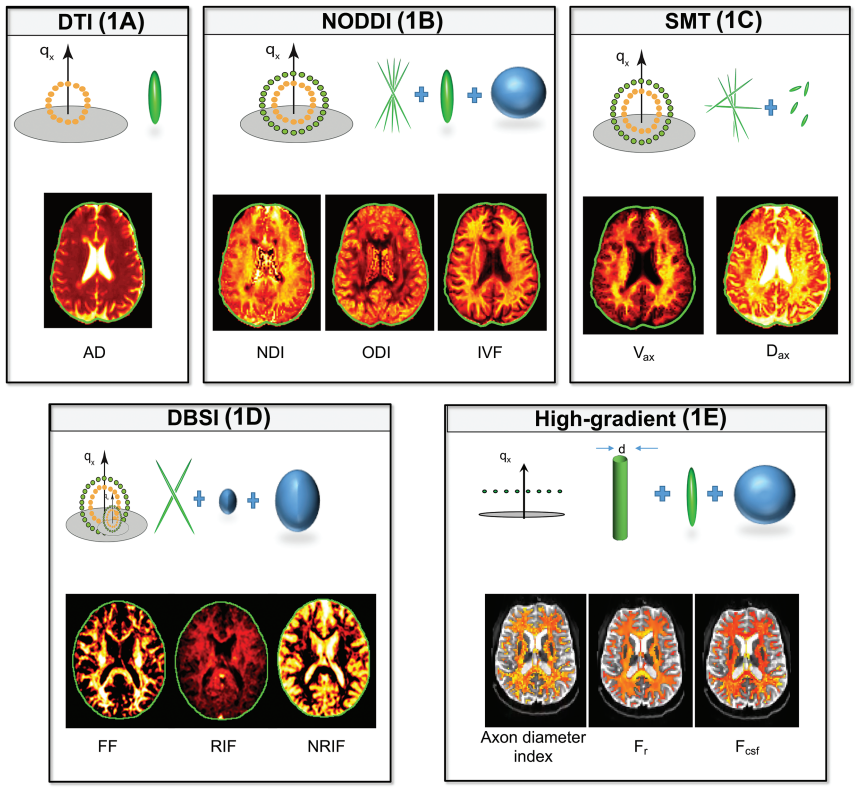

ON-LINE FIGURE. Diffusion-based MR imaging methods. *A*, DTI assumes that signals from each single imaging voxel arise from a single compartment with diffusion modeled as a 3D Gaussian process (ie, a single tensor). *B*, NODDI assumes that signals arise from 3 tissue compartments, ie, axons/dendrites described as sticks (with zero radius) oriented with a spherical Watson distribution, extracellular hindered diffusion described as a single anisotropic tensor, and free water diffusion described as an isotropic tensor. *C*, Multicompartment microscopic diffusion MR imaging with SMT assumes that signals arise from 2 tissue compartments, ie, axons/dendrites described as sticks oriented in arbitrary directions and hindered extracellular diffusion described as anisotropic tensors oriented in arbitrary directions (Part D, courtesy of Drs Anne Cross, Sheng-Kwei Song, and Peng Sun at Washington University). DBSI assumes that signals arise from 3 tissue compartments, ie, anisotropic compartments with an orientation distribution function such as axons, an isotropic restricted compartment such as cells, and an isotropic unrestricted compartment such as CSF (Part E, courtesy of Drs Susie Huang and Eric Klawiter at Harvard University). The high-gradient diffusion imaging assumes that signals arise from 3 compartments, ie, cylindric parallel axons with a finite axon diameter, extracellular space described as an anisotropic tensor, and isotropic free water. qx indicates the directionality and magnitude of diffusion weighting; F_{csf}, free water fraction; F_r, restricted fraction; RIF, restricted isotropic diffusion tensor fraction; NRIF, nonrestricted isotropic diffusion tensor fraction.

On-line Table 1: MR imaging indices derived from different diffusion-based MR imaging models as described in the literature with different nomenclature with their biologic proxy

MR Imaging Model	Index	Biologic Proxy
NODDI	NDI, V_{ic}, V_{in}, f_{icvf}	Intracellular volume fraction (volume of a voxel occupied by intra-axonal water)
	ODI	Neurite orientation dispersion index (represents the degree of structural orientation coherence)
	IVF, V_{iso}, f_{iso}	Isotropic volume fraction (volume of a voxel occupied by intra-axonal water)
SMT	V_{ax}	Intra-axonal volume fraction (volume of a voxel occupied by extra-axonal water)
	D_{ax}	Intra-axonal diffusivity, along the axis (represents the degree of water molecule movement parallel to the axons)
DBSI	RD	Radial diffusivity (represents the degree of water molecule movement perpendicular to the axial diffusion direction)
	AD	Axial diffusivity (represents the degree of water molecule movement parallel to the axial diffusion direction)
	FF	Fiber fraction (represents the volume of a voxel occupied by axonal fiber tracts)
	FA	Fractional anisotropy (represents the measure of directionality of water diffusion)
HGD	Axon diameter	Represents the volume-weighted mean axon diameter
	F_r	Restricted fraction, represents the axonal volume fraction in each voxel
	F_{csf}	Free water fraction, represents the fraction of free water in each voxel
	Axon density	Represents the axon density in the plane perpendicular to the axon direction

Note:—FA indicates fractional anisotropy; HGD, High-Gradient Diffusion MR Imaging; F_r, restricted fraction; F_{csf}, free water fraction.

On-line Table 2: Correlations between clinical and imaging features of disease and multicompartment diffusion MR imaging–derived metrics

MR Imaging Model	Study	Sensitivity to Tissue Injury and Clinical Metrics
NODDI	Granberg et al[14] (26 patients with stable relapsing-remitting MS [≤5 years of disease] and 24 healthy controls)	Higher values of ODI ($P < .001$) in WM lesions compared with normal-appearing WM, lower values of NDI in WM lesions compared with normal-appearing WM ($P < .001$) and in normal-appearing WM compared with normal WM of healthy controls ($P < .05$)
		ODI in the left primary motor and somatosensory cortices was associated with the Expanded Disability Status Scale[19] score
	Spanò et al[18] (15 patients with relapsing-remitting [2–18 years of disease], 15 patients with secondary-progressive [10–30 years of disease], and 20 healthy controls)	Higher values of ODI ($P < .05$) in several cortical and subcortical WM and GM areas ($P < .05$) compared with healthy controls
		ODI values in the right thalamus were associated with disability on the MS Functional Composite score[44] in patients with secondary-progressive MS ($r = -0.74$, $P < .01$)
		ODI measured in cortical and subcortical WM correlated with disability on the MS Functional Composite score and the Expanded Disability Status Scale in patients with both secondary-progressive ($r = -0.69$, $P < .01$, and $r = 0.65$, $P < .01$, respectively) and relapsing-remitting MS ($r = -0.45$, $P = .05$, and $r = 0.49$, $P < .05$, respectively)
		NDI measured in cortical and subcortical WM correlated with disability on the MS Functional Composite score ($r = 0.63$, $P = .01$) and the Expanded Disability Status Scale ($r = -0.59$, $P < .05$) only in patients with secondary-progressive MS
	Schneider et al[15] (5 patients with stable relapsing-remitting MS [6–16 years of disease] and 5 healthy controls)	Lower values ($P < .01$) of NDI and ODI were observed in WM lesions compared with normal-appearing WM and in normal-appearing WM compared with normal WM ($P < .05$ for ODI only)
	Chen et al[12] (18 patients with relapsing-remitting MS [6–18 years of disease] and 9 healthy controls)	Lower values ($P < .05$) of NDI and ODI and higher values of IVF ($P < .01$) in chronic black holes compared with WM-lesions and in the latter versus normal-appearing white matter (for NDI only, $P < .001$)
	Mustafi et al[16] (4 patients with relapsing-remitting MS, 1 with secondary-progressive MS, and 1 with clinically isolated syndrome; 1–20 years of disease)	Lower values of V_{ic} in lesions compared with perilesional tissue ($P < .01$), perilesional tissue compared with normal-appearing WM ($P < .05$), and the latter compared with lesions ($P < .01$)
	By et al[13] (6 patients with relapsing-remitting MS [1–17 years of disease] and 8 healthy controls)	Higher values of ODI ($P < .001$) in spinal cord lesions compared with spinal cord normal-appearing WM
		Higher values of ODI ($P \leq .01$) and lower values of NDI ($P \leq .01$) in spinal cord normal-appearing WM and normal-appearing GM compared with healthy controls
	Collorone et al[17] (28 patients with relapsing-remitting MS [3–13 years of disease] and 20 healthy controls)	Lower values of NDI ($P < .05$) in brain and spinal cord normal-appearing WM compared with healthy controls
		NDI values measured in the normal-appearing WM of the spinal cord showed an association with the Expanded Disability Status Scale score ($r = -0.46$, $P < .05$)
SMT	Bagnato et al[22] (18 patients with relapsing-remitting MS, 3 with secondary-progressive MS [6–18 years of disease], and 9 healthy controls)	In brains, V_{ax} ($P < .001$) and AD ($P < .001$) differed between chronic black holes and WM-lesions as well as between WM-lesions and normal-appearing WM ($P < .001$); D_{ax} differed between chronic black holes and WM-lesions ($P < .01$), but not between WM-lesions and normal-appearing WM
		A trend between V_{ax} measured in WM-lesions and the Timed 25-Foot Walk test scores ($r = -0.42$, $P = .07$)

Continued on next page

On-line Table 2: Continued

MR Imaging Model	Study	Sensitivity to Tissue Injury and Clinical Metrics
	By et al[23] (6 patients with relapsing-remitting MS [1–17 years of disease] and 8 healthy controls)	In spinal cords, decreased values of V_{ax} ($P < .05$) were observed in WM lesions compared with normal-appearing WM and in normal-appearing WM compared with normal WM of healthy controls ($P < .05$); nearly significant decreased D_{ax} was also observed in WM lesions ($P = .08$) and normal-appearing WM ($P = .05$) compared with normal WM of healthy controls
HGD	Huang et al[37] (23 patients with relapsing-remitting MS [3–17 years of disease], 7 with secondary-progressive MS [3–17 years of disease], and 23 healthy controls)	Increased axonal diameters ($P < .05$), decreased ($P = .01$) restricted volume fraction (and axonal density) in WM lesions compared with the normal-appearing WM of the corpus callosum, increased axonal diameters ($P < .01$) and decreased restricted volume fraction ($P < .05$) and axonal density ($P = .001$) in normal-appearing WM in patients with MS and healthy controls, increases in axonal diameters ($P < .01$) and decreases in axonal density ($P < .01$) in the normal-appearing WM of patients with secondary-progressive MS compared with patients with relapsing-remitting MS Correlations ($P \leq .05$) were seen between axonal diameters and the Expanded Disability Status Scale score ($r = 0.56$), the MS Functional Composite score ($r = -0.49$), the Symbol Digit Modalities Test score ($r = -0.59$), and the Brief Visuospatial Memory Test score ($r = -0.63$).

Note:—HGD indicates High-Gradient Diffusion MR Imaging.