an individual may be diagnosed with PD in more of a moderate stage rather than earlier and the disease may have already progressed to some degree. In order to analyze the progression of this disease, the Hoehn and Yahr scale was developed, which classifies the disease as a series of five different stages, respectively increasing in severity as you move up the scale. In a general sense, the first and second stages are indicative of mild PD, the full third stage represents moderate PD, and the fourth and fifth stages constitute what would be considered severe PD. The first stage is characterized by general unilateral involvement of the body and minimal impairment or deficits. The main symptoms include tremor, rigidity, and poor condition in the arms or legs. The face may also be affected on one singular side and pose resemblance to the condition of Bell's palsy. This stage is often missed entirely and a proper diagnosis of PD is typically made during a later phase. After time has passed, in some cases months and others years, symptoms start to develop bilaterally, typically

indicating the origins of the second stage. These may include bilateral loss of facial expressions, also known as masking, speech abnormalities, softer voice, slurred speech, generalized slowness, and rigidity of the trunk of the body. Individuals at this stage are still capable of carrying out tasks of daily living. If the symptoms are properly reflected bilaterally at this phase, it simplifies a PD diagnosis. However, if the only symptoms at this point are rigidity and slowness, this phase may still be mistaken for typical adult aging. The third stage, recognized as moderate PD, is generally characterized by an overall loss of balance and inability to react promptly to protect oneself from falling. An individual may still be able to perform activities of daily independent living. All other aspects of PD are present at this point enough to make a conclusive diagnosis of PD. Also identified as the beginning of severe PD, stage four entails the disease being fully developed within the body. The affected individual is still able to walk and stand unassisted, but clearly appears to be disabled and impaired. The transition from the third to the fourth stage is marked by the inability of the individual to live and function on their own. The fifth and final stage of PD is distinguished as the individual is typically confined to a wheelchair or permanently bedridden. The individual is unable to rise or stand on their own, and are in greatest danger of falling as they are prone to freeze up when standing, as well as stumble when walking ("Five Stages of Parkinson's", 2018).

Although the majority of the incidence of PD happens to be spontaneous and accounts for approximately 85 or 90 percent of all cases, the other 10-15 percent of cases are thought to occur genetically. Scientists and researchers believe that in order to inherit PD, it is not simply a mutation of a singular gene that would result in the condition, but rather a complex interaction of multiple factors, even outside of the genetic realm. For instance, there are also environmental

factors that may place individuals at higher risk of developing PD. Some of these factors include but are not limited to age, gender, area of residence, occupation, pesticide or herbicide exposure, and several others ("What is Parkinson's", 2018).

The first study pertaining to PD specifically focuses on the analysis of sleeping patterns in an attempt to define the circadian phenotypic expressions of individuals with early-stage PD. Prior to conducting their study, the research team noted that in a survey conducted of nonmotor symptoms of Parkinson disease, 64 percent of participants reported suffering from sleep problems, the second greatest nonmotor complaint among PD patients. This survey acted as the driving force for the team to conduct their own study, given their prior awareness of sleep problems linked to the presence of the disease, and the lack of general knowledge regarding the cause of the condition.

The study consisted of an initial assessment with a total of 239 participants, further specified to a more comprehensive case-control subgroup of 45 individuals; 30 of which were diagnosed with early-stage Parkinson disease, and the other 15 acting as healthy control individuals. In terms of data collection for the study, all participants were asked to keep sleep diaries, as well as wear an activity tracking monitor on their non-dominant wrist continuously for a period of two weeks prior to the sleep study. The study itself entailed a polysomnographic assessment over two consecutive nights in which sleep patterns could be tracked and recorded. Patients were also equipped with a venous cannula to allow for blood collection without disturbing the sleep cycles of the subjects. Other than getting up to go to the bathroom, the participants were asked to remain sedentary. Meals were distributed to all participants at fixed

times, daytime naps were prohibited, and the temperature of the environment was maintained at a consistent 21 degrees celsius, or approximately 70 degrees fahrenheit.

The researchers were able to reach several conclusions. Patients newly diagnosed with PD were more likely to report frequent sleep complaints, which correlated with a general poorer quality of life when compared to controls. The researchers noticed that the altered levels of circulating hormones in the body due to PD resulted in abnormal micro-shifts in sleep tendencies specific to PD patients. These shifts include increased sleep latency, or the amount of time required for an individual to fall asleep, overall reduced efficiency of sleep, and reduced REM sleep when analyzing the sleep cycle as a whole. Additionally, it was noted that the patients diagnosed with early-stage PD had a greater tendency towards hypersomnolence than controls. This means that the PD patients were more likely to experience excessive daytime sleepiness, or extended periods of sleep during the evening. They also concluded that there was greater evidence of destructuring of sleep cycles in patients at more advanced stages of PD, supporting its progressive nature as a disease. While declined activity of the SCN in healthy adults leads to sleep-wake disruptions and decreased production of melatonin, these effects are likely amplified and worsened for those with PD.

This study supported hypotheses of disturbed sleep cycles in the presence of PD pathology, however more research should be conducted on this issue in order to better pinpoint causes and develop concrete treatments for the disease. One major critique of this study would be that the number of participants in the sleep study (the major component for providing results and data for analysis) was relatively small. Had this group of participants been larger, the

researchers would have possibly drawn the same conclusions, but would have greater certainty of their findings as reflected by a larger target population (Breen et al., 2014).

The second study placed more of a focus on individuals with PD that experienced some degree of hallucinations as a side effect of the disease. Specifically, it addresses the relationship between the presence of hallucinations in patients with PD and altered circadian rhythms. After reviewing pre-existing literature, the research team noticed that some of the primary complaints of those with PD were related to sleep disturbances, however not much research had been done to investigate the relationship between the disease and circadian rhythms. The researchers also believed that the pathology of PD on the body acts as a mechanism to expedite signs and symptoms that would typically develop and become more prominent with the passage of time and growing older naturally. Before discussing their study, the researchers provided establishing background information to help familiarize the reader with the disease. For example, they mention that PD is one of many degenerative diseases, and that it is comprised of sleep fragmentation and excessive daytime sleepiness, which paired together led themselves to altered biological rhythms.

In this study, the researchers had two main hypotheses: first, that patients with PD would display altered rest-activity rhythms when compared to controls, and second, that a positive correlation was observed between the amount of disturbance and age as related to cognitive impairment. The study consisted of 79 total participants. 50 of the total participants were adult PD patients, 27 of whom suffered from hallucinations, and 23 that did not have hallucinations. The remaining 29 individuals were healthy adult control subjects. The controls did not report any neurological diseases, sleep disorders, or indications of dementia. Periods of rest-activity

were measured using actigraph monitors, specifically uniaxial accelerometers, worn on the non-dominant wrists of the participants. These devices were used to measure gross motor activity, and would provide the researchers with data about the participants' periods of frequent motor activity. The hallucinations were assessed with interviews conducted in which the researchers asked the participants questions about the frequency and subject matter of hallucinations they had experienced within three months prior to the study. All data was recorded from the patients' respective homes remotely, and all were instructed to carry out normal daily activities. The participants were asked to wear the actigraph devices for one week and measurements were recorded at 30-second epochs.

The research team found that all of the individuals with PD, both the standard and hallucinating forms, had lower recorded peaks and bursts of activity when compared to the healthy control subjects. These results likely reflect the fact that PD has debilitating effects on motion and movement, and therefore levels of activity would be expected to be lower than the average healthy individual. Additionally, when comparing the frequency of activity of the PD patients against the controls, it was noted that the PD group had a greater tendency to often transition from high to low activity periods, making their activity levels less predictable than the average control individual. The researchers also noticed that subjects with both PD and hallucinations had higher levels of activity and more fragmented sleep cycles than those that did not experience hallucinations. Ultimately, the presence of PD was described as simply exaggerating the effects of normal aging on circadian rhythms, however at a quicker rate than a healthy control individual. One constant connection the researchers of this study made was the

similarity in results of this PD study to other studies focused on AD, with the exception of the underlying pathologies of the respective diseases.

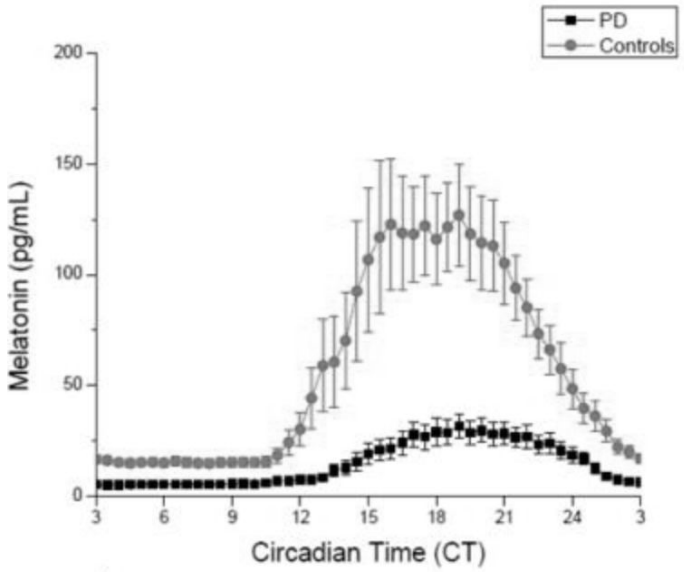
Some possible problems with this particular study were discussed at the end of the article. First, the researchers mentioned that in order to treat some of the symptoms of PD, specific cycles and timing of treatment regimens were required, which may have imposed a pre-existing cyclical framework on these patients who they were trained to operate around. In addition, due to the cognitive impairment and deficits of PD patients, it was difficult for proper compliance of the participants to maintain sleep diaries independently, some of whom did not have caretakers to help them (Whitehead et al., 2008).

The third study mainly focused on the discovery of more information regarding the relationship between the presence of PD and its pathophysiological impact on biological circadian rhythms. The research team wanted to investigate and analyze the endogenous secretion of the neurotransmitter melatonin in individuals affected by PD. Prior to deciding to conduct their own study, the researchers found other experimentation conducted which indicated that subjects with PD suffered from a variety of skewed circadian rhythms and biological levels. The findings included fluctuations in blood pressure, heart rate, impaired sleep-wake cycles, and variations in cortisol and melatonin levels present. From these discoveries, the researchers chose to conduct their own study with a specific focus on the impact of the disease on melatonin production, and its possible stimulation of excessive daytime sleepiness in PD individuals.

The setup for this study consisted of a total of 35 participants. 20 individuals were patients with PD, and the remaining 15 participants served as control subjects. Each of the control individuals were matched in age to their PD counterpart within the study. The PD

patients were recruited from the Parkinson's Disease and Movement Disorders Center of Northwestern University. Contrastingly, the controls were recruited through advertising in the local Chicago area and the Aging Research Registry within the Northwestern Buehler Center on Aging. Specific exclusion criteria were detailed in order to select specific participants for this study. The criteria included a proper idiopathic diagnosis of PD as per the definition provided by the UK Parkinson's Disease Society Brain Bank, ensuring the PD patients were between stages two to four on the Hoehn and Yahr Scale, and that they did not have either an atypical form of PD nor cognitive impairment or depression. The same criteria, where applicable, was applied when selecting comparable control individuals. This study uniquely took form as a cross-sectional study that was conducted between the dates of January 1, 2009 to December 31, 2012. The participants were asked to maintain a consistently regular sleep schedule for two weeks prior to the initiation of the study and to keep corresponding sleep journals as a physical record. Participants were admitted to the clinical research unit at the Northwestern Memorial Hospital. The participants were fitted with intravenous catheters in the forearm for ease when taking blood samples each half hour of a 24 hour period to analyze the blood serum hormone levels (specifically, assays for melatonin levels).

Ultimately, the researchers were able to conclude that there were overall lower melatonin levels and amplitudes in the PD patients when compared to the control subjects. Specifically, those patients that suffer from excessive daytime sleepiness exhibited the greatest amount of impairment in regards to circadian melatonin secretion. This provided evidence for the importance of maintaining proper circadian cycles upon the manifestation of the symptom of excessive sleepiness within PD.



A comparison of plasma melatonin levels in PD patients and controls (Videnovic et al., 2014).

The researchers noted that these results vary from other previous studies conducted, in which no difference in melatonin levels was found when comparing the PD patients to the control subjects. They attribute these possible differences to the fact that very different methods were used among the two studies to obtain the aforementioned results. Additionally, the researchers noted that in their particular study, blood samples were obtained every half hour, compared to previous studies in which blood was sampled every one to two hours. The greater frequency of sampling blood melatonin levels allowed the research team to obtain more accurate results and increased the ability of analyzing the timing of the melatonin rhythm (Videnovic et al., 2014).

Generally, across the three PD studies, several conclusions were reached. PD participants reported a generally poorer quality of life. Immunoassay results revealed altered levels of circulating hormones in the body which resulted in shifts specific to PD pathology, including increased sleep latency, reduced efficiency of sleep, and reduced REM sleep.

Specifically, PD patients were observed as having lower blood serum melatonin levels and impaired melatonin secretion, providing an explanation for the physical manifestation of excessive daytime sleepiness in these individuals. A positive correlation was observed between increasing destructuring of sleep cycles and the stage and severity of the disease. Finally, analysis of actigraph monitored activity revealed that PD patients reported overall lower activity levels than controls. This may be attributed to some degree of motor loss resulting from deterioration of the substantia nigra in the brain.

Cancer

Cancer can generally be described as the uncontrolled division of cells, forming malignant masses and destroying native body tissue. It is a unique type of disease as it is able to affect virtually any system or organs of the human body. Additionally, it has the potential to break off and spread throughout the body beyond the point of origin, a property known as metastasis. In a normally functioning human body, old and damaged cells are typically broken down and replaced by healthy cells. In the case of cancer, the old and damaged cells manage to survive, and new replacement cells are produced in excess where they are not needed. The uncontrolled division and replication of these cells leads to tumorigenesis, the precursor of cancer.

Looking at cancer in more of a general sense, it is a disease that is solely caused by genetics. This means that genetic mutations or modifications may be inherited or passed down from biological parents. On the other hand, genetic changes may arise over time as a result of either cellular errors upon division, or some environmental exposures including ultraviolet radiation emitted by the sun or inhaling tobacco smoke. From one individual to another, cancer is unique in that it may contain any variety or combination of genetic alterations, and even within the same tumor, there may be different types of mutations. In the cases of metastatic cancers, the secondary tumor is still named after the primary form, as it contains the same type of cells as the original form. For instance, in the event that lung cancer should metastasize and travel to the brain, the secondary tumor would be identified as metastatic lung cancer rather than brain cancer.

This disease is also known to take on a variety of prominent forms, detailed as the following. Carcinomas are the one of the most common forms of cancer, which are formed by

epithelial cells, typically impacting either the skin of the lining of various internal organs. Sarcomas tend to take form in bone, muscle, fat, blood and lymphatic vessels, and other fibrous tissues like tendons and ligaments. Leukemias originate in the blood-forming section of bone marrow, and are not manifested as physically solid tumors, but rather exist within the fluid of the blood space. Lymphomas refer to cancer of lymphocytes, specifically in T cells and B cells. Multiple myeloma is the type of cancer that originates in plasma cells, and the abnormal cells accumulate in the marrow and form tumors. Melanomas pertain to cancer of melanocytes, the pigment-producing cells of the body, and while they typically form on the skin, they can also form in other pigmented tissue areas including the eyes. For the brain and spinal cord, the cancer is named after the type of cell that the mutation originated in.

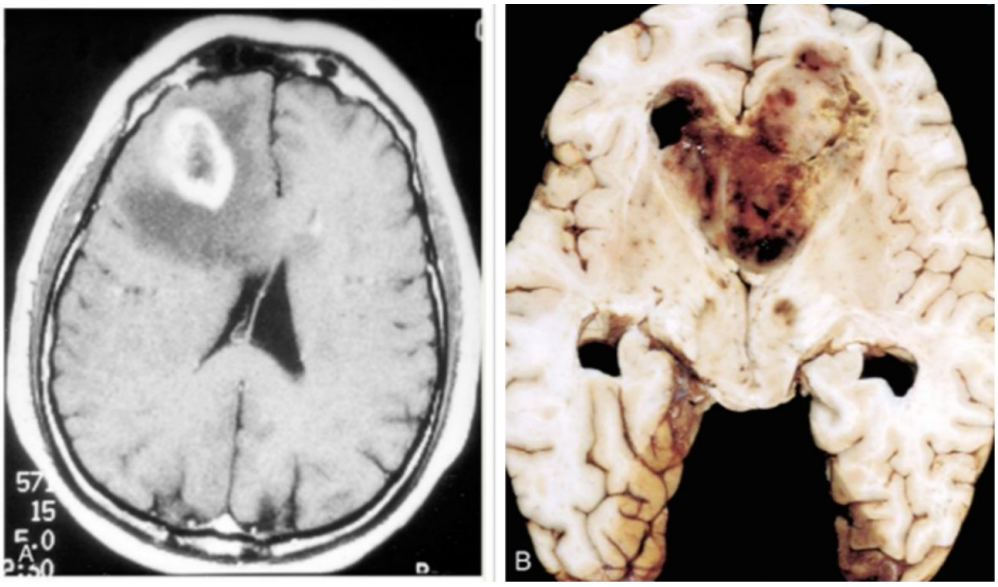


Figure A shows a computed tomographic (CT) scan with contrast of a large tumor in the cerebral hemisphere of the brain. Figure B shows a necrotic, hemorrhagic, infiltrating mass of tumor in the brain ("Section IV: Biological Factors Contributing to Pathophysiology", p.566).

Additionally for brain cancer, tumors may be either benign or malignant. Although there are multiple different types of cancer, those that involve or are related to the brain are the most likely

to have a direct impact on the SCN, and ultimately the modification of circadian rhythms. Brain cancer specifically can be designated as having either originated in the brain, also known as a primary tumor, or may spread to the brain from a different location, known as a secondary tumor. Specifically for brain cancers, there is greater likelihood that they were formed as a result of metastasis from a different tumor as opposed to originating within the brain ("What is Cancer?", 2015).

As cancer is able to take on a variety of forms, this warrants the plethora of possible associated signs and symptoms. Although the list of all cancer symptoms may be quite extensive, some of the most general and common include the following. Individuals may experience changes of the skin, including the presence of new moles or spots, or open wounds or sores that do not appear to heal properly. Additionally in terms of the skin, there may be hyperpigmentation and darkening of tissue, increased sensation of itching, and possible excessive hair growth. There is the possibility of unexplained weight loss, typically a concern when the loss is ten or more pounds, and most commonly correlated with stomach, esophageal, pancreatic, or lung cancers. Fever is also a common symptom of cancer, more likely to occur in the event of metastatic cancers, and can make it more difficult for the body to fight off infection. It is also quite common for these individuals to experience fatigue, and generally feeling more weakened and tired than normal. Other more specific signs and symptoms that exist typically are associated with specific forms of cancer. For instance, a change in bladder habits or function may be associated with either bladder or prostate cancer, a nagging cough a characteristic of lung cancer, and thickening of tissue or lumps forming in the body usually associated with breast or testicular cancers ("Signs and Symptoms of Cancer", 2014).

When we hear cancer diagnoses discussed, there is also typically an assigned stage which identifies the degree of progression or aggression of the cancer. Typically, doctors use the TNM system in order to describe what stage a cancer has taken. TNM is an acronym, and its components assess the tumor, nodes, and metastasis of each individual case or incidence of cancer. When analyzing the tumor as a whole, the criteria of focus pertain to both the size and location of the initial or primary tumor. When providing numerical representation of the tumor, the letter "T", accompanied by a number ranging from zero to four, is used to describe both the size and location of the tumor. The second element is to see whether or not the cancer has managed to spread to the lymph nodes. If this is the case, this section also involves searching for how many of the nodes have been compromised. This information is represented by the letter "N", paired with a number ranging from zero to three, in order to indicate the relative quantity of affected nodes. The greater the amount of compromised nodes, the larger the number from the scale. The final factor addresses the degree of metastasis throughout the rest of the body, and also contributes toward identifying possible secondary tumors. The letter "M" is used to indicate metastasis, with "M0" representing no spread, and "M1" when the cancer has spread. Another sector of staging consists of determining whether a case is in a clinical or pathological stage. An individual diagnosed as having clinical stage cancer means that they were diagnosed as a result of tests, images, or scans, so long as they occurred before any surgical procedures. On the other hand, an individual would be recognized as having pathological stage cancer if the discovery was made during a surgery. Pathological staging better provides significant information in helping to decide on a prognosis when compared to clinical staging.

In addition to the TNM system, most cancers are generally acknowledged as having four distinct stages. Occasionally, cancer may be recognized as being stage zero, in which the cancer is *in situ*, or still located in its place of origin. At this stage, cancer is plausibly treatable and can be easily removed fully with surgery. Stage one is typically characterized by a small tumor in size that has not begun to spread into neighboring tissue, and often referred to as early-stage cancer. Stages two and three are generally indicative of larger developed tumors that may have begun to grow into neighboring tissue and some lymph nodes, without spreading throughout the remainder of the body. The final and most severe is stage four, in which the cancer has metastasized and spread beyond its point of origin to other locations within the body. By this point, the cancer is referred to as advanced ("Stages of Cancer", 2018).

Currently, there are a variety of different treatment options to try and beat cancer. One of the more popular treatment methods when appropriate is to undergo surgery. A surgical procedure can be performed in order to debulk and remove a portion of a tumor, remove an entire tumor, or to correct symptoms of discomfort including pain or pressure. Another treatment option comes in the form of radiation therapy, utilizing the same radiation that at low doses can be used to perform x-ray scans. However, when being used to target cancer cells, a higher dose can be used to kill the malignant cells and shrink tumors. One of the other options we commonly associate with the treatment of cancer is chemotherapy. This method uses chemicals or drugs in order to target cancer cells, and can be given in a variety of ways including orally, intravenously, or topically. Another viable option for treatment would be immunotherapy, in which biological substances produced by living organisms are used to enhance the body's natural immunity in fighting cancer. Targeted therapy is a more specific

option in which an individual case of cancer is analyzed in order to best decide how to attack the malignant cells. This method seeks changes in the cancer cell that indicate how they mutate, grow, and spread, and are typically treated in the form of either small-molecule drugs or monoclonal antibodies. The small-molecule drugs are best used to enter the cell, whereas the monoclonal antibodies attach to specific markers on the outer surface of the cells. Hormone therapy, also known as endocrine therapy, is a form of treatment that attempts to halt or terminate the growth of cancer cells which utilize hormones, and typically is used to treat cases of both prostate and breast cancers. Stem cell transplants may also be used as a viable method for cancer treatment in order to replace blood-forming cells necessary to have a properly functioning immune system, and the best chance at fighting the cancer. These stem cells may be harvested from the individual themself, or may be donated from a different individual, not necessarily related by blood. The final method is known as precision or personalized medicine, in which doctors hand-pick a combination of specific treatments to target the genetic makeup for each unique case ("Types of Cancer Treatment", 2017). Many of these methods can be quite costly, and specific forms of cancer still require many years of research and testing in order to find proper definite remedies.

The first source related to cancer focuses mostly on the general relationship between cancer cells and their impact on circadian rhythm as they alter natural processes of human physiology. Scientists are aware that in order for tumors to grow and develop, excess amounts of nucleic acids and proteins must be produced in order to prepare for the replication of cellular matter. While the protein synthesis is rapidly increasing, there are a certain percentage of proteins that will not be properly folded. These malformed cells trigger the unfolded protein

response (UPR) which acts by slowing new protein synthesis in order to properly fold the misshapen proteins. The intriguing factor came from the discovery that cancer cells learned how to take advantage of the UPR mechanism and process of delaying protein synthesis in order for them to thrive in otherwise quite toxic situations. It is known that the UPR and circadian rhythms are somehow linked to one another, however it was not known what the exact relationship between the two was. J. Alan Diehl, Ph.D. and colleagues, from the MUSC Hollings Cancer Center, conducted a series of experiments in order to learn more about the correlation between cancer pathology and circadian cycles. These experiments utilized both human and rat subjects, the human participants simply being observed, and the rats as test subjects which were provided experimental treatment in order to identify modifications.

The group's main question before going into the experiments was whether the misfolded proteins themselves may alter circadian rhythm of cancer cells. In their first set of experiments, the research team used chemicals to induce the UPR mechanism in osteosarcoma cells. Researchers concluded from these experiments that when activated, the UPR mechanism impacted levels of a protein known as Bmal1, a transcription factor that fluctuates depending on environmental expression of relative light or dark. Specifically, the Bmal1 levels remained low during periods of both light and dark, and as a result shifted circadian cycles. This would indicate that the compromised UPR mechanism was modified in favor of the cancer cells, but resulted in the inability to discern between day and night and respond accordingly. In order to support their findings, they conducted a follow-up experiment in which the main parts of the UPR mechanism were removed from the cancerous cells. Upon this trial, the phase shift did not occur.

In the next set of experiments, the researchers investigated the manipulated UPR mechanism in a group of rats. Essentially, this round of experimentation revealed that the UPR process acts almost as an intermediate liaison between the processing of light and dark cycles, and is essentially responsible for establishing stable circadian cycles. Again, the researchers were able to note that as the levels of the Bmal1 protein decreased, the UPR was increasingly activated, similar to what was observed from the first set of experiments. In order to verify their results, the researchers conducted another round of experiments in which the rats were subjected to a sudden reverse of their light and dark cycles. As a result, their levels of Bmal1 were no longer fluctuating, but rather reaching a point of consistency.

Between both of the sets of experiments, the research team was able to reach some valuable conclusions. First, they identified a relationship between UPR and Bmal1 protein production which is greatly influenced by varying light and dark cycles. Additionally, they concluded that UPR itself may have an impact on causing phase shifts in circadian genes and ultimate biological expression. Finally, the researchers deemed UPR responsible for causing the overall loss of Bmal1 proteins, allowing for rampant tumor growth and providing a favorable environment for cancerous cells to thrive within the body (Medical University of South Carolina, 2017).

The second source related to cancer takes the form of a scientific review by Christos Savvidis and Michael Koutsilieris, scientists studying endocrinology and metabolism, as well as physiology. These scientists reviewed a vast quantity of previously conducted studies regarding components of the relationship or link identified between circadian rhythms and cancer. It is mentioned that both standard healthy cells, as well as pathogenic cancer cells, maintain circadian

time and are regulated by their expression of similar clock genes. Additionally, when analyzing epidemiological studies, it was discovered and correlated that there was greater incidence and poorer prognosis of breast cancer in populations with distorted circadian cycles.

From the compiled studies, the researchers of this article concluded that the disruption of circadian rhythms was present in a variety of different cancer forms. They also mention that there is increasing evidence being discovered to further solidify the relationship between cancer pathogenesis and dysfunction observed within circadian cycles. For instance, one of the many studies detailed the pathogenesis of prostate cancer. That particular population-based case-control study detailed that there was evidence of a link between modified circadian genes and the development of prostate cancer. In the normally functioning male human body, clock genes and androgen receptors are expressed with typical circadian cycles. However, when circadian clock genes such as *Per1* are improperly functioning, they block the androgen receptors which may be associated with the initiation of cancer within the prostate.

The authors of this source also drew several other significant conclusions after analyzing all of the studies. They stated that a portion of cancer cell growth is due in part to clock gene regulation of the human body, and that unregulated clock genes also contribute to progression, metastasis, and angiogenesis of various forms of cancer. When specifically investigating the relationship between melatonin levels and cancer, the authors also arrived at some conclusions. For example, one of the studies made a great discovery from activating melatonin receptors in patients with breast cancer. The increased melatonin levels inhibited the process of transduction, the transfer of foreign DNA into native cells, among cancer cells. The process helped contain the growth of a cancerous tumor. Additionally, a separate study discussed that in patients with

untreated non-small-cell lung cancer, measured levels of both melatonin and cortisol were lower than expected of a healthy individual, suggesting some degree of neuroendocrine dysfunction within the brain. The properly functioning endocrine system would assess the needs of the body, and regulate hormone levels accordingly. When the system is disrupted, the hormone levels are in turn impacted and unable to be properly regulated.

The authors of this source conclude that there is likely some sort of relationship between improper regulation of clock genes and disrupted circadian cycles and the encouragement of cancer pathogenesis (Savvidis and Koutsilieris, 2012). As we have turned to adapting more modern lifestyles, humans have begun to induce circadian disruptions by introducing external sources of light at nighttime, and some interactions between our genes and ever-changing environment. Hopefully, with this new information, we will one day be able to create more efficient and specific remedies to eradicate certain forms of cancer.

The third source shifts focus more towards how psychosocial effects impact cancer growth and development, and in turn create an impact on natural circadian cycles. As mentioned in the abstract, the more severe the incidence or case of cancer, the more likely an individual will experience greater disruption of circadian rhythms. Specifically, the disruptions may take the form of complete phase shifts, altered amplitudes of activity, and inconsistent peaks and troughs of various endocrine, metabolic, immunological, and rest-activity cycles.

One specific section of this journal article details observations made from a collection of studies regarding the relationship between circadian rhythms and cancer incidence. One of the larger findings provided a link between increased risk of developing breast cancer after working extended nighttime shifts of a job. The hypothesis of the study suggests that the exposure to

light during late evening time leads to the suppression of anticipated naturally-produced melatonin. With the presence of melatonin in the body, a typical response in women is to withhold estrogen production. In the absence of melatonin to act as a regulating mechanism, excessive estrogen is produced, likely resulting in a higher incidence of breast cancer. Additionally, shift work forces an individual to alter their typical rest-activity cycle in order to adapt to working conditions. This imposed shift of a circadian cycle is also likely responsible for encouraging cancer development.

The next important section discusses the relationship between circadian rhythms and cancer progression. It was observed that in patients with breast, prostate, ovarian, stomach, and colon cancers, the disruption of circadian cycles was evident across multiple body systems. For instance, the endocrine system is impacted by modifying the levels of cortisol, melatonin, prolactin, thyroid stimulating hormone, growth hormone, luteinizing hormone, and follicle stimulating hormone. Metabolic levels, including temperature, proteins, and enzymes, as well as immunological rhythms are also modified, with greater level of disturbance in more severe cases. These markers may serve as indicators of the status of a tumor and provide healthcare professionals with useful information when assessing their patient. Other mentioned prospective studies have analyzed the ability of using circadian rhythms as a possible indicator of cancer prognosis. For instance, one study researched the link between the relative presence of natural killer (NK) cells and the progression of breast cancer cases. NK cells have the ability to kill cancerous cells, however as their cytotoxicity decreases, there was an observed correlated rise in breast cancer development.

With final remarks, the authors also mention that disrupted circadian cycles reduce the efficiency and potency of some cancer treatments (Sephton and Spiegel, 2003). Based on observations and recorded patterns of unique cycles of individuals, practitioners are able to precisely administer cancer treatments during periods when toxicity will be at its lowest, and efficiency at its highest in order to give the patient the best possible treatment. A better understanding of the relationship between circadian cycles and their altered timing under the control of cancer is crucial in understanding how to approach treatment, whether a psychosocial or biomedical intervention.

The fourth and final source provides substantial general information regarding components of circadian regulation and their importance, followed by how the factors are modified or impacted with the presence of cancer. Specifically, this source focuses on hematopoietic and hormone-related malignancies that give rise to breast and prostate cancers. Hematopoiesis is the biological process in which new blood cells are formed from stem cells. When circadian rhythms are normal, hematopoiesis functions properly with the successful creation of new blood cells. However, if levels of the *Per* clock genes are lower than required to function, this process is disrupted. The suppression of *Per* genes can be observed in a variety of leukemias and lymphomas. As these genes are restrained, circadian cycles are impaired which could be a potential source for encouraging cancerous growth. Due to their unassigned nature, we may be able to develop a form of cancer treatment in which stem cells can be used to specifically target malignant cancerous material.

Many endocrine and metabolic hormones are regulated by a variety of circadian cycles which depend on daytime and nighttime fluctuations. Therefore, an increasing amount of

studies provide evidence of a link between circadian modifications and endocrine malignancies. Most notably, a number of epidemiological studies have formed a clear connection between circadian disruption and increased risk of developing breast cancer. In breast cancer cases, it is noted that there are identified mutations in both the *Per1* and *Per2* genes, which provides grounds indicating altered circadian cycles which may lead to tumorigenesis. Additionally, similar mutations and reduced quantities of the crucial *Per* clock genes were widely observed across many instances of prostate cancer from epidemiological studies. Less is known about the impact of altered clock genes in males impacting the prostate when compared to the incidence of breast cancer, however the foundational causes appear to be similar (Gery and Koeffler, 2010).

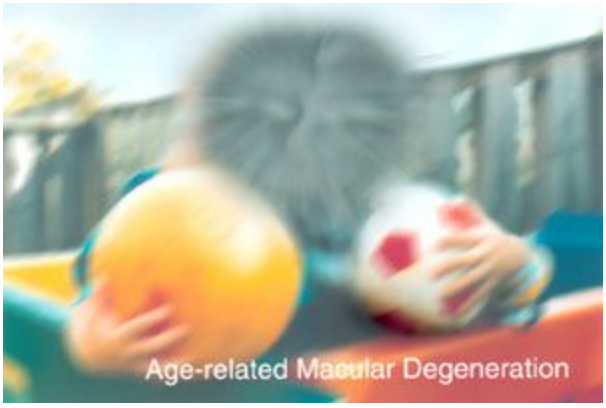
Among the multiple studies related to cancer, multiple conclusions were drawn. Regarding the UPR mechanism, some cancer cells gained the ability to utilize the process in order to develop and thrive in situations that would otherwise be toxic, rendering the cancer cells ineffective. Additionally, the UPR mechanism itself has an impact on causing phase shifts in circadian genes and their biological expression. In general, circadian dysregulation may also result in the reduced effectiveness of various cancer treatments. Finally, unregulated clock genes, such as the *Per* genes, can contribute towards the progression, metastasis, and angiogenesis of various forms of cancer.

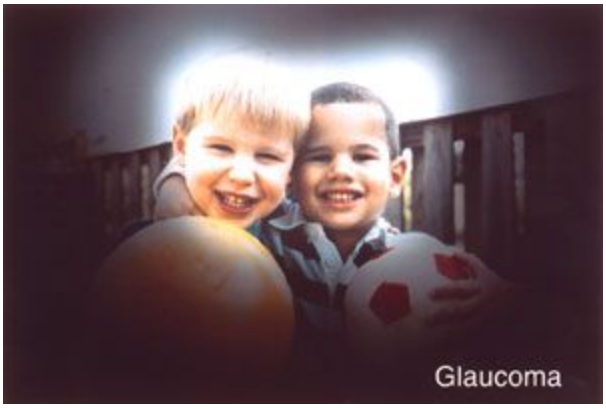
Blindness

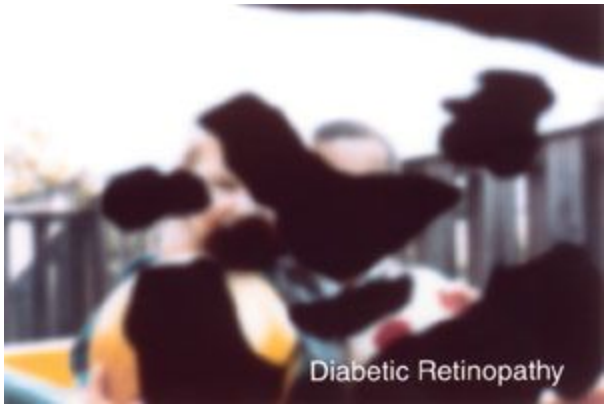
Blindness can be defined in a variety of different technical ways, but as a general statement, it entails an individual that experiences some degree of vision loss. As compared to the previous illnesses discussed, blindness differs in that this type of impairment is associated with the loss of a sensation, as opposed to a direct internal pathological condition. Vision loss itself may described in either one of two ways: partial or complete. An individual with partial vision loss entails that they have a very limited percentage of vision, yet are still somewhat able to see. On the other hand, complete vision loss indicates that an individual is not able to see anything at all, including perception of light or darkness of the surrounding environment. Vision loss may also happen suddenly, or may progressively worsen over time. An individual may be blind at birth if they are born prematurely, however majority of cases are acquired or develop with age or other circumstances. Specifically, majority of visually impaired individuals are over the age of 50. By definition of the law of the United States, an individual is deemed legally blind if their vision is worse than 20/200 with the aid of either glasses or contact lenses. This means that the person in question would be able to see at 20 feet what a normal person can see from 200 feet away. It is estimated that globally 1.3 billion people have some degree of visual impairment as of current time ("Blindness and Vision Loss", 2016; "Vision Impairment and Blindness", 2018).

There are multiple different causes of blindness, however the most common include cataracts, age-related macular degeneration, glaucoma, and diabetic retinopathy. A cataract is typically defined as when the lens of the eye, which is typically transparent, develops a layer of a cloudy film across its surface. This film in turn blocks and impacts the amount of light necessary

for proper visual transmission of one's surroundings. In standard physiology, the role of the lens is to focus the perceived light against the retina in the interior of the eye in order to transmit visual information. In the case of cataracts, the cloudy appearance of the lens casts a blurry light against the retina wall, producing a perceived blurry vision of the environment. Next, we have age-related macular degeneration which specifically impacts and blurs the central sector of the field of vision. This type of visual impairment comes in two forms: wet and dry. In its wet form, leaky blood vessels grow underneath the surface of the retina. On the other hand, dry macular degeneration entails the deterioration of the center of the retina itself. Glaucoma is an overarching name for a group of diseases related an increase of pressure in the eye, resulting in distorted and impaired vision. Specifically with glaucoma, one's vision appears as if they are viewing their surroundings through a tunnel of sorts, with a blurred and darkened vignette around the perimeter of the field of view, and with potential to worsen or even darken over time. Finally, diabetic retinopathy indicates an eye disease in which the blood vessels of the retina are impacted. The pathology of diabetes renders the small blood vessels of the retina weak, causing possible occlusion or even deterioration. With the ever-growing prevalence of acquired diabetes in middle-aged adults, there is correspondingly a rise in prevalence of diabetic retinopathy among this population. Beyond these four primary causes, other possible but less likely causes include surgical complications, tumors, strokes, and several others ("Blindness and Vision Impairment", 2017). In terms of diagnosis, various forms of visual impairment of blindness can be recognized in dilating the eyes during an examination in order to assess various components including the cornea, lens, and retina. On the next page are manipulated depictions of what an individual's field of view would appear like with the visual impairments discussed in detail.







These photographs depict what a typical field of view would appear as under normal circumstances, as well as for individuals with cataracts, age-related macular degeneration, glaucoma, and diabetic retinopathy ("Eye Disease Simulations", *National Eye Institute of NIH*).

The first source related to blindness investigates the relationship between disrupted circadian sleep cycles in blind individuals, as well as possible treatment with supplemental melatonin. For blind individuals, visual cues cannot be transmitted from the retina of the eye to the brain, resulting in an impaired circadian clock, and in turn, disrupted biological rhythms. Without the proper transmission of visual information, it becomes difficult for the body to synchronize its daily physiological activity and behaviors. Although a variety of components contribute to the maintenance of regulated circadian rhythms, one of the primary and most evident shifts is observed with either the presence or absence of light in the surrounding environment.

One of the studies discussed findings that in their blind subjects, a majority had developed their own abnormally entrained circadian rhythms, or completely shifted to free-running rhythms. The same study also provided a relationship indicating that the greater the severity of the visual impairment or loss of vision, the more abnormal their respective circadian cycles were. Another study consisted of 388 blind subjects provided results indicating more disturbed sleep cycles in those with a total loss of light perception when compared with individuals having only some degree of perceived light. Another interesting point mentioned was that in the individual with abnormal circadian rhythms, more daytime naps were taken than when compared with control subjects having normal circadian cycles. A likely explanation is attributed to the brain's inability to properly discern between daytime and nighttime, placing the body in a state of fatigue as it struggles to adapt to some form of abnormal rhythm. The general fatigue would provide a reasonable explanation for the increasing amount of naps taken. Although differences were noted between blind individuals when compared to visually-able

control subjects, and even among varying degrees of severity of visual impairment, none of the studies noted any significant differences between those suffering from congenital blindness when compared to those with acquired blindness.

One of the other crucial components discussed in this particular source is related to the use of external melatonin as a possible treatment to regulate circadian cycles. Depending on the timing on when it is dispensed, the provision of administered melatonin can either advance or delay the timing of the circadian clock of the human body. The authors of this source mention how studies in relatively recent years successfully entrained individuals with free-running rhythms by implementing the use of supplemental external melatonin. Additionally, the use of melatonin for this sort of therapy was also proven to improve sleep and reduce the amount of daytime naps taken by visually impaired individuals. With this information, the hope is for researchers to develop a more established form of treatment to reduce some of the inconvenient symptoms associated with abnormal circadian cycles (Skene and Arendt, 2006).

Most totally blind individuals experience free-running rhythms that are out of sync with those that would be considered normal, resulting in insomnia and daytime sleepiness. For these individuals, rhythms essentially need to be reset in order in order to follow a more true 24 hour cycle. The study was described as a "crossover study", in which the participants were provided different treatments over a period of time.

In specific terms of the experimental design, seven subjects were selected as participants and were deemed completely blind after an ophthalmologic examination. These individuals also were specifically selected because they had free-running cycles, a key component of the study. Other than being blind, the subjects were relatively healthy individuals. Upon random selection,

half of the participants were selected to receive ten milligrams of melatonin, while the other half received a placebo, with both pills being administered approximately one hour before the specified bedtimes of the patients. This system remained in place for approximately one montht, varying depending on each subject's free-running cycle. Measurements of melatonin levels were taken on chosen days via blood samples every hour for a full 24 hours, and additional melatonin would not be supplied these days as to not skew the results. Additionally, sleeping patterns were recorded via polysomnography.

Ultimately, the researchers found that, with cycles averaging approximately 24.5 hours in a 24 hour period, the individuals given the placebo were completely unaffected. For these individuals, the cycles were still free-running as anticipated. However, in six of the seven subjects that received the supplemental melatonin, circadian rhythms were entrained, and the subjects were able to sleep more efficiently. These subjects spent less time overall awake after the initial onset of sleep in the evening. The efficiency and quality of sleep was improved with melatonin treatment. After the initial study, three of the original subjects participated in another trial which provided the same ten milligram supplement of melatonin on a daily basis until entrainment was achieved. At that point, the dose was reduced to simply half a milligram daily for a period of three months. Even after the drastic reduction in the dose of the melatonin supplement, the entrainment still persisted.

This experiment provided crucial findings linking the provision of supplemental melatonin and entrainment of free-running circadian cycles in completely blind individuals (Brandes et al., 2000). One major critique I have of this study would be that the sample size was relatively small. Although I do understand that the small sample size allowed the researchers to

specifically analyze the changes and modifications of rhythms in each of the individual subjects, it would be in their best interest to replicate this study on a larger scale with more participants to substantially support their results.

Between the sources pertaining to blindness, we were able to learn important information. For instance, in visually impaired individuals, specifically prominent in those completely blind, free running rhythms occur, which are out of sync with standard rhythms, resulting in insomnia and increased tendencies of daytime sleepiness. As visual cues cannot be easily transmitted from the retina to the optic nerve and eventually the brain, one's lack of visual perception of their surroundings results in an impaired circadian clock. Additionally, these sorts of erratic or altered cycles can be treated with supplemental melatonin in order to normalize cycles and return to resemble a standard 24 hour cycle. Finally, although both groups were deemed equally blind, no significant differences were found between those with congenital blindness versus acquired blindness.

Findings of Huntington's Disease

In the process of preparing material for this thesis, I also collected research pertaining to Huntington's disease (HD) as a fifth pathological factor for discussion. Although this disease will not be discussed in full detail, I found it important to relay my findings. The three sources I gathered pertaining to Huntington's disease ended up providing similar results as those concluded from Alzheimer's disease and Parkinson's disease. Specifically, they recounted that under the pathology of HD, changes were observed notably in the SCN of the hypothalamus, the master circadian pacemaker of the body, similar to AD. HD patients also displayed greater daytime dysfunction and delayed sleep onset when compared to controls. In addition to the shifted acrophase of sleep, it was also generally observed that HD patients were significantly more active during nighttime when compared to controls. Under a more physiological lens, one of the studies specifically focused on the levels of melatonin in HD patients, and reported that HD patients had lower recorded plasma melatonin levels than their respective control counterparts. Finally, in similar fashion shared by both AD and PD, HD patients reported greater loss of circadian function as the disease progressed in the subjects.

Comparison and Conclusion

After analyzing studies pertaining to the four different diseases, it is evident that they each have some degree of impact on circadian rhythms and cycles within the body. The findings under Alzheimer's disease and Parkinson's disease were similar in that they both resulted in lower recorded amounts of daily activity and general fatigue. Additionally, it was characteristic of both of the diseases to display increasing severity of circadian disruption with the progression of the diseases respectively. The findings from both of the diseases were also found and briefly mentioned as similar to those of Huntington's disease. On the other hand, the effects of cancer on circadian rhythms took more of an internalized toll across the body rather than just the brain specifically, as was the case for both AD and PD. Cancer was unique in that the pathological cells learned how to take advantage of the body's natural biological processes in order to thrive and grow in otherwise quite toxic environments. Finally, with blindness and the loss of visual sensation or visual impairment, the pathway of processing observed external stimuli was absent, resulting in a haphazard perception of a 24 hour period of day and night.

Glossary

Acrophase: Indicative of a peak point or crest of a recorded cycle.

Chronobiology: A word of Greek origin, derived from the words ‘chronos-’ meaning time, and biology, the study of living things. A subsector in the field of biology, specifically focused on inspecting and analyzing the cyclical patterns resulting from living organisms and their responses to both solar and lunar rhythms.

Circadian: A word of Latin origin, the definition can be broken down into two fragments. The first being ‘circa-’, translating to “about”, and the second piece ‘dies-’ meaning “day”, providing a general unified definition of something that occurs within the period of one full day.

Diurnal: An alternate word indicative of an event or pattern that occurs during the day. These events differ from circadian events in that they vary with time of day. Additionally, they may either be light driven or clock driven, allowing for the variable factor of time.

Endogenous: An adjective indicating something of internal origin. In a biological context, something endogenous can range from microscopic substances at the cellular level, or may be as complex as various internal mechanisms or processes.

Entrainment: A phenomenon dependent on environmental oscillation and cues. A process that occurs to optimally achieve synchronicity among various processes or behaviors within a single being. With respect to studies focused on circadian rhythms, a modification or alteration of either a phase or period of circadian cycles as a result of exposure to external light.

Free-running: A sleep pattern not properly entrained to a natural 24 hour cycle.

Melatonin: A hormone commonly associated with inducing the sensation of sleep.

Substantia Nigra: Located within the brainstem of the brain, specifically in the midbrain section, and is primarily responsible for the production of the neurotransmitter dopamine via dopaminergic neurons.

Sundowning: A phenomenon generally describing heightened intervals of active behavioral symptoms, especially during afternoon and evening periods in a day.

Suprachiasmatic Nuclei (SCN): commonly referred to as the "master clock", this section of the hypothalamus of the brain forms a connection between the nervous and endocrine systems, and is responsible for overseeing all mechanisms and rhythms for all cells of the human body.

Zeitgeber: A word of German origin, and formally acknowledged as the combination to two other individual German words. The fusion of both 'zeit' meaning time, and 'geber' meaning giver literally translates to 'giver of time'. With contextual relevance to this thesis, this word is representative of natural or environmental cues provided by one's surroundings. For instance, shifts between periods of lightness to darkness, or temperatures from warm to cool, function as indicators of passage of time.

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