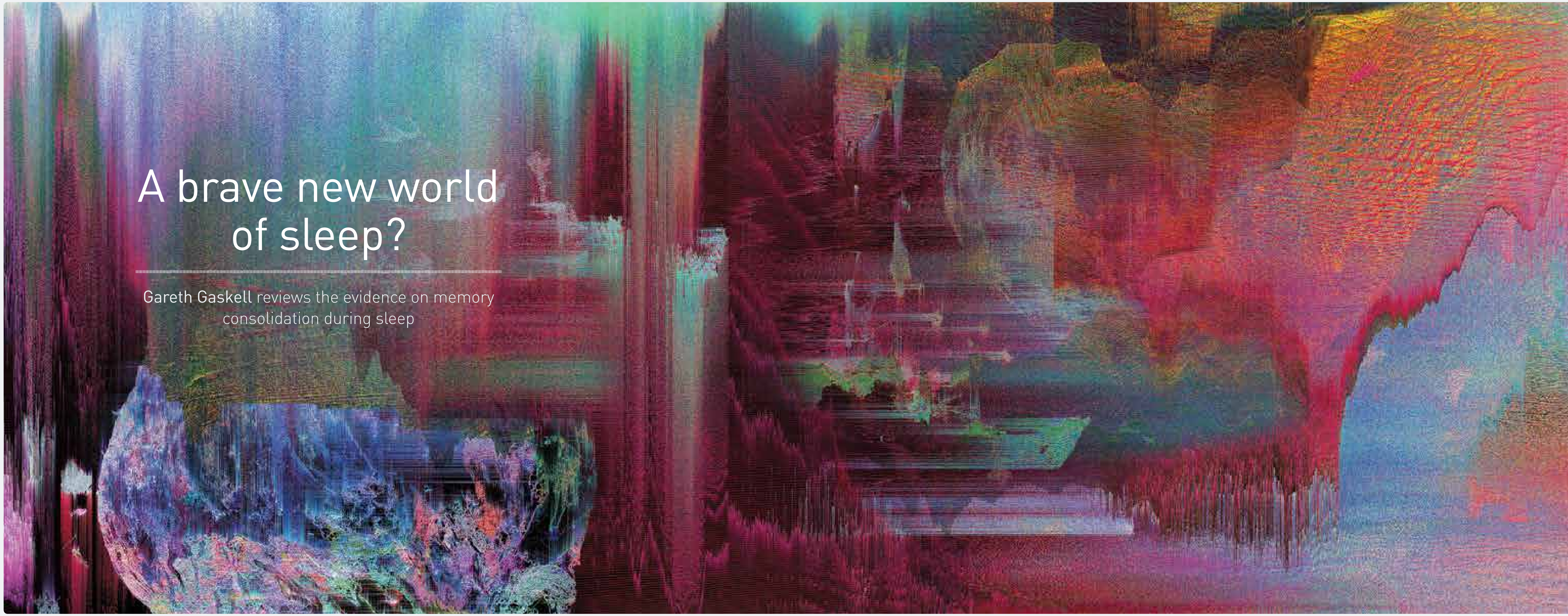

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A brave new world of sleep?

Gareth Gaskell reviews the evidence on memory consolidation during sleep

Does sleep provide an opportunity to reorganise the mind?

Sleep is an enigma. Ask a set of experts a simple question like 'What is sleep?' and you get a remarkable range of answers. Similarly, researchers will provide a multitude of responses to the question 'Why do we sleep?'. Some will point to the value of energy conservation, with an analogy to hibernation or dormancy. Others will argue that sleep provides an opportunity to repair cells, either across the body or more specifically in the brain.

To some extent, the expectation of a single purpose of sleep is unrealistic. What is the purpose of a mouth? One could point to the central role of the mouth in eating, drinking, breathing and speaking, as well as many other more subtle roles (e.g. smiling, kissing, fighting, holding). The truth is that sleep – like the mouth – has many purposes, but it is becoming clear that one of the key benefits that sleep confers is the opportunity to revise, reorganise and strengthen our memories so that we can extract the most useful information from recent experiences and optimise our use of these memories when we wake up.

Research on this process of *consolidation* has a rich history, but our understanding of the specific involvement of sleep in this process has only really been identified in the last decade or so, with recent developments leading to a clearer understanding of both the cognitive impact of sleep on memory and the brain mechanisms that underpin this process. In this article I will describe some of the landmark studies that have helped us to reach this position, and discuss some of the new areas in which we need to conduct more research in order to evaluate the role of sleep in memory consolidation.

Sleep and consolidation

As part of the wonderfully named series of 'Minor studies from the Psychological Laboratory of Cornell University', Jenkins and Dallenbach in 1924 reported a historic study comparing forgetting of nonsense syllables after different time intervals spent awake during the day or asleep at night. Despite testing only two participants, their results were very clear. Forgetting increased as a function of time spent awake in a very orderly fashion. However, time spent asleep led to substantially less forgetting, and beyond a certain point there was no further cost to extra time spent asleep. The authors, quite properly, argued that this result could be explained in terms of interference: when we are awake we form new memories, and these may obscure or overwrite our previous memories. In sleep we are protected from this interference by the sensory barrier that sleep imposes.

But is there more to the involvement of sleep than merely a passive barrier? For decades, this issue remained stubbornly resistant to a solution. However, an increasing conceptualisation of sleep as a *structured hierarchy* of states and events rather than as a single entity has eventually led us to the understanding that there is indeed more to sleep than just passive protection. For example, we tend to have quite different sleep properties early in the night compared with closer to the morning. Soon after falling asleep we tend to descend into deep or slow-wave sleep, which is marked by very strong oscillations with a low frequency across the surface of the brain. Later in the night the oscillations in the brain have a broader range of frequencies, often coupled with rapid eye movements (REM sleep), which are strongly associated with dreams. An ingenious study from Jan Born's lab in Bamberg exploited this dissociation to see whether early night and later night sleep would have the same effect on forgetting as the passive account would predict. In fact they found that the benefit of sleep depended on the type of memory. Early sleep was particularly useful for preserving memories of facts or associations, whereas late sleep was useful only for retaining newly acquired skills. This kind of result is hard to explain in terms of simply resistance to interference. Instead we now think of sleep as having an active role in the protection of memories, through the process of memory consolidation.

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Current thinking on the mechanisms underlying this active process requires even further fractionation of the state of sleep. There is a strong and fruitful tradition of thinking about sleep in terms of a handful of stages, with REM and slow-wave sleep being key examples. But even these divisions are too broad, and one key theory of memory consolidation developed in Italy by Tononi and Cirelli focuses on oscillations within a particular frequency band as a means of refreshing the plasticity of synapses ready for the next day of learning.

Another theory, which probably dominates thinking at the moment, builds on generations of research on amnesia and conceptualises sleep as playing a vital role in the cross-talk between different parts of the brain. According to the notion of *systems consolidation* we have one part of the brain centred on the hippocampus that is particularly effective at forming new memories and retaining them in the short term. However, long-term retention depends on building links in the cortex, and hippocampal replay during sleep offers an opportunity for newly formed memories to be transferred from hippocampus to cortex. This transfer isn't completed overnight, but we are still able to find memory changes as a consequence of sleep after one night, or even sometimes after a short nap. A recent study by Staresina and colleagues recorded brain activity from patients undergoing surgery for epilepsy and was able to characterise the brain mechanisms underlying consolidation in unprecedented detail. They found a beautiful interplay of neural oscillations, with three different components acting in perfect synchrony to make sure that the hippocampus and cortex are prepared to talk to each other before a swift pulse of activity transfers information from one to the other.

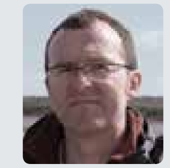
Can we enhance our memories in sleep?

The sad truth is that despite consolidation many of our memories are forgotten or at least weakened to the point where we find it hard to retrieve them. But what if we could hook ourselves up to brain enhancement systems to boost our memories? Given that we are now beginning to understand the mechanism by which the brain consolidates memory, this kind of acceleration of consolidation has become a realistic goal.

One method builds on our understanding of the oscillations in the brain that relate to consolidation. It is fairly straightforward to enhance these oscillations, by electrical stimulation or even repeated bursts of sound at a particular frequency (a bit like a bedroom clock running slightly slow). The stimulation strengthens the natural waves in the brain and results in better consolidation, making a measurable difference to people's performance in memory tests the following morning.

The enhancement of oscillations is a fairly blunt tool in that all it can do is strengthen consolidation across the board (and to be honest, the effects on memory are not dramatic – it's not going to be a way of acing an exam if you haven't done the work). A second method is if anything even more exciting in that it provides a way of picking out specific memories for preferential treatment. This targeted reactivation method works by associating new memories with a stimulus that can then be presented to people as they sleep. Smells work well for this, as do sounds. For example, a study at Northwestern University led by John Rudoy had people learn about the location of various objects on a screen in front of them with the typical sound of each object (e.g. the whistle of a kettle) being played as they learned. Some of these sounds were then played over loudspeakers during sleep, and the memories associated with these sounds were retained better than the control memories that were not reactivated in sleep.

This method is promising (if slightly disturbing) in that it provides a way of manipulating memories as we sleep. It could be used to select the aspects of the day's experience to be enhanced, possibly to the detriment of the unselected aspects. The potential for therapy has so far just been touched on by looking at whether negative gender or race biases could be counteracted by forming more positive associations that were then reactivated during sleep using this method, with some modest success. Nonetheless, the immediate benefit of all these enhancement methods has been to contribute to our understanding of how sleep operates to consolidate memory.



'In recent years I have branched out into sleep and memory research after becoming intrigued by the question of how we can learn and retain new words. York has a newly built three-bedroom Sleep, Language and Memory lab, where willing volunteers sleep in style (covered in electrodes!) after learning new languages.'

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Targeted reactivation comes close to the idea of sleep-learning or hypnopaedia, as featured in many works of fiction such as Huxley's *Brave New World*. The key difference is that the targeted memories are already in place by the time of reactivation. Sleep-learning refers to the idea that we could form a new memory via first exposure during sleep. Is this possible? Certainly a quick web search will find plenty of websites and apps that try to convince you to part with your money to give it a try. However, real scientific studies have for decades suggested that the only cases where learning appears to take place overnight are ones where the participants are momentarily awoken. It seems that we cannot form new memories in our sleep. This makes a lot of sense, given what we now know about consolidation. The great advantage of sleep as an offline state for consolidation is the fact that we can use the hippocampus in replay rather than record mode. Doing both at the same time may be too much to ask.

Having said that, there are a few suggestions that very simple forms of learning are possible in sleep. Arzi and colleagues in Israel have studied the learning of associations in sleep using conditioning techniques, finding that new associations can be formed between tones and smells. Again the therapeutic angle is interesting, with a later study from this group suggesting that aversive conditioning in sleep (associating the smell of cigarettes with rotten eggs) can influence smoking behaviour on subsequent days. So there is really a slight blurring of the boundaries between sleep and wake. Wake is largely for encoding of memories (but actually quiet wakefulness can help consolidation a little) and sleep is largely for consolidation of memories (but perhaps we can encode the simple stuff).

Learn a language while you sleep

Our own work on consolidation has focused on the relationship between sleep, consolidation and language learning. The ability to communicate through language is one of the defining human traits, and the vast bulk of psycholinguistic research has failed to consider the memory processes involved in language learning beyond the first encoding. Furthermore, first language learning is not merely a matter of concern in child development. Even in adulthood we are expanding our vocabulary at a rate of perhaps a word every couple of days. Work in our lab in York has shown that overnight consolidation is an important aspect of learning vocabulary, and the changes that take place through consolidation are more than simply a strengthening of word representations. One important property is the connection of new words to their neighbours in the mental dictionary or 'lexicon' of the language user. It is useful to think of the lexicon as a network of interconnected nodes. When we hear a word, we activate this network and a competitive process separates the identified word from its similar sounding neighbours. For example, in order to recognise the spoken word *breakfast* we need to separate it from similar alternatives such as *bread*, *breath* and *breast*, and this competition process takes time. For many people in the UK and beyond, this competition process got just a little bit harder over the last year when a new word *Brexit* suddenly became a very common word and so acted as a competitor to *breakfast*, slowing down its recognition. This may be the one and only way in which Brexit can be argued to have led to greater integration.

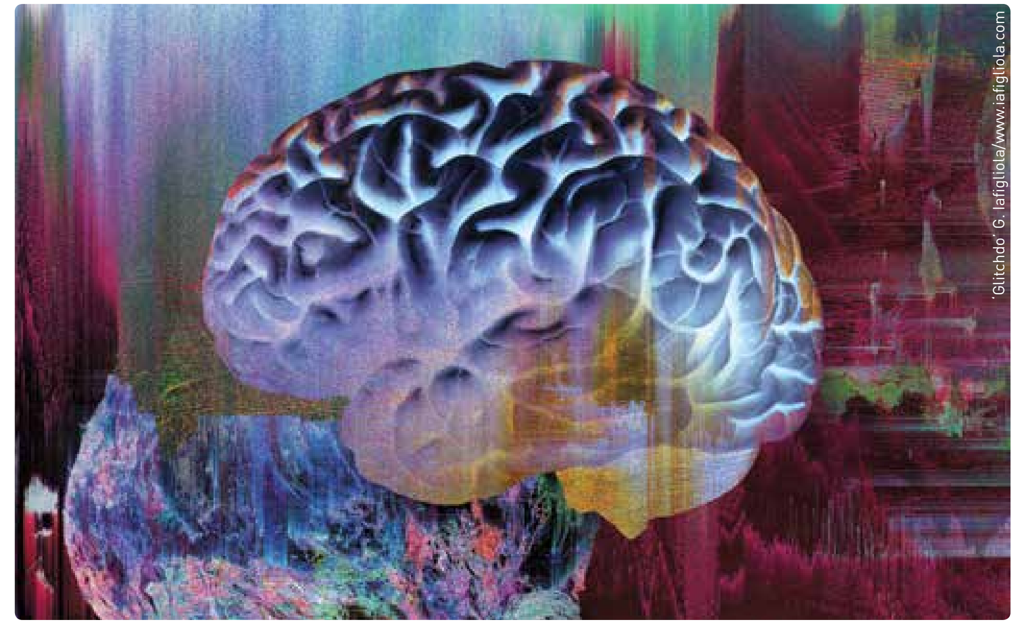
Our work has shown that this integration of a new word is not a property that is immediately available after encoding. Instead it emerges after consolidation, associated with sleep. Returning to the systems consolidation model, this makes sense. The words that we have known for years such as *breakfast* and *bread* reside in certain parts of the cortex, and a new word is unable to contact these words easily to engage in competition without some transfer from hippocampus to neocortex taking place. This is an example of how sleep can do more than just make a new memory robust. It may also alter the structure of memory and its relationship with other memories, old and new, often leaving the consolidated memory better able to serve us in our everyday life.

The influence of sleep also shows up in tests of automaticity in access to word meanings. For example, new colour words learned as part of a foreign language show stronger Stroop effects after a consolidation period, suggesting that their meanings are more readily available and accessed in a more obligatory manner when they have become consolidated. Again this might reflect the properties of the neural routes to information. Access to meaning via the hippocampus is likely to be less direct and perhaps more intentional than a direct cortical route that emerges after consolidation.

Furthermore, the effects of consolidation are not just seen for words. All languages have constraints about the ways in which speech sounds can combine to form words. For example, in English /sl/ is an acceptable combination of sounds as in the word *sleep*, but /sr/ is not. These constraints are not just abstract facts about the language; they have psychological reality and even influence our speech errors (e.g. when intending to say 'sleep' you might mistakenly say 'sneep' but you are very unlikely to say 'sreep'). It also turns out that these constraints are quite malleable, so that people can pick up on new constraints in the lab with their speech errors again influenced. Sleep once again has a role to play in this plasticity of the language system. Simple constraints involving single sounds can be picked up straight away, but complex constraints involving combinations of sounds emerge in our speech errors only after sleep. So sleep here seems to be taking a set of examples from our recent experience in language and extracting the abstract core of this knowledge in order to use this knowledge in a more effective and generalised way after sleep.

Where next?

Although we are building towards a good understanding of how and why sleep aids in the consolidation and integration of memories, this understanding largely applies to healthy adults, and indeed in many cases adults of a typical university student age, since these are the people who tend to sign up for sleep experiments. Researchers have certainly looked at a wider range of ages, but evidence remains patchy. For example, there are substantial changes in the quality and quantity of sleep as we age, and some of the oscillations that turn out to be so important for memory consolidation can wax and wane across the lifespan. One example is slow oscillation activity, which may operate to orchestrate the chain of events that lead to hippocampal replay and memory consolidation. This activity is very strong in children and peaks at about 10 years of age, before gradually declining as we get older. What is the significance of this developmental change? It is tempting to argue that the heightened activity in childhood can mean stronger memory consolidation effects for humans just when they really need it, but comparative studies are few and far between. We know for example that children, like adults, can show consolidation effects in the integration of new vocabulary items, and these effects look on face value to be stronger. But we still know very little about the neural events that underpin these effects in children, and there are many other differences between children and adults (e.g. the size of their vocabulary) that could also have an explanatory role. There are also important changes that take place in the development of the brain's circuitry that need to be taken into account, particularly related to the development of the hippocampus.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In parallel with research into the developmental trajectory of sleep and consolidation, it is becoming increasingly important to examine the involvement of sleep in individual differences in learning, and in the subgroups of children and adults where learning development is impaired. Here we are in a state of substantial ignorance. All kinds of developmental disorders are associated with overt sleep problems, such as difficulty establishing a bedtime routine or difficulty maintaining sleep. But the studies that have examined the structure of sleep – which has turned out to be so important in understanding memory consolidation – have been very small scale and hard to interpret. Most of these disorders will not be defined by the sleep problems, nonetheless atypical consolidation might play a role in the progress of the disorder and the development of the symptoms. As a small step in this direction our group recently investigated the role of consolidation in the learning of vocabulary in autism. Whereas a control group of children showed the standard pattern of integration of new words only after sleep, children with autistic spectrum disorder showed almost the reverse pattern, and most importantly did not demonstrate a consolidation effect in terms of our measure of how well new words have been integrated with the ones that are already known (the 'Brexit' test).

Finally, a similar argument can be made for a greater focus on older adults. It is well understood that slow-wave sleep becomes scarcer in the older people, and the slow oscillations themselves become weaker. A handful of studies have also looked at memory consolidation on older adults, with the evidence suggesting that sleep has the same beneficial effect on memory as we grow older. So sleep still helps to retain memories at this age, but there is less of the really beneficial sleep to stimulate consolidation. Intriguingly, a few studies have looked at some of the ways in which sleep oscillations can be enhanced as described above to see whether memory is improved in older adults. Unfortunately though the evidence is mixed, and more research here is needed. The stakes are high, as researchers at Berkeley have found evidence that sleep disturbance may be causally implicated in the progress of Alzheimer's disease, and have argued that specific tests for sleep disruption could provide an early indicator of susceptibility to Alzheimer's.

This recent development is a good example of how sleep and memory research is extending its tentacles into areas of science that a decade or two would have seemed fanciful or laughable. I remember reading a psychology textbook at University in the late 1980s that covered the cognitive psychology of sleep in a couple of turgid paragraphs. There was simply nothing to say. Now it seems like everywhere we look there is a potentially significant sleep angle and sleep is portrayed in the popular press as a universal panacea. Where will it end?

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