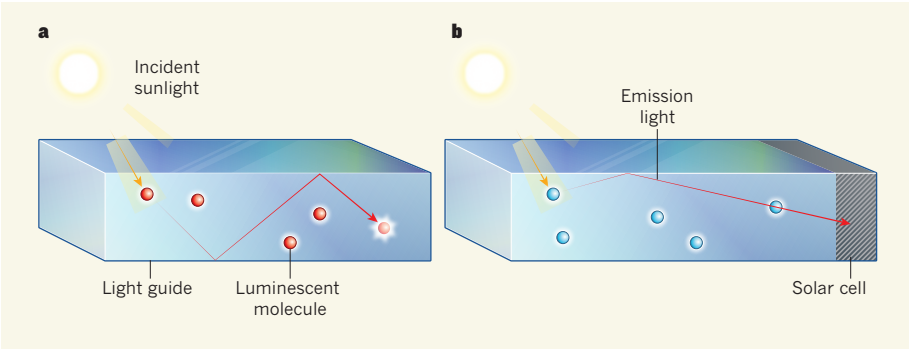

Figure 2 | The working principle of the luminescent solar concentrator. **a**, Incident sunlight (orange arrow) enters a polymer light guide and is absorbed by luminescent molecules. Light losses from reabsorption of emitted light (red arrow) are a consequence of using luminescent molecules that have overlapping absorption and emission spectra. **b**, Bradshaw *et al.*[1] describe luminescent nanocrystals (blue circles) that exhibit practically no overlap in their absorption and emission spectral profiles, and thus, no reabsorption. This results in more light being directed towards the light guide's small solar cell, which converts the exiting light into electrical current.

Cd^{2+}/Mn^{2+}-doped ZnSe/ZnS nanocrystals absorb less of the incident solar spectrum than CdSe/CdS nanocrystals, they could outperform the latter in long light guides.

The fluorescence yield has often been considered the defining factor for LSC dye selection. However, Bradshaw *et al.* introduce and analyse CdSe nanocrystals doped with copper ions ($Cd_{0.999}Cu_{0.001}Se$) which, despite having a fluorescence yield of less than 40%, exhibit broad absorption of incident light and large Stokes shifts that exceed the current leading luminophores in LSCs. Their result suggests that broad-spectrum incident-light absorption and large Stokes shifts are more important than fluorescence yields for obtaining high-output emission in metre-scale LSCs.

If these nanocrystal materials, measured by Bradshaw *et al.* in solution, can be produced in bulk quantities and incorporated uniformly into solid polymeric light guides, and have long-term stability in sunlight, a major step forward in LSC performance may soon be realized. And once polymer sheets are available that contain such luminophores with good absorption in the peak of the solar spectrum, it will be possible to tackle the second major loss mechanism of LSCs, which is emission through the top and bottom surfaces of the light guide. This can be overcome by applying selective reflectors to the LSC surface[5]. Successful outcomes on all these fronts could increase the efficiencies of LSCs to levels that would enable their use in large-area urban settings. ■

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NEUROSCIENCE

Spotlight on deep-brain stimulation

Taking inspiration from a modern technological advance, a classic technique — low-frequency electrical stimulation of a deep-brain region — has been refined to combat cocaine addiction in experiments in mice.

ALIM LOUIS BENABID

Electrical stimulation of deep-brain regions is used to treat a range of human disorders, from Parkinson's disease to obsessive-compulsive disorder. But despite the fact that this technology is almost 30 years old, the mechanism by which it works is still unknown, making improvements difficult. By contrast, optogenetics, in which light-responsive proteins are engineered to regulate gene expression in target cells, is a more recent, well-understood technology, but cannot currently be used in humans. In a paper published in *Science*, Creed *et al.*[1] take inspiration from optogenetics to forge a fresh approach to treating cocaine addiction in mice, using a refined version of deep-brain stimulation (DBS). The results of the study suggest that the cellular mechanisms by which DBS modulates neural networks could be better understood, and that knowledge from optogenetics might inspire ways of improving DBS.

DBS induces different effects depending on the frequency of the stimulation. Low-frequency stimulation (LFS) typically causes neuronal excitation, through well-understood mechanisms that follow the classical principles of neurophysiology. But high-frequency stimulation (HFS), which is a powerful and flexible surgical tool, does not seem to follow these standard rules. HFS mimics the effects of lesioning techniques, in which cells are destroyed or removed from the brain, indicating that HFS is not excitatory. Indeed, HFS seems to inhibit neuronal impulses overall, but, paradoxically, the termini (axons and fibres) of some neurons seem to be excited by HFS (ref. 2). There is no clear explanation for this contradictory effect, although observations in both experimental and human situations suggest that there are several underlying mechanisms at work[3,4].

In addition to its poorly understood mechanism, DBS lacks spatial specificity, regardless of the frequency. DBS-induced electrical pulses provoke changes in electrical fields that spread unevenly in all directions, depending on spatial differences in tissue conductivity. Furthermore, differences in the neuronal make-up of a tissue can affect excitability, and so DBS can modulate different functions in tissues that have different neuronal compositions[5]. In short, it is hard to predict exactly what effects DBS will have.

By contrast, the beauty of optogenetics lies in the ability to precisely plan an experimental set-up. The type of light-sensitive protein used to engineer the cells tells us which neurons will be stimulated — and in response to which specific wavelength of light[6]. Furthermore, we can exercise a high level of spatial and functional control by restricting the diffusion of the light to small subsets of cells. We understand what we are doing, and where.

Using optogenetics to inspire DBS strategies might provide a way of gleaning a better understanding of the mechanisms underlying DBS[7]. For instance, applying the knowledge gained from optogenetics to identify drugs that could be combined with DBS to modulate neuronal activity might produce effects that are different from those obtained using DBS alone. This approach would, in effect,

create a hybrid tool that might have enhanced power and a broader ability to reverse harmful neuronal activity in pathological conditions.

Creed and colleagues set out to investigate this possibility using a mouse model of cocaine addiction. In these mice, cocaine is injected directly into different parts of a brain region called the nucleus accumbens (NAc), inducing long-term neuronal depression or potentiation (a decrease or increase, respectively, in the responsiveness of neurons to incoming neural impulses). This alters transmission across the synaptic junctions of NAc neurons and thus specifically alters motor behaviour — a well-known effect of cocaine addiction. Previous work shows that DBS in the NAc has only a transient effect on addictive behaviour in this mouse model, but there is evidence that optogenetic stimulation of the metabotropic glutamate receptor protein (mGluR) has a longer-lasting effect. Optogenetic activation of mGluR restores normal synaptic transmission and erases addiction behaviours by depressing the activity of a population of NAc neurons that express the D1 dopamine-receptor protein and show increased activity in response to cocaine addiction.

The authors confirmed this optogenetic effect, and used the biological basis of the technique to try to determine how DBS could be modified, refined or combined with drugs to improve its effectiveness. They manipulated the parameters of DBS, using HFS or LFS, in the core or in the shell of the NAc (its two subregions), and with or without injection of D1-receptor antagonists into the NAc. They discovered that when acute LFS was refined by inhibiting D1 receptors, the response mimicked optogenetic mGluR-dependent restoration of synaptic transmission, and had a long-lasting ability to abolish addictive behaviours. The authors conclude that approaches such as this, which combine two treatments, might open up new therapeutic avenues.

But such combination studies are somewhat difficult to interpret, in part because of the different spatial scales over which each technique acts. Optogenetics is focal and specifically acts only on chosen neurons, but DBS, at whatever frequency, acts on larger regions and activates both excitatory and inhibitory neurons indiscriminately[8]. The authors predict that tailoring DBS by taking inspiration from optogenetics might lead to long-lasting, if not permanent, treatments. This would be a major improvement, and would increase its range of applications. Furthermore, the study's results point to other ways of treating patients with cocaine addiction or other pathological conditions — systemic administration of D1-receptor antagonists, for instance, or the use of 'double-channel' strategies that involve targeted delivery of both DBS and pharmacological agents (or optogenetically activated proteins) to the same brain region or to two different sites.

Achieving these improvements will not be straightforward. Sophisticated techniques will be required to achieve optogenetic or pharmacological modification of human synapses. If the effects are not permanent, strategies must be developed to enable the repeated introduction of drugs or genetic constructs to the appropriate brain region. Furthermore, treatment of some behaviours might require DBS or combination therapies at more than one site, or over large regions. Such advances might become possible through the development of nanotechnologies[9].

It is difficult to analyse different complex effects in a tiny region of the mouse brain and extend those findings to humans. This is why optogenetics, for the time being, remains at the periphery of human therapeutic applications. The possibilities opened up by Creed and colleagues' study might help us to cross this frontier. ■

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CANCER IMMUNOTHERAPY

Dendritic-cell vaccines on the move

Vaccines that induce an antitumour immune response are disappointingly ineffective in treating patients with cancer. Pre-conditioning the vaccination site to induce inflammation might provide a way to improve this therapy. SEE LETTER P.366

RACHEL LUBONG SABADO & NINA BHARDWAJ

Dendritic cells (DCs) are often called nature's adjuvants because of the way in which they help to initiate an immune response. Found throughout the body, the cells acquire and process antigens (the molecules recognized and bound by antibodies) from pathogens and tumours. They then migrate to lymph nodes and activate T cells, which in turn induce protective immune responses. These properties have driven attempts to develop vaccines containing DCs loaded with tumour antigens, with the aim of inducing antitumour immune responses in patients with cancer[1]. But this strategy has fallen short of expectations. In this issue, Mitchell *et al.*[2] (page 366) show how simply improving DC migration to lymph nodes dramatically enhances antitumour responses in humans and mice, pointing to a way to optimize the use of DC vaccines.

There is a general consensus that DC vaccines can safely induce long-lasting antitumour immune responses. These vaccinations have produced encouraging, if modest, clinical results in some patients with advanced cancers[3]. For instance, the vaccine sipuleucel-T (the only cell-based cancer vaccine approved for use in the United States) increases median survival times by four months in patients with prostate cancer[4]. But several factors might be limiting the efficacy of DC vaccines: the source and type of DCs used; the site and frequency of injection; and the ability of DCs to migrate to lymph nodes. Moreover, the injected DCs may not themselves directly instigate an immune response, but instead might act indirectly through DCs already present in the lymph node[5].

Less than 5% of cells in a DC vaccine reach the lymph nodes[6]. In mice, DC migration can be improved either by injecting activated DCs or by pre-conditioning the vaccination site in the skin with the inflammatory molecule TNF-α (ref. 7). Mitchell and colleagues therefore investigated whether pre-conditioning the DC vaccine site to generate local inflammatory responses might enhance DC migration in humans. To do this, they used a tetanus/diphtheria (Td) toxoid vaccine. Most people have been exposed to this toxoid during childhood vaccinations, and re-exposure activates a subset of T cells called memory $CD4^+$ T cells that recognize only the Td antigen and mount a strong and rapid inflammatory immune response in its presence.

Glioblastoma multiforme (GBM) is an aggressive brain tumour in which cells specifically express pp65, an antigen from a common