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Research Article

Guiding Diffusion of Magnetic Nanoparticles from Nose to the Brain Using Permanent Magnet is Theoretically Feasible but Practically Challenging

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Abstract

The blood-brain barrier (BBB) presents a significant challenge in delivering medications to the brain, impeding direct targeting of specific brain regions in humans. Currently, effective methods for overcoming this protective barrier are limited. Targeted drug delivery to the brain from the nose has been utilized successfully, albeit the delivered dose of medication directly to the brain predominantly depends on circulation. One promising strategy involves guiding magnetic nanoparticles through the cribriform plate from the nose to the brain. Unlike other areas, the nose and circumventricular organs provide a less restrictive pathway where the BBB is permeable. The concept of guiding the diffusion of magnetic nanoparticles through the cribriform plate appears feasible in theory. However, the complexity of such a delivery system necessitates a heuristic approach for practical implementation. In our recent study, we attempted to guide the diffusion of fluorescent magnetic nanoparticles using neodymium magnets in different media and animal brain tissues. Although, we did not successfully demonstrate this method of delivery with simplistic approach, we argue that an interprofessional effort is essential to tackle this mode of drug delivery by passing the challenges posed by the BBB and to innovate targeted drug delivery solutions for the brain. By leveraging diverse perspectives and specialized knowledge, we can advance towards more effective therapies that harness the potential of magnetic nanoparticle technology for neurological treatments.

Keywords: magnetic nanoparticles, targeted drug delivery, nasal drug delivery, bypass blood brain barrier, olfactory epithelium

INTRODUCTION

Despite significant advances in neuropsychiatry over the past century, delivering medications to the central nervous system (CNS) remains challenging. Systemic administration of psychotropic medications often leads to poor patient compliance, which is suboptimal among individuals with psychiatric disorders[2–4]. One of the primary reasons for treatment discontinuation is the systemic side effects associated with psychotropic medications[3]. To mitigate these side effects, it is essential to deliver psychotropic agents directly to the brain, ideally targeting specific regions within the CNS. However, achieving this goal is complicated by numerous obstacles, foremost among them being the blood-brain barrier (BBB)[5,6].

The blood-brain barrier (BBB) confers partial privilege to the central nervous system (CNS)(9). Despite its incomplete isolation of the brain, the BBB poses a significant obstacle to delivering drugs directly to the CNS. For medications and pharmaceutical agents that do manage to cross the BBB, their delivery tends to be diffuse throughout the CNS. There are limited "windows of opportunity" available for targeted treatment of CNS pathologies. Unlike most areas of the brain, circumventricular organs (CVOs) and the nasal cavity naturally lack a BBB[7]. While CVOs are inaccessible from the periphery, the nasal cavity theoretically becomes a crucial pathway for targeted drug delivery to the CNS.

Although the absence of the blood-brain barrier (BBB) in the olfactory system presents an opportunity to deliver therapeutic or diagnostic agents directly to the central nervous system (CNS), the extent of this opportunity is limited. For instance, the olfactory neuroepithelium (ONE) comprises only a small portion of the nasal cavity mucous membrane, accounting for approximately 5% of the total mucosal surface. Furthermore, evidence suggests that with aging, both the number of olfactory

sensory neurons (OSNs) and the width of the cribriform plate foramina decrease[12,17–19]. These challenges diminish the efficacy of the olfactory system as an optimal option for targeted drug delivery.

To achieve sufficient drug delivery to the brain via the nasal route, large doses of medications may be necessary. However, the nasal mucous membrane is highly vascularized, which could result in significant systemic distribution of drugs, similar to other routes of medication delivery [20]. Therefore, while the olfactory route holds promise, optimizing its potential for CNS drug delivery requires addressing these anatomical and physiological challenges.

One theoretically promising method to enhance targeted drug delivery to the central nervous system (CNS) leverages the absence of the blood-brain barrier (BBB) around ascending fibers originating from the olfactory neuroepithelium (ONE). This method involves the guided transport of magnetic nanoparticles loaded with psychopharmacological agents. In various other organs, it has been demonstrated that magnetic nanoparticles can be directed to deliver drugs to specific regions, such as tumors, achieving significantly higher concentrations compared to systemic delivery [21–23]. Extending this approach to transport medications from the nasal cavity directly to the brain represents a theoretically viable option that warrants exploration. By harnessing magnetic nanoparticle technology, it may be possible to overcome the challenges posed by the BBB and achieve targeted drug delivery to specific regions within the CNS. Continued research and development in this area could lead to innovative therapies with enhanced efficacy and reduced systemic side effects.

To assess the potential use of magnetic nanoparticles for targeted drug delivery to the central nervous system (CNS), two approaches stand out among many. A goal-directed probabilistic approach, based on biological or mathematical modeling, would ideally be the optimal method. However, due to the complexity involving multiple variables in guiding nanoparticle diffusion under a relatively weak force like that of a permanent magnet, a heuristic approach is more practical economically and logistically.

With this rationale in mind, our current study undertakes the initial step to establish the feasibility of guiding the diffusion of magnetic nanoparticles using permanent magnets. Before exploring the feasibility of drug delivery to the CNS using magnetic nanoparticles, it is crucial to demonstrate that targeted delivery to specific regions of the CNS is both achievable and safe.

Our primary objectives in this project were twofold:

1. Evaluate the feasibility of guiding the diffusion of magnetic nanoparticles within brain tissue.
2. Validate the selective diffusion of these magnetic nanoparticles using various imaging technologies.

Before commencing the project, we hypothesized that guiding the diffusion of magnetic nanoparticles using permanent magnets is feasible and can be monitored in real-time. These initial steps are essential to lay the groundwork for potential advancements in targeted drug delivery to the CNS using magnetic nanoparticle technology.

MATERIALS AND METHODS:

We acquired nano-screenMAG-ARA from Chemicell.com [24]. Additionally, we purchased three types of Neodymium magnets: a neodymium magnet N40 with a diameter of 12.7 mm, a hole diameter of 6.5 mm, and a thickness of 3.18 mm; a neodymium cube measuring 4.76 mm x 4.76 mm x 4.76 mm; and a neodymium N48 cylinder with dimensions of 25.4 mm x 25.4 mm. These magnets have been previously employed in biomedical research[25,26]. Brain and spinal cord tissues were obtained through collaboration with faculty at Howard University College of Medicine. The Malvern Zetasizer Nano S90 was utilized to measure particle sizes, and sonication was employed to standardize particle sizes. For visualizing particle diffusion in various media and tissues, we utilized the PerkinElmer IVIS® Spectrum imaging system and the Olympus Fluoview 300 confocal microscope. Brain tissue imaging was conducted using the Bruker AV400 9.4 Tesla (400 MHz), 89 mm vertical bore MRI/MRS system.

Figure 1: A Zetasizer; B: Sonicator; C: PerkinElmer IVIS Spectrum imaging system; D: Bruker MRI; E: vial of nanoparticles F: vial of the nanoparticle as imaged under PerkinElmer IVIS system

In summary, our study proceeded through several key phases to evaluate the behavior of magnetic nanoparticles under the influence of neodymium magnets:

1. Initially, we investigated whether neodymium magnets could attract the magnetic nanoparticles.
2. Next, we utilized agarose gel of varying viscosities, along with water and oil, to conduct a gross examination of nanoparticle diffusion when exposed to permanent magnets.
3. Subsequently, we injected the nanoparticles into tissue samples and visually observed their diffusion using the PerkinElmer IVIS® Spectrum imaging system (epifluorescence with filter pairs excitation: 570nm, emission: 620nm) and confocal microscope.
4. Lastly, we injected nanoparticles into the nasal cavity of freshly acquired rodent skulls. After removing the dentary, occipital, temporal, and part of the frontal bones, we placed the samples on a neodymium N48 grade magnet. We then monitored the samples immediately and 24 hours later using the PerkinElmer IVIS® Spectrum imaging system (epifluorescence with filter pairs excitation: 570nm, emission: 620nm) and the Bruker AV400 9.4 Tesla (400 MHz), 89 mm vertical bore MRI/MRS systems using a 25mm ID volume coil. Rapid Acquisition with Refocused Echoes (RARE) fast spin echo MRI images were acquired with echo time = 20ms, repetition time = 2000ms, acceleration factor = 8, number of averages = 9 and voxel size = 100×50×300µm. Fast Low Angle Shot (FLASH) gradient echo images were acquired with echo time = 5.4ms, repetition time = 518ms, flip angle = 30°, number of averages = 32, voxel size = 100×62×500µm.

These steps allowed us to comprehensively assess the potential for guiding magnetic nanoparticles within biological tissues and towards specific regions using magnetic fields.

RESULTS:

As expected, the permanent magnets successfully attracted the magnetic nanoparticles in both water and oil media (Figure 2). In water, the particles dispersed readily, and the magnets were effective in clearing the particles within a short period. However, in oil media, the particles remained in globular form without dispersing, and they varied in size (approximately <3mm in diameter) (Figure 3). Even after removing the magnets, the nanoparticles retained their globular shape in the oil medium.

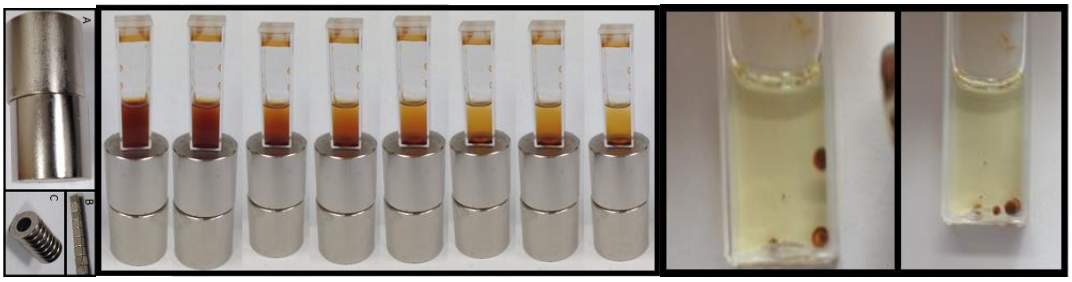

Figure 2. Various sizes of neodymium magnets were employed in these experiments. In water, the magnetic nanoparticles were effectively cleared from both water and oil media. However, in the oily medium, the nanoparticles remained in globular form despite the magnetic field.

Using the Malvern Zetasizer Nano S90, we discovered that the actual size of the nanoparticles was significantly larger than the size advertised by the manufacturer at the provided concentration. Despite employing sonication and reducing the nanoparticle concentration, the particle sizes consistently remained larger than the manufacturer's specifications. The most consistent results were achieved at a concentration of 0.025 mg/ml (Figure 3).

Figure 3: The actual size of fluorescent magnetic nanoparticles was measured at various dilutions using the Malvern Zetasizer Nano S90.

To assess the viability of this drug delivery method, it is crucial that guided diffusion occurs rapidly. To evaluate this, we utilized various concentrations of agarose gels to monitor the movement of nanoparticles under the influence of external permanent magnets. Below a concentration of 0.25%, agarose gel was observed to be pulled along with the nanoparticles by the magnets. This movement was clearly visible using an optical imaging system (Figure 4). The particles were immediately attracted and pulled by the magnets within the first few minutes.

Achieving similar results in more viscous gels or tissue samples would be a significant milestone, indicating that the application of permanent magnets does not require prolonged exposure to influence the diffusion of magnetic nanoparticles. This rapid response is crucial for the practical implementation of this drug delivery approach.

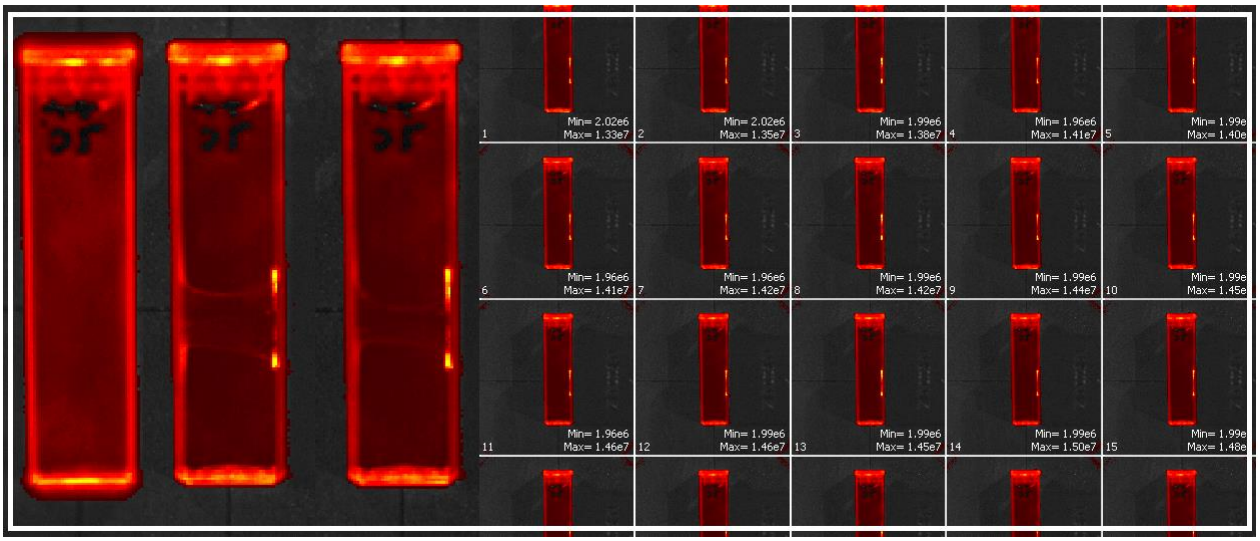

Figure 4. In thin agarose gel, the majority of particles were attracted to the magnet shortly after its application. However, in thicker gels, we observed no noticeable movement of the particles, either visually or under the optical imaging system.

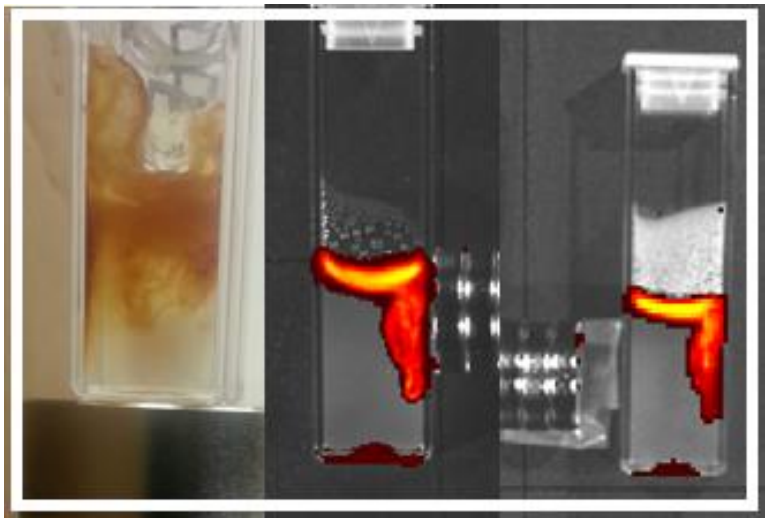

Figure 5. In thicker agarose gel, we did not observe the phenomenon observed in Figure 4. Specifically, there was no noticeable attraction or movement of the particles towards the magnet.

In tissue samples, we did not observe any significant diffusion of nanoparticles in our experiments. In fixed spinal cord tissue, we found that there was no diffusion beyond the site of injection (Figure 6); any diffuse color change observed was attributed to artifact rather than actual diffusion. Confocal microscope images further confirmed the absence of nanoparticle diffusion beyond the injection points. This lack of diffusion was consistent across both fixed and fresh tissue samples.

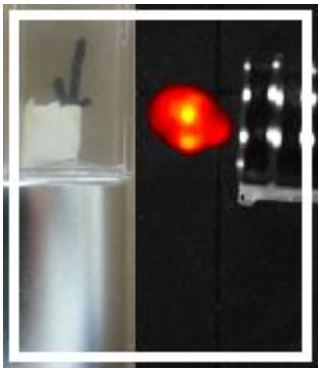

Figure 6. The application of permanent magnets had no discernible effect on the diffusion of particles in fixated spinal cord tissue.

When nanoparticles were injected into the nasal cavity, we did not observe movement of the particles when permanent magnets were applied. However, over time, the particles diffused to the orbital cavity but did not reach the brain. Confocal microscopy also did not reveal significant diffusion of nanoparticles far from the site of injection. Additionally, MRI imaging did not show substantial distortion due to the presence of magnetic nanoparticles (Figure 7).

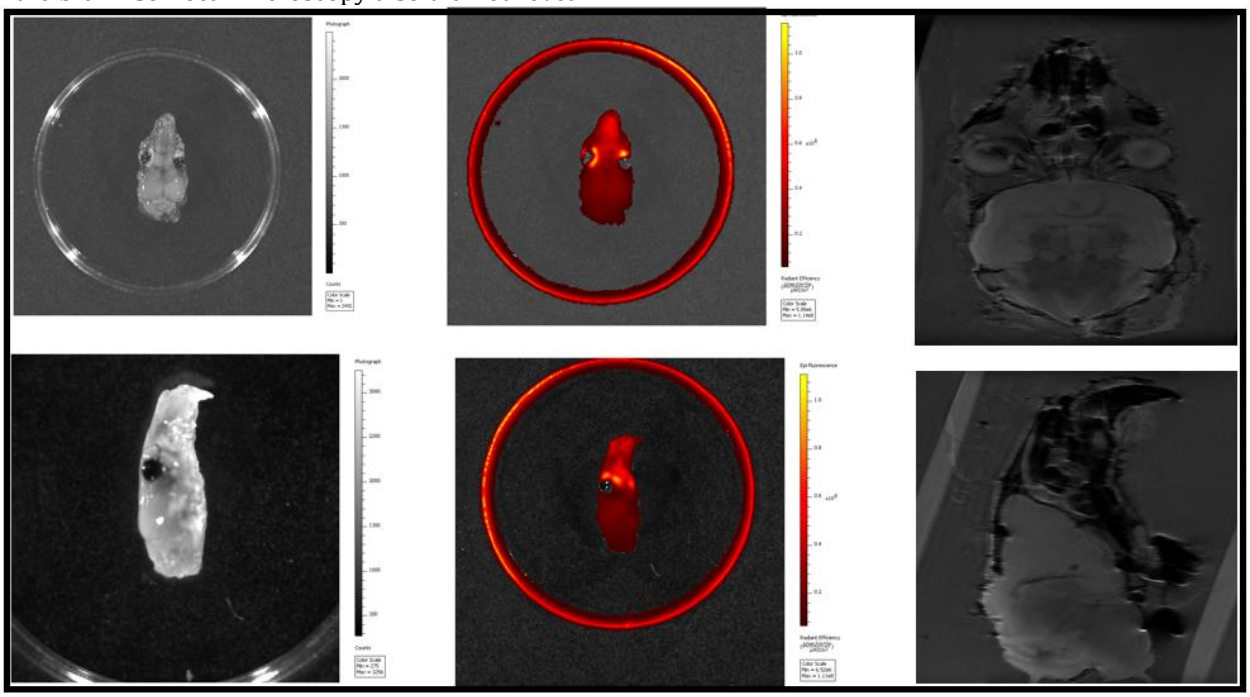

Figure 7: Twenty-four hours after injecting fluorescent nanoparticles into the nasal cavity, we observed no diffusion of particles across the cribriform plate into the brain. Furthermore, the presence of magnetic particles did not noticeably affect the quality of MRI images.

DISCUSSION:

In this hypothesis-driven heuristic approach, our primary objective was to guide the diffusion of magnetic nanoparticles within a simple system comprising permanent magnets, magnetic nanoparticles, and various media. Overall, we did not succeed in achieving this goal. However, we did make partial progress toward one of our aims: we successfully tracked the real-time diffusion of nanoparticles over short periods using various visualization techniques.

Despite our efforts, our simplistic approach did not allow for the directable diffusion of nanoparticles using permanent magnets in thicker media or tissue samples. Nevertheless, our findings provide valuable insights for future studies in this area of research. While our study did not achieve the intended outcome, it underscores the challenges and complexities involved in guiding the diffusion of magnetic nanoparticles with the aid of permanent magnets.

Previous research has demonstrated the feasibility of manipulating magnetic nanoparticles for various biomedical applications [25,26]. However, translating this capability into a reliable method for targeted drug delivery remains challenging, particularly in complex biological environments [26].

Moving forward, exploring alternative methods and technologies, such as magnetic levitation systems or advanced magnetic field configurations, may offer new

avenues to enhance the precision and efficacy of nanoparticle-guided delivery systems [27,28]. Despite the practical challenges, the potential benefits of utilizing magnetic nanoparticles and permanent magnets in psychopharmacological interventions remain promising, warranting continued investigation and innovation in this field.

Our disappointing efforts here underscore the importance of interprofessional collaborations between psychiatrists and other scientific disciplines to develop technologies tailored specifically to psychiatry. Without such collaborations, progress in this field may be limited. For instance, the complex mathematics involved in designing models that simulate the diffusion of magnetic nanoparticles under the influence of permanent magnets in the nasal cavity would likely be beyond the expertise of most psychiatrists. Similarly, understanding the nuanced needs of psychiatric patients may appear overly simplistic to physicists and mathematicians who are not familiar with clinical practice.

By fostering collaboration between clinicians and non-medical scientists, we can accelerate the discovery of innovative methodologies for treating and diagnosing mental disorders. This collaborative approach leverages diverse expertise and perspectives, bridging gaps between theoretical knowledge and practical application in psychiatric care. Ultimately, such partnerships hold great potential to drive meaningful advancements in psychiatric therapies and diagnostics.

In this small study, conducted without true interprofessional collaboration, we employed a heuristic approach. Heuristic approaches are commonly utilized in social sciences and psychiatry [29–31] and also find value in physical sciences and biomedical research [29]. For instance, animal models are often heuristic analogies intended to represent causal similarities of human pathologies, despite their limitations[33–35]. These heuristic approaches may still be effective in guiding future more goal directed outcome specific research[33,34]. While such heuristic approaches may not fully replicate biological complexity, they can still guide more targeted and outcome-specific research in the future [33, 34].

In biomedical research, heuristic models prove especially beneficial when faced with numerous confounding factors and limited prior data availability. Simplified biological or computerized models often fail to capture the full complexity of living organisms due to the intentional reduction of variables[33,36]. Thus, while probabilistic models, particularly computerized ones, may not fully represent biological systems as intended, heuristic approaches help narrow down factors that can be considered in probabilistic modeling.

Addressing challenges encountered in heuristic systems can inform updates to probabilistic models, facilitating iterative improvements [33, 34, 36]. Despite our study not achieving its objectives, we do not view our efforts as futile. Our findings can serve as a foundation for future studies, particularly those conducted in collaboration with physicists, computer scientists, and psychiatrists. By pooling resources and expertise across disciplines, future research endeavors can build upon our insights to design more robust and effective studies in psychiatric technology and treatment methodologies.

Conflict of Interest: NIL

Authors Contribution: All authors equally contributed in this research work.

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