using intracellular recordings: instead of performing spike-triggered averaging from the whisker stimulus, they performed a voltage-weighted averaging from the continuously varying intracellular voltage signal (**Fig. 1b**). The result is an approach that can provide a robust characterization of the spatiotemporal receptive field properties, and thus feature selectivity, with substantially less observation time and without any required spiking activity. The authors go on to show the explicit relationship between the voltage-weighted average and the classical spike-triggered characterization. Furthermore, they achieved layer specificity using histological analysis to quantify cell morphology and cortical depth.

Beyond the technical advance, however, Ramirez *et al.*[2] have made several scientific advances that will certainly prompt many further investigations. Although often not described as such, the receptive field of a sensory neuron is not an invariant property of the neuron and the circuit in which it is embedded but instead reflects a complex interplay between the circuitry and the way the circuit is engaged by the sensory input. Ramirez *et al.*[2] found that the complex, spatiotemporal tactile patterns that they presented led to sharpened receptive fields, in contrast with the broad, diffuse receptive fields that they observed for simple, single-whisker stimuli that have been classically used. Counterintuitively, this complex sensory stimulation corresponded to a facilitative surround influence, in contrast with the findings in a range of previous studies. The authors suggest that the sharpening of the receptive fields that they observed for complex stimuli reflects an adaptation that may shift the pathway from a regime in which inputs are encoded for detection to a regime in which enhanced acuity might facilitate sensory discrimination, as shown in recent studies[8,9]. They further found distinct receptive field properties from layer 2/3 neurons that have not been well described from this functional perspective, owing in large part to the sparse firing activity in these layers. This begs the question, as asserted by Barth and Poulet[7], as to whether the lack of functional characterization of layer 2/3 neurons might perhaps be a result of experimentally impoverished inputs. In contrast, however, Ramirez *et al.*[2] provide evidence that even rich spatiotemporal tactile inputs are often insufficient to drive spiking activity in layer 2/3. The implications for these findings are that superficial layers may not be purely responsive to sensory input in a simple way but are instead part of a more integrative, cross-laminar computation. These findings are consistent with recent behavioral studies in rodent primary visual cortex that show an increase in layer 2/3 activation during locomotion[10,11], potentially as part of a sensorimotor integration framework.

What remains, in this pathway and other sensory pathways, is connecting the dots between feature selectivity and the natural world that we live in. For example, we presume that, because the visual world is made up of objects that have boundaries, the complex natural scene must be comprised of oriented edges that engage this ubiquitous feature selectivity in visual cortex. However, the relationship between simple feature selectivity and the natural world is very poorly understood, especially in the context of a dynamically varying environment. So what is the needle in the haystack for the vibrissal system? Ramirez *et al.*[2] have provided a layer-by-layer analysis of the encoding of somatosensory information in the rodent vibrissal pathway using complex sensory inputs that identify nontrivial multi-whisker interactions that directly affect feature selectivity. This work begins to identify the processing roles of each cortical layer, even those with little to no spiking activity, in response to complex sensory inputs. Although our understanding of how feature selectivity gives rise to perception is still limited, the work from Ramirez *et al.*[2] sets the stage for a range of investigations that may help us to more fully understand the complex coding of the sensory world across cortical laminae that forms the substrate of basic computations.

COMPETING FINANCIAL INTERESTS
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The (gamma) power to control our dreams

Jessica D Payne

Stimulating the brain in the gamma frequency range, which is the frequency band most often associated with conscious awareness in the awake state, boosts the ability to engage in lucid dreaming during REM sleep.

I have long been fascinated by dreams, both personally and scientifically. Early in graduate school, I tried to keep this interest hidden for fear of being perceived as 'far out' or lacking in scientific credibility. But what was this state of consciousness that allowed us to defy the laws of physics, to connect fragments of our experience in creative, even preposterous ways and to sometimes become aware of these experiences as they unfolded in our sleeping minds? In spite of my long-held interest in dreams, however, even I was shocked to learn that lucid dreaming—the phenomenon in which a dreamer becomes aware that he or she is dreaming and can potentially exert control over the dream—was a distinct cognitive state whose existence has quite a bit of scientific support[1,2]. Lucid dreaming finds its strongest support yet in a study published in this issue of *Nature Neuroscience*, in which Voss *et al.*[3] demonstrate that lucid dreaming can be experimentally triggered by stimulating the brain at a frequency associated with conscious awareness.

Lucid dreams are believed to occur exclusively during rapid eye movement (REM) sleep, which is an active brain state that is similar in some respects to wakefulness. Usually, the REM-sleep dreamer uncritically accepts the bizarre and disjointed themes of dreams as normal. As protagonist Dom Cobb explains in the science fiction heist thriller film *Inception*, which was inspired by lucid dreaming,

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"it's only when we wake up that we realize something was actually strange." Part of learning to lucid dream, as outlined by Stephen LaBerge (arguably the biggest scientific advocate of lucid dreaming) in his 1991 book *Exploring the World of Lucid Dreaming*[4], involves training yourself to notice these bizarre elements to help you realize that you are asleep.

Early studies of lucid dreaming demonstrated that REM-sleep dreamers can signal to researchers that they have become lucid in their dream by moving their eyes in an agreed upon series of movements (for example, left, right, left, right—this being necessary because, although the eyes can move freely, the rest of the body is paralyzed during REM sleep as an important safeguard against acting out dreams). These eye movements coincide with elevated levels of respiratory, cardiovascular and neurological activity in the absence of signs of arousals or awakenings in the electroencephalogram that might otherwise explain the lucidity[1,2]. These studies suggested that lucid dreamers can remember to perform predetermined actions and signal to the laboratory while they are asleep—a task that would certainly require conscious awareness.

More recent studies have shown that lucid dreams are associated with increased phase synchrony and elevated frequency-specific activity in the lower gamma frequency band, centered around 40 Hz, especially in the frontal and temporal regions of the brain[5–7]. Activity in this frequency band is associated with conscious awareness and executive function, both of which are typically not available during REM-sleep dreams[7]. Although such findings are fascinating, they also raise a key question: does gamma activity trigger lucid dreaming or does lucid dreaming trigger gamma activity? In an effort to tackle this difficult question of causality, Voss *et al.*[3] stimulated the brain at different frequencies to determine whether gamma activity is a necessary condition for lucid dreaming to occur. Using a relatively new method of brain stimulation called transcranial alternating current stimulation (tACS), the authors applied currents through the skull over frontal and temporal electrode sites with weak alternating current. They stimulated at frequencies of 2, 6, 12, 25, 40, 70 and 100 Hz, as well as under a sham condition where no current flow was applied. Stimulating at these frequencies entrains neural oscillations in underlying brain regions in a frequency-specific fashion. This allowed the authors to explore whether stimulation would influence dreaming and, if so, whether lucid dreams require gamma stimulation or rather can also be achieved via stimulation with other (faster or slower) frequencies.

Following approximately 2 min of unambiguous REM sleep, the researchers applied tACS stimulation. They then awakened participants and asked them to rate their dream consciousness on an analytically derived and validated scale that assesses dream lucidity. This LuCiD scale assesses several features of lucid dreaming, including insight into the fact that one is dreaming, control over the dream plot and the tendency to take on a third-person perspective in the dream.

As predicted, lucid dreams were most prominent during stimulation at 40 Hz, with 77% of subjects reporting lucidity following stimulation. The next most effective stimulation frequency was 25 Hz, with 58% of subjects reporting lucidity. Notably, electroencephalographic power in the lower gamma band was increased following stimulation at these frequencies regardless of whether lucidity was attained, but the increase was much stronger when lucid dreams were reported. This may suggest a reciprocal effect of induced brain activity and conscious thought. Moreover, increases in 40-Hz frequency band activity induced by stimulation were positively correlated with scores on the LuCiD scale: specifically, with the level of insight participants had into the fact that they were dreaming and with the degree to which they viewed themselves acting in the dream from a third-person perspective.

These results provide compelling evidence that the ability to become consciously aware during REM sleep dreams is specifically related to gamma activity, as the effect was not observed when stimulating at lower or higher frequencies. If this result is confirmed, it will raise important questions for the treatment of psychiatric conditions such as depression and anxiety disorders, including post-traumatic stress disorder (PTSD). PTSD is characterized by symptoms including reoccurring nightmares that often replay a single traumatic event. Even outside diagnosed PTSD, it is estimated that about 8 percent of adults suffer from chronic nightmares[8,9]. Although studies are under way that try to teach participants to lucid dream and thereby alter the endings of their nightmares[10], achieving lucidity is not always successful (and even if achieved, lucidity may not always help us prevail in our nightmares, as anyone who has seen *A Nightmare on Elm Street 3* can attest). Perhaps stimulation, in a manner similar to that done by Voss *et al.*[3], would boost the success of this treatment.

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Figure 1 Brain stimulation in the gamma frequency range during REM sleep enhances lucid dreaming. Voss *et al.*[3] report that gamma stimulation during REM sleep enhances the ability to gain conscious awareness in dreams. Through achieving such lucidity, the sleeper in this image gains control over her dream and is able to fly.

Both sleep stimulation and targeted memory reactivation techniques are becoming increasingly common in the scientific literature. This has me wondering whether we might soon begin using them, not just for therapeutic applications, but also for various types of cognitive enhancement. For example, a study by Marshall *et al.*[11] demonstrated that boosting slow oscillatory activity (<1 Hz) during non-REM sleep improves the recall of word pairs memorized the previous night. These results provided the first evidence for a causal contribution of slow oscillations to sleep-dependent memory consolidation. Might we one day use such stimulation to improve memory performance or stave off age-related memory decline? After all, it is not hard to imagine a future in which stimulation devices are made portable (**Fig. 1**), although certainly issues of ethics and safety (that is, whether regular use of such procedures could be harmful) would have to be addressed.

Or perhaps we will find another way to boost neurocognitive processing during sleep. Several studies have shown that sleep aids memory processing by demonstrating that a sensory cue (an odor, a sound), if originally paired with a memory at the time of learning, can improve memory retention when that cue is covertly redelivered during sleep. In a recent study by Diekelmann *et al.*[12], participants were trained on a task similar to the memory game Concentration either in the presence or absence of an odor that would later serve as a memory cue. They then

either stayed awake or went to sleep, during which time they were reexposed to the odor. Odors applied during non-REM, slow-wave sleep stabilized memories and benefited subsequent task performance.

When memory cues are reapplied during REM sleep, however, new evidence suggests that higher level cognitive abilities such as generalization and integration benefit instead[13,14]. Thus, although presenting cues during slow-wave sleep may promote veridical memory consolidation, presenting cues during REM sleep may ultimately favor the ability to integrate and recombine elements of knowledge to make creative connections. What if we could gain some measure of control over the creative processes of REM sleep, which, unlike non-REM sleep, might ultimately be more about creation and less about retrospection and replay of memories? By becoming lucid, perhaps we could learn to exert control over how dream fragments are connected, rather than passively watching as the bizarre and (at times) seemingly useless themes of REM sleep dreams unfold in our minds.

In *Inception*, dream 'architect' Ariadne can build cities from scratch in a lucid act of "pure creation," and discoveries ranging from the molecular structure of benzene to the plot for the *Strange Case of Dr. Jekyll and Mr. Hyde* have been attributed to dreams. It will be fascinating to determine whether we can boost the brain's ability to create during REM sleep, in a manner similar to boosting its ability to remember during non-REM sleep, and to discover whether lucid dreaming can be used to enhance and refine the process of creation.

COMPETING FINANCIAL INTERESTS
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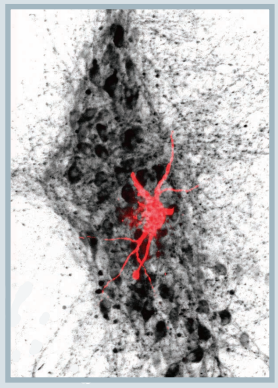
Pacemaker's burden



Neurons of the locus coeruleus (LC) in the brainstem innervate various regions throughout the brain and modulate sleep, wakefulness, arousal, attention and memory. LC neurons are a major source of noradrenaline in the CNS, and these neurons fire steady and spontaneous action potentials at a relatively high frequency. These neurons, however, are also extremely vulnerable as we age, and LC neurons are lost in neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease. Their loss may contribute to some of the symptoms of these disorders, such as excessive daytime sleepiness and memory deficits. Why is this neuronal population so vulnerable to aging and stress? A study in this issue of *Nature Neuroscience* provides some clues to this question and shows that the pacemaking properties of LC noradrenergic neurons may be partly responsible. On page 832, Sanchez-Padilla *et al.* report that the pacemaking properties of LC neurons depend on the opening of voltage-dependent calcium channels (VDCCs); although the resulting influx of calcium and dendritic calcium oscillations are necessary to maintain pacemaking, they also cause mitochondrial stress, a phenomenon that is aggravated in a mouse model of Parkinson's disease.

Sanchez-Padilla *et al.* used *ex vivo* slice electrophysiology of 3–4-week-old mice to show that LC neurons—as seen in the image with a biocytin-labeled neuron counterstained with streptavidin-conjugated to Alexa 594 (in red) overlaid on neurons immunoreactive for tyrosine hydroxylase (in black and white)—are indeed autonomous pacemakers. Using pharmacological agents, the scientists established that L-type voltage-gated calcium channels contribute to this pacemaking activity. By pharmacologically blocking mitochondrial Ca^{2+} entry via junctions between the endoplasmic reticulum and mitochondria, they found that calcium fluctuations are associated with mitochondrial oxidative stress. Previous studies by this laboratory had suggested that mitochondrial Ca^{2+} entry in dopaminergic neurons of the substantia nigra can increase mitochondrial oxidative stress. Similarly, LC neurons also exhibited an increase in mitochondrial oxidant stress (as measured by a mitochondrially targeted ratiometric redox probe) that was blocked by inhibitors of L-type VDCCs or the mitochondrial Ca^{2+} uniporter. This mitochondrial oxidative stress was exacerbated in the DJ-1 null mouse, a genetic model of early onset Parkinson's disease. Nitric oxide (NO) production was also correlated with high mitochondrial stress in LC neurons and pharmacologically blocking NO synthase activity diminished mitochondrial oxidative stress.

The activity of LC neurons is known to vary with behavioral states. During arousal, for example, an increase in LC firing is mediated by orexin (released by the hypothalamus), and subsequent noradrenaline released to various neocortical regions can sharpen attention and modulate cognitive function. Surprisingly, the current study found that exogenous orexin can attenuate mitochondrial oxidative stress of LC neurons, even though it also increased LC spontaneous spiking. This effect was, however, correlated with a reduction in the amplitude of dendritic Ca^{2+} oscillations in the LC neurons. Other extrinsic signals, such as high carbon dioxide, which increases spiking activity, increased oxidative stress in LC neurons, suggesting that pacemaking-dependent oxidative stress in the LC is subject to dynamic modulation by extrinsic signals.

This work presents some tantalizing clues as to why LC neurons may be susceptible to substantial neurodegeneration in Parkinson's disease and adds to the evidence suggesting that, although L-type calcium channels are important for maintaining autonomous spiking in some neuronal populations, they may also cause increased mitochondrial stress in these neurons. Targeting these channels may be useful to combat some of the non-motor symptoms of Parkinson's disease.

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