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MOOD DISORDERS

The dark night

The causal relationships between lack of sleep and mood disorders remain murky. But one thing is clear as day: better sleep can have psychological benefits.

BY SARAH DEWEERDT

One of the few personal touches in psychiatrist Murray Raskind's small, windowless office is a yellowing photograph of a young man in military garb. The man is crouching on the ground, leaning against his rifle for balance, and looks up at the camera with haunted eyes. It is a portrait of a soldier suffering from combat-related post-traumatic stress disorder (PTSD).

The man in the photo is Don Hall, who fought in Vietnam during the brutal Tet Offensive in 1968. When Raskind met him in the mid-1990s, Hall was plagued by recurrent nightmares, replaying his combat experiences as if they were on videotape, night after night for nearly 30 years. "That's a hallmark of combat PTSD," says Raskind, director of the VA Northwest Mental Illness Research, Education and Clinical Center in Seattle, Washington, who discovered that a common blood-pressure medication can alleviate these nightmares.

The symptoms of PTSD include anger and irritability, feeling numb and detached, and difficulty concentrating. "But as far as the veterans are concerned, their problem is they can't sleep," Raskind says. "And when they have a bad night with nightmares, the next day they're in a bleak mood."

The role of combat nightmares in PTSD is particularly dramatic, but sleep abnormalities are associated with nearly all mood and anxiety disorders. Depression often leads to insomnia, or sometimes to sleeping more than normal or having trouble getting out of bed. During manic episodes, many people with bipolar disorder — a condition characterized by bouts of high-energy frenzy alternating with depression — seem to need very little sleep, getting by on just a few hours a night for days on end.

Sleep disruptions are so common that they even form part of the diagnostic criteria for these disorders. "Mood dysregulation and sleep dysregulation seem to go hand in hand," says Matthew Walker, a sleep researcher at the University of California, Berkeley.

DISTRESS SIGNALS

The link between sleep disruption and psychiatric disorders is well established, but the causal relationships are less clear. Do sleep disturbances trigger episodes of these disorders, or do mood and anxiety disorders lead to difficulty sleeping? Both could be true. "It's a two-way street," says Walker. It's also possible that some other underlying problem in the brain interferes with both mood and sleep.

There is ample evidence that sleep and mood are entangled at the very root. People who sleep poorly are more likely to develop depression than those who sleep well[1], for example. Insomnia is often the first symptom of an episode of depression to appear, and often the last to go. And treatments including antidepressants and psychotherapy are less effective in people with both depression and insomnia than in those with depression alone[2].

Loss of sleep also often heralds an episode of mania in bipolar disorder. Similarly, sleeping too much is linked to depressive episodes. One study found that depriving people with bipolar disorder of sleep triggered mania or hypomania — a less intense episode that often precedes mania — in about 10% of patients[3].

People with bipolar disorder and their unaffected relatives are also more likely to be night owls — they have what sleep researchers call a 'delayed sleep phase'. Such observations suggest there may be a circadian component to sleep disruptions in mood disorders (see 'Stepping out of time', page S10).

Bolstering the circadian link, some patients show a seasonal pattern of bipolar symptoms, says Ruth Benca, a psychiatrist at the University of Wisconsin in Madison. They exhibit peaks of suicidal behaviour in spring and autumn, when day length changes most rapidly.

But other patients with bipolar disorder may have normal circadian rhythms, despite showing extremely chaotic sleep patterns, says psychologist Ellen Frank at the University of Pittsburgh in Pennsylvania.

The sleep problems associated with mood disorders go beyond the usual tossing and turning. Electroencephalography (EEG) studies

reveal abnormalities not just in how much and when these patients sleep, but also in how their brains function during sleep. Compared with healthy people, bipolar disorder sufferers are more likely to show a variety of abnormalities, such as more time in light sleep and waking up more often. They therefore spend less time in the deepest phase of sleep, known as slow-wave or delta-wave sleep. "For whatever reason, their brains don't seem to be able to make these delta waves that we believe are associated with the restorative aspect of sleep," Frank says.

In another EEG study, Benca and colleagues found that people with depression do not show the expected change before and after sleep in a measure of brain function associated with slow-wave sleep. The brain's electrical response to a sound, known as an auditory evoked potential, is normally larger before sleep than on waking, but those with depression don't show this decline. "Depressed people's brains don't reset the same way between the night and the morning as the control subjects," Benca says.

This finding is striking, she adds, because the study participants did not have bad insomnia. But Benca cautions that these abnormalities may or may not be connected to the symptoms that people with mood disorders experience during the day. Perhaps sleep simply removes the variables and distractions of the daytime and reveals how the brains of people with mood disorders function differently overall.

NEGATIVE IMAGES

To untangle these relationships, scientists are probing the neural basis of the connection between sleep and emotional state. In one of the first such studies, Walker and his colleagues performed brain scans on healthy adults — some of whom were well rested while others had been kept awake for 35 hours — as they were shown a series of images ranging from neutral to gory and unpleasant, such as mutilated bodies or children with tumours.

Viewing negative images activates the amygdala, an area of the brain involved in the formation of memory associated with emotional events, such as frightening experiences, the researchers found. Both groups had similar reactions when shown neutral images, but the amygdala's response to the negative images was about 60% greater in the sleep-deprived group[4].

"When you take a healthy brain and take sleep away, you can produce patterns of brain activity that look not dissimilar to some psychiatric disorders," Walker says. Similar overactivity in the amygdala is also seen in mood disorders, and unpublished data from Walker's lab suggest that a lack of sleep can mimic some of the brain processes seen in anxiety disorder.

Paradoxically, some depressed patients who are deprived of sleep for a night have diminished symptoms the next day, suggesting an antidepressant effect. It is thought that sleep deprivation dampens excess activity in one area of the brain, the anterior cingulate cortex, which is characteristic of depression[5]. Once they can sleep again, the depression returns, so sleep deprivation isn't a viable treatment. But the finding has spurred research to find out which types of sleep are involved in this effect.

Some evidence points to rapid eye movement (REM) sleep. For example, tricyclic antidepressants are thought to work by disrupting REM sleep. In some cases, an antidepressant's efficacy is correlated with how well it suppresses REM sleep, Benca says. But this may not be the whole story. Benca's group showed that disrupting the ability to produce slow waves during deep sleep has an antidepressant effect[6], which "opens the possibility that somehow manipulations of slow-wave activity might be effective".

Research from Walker's lab suggests a possible mechanism for this effect. They found that when healthy but sleep-deprived people view a series of neutral or positive images, they classify more of the images as positive than people who are well rested[7]. They also show greater brain activity in the mesolimbic system, a brain network thought to be associated with reward, suggesting that a lack of sleep increases activity in the brain's pleasure centre. These results are the flip side to Walker's earlier finding of greater responses to negative images in his overtired volunteers: sleep deprivation increases what researchers call emotional reactivity in general.

DON HALL

A haunted-looking Don Hall in Vietnam.

OVERNIGHT IMPROVEMENT

The causal relationships between sleep and mood aren't yet clear, but the implication for treatment is: get people sleeping better. "These sleep problems are very modifiable," says Allison Harvey, a clinical psychologist at the University of California, Berkeley. "Simple, powerful behaviour modifications can yield fairly startling improvements in both the sleep and the disorder."

For example, Frank and her colleagues have developed an approach to treating bipolar disorder that encourages patients to keep to a regular daily schedule of waking up, eating, socializing and going to bed. This method, Frank says, "seems to be protective against new episodes of bipolar disorder, and to help people come out of their depression more quickly". That's particularly important, she adds, because although drugs can keep mania in check, bipolar depression is not as easily controlled.

Harvey and her colleagues have begun to apply similar principles to unipolar depression. She has unpublished data suggesting that patients who are coached to improve their sleep are less likely to have a relapse of depression. Another group has shown that using cognitive behavioural therapy to treat insomnia (see 'Chasing the dream', page S16) improves the effectiveness of treatment for depression[8].

Walker refers to sleep as "overnight therapy". In REM sleep — the phase in which most dreaming occurs — the brain's production of noradrenaline (also known as norepinephrine) shuts down. Noradrenaline is the brain's form of the stress hormone adrenaline, so its absence during REM sleep creates a soothing neurochemical environment in which the brain can process tumultuous events. "It essentially takes the sharp edges off these emotional experiences," Walker says.

This process goes awry in PTSD, he thinks, as PTSD sufferers have too much noradrenaline and not enough REM sleep. Interestingly, the treatment for trauma nightmares that Raskind discovered, a blood-pressure drug called prazosin, blocks noradrenaline receptors in the brain.

A couple of weeks after starting prazosin, Hall told Raskind he was sleeping through the night for the first time since his military service in Vietnam. "I thought, man, I didn't know I was such a good psychotherapist," Raskind recalls. "I was sure this was a placebo effect." But Raskind gave the drug to a second Vietnam veteran suffering from PTSD, and his nightmares got better too. Randomized trials have since shown that prazosin reduces trauma nightmares, improves sleep, and diminishes other symptoms of PTSD in combat veterans[9]. About 70,000 US army veterans now take the drug.

Raskind reports that as long as Hall continues taking prazosin, his nightmares are kept at bay. And it shows. Raskind keeps another photo in his office, from Hall's recent wedding, showing a man who looks older but also more at peace: a portrait of the role of a good night's sleep in healing the mind. "He looks a lot better here than he did with that furrowed brow," Raskind says. "Notice the brow difference — that's the prazosin effect." ■

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