Showalter and colleagues note that the volume of Hippocamp is only 2% of that missing from the Pharos impact basin, the volume of particles in the Phoebe ring would fill a crater that is only 1 km wide[12] (by comparison, Jason is about 100 km in diameter[13]). Clearly, the impacts that produced these revealing scars generated much more debris than remains today in the form of a dust ring or a tiny moon.

Whether Hippocamp formed in place from material that did not originate from Proteus or was born of Proteus remains to be determined. Nevertheless, applying the techniques that were used to find it might result in the detection of other small moons around giant planets, or even planets that orbit distant stars. ■

Anne J. Verbiscer *is in the Department of Astronomy, University of Virginia, Charlottesville, Virginia 22904, USA.*
e-mail: verbiscer@virginia.edu

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METABOLISM

How broken sleep harms blood vessels

The link between sleep and cardiovascular disease is poorly understood. Findings in mice now show that disrupted sleep causes the brain to signal the bone marrow to boost white blood cell production, damaging blood vessels. SEE LETTER P.383

ALAN R. TALL & SANJA JELIC

Most people have at some point echoed Macbeth's complaint about the loss of "sleep that knits up the ravelled sleeve of care". Sleep disorders, such as obstructive sleep apnoea (when breathing temporarily stops, causing both sleep disruption and lack of oxygen in blood) and sleep deprivation, have been associated with an increased risk of atherosclerosis and its harmful cardiovascular effects[1,2]. Atherosclerosis is characterized by the formation of 'plaques' in arteries, as white blood cells enter the artery wall, take up cholesterol and other substances from the blood and trigger an inflammatory response. However, the mechanisms linking sleep disruption and atherosclerosis have been largely unknown. McAlpine *et al.*[3] show on page 383 that persistent sleep disruption causes the brain to signal the bone marrow to increase the production of white blood cells.

McAlpine *et al.* studied mice that were prone to developing atherosclerosis. The authors induced sleep fragmentation by moving a bar intermittently across the bottom of the animals' cages during their sleep period (Fig. 1), and compared these animals with animals that slept normally. They found that mice with sleep fragmentation had more-severe atherosclerosis, which was paralleled by increases in the production of white blood cells in the bone marrow and in the numbers of monocytes and neutrophils — two types of white blood cell — in the blood. These effects were absent if the bar was moved when the mice were fully awake. Stress activates the sympathetic nervous system (which is associated with the 'fight-or-flight' response), and such activation increases the production of white blood cells and atherosclerosis in other experimental settings[4]. However, the authors did not find evidence for a role of sympathetic activation in their setting.

Next, McAlpine and colleagues performed a systematic examination of sleep-regulating proteins in the hypothalamus, a part of the brain that controls metabolic responses in the body. They discovered that expression of the protein hypocretin (also called orexin) was markedly reduced in the sleep-disturbed mice, compared with the control mice. Hypocretin promotes wakefulness, and increases food intake and the activity of the sympathetic nervous system[5]. Low expression of hypocretin has been seen in individuals with narcolepsy, a rare disorder that makes people fall asleep during the day[5].

McAlpine *et al.* observed that, like the mice with sleep fragmentation, genetically engineered mice unable to express hypocretin produced more white blood cells and had

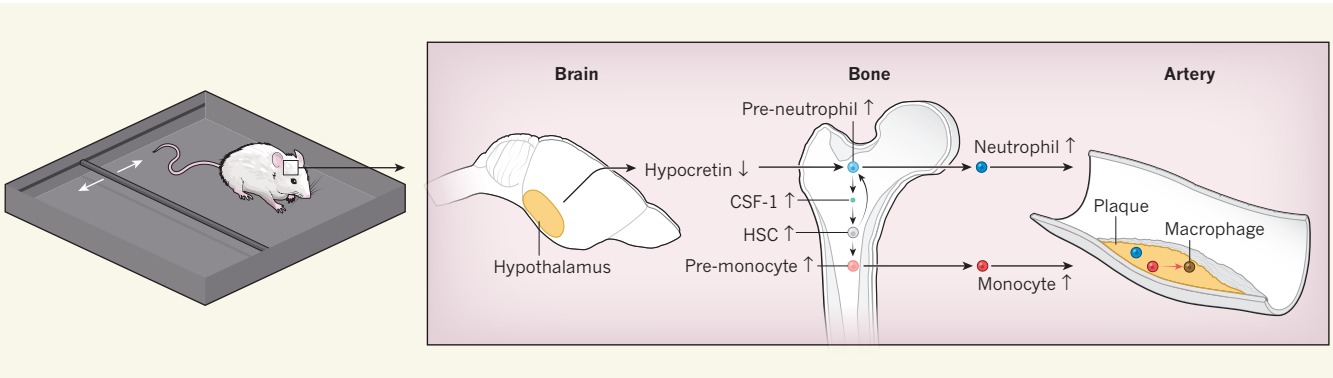

Figure 1 | Sleep fragmentation accelerates atherosclerosis. McAlpine *et al.*[3] induced long-term sleep fragmentation in mice by moving a bar across the bottom of their cages during their sleep period. Such treatment reduces the levels of the protein hypocretin, which is produced in the brain's hypothalamus. Hypocretin receptors are present on cells in the bone marrow (pre-neutrophils) that will develop into a type of white blood cell called a neutrophil. Pre-neutrophils sense the lack of hypocretin and produce increased amounts of a protein known as colony-stimulating factor-1 (CSF-1). Uninhibited CSF-1 production stimulates stem cells that give rise to all types of white blood cell (haematopoietic stem cells; HSCs) to produce increased numbers of pre-neutrophils and pre-monocytes (white blood cells that will develop into monocytes). Mature neutrophils and monocytes migrate to arterial walls, where the monocytes develop into macrophage cells. Macrophages and, to a lesser extent, neutrophils promote the formation of plaques, a hallmark of atherosclerosis — a condition that can have harmful cardiovascular effects.

increased atherosclerosis compared with mice that were able to express hypocretin. Giving hypocretin to mice that had sleep disruption reduced white blood cell production and decreased the severity of atherosclerosis, suggesting that reduced hypocretin levels have a major role in atherosclerosis driven by sleep fragmentation.

Probing further, McAlpine *et al.* found that sleep disruption decreased hypocretin levels in the animals' blood and bone marrow. This protein has two receptors in cells, one of which is highly expressed in the subset of bone marrow cells that gives rise to neutrophils. These pre-neutrophils responded to decreased amounts of hypocretin by increasing the production of colony-stimulating factor 1 (CSF-1), a protein that promotes the production of white blood cells from stem cells in the bone marrow. The authors also found that CSF-1 deficiency in bone marrow cells counteracted the increased production of monocytes and the accelerated atherosclerosis caused by hypocretin deficiency or sleep fragmentation. These results suggest that the reduction of hypocretin levels caused by sleep disruption stimulates CSF-1 production, and that this increases the production of monocytes and promotes atherosclerosis.

Although the hypocretin–CSF-1 pathway seems to be the major mechanism linking sleep fragmentation to the production of white blood cells and atherosclerosis, there are hints that other mechanisms could also be involved. For example, McAlpine *et al.* observed that CSF-1 deficiency in bone marrow cells did not reduce the elevated numbers of neutrophils in blood caused by hypocretin deficiency or sleep fragmentation. This suggests that other, CSF-1-independent, pathways increase neutrophil production during sleep disruption. Of note, neutrophils can contribute to the formation of atherosclerotic plaques, even if their role is less important than that of monocytes. Furthermore, in addition to increasing monocyte numbers in blood, CSF-1 affects the artery wall directly, for example by stimulating the maturation of monocytes into macrophage cells[6]. This influence of CSF-1 on artery walls might have contributed to the protective effects of CSF-1 deficiency in mice with sleep fragmentation.

McAlpine *et al.* observed a decrease in hypocretin expression and an increase in the production of white blood cells only after 12 weeks of sleep disruption. Although this might suggest that the brain undergoes structural changes that lead to loss of hypocretin-producing neurons, this possibility was not supported by the authors' assessment of the number of dead cells in the hypothalamus. Narcolepsy can be caused by the loss of hypocretin-producing neurons[5], and one of the hallmarks of this disease is fragmented sleep[7]. Together with the present study's findings, which indicate that sleep fragmentation causes hypocretin deficiency, this suggests that a bidirectional relationship might exist between the two conditions.

Although sleep disruption did not affect the animals' body weight, it reduced food intake, as expected when hypocretin levels are low. The maintenance of body weight despite reduced food intake implies that the mice used less energy. Given that hypocretin increases energy expenditure through signalling by the hormone leptin[8], these findings indicate that hypocretin deficiency might lead to reduced leptin signalling in mice that have sleep fragmentation. Moreover, white blood cell production is increased in leptin-deficient mice[9]. This suggests that metabolic disturbances beyond those studied by McAlpine *et al.* might contribute to the increased production of these cells and the worsening atherosclerosis in mice with sleep disruption.

Study of the relationships between sleep disorders and metabolic and cardiovascular disorders is in its infancy. McAlpine *et al.* have uncovered a previously unknown mechanism that has possible therapeutic implications. The drug suvorexant, a blocker of hypocretin receptors, was approved in 2014 for the treatment of insomnia. The present study raises the question of whether such therapies could have harmful cardiovascular consequences. Effects observed in mouse studies often do not translate well to humans, and suvorexant did not increase total white blood cell counts in one observational human study[10]. Nevertheless, continued surveillance of people receiving this drug might be warranted. Future studies might further unravel the links between sleep disorders and cardiometabolic risk, and lead to new therapeutic strategies for treating these highly prevalent disorders. ■

Alan R. Tall *and* **Sanja Jelic** *are in the Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York, New York 10032, USA.*
e-mails: art1@cumc.columbia.edu; sj366@cumc.columbia.edu

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CITATION METRICS

Small-team science is beautiful

The application of a new citation metric prompts a reassessment of the relationship between the size of scientific teams and research impact, and calls into question the trend to emphasize 'big team' science. SEE LETTER P.378

PIERRE AZOULAY

The current infatuation with large-scale scientific collaborations and the energy they can bring to a scientific domain owes much to the robust correlation that exists between citation impact and team size. This relationship has been well documented in the emerging 'science of science' field[1]. On page 378, Wu *et al.*[2] use a new citation-based index to nuance this conventional wisdom. They find that small and large teams differ in a measurable and systematic way in the extent of the 'disruption' they cause to the scientific area to which they contribute.

Scientists have long had a love–hate relationship with citation metrics. When it comes to recognizing and promoting individuals (or even teams), why would researchers ever rely on proxies of questionable validity, rather than engage with the scientific insights proposed in a paper or by a particular scientist? And yet, precisely because they encode the recognition of one's peers, citations occupy a central place in the complex web of institutions and norms that allow for the smooth functioning of the scientific enterprise.

But what is the meaning of a citation? Scientists cite previous work for many reasons. Sometimes their purpose is to acknowledge an intellectual debt. More rarely, it is to criticize the work that came before them[3]. Citation behaviour can also reflect strategic considerations, such as currying favour with referees or editors, or status-based considerations, as when an author cites well-known authorities in the field without engaging with the substantive content of their work. Moreover, citation counts are obviously affected by field size and cross-domain citation norms, which makes it