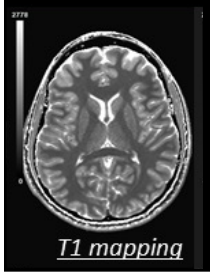
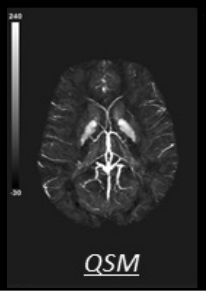
Applications of STAGE Imaging in Neurodegenerative Diseases

E. Mark Haacke, PhD
Prof. Of Radiology, Wayne State University





1

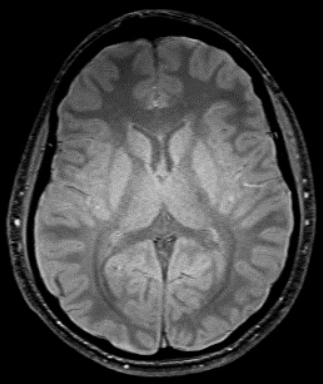
STAGE: Standardization of MR Imaging

- STAGE stands for STrategically Acquired Gradient Echo imaging.
- The STAGE imaging protocol is a rapid, multi-contrast sequence and software approach to gain the maximum amount of information with the highest resolution in the least amount of time.
- STAGE provides 15 pieces of information, 8 qualitative/7 quantitative.
- Depending on the resolution, echo times and repeat times chosen, ***STAGE can be run in 4-6 minutes clinically*** for 2mm or 6-9 minutes for 1.34mm thick slices with an in-plane resolution of 0.67 x $1mm^2$.

2

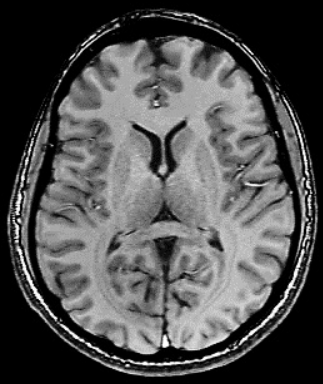
Structural STAGE using ME SWI

SPIN DENSITY WEIGHTED



A: FA=6°, TE=7.5

T1 WEIGHTED



B: FA=24°, TE=8.75

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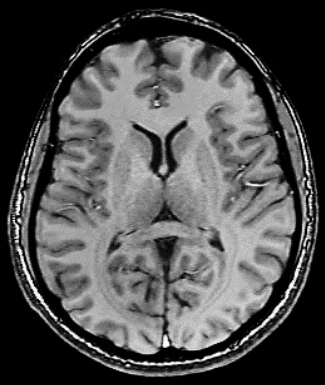
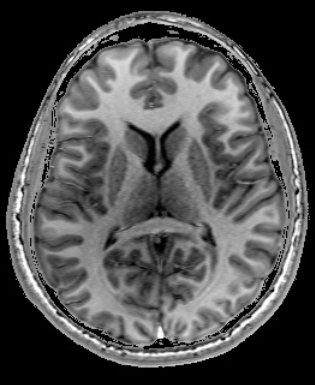
Improved T1W (T1WE) Image using STAGE

T1 WEIGHTED



FA=24°, TE=8.75

IMPROVED T1 WEIGHTED



STAGE T1WE

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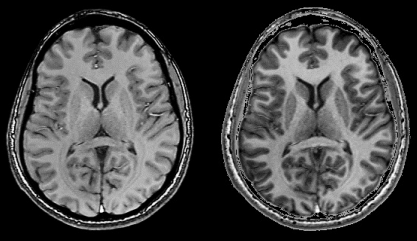
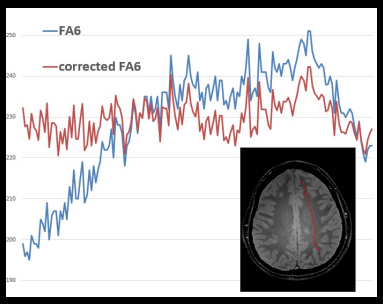
STAGE T1 Weighted Enhanced (T1WE)



A B



A): Conventional T1W (FA=24º).

B): STAGE T1WE: improved image homogeneity and GM/WM contrast.

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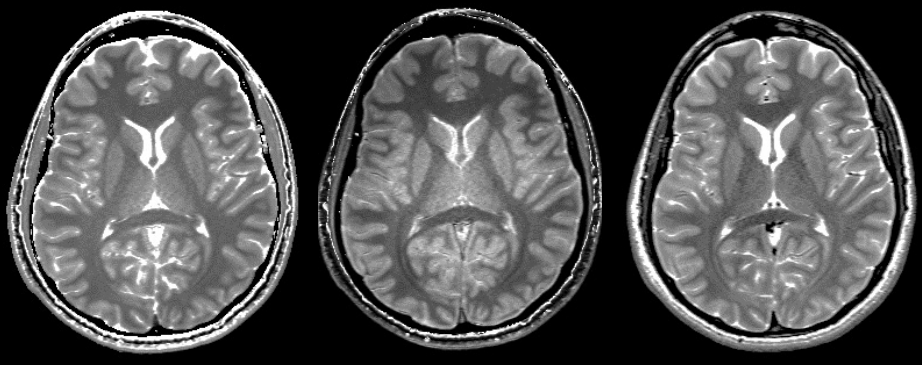
T1 MAP, PD MAP and T2W images



T1 MAP PD MAP T2W (2D T2 TSE)

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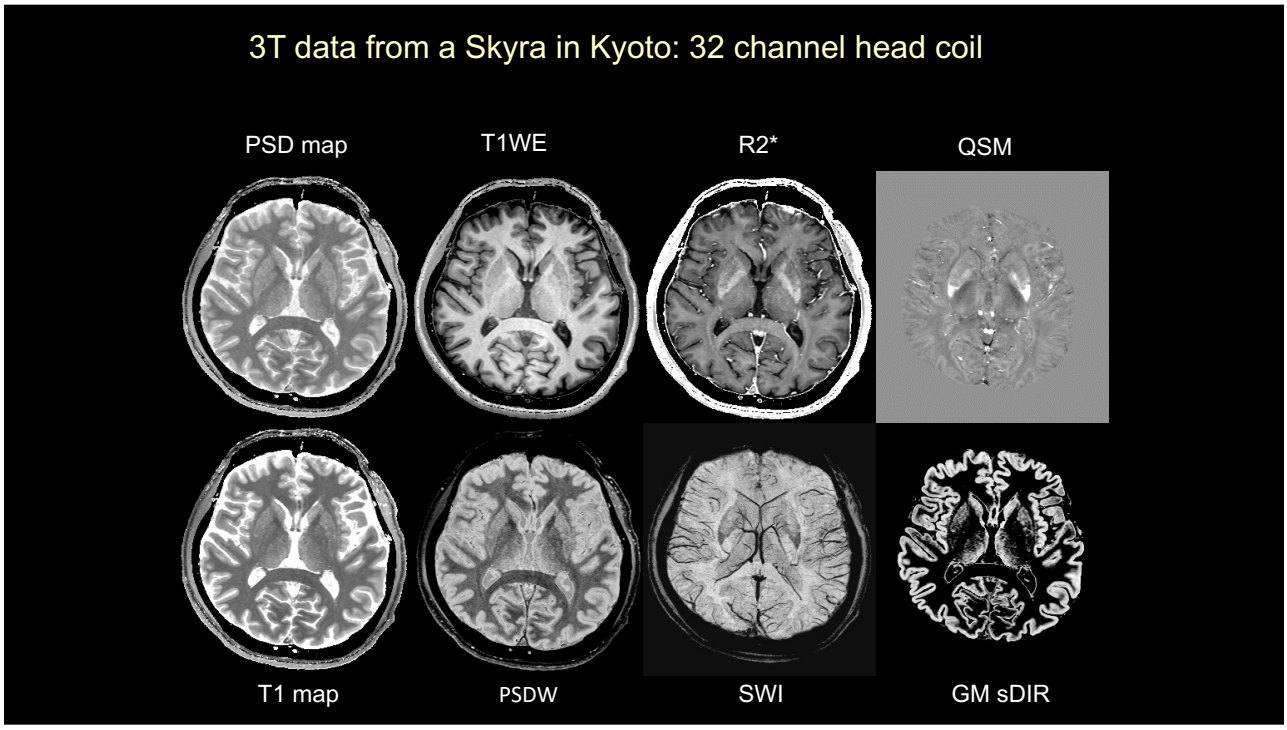
6


3T data from a Skyra in Kyoto: 32 channel head coil
PSD map
T1WE
R2*
QSM
T1 map
PSDW
SWI
GM sDIR

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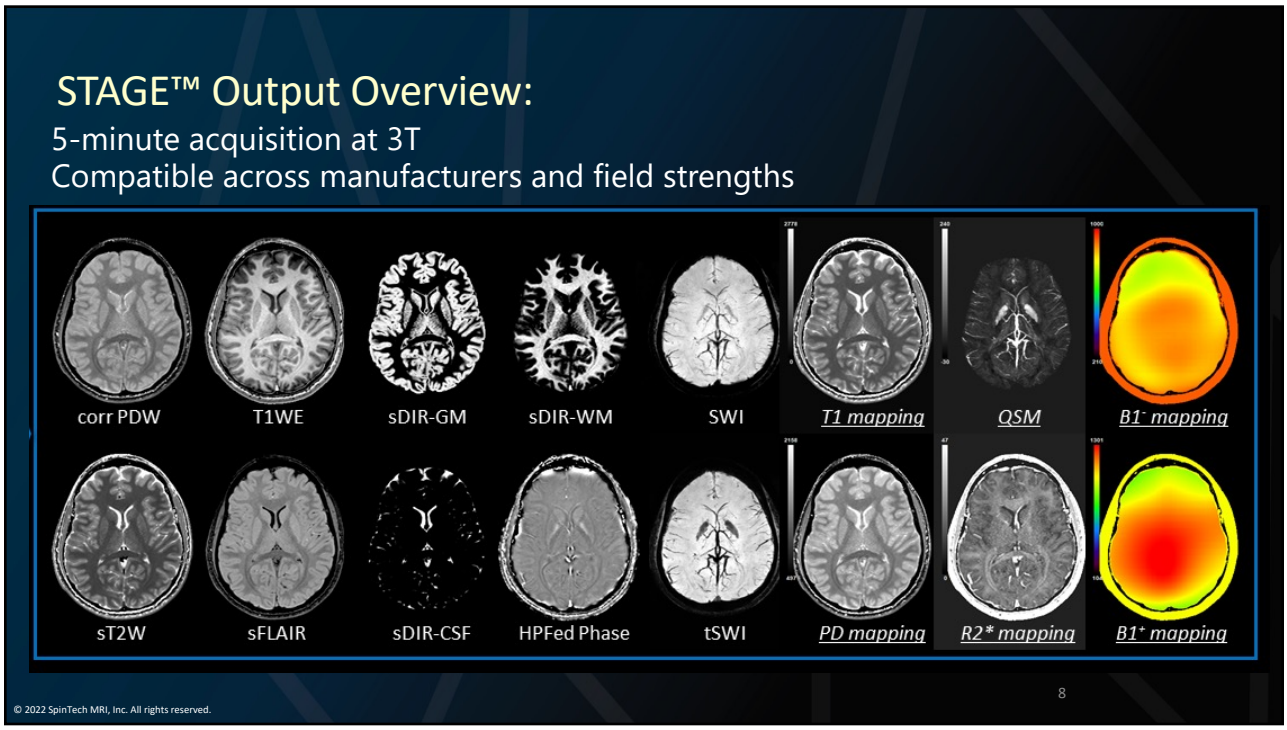
STAGE™ Output Overview:
5-minute acquisition at 3T
Compatible across manufacturers and field strengths
corr PDW
T1WE
sDIR-GM
sDIR-WM
SWI
T1 mapping
QSM
B1⁻ mapping
sT2W
sFLAIR
sDIR-CSF
HPFed Phase
tSWI
PD mapping
R2* mapping
B1⁺ mapping
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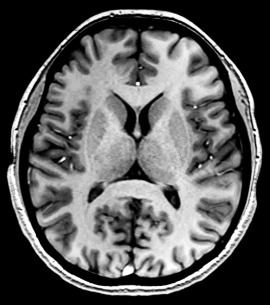
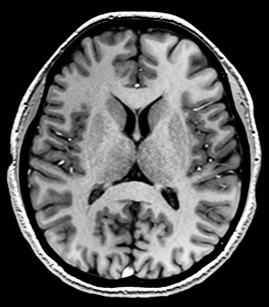
Comparison of 2min, 2mm and 3min, 1.34mm short TR T1W STAGE Protocols: 0.67mm x 1mm in-plane resolution, TE = 5ms

TH=2mm; 2 min per FA



TH=1.34mm; 3 min short TE



According to our experience, the resolution of 0.67mm x 1mm x 1.34mm is an optimal cutoff above which the images appear blurry and below which the images take too long to collect and are much noisier.

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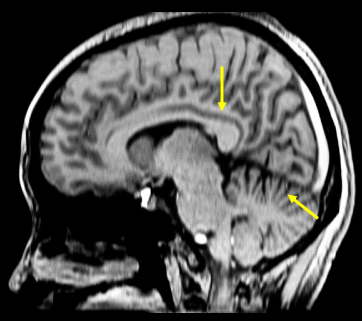
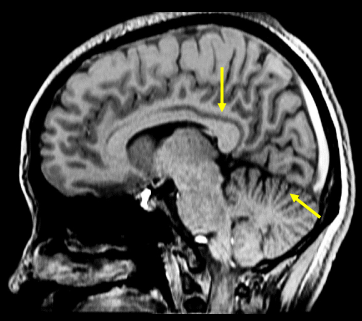
Comparison of 2min and 3min T1 STAGE Protocols: 0.67mm x 1mm in-plane resolution, TE = 5ms

TH=2mm; 2 min per FA



TH=1.34mm; 3 min per FA



After reformatting from the transverse to the sagittal plane, the 2minute 2mm thick images look blurry (although maybe still acceptable for many clinical applications) compared to the 3 minute 1.34mm thick images.

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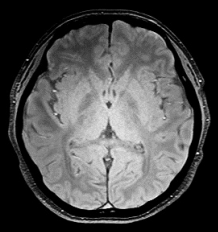
SHORT TR DOUBLE ECHO (5,10ms) HIGH BW STAGE

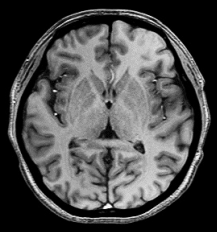
0.67mm x 1mm x 1.34mm – two 3 minute scans

PSDW

T1W

FA 6°, 5ms
1.34mm thick
BW=200Hz/px



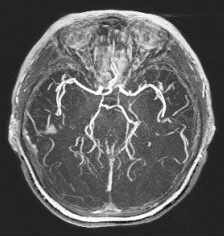


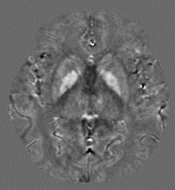
FA20°, 5ms
1.34mm thick
BW=200Hz/px

MRA

QSM

From TEs
5/10ms





From TEs
5/10ms

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TRUE PD MAP
From 3 echo STAGE

0.67mm x 1.0mm
x 1.34mm (3D)

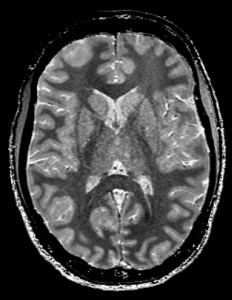
CROWN (Constrained Reconstruction of White Noise) is my answer to enhanced SNR using AI.

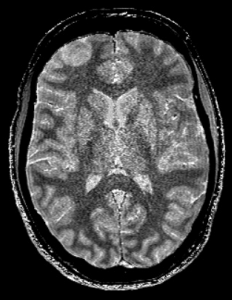
CROWN is self trained algorithmically and needs no further training.

iPAT2
(9min 32sec)

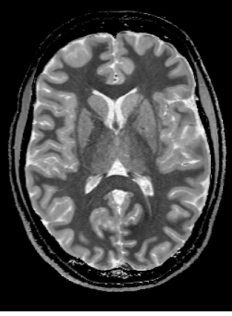
iPAT2x2
(4min 32sec)

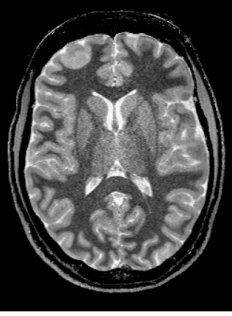
Pre-CROWN





Post-CROWN





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Applications of STAGE to Parkinson's Disease

- Parkinson's disease (PD) is believed to be the second most common neurodegenerative disease in developed countries with the number of cases expected to increase to 12 million by 2040.
- Differentiating between movement disorders can be difficult and take years to properly diagnose.
- These include: idiopathic PD (IPD), Multiple System Atrophy (MSA), Essential Tremor (ET), Progressive Supranuclear Palsy (PSP), Lewy Body with Dementia (LBD), and REM Sleep Behavior Disorder (RBD).
- STAGE offers a comprehensive PD protocol that provides for quantitative and qualitative MR imaging biomarkers representing changes in neuromelanin in the substantia nigra and locus coeruleus as well as the iron content throughout the deep gray matter (DGM) structures using a template based automatic segmentation of the DGM.
- Visualizing the DGM through their iron content can play a key role in deep brain stimulation (DBS) surgical planning for differentiating between the substantia nigra and subthalamic nucleus.

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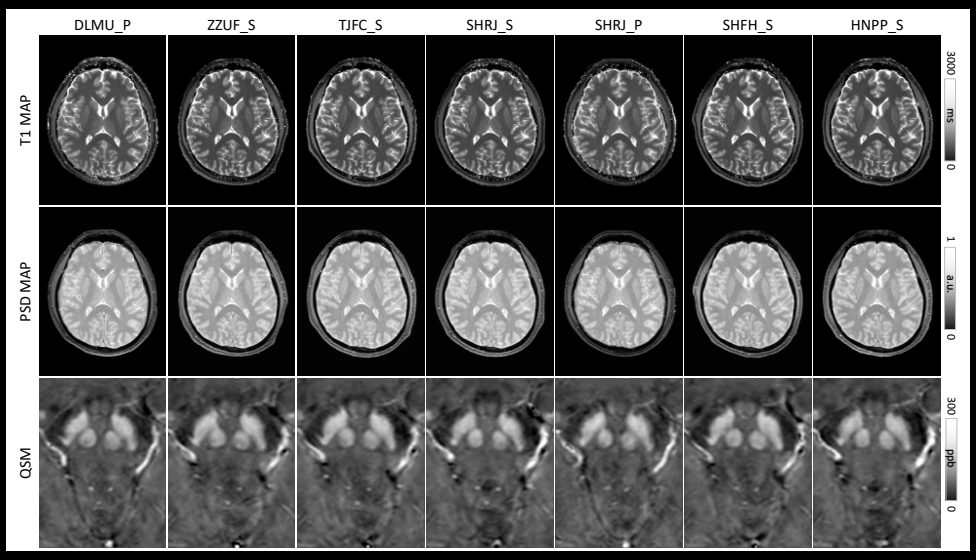
STAGE Across 7 Sites and 2 Manufacturers



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Specific indications of STAGE for PD

- **PSD:** Gives quantitative water content within white matter (WM) lesions.
- **PSD:** May provide a means to monitor neuromelanin (NM) without MTC.
- **True SWI:** Shows the nigrosome-1 (N1) sign which is key for interpreting NM degeneration and distinguishing PD from ET and healthy controls.
- **QSM:** Provides iron content for all the deep gray matter, including the midbrain.
- **QSM:** Makes it possible to delineate the SN from the STN.
- **sDIR images:** Map whole brain CSF, GM and WM atrophy longitudinally.
- **T1maps:** Quantify T1 and relate this tissue contrast.

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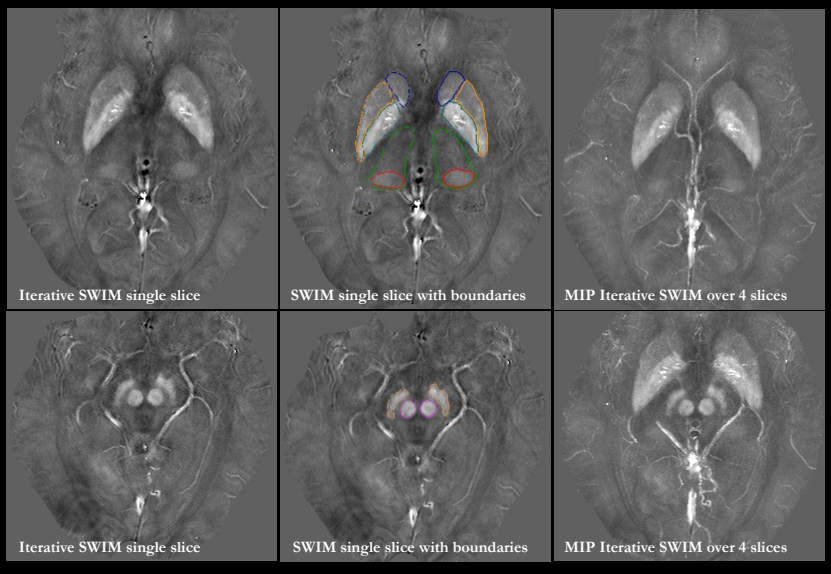
QSM of the Midbrain and Basal Ganglia for a Normal Subject



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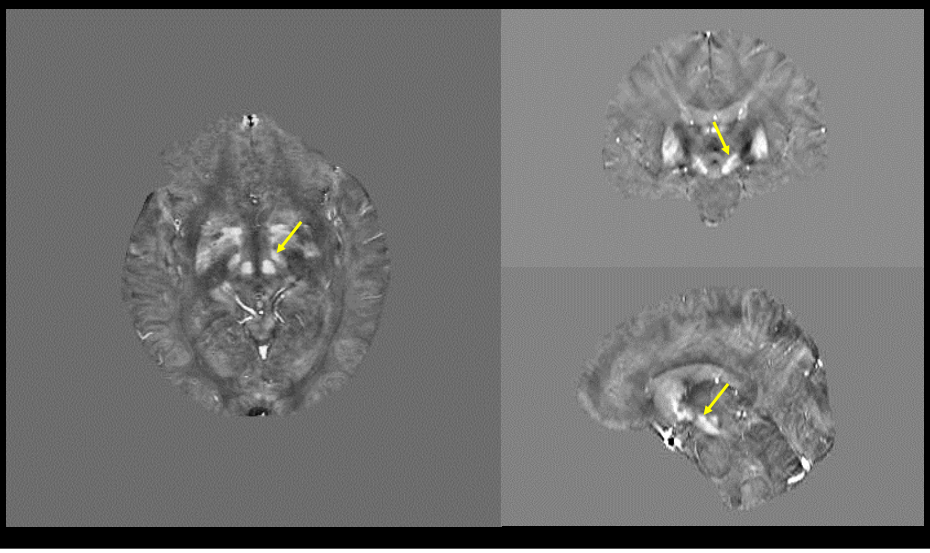
3D view of the Subthalamic Nucleus on QSM:

Visualizing the deep gray matter and the subthalamic nucleus in particular is vitally important for DBS planning



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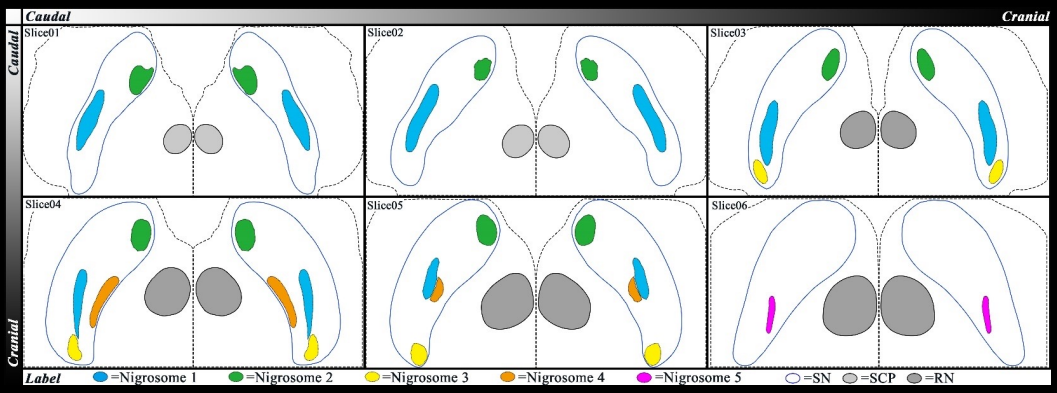
The N1-N5 nigrosome neuromelanin territories



- 60% of NM dopaminergic neurons are in the SN (Calbindin positive), another 40% are in the N1-N5 regions
- The N1-N4 structures are located below the rostral exit of the third cranial nerve.
- The N1 structure is larger, located posteromedially, can cover up to 5 mm in length and is adjacent to N3 posteriorly.
- When NM-MRI slice thickness is 1.34mm, N1 structures can be observed in 2-3 slices caudally.
- In PD, the severity and order of loss of NM occur as follows: N1>N2>N4>N3>N5.

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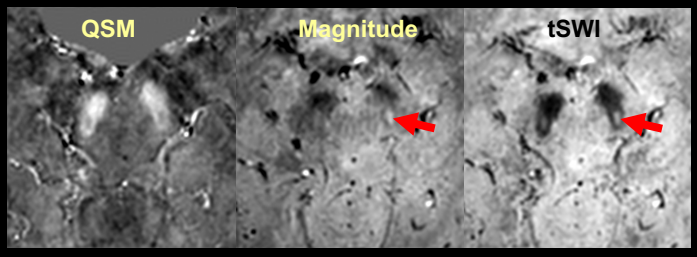
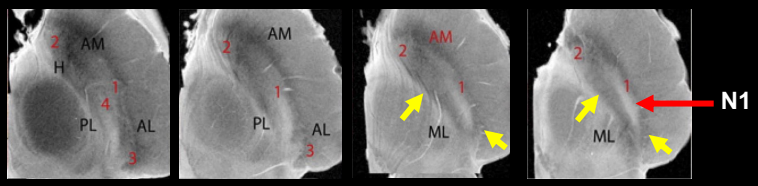
Imaging the swallowtail or N1 sign

tSWI most consistently depicts the N1 territory



SWI 0.67mm isotropic resolution



60% of NM dopaminergic neurons are in the SN (Calbindin positive), another 40% are in the N1-N5 regions

L.A. Massey et al. NeuroImage: Clinical 13:154;2017

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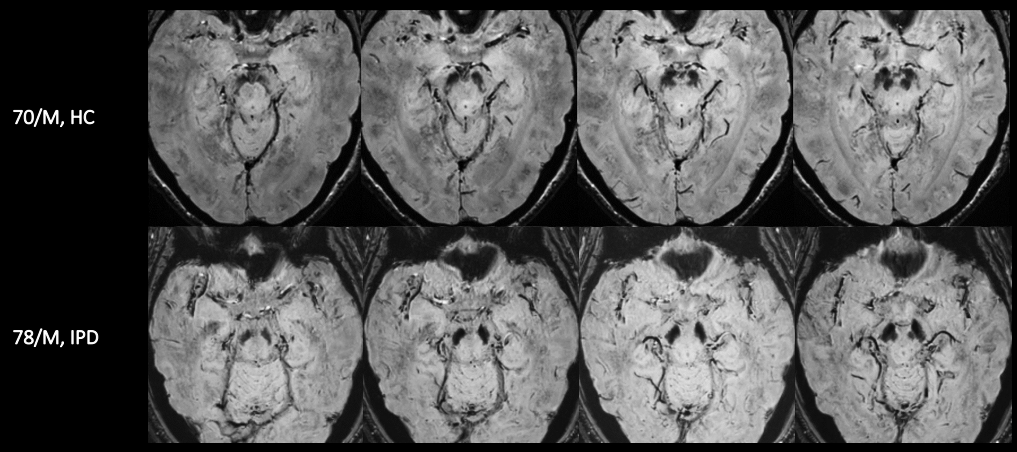
N1 sign in HC vs. IPD

Presence and absence of the N1 sign in HC and PD subjects.



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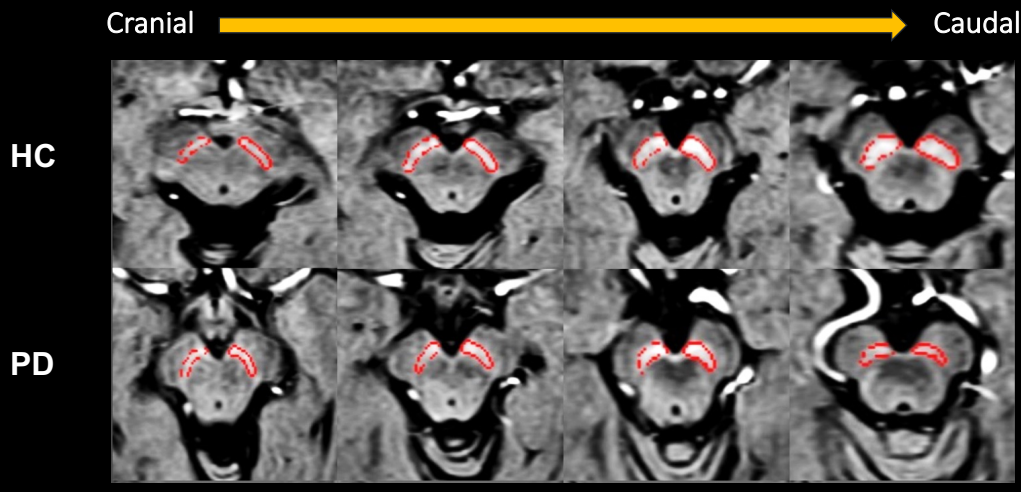
NM, iron and their overlap in the SN using MTC STAGE



3D regions of interest depicting putative NM content (red) on four consecutive slices on MTC data for a healthy control (61y), and a Parkinson's disease (PD) patient (64y)

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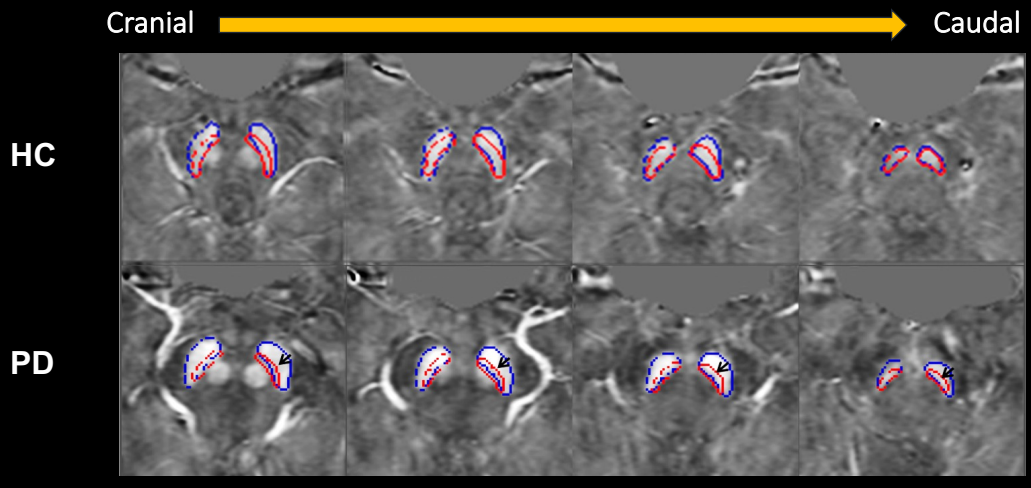
NM, iron and their overlap in the SN using MTC STAGE



3D ROIs depicting putative NM content (red) from MTC data superimposed on the corresponding MTC-QSM data with the SN (blue) already traced on them for a HC (66y), and a PD patient (66y).

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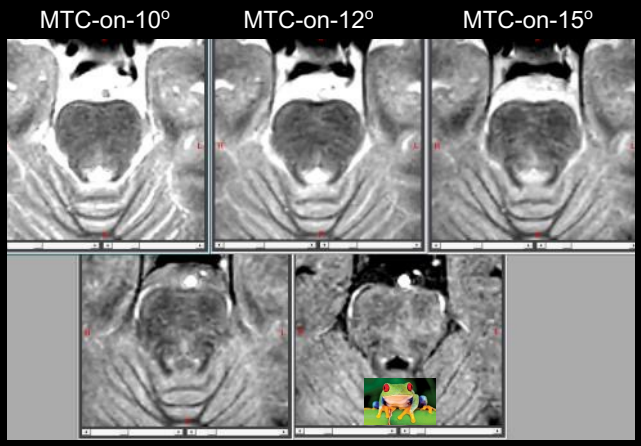
The Choice of Optimal FA in MTC Imaging Using STAGE



The ability to optimize the locus coeruleus visibility depends on understanding the tissue properties and the system capabilities.

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Neuromelanin in the LC seen with "The Red Eyed Bamboo Tree Frog Sign" or the "Frog Eyes" sign

Liu Y, Li J, He N, Chen Y, Jin Z, Yan F, Haacke EM.

Optimizing neuromelanin contrast in the substantia nigra and locus coeruleus using a magnetization transfer contrast prepared 3D gradient recalled echo sequence.

Neuroimage. 2020:218:116935. doi: 10.1016/j.neuroimage.2020.116935. PMID: 32413460.

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STAGE Imaging of Multiple Sclerosis: MS Pathology

- MS is a disease of uncertain etiology with a wide range of symptoms including but not limited to:

Cognitive decline	brain fog	incontinence
loss of muscle coordination	emotional disturbance	loss of ambulation

- MS is diagnosed using MRI via the McDonald criteria involving dissemination in space and time.
- Peri-ventricular, peri-venous lesions are seen throughout the brain and spinal cord, affecting the central nervous system.
- Lesions are typically identified in T2 FLAIR or T1W images, due to their inflammatory nature.
- MS is still thought to be auto-immune in nature, but may in fact be related to:
  - having had Epstein-Barr virus, and
  - a disruption of the endothelium leading to extravasation of lymphocytes.
- Chronic lesions can lead to loss of blood supply and tissue necrosis.

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Challenges in Imaging MS

- MS has long been a difficult syndrome to diagnose.
- It has many mimics all showing white matter lesions.
- Some can be separated using the 50% central vein sign rule.
- There may be substantial discordance between conventional MRI findings and clinical syndrome, therefore additional information is needed from imaging examinations
- Recent progress suggests it is possible to differentiate inflammatory from demyelinating inflammatory lesions. The ability to distinguish these states may provide an opportunity for improved therapy.

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Specific indications of STAGE for MS

A) PSD: Gives quantitative water content within white matter (WM) lesions.
B) PSD: At long TE, this provides clear images of WM comparable to FLAIR.
C) T1WE: Shows strong GM/WM contrast, dark for lesions with high water content.
D) SWI/SWI-FLAIR: Shows the central vein sign that is key for interpreting MS.
E) QSM: Provides iron content in the deep gray matter.
F) QSM: Increased susceptibility in WM lesions represents demyelination.
G) sDIR images: Map whole brain CSF, GM and WM atrophy longitudinally.
H) T1maps: Quantify T1 and are used to help produce CROWN images.

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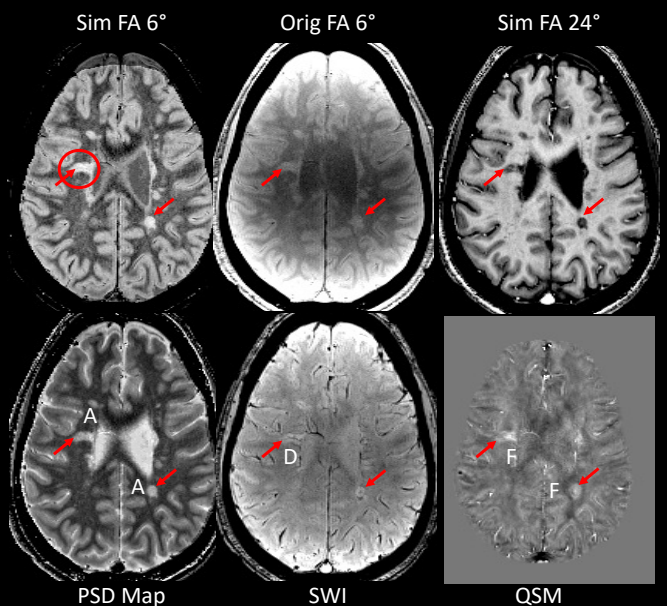
Overview of STAGE results from an MS patient

0.67×1×2 mm^3 (interpolated to 0.67×0.67×2 mm^3)

NAGM has water content (PSD ≈ 0.80 to 0.84)
Images courtesy of Sagar Buch.

- The lesion marked (red circle) and the one at 9 o'clock have abnormally high water content (PSD ≈ 0.92).
- These lesions will look particularly dark on T1W scans because of their high water content relative to the usual MS lesions.



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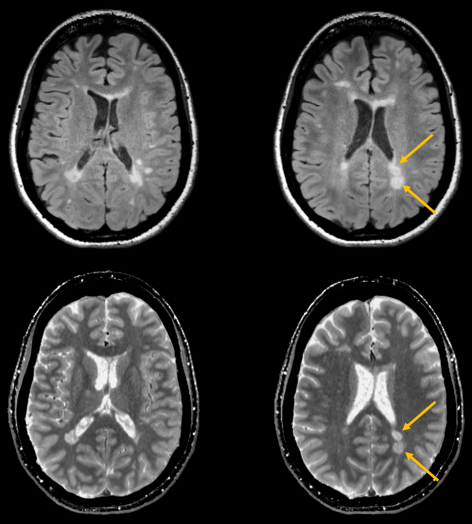
STAGE PSD MAP:
FLAIR versus water content (PSD)

FLAIR

PSD



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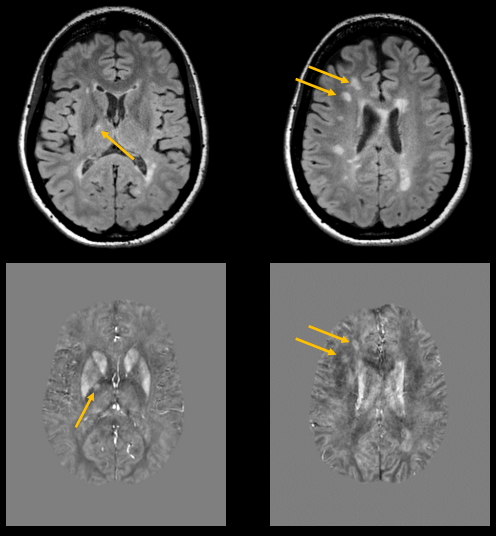
STAGE PSD MAP:
FLAIR versus susceptibility

FLAIR

QSM



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MS MRI Future Directions

- Using STAGE for rapid tissue property mapping
- Mapping water content of lesions
- Measuring venous abnormalities with MICRO
- Measuring flow deficits in the medullary veins
- Measuring flow deficits in the ependymal veins
- Mapping inflammation at the vessel wall pre WMH
- Differentiating demyelinating lesions from purely inflammatory lesions.

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STAGE Summary

- 4-6 minute 3D whole brain acquisition at 3T
- Enhanced image contrast with quantitative outputs
- Manufacturer agnostic across field strengths
- Standardized data across systems
- Uniform images for all coil types and field strengths
- New biomarkers for better understanding MS and PD

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