

Neuroscience and Psychiatry

Neuromelanin-Sensitive Magnetic Resonance Imaging as a Proxy Marker for Catecholamine Function in Psychiatry

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The catecholamine neuromodulators dopamine and norepinephrine play key roles in cognition and psychiatric pathophysiology. Much of the evidence for this comes from human studies using positron emission tomography (PET), which allows direct, *in vivo* measurement of aspects of catecholamine function, such as synthesis or transmission. However, the invasiveness and high degree of specialization associated with PET limit its applicability for clinical use and research, especially in pediatric populations and repeated, longitudinal assessments of illness course and treatment response. This underscores the need for biomarkers that, like PET-based measures, reflect neurobiological processes relevant to illnesses and treatments but are more scalable and easily acquired.

Neuromelanin-sensitive magnetic resonance imaging (NM-MRI)¹ may fit these criteria. Neuromelanin (NM) is a dark pigment produced from catecholamine metabolism via iron-dependent oxidation. It accumulates gradually over the life span in granules stored in the body of catecholamine brainstem neurons (Figure). This creates a lasting record of the history of catecholamine turnover, because NM granules, which contain NM-iron complexes alongside proteins and lipids, cannot be removed from neurons; they are only cleared from tissue following cell death in neurodegenerative conditions such as Parkinson disease. The paramagnetic properties of NM-iron complexes make it possible to image them noninvasively using MRI. Neuromelanin-sensitive MRI localizes NM-rich nuclei, such as the dopaminergic substantia nigra (SN) and ventral tegmental area (VTA) and the noradrenergic locus coeruleus (LC), as hyperintense regions through a combination of T1 effects and direct or indirect magnetization transfer effects, in gradient-echo sequences with a magnetization-transfer pulse or turbo-spin-echo sequences, respectively.² Specifically, paramagnetic melanin-iron complexes in synthetic phantoms cause a T1 shortening that reduces magnetization-transfer effects and is thought to underlie the NM-MRI contrast.³ The relative content of macromolecules vs water further influences magnetization transfer and NM-MRI *in vivo*: local NM-MRI contrast in SN-VTA and LC seems to be partly driven by the large size and high water content of catecholamine neurons relative to surrounding white-matter tissues rich in macromolecules.⁴ Despite this nonspecific, still-debated contrast mechanism, NM-MRI hyperintensities in SN-VTA and LC colocalize and correlate with counts of NM-positive catecholamine neurons in postmortem histology.² Furthermore, cell loss in these regions is associated with decreases in the NM-MRI signal, such as those reliably observed in Parkinson disease,⁵ which tend to parallel the loss of catecholamine neuron terminals in target regions in studies imaging transporter density.⁵ However, until recently, it was unclear whether in addition to use as a catecholamine cell loss marker in neurodegenerative conditions, NM-MRI could also be used as a catecholamine function marker in nonneurodegenerative conditions, eg, those most relevant in psychiatry.

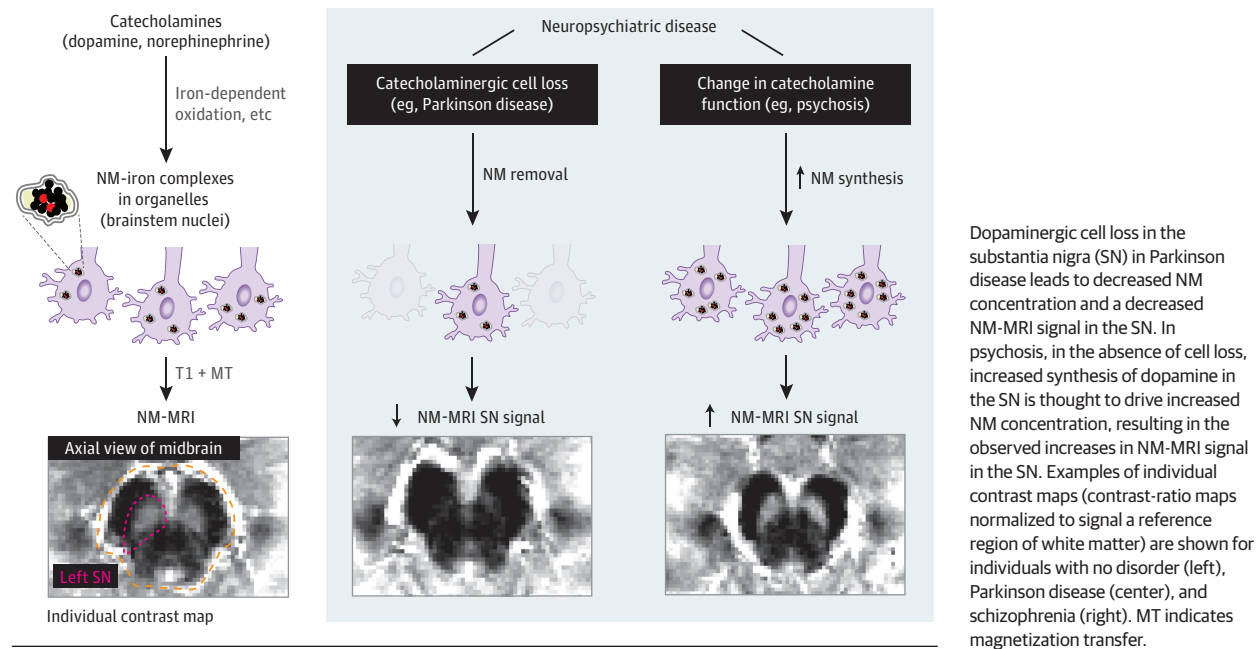
A recent study⁶ showed that NM-MRI is sensitive to variability in NM concentration in postmortem SN tissue, even in the absence of neurodegeneration. Even more critically, it showed a correlation of the SN NM-MRI signal with a PET measure of dopamine function indexing storage and (amphetamine-induced) release capacity of dopamine in the dorsal striatum.⁶ This is consistent with the seminal preclinical finding² that pharmacological induction of dopamine synthesis enhances NM accumulation. The NM-MRI signal also correlated with a functional MRI readout of local neural activity in SN.⁶ Thus, beyond the structural information provided by NM-MRI and its ability to localize NM-rich structures, emerging evidence suggests the intensity of the NM-MRI signal provides quantitative information about the molecular composition of the tissue, in particular NM concentration, which can serve as an indirect proxy for dopamine function.

Mounting evidence further suggests that NM-MRI may capture catecholamine dysfunction in psychiatric disorders without known catecholamine cell loss.^{1,6-9} For example, consistent with the established finding of excess nigrostriatal-dopamine function in psychosis, increased NM-MRI signaling was observed in patients receiving medication^{1,8} and more recently in patients and individuals at clinical high risk who were unmedicated as a function of psychosis severity.⁶ A more detailed topographical characterization of signal patterns across voxels, afforded by an anatomical resolution of NM-MRI up to an order of magnitude higher than PET, further revealed that SN alterations predominate in subregions projecting to the associative dorsal striatum. Other NM-MRI studies have reported alterations of the SN and LC in major depressive disorder^{1,9} and cocaine addiction.⁷

These and other data show the potential of NM-MRI for developing psychiatric biomarkers. One desirable feature of NM-MRI in this regard is its stability. The slow accumulation of NM likely makes NM-MRI stable over relatively long time scales and insensitive to short-term factors. Indeed, NM-MRI shows excellent test-retest reliability,¹⁰ even for voxelwise analyses.⁶ Its stability and noninvasiveness situate NM-MRI well for potential development of risk or prognosis biomarkers, including in pediatric populations, and possibly monitoring treatment response once the time scale of observable NM-MRI changes and their susceptibility to treatment are determined.⁹ If shown to provide a longer-term readout of catecholamine function, NM-MRI could complement acute PET measures in the same way that, in diabetes, glycated hemoglobin measurements complement acute glycemic levels by indexing longer-term glycemic control.

For NM-MRI to fulfill its potential, however, important outstanding questions need to be addressed. First, further work should assess the specificity of NM-MRI to NM concentration vs other factors, such as macromolecule content. Further refinement of NM-MRI sequences may maximize their specificity and resolu-

Figure. Mechanisms and Clinical Applications of Neuromelanin-Sensitive Magnetic Resonance Imaging (NM-MRI)



tion. Second, even in the unlikely case that NM-MRI signal corresponded perfectly to NM concentration, NM concentration will reflect a combination of processes affecting the cytosolic concentration of catecholamines, including synthesis and vesicular transport, and the various steps involved in NM synthesis and accumulation. Assessing the extent of their relative contributions to variability in NM-MRI signal in health and disease, perhaps through triangulation with PET measures, is thus critical. Third, further study is needed regarding the specific association of regional

NM-MRI signals with the function of different catecholamine pathways. Furthermore, the ability of NM-MRI to measure NM concentration in the LC still requires direct confirmation. Finally, development of harmonization protocols will facilitate multisite studies likely required for biomarker development. We hope that this work and proposed future directions will guide further development of NM-MRI as a valuable tool for elucidating disease mechanisms and ultimately informing clinical decisions in psychiatry.

ARTICLE INFORMATION

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