Play It Nan▶: Acoustically and Molecularly Driven mRNA Delivery to the Brain for Treating Neurological Disorders

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Why Does It Matter?

Delivering therapeutics to the brain is consistently stymied by the restrictive blood-brain barrier (BBB), leaving hundreds of millions with untreated neurological disorders. While mRNA-based therapies offer a powerful route for protein production within diseased cells, achieving high-efficiency, neuron-selective delivery remains a primary hurdle. This research introduces a dual-modality paradigm that synergizes molecular engineering with physical modulation. By combining AI-validated, ligand-functionalized LNPs, specifically acetylcholine-conjugated particles, with non-invasive, low-frequency acoustic stimulation, we demonstrate a dramatic increase in delivery efficiency. This "acoustic gating" not only amplifies LNP internalization tenfold in neurons but also enables systemic mRNA delivery to deep-brain regions that are otherwise difficult to reach. By bridging the gap between rational chemical design and audible mechanical stimulation, this modular platform establishes a predictive and highly efficient route for CNS gene therapy, paving the way for non-invasive, precision treatment of neurological conditions.

The Idea

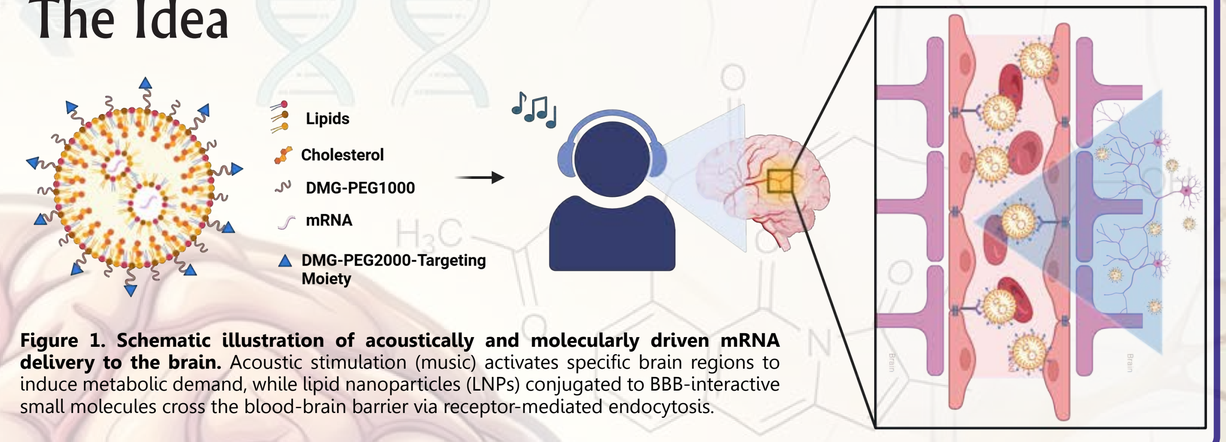
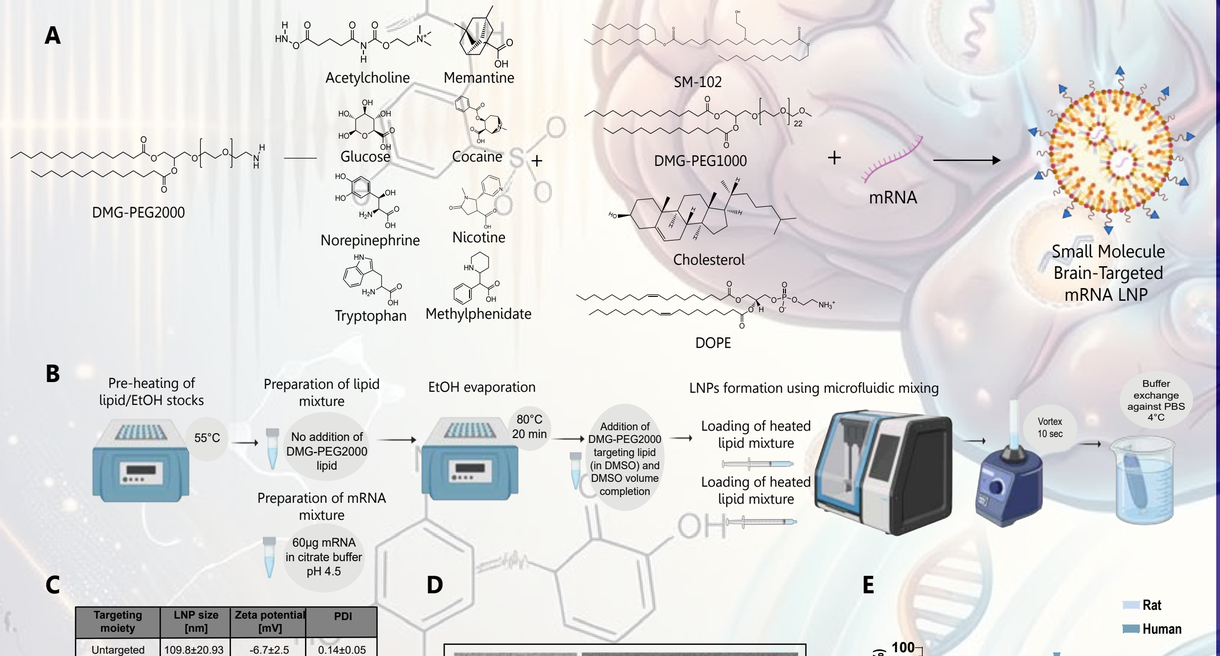


Figure 1. Schematic illustration of acoustically and molecularly driven mRNA delivery to the brain. Acoustic stimulation (music) activates specific brain regions to induce metabolic demand, while lipid nanoparticles (LNPs) conjugated to BBB-interactive small molecules cross the blood-brain barrier via receptor-mediated endocytosis.

Synthesis and Physicochemical Characterization



Targeting moiety	LNP size [nm]	Zeta potential [mV]	PDI
Untargeted	109.8±20.93	-6.7±2.5	0.14±0.05
Glucose	155.1±21.1	-9.6±2.2	0.08±0.04
Methylphenidate	141.9±10.9	-8.6±1.1	0.18±0.05
Memantine	153.9±19.7	-11.8±2.9	0.31±0.05
Acetylcholine	149.1±10.58	-13.4±1.6	0.13±0.05
Cocaine	148.6±15.1	-12.2±2.1	0.19±0.08
Tryptophan	147.7±9.2	-12.6±0.3	0.12±0.08
Nicotine	161±13.5	-10.7±4.1	0.10±0.05
Norepinephrine	155.5±17.6	-13.6±5.7	0.18±0.07

Figure 2. Engineering brain-targeted (BT) mRNA-loaded LNP library. (A) BT-LNP library formulated with small-molecule derivatives; Tryptophan used in native form. **(B)** Microfluidic mixing optimized for PEG–small-molecule lipids, with DMSO replacing EtOH and temperature adjustment for solubility and performance. **(C)** Physicochemical properties (size, zeta potential, PDI; mean ± SD, n=3). **(D)** Cryo-TEM confirmed uniformity and size distribution; Glucose-LNPs shown (scale bar = 200 nm). **(E)** BBB crossing potential predicted with rat/human model. Acetylcholine showed highest BBB interaction/uptake; untargeted = methyl control.

Low-Frequency Stimuli Enhance LNPs Uptake

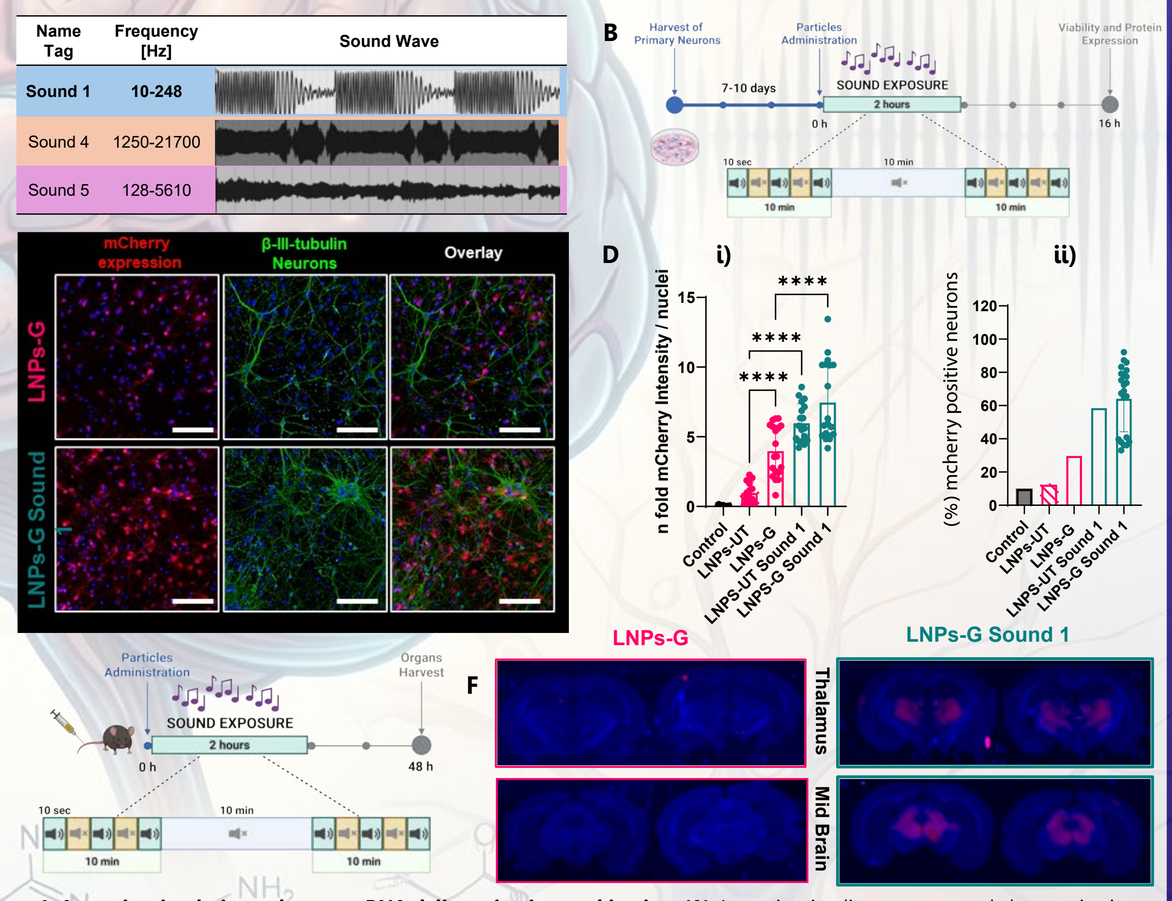


Figure 4. Acoustic stimulation enhances mRNA delivery in vitro and in vivo. (A) Acoustic stimuli parameters and characterization. **(B)** Experimental workflow for primary cortical neuron cultures exposed to sound. **(C)** Representative confocal images of primary neurons 24 h post-treatment; mCherry (red), b-III-tubulin (green), and DAPI (blue). Scale bars: 50 µm (main) and 25 µm (zoom). **(D)** Quantification of mCherry expression: **(i)** normalized to nuclei count and **(ii)** percentage of b-III-tubulin positive neurons, showing significant sound-induced enhancement (****p<0.0001). **(E)** Schematic of in vivo experimental setup following IV administration and sound exposure. **(F)** Representative brain sections showing regional specificity in the midbrain and thalamus, indicating enhanced LNP uptake in auditory-processing regions. Scale bar: 5000 µm.

Functional Evaluation of mRNA Delivery

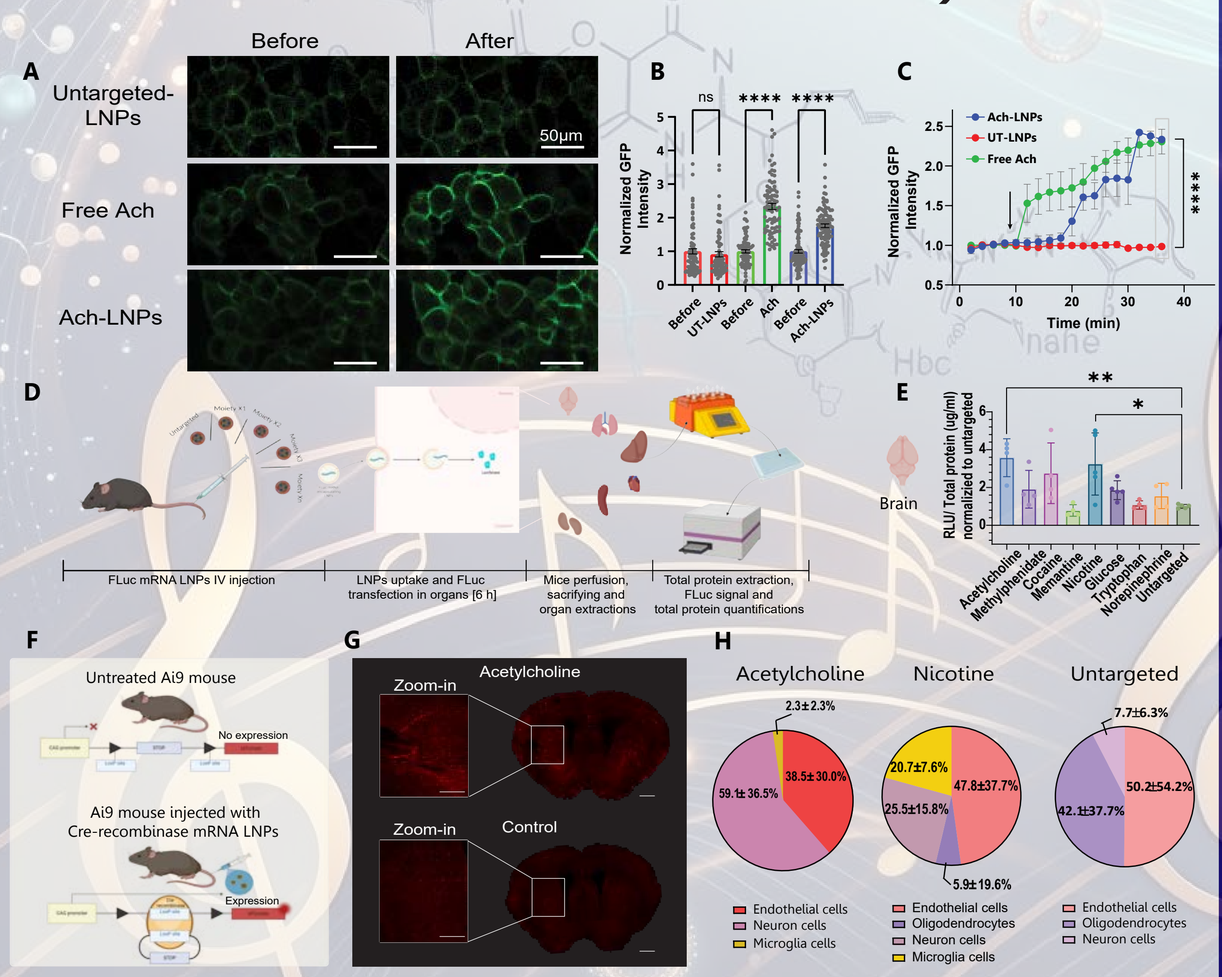


Figure 3. In vitro and in vivo validation of brain-targeted (BT) mRNA-LNPs. (A) Representative images of HEK293-AchLightG cells showing sensor activation (GFP) 35 min post-treatment with free Ach (100 µM) or Ach-LNPs. Scale bar: 50 µm. **(B)** Quantification of normalized GFP intensity (n≥80). **(C)** Activation kinetics post-treatment (arrow denotes injection); ****p<0.0001. **(D)** Bioluminescence-based assessment of FLuc-mRNA biodistribution and **(E)** brain-specific transfection efficiency following IV injection. **(F)** Evaluation of cell-type selectivity using Ai9 Cre reporter mice. **(G)** Representative brain sections 48 h post-injection show tdTomato expression localized primarily .in BBB endothelial capillaries. Scale bars: 1000 µm (main) and 100 µm (zoom). **(H)** Distribution of LNPs across major neural cell populations

Sound Stimuli with Clinical Therapy Potential

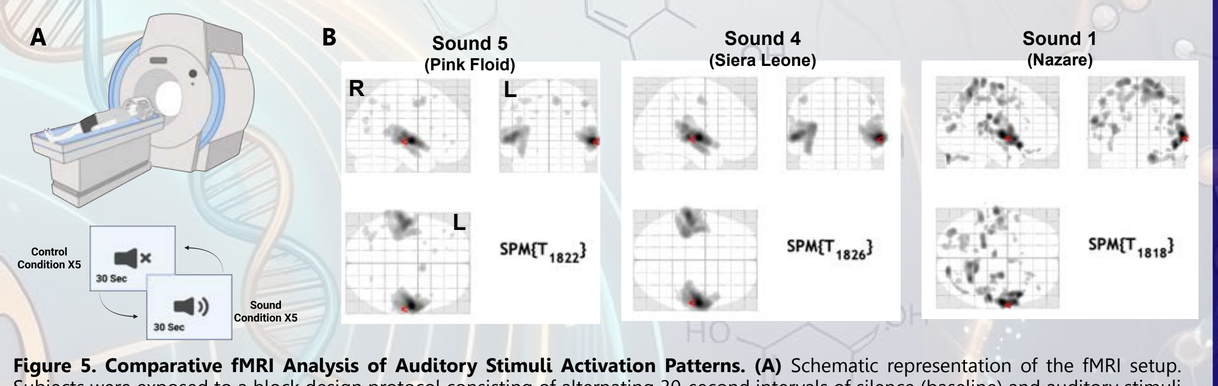


Figure 5. Comparative fMRI Analysis of Auditory Stimuli Activation Patterns. (A) Schematic representation of the fMRI setup. Subjects were exposed to a block design protocol consisting of alternating 30-second intervals of silence (baseline) and auditory stimuli (sound). Bold-fMRI scans were used to map neural activation. **(B)** Functional MRI activation maps (p < 0.05, FWE-corrected) showing brain responses to three distinct auditory stimuli. The analysis demonstrated that Sound 1 induced a broader and more widespread brain activation pattern compared to the other two auditory conditions.

Take Home Message

Synergistic Delivery: Combining Ach-LNPs with acoustic gating overcomes the BBB.

Acoustic Power: Sound stimuli amplify mRNA internalization up to 10-fold.

Personalized Precision: fMRI-guided sound protocols enable patient-specific brain targeting.

Modular Platform: A predictive route for non-invasive CNS gene therapy.

Acknowledgements & References

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- Mora-Raimundo, P., M., Gilon, A., Kadosh, H. et al. Music enhances lipid nanoparticle brain delivery and mRNA transfection in brain cells. Journal Of Controlled Release (October 2025).

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