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# Micro- and nanorobots for biomedical applications in the brain

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Micro- and nanorobots hold great potential to overcome brain barriers for the treatment of brain diseases. They can be delivered to the brain by local injection, intranasal application, or systemic administration. Combining active propulsion with biological and chemical approaches or external physical stimuli can improve brain targeting.

## Barriers in the brain

The brain is the command centre of the nervous system, controlling and organizing vital functions and behaviours in the living body. It has unique and sophisticated barrier systems, such as the blood–brain barrier (BBB), which maintains and regulates brain homeostasis. The BBB restricts the entry of small and macromolecules, as well as of potentially toxic agents, into the central nervous system (CNS). The BBB also restricts the amount of drugs that can be delivered to the CNS, limiting their therapeutic efficacy for the treatment of brain diseases. Moreover, surgical treatment of brain-related diseases often requires invasive and severe operations. Thus, minimal and non-invasive therapies for brain diseases are highly desired to reduce mortality and associated disabilities.

## Micro- and nanorobots

Micro- and nanorobots, here defined as micro- and nanoscale objects with the ability to move and execute specific functions, hold great potential to improve therapeutic regimes in brain regions[1]. Micro- and nanorobots exhibit minimal invasiveness, enhanced transport and therapeutic efficacy, and reduced side effects compared to traditional therapeutic approaches, such as local injection or systemic administration of drugs that passively diffuse to target sites. However, achieving effective locomotion is challenging at the micro- and nanoscale owing to the low Reynolds number of fluids (for example, blood and mucus) and Brownian motions. Therefore, a swimming strategy needs to be designed that breaks system symmetry to induce translational movement. According to their power sources, the propulsion of micro- and nanorobots can be classified into chemical propulsion, external-stimuli propulsion (with light, electrical, magnetic or ultrasound field) and biohybrid propulsion[1]. Proof-of-concept medical applications of micro- and nanorobots have been demonstrated in various physiological regions, such as the gastrointestinal tract, kidney, vitreous humour, lung and brain. For example, antibiotic-loaded algae-based microrobots enable robust motion in lung fluid through intratracheal administration. The microrobots can prolong tissue retention and improve the therapeutic outcome in a mouse model of acute bacterial pneumonia[2].

## Introducing robots into the brain

Micro- and nanorobots can overcome brain barriers to improve drug delivery by local injection, intranasal transport or systemic delivery[3] (Fig. 1). Local injection assisted by needles or catheters can introduce micro- and nanorobots to the lesion site instantly and precisely. The active propulsion of robots can then overcome limitations often associated with the local administration of drugs, such as poor drug distribution and the difficulty to reach lesions at a microscopic level. In addition, intranasal transport can provide a rapid and non-invasive or minimally invasive option to effectively deliver the robots to the CNS, bypassing the BBB through the olfactory mucosa.

Systemic delivery is a promising alternative for delivering micro- and nanorobots to the brain. Although efficient barrier penetration remains challenging, systemic delivery offers non-invasive access to the brain through the circulatory system. Enhanced BBB penetration could be achieved by chemical and biological modifications of micro- and nanorobots to achieve receptor-mediated transcytosis (RMT), or by exploiting external physical stimuli. The most widely studied approach to penetrate the BBB is harnessing receptors that are overexpressed on the luminal surface of brain endothelial cells. By conjugating specific ligands on the surface of micro- and nanorobots, the robots can target brain endothelial cells and form a ligand–receptor complex for selective RMT. Cell-mediated delivery is another pathway to penetrate the BBB by hitchhiking on immune cells, such as macrophages and neutrophils, that can cross the BBB in neuroinflammatory conditions through the chemotactic effect. Alternatively, temporal disruption of the BBB by applying external physical stimuli, such as focused ultrasound, magnetic fields and near-infrared laser irradiation, can non-invasively open the endothelial tight junction at the region of interest. The combination of active propulsion and external stimulation could serve as a powerful delivery approach to the brain.

## Applications in the brain

Micro- and nanorobots with active propulsion offer a promising way to design motile vehicles that transport drugs to the brain. A biocatalytic nanorobot encapsulating glucose oxidase and catalase is capable of chemotactic motion towards glucose gradients for drug delivery in the brain[4]. To improve BBB penetration, nanorobots can be functionalized with the peptide angiopep-2, which targets the low-density lipoprotein receptor-related protein 1 that is overexpressed on brain endothelial cells, triggering RMT. The combined effects of propulsion and RMT can improve BBB penetration and in vivo drug delivery efficiency in rats. Neutrophil-based microrobots (neutrobots) are fabricated by coating paclitaxel-loaded magnetic gels with *Escherichia coli* membranes, which can then be phagocytosed by neutrophils[5]. The *E. coli* membrane improves phagocytosis efficiency and minimizes drug leakage. Such neutrobots can thus penetrate the BBB to reach glioma tumour cells in glioma-bearing mice, owing to the synergistic functions of magnetic propulsion and chemotactic dynamics in the presence

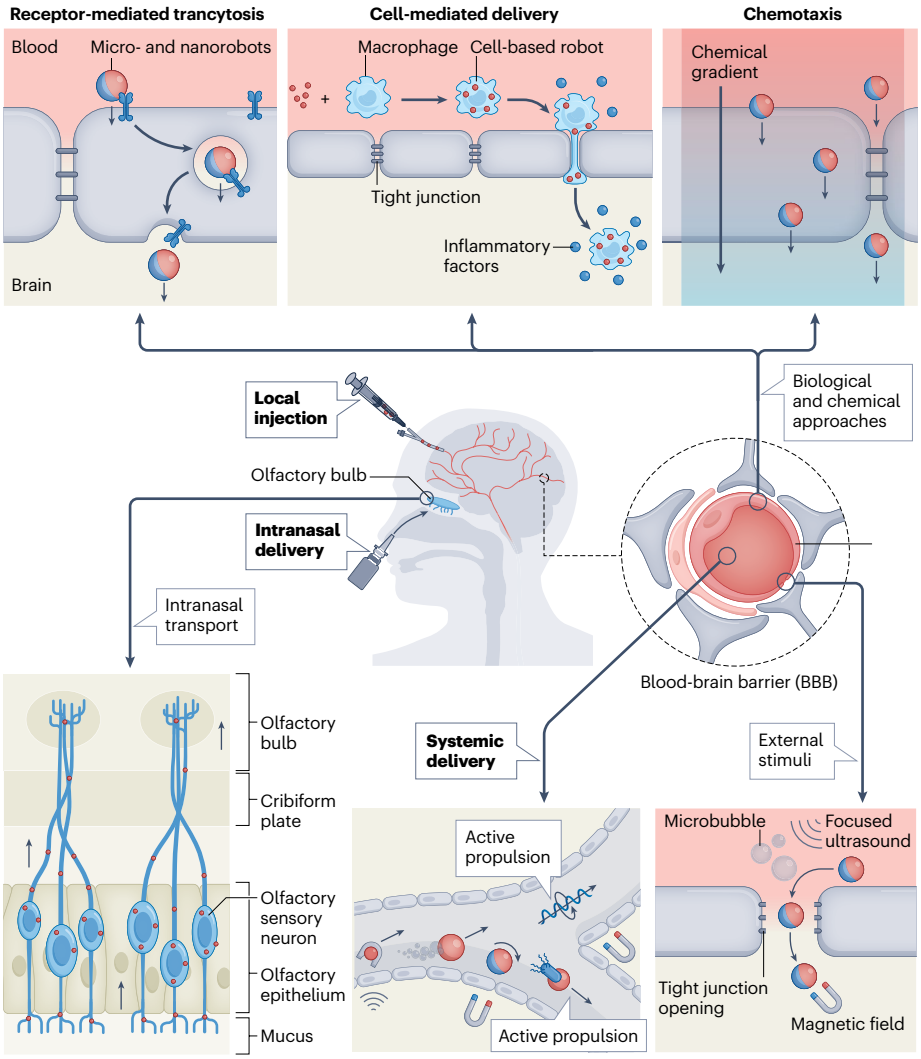


**Fig. 1 | Strategies to introduce micro- and nanorobots into the brain for drug and cell delivery.** Local injection, intranasal transport and systemic delivery. The penetration of the BBB and the efficiency of systemic delivery can be improved using biological and chemical approaches (for example, receptor-mediated transcytosis, cell-mediated delivery and chemotaxis) and external physical stimuli (such as focused ultrasound and magnetic field), along with the active propulsion of micro- and nanorobots.

of a chemokine gradient. Biofluid-powered magnesium-based microrobots can remove reactive oxygen species for acute ischaemic stroke treatment in the brain[6]. The magnesium–water reaction produces hydrogen bubbles for propulsion, which also serve as therapeutic agents to relieve oxidative stress at the stroke site caused by overexpressed reactive oxygen species, and downregulate the expression of inflammatory factors.

Integrating active propulsion with multifunctional cells can provide motile medical robots for brain-targeted delivery. Magnetically actuated scaffold-type microrobots enable precise ex vivo stem-cell delivery and transplantation in rat brain blood vessels[7]. The nasally administered magnetically actuated cell-based robots can bypass the BBB and migrate from the olfactory bulb to the cerebral cortex of the mouse brain[8].

In addition to drug and cell delivery, motile nanorobots could act as surgeons to modulate cellular activities for neurostimulation. Magnetically powered helical microrobots, prepared by coating iron oxide and piezoelectric barium titanate nanoparticles onto a *Spirulina platensis* template, can target neural stem cells upon magnetic control and generate an electric stimulus under an acoustic field to regulate neural stem-cell differentiation[9]. A rotating micromotor powered by light can induce shear force around the nerve axon, leading to controlled growth direction of the axon[10].

Medical imaging technologies are essential in navigating these robots in deep tissues. Furthermore, micro- and nanorobots could potentially improve brain imaging by carrying an imaging contrast agent. For example, Au/Ni/$SiO_2$ microrobots can be manipulated in the murine cerebral vasculature using real-time visualization by photoacoustic imaging, paving the way to precisely and safely operate these robots in the brain[11].

## Outlook

Spatiotemporally controllable micro- and nanorobots hold potential as an intelligent medical platform that can overcome many limitations of drug delivery to the brain. However, challenges remain in leveraging the full potential of micro- and nanorobots for applications in the brain. The propulsion mechanism should be carefully selected according to the application; for example, chemically powered robots may have a limited lifetime or propulsion speed, and fuel-free robots may require a high external energy supply. To improve the efficiency of delivery to the brain, the design of micro- and nanorobot carriers could benefit from nanomedicine technologies (for example, integration with multifunctional materials, such as imaging contrast agents and targeting ligands). Additionally, for in vivo brain applications, micro- and nanorobots should be biodegradable and biocompatible to minimize toxicity. A key starting point is to use approved biocompatible materials to reduce concerns of toxicity and avoid unnecessary attempts. Thus far, studies have mainly focused on how to deliver micro- and nanorobots to the brain and how to propel them once within, but these lack in-depth clinical evaluation of in vivo mechanisms. More efforts should be devoted to designing adaptive, biocompatible and cost-effective micro- and

nanomachines with multiple integrated features (for example, imaging, motion control and delivery) to accelerate the translation of lab research to clinical applications in the brain.

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## Competing interests

The authors declare no competing interests.