ON-LINE APPENDIX

Detailed Search Strategies and Eligibility Criteria

MEDLINE. Spinocerebellar ataxia* OR SCA OR autosomal dominant cerebellar ataxia* AND Magnetic Resonance Imaging OR MR imaging OR NMR OR spectroscopy OR volumetry OR morphometry OR gray matter atrophy OR regional atrophy OR white matter atrophy OR DTI OR tractography OR diffusion tensor.

Cochrane. Spinocerebellar ataxia AND Magnetic Resonance Imaging.

LILACS. MR imaging OR MR imaging AND SCA OR spinocerebellar ataxia.

Eligibility Criteria

First phase (articles reviewed at the abstract).

Inclusion Criteria

Population. 1) Symptomatic individuals with a molecular diagnosis of a dominant PolyQ-SCA (SCA1, SCA2, SCA3, SCA6, and SCA7); 2) asymptomatic carriers of dominant PolyQ-SCA mutation; 3) ≥20 individuals per group in symptomatic patients; and 4) ≥10 individuals per group in asymptomatic carriers.

Exclusion Criteria

1) Study design: case report and review studies

2) Absence of molecular diagnosis of PolyQ-SCA mutations

3) Fewer than 20 individuals per group in symptomatic patients

4) Fewer than 10 individuals per group in asymptomatic carriers.

Second Phase

Inclusion Criteria. 1) Population: symptomatic individuals with a molecular diagnosis of a dominant PolyQ-SCA (SCA1, SCA2, SCA3, SCA6, and SCA7); asymptomatic carriers of dominant PolyQ-SCA mutation; ≥20 individuals per group in symptomatic patients; ≥10 individuals per group in asymptomatic carriers; the group of patients representing >5 different families; prospective studies with ≥15 individuals and studies on presymptomatic individuals with ≥10 subjects; at least 1 of the following about studied subjects: age, age at disease onset, CAG repeat length on the expanded allele, or scores obtained from a validated ataxia scale should be reported.

2) Study design: systematic review, randomized clinical trial, cohort, case-control, or case series

3) Equipment and imaging protocols

4) CNS MR imaging with ≥1.5T field

5) Image processing by using volumetric analysis, MR spectroscopy, diffusion tensor imaging, tractography, or other MR imaging quantitative techniques.

Exclusion Criteria. 1) Study design: case reports or reviews, other than systematic; 2) population: absence of a healthy control group; <20 individuals per group; group of patients representing <5 different families; and 3) equipment and imaging protocols: qualitative CNS MR imaging analysis, neuroimaging studies other than MR imaging, and MR imaging with <1.5T field.

On-line Table 1: Main infratentorial findings

Study	SCA	No.		Cerebellum						Brain Stem				Cervical Spine
				Total	Hemispheres	Vermis	Dentate	Peduncle	Other Nuclei	Total	Midbrain	Pons	Medulla Oblongata	
VBM														
Della Nave et al, 2008[18] (SPM2; 1.5T); cross-sectional	SCA2	20	GM	NA	↓ [a,b] ICARS: $R = -0.53$	↓ [a,b] ICARS: $R = -0.53$	NA	NA	NA	NA	NA	NA	NA	NA
			WM		↓ [a,b] ICARS: $R = -0.54$	=	NA	↓ [a,b] ICARS: $R = -0.54$	NA	NA	↓ [a,b] ICARS: $R = -0.54$	↓ [a,b] ICARS: $R = -0.54$	=	NA
Schulz et al, 2010[29] (SPM5 and Toolbox; 1.5T); cross-sectional	SCA1	48	GM	NA	↓	↓	↓	NA	NA	↓	NA	=	=	NA
			WM	NA	↓	↓	NA	↓	NA	↓	↓	↓	=	NA
	SCA3/MJD	24	GM	NA	↓	↓	=	NA	NA	NA	NA	=	=	NA
			WM	NA	↓	↓ [e]	=	↓	NA	↓	↓	↓	=	NA
D'Abreu et al, 2012[16] (SPM2, 2T); cross-sectional	SCA3/MJD	45	GM	↓ [a] ICARS: $R = 0.730$	=	↓ [a] ICARS: $R = 0.730$	NA	NA	NA	↓	↓	↓	↓	NA
			WM	↓	↓	=	NA	=	NA	=	=	=	=	NA
D'Abreu et al, 2012[16] (SPM2, 2T); longitudinal data; follow-up: 1 yr	SCA3/MJD	45	GM	↓	=	=	=	=	=	=	=	=	=	NA
			WM	=	=	=	=	=	=	=	=	=	=	NA
Guimarães, et al, 2013[24] (SPM8, 3T); cross-sectional	SCA3/MJD	38	GM	NA	↓ [a] SARA: R = NA	↓	=	=	↓	=	=	↓ [a] SARA: R = NA	↓	NA
			WM	NA	↓ [a] DD: R = NA; SARA: R = NA; ICARS: R = NA	↓ [a] DD: R = NA; SARA: R = NA; ICARS: R = NA	↓ [a] DD: R = NA	↓	↓ [a] DD: R = NA	↓ [a] DD: R = NA; SARA: NA; ICARS: R = NA	=	↓ [a] DD: R = NA	↓ [a] DD: R = NA	NA
Reetz et al, 2013[17] (SPM8; 1.5T)[a]; longitudinal data; follow-up: 2 yr	SCA 1	37		↓ [a] CAG_{exp}: $R = -0.480$	↓	=	=	=	=	↓	↓	↓ [a] CAG_{exp}, $R = -0.470$	=	NA
	SCA3/MJD	19		=	=	=	=	=	=	=	=	=	=	NA
Surface-based analysis														
de Rezende et al, 2015[32] (FreeSurfer, 3T); cross-sectional	SCA3/MJD	49	GM	↓	NA	NA	NA	NA	NA	↓ [a] SARA: $R = -0.581$	NA	NA	NA	NA
			WM	↓ [a] DD: $R = 0.543$	NA	NA	NA	NA	NA	↓ [a] SARA: $R = -0.581$	NA	NA	NA	NA
Hernandez-Castillo et al, 2015[28] (FSL; 3T)	SCA7	24	GM	NA	↓ [a] SARA: $R = -(0.640–0.817)$	NA	NA	NA	NA	=	=	=	=	NA
Semiautomatized volumetric analysis														
Schulz et al, 2010[29] (1.5T); cross-sectional	SCA1	48		↓	↓	↓	NA	NA	NA	↓ [a] SARA: $R = -0.447$	=	↓ [a] DD: $R = -0.311$; SARA: $R = -0.531$	↓	NA
	SCA3/MJD	24		↓ [a]	↓ [a] SARA: $R = -0.459$	↓	NA	NA	NA	↓	↓	↓ [a] SARA: $R = -0.560$	↓ [a] SARA: $R = -0.479$	NA
Fahl et al, 2015[33] (3T); cross-sectional	SCA3/MJD	48		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	↓ [a] DD: $R = -0.629$; SARA: $R = -0.367$
Reetz et al, 2013[17] (1.5T, SPM8)[d]; longitudinal data; follow-up: 2 yr	SCA 1	37		=	↓ ↓ [a] CAG_{exp}: $R = -(0.370–0.380)$	=	NA	NA	NA	↓ ↓	=	↓	=	NA
	SCA3/MJD	19		=	=	=	NA	NA	NA	↓	=	↓	=	NA
MR spectroscopy														
Lei et al, 2011[20] (1.5T); cross-sectional	SCA3/MJD	36	NAA/Cr	NA	↓	↓	↓ [a] DD: $R = 0.421$; SARA: $R = 0.452$	↓ [a] AO: $R = -0.354$; SARA: $R = 0.954$	NA	NA	NA	NA	NA	NA
			NAA/Cho	NA	=	↓ [a] SARA: $R = 0.954$	↓	=	NA	NA	NA	NA	NA	NA
			Cho/Cr	NA	=	=	=	=	NA	NA	NA	NA	NA	NA
Wang et al, 2012[22] (1.5T); cross-sectional	SCA3/MJD	48	NAA/Cr	NA	↓ [a] SARA: $R = -(0.536–553)$	↓ [a] SARA: $R = -0.748$	NA	NA	NA	NA	NA	NA	NA	NA
			Cho/Cr	NA	=	↓	NA	NA	NA	NA	NA	NA	NA	NA

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On-line Table 1: Continued

Study	SCA	No.		Cerebellum						Brain Stem				Cervical Spine
				Total	Hemispheres	Vermis	Dentate	Peduncle	Other Nuclei	Total	Midbrain	Pons	Medulla Oblongata	
Lirng et al, 2012[21] (1.5T); cross-sectional	SCA3/MJD	58	NAA/Cr	NA	↓[a] SARA: R = NA	↓[a] SARA: R = NA	NA	NA	NA	NA	NA	NA	NA	NA
			NAA/Cho	NA	↓[a] SARA: R = NA	↓[a] SARA: R = NA	NA	NA	NA	NA	NA	NA	NA	NA
Lopes et al, 2013[26] (3T); cross-sectional	SCA3/MJD	32	NAA/Cr + PCr	NA	↓	NA	NA	NA	NA	NA	NA	NA	NA	NA
			NAA + NAAG/ Cr + PCr	NA	↓	NA	NA	NA	NA	NA	NA	NA	NA	NA
			Glu/Cr + PCr	NA	↓	NA	NA	NA	NA	NA	NA	NA	NA	NA
Adanyeguh et al, 2015[19] (3T); cross-sectional	SCA3/MJD	21	mIns		NA	↑	NA	NA	NA	NA	NA	↑	NA	NA
			Cr		NA	↑	NA	NA	NA	NA	NA	↑[a] SARA: R^2 = 0.414	NA	NA
			NAAG		NA	=	NA	NA	NA	NA	NA	=	NA	NA
			GABA		NA	=	NA	NA	NA	NA	NA	=	NA	NA
			GPC		NA	=	NA	NA	NA	NA	NA	=	NA	NA
			ChoP		NA	=	NA	NA	NA	NA	NA	=	NA	NA
			Other		NA	=	NA	NA	NA	NA	NA	=	NA	NA
DTI														
Guimarães et al, 2013[24] (3T); cross-sectional	SCA3/MJD	38	FA	↓	↓	=	↓	↓	↓	↓	↓	↓[a] DD: R = 0.400	=	NA
			AD	↑	↑	=	↑	↑	↑	↑	↑	↑	=	NA
			RD	↑	↑	=	=	↑	↑	↑	↑	↑	=	NA
			MD	=	=	=	=	=	=	=	=	=	=	NA

Note:—NAAG indicates *N*-acetylaspartylglutamate; PCr, phosphocreatine; AO, age at onset; CAGexp, length of the expanded CAG repeat; DD, disease duration; NA, not available; ↓ ↓, this SCA presents more marked atrophy than another SCA subtype in the same study; ↓, decrease; ↑, increase; =, no difference in the parameter or region atrophy comparing with controls (cross-sectional) or with time (longitudinal); GPC, glycerophosphorylcholine; ChoP, phosphorylcholine; MD, mean diffusivity.

[a] Significant correlation of region-specific volume atrophy with clinical scales, disease duration, CAGexp, or age at onset.

[b] Significant correlation of grouped GM and WM alterations with clinical scales, disease duration, CAGexp; individual region-specific correlations not provided.

[c] Significant correlation with neuropsychological tests.

[d] The study of Reetz et al[17] used $P < .001$ as threshold for significant difference.

[e] Differences between right and left sides.

On-line Table 2: Main supratentorial findings

Study	SCA	No.		Caudate	Putamen	GPi	Lentiform	Claustrum	Thalamus	Hemispheres	Temporal Lobe	Frontal Lobe	Parietal Lobe	Occipital Lobe	Limbic Lobe	Corpus Callosum
VBM																
Della Nave et al, 2008[18] (SPM2; 1.5T); cross-sectional	SCA2	20	GM	=	=	=	=	=	=	=	=	=	=	=	=	NA
			WM	NA	NA	NA	NA	NA	NA	=	=	=	=	=	=	=
Schulz et al, 2010[29] (SPM5 and Toolbox; 1.5T); cross-sectional	SCA1	48	GM	↓	=	=	=	=	=	=	↓	=	=	=	=	NA
	SCA3/MJD	24	GM	=	=	=	=	=	=	=	=	=	=	=	=	=
D'Abreu et al, 2011[31] (SPM2); cross-sectional	SCA3/MJD	45	GM	NA	NA	NA	NA	NA	↓	NA	NA	NA	NA	NA	NA	NA
D'Abreu et al, 2012[16] (SPM2, 2T); cross-sectional	SCA3/MJD	45	GM	↓	NA	NA	↓	↓	↓ [c]	NA	↓ [a] ICARS: $R = 0.717$	↓ [a]	↓ [a] ICARS: $R = 0.569$	↓ [a] ICARS: $R = 0.443$	↓ [a] age and CAG_{exp}	NA
			WM	NA	NA	NA	NA	NA	NA	=	=	=	=	=	=	=
D'Abreu et al, 2012[16] (SPM2, 2T); longitudinal; follow-up: 1 yr	SCA3/MJD	45	GM	=	=	=	=	=	=	=	=	=	=	=	=	NA
			WM	NA	NA	NA	NA	NA	NA	=	=	=	=	=	=	=
Reetz K, et al, 2013[17] (SPM8; 1.5T); longitudinal; follow-up: 2 yr	SCA 1	37		=	↓	↓	=	=	=	=	=	=	=	=	=	=
	SCA3/MJD	19		=	↓	↓	=	=	=	=	=	=	=	=	=	=
Surface-based analysis																
de Rezende et al, 2015[32] (FreeSurfer 3T); cross-sectional	SCA3/MJD	49	GM	↓	↓	↓	NA	NA	↓ [a,c] SARA: $R = 0.717$	NA	↓ [a] AO: $R = 0.239$; DD: $R = 0.223$; SARA: $R = -(0.302–311)$	↓ [a,b] SARA: $R = -(0.303–354)$	↓ [a] AO: $R = 0.386$; DD: $R = 0.376$; SARA: $R = -0.311$	↓	↓	NA
Hernandez-Castillo et al, 2015[28] (FSL; 3T)	SCA7	24	GM	=	=	=	=	=	=	=	↓ [a] SARA: $R = -(0.725–799)$	↓	↓	↓	=	NA
Semiautomatized volumetric analysis																
Schulz et al, 2010[29] (1.5T); cross-sectional	SCA1	48		↓	↓	NA	NA	NA	NA	=	↓	=	=	=	NA	NA
	SCA3/MJD	24		↓ [a] SARA: $R = -0.455$	↓	NA	NA	NA	NA	=	↓	=	=	=	NA	NA
D'Abreu et al, 2011[31]; cross-sectional	SCA3/MJD	45		NA	NA	NA	NA	NA	↓	NA	NA	NA	NA	NA	NA	NA
Reetz et al, 2013[17] (1.5T); longitudinal; follow-up: 2 yr	SCA 1	37		↓	↓	NA	NA	NA	NA	=	=	=	=	=	NA	NA
	SCA3/MJD	19		↓	↓	NA	NA	NA	NA	=	NA	NA	NA	NA	NA	NA
MR spectroscopy																
D'Abreu et al, 2009[25] (2T); cross-sectional	SCA3/MJD	40	NAA/Cr	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	↓
			Cho/Cr	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	=
D'Abreu et al, 2012[16] (2T); longitudinal; follow-up: 1 yr	SCA3/MJD	40	NAA/Cr	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	=
DTI																
Guimarães et al, 2013[24] (3T); cross-sectional	SCA3/MJD	38	FA	=	=	=	=	=	=	NA	=	=	=	=	=	=
			AD	=	=	=	=	=	↑	NA	=	=	=	=	=	=
			RD	=	=	=	=	=	↑	NA	↑	↑	↑	=	=	↑
			MD	=	=	=	=	=	=	NA	=	=	=	=	=	=

Note:— ↓ indicates decrease; ↑, increase; =, no difference in the parameter or region atrophy compared with controls (cross-sectional) or with time (longitudinal); NA, not available; No., number of individuals per group; GPi, internal globus pallidus; AO, age at onset. CAGexp, length of the expanded CAG repeat; DD, disease duration; MD, mean diffusivity.

[a] Significant correlation of region-specific volume atrophy with clinical scales, disease duration, CAGexp or age at onset.

[b] Differences between right and left sides.

[c] Inclusion of the same cohort of patients, repeat data.

On-line Table 3: Volumetric and surface analysis extraction table[a]

Author, Year/Country Design/Medical Scenario Population	Sample Size	Outcomes	Acquisition, Postprocessing	Main Findings	Correlations	Limitations
Della Nave et al, 2008[18]/Italy Case-control/single center Consecutive patients with SCA2 and healthy age- and sex-matched controls	20 Individuals with SCA2 10 Women Age, 49 ± 12 yr CAG_{exp}: 39 ± 3 Disease duration, 6.97 ± 3.19 yr ICARS, 32 ± 16 IACRS, 14 ± 16 20 Controls 10 Women Age, 47 ± 10 yr	Differences in GM and WM volumes between patients and controls	1.5T system VBM-SPM2-Schmahmann[42] MRI atlas of the human cerebellum, anatomic reference GM, WM, or CSF in the ROI calculated as average values, taking into account that in the voxels contained in the ROI, the possible value of GM, WM, or CSF is between 0 (null) and 1 (100%)	GM loss ($P < .005$) was symmetric in cerebellar vermis and in cerebellar hemispheres with sparing of vermian lobules I, II (lingula) and X (nodulus) and of hemispheric lobules I, II (lingula) and crus II WM loss ($P < .05$) was observed symmetrically in the peridentate regions, middle cerebellar peduncles, dorsal portion of the pons and in the superficial portion of the cerebral peduncles No GM or WM volume loss was observed in cerebral hemispheres Increase in CSF spaces in posterior fossa of patients with SCA2: more marked on prepontine, ambiens and magna cisterns and in the lateral CSF spaces ($P < .001$ for all comparisons)	Clinical scales ICARS Cerebellar GM ($R = -0.53$) WM volume in the peridentate regions, middle cerebellar peduncles, dorsal pons, and cerebral peduncles ($R = -0.54$) CSF volume in the posterior cranial fossa ($R = 0.45$) IACRS Cerebellar GM ($R = -0.54$) WM volume in the peridentate regions, middle cerebellar peduncles, dorsal pons, and cerebral peduncles ($R = -0.49$) Disease durations and GM and WM correlations were referred to as borderline (P value not given) No significant correlations with CAG_{exp} were observed	Date of data collection not reported P values of simple correlation tests were not provided Both GM and WM alterations were grouped to perform correlation analysis; therefore, specific region atrophy correlations with clinical and molecular finding was not provided
Schulz et al, 2010[29]/Germany, Belgium, Italy, the Netherlands, France, Spain, and Poland Case-control/multicenter: 9 European centers of EUROSCA Consecutive patients with SCA1, SCA3/MJD, and SCA6; healthy age- and sex-matched controls Collection data: between July 2005 and August 2006	48 Individuals with SCA1 Age, 44.3 ± 11.9 yr 17 Women Disease duration, 8.1 ± 4.5 yr SARA, 12.0 ± 5.2 UHDRS-IV, 21.2 ± 4.7 24 Individuals with SCA3/MJD Age, 47.3 ± 11.4 yr 13 Women Disease duration, 11.7 ± 6.0 yr SARA, 12.0 ± 5.7 UHDRS-I, V, 20.3 ± 4.5 32 Controls Age, 49.8 ± 16.2 yr 18 Women SCA6 data were excluded due to sample size of 10	Differences of volumetric analysis between SCA subtypes and controls and between each SCA subtype	1.5T system VBM SPM5 and VBM Toolbox Segmentation of gray matter, white matter, and CSF; iterative segmentation approach Volumetric analysis, manual presegmentation, Talairach grid MRI datasets analyzed by 1 blinded investigator Volumetry, presegmentation and automated Region segmentation; calculation of the volumes: multiplying the number of voxels per ROI and the voxel size	VBM SCA 1 versus controls: Loss of gray matter volume ($P < .001$) in the cerebellar hemispheres, vermis, brain stem, caudate nucleus, and temporal lobes; white matter loss in brain stem, pons, middle cerebellar peduncles, cerebellar hemispheres, and midbrain; all hemispheric and vermal cerebellum lobules were involved SCA3/MJD versus controls: Loss of gray matter volume in cerebellar hemispheres, vermis, but almost none in the pons, basal ganglia, and cerebral hemispheres; white matter loss in brain stem, pons, midbrain, cerebellar peduncles, and cerebellar hemispheres; atrophy affected the hemispheric lobules I–VI; atrophy in the vermis spared the lobules VII and VIII Total intracranial volumes were not different between groups Semiautomated volumetric analysis SCA1 × controls: Atrophy ($P < .05$) on brain stem, pons, medulla, cerebellum, cerebellar hemispheres, and vermis, caudate, putamen, temporal lobes SCA3/MJD × controls: Atrophy ($P < .05$) on brain stem: midbrain, pons, medulla, cerebellum, cerebellar hemispheres and vermis, caudate, putamen, temporal lobes SCA1 × SCA3/MJD: Cerebellum, cerebellar hemispheres, and putamen with more marked atrophy in SCA1 ($P < .05$); midbrain and parietal lobes with more marked atrophy in SCA3/MJD ($P < .05$) Region-specific atrophy Cohen effect size had similar results in SCA1 and SCA3/MJD; most pronounced atrophy was in total brain stem, pons, and medulla; less volume loss in cerebellar structures, and least volume loss in the putamen and caudate nucleus	SCA 1 Clinical scales SARA Brain stem ($R = -0.447$, $P < .001$) Pons ($R = -0.531$, $P < .001$) UHDRS Brain stem ($R = -0.376$, $P < .01$) Pons ($R = -.438$, $P < .001$) Disease duration: Pons ($R = -0.311$, $P < .05$) The length of CAG_{exp} did not correlate with any region degree of atrophy In SCA1, the pons volume explained 28% of the variance of SARA on regression analysis [$F(1;46) = 18.0$, $P = .001$] SCA3/MJD Clinical scales SARA Brain stem ($R = -0.677$, $P < .001$) Midbrain ($R = -0.467$, $P < .05$) Pons ($R = -0.560$, $P < .01$) Medulla ($R = -0.479$, $P < .01$); total cerebellum ($R = -0.451$, $P < .05$) Cerebellar hemispheres ($R = -0.459$, $P < .05$) Caudate nucleus (-0.455, $P < .05$) CAG_{exp} and disease duration did not correlate with regional of atrophy In SCA3/MJD, the stepwise inclusion of pons and medulla together explained 53% of the variance in SARA in the linear regression model [$F(2;21) = 11.7$, $P < .001$]	CAG_{exp} repeats per group not provided; no other major limitation
D'Abreu et al, 2011,[31]/Brazil Case-control/single center SCA3/MJD and healthy controls	45 Individuals with SCA3/MJD Age, 46.2 ± 13.2 yr Disease duration, 9.9 ± 6.1 yr CAG_{exp}, 66 52 Controls Age- and sex-matched	MRI findings of thalamus correlations with clinical and genetic markers of the disease	Tesla system not informed Automated thalamic volume preprocessed: MarsBar volume toolbox[b] to SPM2 and selected thalamic ROIs; manual segmentation of the thalamus display software	Significant thalamus atrophy in patients on automated analysis ($P = .01$) Smaller thalamic volume in patients with SCA3/MJD (7862.5 ± 712.5 mm^3) compared with controls (8592.3 ± 712.5 mm^3; $P < .001$) on manual segmentation	No significant correlation of thalamus atrophy with CAG repeat length, disease duration, and age of onset or age On manual measurement, patients with dystonia had smaller thalamic volumes than patients without dystonia ($P = .049$)	Origin of patients and controls and period of data collection not reported No information about manual analysis blinding was provided Tesla system not provided; authors confirmed that they used Tesla system ≥1.5T

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On-line Table 3: Continued

Author, Year/Country Design/Medical Scenario Population	Sample Size	Outcomes	Acquisition, Postprocessing	Main Findings	Correlations	Limitations
D'Abreu et al, 2012[16]/Brazil Case-control/single center Consecutive patients with SCA3/MJD and healthy controls	45 Individuals with SCA3/MJD Age, 47.02 ± 12.23 yr 15 Women Age of onset, 37.04 ± 11.05 yr Disease duration, 9.97 ± 6.13 yr CAG_{exp}, 72 (range, 65–81) ICARS, 36.36 ± 18.5 51 Controls Age, 44.08 ± 11.78 yr	Differences in GM and WM density between patients and controls	2T system VBM: MarsBar software[b] on SPM2 to extract the GMD in selected ROIs	Significant decreases in GMD ($P < .01$) in the cerebellum and vermis, brain stem (medulla, pons, and midbrain), lentiform nucleus, caudate nucleus, claustrum; frontal lobes (precentral; inferior, superior, and middle frontal gyri; paracentral lobule); parietal lobes (postcentral gyrus; precuneus; inferior, superior, angular, and supramarginal gyri); temporal lobes (fusiform gyrus; insula; middle, superior temporal gyrus); occipital gyrus (cuneus, inferior occipital gyrus, lingual gyrus, middle occipital gyrus, superior occipital gyrus); limbic lobe (cingulate cortex; parahippocampal gyrus); and thalami WM abnormalities were observed only in the deep cerebellar WM No changes in GMD and WMD between MRIs after 1 yr of follow-up	CAG number, disease duration, and age were significant factors in the determination of the GMD in areas 3, 4, 5, and 6 of the cerebellum; left anterior cingulate gyrus; inferior (bilateral), middle (left), and superior (left) frontal lobes; fusiform gyrus (bilateral); Heschl gyrus (bilateral); insula (bilateral); lingual gyrus (bilateral); paracentral lobule (bilateral); postcentral gyrus (left); precentral gyrus (bilateral); precuneus (left); rolandic area (bilateral); supplementary motor area (left); inferior (left), middle (left), and superior temporal gyri (bilateral); all vermian areas Age and CAG length were the most frequent factors in the determination of ROI densities, while disease duration was only an independent factor in the middle frontal gyrus orbicular part; age was the most frequent independent determinant of ROI density ROIs that were important determinants of the final ICARS score: cerebellum, vermis, frontal, parietal, temporal, and occipital lobes	Origin of patients and controls (and sex proportion of controls) and period of data collection not reported 95% CIs were not reported
Guimarães et al, 2013[24]/Brazil Case-control/single center, specialized neurology department Patients with SCA3/MJD and healthy age- and sex-matched controls Collection data: 2009–2011	38 Individuals with SCA3/MJD Age, 40.38 ± 12.12 yr 17 Women CAG_{exp}, 68.08 ± 4.5 ICARS, 32.08 ± 14.01 SARA, 14.65 ± 7.33 38 Healthy controls Age, 46.86 ± 12.07 yr 18 Women	Differences in infratentorial regions between groups and the correlation with other disease markers	3T system Volumetric (3D) T1 gradient-echo images acquired in the sagittal plane with 1-mm section thickness VBM: SUIT toolbox with SPM8/DARTEL[d]	WM infratentorial structure atrophy ($P < .05$): cerebellar areas: tonsil, posterior lobe, culmen, declive, vermis, dentate, uvula, posterior cingulate, fastigium, tuber, nodule, and cerebellar peduncles; brain stem: right brain stem, medulla, pyramids, and pons GM infratentorial structure atrophy ($P < .05$): cerebellar areas: posterior lobe, vermis, tonsil, inferior semilunar lobule, declive, uvula, fastigium, and tuber; brain stem: pons, pyramids, and medulla	WM Disease duration: Negative correlation ($P < .05$) with brain stem: pons, midbrain, pyramids, cerebellum: anterior and posterior lobes, cerebellar tonsil, culmen, dentate, uvula, fastigium, vermis, tuber, and declive Clinical scales (SARA and ICARS): Negative correlation ($P < .05$) with brain stem: left and right brain stem, midbrain, cerebellum, posterior and anterior lobe, culmen and vermis GM Clinical scales (SARA): Negative correlation ($P < .05$) with brain stem: midbrain, pons cerebellum: anterior and posterior cerebellar lobe	95% CIs were not reported The magnitude of the correlations of regional atrophy with other markers was not provided, only the significance
Lopes et al, 2013[26]/Brazil Case-control/single center Exploratory study Patients with SCA3/MJD and healthy controls matched for age, sex, and educational level	32 Individuals with SCA3/MJD Age, 46.97 ± 12.06 yr 17 Women Mean educational level, 10.40 ± 4.27 yr Age at onset, 36.72 ± 10.91 yr (range, 15–58 yr) Disease duration, 10.09 ± 5.78 yr, CAG_{exp}, 69.0 ± 5.0 SARA, 13.6 ± 6.3 32 Controls Age, 46.78 ± 11.47 yr 17 Women	Correlation between the cognitive findings and GM volume, WM integrity, cerebellar metabolite concentration, clinical and genetic data	3T system VBM: VBM Toolbox SPM8	VBM: Differences between groups in the GM volume at right and left cerebellum, right putamen, left posterior cingulum, left superior parietal lobe (Brodmann area = 7) and left precentral gyrus (Brodmann area = 7)	VBM and cognitive test not reported; this was not an outcome of interest for this review	Origin of patients and controls and period of data collection not reported 95% CIs were not reported Some analyses were not corrected for multiple comparisons due to the exploratory nature of the study

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On-line Table 3: Continued

Author, Year/Country Design/Medical Scenario Population	Sample Size	Outcomes	Acquisition, Postprocessing	Main Findings	Correlations	Limitations
Reetz et al, 2013[17]/Germany, Belgium, Italy, the Netherlands, France, and Poland Case-control/multicenter (EUROSCA centers), specialized neurology departments Patients with SCA1, SCA3/MJD, and SCA6; healthy age- and sex-matched controls Baseline collection data: November 2005–March 2007 Follow-up: January 2007–December 2008	63 (SCA1, $n = 37$; SCA3/MJD, $n = 19$; SCA6, n = 7) of the 82 patients who were studied at baseline (Schulz et al, 2010[29]) were available for follow-up; 19 (23%) dropped out 37 Individuals with SCA1 (48 at baseline) Age, 43.32 ± 11.14 yr 16 Women CAG_{exp}, 48.9 ± 6.06 Disease duration, 6.97 ± 3.19 yr SARA, 11.63 ± 4.56 INAS, 5.43 ± 2.12 SCAFI, −0.18 ± 0.71 UHDRS-IV, 21.33 ± 4.58 37 SCA1 controls Age, 43.43 ± 11.17 yr 16 Women 19 Individuals with SCA3/MJD (24 at baseline) Age, 46.79 ± 10.15 yr 10 Women CAG_{exp}, 71.1 ± 2.49 Disease duration, 9.11 ± 6.04 yr SARA, 12.08 ± 5.68 INAS, 5.44 ± 2.07 SCAFI, 0.46 ± 0.81 UHDRS-IV, 20.61 ± 4.05 19 SCA3/MJD controls Age, 46.35 ± 10.58 yr 10 Women SCA6 data were excluded due to sample size of 7 (10 at baseline)	ROI volume loss progression in different genotypes across time SRM for clinical scales and neuroimaging Correlation between regions with volume loss and clinical variables	1.5T system Semiautomatic technique; blinded volumetric processing; ROI: 1) brain stem subdivided into medulla oblongata, pons, and mesencephalon; 2) cerebellum subdivided into the right and left cerebellar hemispheres and vermis; 3) caudate and putamen nucleus; 4) the cerebrum VBM: SPM8 and the VBM Toolbox 8 Percentage change of volume loss: calculated with baseline and follow-up normalized values for each ROI, corrected for visit interval The standardized response mean (SRM): mean score change/standard deviation (SD) of score change.	**Semiautomated analysis:** longitudinal % normalized volume loss in genotypes compared with controls Group vs time SCA1: Brain stem: −0.36 ± 0.22, $P < .05$; Pons: −0.34 ± 0.23, $P < .005$; Right putamen: −0.86 ± 0.53, $P < .05$; Left putamen: −0.81 ± 0.53, $P < .05$; Left caudate: −0.79 ± 0.66, $P < .05$; Left cerebellar hemisphere: −0.32 ± 0.44, $P = .052$ SCA3/MJD: Brain stem: −0.20 ± 0.19 ($P < .05$); Pons: −0.41 ± 0.6 ($P < .005$); Right putamen: −0.38 ± 0.33; Left putamen: −0.53 ± 0.36; Left caudate: −0.48 ± 0.38 The remaining regions showed no significant interactions or main effects Group vs group: SCA1 showed an increased rate of volume loss in the brain stem ($P < .05$), left cerebellar hemisphere ($P < .05$), and putamen ($P < .05$) compared with SCA3/MJD; the degree of change in the pons ($P < .0001$) was similar in patients with SCA1 and SCA3/MJD **VBM** SCA1 GM volume atrophy in the brain stem, left anterior and posterior cerebellum, and the right putamen and pallidum ($P < .001$) SCA3/MJD The main effect restricted to bilateral putamen and pallidum **SRM** Clinical scales with significant changes with time SCA1 SARA = 1.2 UHDRS-IV = −0.1 SCA3/MJD SARA = 1.4 UHDRS-IV = −0.6 MRI volume loss with time SCA1 Brain stem: −1.6 Pons: −1.5 Putamen: −1.3 Caudate: −1.2 Cerebellum: −0.7 SCA3/MJD Brain stem: −1.1 Pons: −0.9 Putamen: −1.5 Caudate: −1.6	Clinical vs MRI findings: CAG_{exp} correlated inversely with change on the left ($R = −0.370$, $P < .05$) and right cerebellum ($R = 0.380$, $P < .05$) in the SCA1 group; the same pattern was found when using VBM data for cerebellum ($R = −0.48$, $P < .005$) and pons at the cluster level ($R = −0.47$, $P < .005$) Disease duration showed no significant association with changes on the clinical variables or with changes on brain volume loss Association measures between localized volume reduction and the change on the various clinical variables revealed no significant findings	19 Dropouts (23% of sample), reasons for losses were reported Follow-up was reported to be 2 yr, but authors provided only the period of data collection

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On-line Table 3: Continued

Author, Year/Country Design/Medical Scenario Population	Sample Size	Outcomes	Acquisition, Postprocessing	Main Findings	Correlations	Limitations
Jacobi et al, 2013[30]/Germany, Belgium, Austria, Italy, France, Spain, Hungary, and Poland Case-control/multicenter: 8 European centers Relatives of patients with SCA with the following 3 criteria: ●Offspring or sibling of an individual with SCA1, SCA2, SCA3, or SCA6; ●Age, 18–50 yr if directly related to individuals with SCA1, SCA2, or SCA3, and 35–70 yr if directly related to individuals with SCA6 ●No ataxia (SARA < 3) Data were collected between September 2008 and December 2011	26 SCA1 carriers Age, 26 yr (range, 22–30 yr) 23 Women Estimated time from onset: −11 yr (−14 to −8) yr 13 SCA1 noncarriers Age, 28 yr (range, 22–36 yr) 8 Women 11 SCA6 carriers Age, mean, 4 yr (range, 42–49 yr) 6 Women Estimated time from onset: −20 yr (−23 to −16) yr Pooled noncarriers ($n = 33$) Data from SCA2 and SCA3/MJD carriers was excluded due to sample sizes of 4 and 9, respectively.	Differences in volume in semiautomated and VBM analysis between groups and the correlation with disease markers	1.5T system VBM: SPM8, VBM8, and the spatially unbiased Infratentorial Toolbox (Version 2.5.3)[c] Semiautomated, quantitative volumetry: brain stem volume, cerebellar volume, and total intracranial volume MRI volumetric analysis was performed by 1 investigator blinded to carrier status	Presymptomatic SCA1 VBM: GM loss ($P < .001$) in the medulla oblongata, pons, lobule IX of the cerebellum Semiautomated volumetric analysis ($P < .05$): Lower brain stem volumes of SCA1 carriers than of pooled noncarriers Presymptomatic SCA6 No differences in VBM or semiautomated volumetric analysis between carriers and noncarriers	None	Only 30% of the studied individuals underwent MRI No other major limitation
de Rezende et al, 2015[32]/Brazil Case-control/single center, specialized neurology and neurogenetics department Patients with SCA3/MJD and healthy controls Data were collected between 2009 and 2013	49 Individuals with SCA3/MJD Age, 47.7 ± 13.0 yr 22 Women Age at onset, 37.5 ± 12.5 yr Disease duration, 10.00 ± 4.7 yr CAG_{exp}, 72.1 ± 4.2 SARA, 14.7 ± 7.3 Patients with dystonia ($n = 19$, (39%) 49 Controls Age, 47.5 ± 12.7 yr 22 Women	Differences in cortical thickness and subcortical volumes between groups and its correlation with other disease markers	3T system Cortical thickness: FreeSurfer software, Version 5.3	Cortical thickness Vertex-wise analysis Significant reduction in patients with SCA3/MJD in left hemisphere: superior frontal ($P = .013$), superior temporal ($P = .027$), precentral cortices ($P = .021$) Right hemisphere: superior frontal cortex ($P = .014$) Atlas of Desikan et al[41] Significant cortical thinning in patients with SCA3/MJD in left hemisphere: middle occipital gyrus, precentral gyrus, anterior transverse temporal gyrus, posterior ramus of the lateral sulcus, inferior part of the precentral sulcus, superior temporal sulcus Right hemisphere: paracentral lobule and sulcus, middle posterior part of the cingulate gyrus and sulcus, short insular gyri, superior occipital gyrus, angular gyrus, precentral gyrus; posterior ramus of the lateral sulcus, central sulcus, marginal branch of the cingulate sulcus, medial occipitotemporal sulcus, and lingual sulcus Subcortical volumetric analyses Significant reductions in patients with SCA3/MJD in left hemisphere: cerebellar WM, cerebellar GM, thalamus, caudate, putamen, pallidum, ventral diencephalon Right hemisphere: cerebellar WM, cerebellar GM, thalamus; caudate, putamen; pallidum, ventral diencephalon, brain stem Both hippocampi were also atrophic in the SCA3/MJD group ($P < .001$)	Cortical data SARA Left precentral gyrus ($R = -0.302$, $P = .035$) Anterior transverse Temporal gyrus ($R = -0.303$, $P = .034$) Superior temporal sulcus ($R = -0.354$, $P = .013$), Caudal middle frontal cortex ($R = -0.330$, $P = .02$) Paracentral cortex ($R = -0.311$, $P = .03$) Transverse temporal cortex ($R = -0.346$, $P = .015$) Multiple regression: Age, age at onset, and disease duration were independently correlated with the thickness of the right angular gyrus (R-adjusted = 0.662; $P < .001$) Left caudal middle frontal cortex (R-adjusted = 0.569; $P < .004$) Right posterior ramus of the lateral sulcus (R-adjusted = 0.603; $P = .001$) No correlation between the length of the expanded CAG repeat and thickness measurements Neuropsychological tests not reported; this was not an outcome of interest for this review Subcortical data SARA Brain stem ($R = 0.581$, $P < .001$) Left thalamus volume ($R = 0.624$, $P < .001$) Ventral diencephalon, both at right ($R = 0.575$, $P < .001$) and left ($R = 0.641$, $P < .001$) Duration of the disease: Left ($R = 0.619$, $P < .001$) and right ($R = 0.578$, $P < .001$) ventral diencephalon and right cerebellar white matter ($R = 0.543$, $P = .001$) No correlations between subcortical volumes and age, age at onset and CAG_{exp} were found	Origin of controls not reported

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On-line Table 3: Continued

Author, Year/Country Design/Medical Scenario Population	Sample Size	Outcomes	Acquisition, Postprocessing	Main Findings	Correlations	Limitations
Fahl et al, 2014[33]/Brazil Case-control/single center, specialized neurology and neurogenetics outpatient clinics Consecutive SCA3/MJD and healthy age- and sex-matched controls	48 individuals with SCA3/MJD Age, 47.7 ± 12.9 yr 22 Women Disease duration, 9.00 ± 4.4 yr CAG_{exp}, 70.1 ± 5.4 SARA, 14.2 ± 7.1 48 Controls Age, 47.7 ± 12.9 yr 22 Women	Differences in the cervical cord area and eccentricity between groups and its correlation with other disease markers	3T system SpineSeg for the quantitative analyses of the cervical cord; measurements of the cervical spinal cord were determined from sections obtained perpendicular to the lower limits (base) of the 2nd and 3rd cervical vertebrae CA and CE of the cord were used for analysis FreeSurfer, Version 5.3, was used to segment automatically the cerebellum and calculate its total volume All measurements were performed by a single evaluator, blinded to the clinical status of the subjects	SCA3/MJD versus controls CA (49.5 ± 7.3 vs 67.2 ± 6.3 mm^2, $P < .001$) CE (0.79 ± 0.06 vs 0.75± 0.05, $P = .005$)	Disease duration was the only variable associated with CA ($R^2 = 0.343$, $R = -0.629$, $P = .025$) in the multiple variable regression model After covariation for disease duration and cerebellar volume, CA was independently associated with SARA scores; the model explained 49.1% of SARA variance ($R = -0.367$, $P = .010$) with cord area	Origin of controls and period of data collection not reported
Hernandez-Castillo et al, 2015[28]/Mexico Case-control/Universidad Nacional Autonoma de Mexico Patients with SCA7 with CAG expansions >40; healthy age- and sex- matched controls	24 Individuals with SCA7; age, 39.8 ± 15.18 yr 10 women Disease duration, range, 1–21 yr CAG_{exp}, range, 41–71 SARA, range, 4–29.5 24 controls Mean age, 38.4 ± 15 yr 10 women	Differences in supra- and infratentorial regions between groups and the correlation with SARA	3T system; surface-based analysis: FSL; images corresponding to the GM were aligned to Montreal Neurological Institute-152 standard space by a nonlinear coregistration; GMV images, loaded in Matlab 2014a,[e] and a voxelwise partial correlation were calculated using in-house functions	Right anterior cerebellum showed the greatest amount of atrophy, followed by the left posterior cerebellum in SCA7; gray matter decreases in the SCA7 group compared with controls were also seen in the cuneus, precuneus, pre-/postcentral gyri, inferior frontal gyrus, and temporal regions	Significant negative correlations were found between GMV and SARA scores in the SCA7 group; these regions included the bilateral anterior and posterior cerebellum, the left parahippocampal gyrus, bilateral precentral gyri, bilateral cingulate gyri, bilateral insula, and bilateral inferior frontal gyri	Selection: neither information on origin of patients and controls nor period of data collection reported; 95% CIs were not reported

Note:—IACRS indicates Inherited Ataxia Clinical Rating Scale; ICARS, International Cooperative Ataxia Rating Scale; INAS, Inventory of Non-Ataxia Signs; SCAFI, spinocerebellar ataxia functional index; UHDRS, Unified Huntington's Disease Rating Scale; EUROSCA, European Integrated Project on Spinocerebellar Ataxias, http://www.eurosca.org/; SpineSeg , Spinal Cord Segmentation, http://www.lni.hc.unicamp.br/app/spineseg/;, CA, cross-sectional area; CE, cross-sectional eccentricity; GMV, gray matter volume; GMD, gray matter density; WMD, white matter density.

[a] Data are shown as mean ± SD on sample size column.

[b] https://sourceforge.net/p/marsbar/mailman/message/24774013; and www.bic.mni.mcgill.ca.

[c] http://www.diedrichsenlab.org/imaging/suit.htm.

[d] Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra.

[e] MathWorks, Natick, Massachusetts. http://www.diedrichsenlab.org/imaging/suit.htm.

On-line Table 4: MR spectroscopy extraction table[a]

Author, Year/Country Design/Medical Scenario Population	Sample Size	Outcomes	Acquisition, Postprocessing	Main Findings	Correlations	Limitations
D'Abreu et al, 2009[25]/Brazil Case-control/single center Patients with SCA3/MJD and healthy controls	40 Individuals with SCA3/MJD Age, 44.6 ± 12.28 yr 18 Women Age of onset, 34.6 ± 12.2 yr Disease duration, 9.6 ± 4.7 yr CAG_{exp}, 66 (range, 61–75). 27 Controls Age, 31.4 ± 13.6 yr	Spectroscopy findings correlated with clinical findings and ICARS score	2T system Single-voxel ^{1}H-MRS PRESS sequence 16 ROI: superoposterior region of the left hemisphere at the level of the corpus callosum (large amount of white matter without the contamination of CSF and gray matter) Spectra postprocessed with the software supplied by the machine manufacturer[b] NAA at 2.01 ppm, choline-based compounds at 3.2 ppm, and creatine- and phosphocreatine-containing compounds at 3.0 ppm; we scaled the spectra in relation to creatine values; NAA/Cr and Cho/Cr ratios were used for analyses; MRS analyses were blinded	^{1}H-MRS: Mean NAA/Cr ratios were 1.63 ± 0.41 (range, 1.15–2.76) in SCA3/MJD and 1.97 ± 0.51 (1.50–2.92) in the control group (U test = 219.0; $P < .001$). Mean Cho/Cr ratio in SCA3/MJD was 0.93 ± 0 .15 (range, 0.7–1.18) and in the control group, 0.97 ± .12 (range, 0.7–1.23) There was no significant difference in Cho/Cr ratios 4 Subjects were excluded from the MRS analysis due to poor quality of spectra	There was no significant correlation between NAA/Cr ratios and clinical and genetic variables, including disease duration, ICARS score and CAG ($F = 2.477$ and $P = .102$)	Origin of patients and controls and period of data collection not reported Only 15 patients and 15 controls were age-matched, and only 11 were sex-matched The authors provided data of these 15 age-matched individuals that had similar results; however, these results were not included in the present review due to the small number of patients
Lei et al, 2011[20]/China Case-control/single center; Neurodegenerative Disorders Clinics at a university hospital from 2007–2009 Patients with SCA3/MJD and healthy controls matched for age	36 Individuals with SCA3/MJD Age, 36.67 ± 6.04 yr 18 Women Disease duration, 4.50 ± 2.60 yr CAG_{exp}, 75.53 ± 4.3 SARA, 10.21 ± 3.56 27 Controls Age, 31 ± 7.35 yr 14 Women	Difference between metabolites and metabolite ratios between cases and controls and its correlations with other disease markers	1.5T system Conventional SE was performed to obtain T1W1 horizontal axial position, median sagittal position, and coronal position (TR, 838 ms; TE, 12 ms; layer thickness, 6 mm; layer gap, 0; FOV, 230; NEX, 2; matrix, 256 × 256) and FSE T2WI (TR, 4000 ms; TE, 95 ms; echo train, 15; layer thickness, 6 mm; layer gap, 0; FOV, 230; NEX, 2; matrix, 256 × 256) axial images ROI positioning was manual; acquisition included vermis of cerebellum, middle cerebellar peduncle, right-sided cerebellar cortex, and right-sided cerebellar dentate nucleus; voxel size, 15 × 10 × 15 mm SVS-SE, 135 sequences (TR, 1500 ms; TE, 1500 ms; acquisitions, 192) to perform single-voxel signal acquisition MR signals of NAA, Cho, Cr and the ratios NAA/Cho, NAA/Cr, and Cho/Cr were calculated	NAA/Cr reduced in patients with SCA3/MJD in dentate nucleus ($P = .003$), cerebellar cortex ($P = .001$), vermis ($P < .001$), and middle cerebellar peduncle ($P < .001$) NAA/Cho reduced in patients with SCA3/MJD in dentate nucleus ($P = .001$) and vermis ($P < .001$)	NAA/Cr of dentate nucleus was directly correlated with disease duration ($R = 0.421$, $P = .011$), CAG_{exp} ($R = 0.415$, $P = .012$), and SARA score ($R = 0.452$, $P = .006$); Middle cerebellar peduncle was inversely correlated with age at onset ($R = -0.354$, $P = .034$) and directly with SARA ($R = 0.954$, $P = .010$) Cho/Cr of dentate nucleus was directly correlated with SARA ($R = 0.360$, $P = .031$); cerebellar cortex was inversely correlated with disease duration ($R = -0.347$, $P = .038$), CAG_{exp} ($R = -0.497$, $P = .002$), and SARA ($R = -0.389$, $P = .019$) Vermis was directly correlated with SARA ($R = 0.954$, $P = .002$) NAA/Cho of cerebellar cortex was directly correlated with disease duration ($R = 0.368$, $P = .027$), CAG_{exp} ($R = 0.562$, $P < .001$), and SARA ($R = 0.458$, $P = .005$); vermis was directly correlated with SARA ($R = 0.954$, $P = .010$)	No information about blinding for ROI positioning 95% CIs were not reported Authors did not comment on the discrepancy in the between-group and correlation analyses, in which reduced spectroscopy ratio regions had direct correlation with clinical data that increase with disease severity, except for Cho/Cr of the cerebellar cortex, which was inversely correlated these variables
Wang et al, 2012[22]/Taiwan Case-control/single center; Taipei Veterans General hospital from March 2004–March 2010 Patients with SCA2, SCA3/MJD, and SCA6; healthy controls matched for age, sex	48 Individuals with SCA3/MJD (43 patients with SCA3/MJD underwent MRI) Age, 48.8 ± 11.4 yr Disease duration, 8.7 ± 6.2 yr CAG_{exp}, 73.1 ± 4.0 Age of onset, 40.1 ± 10.5 yr SARA, 14.1 ± 8.0 44 Controls Age, 51.1 ± 18.0 yr Data from SCA2 and SCA6 were excluded due to sample sizes of 12 and 8, respectively	Outcomes of interest: difference among groups in NAA/Cr in the vermis (denoted V-NAA), right cerebellar hemisphere (R-NAA), and left (L-NAA) cerebellar hemisphere; and Cho/Cr ratio in these same regions	1.5T system Axial T1-weighted (TR, 8.58 ms; TE, 3.62 ms; TI, 400 ms; section thickness, 1.5 mm) Axial, T2-weighted, fast SE sequence (TR, 4000 ms; TE, 256.5 ms; section thickness, 5 mm) Single-voxel analysis in cerebellar vermis and hemispheres; metabolite intensity ratios were calculated automatically at the end of each single-voxel acquisition	Spectroscopy NAA/Cr ratio decreased in the cerebellar hemispheres and the vermis in SCA3/MJD ($P < .001$) V-Cho/Cr reduction ($P = .025$), with no changes in cerebellar hemispheres in SCA3/MJD	Clinical Measurements Age, disease duration, and age of onset, CAG repeats R-NAA/Cr ($R = -0.553$, $P < .001$), V-NAA/Cr ($R = -0.748$, $P < .001$), and L-NAA/Cr ($R = -0.536$, $P < .001$) presented an inverse correlation with SARA No correlation was found for MRS ratios with CAG_{exp} R-NAA/Cr decrease with age in controls ($R = -0.352$, $P < .05$) and patients with SCA3/MJD ($R = -0.572$, $R = .001$); V-NAA/Cr ($R = -0.364$, $P < .05$) and L-NAA/Cr ($R = -0.566$, $R = 001$) decrease with age only in patients with SCA3/MJD Control subjects R-NAA ratio decreased with increasing age ($R = -0.352$, $P = .05$); L-NAA ($R = -0.320$ and $P > .05$) and V-NAA ($R = 0.043$ and $P > .05$) ratios exhibited no change with age (not normally distributed)	Sex distribution not described; demographic data were reported for all the screened population in the study, and not only for the individuals who underwent MRS Some patients had repeat MRS measures in the study; however, the exact number of patients and intervals was not reported Many of the performed analyses were based on statistical models; the study did not evaluate the target parameter as disease progression with time and MRS findings in presymptomatic individuals

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On-line Table 4: Continued

Author, Year/Country Design/Medical Scenario Population	Sample Size	Outcomes	Acquisition, Postprocessing	Main Findings	Correlations	Limitations
Lirng et al, 2012[21]/Taiwan Case-control/single center; specialized neurology department Patients with SCA1, SCA2, SCA3/MJD, SCA6, SCA17, and MSA-C; healthy, age- and sex- matched controls Baseline collection data: 2004–2010	58 Individuals with SCA3/MJD Age, 50.0 ± 12.7 yr Disease duration, 8.9 ± 6.2 yr CAG_{exp}, 73.2 ± 3.9 44 Controls Age, 51.1 ± 17.9 yr Data from SCA1, 2, 6, and 17 were excluded due to sample sizes of 4, 16, 10, and 6, respectively; MSA-C data were not analyzed because of our eligibility criteria	Comparison of the metabolic parameters on MRS between patients with SCA and healthy controls and between SCA subtypes and MSA-C Correlation of the MRS ratios with other disease markers	1.5T system MRI acquisition protocol for axial T1-weighted 3D fast spoiled gradient-recalled acquisition in steady-state images (TR, 8.58 ms; TE, 3.62 ms; TI, 400 ms; voxel resolution, 0.75 × 0.75 × 1.5 mm^3) and an axial T2 fast SE sequence (TR, 4000 ms; TE, 256.5 ms; voxel resolution, 348 × 512) Proton MRS was recorded in cerebellar hemispheres and cerebellar vermis by using single-voxel stimulated echo acquisition mode sequence Metabolite-intensity ratios: automatically calculated at the end of each single-voxel acquisition, including NAA/Cr and Cho/Cr	SCA3/MJD Cerebellar hemispheres ($P < .05$) NAA/Cr, 0.84 ± 0.14 NAA/Cho, 1.25 ± 0.16 Cerebellar vermis ($P = .05$) NAA/Cr, 0.79 ± 0.1. NAA/Cho, 1.20 ± 0.13 Early-stage (SARA < 10) SCA3/MJD ($n = 20$) Cerebellar hemispheres ($P < .0005$) NAA/Cr, 0.9 ± 0.1 NAA/Cho, 1.3 ± 0.1 Cerebellar vermis NAA/Cr, 0.8 ± 0.1 ($P < .002$) NAA/Cho, 1.2 ± 0.1 ($P < .007$)	Inverse correlation between MRS ratios (NAA/Cr, NAA/Cho, Cho/Cr in the cerebellar hemispheres and vermis) and SARA scores in SCA3/MJD; the lower the metabolite ratio, the higher the SARA scores NAA/Cho correlated with disease duration ($P = .037$ in the cerebellar hemispheres; $P = .006$ in the vermis); disease duration did not correlate with NAA/Cr or Cho/Cr in cerebellar hemispheres or vermis	Sex distribution not described The *R* and *P* values for the correlations between MRS and SARA in the different SCAs were not provided The correlations between MRS and disease duration is provided with the overall data and not for each SCAs subtype
Lopes et al, 2013[26]/Brazil Case-control, exploratory study, single center Patients with SCA3/MJD and healthy controls matched for age, sex, and educational level	32 individuals with SCA3/MJD (26 analyzed for MRS-c) Age, 46.97 ± 12.06 yr 17 Women Age at onset, 36.72 ± 10.91 yr (range, 15–58 yr) Disease duration, 10.09 ± 5.78 yr (range, 2–30 yr) CAG_{exp}, 69.0 ± 5.0 (range, 62–81) SARA, 13.6 ± 6.3 (range, 4.5–30) 32 Controls (26 analyzed with MRS-c) Age, 46.78 ± 11.47 yr 17 Women	Outcomes of interest: correlation between the cognitive findings and GM volume, WM integrity, cerebellar metabolite concentration, clinical and genetic data	3T system MRS: spectra acquired with a PRESS sequence (TR/TE, 2000/144 ms; 128 scans; 2-kHz bandwidth; 1024 data points), using a single voxel of 1.5 cm^3 placed over the white matter in the left cerebellum Quantification of the spectra performed with software LCModel[c] Evaluated metabolites: NAA, NAA + NAA + NAAG, total creatine (Cr + PCr), Glu, Glu + Gln, PCh, PCh + GPC + PCh, and mIns	MRS-c reduced relative metabolite concentrations in patients with SCA3/MJD compared with controls NAA/Cr + PCr (0.76 ± 0.15 vs 0.98 ± 0.19, $P = .001$) NAA + NAAG/Cr + PCr (0.88 ± 0.15 vs 1.28 ± 0.41, $P = .001$), Glx/Cr + PCr (0.37 ± 0.09 vs 0.47 ± 0.15, $P = .035$) No difference in Glu/Cr + PCr (0.35 ± 0.10 vs 0.44 ± 0.17, $P = .11$) PCh + PCr (0.22 ± 0.06 vs 0.25 ± 0.08, $P = .13$) GPC + PCh/Cr + PCr (0.24 ± 0.04 vs 0.27 ± 0.05, $P = .098$) mIns/Cr + PCr (0.83 ± 0.20 vs 0.81 ± 4.09, $P = 1.00$)	MRS-c and cognitive test correlations were not reported; these were not an outcome of interest for this review No significant correlation between the cognitive findings and CAG expansion length, duration and disease severity were found; the correlation between VBM, DTI, and MRS-c findings and CAG expansion length, duration, and disease severity was not performed	Origin of patients and controls and period of data collection not reported 6 (18%) Cases were excluded from MRS-c analysis without reason Some analyses were not corrected for multiple comparisons due to the exploratory nature of the study
Adanyeguh et al, 2015[19]/France Case-control/single center Patients with SCA1, SCA2, SCA3/MJD, and SCA7; healthy age-and sex-matched controls Baseline collection data: 2004–2010	21 Individuals with SCA3/MJD Age, 51 ± 12 yr 12 Women Disease duration, 9 ± 5 yr CAG_{exp}, 69 ± 6 33 Controls Mean age, 48 ± 13 yr 18 Women Data from SCA1, 2, and 7 were excluded due to sample sizes of 16, 12, and 12	Outcomes of interest: Difference in vermis and pons metabolites in each SCA versus control Correlation between the metabolite and SARA score, CAG repeat length, and disease duration	3T system MRS: modified semiadiabatic localization by adiabatic selective refocusing (semi-LASER) sequence 3D T1-weighted volumetric images (TR, 2530 ms; TE, 53.65 ms; 1-mm isotropic; FOV, 256 × 176 mm^2; matrix size, 256 × 256) were acquired for spatial normalization and localization of brain volumes; shimming was performed on a 25 × 10 × 25 mm^3 VOI in the vermis, and a 16 × 16 × 16 mm^3 VOI in the pons, using a fast automatic shimming technique with echo-planar signal trains using mapping along projections, FAST(EST)MAP Spectral processing and metabolite quantification: LCModel, with the following metabolite profile: alanine, ascorbate, aspartate, creatine, GABA, GPC, PCh, phosphocreatine, glucose, glutamine, Glu, glutathione, myoinositol scyllo-inositol, lactate, NAA, NAAG, phosphorylethanolamine, taurine, and experimentally measured macromolecules	SCA3/MJD Vermis: Reduced NAA ($P < .001$) Glu ($P < .01$) Increased mIns ($P < .001$) Cr ($P < .001$) Pons: Reduced NAA ($P < .001$) Glu ($P < .01$) Increased mIns ($P < .001$) Cr ($P < .05$)	A strong inverse correlation was found between SARA scores and NAA in SCA3/MJD pons ($R^2 = 0.667$, $P = .002$) Cr also strongly correlated with SARA scores in SCA3/MJD pons ($R^2 = 0.414$, $P = .039$) SARA scores correlated with mIns in the pons of patients with SCA3/MJD ($R^2 = 0.470$, $P = .027$) CAG_{exp} and disease duration did not correlate with the concentration of any neurochemical evaluated	No major

Note:—MRS-c indicates MR spectroscopy cerebellum; PRESS, point-resolved spectroscopic sequence; SE, spin-echo; PCh, phosphorylcholine; LASER, localization by adiabatic selective refocusing; FAST(EST)MAP https://www.cmrr.umn.edu/downloads/fastmap/fastestmap.pdf; V-NAA, NAA/Cr in the vermis; R-NAA, NAA/Cr in the right cerebellar hemisphere; L-NAA, NAA/Cr in the left cerebellar hemisphere; MSA-C, multiple system atrophy, cerebellar type; NAAG, N-acetyl-aspartyl-glutamate; GPC, glycerophosphorylcholine.

[a] Data are shown as mean ± SD on sample size column.

[b] 2T Prestige; Elscint Haifa, Israel.

[c] http://www.lcmodel.com/.

On-line Table 5: DTI extraction table[a]

Author, Year/Country Design/Medical Scenario Population	Sample Size	Outcomes	Acquisition, Postprocessing	Main Findings	Correlations	Limitations
Guimarães et al, 2013[24]/Brazil Case-control/single center; specialized neurology department Patients with SCA3/MJD and healthy age and sex matched controls Collection data: 2009–2011	38 Individuals with SCA3/MJD Age, 40.38 ± 12.12 yr 17 Women CAG_{exp}, 68.08 ± 4.5 ICARS, 32.08 ± 14.01 SARA, 14.65 ± 7.33 38 Controls Age, 46.86 ± 12.07 yr 18 Women	Differences in FA, AD, RD, and MD in different areas between groups and the correlation with other disease markers	3T system DTI via a 32-direction noncollinear echo-planar sequence Data processing: Tract-Based Spatial Statistics (TBSS, FSL software)[b]	MD: No significant differences were found between groups FA: Reduction ($P < .05$) in SCA3/MJD: Brain stem: including pons, midbrain; bilateral cerebellum: anterior lobe, right posterior lobe, nodule, culmen, dentate, fastigial, lingual, and superior, middle, and inferior cerebellar peduncles RD: increased ($P < .01$) in SCA3/MJD: Brain stem: pons, midbrain, Bilateral cerebellum: anterior lobe, cerebellum posterior lobe, culmen, fastigium, dentate, tonsil, lingual, pyramids, uvula, declive, and cerebellar peduncles. Supratentorial: thalamus, bilateral cerebral WM, and frontal, temporal and parietal lobes AD: increased ($P < .01$) in SCA3/MJD: Brain stem: pons and midbrain Bilateral cerebellum: anterior and posterior lobes, culmen, fastigium, lingual Right thalamus	FA Pons: correlation between FA and disease duration ($R = 0.4$, $P = .01$) No other significant correlations	95% CIs were not reported The magnitude of the correlations with other markers was not provided, only the significance

Note:—MD indicates mean diffusivity.

[a] Data are shown as mean ± SD on sample size column.

[b] http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS.

On-line Table 6: Other MRI methods extraction table

Author, Year/Country Design/Medical Scenario Population	Sample Size	Outcomes	Acquisition, Postprocessing	Main Findings	Correlations	Limitations
Relaxometry						
Guimarães et al, 2013[24]/Brazil Case-control/single center; specialized neurology department Patients with SCA3/MJD and healthy age- and sex-matched controls Collection data: 2009–2011	38 SCA3/MJD individuals Age, 40.38 ± 12.12 yr 17 Women CAG_{exp}, 68.08 ± 4.5 ICARS, 32.08 ± 14.01 SARA, 14.65 ± 7.33 38 Controls Age, 46.86 ± 12.07 yr 18 Women	Differences in T2 relaxation time in different areas between groups and the correlation with other disease markers	3T system T2-relaxometry images, acquired with a multiecho T2-weighted sequence in a plane perpendicular to the long axis of the hippocampus; 36 sections with 3-mm thickness After voxel 3D medical image visualization and interactive volume segmentation; software from UNICAMP[b] was used to convert, visualize, and segment the ROIs in the cerebellar WM bilaterally; a circular ROI was placed at each structure, and the T2 relaxation times were automatically calculated	Decreased in the WM of the right cerebellar hemisphere (88.8 × 82.2 ms; $P = .032$) No other differences were observed	No significant correlation between T2 relaxation times and other disease markers	95% CIs were not reported The magnitude of the correlations with other markers was not provided, only the significance
MRI perfusion						
Xing et al, 2014[23]/China Case-control/single center; specialized neurology and genetics departments Symptomatic and presymptomatic individuals with SCA3/MJD; healthy age- and sex-matched controls; all individuals were Han Chinese Collection data: July 2012–February 2013	22 Individuals with SCA3/MJD Age, 43.55 ± 5.86 yr 9 Women 25 Controls Age, 38.44 ± 12.31 yr 16 Presymptomatic individuals with SCA3/MJD Age, 29.56 ± 8.39 yr 8 Women 23 Controls to presymptomatic SCA3/MJD group Age, 33.3 ± 10.19 yr	rCBF maps to evaluate cerebral perfusion with ASL MRI perfusion-weighted imaging	3T system Axial and coronal T2-weighted images: TR, 4480 ms; TE, 120 ms; FOV, 240; section thickness, 5 mm; intersection gap, 1.5 mm; and matrix, 320 × 288; sagittal T1-weighted images: TR, 2650 ms; TE, 24 ms; FOV, 240; section thickness, 5 mm; intersection gap, 1.0 mm; and matrix, 320 × 256; FAIR sequence of the ASL: flip angle, 90°; TR, 3500 ms; TE, 16.1 ms; FOV, 240; matrix 96 × 96; no gap; section thickness, 1.5 mm The ASL perfusion MRI results were analyzed with FuncTool perfusion software[c] following a general kinetic model The ROI in the bilateral precentral gyrus and cerebral peduncle was 36 voxels; the ROI in the bilateral frontal white matter, posterior limb of the internal capsule, cerebellar white matter, and cerebellar cortex was 48 voxels; the ROIs that outlined the pons and bilateral cerebellar dentate nucleus were hand drawn on the FAIR images that showed the largest sizes of these regions Single physician blinded to the clinical data performed all measurements	rCBF of pons, dentate nucleus, and cerebellar cortex was significantly lower in the patients with SCA3/MJD than in the control group rCBF of dentate nucleus and cerebellar cortex was significantly lower in the presymptomatic individuals with SCA3/MJD than in the control group No significant difference was found between the rCBF of the 11 symptomatic (age, 39.18 ± 3.54 yr) and 9 age-matched presymptomatic (age, 35.11 ± 6.15 yr) individuals with SCA3/MJD	Not performed	Correlation with other disease markers was not performed to further validate the findings The number of subjects changed according to the comparison, with insufficient power to compare presymptomatic and symptomatic individuals with SCA3/MJD The number of families was not provided; CAG_{exp} repeat number was not provided
FD analysis						
Wang et al, 2012[22]/Taiwan Case-control/single center; specialized hospital Healthy age- and sex-matched controls Collection data: 2005 to February 2012	48 Individuals with SCA3/MJD Age, 48.13 ± 11.7 yr 21 Women 50 Controls Age, 48.24 ± 13.95 yr 25 Women	FD analysis of cerebral and cerebellar cortex and the correlation with disease parameters, MMSE, and EEG	1.5T system T1-weighted image of each participant was reformatted into an axial image and converted to the Analyze format by using MRIcro[d] software; normalization process was conducted using DiffeoMap[e] Data processing was conducted using the SPM5 toolbox, IBASPM[f] toolbox in Matlab 7.0 software. Fractal analysis: 3D box-counting method of 97 regions of gray matter from the entire brain	3D-FD values of the cerebellar cortex and cerebral cortex of the patients with SCA3/MJD were decreased 3D-FD analysis indicated that 37 parcellated regions of the cerebral and cerebellar cortices exhibited significant regional variation in patients with SCA3 compared with the controls Among the parcellated regions, 32 were located in the cerebral cortex and 5 were located in the cerebellar cortex; the posterior lobe of the cerebellar cortex showed significant decrease in patients with SCA3	Significant correlation between decreased 3D-FD values of both the cerebral and cerebellar cortices and disease duration; significant correlations ($P < .05$) were found between disease duration and the 3D-FD values of 37 specific regions, including the anterior and posterior lobes of the cerebellar cortex; and frontal, parietal, occipital, and temporal lobes; and limbic and subcortical regions of the cerebral cortex Significant correlation between the 3D-FD values of the cerebellar cortex and SARA scores ($R = -0.3346$; $P = .023$); the mean 3D-FD values of the patients with SCA3/MJD at the early stage were greater than those at the late stage of the disease	The number of families was not provided; CAG_{exp} repeat number was not provided

Note:—EEG indicates electroencephalogram; MMSE, Mini-Mental State Examination FD, fractal dimension; rCBF, regional cerebral blood flow; ASL, arterial spin-labeling; FAIR, flow-sensitive alternating inversion recovery.

[a] Data are shown as mean ± SD on sample size column.

[b] UNICAMP software; https://sourceforge.net/projects/unicamp/.

[c] GE Healthcare, Milwaukee, Wisconsin.

[d] http://www.mccauslandcenter.sc.edu/mricro/mricro/mricro.html.

[e] https://www.mristudio.org.

[f] http://www.thomaskoenig.ch/Lester/ibaspm.htm.