State of the art: Sleep

JIM HORNE *discusses the latest research on sleep, dreaming and sleep deprivation.*

FOR me, one of the greatest mysteries of sleep is why so few psychologists seem to be interested in the subject. Sleep occupies so much of our time that it is arguably the commonest form of human behaviour, and it is associated with one of the most frequent complaints brought to the GP: also well within the repertoire of the psychologist. Loss of sleep is linked with some of the worst man-made disasters or near disasters, is a major cause of road traffic death and, every year, involves countless millions of pounds of product sales to avoid it. For most of us the explanation for sleep is simple and pragmatic – oblivion.

From plants to people

For most living organisms sleep or its like is a simple matter. All forms of life display regular daily periods of rest that are largely governed by a circadian rhythm. Even plants rest at night, when photosynthesis ceases. For animals, sleep is also typified by a retreat to a sleeping site, cessation of physical activity, adoption of a typical body posture, and a marked reduction in behavioural responsiveness. (Maybe some of these criteria could still apply to plants?)

But for animals with a distinct brain, whether it be an octopus, insect, fish, frog or human, this is this organ that shows the most distinctive changes during sleep, and where the control mechanisms for sleep are to be found.

With humans and other advanced mammals, focusing on the brain is particularly appropriate for the understanding of their sleep, as it is the cerebrum for which sleep provides the vital function. In less cerebrally advanced small mammals, sleep has a more basic role, because of their need for a high energy intake. In such animals sleep provides the only real opportunity for physical rest from otherwise constant activity, as well as confining them to the thermal insulation and safety of a nest. In all these respects, sleep conserves much energy, especially when it can also develop into a torpor (whereby metabolic rate and body temperature drop significantly for a few hours during sleep).

Humans, like most large mammals, do not have this ability, but we can physically rest and relax quite adequately during wakefulness owing to an advanced cerebrum to provide for the accompanying advanced behaviour that facilitates this inactivity, such as thinking, reading, listening, watching, talking, and so on. As this is beyond the capacity of small mammals, sleep is their only immobiliser and energy saver. For humans, though, the energy saved by being asleep throughout the night rather than sitting relaxed but awake, is trivial – the energy equivalent to a slice of bread.

Thus, sleep serves more than one

function, probably changing its emphasis with evolution, body size, need to conserve energy, cerebral development, and amount of relaxed wakefulness. Indeed, for humans, there is little or no evidence that any other organ apart from the cerebrum undergoes any heightened degree of recovery during sleep compared with relaxed wakefulness. Other organs recover equally effectively (and probably more so) during relaxed wakefulness. This is especially the case as more nutrients are usually available to the cell at this time, in contrast with the typically fasting state of night-time sleep (Horne, 1988).

How much sleep do we need?

When confined to cages, stables or otherwise restricted, most mammals sleep longer than when free. The well-fed cat sleeps much more than one that has to hunt for its living. What is the norm for their sleep? Are they chronically sleep-deprived in the 'wild', or do they sleep to excess when they are constrained? But it is human sleep that is the real focus for this ongoing debate among sleep researchers (e.g. Dement, 2000; Harrison & Horne, 1995). Doubtless, one's need for sleep alters as the night progresses, initially serving more important purposes, then changing to those of less benefit, and eventually to a sleep that is perhaps superfluous, luxurious and just pleasant to take. If encouraged to do so, healthy people can sleep two or more hours beyond their daily norm. Compare sleep with eating and drinking – a certain amount is vital, but we can easily consume more than we really need. It is pure indulgence, so why should this not also be the case for the extra sleep? Alternatively, many sleep researchers, particularly in the USA, argue that indeed we do need this extra sleep, otherwise we would not be able to take it (e.g. Dement, 2000).

Sleeping one or two hours beyond our daily norm leads to only marginal improvements in daytime alertness (Harrison & Horne, 1996), mainly in the early afternoon, when the 'afternoon dip' in alertness is eliminated. If this extended sleep regimen is continued for a week or so, night-time sleep quality deteriorates, so it takes longer to fall asleep at night and one wakes up more frequently. In effect, sleep is stretched out, inefficiently, to fill the greater time available. A better remedy for those affected by afternoon sleepiness is not to extend night-time sleep this way, but simply to take a 10-minute afternoon nap instead (Horne & Reyner, 1996).

Longer sleepers do not have a greater

Insufficient sleep can be hazar dous

life expectancy, and neither do shorter sleepers die earlier. A six-year prospective follow-up study by Kripke *et al*. (1998) of over one million Americans found that when daily habitual sleep exceeded seven and a half hours in apparently healthy people, mortality rates rose. Furthermore, Kripke and Marler (2000) reported that sleeping less than seven hours a day predicted no significant increase in mortality when the usual confounds such as heart disease, smoking, and obesity were removed. Surprisingly, those respondents reporting having insomnia had a significantly lower mortality risk, unless they also took sleeping tablets, when the risk rose significantly. Sleeping tablets are probably not the cause, but there are interesting implications. The most recent study by this group (Jean-Louis *et al*., 2000), looking at sleep satisfaction, found it to be coupled with the perception of having a healthy life, not with longer sleep.

Symptoms associated with persistent insomnia are largely unconnected with insufficient sleep, as indicated by the recent authoritative review by the American Academy of Sleep Medicine (Sateia *et al*., 2000):

> *…no consistent picture of the daytime consequences of clinical insomnia has emerged. The ultimate significance of insomnia lies, at least in part, on such consequences. Current data seems to suggest that the daytime consequences which are associated with an insomnia complaint may not be due to sleep deprivation, but instead, to hyperarousal which gives rise to both sleep disturbance and waking complaints. To the extent that this is true, it suggests that evaluation and treatment efforts might be most effectively aimed at this underlying arousal.* (p.254)

The key symptom of insufficient sleep, sleepiness, can be hazardous and cause serious accidents. Nevertheless, there is little evidence that insomniacs are in such danger. On the other hand, in our increasingly 24-hour society, people take risks in having too little or no sleep for a night or so. Sleepiness is a common killer on our roads, especially when speeding along a dull and monotonous motorway (Horne & Reyner, 1999). These are not 'accidents' but inexcusable and easily preventable crashes, as drivers are quite aware of heightened sleepiness well beforehand and have had adequate opportunity to avoid the situation (Reyner & Horne, 1998).

Sleep and mood are interlinked in intriguing ways that are still not understood. Healthy, happy, naturally very short sleepers usually feel on top form, even euphoric. Patients with mania take little or no sleep during eruptions of the illness. On the other hand, when sleep is shortened to around four hours for one night in severely depressed patients, there is often a rapid improvement in mood for as long as they remain awake (Wu & Bunney, 1990). Unfortunately, the ensuing sleep soon leads to a relapse.

Dreaming

To varying extents, mental activity continues throughout all sleep, with the intensely visual and vivid form dreaming largely confined to REM sleep. However, these are just bedfellows, as REM control mechanisms are located in the brainstem and midbrain, whereas the neuroanatomical basis of dreaming clearly lies in higher centres. Further indications that REM sleep and dreaming are independent processes are reflected in the rapid eye movements of REM sleep. These are unlikely to be associated with dream imagery, especially as most of dreaming contains no eye movements at all. Solms (in press) has reported many cases of dreamless REM sleep among neurological patients. He surmised that if dreams were in some way

WEBLINKS

European Sleep Research Society: *www.esrs.org/*

Sleep Research Centre at Loughborough University: *www.lboro.ac.uk/departments/hu/groups/sleep/index.htm*

Sleep Research Society: *www.srssleep.org/*

International database on many aspects of sleep: *bisleep.medsch.ucla.edu/*

the 'guardians of sleep' as proposed by Freud, then patients no longer capable of dreaming should sleep less well. This was not the case, as half these patients slept better and half slept worse than before their illnesses.

We are easily aroused from REM sleep by external stimuli signifying possible danger or having other emotional content. In contrast, there is a high arousal threshold for meaningless, non-threatening stimuli that can even be incorporated into dreams. Interestingly, during REM sleep one has a greater level of awareness of the outside world than is the case with non-REM sleep. Given the potential fragility of REM sleep with respect to emotive external stimuli, and that dreams can have so much emotional content, it is remarkable that we do not wake up more frequently during dreaming, other than from the more frightening nightmares. It seems that the dreamer is disembodied or protected from the emotional content of the dream.

The highly active amygdala during this state (Maquet, 2000) may be the real guardian of sleep, blocking these potential emotions in order to maintain the integrity of sleep, whilst allowing the detection of outside threats (Horne, 2000). Such disembodiment is reflected not only by the paralysis of much of the body (atonia) during REM sleep, but in a generalised physiological unresponsiveness, when, despite the emotional content of dreams, mean heart rate, blood pressure, adrenaline and cortisol output all remain unchanged. The rise in cortisol levels during the latter part of our night's sleep is largely a circadian phenomenon, not really connected with sleep.

Inasmuch as dreams are composed of a distorted mixture of a person's recent waking thoughts and events, then the 'analysis' of dreams can only be achieved by knowing about these idiosyncrasies. Interpretation by people who are unfamiliar with these experiences is usually nonsense, and the fantasy largely exists within the mind of these dream interpreters rather than that of the dreamer. People spend about 100 minutes a night dreaming, but can seldom recollect more than the last few minutes prior to an awaking. It implies that dreams are meant to be forgotten, having little more than entertainment value in being the nightly 'cinema of the mind'. This is not to dismiss the importance of REM sleep and dreams, as they keep the slumbering brain stimulated, preoccupied and 'toned up' in preparation for wakefulness (Horne, 2000).

In many respects REM sleep is very similar to wakefulness than non-REM sleep, to the extent it could be seen as 'non-wakefulness' whereby wakefulness is switched off rather than sleep being switched on. I argue (Horne, 2000) that this similarities much more than implied by the term 'paradoxical sleep', used as a synonym for REM sleep in animals.

REM sleep seems somewhat dispensable: people can quite easily be deprived of most if not all of it for months at a time, for example during medication by most tricyclic antidepressants. Cessation of this treatment leads to only relatively small rebounds of REM sleep. If it has a key role with memory consolidation, as is often believed, then such a prolonged suppression of REM sleep should have a major impact on at least some aspect of memory, which is not the case (Horne, 2000).

Whatever REM sleep's function may be, it seems to centre on the developing mammalian brain, as in most mammals REM sleep is at its most prolific in the foetus and neonate. This has given rise to perhaps the most plausible explanation, that REM sleep aids brain development by providing substitute stimulation, owing to the relative lack of external stimulation from within the uterus (Roffwarg *et al*., 1966).

Sleep deprivation

The effects of sleep deprivation Total sleep deprivation in humans is surprisingly uneventful for most organs other than the cortex. But there are still gaps in our knowledge, especially in relation to the immune system, where sleep loss causes changes to certain aspects of host defence. In this difficult area of research it is too easy to jump to wrong conclusions, and these changes should not be seen as impairments but best described as an increased surveillance by the immune system, returning to normal after recovery sleep (e.g. Dinges *et al*., 1995). Recent reports even point to sleep loss boosting host defence and helping to ward off tumour growth and infection (Bergmann *et al*., 1996a; Renegar *et al*., 2000).

Over the last 20 years, pioneering research into sleep deprivation (using rats) has been undertaken at the Chicago University Sleep Laboratory (Rechtschaffen, 1998). Animals totally sleep deprived die after about 14 days, for reasons that are still not clear. Animals allowed to sleep near this end point quickly and fully recover. During the sleep loss there is an initial body temperature rise, that returns to normal for a while. Animals eat voraciously, lose weight and develop peculiar, non-infected skin lesions. In the final stage of deprivation body temperature falls once more, and weight loss continues. Although host defence eventually collapses, it may or may not be the primary cause of death.

Whilst Eversen (1993) argues that this deprivation causes widespread systemic infections due to the failure of host defence,

with the accumulation of bacterial toxins and death through septicaemia, Bergmann *et al.* (1996b) dismiss this interpretation. They point to their own work showing that sleep-deprived rats have little by way of serious infections, and that treating animals with antibiotics to remove any signs of infection neither affects their temperature and weight changes nor prolongs progression towards death. There are no signs of brain pathology in these animals, and it is as if they just give up.

Numerous studies have deprived humans of sleep, usually for one to three nights, and a few for five to eight nights (Horne, 1988). The circumstances are much more pleasant than those for the rat, of course, and there are no reports of physical illness or other adverse physiological signs – there is just a general slowing up. There are only minor changes to thermoregulation, with body temperature dropping by about 0.5°C. Such an uneventful outcome is not what one would expect if sleep was a condition of heightened body repair (excluding the brain); and it seems that, for humans at least, restorative processes are carried out effectively during the wakefulness of sleep deprivation. Although a recent report by Spiegel *et al.* (1999) claims that human sleep loss causes metabolic and endocrine impairments, the significant effects were in comparison only with recovery days, not with the normal baseline.

Testing sleep deprivation effects in humans Most standard psychological tests used in human sleep deprivation research are generally unhelpful from the viewpoint of sleep function (Harrison & Horne, 2000), being far too simple, unstimulating and tediously boring. Boredom facilitates sleepiness even in mildly sleepy people (Mavjee & Horne, 1994), and is why vigilance and reaction time tasks are so sensitive to sleep loss: the sleepy brain increasingly needs motivating sensory stimulation to keep it awake. When sleep-deprived people are encouraged to apply more compensatory effort to an otherwise dull task, then the deficit can be reversed, at least for a while. Lapsing ('microsleeps') is probably the explanation for the performance failures (Dinges & Kribbs, 1991) as when a sleepy person is not lapsing, reaction times are normal.

A traditional line of thinking is that short and interesting tasks, typified by convergent logical tests, are insensitive to sleep deprivation. Nevertheless, if they are simple and repetitive, then such tasks can still be sensitive to sleep loss, again because of monotony and boredom.

So it might be surprising that certain short, novel, divergent and interesting tasks, for example of verbal fluency, and nonverbal planning, are sensitive to sleep loss (Horne, 1988). The reason seems to be that, unlike the logical tasks, they rely heavily on the prefrontal cortex. This region is one of the hardest-working cortical areas during wakefulness. If sleep provides cortical recovery following wakefulness, then this area might be more vulnerable to sleep loss (Horne, 1993). The prefrontal cortex is also responsible, for example, for directing and sustaining attention, inhibiting distraction, aspects of working memory, and flexible thinking. Such skills are also impaired by short-term sleep deprivation (cf. Harrison & Horne, 2000), despite the participants' best efforts to perform well, even following caffeine at a dose that returns reaction time and sleepiness to normal levels (Harrison *et al.*, 1997).

The prefrontal cortex in sleep deprivation Normally, the cortex is unable to 'switch off' to any extent, outside sleep. Even when we lie down, turn off the light, relax but remain awake, block out sound and try and clear the mind of all thoughts, the cortex is always in a state of quiet readiness, prepared to respond immediately to any stimulus. In this respect, the waking cortex is like a computer, where the power consumption is near to its peak, whether it is idling on standby, awaiting instructions, or is involved with programs and taking in information. If some form of rest is required for the recovery of cerebral function, then only sleep seems able to provide this facility, which seems to be why the obvious effects of human sleep deprivation is with behaviour. For the more advanced mammalian cerebrum, this role for sleep is of particular importance, whereas for the less cerebrally advanced rodent it may be less so.

Recent brain-imaging studies, in the USA, with similarly sleep-deprived people, confirm that the prefrontal cortex indeed shows particularly profound changes with sleep loss (Drummond *et al.*, 2000; Thomas *et al.*, 2000). Moreover, other cortical regions usually not involved with tasks having a prefrontal focus, become more active, as if to compensate (Drummond *et al.*, 2000).

Interestingly, in young adults the effect of 36 hours of sleep deprivation on these prefrontal neuropsychological tests is similar to that of normal healthy ageing – equivalent to about 60 years of age (Harrison *et al.*, 2000). Healthy ageing also leads to a preferential impairment of the prefrontal cortex, whereas psychological tasks not so oriented to this area are less sensitive both to sleep deprivation and to ageing. This does not imply that an aged brain is a sleep-deprived brain, merely that regions of the waking cortex working the hardest are more vulnerable to both these factors.

The type of sleep that seems to be associated with cerebral recovery is reflected by slow wave ('delta') activity in the EEG (Horne, 1988). It is the form of sleep most highly correlated with the length of prior wakefulness, appears early on in sleep, and takes priority over all other sleep states, including REM sleep. Also it is most apparent in the prefrontal area (Werth *et al.*, 1997). Brain imaging during sleep shows that the greatest degree of cerebral shutdown occurs during slow wave activity; more so in the prefrontal region (Maquet, 2000).

Sleep deprivation and human error No doubt the prefrontal approach to sleep deprivation will turn out to be too simple. Nevertheless, it does have several real-world implications, especially for decision makers (including junior hospital doctors) obliged to go without sleep in an emergency. If there is a need to deal with surprise and the unexpected, be innovative, think flexibly, avoid distraction, make risk assessments, be aware of what is feasible, appreciate one's own capabilities, and communicate clearly, then these are the very behaviours that are likely to be dependent on a fully functioning prefrontal cortex, and are the most likely to begin to fail with sleep deprivation (Harrison & Horne, 2000).

It may be a coincidence that renowned disasters or near-disasters due to human error and concerning nuclear power plants, such as Chernobyl, Three Mile Island, Davis-Beese (Ohio) and Rancho Seco (Sacramento), all occurred in the early morning, and involved failure to contain otherwise controllable but unexpected and unusual mechanical or control room malfunctions. With all four, experienced control room managers misdiagnosed and failed to appreciate the extent of the fault, then embarked on courses of action that were inappropriate. They continued to persevere in this way in spite of clear indications that their original assessment

was wrong. Of course, it is difficult to say how much of this could have been due to sleep deprivation rather than to stress and panic. But sleep deprivation certainly played a crucial role in the fateful dawn decision to launch the space shuttle *Challenger*. The Presidential Commission (1986) cited the contribution of human error and poor judgement related to sleep loss and shift work during the early morning hours. Key managers had less than two hours sleep the night before and had been on duty since 1am. The report further commented that 'working excessive hours, while admirable, raises serious questions when it jeopardises job performance, particularly when critical management decisions are at stake' (p.5).

ASSOCIATED PRESS

Sleep deprivation played a crucial role in the decision to launch the space shuttle *Challenger*

Conclusion

Sleep is the natural state of unconsciousness. It promotes consciousness in the form of heightened waking awareness of oneself and one's environment. Without sleep, thinking becomes clouded, we become automatons and we lose our unique behaviour. Sleep is too complex a state to be seen as 'oblivion', especially as so many brain systems are involved in its regulation. If it was just 'non-behaviour', then why would its loss lead to sleepiness, especially when the latter is so hazardous and there is no eventual override mechanism to profound sleepiness? To understand sleep better we must await further technological advances with which to see inside the sleeping brain at the cellular level, and not just the neurone – glial cells may have the answer. But we will be little the wiser without knowing about the behavioural sequelae of such cellular events.

■ *Professor Jim Horne is at the Sleep Research Centre, Human Sciences Department, Loughborough University, Leicestershire LE11 3TU. Tel: 01509 223004; fax: 01509 223940; e-mail: j.a.horne@lboro.ac.uk.*

References

Bergmann,B.M.,Rechtschaffen,A.,Gilliland, M.A., & Quintans, J.(1996a).Effect of extended sleep deprivation on tumour growth in rats. *American Journal of Physiology, 271*, R1460–R1464.

Bergmann,B.M.,Gilliland,M.A., Feng,P-F, Russell, D. R.,Shaw, P,Wright,M., Rechtschaffen,A., & Alverdy, J. C. (1996b).Are physiological effects of sleep deprivation in the rat mediated by bacterial invasion? *Sleep,19*, 554–562.

Dement, W. C. (2000). *The promise of sleep*. New York: Bantam Doubleday Dell.

Dinges, D. F.,Douglas,S. D.,Hamarman,S., Zaugg,L., & Kapoor, S.(1995).Sleep deprivation and human immune function. *Advances in Neuroimmunology, 5*, 97–110.

Dinges, D. F., & Kribbs, N.B.(1991). Performing while sleepy:Effects of experimentally induced sleepiness. In T. H Monk, T. H.(Ed.), *Sleep, sleepiness and performance* (pp. 97–128).Winchester: John Wiley.

Drummond,S. P.A.,Brown,G.A., Gillin J. C., Stricker, J.L., Wong,E. C., & Buxton, R. B.(2000).Altered brain response to verbal learning following sleep deprivation. *Nature, 403*, 655–657.

Eversen C. A.(1993). Sustained sleep deprivation impairs host defence. *American Journal of Physiology, 265*, 1148–1154.

Harrison,Y., & Horne, J.A.(1995). Should we be taking more sleep? *Sleep,10*, 901–907.

Harrison,Y., & Horne, J.A.(1996).Long-term extension to sleep – Are we chronically sleep deprived? *Psychophysiology, 33*, 22–30.

Harrison,Y., & Horne, J.A.(2000).The impact of sleep loss on decision making: A review. *Journal of Experimental Psychology:Applied, 6*, 236–249.

Harrison,Y.,Horne, J.A., & Rothwell,A. (1997). Sleep loss performance decrements on frontal lobe tasks show no improvement with caffeine. *Sleep Research,26*, 616.

Harrison,Y.,Horne, J.A., & Rothwell,A. (2000).Prefrontal neuropsychological effects of sleep deprivation in young adults: A model for healthy aging? *Sleep, 23*, 1067–1071.

Horne, J.A.(1988). *Why we sleep:The functions of sleep in humans and other mammals*. Oxford:Oxford University Press.

Horne J. A.(1993). Human sleep, sleep loss and behaviour: Implications for the prefrontal cortex and psychiatric disorder. *British Journal of Psychiatry, 162*, 413–441

Horne, J.A.(2000). REM sleep – by default? *Neuroscience and Biobehavioural Reviews, 24*, 777–797.

Horne, J.A., & Reyner, L.A.(1996).Driver sleepiness: Comparisons of practical countermeasures – caffeine and nap. *Psychophysiology, 33*, 306–309.

Horne, J.A., & Reyner, L.A.(1999).Vehicle accidents related to sleep: A review. *Occupational and Environmental Medicine, 56*, 289–294.

Jean-Louis,G.,Kripke, D. F., & Ancoli-Israel, S.(2000). Sleep and quality of well-being. *Sleep,23*, 1115–1121.

Kripke, D. F.,Klauber, M.R.,Winguard, D. L., Fell,R.L.,Assmus,J. D., & Garfinkel,L. (1998).Mortality hazard associated with prescription hypnotics. *Biological Psychiatry, 43*, 687–793.

Kripke, D. F., & Marler, M.R.(2000). Insomnia is not a mortality risk factor: Maybe it's good for your patients! *Sleep,23* (Suppl 2),A49.

Maquet, P. (2000). Functional neuroimaging of normal human sleep by positron emission tomography. *Journal of Sleep Research,9*, 207–232.

Mavjee,V., & Horne, J.A.(1994).Boredom effects on sleepiness/alertness in the early afternoon vs early evening,and interactions with warm ambient temperature. *British Journal of Psychology, 85*, 317–334.

Presidential Commission (1986). Human factors analysis. In *Report of the Presidential Commission on the Space Shuttle Challenger Accident* (Vol II, Appendix G).Washington,DC:US Government Printing Office.

Rechtschaffen,A.(1998).Current perspectives on the function of sleep. *Perspectives in Biology and Medicine, 41*, 359–390.

Renegar, K.B.,Crouse, D.,Floyd,R.A., & Krueger, J.(2000).Progression of influenza viral infection through the murine respiratory tract:The protective role of sleep deprivation. *Sleep,23*, 859–863.

Reyner, L.A., & Horne, J.A.(1998).Falling asleep at the wheel: Are drivers aware of prior sleepiness? *InternationalJournal of Legal Medicine, 111*, 120–123.

Roffwarg,H. P.,Muzio, J.N., & Dement, W. C. (1966). Ontogenetic development of the human sleep–dream cycle. *Science, 152*, 604–619.

Sateia,M.J.,Doghramji,K.,Hauri, P. J., & Morin, C. M.(2000). Evaluation of chronic insomnia. *Sleep,23*, 243– 308.

Solms,M. (in press).Dreaming and REM sleep are controlled by different brain mechanisms. *Behavioral and Brain Sciences*.

Spiegel K., Leproult,R., & Van Cauter E. (1999). Impact of sleep debt on metabolic and endocrine function. *The Lancet,354*, 1435–1439.

Thomas,M. *et al.* (2000). Neural basis of alertness and cognitive performance impairments during sleepiness. I:Effects of 24h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research, 9*, 335–352.

Werth,E.,Achermann, P. R.,Borbély, A.A. (1997).Fronto-occipital EEG power gradients in human sleep. *Journal of Sleep Research,6*, 102–112.

Wu,J. C., & Bunney, W. E.(1990).The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *American Journal of Psychiatry, 147*, 14–21.