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Machine Learning Approach for Early Suppression of Fatal Familial Insomnia Via Symptoms

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Background: A unique neuro-generative disorder that turns healthy into fatal, as time progresses is said to be a prion disease. This disease is instigated bythe abnormal variant of PRNP gene which initiates Prion Protein (PrP) deep inside the brain, which is noxious to the body, mostly to the brain cells. Many clinical trials have been conducted, but no effective treatment has been discovered.Also, there are several diseases caused due to prions, and one among them is Fatal Familial Insomnia (FFI).
Objective: Since for the analysis or for identifying any disease, majority of the tests were performed invasively and MRI, CT Scan costs a lot for a normal individual. So, this work chiefly concentrates on suppressing FFI using EEG as a biomarker as it is taken non-invasively, cost effective and thereby predicting the insomniacs with the help of machine learning approach is easier for a medical personal.
Materials & Methods: Three subjects (two diseased and one Normal) EEG is collected, noise removal using window techniques was done and further features like standard deviation, variance, Kurtosis, etc., are extracted and fed to the Support Vector Machine (SVM) classifier for classification. This classifies subjects in short time.
Results: The performance metrics were computed in identifying the diseased from normal and obtained sensitivity of 67.8%, accuracy of 85.9%, specificity of 87.9%, and precision of 84.5%.
Conclusion: Using this, doctors on easy identification of insomniacs from the healthy can give the required treatment to suppress the initial symptoms, enhance the patient's life, and reduce the risk of FFI, most importantly without any need of invasive methods. Further it will be useful to identify the insomniacs without having family history too.

Keywords: Prion, Fatal Familial Insomnia, Insomnia, EEG, Support Vector Machine.

1. Introduction

Among all the biological systems of the human body, the most complex one is the human brain. It occupies 2% weight of the human body and consumes 20% oxygen of the total body and cardiac output of 15%. Moreover, when the brain is in running mode, generally, a matured brain contains nearly 100 billion nerve cells that process the information and are termed, neurons. These neurons along with glial cells form brain tissues. They have control of task-induced responses, gestures, perceptions, vehemence, communication, memory, and intelligence. The human brain consists of three main parts: Cerebrum, Cerebellum, and brain stem. The cerebrum takes control of sensory and motor information. In the centre of the cerebrum, the thalamus is located deep within the brain and appears small in the shape of an egg. Moreover, it plays a crucial role in disseminating sensory information to the cerebral cortex and synchronizing sleep and wakefulness. The specific proteins found in the thalamus can vary depending on the nature of the cell and its function.

Like all other parts of the brain, the thalamus contains proteins. These proteins help to regulate many bodily functions, including sleep, appetite, and body temperature. When a misfolded PrP starts rising in the thalamus, it starts diminishing the neurons. The source of this infectious protein is unknown, yet it may sometimes be caused by consuming infectious meat products.

2. Types and Causes of Prion diseases:

Creutzfeldt-Jakob Disease:

Creutzfeldt-Jakob Disease is known as CJD and is caused due to prions. It can be sporadic, inherited, or acquired. This disease came into existence in the 1990s, when a few people in the United Kingdom developed variant CJD (v CJD) after consuming diseased cattle meat. Later on, this hasn't been linked to eating beef. A person suffering from CJD is first observed to have mental ability changes, followed by early symptoms like personality changes, Memory loss, blurry vision, blindness, insomnia, coordination problems, and trouble speaking & swallowing. Death usually occurs in a year, after experiencing medical issues which are associated with the disease. This often affects the people in the age group of 40’s.

Kuru:

Kuru is a rare, fatal brain disorder. It was observed in New Guinea from 1950’s to 1960’s. The disease came into life as a result of ritual cannibalism practices among the Fore, in which relatives prepared and consumed the tissues of deceased family members. The contaminated brain tissue with kuru was highly infectious and was transmitted either by eating or coming in contact with the wounds. But after the dissuasion of the government, it was almost vanished. It highly affects the cerebellum with unsteady gait, tremors, mood swings, and slurred speech as initial symptoms, eventually, they found it difficult to stand or eat, and they died in a coma state within 6 to 12 months.

Fatal Familial Insomnia:

It is known as FFI, with a hallmark symptom of Insomnia ("Fatal Insomnia - Neurologic Disorders". Merck Manuals Professional Edition. Retrieved 17 May 2019).The human thalamus contains many healthy proteins (PrP^{C}) and when it comes in contact or mutation with

the abnormal prion (PrP^{SC}), even the healthy ones turn unhealthy. This action follows the multiplication process and gets replicated. The symptoms start with extreme Insomnia, inability to maintain body temperature, cognitive impairment, loss in weight and memory, Dementia, which leads to difficulty in coordinating activities, and Hypertension.

There are four stages in FFI. In stage one, sleeplessness starts to increase and mental symptoms like fear, paranoia, and panic episodes are found to be seen. Patients experience this for over four months. In stage 2, that is during the next five months of stage 1 psychiatric problems intensify and patients experience hallucinations. Stage 3 is a three-month period in which the affected suffers a severe disturbance in the sleep-wake cycle. The fourth stage is a terminal stage that may last six months or longer. During this period, patients experience cognitive deterioration, dementia, and difficulty in moving and talking. Death generally results within 7-36 months after the onset of symptoms and is caused by cardiac issues or infections in the brain, heart, lungs, and stomach.[10]

3. Methods to identify prion diseases:

Initially, it was observed that FFI is seen in people with a family history of FFI. But later, it appears to be found in people where family history is absent too and is termed as sporadic fatal insomnia. Though there is no cure for FFI, early diagnosis managing prion diseases, and providing supportive care play an essential role.

(i). Clinical and Neurological Tests

(ii). Diagnostic Tests: Electroencephalogram (EEG) , Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Cerebro Spinal Fluid (CSF), Brain Biopsy.

In this work, the EEG signal is utilized as a biomarker, as it is a non-invasive method and doesn't harm or stress the patient. So, by identifying people EEG with initial symptoms and giving them proper treatment at an early stage, death caused by FFI can be reduced and patients can be saved from untimely deaths.

4. Related work

This section portrays the literature on fatal familial insomnia, a degenerative brain disease that distracts the patterns of sleep giving rise to extreme insomnia and dementia, which are the prominent symptoms to be controlled or else lead to sleepwalking, hallucinations, depression, and finally to death.

FFI has three cardinal features -insomnia, dysautonomia, and neurological motor disturbances.[4]Spanish family members (mother and two of her offspring) who suffered from a rapidly progressing disease with insomnia and behavioural changes as the early symptoms are examined and were found to be fatal between 5 and 10 months after the onset of illness.[3]Treating insomnia may extend the life of FFI patients and can save them from untimely deaths.[8]

The data of 56 prion-diseased patients of which 12 are of FFI are taken and CSF samples of 54 were collected and RTQuIC analysis was performed to identify the abnormal protein. After

the analysis, the author observed that many of the patients are not only insomniacs but also suffering from Dementia.[9] The data of 41 FFI patients is utilized for the analysis, from the Gottingen University- CJD Surveillance Unit and developed a diagnostic algorithm that improves the clinical diagnosis of FFI and provides information regarding whom the PRNP analysis should be done without having a family history.[1]The data of 110 prion patients has chosen, of which 7 are FFI. CSF samples were taken from all the patients and analysed for abnormal prion protein through RTQuIC method. After the analysis, it was observed that most of the patients are going through dementia, and it concluded that this method should be a part of a clinical workup for progressive dementia cases. [12]

In the case study of a 42-year-old male government employee, it is observed that, for the past8months, the patient suffered from symptoms like insomnia and hallucinations. Later in 3 months, his weight is reduced by nearly 20kgs. After 8months, he visited the physician and underwent PRNP analysis. The result declared positive FFI, and he was given medication for 3 months. After this period, he was found to be dead. The author concluded that though Insomnia is complex in FFI, agrypnia excitata, and apnea can also be treated as indicators of FFI.[2]A case study on a 58-year-old female is conducted. At first in the year 2013, the subject was identified with insomnia, and later in the year 2014, the patient suffered severe tremors, changes in character, cognitive impairment, and autonomic disturbances. A brain biopsy was done during this period and found to have abnormal proteins, hampering the brain activities, and thereby at the start of 2015,she was found to be dead.[15]

Study of 40 FFI patients in China is chosen, out of which 27 have a clear family history and the remaining don't. CSF samples of all 40 were examined thrice by an RTQuIC test. If any of the samples displayed positive results twice, the samples of those concerned patients are summarized to be identified with positive FFI. [14]A clinical diagnostic criteria algorithm is developed which is applicable to both FFI and CJD patients. Information about the patients who may have possible FFI, probable FFI, and definitive FFI is predicted.[11]Studies show that CT, MRI, and IHC don't give a clear picture of the disorder until the ending stage of the disease. Whereas the RTQuIC test and Protein misfolding cyclic amplification (PMCA) tests can identify the PrPSc concentrations in the patients of FFI. The author finally deduced that the PMCA test cannot trace the misfolded prion concentrations in other neurodegenerative diseases. [6]

A 46-year-old male case study, suffering from FFI has presented and in his observations cranial magnetic resonance, electroencephalogram, and (CSF) did not show any findings. Yet, the genetic study demonstrated the missense mutation c.532G > A (p.Asp178Asn) is compatible with FFI. Furthermore, the post-mortem study revealed the synaptic deposits of PrPSc in the entorhinal cortex and the thalamus, confirming FFI diagnosis.[5]An overview of the recent clinical utility of CSF-based biomarkers, neuro diagnostic testing, and brain imaging in the diagnosis of prion disease are provided. One of the observations is that EEG remains an important neuro diagnostic test in identifying prion disease, primarily for ruling out more common pathologies. EEG can be an important clinical clue if periodic short-wave complexes (PSWCs) are attained. [13]

Large number of patients' data has taken and diagnosed FFI by genetic testing. From their case series and from the literature review it was observed that patients suffered highly from

Insomnia (87.0%) and rapidly progressive dementia (RPD; 83.2%). This was seen in the age group of range (17–76) years, and most of the patients died and the disease duration was in the range of (02–48) months.[7] A case report of a 28-year-old FFI patient, who was vaccinated against COVID-19 during the COVID-19 pandemic and doesn't have any family history of FFI is investigated. The report shows an elevation of white blood cells in the CSF sample and concludes that timely detection of Tau protein in CSF fluid is helpful for early prediction of FFI, and precise diagnosis relies on genetic testing only.[16]

5. Proposed Method:

In general, prion diseases like CJD and FFI occur very rarely, and both have nearly common symptoms, and one among them is Insomnia. Most importantly, in some South Asian countries, there are few rural and urban areas, where some physicians are not aware of identifying such diseases too. Since there is no cure for fatal familial insomnia, it's very horrendous for a person and his family to face the symptoms of FFI as they don't even know why it's happening to them. Also, in terms of price, many of them cannot afford diagnostic tests like CT, PET, MRI scans, CSF analysis, PRNP analysis, etc., and that to its very complicated without performing any tests, to know, whether any person has these diseases with or without family history too. So, keeping all these in mind, the main goal of this work is to suppress the rate of FFI cases, by simply identifying the symptoms i.e., insomniacs and giving a proper treatment for it. By lessening the effects of insomnia, the lives of patients can be saved from untimely deaths. For this purpose, as shown in Figure 1, EEG signals of three subjects (A, B, C) were chosen to predict insomnia from the normal, a hallmark symptom of FFI. The methodology is as follows:

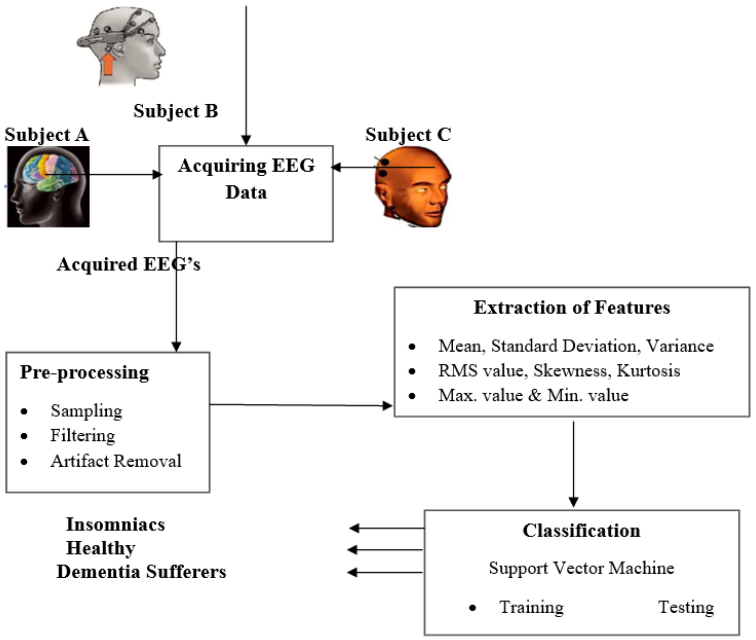

Figure 1: Block Diagram of Proposed work

(i). EEG signal acquisition: EEG signals are acquired from subjects A, B, and C and the signals are then pre-processed using window techniques to remove noise and artefacts.

Subject A: Male around 32 years of age, an employee in an industry. Initially experienced anxiety and gut problems in 2022. After visiting the gastroenterologist, on using medicines for 04 months, the gut problems were rectified. But after 02 months, he noticed a gradual loss of weight and found himself having difficulty falling asleep and memorizing things that were happening in a day. On consulting the physician, he was diagnosed with insomnia (initial stage) and was advised to use Trazonil 50mg and Zolpidem 5mg, and further sleeplessness and anxiety were reduced to the maximum extent and became normal.

Subject B: A male aged < 62 years, a retired employee, was attacked with the coronavirus in 2021 and after receiving proper medication, the person is stable. Once, he became free from the virus, was vaccinated against COVID-19 at the end of 2021. Though his body temperature was normal, and consciousness was clear, at night, he started experiencing excessive sweating, and difficulty to breath and sleeping in 2022, after retirement. During the day he frequently experienced headaches, joint pains, and chest pain. So, the subject visited several hospitals and finally, he was concluded to have excessive insomnia. Several diagnostic tests were performed, in which genetic testing is one of them. He was found to have a possible FFI and as there is no cure for it, medication was given for 6 months with monthly hospital visits. Even after medication, he suffered from severe hallucinations- seeing the dead, gait disorders, and finally was deceased in May 2023 due to a massive heart attack. Brain biopsy of the deceased is not accepted by his family.

Subject C: A female aged 55 years is a homemaker and lives in a rural area. The subject suffered from severe diarrhoea in Dec-2021, after consuming the meat which was stored in the refrigerator for 7 days. Later the subject encountered many sleepless nights, which drove her into depression. Several clinical and diagnostic tests were performed on her, and physicians confirmed that she had dementia. Moreover, after knowing this, she was bedridden and died within 10 months that is in September 2022.

(i). In the pre-processing stage, the raw EEG signal is down-sampled at 250 Hz to accelerate the computation. Raw EEG signals are filtered through a 1–50 Hz band pass filter to detach inapt artefacts.

(ii). Decomposition of EEG signal: As portrayed in Table1, the acquired EEG signal is first decomposed into frequency bands and thereby the statistical features mean (μ), variance (V),standard deviation (SDE), RMS value (RMS), kurtosis(KUR) and Skewness (SK) are calculated, for all the subjects (Dementia, Normal and Insomniac) as shown in Table 2, Table 3,& Table4.

Table 1: Decomposition of EEG

Frequency Range (Hz)	Decomposition Co-efficient	Frequency Band
0.5-5	*A4*	*Delta*
5-8	*D4*	*Theta*
8-16	*D3*	*Alpha*
16-32	*D2*	*Beta*
32-64	*D1*	*Gamma*

Table 2: Extracted features of Dementia person

Parameters	Gamma	Beta	Alpha	Delta	Theta
Dementia_max	5031.1	3472	3943.1	5978.2	17518
Dementia_min	-5999.1	-3499.4	-4068.1	-6195.9	-10610
Dementia_M	-0.023228	-0.29147	-5.0927	11.417	260.99
Dementia_SDE	235.47	293.95	609.47	1098	3400.1
Dementia_SK	-1.6618	-0.33108	-0.47323	-0.25655	0.75468
Dementia_KUR	440.22	119.51	39.826	20.152	12.41
Dementia_RMS	235.43	293.81	609.08	1096.8	3456.1
Dementia_V	1.5368e+05	1.9978e+05	1.0231e+06	2.9003e+06	1.8799e+07

Table 3: Extracted features of Healthy person

Parameters	Gamma	Beta	Alpha	Delta	Theta
Normal_max	678.45	837.39	1918.3	2797.4	14746
Normal_min	-686.72	-810.21	-1913.1	-2684.2	-6326.1
Normal_M	-0.13811	-0.44486	-0.13634	-3.393	4222.7
Normal_SDE	78.997	127.75	316.39	525.34	4124
Normal _SK	-0.2163	1.932	-0.347	-0.0571	0.1825
Normal_KUR	268.13	79.31	30.78	19.3152	8.31
Normal_RMS	46.63	127.69	316.4	545.76	10391
Normal_V	53145	1.2382e+05	4.6103e+05	1.0104e+06	1.0108e+08

Table 4: Extracted features of Insomniac

Parameters	Gamma	Beta	Alpha	Delta	Theta
Insomnia_max	876.55	1269.8	2798	4849.8	10605
Insomnia_min	-900.15	-1180.2	-3118.7	-4833.4	-20618
Insomnia_M	-0.0529	-0.20662	-3.1964	0.88387	-5045.5
Insomnia_SDE	78.966	163.9	493.99	924.98	5462.5
Insomnia_SK	-3.2618	-1.346	1.328	-0.5655	-0.958
Insomnia_KUR	419.8	156.74	86.31	42.65	17.612
Insomnia _RMS	58.95	163.83	493.79	924.26	20783
Insomnia_V	27206	1.417e+05	1.2137e+05	1.0104e+06	1.2317e+08

Mean: In simple words it is called an average and is a measure of the central tendency of a dataset. $M = \mu = \frac{1}{N}\sum_{n=1}^{N} x_n$

Variance: It is the dispersion of a set of data points around their mean. Informs how the signal is spread.

$V = \frac{1}{N-1}\sum_{n=1}^{N}(x_n - \mu)^2$

Standard Deviation: Just like variance, it even gives information about, how the signal is spread concerning time.

$SDE = \sigma = \sqrt{\frac{1}{N-1}\sum_{n=1}^{N}(x_n - \mu)^2}$

RMS value: To measure the amplitude of the pre-processed signal, RMS values are calculated.

$RMS = \sqrt{\frac{1}{N}\sum_i x^2}$

Skewness: It provides a measure of the asymmetry of intrinsic brain activity.

$SK = \frac{1}{\sigma^3}\left\{\frac{1}{N-1}\sum_{n=1}^{N}(x_n - \mu)^3\right\}$

Kurtosis: It helps to identify unusual data points that may skew the analysis.

$$KUR = \frac{1}{\sigma^4}\left\{\frac{1}{N-1}\sum_{n=1}^{N}(x_{n-}\mu)^4\right\}$$

(iii). SVM classification:

Support Vector Machine (SVM) is the most powerful machine learning technique in classifying or identifying diseased EEG from the normal. The features extracted using the Daubechies4 wavelet are given to SVM for training, & is able to separate the classes of the original data set correctly. For better classification, the input database given to SVM is split up into a testing dataset and a training dataset. If the classifier undertakes 30% training, the remaining 70% will be given for testing.

Since, three classes were considered – Normal (N), Insomnia (I), and Dementia (D), three binary classifiers, are trained separately for each pair of classes. i.e.,

Classifier 1: N vs. (D, I); Classifier 2: D vs. (I, N); Classifier 3: I vs. (N, D). As a result, a 3X3 confusion matrix is utilized.

6. Performance Metrics:

To evaluate the performance of the SVM classifier, the confusion matrix is considered and the performance metrics like accuracy, sensitivity, specificity, precision, and F1-score are calculated as shown in Table 5.

Table 5: Performance metrics

Parameters	Normal-Dementia	Dementia-Insomnia	Insomnia - Normal	Normal-Dementia-Insomnia
Accuracy	83.2	84.32	84.6	85.9
Precision	83.2	82.9	84.4	84.5
Sensitivity	66.8	65.6	72.1	67.8
F1- Score	0.73	0.75	0.74	0.86
Specificity	85.8	82.68	84.3	87.9

(i). Accuracy (A) for all the three classes is given as,

$$A = \frac{TPi+TPd+TPn}{TPi+TNi+FPi+FNi+TPd+TNd+FPd+FNd+TPn+TNn+FPn+FNn}$$

(ii). Precision (P) for each class is given as,

$$P_{(Insomnia)} = \frac{TPi}{TPi+FPi+FPd}\ ;\ P_{(Dementia)} = \frac{TPd}{TPd+FPn+FNn}\ ;\ P_{(Normal)} = \frac{TPn}{TPn+FPd+FNd}$$

(iii). Sensitivity (S_e) or Recall for each class is given as,

$$S_{e\ (Insomnia)} = \frac{TPi}{TPi+FNi+FNd}\ ;\ S_{e\ (Dementia)} = \frac{TPd}{TPd+FNn+FNi}\ ;\ S_{e\ (Normal)} = \frac{TPn}{TPn+FNd+FNn}$$

(iv). Specificity (S_p) for each class is given as,

$$S_{p\ (Insomnia)} = \frac{TNi}{TNi+FPi+FPd};\ S_{p\ (Dementia)} = \frac{TNd}{TNd+FPn+FNn};\ S_{p\ (Normal)} = \frac{TNn}{TNn+FPd+FNd}$$

(v). F1-score for each class is given as,

$$\text{F1-score}_{(\text{Insomnia})} = \frac{\mathbf{2} * (\boldsymbol{P}(\boldsymbol{Insomnia}) * \boldsymbol{Se}(\boldsymbol{Insomnia}))}{(\boldsymbol{P}(\boldsymbol{Insomnia}) + \boldsymbol{Se}(\boldsymbol{Insomnia}))}$$

$$\text{F1-score}_{(\text{Dementia})} = \frac{\mathbf{2} * (\boldsymbol{P}(\boldsymbol{Dementia}) * \boldsymbol{Se}(\boldsymbol{Dementia}))}{(\boldsymbol{P}(\boldsymbol{Dementia}) + \boldsymbol{Se}(\boldsymbol{Dementia}))}$$

$$\text{F1-score}_{(\text{Normal})} = \frac{\mathbf{2} * (\boldsymbol{P}(\boldsymbol{Normal}) * \boldsymbol{Se}(\boldsymbol{Normal}))}{(\boldsymbol{P}(\boldsymbol{Normal}) + \boldsymbol{Se}(\boldsymbol{Normal}))}$$

Where, TP_i, TP_d, and TP_n represent the true positive cases, FN_i, FN_d, and FN_n represent the false negative cases for each class.

TP_i = The number of instances that were actually insomnia and are correctly predicted as insomnia.

TP_d = The number of instances that were actually dementia and are correctly predicted as dementia.

TP_n = The number of instances that were actually normal and are correctly predicted as normal.

FN_i: The number of instances that were actually insomnia but were incorrectly predicted as dementia or normal.

FN_d: The number of instances that were actually dementia but were incorrectly predicted as insomnia or normal.

FN_n: The number of instances that were actually normal but were incorrectly predicted as insomnia or dementia.

7. Conclusion:

Detecting and diagnosing sleep issues are necessary for maintaining people's health before experiencing any further adverse effects. Early diagnosis of FFI is crucial for initiating treatment and managing symptoms. If there is a family history of FFI, genetic counselling may be recommended to assess the risk of inheriting the condition. While there is no cure for FFI, there are ways to manage the symptoms and improve the quality of life for those affected. Moreover, EEG being a non-invasive technique, its examination of the patients plays a major role in identifying disturbances in the sleep-wake cycle thereby suppressing the symptoms and saving the patients from untimely deaths. For patients suffering from Blood Pressure and Heart Diseases, insomnia can be a part of routine assessment, as most of them experience sleeplessness. In this work, using a machine learning model, insomnia is identified among a group of diseased and normal with an accuracy of 85.9%, precision of 84.5%, Sensitivity of 67.8%, Specificity of 87.9%, and F1 score of 0.86 respectively, which helps to provide a path for physicians to identify the disease at a faster rate, and proper medication can be given to prevent it at an early stage. Early diagnosis, symptom management strategies, and support from loved ones and healthcare professionals can make a significant difference in the lives of individuals with FFI. Maintaining a regular sleep-wake schedule, creating a relaxing bedtime routine, and avoiding caffeine and alcohol before bed can help improve sleep quality, Exposure to bright light during the day can help regulate the body's natural sleep-wake cycle. Also, ongoing research is exploring new treatments and potential cures for FFI.

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