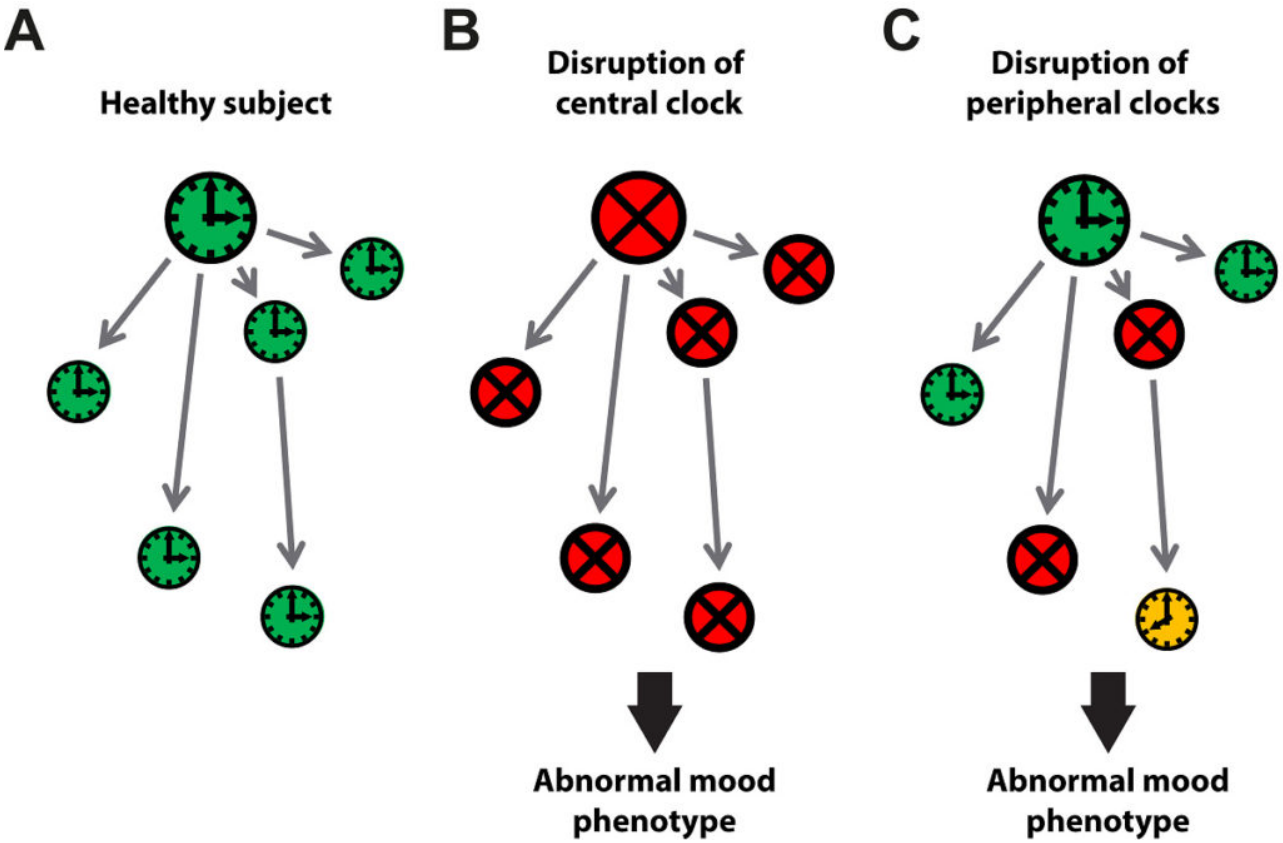
Are we depressed when we miss our inner clock?

All of us have preferred times to wake up and to go to bed. We get hungry at approximately the same times each day and can concentrate better at other times. Such daily rhythms are not just driven by naturally recurring events in our environment, like day and night. Rather, humans and many other organisms, including other mammals, birds, fish, plants, fungi, and even some bacteria, have inherent “circadian” (circa daily) clocks that help them to navigate through the day. The molecular clocks that drive circadian rhythms are present in almost every cell of the body, and synchronize virtually all bodily processes. However, due to everyday obligations imposed by modern life, we cannot always follow the dictates of this internal body clock, and it is perhaps not surprising that disruptions of our natural synchronization can have heavy impacts on our physical and mental health.



A: In healthy subjects, all circadian clocks are functional and synchronized. B: When the central clock is not working, other clocks in the body are not functional as well. This may lead to depression. C: In depressed patients, it might be that only certain clocks in the brain or body are not functional or not properly synchronized (e.g. in the stress system). This might be sufficient to cause depression.

For example, many shift workers, who are forced to work against their internal clock, develop depression. Conversely, depressed people often complain about problems keeping their normal daily routines. They often suffer sleep problems, but feel tired during the day; they are not hungry at regular times and have difficulties following the social rhythms of their family and friends. Although many physicians already treat depressed patients with so-called “chronotherapies” designed to regularize daily rhythms, the question remains: Are disturbed circadian rhythms a result of depression, or are they one of the reasons why depression develops in the first place?

In our study, we tried to determine whether disrupting the circadian clock is sufficient to provoke depression. To understand our approach, it is important to know that circadian clocks in mammals are under control of a small brain area called the suprachiasmatic nucleus (SCN). The SCN is directly connected to the eyes, allowing adjustment of the master SCN clock to daily light/dark cycles. The SCN, in turn, synchronizes circadian clocks in all other cells throughout the body. When the SCN is not working properly, all circadian rhythms in the organism are disrupted.

Accordingly, we developed a new mouse model in which an essential clock gene called *Bmal1* is deactivated only in the SCN. This can be done by precise injecting into the SCN a special virus carrying genetic instructions that locally inhibit expression of *Bmal1*. Thus, the only difference between these mice and control mice is that they have weakened circadian rhythms in the SCN; otherwise, they are exactly the same.

Interestingly, these mice change their behavior in a way that resembles human depression. Compared to their companions with normal circadian clocks, they are less motivated to escape uncomfortable situations, like mild but unpleasant electric shocks, or being hung by their tail for a few minutes. They are also more anxious in that they tend (more than other mice) to avoid potentially dangerous environments. Furthermore, they gain more weight, a feature that is also observed in many depressed patients. Intriguingly, we detected an irregular daily pattern of release of the stress hormone corticosterone in these mice. The stress system plays a central role in mood regulation and is often disturbed in depression. Therefore, this observation may give an initial clue about how disrupted clocks might lead to depression.

For the first time, we have shown that suppressing circadian rhythms in otherwise totally undisturbed animals is enough to cause behaviors similar to human depression. Our data suggest that the stress system is affected when the inner clock is disrupted. Understanding precisely how circadian clock disruption leads to depression in this mouse model will be an important step toward developing new depression treatments that directly target the circadian clock in humans.

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