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CLINICAL INVESTIGATIVE STUDY

Gadolinium-based contrast agent exposures and physical and cognitive disability in multiple sclerosis

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Abstract

Background and Purpose: The clinical correlation of gadolinium-based contrast agents (GBCAs) has not been well studied in multiple sclerosis (MS). We investigated the extent to which the number of GBCA administrations relates to self-reported disability and performance measures.

Methods: A cohort of MS patients was analyzed in this retrospective observational study. The main outcome was the association between the cumulative number of GBCA exposures (linear or macrocyclic GBCA), Patient-Determined Disease Steps (PDDS), and measures of physical and cognitive performance (walking speed test, manual dexterity test [MDT], and processing speed test [PST]). The analysis was performed first cross-sectionally and then longitudinally.

Results: The cross-sectional data included 1059 MS patients with a mean age of 44.0 years (standard deviation = 11.2). While the contrast ratio in globus pallidus weakly correlated with PDDS, MDT, and PST in a univariate correlational analysis (coefficients, 95% confidence interval [CI] = 0.11 [0.04, 0.18], 0.15 [0.08, 0.21], and −0.16 [−0.10, −0.23], respectively), the associations disappeared after covariate adjustment. A significant association was found between number of linear GBCA administrations and PDDS (coefficient [CI] = −0.131 [−0.196, −0.067]), and MDT associated with macrocyclic GBCA administrations (−0.385 [−0.616, −0.154]), but their signs indicated better outcomes in patients with greater GBCA exposures. The longitudinal data showed no significant detrimental effect of macrocyclic GBCA exposures.

Conclusion: No detrimental effects were observed between GBCA exposure and self-reported disability and standardized objective measures of physical and cognitive performance. While several weak associations were found, they indicated benefit on these measures.

KEYWORDS
gadolinium-based contrast agent, magnetic resonance imaging, multiple sclerosis

INTRODUCTION

Gadolinium-based contrast agents (GBCAs) are widely used in MRI with 30 million doses administered per year worldwide.[1] Recent studies have shown gadolinium deposition in the brains of patients receiving GBCA for multiple indications, especially in the dentate nucleus,[2] even in those without brain disease.[3] These findings have raised concerns about the stability of gadolinium chelation and safety.[1] Structurally, GBCAs are classified into linear and macrocyclic types, where linear GBCAs wrap around the gadolinium atom and macrocyclic GBCAs trap the gadolinium atom in a cage-like structure. Animal studies have shown greater GBCA deposition[4] and MRI signal change[5] with linear GBCAs compared to macrocyclic GBCAs. Adverse effects of GBCAs are rare (0.01%-0.03%) and include allergic-like (sneezing, hives, and anaphylactic reaction) and physiologic (nausea and emesis) reactions.[6] Potential long-term effects include nephrogenic systemic fibrosis in patients with chronic kidney disease (<0.07%).[7]

In multiple sclerosis (MS), GBCA is used to detect active lesions as disease surveillance. MS patients receive repeated doses of gadolinium and undergo frequent physical and cognitive examinations. Thus, studying this patient population may reveal possible long-term deposition and potential detrimental neurological effects. Because prospective randomized trials evaluating the effect of GBCA on cognitive and physical functions are not feasible, retrospective studies utilizing routinely acquired data in a large population may be the best alternative to investigate potential associations. Regarding MRI signal changes, several studies have investigated the relationship between GBCA exposure and regional signal changes in the dentate nucleus and globus pallidus,[8–14] as well as areas in deep gray structures (substantia nigra and red nucleus)[15] with most studies finding correlations between GBCA exposure and signal changes. However, many studies were small in MS, with fewer than 100 MS patients. In addition, several studies investigated the association between the signal change and clinical measures, yielding conflicting results.[13,14] At present, the clinical significance of GBCA deposition remains uncertain.

The objective of this study was to investigate the relationship between (1) GBCA exposure and MR signal intensities in the dentate nucleus, globus pallidus, substantia nigra, and red nucleus, and (2) GBCA exposure and clinical disability measures, using a large cohort of MS patients.

METHODS

We performed two analyses: cross-sectional and longitudinal. In the cross-sectional analysis, contrast ratios, defined as a ratio of mean voxel intensity within tissues of interest (dentate nucleus, globus pallidus, substantia nigra, and red nucleus) and that in reference tissues (middle cerebellar peduncle, head of caudate, central medial nucleus of thalamus), as well as disability measures were obtained at a single timepoint in each patient. In the longitudinal analysis, at least two clinical and corresponding standardized MRI sessions on consistent scanners and consistent weight-based contrast dosing were required to investigate the change in contrast ratios and in disability measures related with additional GBCA exposure. The study was approved by the local institutional review board.

Data

MRI and electronic health records from MS patients followed at our center between 2015 and 2018 were included. Based on records of 9612 clinical visits from 4733 unique MS patients, 3397 standardized MRIs within 6 months of a clinical visit were identified. To improve the reliability of record review and reduce patient variability, additional inclusion criteria for cross-sectional analysis were diagnosis in 2004 or later and disease duration less than 12 years.

From the electronic health record, demographic and clinical information were collected, including age at the clinical visit, disease duration based on the diagnosis year and visit date, Patient-Determined Disease Steps (PDDS), and performance measures (walking speed test [WST], manual dexterity test [MDT], and processing speed test [PST]). PDDS is a self-reported disability measure with scores from 0 to 8 ranging from normal to bedridden[16]; WST is an iPad implementation of Timed 25-foot Walk measured as completion time in seconds; MDT is an iPad-adapted version of 9-Hole Peg Test and measures an average of completion time of both hands in seconds; and PST is an iPad implementation of Symbol Digit Modalities Test, reported as the number of correct answers in 2 minutes.[17–19] Increases in PDDS, WST, and MDT and a decrease in PST represent worse outcomes.

To obtain the history of GBCA for each patient, all previous MRI records (brain and other body regions) were retrieved. The specific brand of GBCA used (gadoxetate disodium, gadoversetamide, gadodiamide, gadobenate dimeglumine, gadopentetate dimeglumine, gadoteridol, gadoterate meglumine, gadobutrol, or unknown) was identified. We classified GBCA into linear, macrocyclic, or not-specified types and determined the cumulative numbers of MRI sessions with linear, macrocyclic, and total GBCAs. In this retrospective observational study, we did not have control over the use and the brand of GBCA for each patient. These MRIs were not analyzed; only the date and GBCA information were retrieved, as these scans included nonstandardized scans as well as nonbrain scans.

Image analysis

For the measurements of contrast ratios, standardized MRIs[20] were acquired on six 3T scanners, which included sagittal T1-weighted 3-dimensional magnetization-prepared rapid gradient-echo and sagittal 3-dimesnional fluid-attenuated inversion recovery. Conventional MRI-derived measures of whole brain fraction (WBF) and T2 lesion volume were also calculated using in-house methods.[21,22] Briefly, WBF was a ratio of brain parenchymal volume to the outer contour volume within dura obtained by brain extraction based on nonlocal segmentation technique,[23] and T2 lesions were segmented using

U-net convolutional neural network that had Dice of .699 compared to manual segmentation.

Using an atlas-based algorithm, we segmented the globus pallidus, caudate nucleus head, dentate nucleus, juxta-dentate middle cerebellar peduncles, substantia nigra, red nucleus, and central medial nucleus of thalamus. Briefly, custom nonlinear atlas images were created[24] after lesion-inpainting with FSL[25] from 245 MS patients, not in the study, to the ICBM T1-weighted template.[26] An experienced analyst (KN) manually segmented these structures once on the average template image. The seven regions-of-interest (ROI) were warped to the patients MRIs. Within the ROIs, mean intensities were determined from precontrast standardized scans.

To account for spatial, scanner, and sequence variability, contrast ratios were created using the mean intensities of ROIs divided by the mean intensities of caudate for globus pallidus, central medial nucleus for substantia nigra and red nucleus, and normal-appearing middle cerebellar peduncles for dentate nucleus. T2 lesions were excluded from ROIs to reduce the effect of MS-related white matter abnormality, and segmentation was manually edited when necessary. For the cross-sectional analysis, this image analysis was performed once per patient, and for the longitudinal analysis, it was repeated for the follow-up scans, resulting in multiple contrast ratio measurements in each patient. The longitudinal comparisons for a patient were performed on scans acquired consistently on the same scanners; measurements obtained across different scanners were not included in the analysis.

Statistical analysis

For the cross-sectional analysis, Spearman's rank correlation coefficients (SRCC) were calculated for univariate analyses among all the variables (total number of GBCA exposures, number of linear GBCA exposures, number of macrocyclic GBCA exposures, contrast ratios in the globus pallidus, dentate nucleus, substantia nigra, and red nucleus, WBF, T2 lesion volume [LV], age, disease duration, PDDS, WST, MDT, and PST). Linear models were used to predict the contrast ratio in the ROIs with adjustment for age, disease duration, WBF, T2LV, number of linear GBCA exposures, and macrocyclic GBCA exposures. For clinical correlations, linear models were used to model PDDS, WST, MDT, and PST. For PST and MDT, previous number of examinations were included to account for practice effects.

For the longitudinal analysis, we selected the patients with follow-up scans 0.5-1.5 years apart and grouped them into those with or without at least one GBCA. The effects of additional GBCAs on MRI (as measured by model coefficients), patient-reported outcome, and performance measures were determined using a linear mixed effect model. All available data were included; for example, MRI timepoints could be missing one or more clinical variables. The MRI-dependent variables were contrast ratios, and the clinical dependent variables were PDDS, WST, MDT, and PST. The fixed effects were baseline age, baseline disease duration, baseline WBF, baseline T2LV, dichotomized GBCA status since the baseline MRI (none or any GBCA), and the interaction between GBCA status and interval since baseline scan. A patient random effect was used. Thus, the potential cumulative gadolinium accumulation is accounted effectively as this random patient effect. We used the Bonferroni correction and set the significance level to .003 (16 cross-sectional and six longitudinal analyses) and .0007 in the univariate correlation matrix (70 correlations). We report the raw *p*-values. The analyses were performed with R.

RESULTS

Cross-sectional analysis

For the cross-sectional analysis, records from 1059 patients were obtained. Characteristics are shown in Table 1. Examples of T1 hyperintense regions are shown in Figure 1. A total of 463 patients had never received linear GBCA, 106 patients had never received macrocyclic GBCA, 25 patients received only linear GBCA, 278 patients received only macrocyclic GBCA, and 573 patients received both types. The maximum number of MRI sessions with GBCA was 25. The most common contrast agents were gadopentetate dimeglumine ($n = 1418$ sessions), gadobutrol ($n = 1338$), and gadoterate meglumine ($n = 1961$).

Scatter plots of contrast ratios and number of GBCA MRI sessions are shown in Figure 2 for linear (red), macrocyclic (blue), and total GBCA (black), for the globus pallidus (A) and dentate nucleus (B), showing increase in the slopes of linear GBCA in both structures, but not macrocyclic GBCA. There were no significant correlations in substantia nigra and red nucleus. Linear model adjusting for age, disease duration, WBF, and T2LV showed similar results (Table 2). One administration of linear GBCA was associated with increased contrast ratio ($p < .001$) by 0.3%-0.4% in both the globus pallidus and dentate nucleus (Table 2).

In the univariate analysis of contrast ratios and patient-reported and performance outcomes, the contrast ratios in globus pallidus and substantia nigra showed weak correlations with PDDS, MDT, and PST (Figure 3; $p < .0007$), but not in dentate nucleus or red nucleus.

The comprehensive linear model predicting patient-reported and performance outcomes with all variables (Table 2) showed weak associations between PDDS and linear GBCA exposures and between MDT and macrocyclic GBCA exposures ($p < .003$). The signs of these coefficients indicated that patients were less disabled with greater number of respective GBCA exposures. Excluding the contrast ratios from these models did not change significant variables. In all the models predicting clinical outcomes, T2LV was consistently significant ($p < .001$).

Since it was possible that some patients were followed elsewhere initially and we did not capture their early MRIs and GBCA history, we performed a post hoc sensitivity analysis in the patients who had the first MRI in the diagnosis year or before ($n = 549$). The associations with contrast ratios remained. The magnitude of coefficients for patient-reported and performance measures became smaller and nonsignificant, but their signs remained the same.

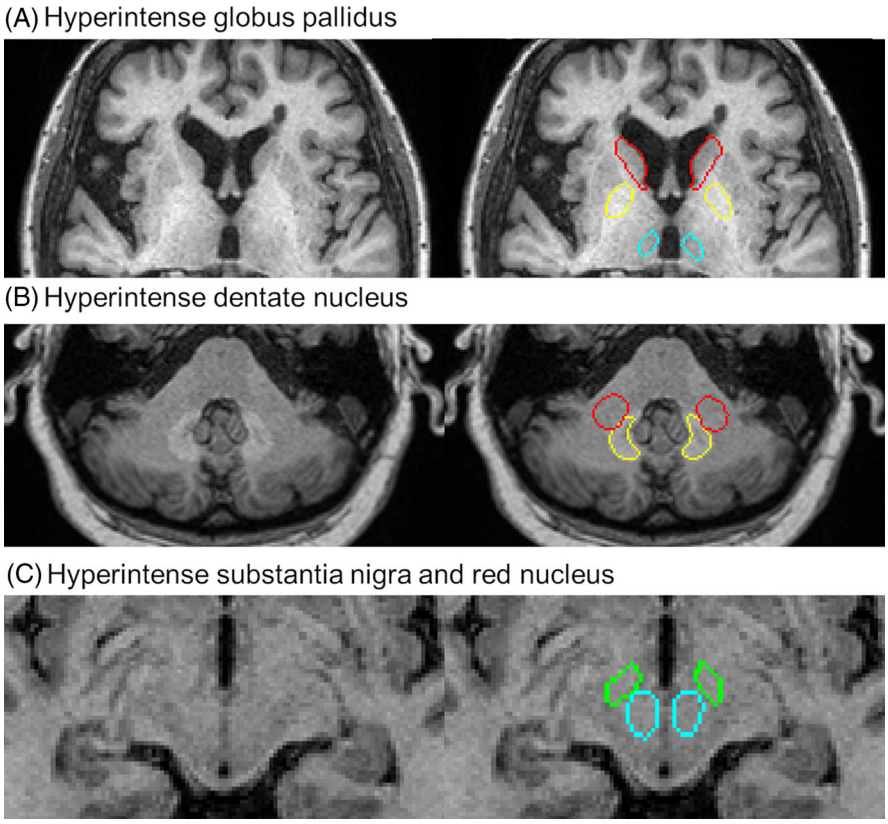

FIGURE 1 Examples of hyperintense globus pallidus (yellow), caudate (red, reference area), and central medial nucleus (cyan) (A), dentate nucleus (yellow) and juxta-dentate white matter (red) (B), and substantia nigra (green) and red nuclei (cyan) (C), overlaid on T1-weighted precontrast scans

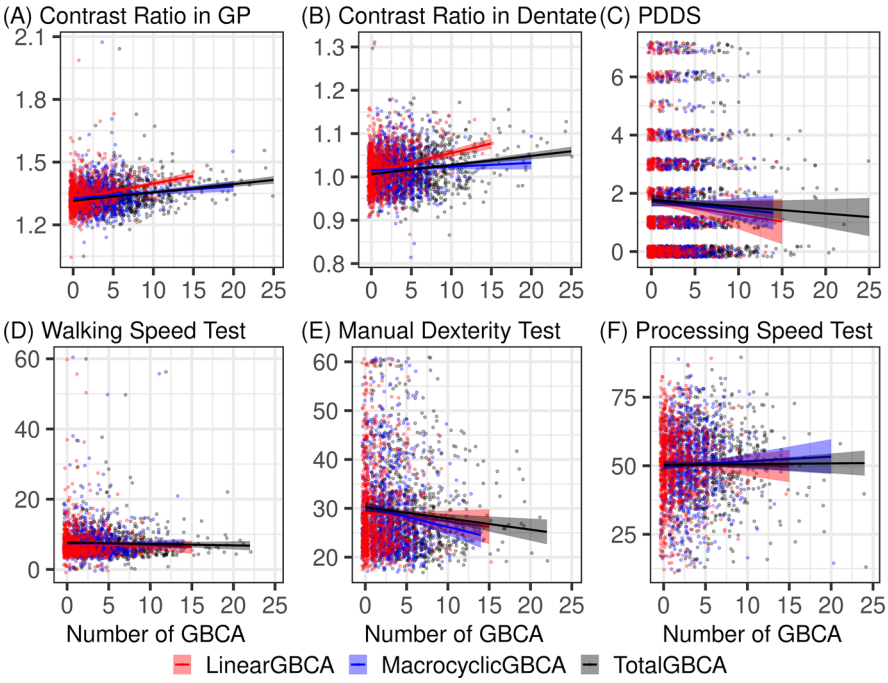

FIGURE 2 Scatterplots of contrast ratios in the globus pallidus (GP, A), dentate (B), patient-determined disease steps (PDDS, C), walking speed test in seconds (D), manual dexterity test in seconds (E), and number of correct answers in processing speed test (F); for total number of gadolinium-based contrast agent (GBCA) exposures (black), for linear GBCA (red), and for macrocyclic GBCA (blue). A jitter is added in both *x*- and *y*-axes for visualization purposes; shaded area represents 95% confidence interval of linear regression lines.

TABLE 1 Patient characteristics for the cross-sectional (left) and baseline characteristics for longitudinal (right) data

		Longitudinal data at baseline			
	Cross-sectional data ($n = 1059$)	GBCA-free group ($n = 46$)	GBCA+ group ($n = 393$)	Total ($n = 439$)	p-value between GBCA± groups
Age, years	44.0 ± 11.2	42.9 ± 10.0	46.3 ± 10.9	45.9 ± 10.8	.049
Female proportion (%)	69.6	73.9	70.2	70.6	.728
Follow-up interval (last visit), years	NA	1.18 ± 0.45	1.12 ± 0.43	1.12 ± 0.43	.370
Number of follow-up MRIs (min, max)	NA	1.39 (1, 2)	1.30 (1, 3)	1.30 (1, 3)	.294
Whole brain fraction	0.820 ± 0.030	0.811 ± 0.032	0.813 ± 0.033	0.813 ± 0.033	.642
T2 lesion volume, ml	23.1 ± 22.1, $n = 1054$	27.8 ± 23.4	28.4 ± 25.7	28.4 ± 25.4	.879
Disease duration, years	6.7 ± 3.8	10.7 ± 7.5	11.5 ± 9.7	11.5 ± 9.5	.593
Globus pallidus contrast ratio	1.354 ± 0.045	1.379 ± 0.061	1.383 ± 0.066	1.382 ± 0.065	.699
Dentate nucleus contrast ratio	1.018 ± 0.034	1.025 ± 0.033	1.024 ± 0.037	1.024 ± 0.037	.859
PDDS	1.65 ± 1.98, $n = 1025$	1.91 ± 2.19, $n = 43$	1.98 ± 2.20, $n = 365$	1.97 ± 2.20, $n = 408$	.847
WST	7.43 ± 4.52, $n = 967$	7.45 ± 3.21, $n = 37$	7.96 ± 5.35, $n = 344$	7.91 ± 5.18, $n = 381$	.574
MDT	29.0 ± 8.7, $n = 999$	26.9 ± 8.2, $n = 36$	30.2 ± 9.0, $n = 364$	29.9 ± 9.0, $n = 400$	.037
PST	50.4 ± 13.2, $n = 895$	48.6 ± 14.0, $n = 40$	48.8 ± 14.0, $n = 333$	48.8 ± 14.0, $n = 373$	.998
Disease modifying therapy					
Monoclonal antibody (alemtuzumab, natalizumab, ocrelizumab, and rituximab), n (%)	380 (36%)	28 (61%)	180 (46%)	208 (47%)	<.001
Other (dimethyl fumarate, fingolimod, glatiramer acetate, interferon, teriflunomide), n (%)	534 (51%)	18 (39%)	179 (46%)	197 (45%)	<.001
Untreated, n (%)	140 (13%)	0 (0%)	34 (9%)	34 (8%)	<.001

Note: All the data represent mean ± standard deviation unless otherwise indicated.
Abbreviations: max, maximum; MDT, manual dexterity test; min, minimum; *n*, number; NA, not available; PDDS, Patient-Determined Disease Steps; PST, processing speed test; WST, walking speed test.

Longitudinal analysis

For the longitudinal analysis, 511 patients with serial MRIs were identified. We removed 7 patients with unknown GBCA and 1 patient with linear GBCA (gadobenate dimeglumine). The remaining patients all received gadoterate meglumine. The criteria of follow-up interval of 0.5-1.5 years yielded 439 patients of whom 46 were GBCA free during the interval, and 393 had at least one GBCA. Their baseline characteristics are summarized in Table 1. The linear mixed effect model showed no significant interaction of time and GBCA status (time × GBCA on Table 2) on contrast ratios in any ROIs ($p > .3$), consistent with the cross-sectional analysis. The results did not change when the difference in contrast ratios was analyzed with a linear model. There was no association of macrocyclic GBCA administration with PDDS, WST, MDT, or PST ($p > .2$).

DISCUSSION

This study aimed to find possible associations between the number of GBCA administrations and self-reported disability and performance measures by analyzing clinical and imaging records from a large number of MS patients. In the cross-sectional univariate analysis, the number of linear GBCA administrations correlated with the contrast ratios in globus pallidus and dentate nucleus but not in substantia nigra and red nucleus. In a univariate analysis, the contrast ratios in globus pallidus and substantia nigra weakly correlated with PDDS, MDT, and PST, which could suggest an association between GBCA accumulation and patient disability. However, a linear model that adjusted for covariates no longer showed these associations. The comprehensive models reveal several associations, but they were not detrimental. In the longitudinal analysis, we failed to show association between GBCA administration and contrast ratios or with clinical outcomes.

In MS patients, given potential breakdown of the blood brain barrier, gadolinium may accumulate to a greater degree than in healthy individuals, but there are no reports that investigate this possibility specifically. When administered intravenously, GBCA is distributed throughout the intravascular compartment. It has been hypothesized that the gadolinium complex would not cross the blood-brain barrier, but recent studies have found gadolinium in autopsied brain sampled from subjects without neurological or renal dysfunction.[3,27] In MS, the blood-brain barrier is permeable during active inflammation, and gadolinium leaks into the interstitial space of the brain parenchyma.

TABLE 2 Coefficients ± standard error of linear models

Contrast ratios and number of GBCA administrations in linear model from cross-sectional data

Dependent variable	Number of linear GBCA	Number of macro-cyclic GBCA	Age (year)	DD (year)	WBF	T2LV (ml)
Contrast ratio in globus pallidus	0.0041 ± 0.0007**	−0.0004 ± 0.0006	−0.0003 ± 0.0001	0.0016 ± 0.0004**	−0.0141 ± 0.0018**	−0.0002 ± 0.0001*
Contrast ratio in dentate nucleus	0.0034 ± 0.0005**	−0.0003 ± 0.0004	−0.0001 ± 0.0001	0.0015 ± 0.0003**	−0.0003 ± 0.0014	0.0000 ± 0.0001
Contrast ratio in substantia nigra	−0.0001 ± 0.0005	−0.0008 ± 0.0004*	0.0006 ± 0.0001**	0.0006 ± 0.0003*	−0.0046 ± 0.0012**	−0.0001 ± 0.0000*
Contrast ratio in red nucleus	−0.0009 ± 0.0004*	−0.0004 ± 0.0003	−0.0002 ± 0.0001**	0.0002 ± 0.0002	−0.0061 ± 0.0010**	0.0000 ± 0.0000

Patient-reported and performance outcomes, contrast ratios, and number of GBCA administrations in linear model from cross-sectional data

Dependent variable	Number of linear GBCA	Number of macro-cyclic GBCA	Globus pallidus	Dentate nucleus	Substantia nigra	Red nucleus	Age (year)	DD (years)	WBF	T2LV (ml)	Number of previous exams
PDDS	−0.1314 ± 0.0328**	−0.0238 ± 0.0266	3.1241 ± 1.5517*	3.6075 ± 1.8839	0.1055 ± 3.2488	7.2290 ± 3.8476	0.0385 ± 0.0068**	0.0183 ± 0.0189	−0.0747 ± 0.0878	0.0161 ± 0.0035**	NA
WST	−0.2334 ± 0.0825*	−0.0163 ± 0.0647	4.0891 ± 3.8161	2.5606 ± 4.6984	1.7716 ± 7.9734	3.3510 ± 9.4671	0.0465 ± 0.0167*	0.0613 ± 0.0467	−0.1426 ± 0.2176	0.0347 ± 0.0090**	NA
MDT	−0.3451 ± 0.1434*	−0.3850 ± 0.1176**	10.7697 ± 6.6974	−7.665 ± 8.22333	18.8329 ± 14.0313	20.5443 ± 16.5540	0.0448 ± 0.0290	0.0832 ± 0.0806	−0.9337 ± 0.3669*	0.1248 ± 0.0141**	−0.5732 ± 0.2151
PST	0.3982 ± 0.2149	0.0404 ± 0.1692*	−14.2062 ± 9.7091	12.4182 ± 11.7327	−30.9886 ± 20.6761	−12.3257 ± 23.8832	−0.3299 ± 0.0424**	0.0842 ± 0.1195	2.3193 ± 0.5302**	−0.1764 ± 0.0202**	1.7586 ± 0.3209*

Linear mixed effect linear model from longitudinal data

Dependent variable	Time interval between scans (year)	Baseline WBF	Baseline T2LV (ml)	Baseline DD (year)	Baseline age (year)	GBCA status	Time interval between scans × GBCA status	Number of previous exams
Contrast ratio in globus pallidus	0.0025 ± 0.0026	−0.0185 ± 0.0029**	0.0007 ± 0.0001**	0.0004 ± 0.0004	0.0003 ± 0.0003	0.0019 ± 0.0072	0.0011 ± 0.0027	NA
Contrast ratio in dentate nucleus	−0.0014 ± 0.0014	0.0007 ± 0.0023	0.0002 ± 0.0001*	0.0000 ± 0.0002	0.0003 ± 0.0002	0.0014 ± 0.0056	−0.0003 ± 0.0015	NA
Contrast in substantia nigra	0.0065 ± 0.0024*	−0.0084 ± 0.0017**	−0.0002 ± 0.0001	−0.0006 ± 0.0003	0.0008 ± 0.0003**	0.0020 ± 0.0044	−0.0026 ± 0.0026	NA
Contrast in red nucleus	0.0065 ± 0.0023*	−0.0047 ± 0.0013**	0.0000 ± 0.0001	−0.0002 ± 0.0003	0.0001 ± 0.0002	−0.0009 ± 0.0035	−0.0017 ± 0.0024	NA
PDDS	−0.0789 ± 0.1376	−0.2961 ± 0.1263*	0.0157 ± 0.0050**	0.0176 ± 0.0182	0.0029 ± 0.0154	0.2429 ± 0.3251	0.0894 ± 0.1457	NA
WST	−0.3941 ± 0.3810	−0.6519 ± 0.3755	0.0357 ± 0.0147*	−0.0230 ± 0.0571	0.0065 ± 0.0488	0.9443 ± 0.9521	0.4368 ± 0.3992	NA
MDT	0.0376 ± 0.9514	−2.1913 ± 0.4900**	0.0729 ± 0.0193**	0.0729 ± 0.1164	−0.0676 ± 0.1125	2.3695 ± 1.3430	−1.0275 ± 0.8663	0.2244 ± 0.2747
PST	0.1776 ± 0.8316	4.6790 ± 0.6997**	−0.1622 ± 0.0277**	−0.0641 ± 0.0995	−0.1208 ± 0.0868	−0.4854 ± 1.7312	0.0231 ± 0.7711	0.5070 ± 0.2425*

Note: The dependent variables are listed on the left column and the independent variables are shown on the first row for cross-sectional and longitudinal analyses.

Abbreviations: DD, disease duration; MDT, manual dexterity test; NA, not available; PDDS, Patient-Determined Disease Steps; PST, processing speed test; T2LV, T2 lesion volume; WBF, whole brain fraction; WST, walking speed test.

*$p < .05$; **$p < .003$.

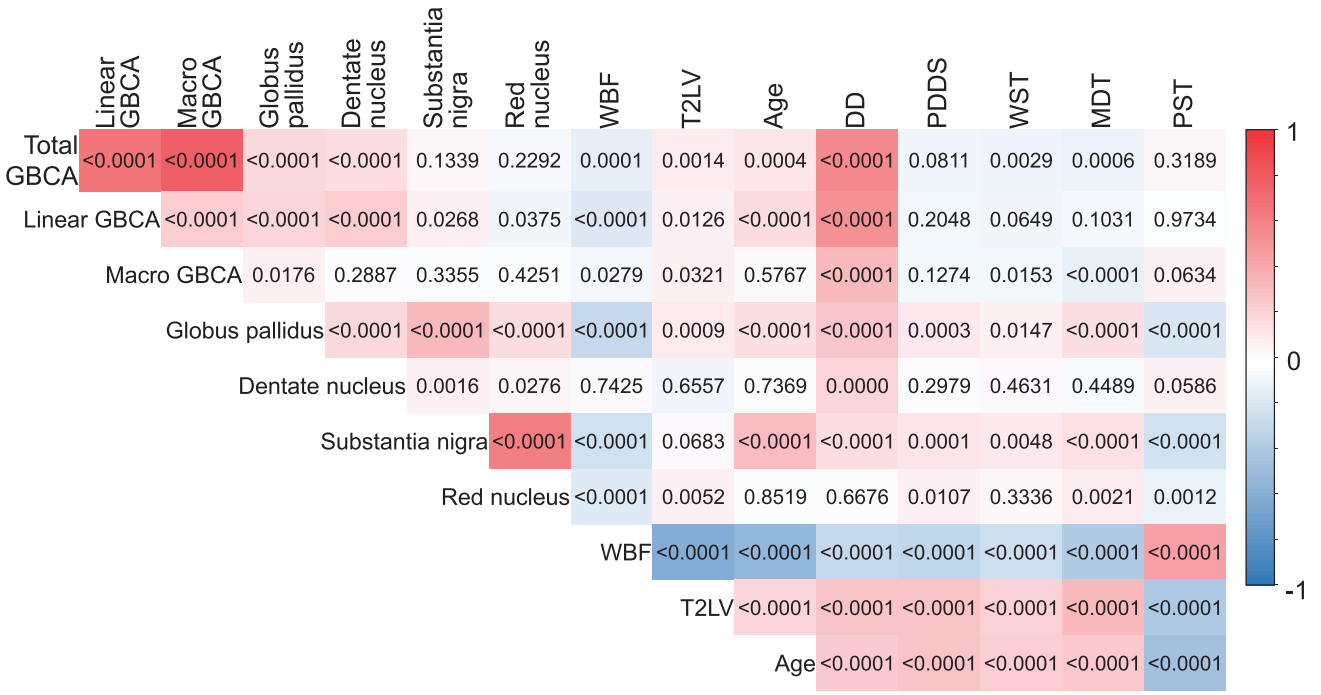

FIGURE 3 Univariate *p*-value matrix using Spearman's rank correlation coefficient. Numbers indicate *p*-values, and the color scale indicates the Spearman's rank correlation coefficient. DD, disease duration; PDDS, Patient-Determined Disease Step; WST, walking speed test; MDT, mean dexterity test; WBF, whole brain fraction; PST, processing speed test; T2LV, T2 lesion volume

Once in the parenchyma, if not excreted rapidly, gadolinium ions may become unchelated. It is not clear if there is a diffuse increase in blood-brain barrier permeability in MS, allowing GBCA to enter the parenchyma without focal active contrast-enhancing lesions. Gadolinium's potential toxic effects on the nervous system are hypothesized to be associated with its competition with calcium ions in voltage-gated calcium channels and binding with phosphate resulting in altered regulation of some cytokines.[28] It is unclear if microglia and macrophages, commonly found in MS active lesions, clear GBCA molecules, free gadolinium ions, or other gadolinium-bound molecules.

Despite the observational nature of the study, weak but significant associations were found between PDDS and linear GBCA, and MDT and macrocyclic GBCA ($p < .003$). However, surprisingly, the results indicated better outcomes with greater GBCA exposures. It is possible that some of the covariates with higher association with performance measures such as T2LV and brain atrophy overshadowed the effect of GBCA. It is also possible that the more frequently scanned patients are more closely monitored, more intensively treated, and, as a result, might have had better outcomes. Some higher efficacy therapies require more frequent MRI surveillance for complications. In fact, the patients on monoclonal antibodies (alemtuzumab, natalizumab, ocrelizumab, or rituximab) had more frequent MRIs on average (mean [standard deviation] 1.164 [0.767] scans/year, $n = 380$) than patients on other therapies (dimethyl fumarate, fingolimod, glatiramer acetate, interferon, or teriflunomide) (1.017 [0.721] scans/year, $n = 534$) or untreated patients (1.061 [0.932] scans/year, $n = 140$). Also, a previous study that examined patients with secondary progressive MS in a clinical trial who received five or more GBCA exposures also showed a trend for better outcome over 2 years on expanded disability status scale and MS functional composite when compared to the group with four or fewer GBCA exposures ($p = .09$).[8] The fact that other variables such as T2LV significantly correlate with clinical outcome measures suggests that the effect of GBCA exposure is smaller or more variable than effects related to the MS disease process.

We have performed post hoc sensitivity analyses on both cross-sectional and longitudinal data by removing covariates. Some additional associations were found in cross-sectional analysis: between linear GBCA and red nucleus contrast ratio, between linear GBCA and substantia nigra contrast ratio, and between macrocyclic GBCA in substantia nigra contrast ratio; and an association was lost in longitudinal study: between linear GBCA and PDDS. However, our overall conclusion did not change.

The results from the longitudinal analysis revealed several associations between contrast ratios and age, disease duration, and WBF even after accounting for the GBCA exposures, suggesting that the patients with more disease burden or even normal aging may have reduced gadolinium clearance and greater retention.[29]

Several limitations exist in this study. We report the measures of physical and cognitive disability commonly used in MS, which capture a range of neurologic dysfunction including overall disability (PDDS), lower extremity function (WST), upper extremity function (MDT), and cognition (PST). While there are no studies to directly associate these performance measures to the health of investigated structures (globus pallidus, dentate nucleus, substantia nigra, and red nucleus), these

structures are associated with motor control and cognitive executive functions. The effects of GBCA on nonneurologic impairment beyond these functions were not evaluated here. Disease-modifying therapy was not formally accounted for in this study. Observational studies often lack correlations between therapies and clinical disability measures as there is no randomization or control over the therapy, and the interpretation of therapeutic effect is typically difficult. Similarly, we did not capture renal function. However, it has been shown that the subjects with normal renal function also have gadolinium accumulation in autopsied brains as measured by inductively coupled plasma mass spectroscopy.[27] Finally, as the study is retrospective and observational, we did not have control over missing data and timing of data collection.

The trade-off between the potential toxicity of GBCA and benefit in medical diagnosis depends on the disease of concern. Here, we focused on MS, one of the most frequently scanned patient groups with almost 1 million patients in the United States.[30] The Consortium of MS Centers 2018 MRI guidelines state that GBCA is indispensable for diagnosis of MS and subsequent monitoring for lesion activity. Subclinical MRI activity can be identified as enhancement of plaques on postcontrast imaging and that information can be used to determine treatment response.[31,32] Since most contrast-enhancing lesions result in T2 lesions, advanced standardization of MRI protocols[33] and image analysis software for new or enlarging T2 lesions may circumvent the need for GBCA during disease monitoring.[22,34,35] Machine learning for prediction of gadolinium-enhancing lesions from noncontrast scans is also active area of research.[36] Furthermore, gadolinium-enhancing lesions are less common than new or enlarging T2 lesions, and presumably less sensitive to subclinical activity.[37] Since there was no detrimental association between performance measures and GBCA exposures, our study suggests that GBCA can be used, but the best practice may be to shift toward standardization of MRI acquisitions and postprocessing in order to reliably capture new T2 lesions.

In conclusion, in our large cohort of MS patients, while signal hyperintensity in the dentate nucleus and globus pallidus correlated with increasing linear GBCA exposures, physical and cognitive worsening was not found, suggesting that routine GBCA use may still be suitable for monitoring MS disease activity.

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