Magnetic particle imaging (MPI) is a new tomographic technique developed in the early 2000s. In contrast to traditional imaging modalities such as MR imaging, sonography, x-ray, and CT, MPI is not a structural imaging technique. Instead, it is a tracer imaging technique similar to PET and SPECT. MPI allows tracking and quantification of tracer materials, specifically magnetic nanoparticles. It is a quantitative 3D imaging technique modeled by the Langevin theory, with the ability to track and quantify nanoparticle concentrations without tissue background noise. It is a promising new imaging technique for multiple applications, including vascular and perfusion imaging, oncology imaging, cell tracking, inflammation imaging, and trauma imaging. In particular, many neuroimaging applications may be enabled and enhanced with magnetic particle imaging. In this review, we will provide an overview of magnetic particle imaging principles and implementation, current applications, promising neuroimaging applications, and practical considerations.

**SUMMARY:** Magnetic particle imaging is an emerging tomographic technique with the potential for simultaneous high-resolution, high-sensitivity, and real-time imaging. Magnetic particle imaging is based on the unique behavior of superparamagnetic iron oxide nanoparticles modeled by the Langevin theory, with the ability to track and quantify nanoparticle concentrations without tissue background noise. It is a promising new imaging technique for multiple applications, including vascular and perfusion imaging, oncology imaging, cell tracking, inflammation imaging, and trauma imaging. In particular, many neuroimaging applications may be enabled and enhanced with magnetic particle imaging. In this review, we will provide an overview of magnetic particle imaging principles and implementation, current applications, promising neuroimaging applications, and practical considerations.

**ABBREVIATIONS:** FFL = field-free line; FFP = field-free point; FFR = field-free region; MPI = magnetic particle imaging; SPIO = superparamagnetic iron oxide; SPION = superparamagnetic iron oxide nanoparticle
Comparison of MPI with common clinical imaging modalities

| Modality               | Ultrasound | CT       | MRI      | PET      | SPECT    | MPI      |
|------------------------|------------|----------|----------|----------|----------|----------|
| Main clinical applications | Structural imaging | Structural imaging | Structural imaging | Tracer imaging | Tracer imaging | Tracer imaging |
| Spatial resolution     | 1 mm       | <1 mm    | 1 mm     | 4 mm     | 3–10 mm  | 1 mm     |
| Temporal resolution    | <1 second  | Microbubbles | Seconds to hours | Minutes  | Minutes | <1 second to minutes |
| Contrast agents/tracers | Low        | Low      | Low      | High     | High     | High     |
| Sensitivity            | Low        | Low      | Low      | High     | High     | High     |
| Patient risk           | Low        | Heating and caviation | Radiation | Heating and peripheral nerve stimulation | Radiation | Heating and peripheral nerve stimulation |
| Cost                   | Low        | Medium   | High     | High     | Medium   | Medium   |

The contrast and signal to noise ratio is excellent with MPI because MPI sees only a tracer and does not see tissue. More specifically, MPI is not affected by the endogenous iron present in the body. It can see only injected SPIONs. This is similar to PET and SPECT, which also have no background signal from tissue. However, PET and SPECT, with imaging times on the order of minutes, are not suited for dynamic imaging applications. PET and SPECT tracers also have half-lives on the order of minutes to hours, while MPI tracers can last for days to weeks. MPI contrast shows the greatest benefits in techniques in which the high contrast can lead to higher accuracy, such as perfusion imaging and cell tracking. This benefit compares favorably with traditional structural imaging techniques such as MR imaging and CT, which can struggle to produce reliable perfusion imaging.

The sensitivity of the technique is because MPI directly detects the electronic magnetization of iron oxide nanoparticles, a magnetization that is large compared with the nuclear magnetization detected in MR imaging. This feature gives MPI a low detection limit, meaning that minute amounts of tracer material can be detected. For example, the iron detection limit was 1.1 ng (SNR = 3.9) in a voxel of tailored MPI tracers using a high-sensitivity FFL scanner with a 5.7-T/m gradient with a native resolution of 800-μm full width at half maximum. The system was also used to detect dilute tracer (550 pg Fe/μL), which could be seen with SNR = 4.9. As MPI systems begin to mature, their sensitivity should continue to improve. Current systems have limits as low as ~200 cells in a voxel, and theoretically, the MPI detection limit may be as little as 1–10 iron oxide cells in a voxel.

**Applications of MPI and Perspectives on Neuroimaging**

**Vascular Imaging.** Currently the standard of care for cerebral blood perfusion imaging is CT perfusion, which poses ionizing radiation risks. MPI is well-suited for measuring perfusion. A study demonstrated imaging of cerebral blood flow in living mice using MPI. This was followed by a demonstration of MPI perfusion in mice for imaging stroke. In our work, we recently measured CBV and CBF in a rat. In addition, we performed in vivo cerebral blood perfusion in stroke mice with MPI (Fig 1), in which an intravenous bolus of iron nanoparticles was administered to mice. Tomographic 3D-MPI was performed using a MOMENTUM MPI system (Magnetic Insight). We
For example, we in
In addition, it
MPI may
in which a transgenic mouse model with bleeding in-
By means of a human glioblastoma mouse model, fluo-
In an-
the impacted animals compared with the controls over a 2-week
brain injury, animals were monitored longitudinally to study ce-
scans for 80 minutes. In another study in a rat model of traumatic
duced in the gut using heparin was imaged with 21 repeat MPI
showed that lower MPI signal (a measure of CBV) is observed
the side of the brain with the stroke lesion.
Another promising application of MPI is to image vasculature.
MPI provides 3D information, and the signal is directly related to
blood volume in a vessel. This is an improvement over 2D tech-
niques such as x-ray or DSA. CT or MR angiography, while pro-
viding 3D images, has background noise from the surrounding
tissue and calcium, which is not a concern for MPI. In MPI, 3D
angiography can be performed using bolus tracking or blood pool
agents. An MPI-specific long circulating nanoparticle can repeat-
edly measure the blood pool with 1 single injection, enabling
tracking of changes from minutes to hours. For example, we
recently demonstrated use of a long circulating tracer to detect gut
bleed, in which a transgenic mouse model with bleeding in-
duced in the gut using heparin was imaged with 21 repeat MPI
scans for 80 minutes. In another study in a rat model of traumatic
brain injury, animals were monitored longitudinally to study ce-
rebral bleeding caused by the impact. We showed differences in
the nanoparticle clearance rate in different regions of the brain in
the impacted animals compared with the controls over a 2-week
period.

MPI is also capable of very fast imaging, similar to x-ray and
DSA, enabling tracking of fast blood flow dynamics. Previously, 1
study demonstrated 3D in vivo imaging of a beating mouse heart
using a clinically approved concentration (<40 μmol [Fe]¹⁻) of
Resovist (ferucarbotran; Bayer Schering Pharma, Berlin, Ger-
many), with a temporal resolution of 21.5 ms, FOV of 1–2 cm, and
resolution sufficient to resolve heart chambers. In addition, it
has been shown that catheters and guidewires can be tracked with
MPI, enabling image-guided interventions.

Oncology. A promising application for MPI is in oncology. MPI
could be used to image tumor vascularization, which may be im-
portant in indicating tumor stage and
treatment efficacy. We recently dem-
strated MPI visualization in a breast can-
cer xenograft model and showed that
MPI can see both the early dynamic con-
trast-enhanced effect of nanoparticles
flowing into a tumor, followed by the
enhanced permeability and retention ef-
fect during the following 48 hours.

In neuro-oncology, conventional MR
imaging and CT lack reliability in assess-
ing the size and location of brain tu-
mors, and they are often not specific
enough to differentiate tumor prog-
ression from other treatment-related
changes. While traditional PET for
glucose metabolism is often used in pe-
ripheral tumor imaging, it cannot pro-
vide good contrast for brain tumors due
to the high levels of glucose metabolism
inherent in the brain, and novel tracers
such as radio-labeled amino acids are re-
quired for better contrast. MPI may
provide a promising alternative, espe-
cially as brain-specific MPI tracers are
developed to improve specificity, enhance retention times, and
reduce potential harm to the patient.

In brain tumor studies, SPION size can be optimized to pas-
ively target and accumulate in a brain tumor because the tumor is
hypervascularized with leaky vessels while the blood-brain barrier
blocks access to healthy brain tissue. Active tumor targeting
can also be achieved via surface chemistry modifications or the
use of magnetic fields. For example, it was shown that lactoferrin-
conjugated nanoparticles can be used to target brain glioma cells
in MPI. By means of a human glioblastoma mouse model, fluo-
rescent magnetic nanoparticles could be magnetically retained in
the neovasculature as well as tissue of the tumor, using a magnetic
micromesh.

MPI can also be used for sentinel lymph node imaging and
hyperthermia treatment. The current state of the art is to use
radioactive colloid tracers, which could be replaced with MPI
tracers. This was demonstrated in a mouse cancer model, in
which magnetic tracer material was seen depositing in tumor tis-
ue and/or sentinel lymph nodes near tumors. In hyperthermia
treatment, magnetic particles injected into tumors can locally
heat the tissue around the FFR. It was demonstrated that the MPI-
measured magnetic particle concentration correlated well with
tumor volume decrease after magnetic hyperthermia. In another
study, it was shown that magnetic nanofibers loaded with
magnetic nanoparticles could be visualized using MPI and used
for magnetic hyperthermia.

Cell Labeling and Tracking. MPI is promising for cell tracking
because the technique is independent of depth in tissue with mil-
limeter-scale resolution, robust linear quantification, and high
sensitivity. We evaluated MPI for tracking of systemically admin-
istered mesenchymal stem cells. Mesenchymal stem cells are of

FIG 1. Perfusion, structural, and histology images from a mouse injected with the nanoparticles.
The parameters were the following: FOV = 4 cm, 35 projections, best image quality, Lodespin
scan mode. A 70- to 100-L intravenous bolus of iron nanoparticles (0.949 mg Fe/mL; core diam-
eter, 27.6 nm) donated by Dr Kannan Krishnan, University of Washington, was administered to
C57Bl/6 stroke mice through tail veins. The mice were sacrificed within 30 minutes postinjection,
and 3D-MPI was performed using a MOMENTUM MPI system. Anatomic images were collected
on the eXplore CT-120 microCT (GE Healthcare, Milwaukee, Wisconsin) and a 7T MR imaging
scanner. Anatomic images were collected on the eXplore CT-120 microCT (GE Healthcare, Milwaukee, Wisconsin) and a 7T MR imaging
scanner. In vivo iron oxide quantification was performed by imaging fiducials containing a known concentration of tracer positioned beside the animal. A. In the 2D coregistered image from CT and
MPI, the MPI signal (red if high, yellow if intermediate, blue if low) from the left hemisphere is less than that from the contralateral side (red spots
indicate vascular structures with high blood volume). B. The high T2 signal (stroke lesion, arrow-
heads) in the left basal ganglia and thalamus. C. The histology image of a perfusion-fixed whole
brain shows the stroke lesion on the left (L). R indicates right.
Intravenous injections are sometimes used to de- 
51,52 
58-61 
or by 
to serve as potential contrast agents for MPI.
The authors demonstrated a detec-
Our proof-of-concept study confirmed that 
As mentioned previously,
There are a number of commercial SPIO agents that 
Blood cell tracking is another 
48 hours and reduced with time.
particular therapeutic interest because they can control inflam-
and modify the proliferation and cytokine production of immune cells.41 Intravenous injections are sometimes used to de-
river mesenchymal stem cells in both animal models and clinical 
Our proof-of-concept study confirmed that >80% of 
In a different study, it was shown that rat and human adult stem cells can uptake SPIIONS 
and they localize in the cytoplasm.64 Blood cell tracking is another application for MPI as a method for increasing circulation time.65 Using red blood cells as the carrier also has the advantage of being able to increase circulation time from minutes to hours.2,46,47 Additionally, there is ongoing work on the development of MPI-tailored nanoparticles, which can be functionalized for efficient targeting and cell labeling. We recently demonstrated that Janus nanoparticles made by encapsulating iron oxide nanoparticles in semiconducting polymers allowed efficient cell labeling and were sensitive enough to track 250 labeled HeLa cells after implantation in mice.9
These cell-labeling and tracking methods may also be applied to neuroimaging. In one study, it was shown that neural grafts could be monitored in rats. This study implanted neural progenitor cells into the forebrain of rats and measured nonsignificant signal decay during 87 days.18 The authors demonstrated a detect-
sensitivity of <1000 cells in a voxel. As commercial development continues, we estimate that the theoretic detection limit may approach as little as 1–10 cells in a voxel. For comparison, these numbers compare favorably with MR imaging, in which the 
first clinical cell-tracking detection limit was 15,000 cells.48 In a preliminary experiment, we administered SPION-la-
ble mouse macrophages to stroke 
mice to test the localization and reten-
tion of signals for stroke monitoring (Fig 
We showed that while the accumula-
tion of iron-labeled cells was highest at 
48 hours, there was still detectable MPI signal at 96 hours postinjection.
Inflammation Tracking. Inflammation is involved in many disease processes, in-
cluding immune disorders, neurologic/neuropsychological disorders, and cancer.
Detection and tracking of inflammation could help with diagnosis and monitor 
treatment outcomes. Unfortunately, cur-
rent practices in tracking inflammation often involve biopsies or imaging methods 
that have low specificity and quantifiabil-
ity. MPI may be a promising quantitative imaging alternative. Previous studies have 
already shown the use of SPIO tracers to target inflammation. SPIOs may be in-
jected intravenously and may be taken up 
at inflammation sites, such as by macro-
phages at active phagocytic sites49,50 or by atherosclerotic plaques.51,52 Previous studies have used MR imaging to detect 
the SPIOns for inflammation tracking.49,50,53,54 However, with high magnetic susceptibility, SPIOs cause a decrease in signal intensity, which could often be confused with signal voids from bone, air bub-
bles, susceptibility blowouts, and imaging artifacts. With the use of 
MPI, SPIOns can be more specifically detected with a higher signal-
to-noise ratio.
Contrast Agent. SPIO contrast agents have previously been developed for MR imaging contrast enhancement. SPIOs are relatively safe for the patient and are biodegradable through the reticuloendothelial system.55 As mentioned previously, 
SPIO agents can achieve long retention times in the body up to 
hours or days when loaded into cells. In PET or SPECT, the 
radioactive tracers have shorter half-lives in the body, espe-
cially for the high-energy probes required in PET. In addition,
due to the short half-life of PET tracers, PET requires a cyclo-
tron on site. In comparison, the SPIOs used in MPI are much more stable and have longer shelf lives with lower production cost.56 There are a number of commercial SPIO agents that 
have either received FDA approval or are in a clinical trial phase57 to serve as potential contrast agents for MPI.58-61 SPIOns have historically been used in humans as MR imaging contrast agents, and 2 tracers, ferucarbotran (Resovist) and ferumoxytol, remain on the market in the European Union/ Asia Pacific and the United States/European Union/Asia Pa-
cific, respectively. These agents have been approved for con-
trast-enhanced MR imaging of the liver/spleen.62,63 MR imaging contrast agents can also be used for MPI. Additionally,
development and synthesis of MPI-tailored contrast agents are an emerging and important field of research.

MPI performance is affected by particle size, size distribution, relaxation properties, surface chemistry, and the environment.\textsuperscript{51,64-66} MPI tracer development has so far been dominated by optimizing for particle core size and size distribution. This is especially important for MPI because particle size directly affects image resolution. We have shown that single-core tracers with core diameters of 26–27 nm provide excellent performance for MPI, and modeling studies predict 25–30 nm as the optimal diameter for iron oxide magnetic nanoparticles, with improved performance for uniform size and optimized magnetic properties.\textsuperscript{67,68} Early research also shows that there is an optimal core size for each operating frequency that is driven by transition of the dominant relaxation effect from Neél to Brownian.\textsuperscript{67,68} Additionally, for in vivo applications, further considerations need to be made for circulation time, biodistribution, and cellular uptake. Thus, new contrast agents more specifically targeted for MPI applications are being actively developed. These new particles are optimized for size and size distributions,\textsuperscript{68,69} quality of crystal structure,\textsuperscript{9} mass sensitivity,\textsuperscript{67} high stability,\textsuperscript{70} rich harmonic spectrum,\textsuperscript{71} and surface chemistry.\textsuperscript{72-74}

Safety Considerations. The current consensus is that MPI is safe to scale to human sizes. The primary concerns for MPI are the safety of the SPIONs and the safety of the time-varying magnetic fields. SPIONs are considered a low risk to patients and are well-tolerated, with some exceptions. First, large concentrations can lead to decreased cell proliferation.\textsuperscript{75} Second, there have been some cases of moderate-to-severe allergic reactions to injections of SPIONs.\textsuperscript{76-78}

There is comparatively less risk in the magnetic fields used by MPI, which is governed by the same limits to peripheral nerve stimulation and specific absorption rate that are seen in MR imaging. In a human subject study, it was found that the safe limit for peripheral nerve stimulation and the specific absorption rate in the chest is about 7 mT, between 25 and 50 kHz.\textsuperscript{79} Cardiac stimulation and peripheral nerve stimulation will not be a limitation for clinical MPI systems.\textsuperscript{79-81} In addition, for applications in which guidewires and catheters are used, heating of the equipment is also a potential concern.\textsuperscript{82}

Practical Considerations. The hardware complexity of MPI is comparable with that of MR imaging. One of the difficult engineering tasks is while MR imaging requires a parts-per-million accurate main magnetic field, MPI requires a parts-per-million accurate sinusoidal drive field.\textsuperscript{83} Both techniques require real-time control of magnetic fields and involve pulse sequences and reconstruction algorithms. In contrast to MR imaging, however, MPI scanning and imaging are straightforward, and we have not found that specialized training is required to acquire or interpret MPI. MPI contrast agents are widely available, easy to handle, and less expensive than commonly used radioactive probes. Like nuclear medicine, it can be helpful to have structural information with which to overlay MPI, and we frequently coregister MPI with CT and MR imaging. Thus, construction of hybrid systems to ease coregistration with anatomic images may be desirable in the future.

CONCLUSIONS

MPI is a novel, promising imaging technique for sensitive, quantitative, and high-resolution in vivo imaging. Preliminary animal studies have shown promising applications, including vascular imaging, oncology imaging, cell tracking, and inflammation imaging. Much development work is being done to further improve imaging design, tracer design, and imaging protocols. With these improvements and the upcoming development of human-sized scanners, MPI has the potential to become a widely adopted clinical tool for neuroimaging.

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