FATAL FAMILIAL INSOMNIA

Literally, insomnia means 'the inability to sleep'. However, the word better describes the various ways in which sleep is *disturbed*. These include:

- Difficulty getting off to sleep (30 minutes or more after going to bed)
- Waking up during sleep
- Waking up too early

Clinicians distinguish between two types of insomnia:

(1) **Primary insomnia:** Sleeplessness that is considered an illness in itself, and cannot be attributed to a medical condition, a psychiatric condition, or the direct physiological effects of a substance (such as stimulant drugs).

(2) **Secondary insomnia:** Sleeplessness that *can* be attributed to the factors identified above. Secondary insomnia is more common than primary insomnia. There are many causes of it. The most common medical conditions are **chronic pain**, **heart disease**, **high blood pressure**, and **Parkinson's disease**. Psychiatric conditions include **depression**, **PTSD**, and **dementia**. Commonly used stimulant drugs include **caffeine** and **nicotine**.

Fatal Familial Insomnia (FFI)

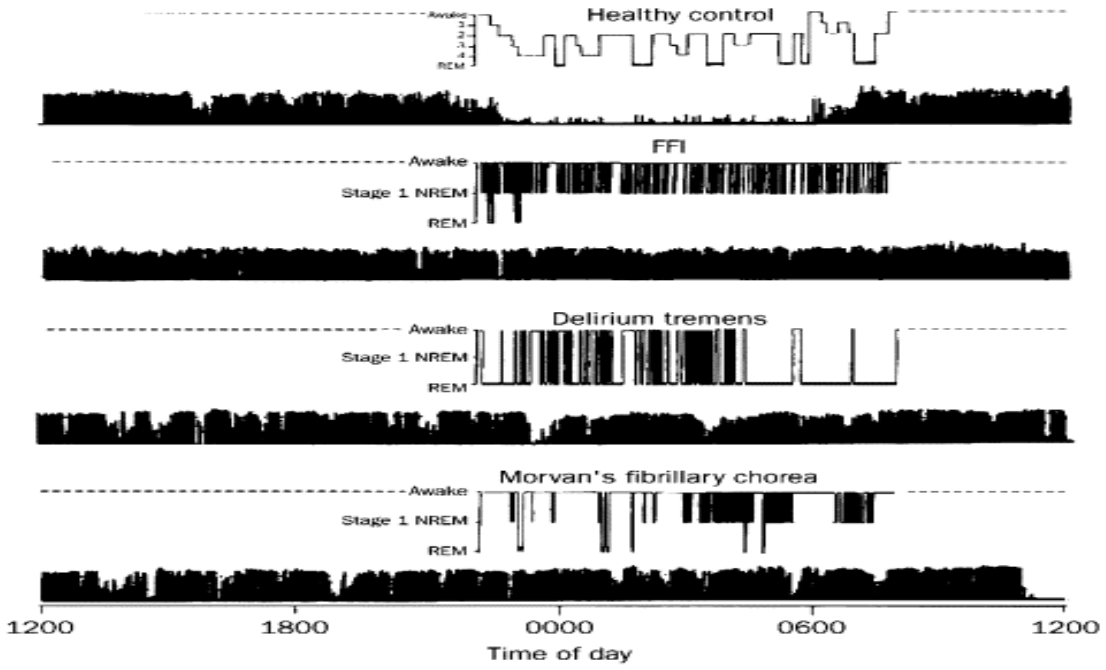
One extremely rare form of secondary insomnia is called **Fatal Familial Insomnia (FFI)**, which has been recognized as a sleep disorder only since 2000, despite the fact that it can be traced back all the way to the 1760s. This is because its symptoms closely resemble other conditions such as dementia, end-stage alcoholism, and encephalitis. FFI typically affects people in their late 40s, although the onset ranges from 25-60 years of age, with an average age of onset of 50 years. As its name suggests, this form of insomnia eventually results in death, which typically occurs within 6 to 36 months. The cause of death is either a coma or some kind of secondary infection.

<u>The stages of FFI</u>

The initial stage involves the person finding it increasingly difficult to fall asleep. This difficulty is associated with panic attacks, paranoia, and

phobias, and lasts for about 4 months. After this, there is a severe and intractable inability to sleep. Slow wave sleep and stage 2 sleep decrease first. Although the EEG may show brain wave activity associated with REM sleep, the person is not asleep and does not show the loss of muscle tone associated with REM sleep. The hallucinations that occur during this second stage are believed to be a result the dreams associated with REM sleep occurring while the person is awake. This stage lasts around 5 months.

Then, the person shows a complete inability to sleep, which is followed by rapid weight loss and limited mental functioning. This third stage lasts for about 3 months. In the final stage, the person shows signs similar to dementia, and becomes unresponsive or mute. However, despite their lack of communication, the person has a clear understanding of what is happening to them. Eventually, and as noted above, the person falls into a coma and dies from total insomnia, or death occurs from some secondary condition.



'Healthy control' participants typically have a 7-8 hour period asleep. In FFI (and other conditions), this does not happen

Another symptom of FFI is *dysautonomia*. This refers to the abnormal functioning of the Autonomic Nervous System (ANS) which regulates things like blood pressure and heart rate. As a result, the person shows high blood pressure, rapid heart rate, sweating, and so on. Other symptoms include difficulty in walking, *myoclonus* (muscle twitching) and

tremor. In the latter stages of FFI, the main cognitive symptoms are poor attention, disorientation, and confusion.

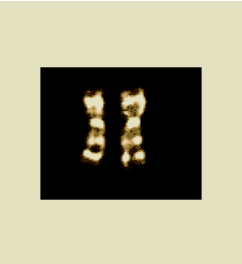
Explanations of FFI

FFI can be traced back to 1765 and a wealthy and respected 36-year-old Venetian doctor known today as '*Subject Zero*'. According to **Max (2006)**, the doctor found that he was able to stay awake all night, and he spent his time either playing cards or studying medicine. However, he sweated profusely during the night, with the result that his servants had to continually supply him with fresh shirts. Within months, the doctor died.

His children were affected in the same way. They began to experience the symptoms of insomnia, and found it increasingly difficult to get to sleep and began to wake earlier and earlier. They also experienced cognitive problems similar to those seen in dementia. After nine months of not sleeping, they too were dead. Although they had been prosperous, the family fell on hard times. Some of them migrated to other parts of Italy and Europe, whilst others went to America.

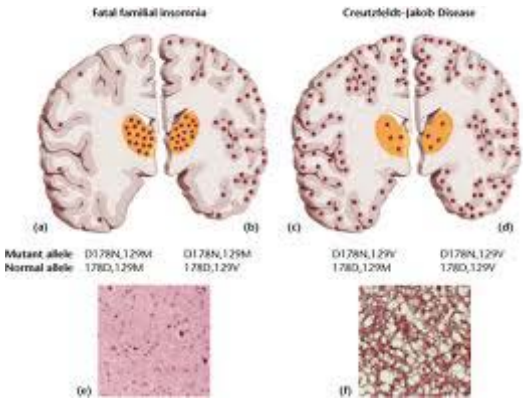
In 1980, a descendant of the family checked into the sleep clinic at Italy's Bologna University with the same symptoms his ancestors had shown. The descendant (a man named Silvano) had been an energetic playboy who had never had any problems sleeping. However, when he checked into the clinic he appeared old and sickly. His motor skills were impaired and his brain function was unusual, since he appeared to be neither awake nor asleep. Silvano told doctors that after his death they could study his brain, and most of what is known now about FFI is a result of research done on Silvano's brain.

The fact that Silvano's condition can be traced all the way back to his ancestor 'Subject Zero' suggests a **genetic** basis to the condition (as is recognized in the term 'familial'). Some genes are responsible for the manufacture of *proteins*, and on the short arm of *Chromosome 20* there is a gene which makes a protein called *PrPc*. In FFI, a genetic mutation results in the substitution of one *amino acid* for another. Amino acids are the building blocks for proteins, and substitution leads to protein folding and dysfunction.



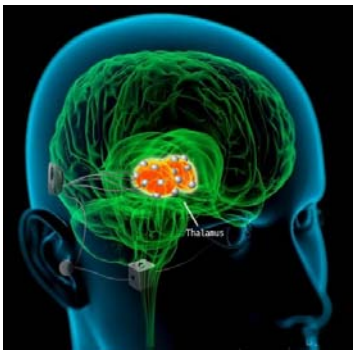
Chromosome 20

In the 1980s, **Stanley Prusiner** coined the term **prion** to describe a mutated protein which permanently affects brain structure. It is now well known that prions are responsible for *Bovine Spongiform Encephalopathy (BSE)* in cattle and its human equivalent *Creuzfeldt-Jacob Disease (CJD)*. FFI is also an example of a **prion disease**.



Like CJD, FFI is a prion disease

In FFI, prions affect the **thalamus**. The thalamus regulates various sensory and motor systems and also regulates sleep. The insoluble proteins cause a build up of plaque, and this increasingly prevents the person from losing consciousness, as though the 'on-off' switch for sleep is stuck in the 'off' position. Although EEG readings may show signs associated with REM sleep during the waking hours, a person is so sleep deprived that they are actually dreaming while awake.



The thalamus

So, FFI is a genetic condition which leads to **brain damage**. Although this is a **reductionistic** explanation, it also happens to be true. FFI is therefore a condition which has a clear *biological cause*, and the environment plays no role whatsoever. The sufferer desperately wants to sleep, but is denied **free-will** by the condition.

Note that FFI can be detected prior to its onset by genetic testing. However, the condition typically manifests itself after a person has had children. If one parent has the gene responsible for FFI, the chance of inheriting it is 50%. Since FFI inevitably leads to death, there are clear **ethical issues** that are raised by this condition.

Notice also that the condition can develop *spontaneously* in people without the inherited mutation. This is called **Sporadic Fatal Insomnia (SFI)**. Although only eight cases of SFI have ever been diagnosed, with seven billion people on the planet it is likely that the mutation will also develop in at least some of them. It seems that as a species we are destined to live with FFI.

One of the most notable cases of FFI is that of **Michael Corke**, a music teacher from Chicago, Illinois. He suddenly began to have trouble sleeping not long after his 40th birthday in 1991, and his health and state of mind quickly deteriorated as his sleeplessness grew worse. Eventually, he couldn't sleep at all, and he was admitted to hospital. Doctors there weren't sure what was wrong with him, and initially diagnosed Multiple Sclerosis. In a bid to send him to sleep in the later stages of the condition, physicians induced a coma with the use of sedatives, but they found that his brain still failed to shut down. Corke died in 1992 a month before his 41st birthday, by which time he had gone without sleep for six months.