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NEUROSCIENCE

Non-invasive and fast control of neural activity

Chemomagnetics enable remote and non-invasive modulation of neural activity in behaving mice.

Controlling neurons with light or chemicals are widely used techniques for manipulating neural activity. Optogenetics affords high temporal control but is invasive as it requires light delivery via optical fibers. Chemogenetics is non-invasive as activation or inhibition of neurons depends on the expression of designer receptors exclusively activated by designer drugs (DREADDs) and the administration of the chemical compound CNO (which activates the DREADDs), but it does not allow the temporally precise manipulation of neuronal activity.

To overcome these limitations, Polina Anikeeva, from the Massachusetts Institute of Technology, along with her team and collaborators, including first author Siyuan Rao, have modified the delivery approach for CNO with the goal of achieving precise control over the neuronal manipulation. To do so, the researchers made use of the properties of magnetic nanoparticles. More specifically, these particles heat up when they are subjected to an alternating magnetic field. The team incorporated the magnetic nanoparticles, together with CNO, into liposomes. When applying an alternating magnetic field, the heat generated by the magnetic nanoparticles eventually leads to a phase transition of the lipids in the liposomes, and CNO is gradually released.

According to Anikeeva, first author Siyuan Rao found that the chemistry was easy, but doing careful biological experiments really took some time. The researchers first tested their chemomagnetic approach with cultured hippocampal neurons. In neurons that expressed DREADDs and were exposed to the CNO-containing liposomes, applying tens of seconds of an alternating magnetic field was sufficient to release CNO and to generate a measurable calcium signal. Moreover, the manipulation was specific, as the cells did not respond if either the DREADDs, CNO or the alternating magnetic field were omitted.

Having established their approach in cell culture, the researchers turned to in vivo experiments. When using their approach to excite neurons in the mouse ventral tegmental area (VTA), they used immunofluorescence analyses to verify that they could elicit neuronal activity as indicated by the expression of c-fos, which is a marker for neuronal activity. In addition, they used fiber photometry to show that magnetothermally mediated release of CNO induces calcium activity in DREADD-expressing animals.

The researchers then sought to manipulate neuronal activity in behaving animals. In a forced swim test, mice typically reduced their motility when undergoing the test multiple times. To conduct chemomagnetic manipulations, the researchers placed the water container within a magnetic coil, such that the swimming mouse would be at the center of the coil and therefore be exposed to a uniform magnetic field. Chemomagnetic manipulation of the VTA abolished the adaptation effect, as mice did not reduce their motility. Moreover, as the VTA also has a role in social preference behavior, the researchers could show that chemomagnetic activation of VTA neurons increases the preference of mice for novel mice as compared to novel objects.

Chemomagnetic manipulation of neuronal activity combines the advantages of both optogenetics and chemogenetics in affording fast and non-invasive control over neuronal activity. These characteristics make the approach particularly suitable for experiments where optical fibers would be a hindrance and where temporal precision is beneficial, such as experiments involving multiple animals or adverse environments, including water.

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Research paper

Rao, S. et al. Remotely controlled chemomagnetic modulation of targeted neural circuits. *Nat. Nanotechnol.* https://doi.org/10.1038/s41565-019-0521-z (2019).