Intracranial Gadolinium Deposition

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MAYO CLINIC

Conflicts of Interest

GE Healthcare – Consultant & Investigator Initiated Research Support (all funds to Mayo); Bracco Diagnostics - Consultant & Investigator Initiated Research Support (all funds to Mayo); Bayer Healthcare – RSNA Grant Research Support (all funds to Mayo).

Intracranial Gadolinium Deposition

IT ALL STARTED with KANDA?

ORIGINAL RESEARCH ■ NEURORADIOLOGY

High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing Cumulative Dose of a Gadolinium-based Contrast Material[1]

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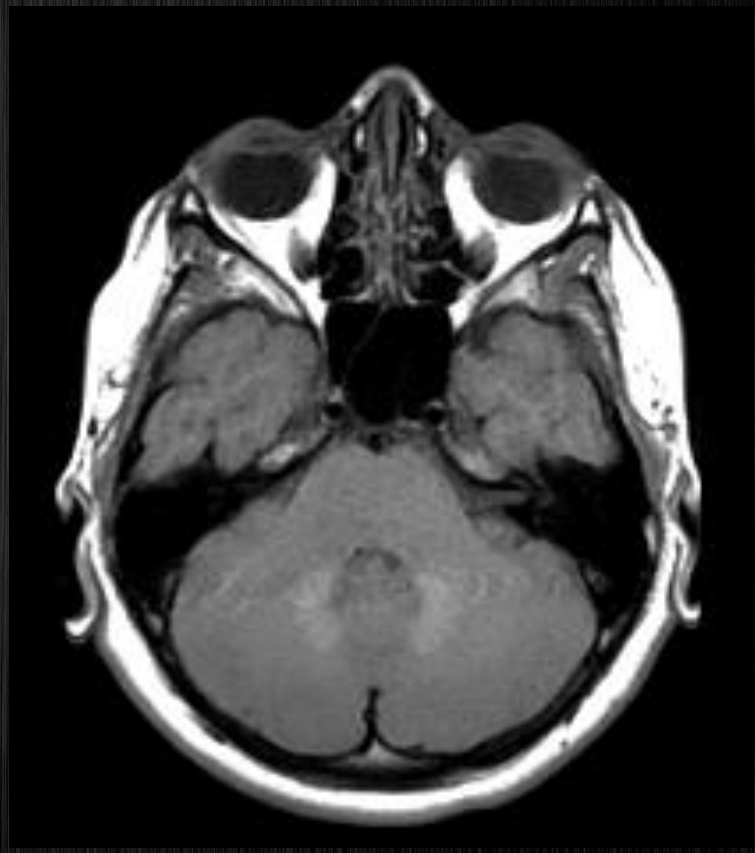
Kazuhiro Kitajima, MD, PhD
Daisuke Takenaka, MD, PhD

Purpose: To explore any correlation between the number of previous gadolinium-based contrast material administrations and high signal intensity (SI) in the dentate nucleus and globus pallidus on unenhanced T1-weighted magnetic resonance (MR) images.

Materials and Methods: The institutional review board approved this study, waiving the requirement to obtain written informed consent. A group of 381 consecutive patients who had undergone brain MR imaging was identified for

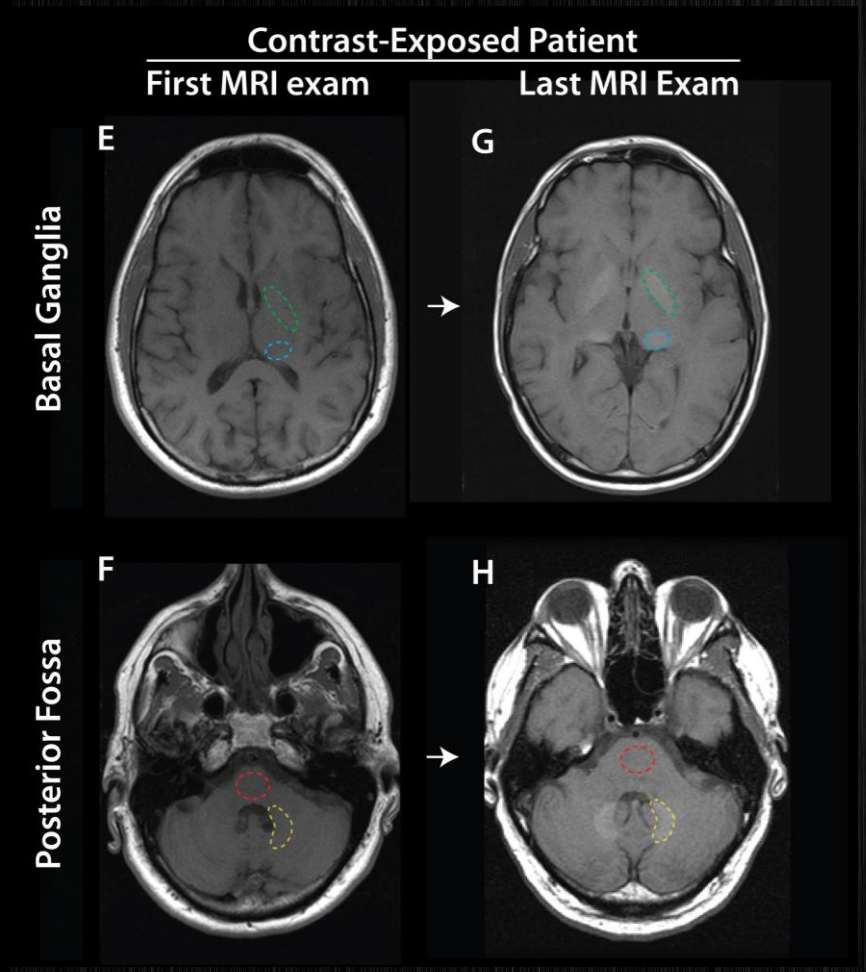
Radiology

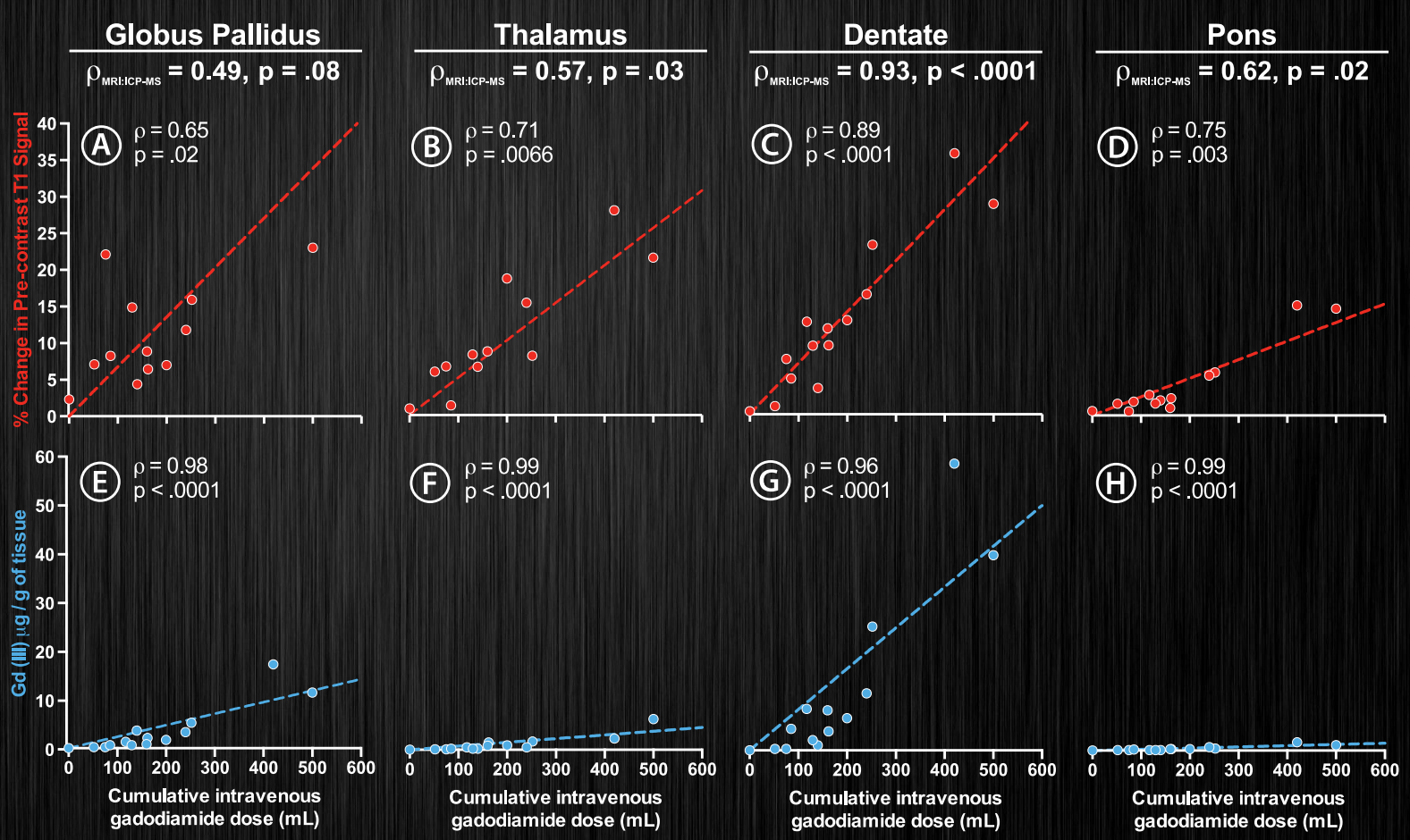


- Have we been misattributing the causes of T1 hyperintensities?
- Are these hyperintensities due to Gadolinium?

Intracranial Gadolinium Deposition

CONFIRMATORY EVIDENCE USING MASS-SPECTROMETRY OF POST-MORTEM HUMAN TISSUE





McDonald et al, Radiology 2015

Intracranial Gadolinium Deposition

CONFIRMATORY EVIDENCE USING MICROSCOPY OF POST-MORTEM HUMAN TISSUE

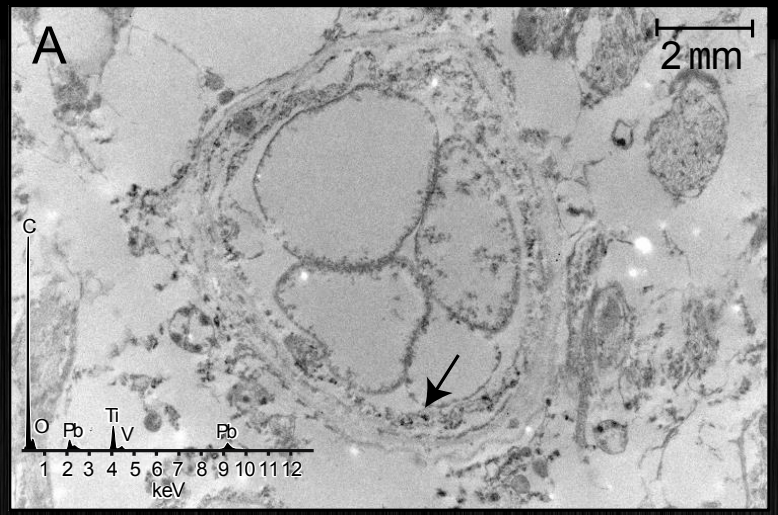
Control Patient

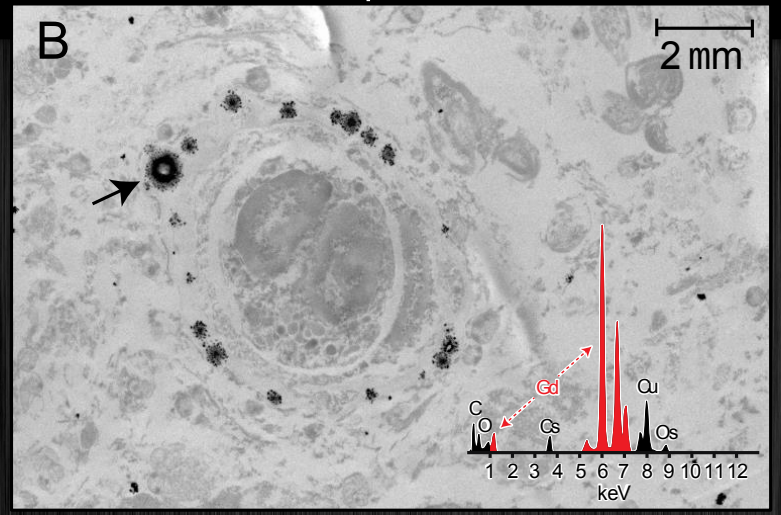
Contrast-Exposed Patient

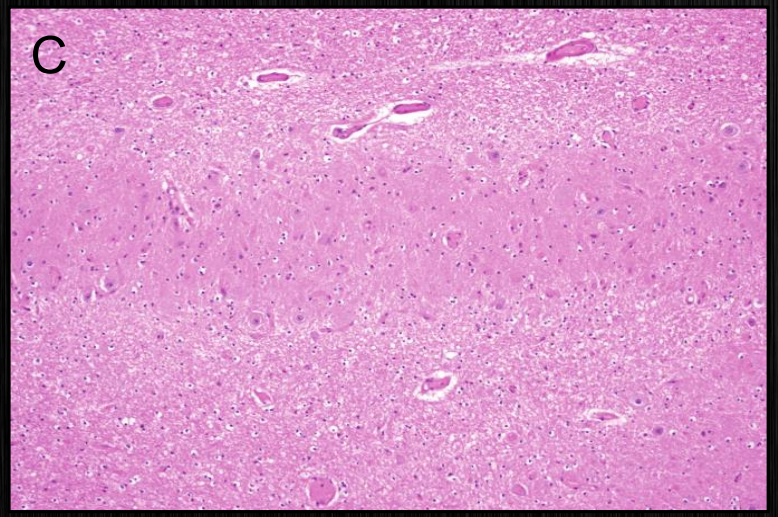
Gadolinium Exposed Patient

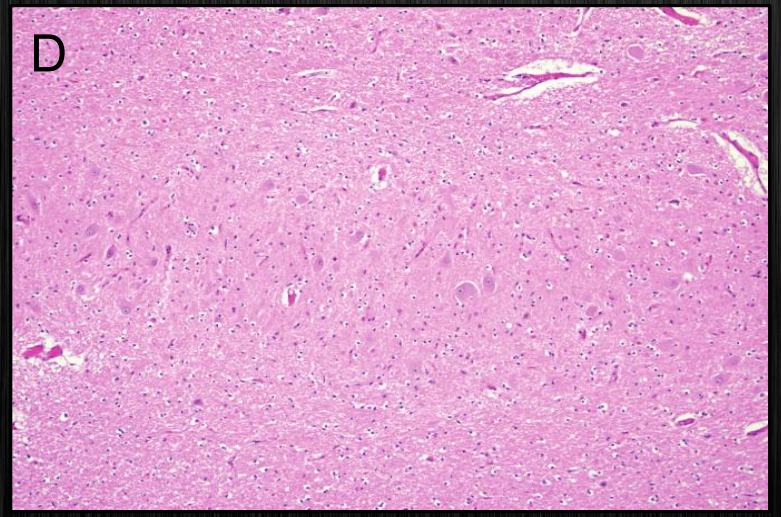
TEM

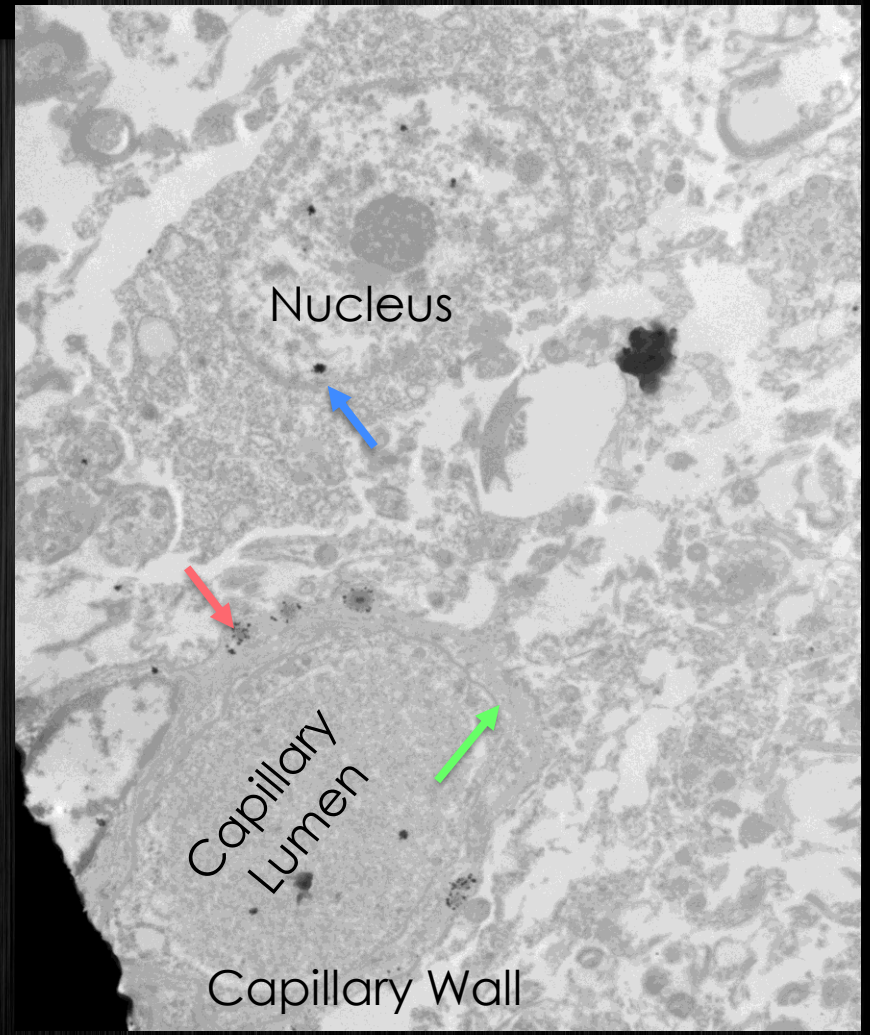
Light Microscopy











McDonald et al, Radiology 2015

Intracranial Gadolinium Deposition

PRECLINICAL MODEL OF GD DEPOSITION

- Gadolinium tissue concentration is not entirely class-dependent
- Gadavist levels are much higher than ProHance, and within 2-4 –fold of linear agents.
- Similar pattern of differentiation is seen in other organs, at higher [Gd].

McDonald et al, Radiology 2017

Gadolinium Deposition

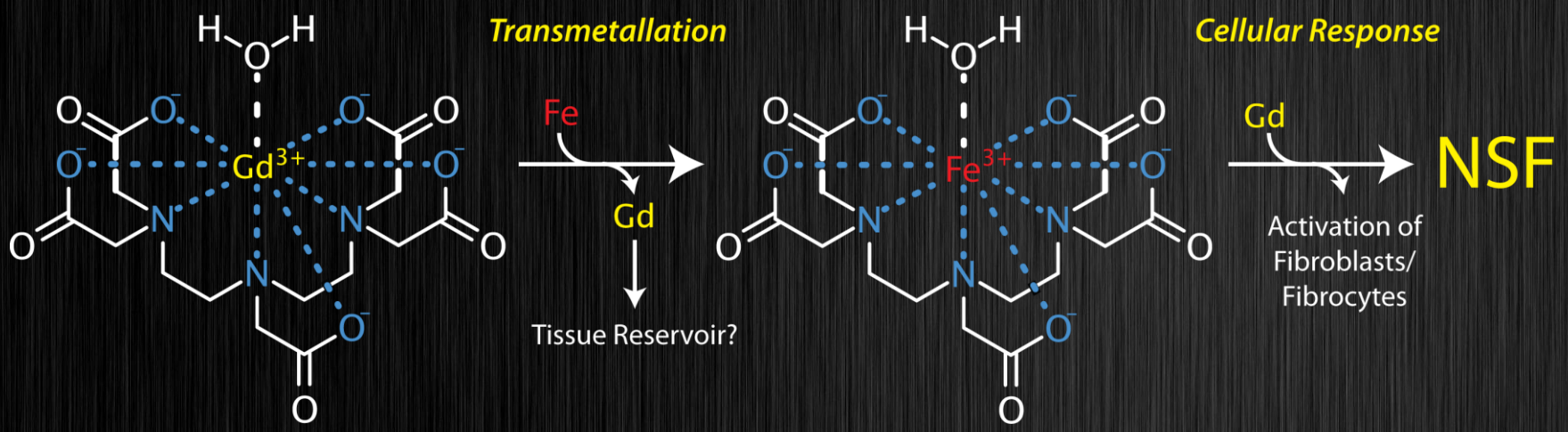
STATUS OF FINDINGS & LINGERING QUESTIONS

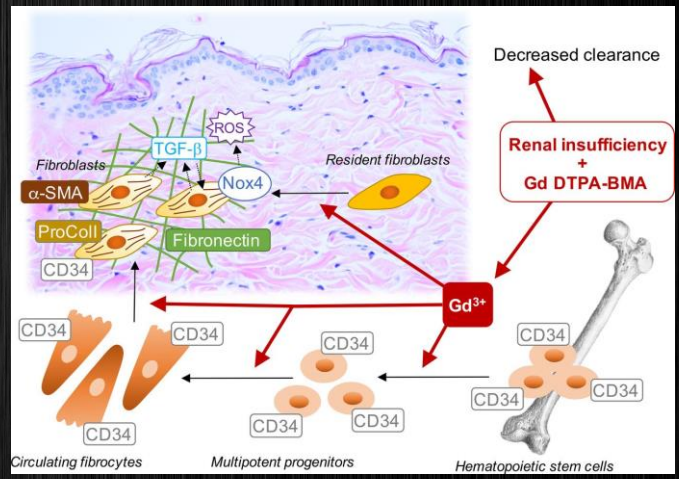
✓ Does Gd accumulate in CNS following GBCA administration? 

1. Is Gd accumulation limited to linear GBCA administration? 
2. What is the chemical form of these deposits? 
3. What is the mechanism of deposition? 
4. Are these deposits biologically active/toxic? 
5. Are there clinical symptoms of Gd deposition? 
6. Is gadolinium deposition the only meaningful safety issue? 
7. How safe are GBCAs – should I be worried? 

QUESTION: Are Gd Deposits Toxic?

NSF & OTHER MECHANISMS





Mechanisms	Study	Species/cells	Reference
Nephrotoxicity (reduced glomerular filtration rate)	In vitro	Renal tubular cells	Heinrich et al. 2007
Nephrotoxicity (acute tubular necrosis)	In vivo	Pigs	Elmstahl et al. 2006
Hematoxicity (reduced WBC count)	Case report	Human	Akgun et al. 2006
Hepatotoxicity (vacuolar degeneration, disorganized hepatic cords)	In vivo	Mice	Chen et al 2015
Pancreatitis	Case report	Human	Blasco-Perrin et al. 2013
Neurotoxicity (myoclonus, ataxia, tremor, neuronal death, and hemorrhage)	In vivo	Rats	Ray et al. 1996
Neurotoxicity (encephalopathy)	Case report	Human	Hui and Mullins 2009

QUESTION: Are Gd Deposits Toxic?

NSF & OTHER MECHANISMS

Mechanisms	Study	Test subjects/cells	Reference
Release of chemokines and subsequent attraction of CD34 + fibrocytes leading to fibrosis	In vitro	Human macrophages	Idee et al. 2014 Del Galdo et al. 2010
Stimulation of the expression and release of the cytokines a/w in tissue fibrosis development	In vitro	Human monocytes	Newton and Jimenez 2009
Induction of expression of a profibrotic chemokines and cytokines: IL-4, IL-6, IL-13, and VEGF in monocytes and type I and II collagen in fibroblasts	In vitro	Human monocytes Human fibroblasts	Wermuth and Jimenez 2014
Inhibition of stretch-activated and voltage-gated calcium channels Blockage of Ca2+-dependent enzymes (S-transferases, dehydrogenases, kinases, ATPase, and glutathione) Disruption of Ca2+ homeostasis	In vitro	Rat and human cells Isolated rat atrium Rat cortical neurons	Mlinar and Enyeart 1993 Laine et al. 1994 Xia et al. 2011
Induction of fibronectin expression, apoptosis, and necrosis in fibroblasts Induction of fibrocyte markers (CD34 and procollagen type I)	In vitro In vivo	Human fibroblasts Rats	Do et al. 2014
Mobilization of Fe and the differentiation of PBMCs into ferroportin-expressing fibrocytic cells	In vitro	Mice	Bose et al. 2015
Apoptosis	In vivo	Alveolar marcrophages Rat cortical neurons Hepatocytes	Mizgerd et al. 1996 Xia et al. 2011 Liu et al. 2003
Elevation of reactive oxygen species	In vivo	Rat cortical neurons Mitochondria	Xia et al. 2011 Liu et al. 2003
Blockage of ATP and ADP hydrolysis via stimulation of angiotensin II AT1 receptors	In vitro	Rat aortic rings	Angeli et al. 2011
Effects on ACE activity via transmetallation with zinc	In vitro In vitro	Rabbit lung ACE Rats	Corot et al. 1998

QUESTION: Are Gd Deposits Toxic?

PHARMACOTOXICITY OF GBCAS

Subclass	Trade Name	LD_{50} µmol/kg	CI µmol/kg	CNS ED_{50} µmol/kg	CI µmol/kg
Linear Non-ionic	Omniscan	208	149-308	47	22-86
Linear Ionic	Magnevist	740	480-1250	73	33-165
Macrocyclic Non-Ionic	Gadovist	86	64-115	18	8-33
Macrocyclic Non-Ionic	ProHance	46	34-62	20	8-29
Macrocyclic Ionic	Dotarem	58	43-78	31	19-44

- Macrocyclic GBCAs actually have significantly lower toxicity thresholds (LD50 & CNS ED50) than linear GBCAs following intrathecal administration in Wistar rat model.

Vogler H, et al. Eur J Radiol, 1995

QUESTION: Are Gd Deposits Toxic?

INCREASED SEIZURE RATE FOLLOWING MAGNEVIST ADMINISTRATION IN CANINE BRAIN FOLLOWING OSMOTIC DISRUPTION OF BBB

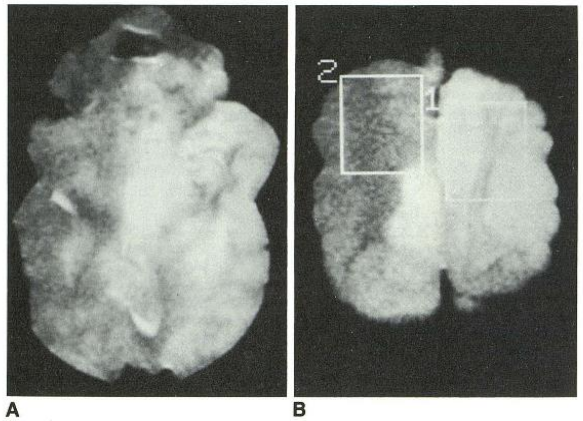
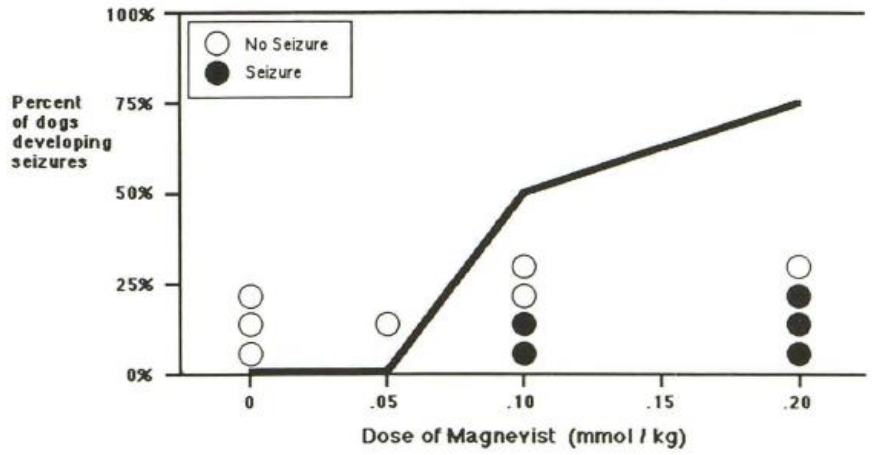


Fig. 2.—*A*, T1-weighted transaxial MR image (350/20/2) in animal 7 given 0.2 mmol/kg gadopentate dimeglumine intravenously after blood-brain barrier disruption and imaged 3 hr after disruption shows marked enhancement in disrupted left cerebral hemisphere.
B, T1-weighted image of same animal shows an example of how calculations were done for the MR ratio. The measured T1 value in area 1 in left cerebral hemisphere measured 274 vs 567 in area 2 in the nondisrupted right cerebral hemisphere, which shows T1 shortening due to enhancement in disrupted cerebral hemisphere.



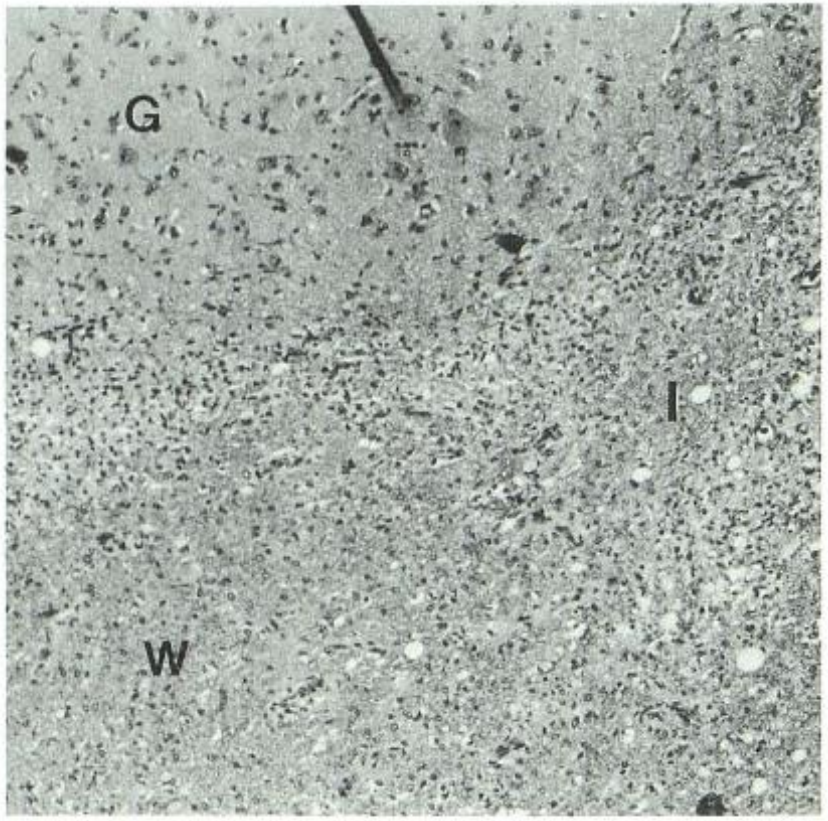


Fig. 4.—Histologic section of left frontal lobe in animal 16 shows small subacute infarct at gray-white junction. I = infarct; G = gray matter; W = white matter. (H and E, original magnification ×250).

Roman-Goldstein SM, et al. AJNR Am J Neuroradiol 1991;12(5):885–890.

QUESTION: Are Gd Deposits Toxic?

BEHAVIORAL CHANGES FOLLOWING GBCA ADMINISTRATION IN RAT BRAIN FOLLOWING OSMOTIC DISRUPTION OF BBB

Table 2. Number of animals showing behavioral changes within 1 h after intravenous injection of contrast agents at a dose of 3 mmol Gd/kg

Contrast agents	*N*	Grade of behavioral change 1	2	3
Gd-DTPA	10	10	0	0
Gd-DTPA-BMA	10	8	1	1
Gd-DO3A-butrol	10	7	2	1
Gd-DO3A-HP	10	1	5	4*†‡

N: number of animals in each group, * $p < .01$ vs. Gd-DTPA, † $p < .01$ vs. Gd-DTPA-BMA, ‡ $p < .05$ vs. Gd-DO3A-butrol.

N: number of animals in each group. * $p < .01$ vs. Gd-DTPA-BMA, † $p < .01$ vs. Gd-DO3A-butrol.

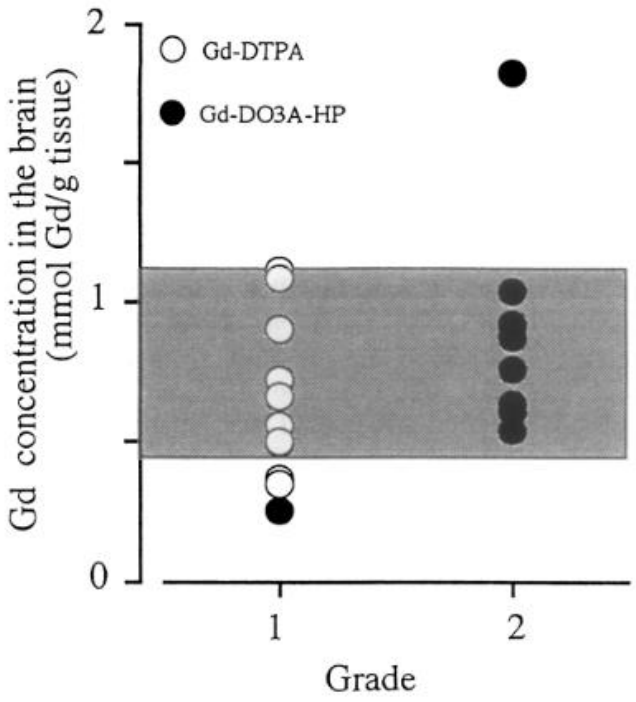


Fig. 1. Correlation between gadolinium concentration in the whole brain and behavioral score for individual animals with blood–brain barrier disruption 30 min after intravenous injection of Gd-DTPA (○) or Gd-DO3A-HP (●) at a dose of 3 mmol Gd/kg.

Takahashi M, et al Magn Reson Imaging. 1996;14(6):619-23.

QUESTION: Are Gd Deposits Clinically Significant?

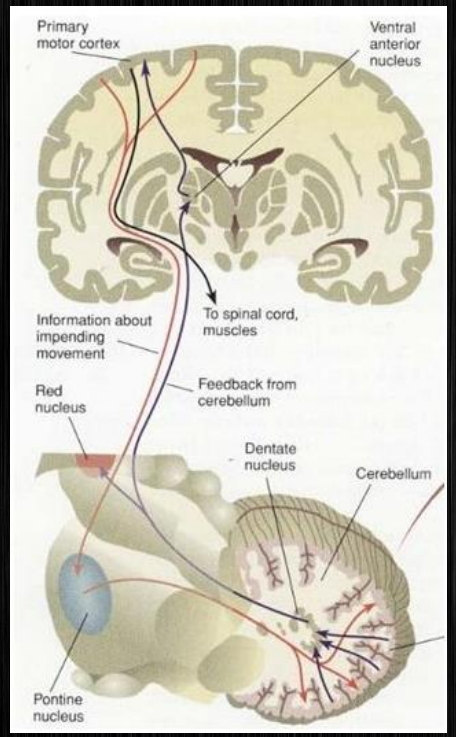
- The Single Most Important Question
- Real World Data: Approximately 400 million doses of IV GBCAs have been administered over the past 30 years (Linear > Macrocyclic) WITHOUT widespread reports of neurotoxicity. However, scientific proof is needed!
- How Do We Go About Testing This?
  1. Preclinical Models
  2. Retrospective Human Data
  3. Prospective Human Data

QUESTION: Are Gd Deposits Clinically Significant?

STRUCTURE-FUNCTION APPROACH TO LOOK FOR SYMPTOMS

Dentate Nucleus

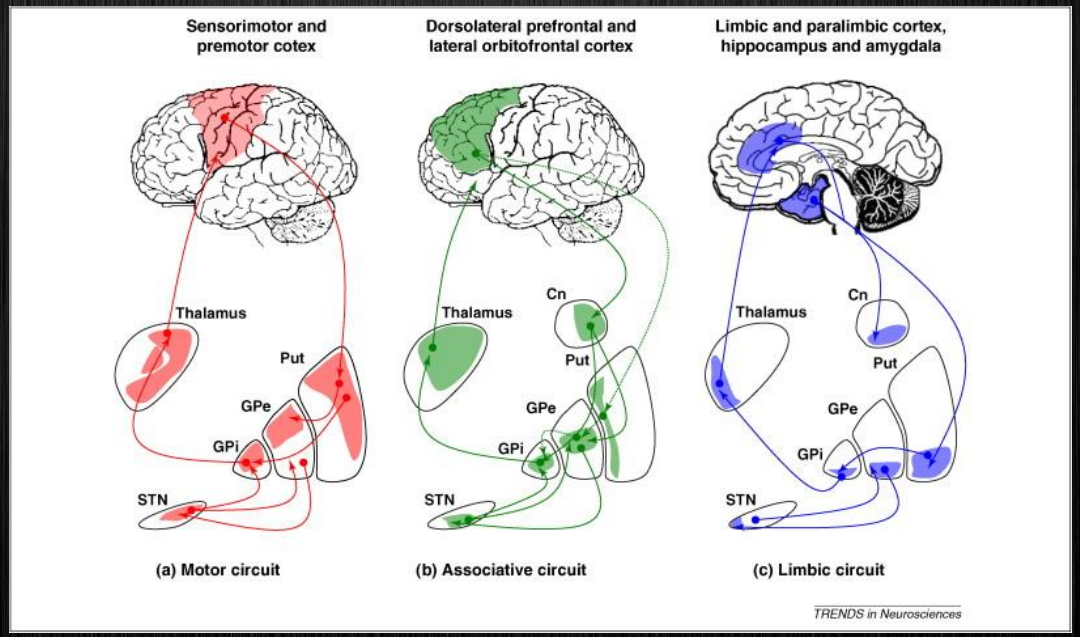
- Coordination (planning and initiation) of limb movement



http://images.slideplayer.com/16/5165960/slides/slide_9.jpg

Basal Ganglia

- learning and memory
- coordination of movement; filtering out undesired movements; posture and balance
- implicated in anxiety and mood disorders



Krack, P., et al. "Deep brain stimulation: from neurology to psychiatry?" Trends in Neurosciences 33(10): 474-484.

QUESTION: Are Gd Deposits Clinically Significant?

WELK STUDY ON PARKINSIONISM IN CANADA

Table 2. New Diagnoses of Parkinsonism After MRIs (Not of the Brain or Spine) With or Without Gadolinium Exposure

Primary Analysis	Entire Cohort (N = 246 557)	Exposed to Only Non-Gadolinium-Enhanced MRIs (n = 146 818)	Exposed to Gadolinium-Enhanced MRIs		HR (95% CI)	*P* Value
			≥1 MRI (n = 99 739)	≥4 MRIs[a] (n = 2446)		
Total follow-up, person-years	991 937	625 185	366 752	6634		
Primary outcome, No. (%)	2861 (1.16)	1697 (1.16)	1164 (1.17)	17 (0.70)		
Rate (95% CI)[b]	2.88 (2.78-2.99)	2.71 (2.59-2.84)	3.17 (2.99-3.36)	2.56 (1.54-4.02)		
Unadjusted analysis[c]		Reference			1.08 (1.04-1.13)	<.001
Adjusted analysis[d]		Reference			1.04 (0.98-1.09)	.18
Sensitivity analysis						
Post hoc analysis 1[e]		Reference			0.99 (0.94-1.03)	.58
Post hoc analysis 2[f]		Reference			1.03 (0.98-1.09)	.29

- Hospital administrative database
- N = 246557 underwent MRI, N = 99739 Gd enhanced MRI
- Gd was not associated with increased incidence of Parkinson disease among pts > 66 years in age

Welk B et al, JAMA 2016

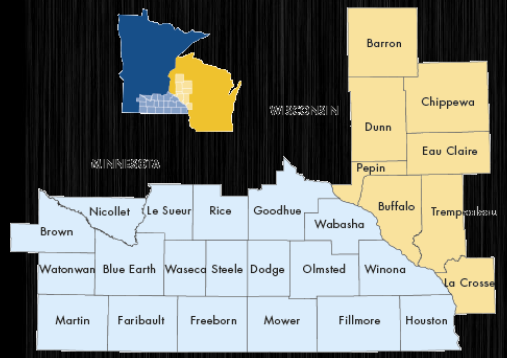
QUESTION: Are Gd Deposits Clinically Significant?

PRELIMINARY PROSPECTIVE HUMAN DATA: MAYO CLINIC STUDY ON AGING

Rochester Epidemiology Project (REP) (1966-current)

- World's largest and longest continuously funded population-based study of human health
- Health records are available over entire lifetime

Mayo Clinic Study of Aging (MCSA) (2004-current)

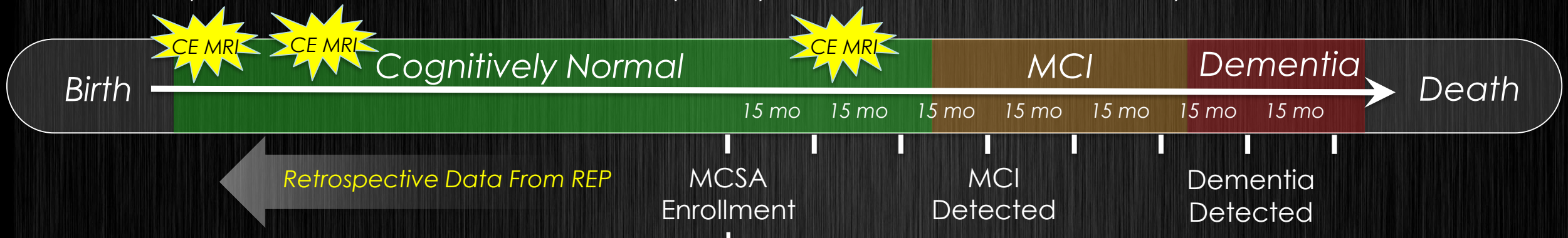


- World's largest prospective population-based cohort to study the prevalence, incidence, and risk factors for dementia
- "Accidentally" studied effects of Gd deposition for 10+ years!
- Augments REP data with routine annual clinical, imaging, and laboratory evaluation used to assess neurologic, neurocognitive, and neuropsychiatric function.

QUESTION: Are Gd Deposits Clinically Significant?

MCSA STUDY DESIGN

Participants underwent contrast enhanced MRIs (CE MRI) for reasons unrelated to MCSA study



Clinical Evaluation

Risk Factor Assessment

- Family & Medical Hx
- Risk Assessment
- Medications
- Demographics
- Neuropsychiatric Inventory
- Clinical Dementia Rating
- Functional Assessment

Neurological Evaluation

- Neurological Interview
- Memory & Orientation
- Short Test of Mental Status
- Modified Hachinski Scale
- Neurological exam
- Modified UPDRS

Neuropsychological Evaluation

- **Memory** Logical memory, Visual Reproduction, AVLT
- **Executive Function** Trails A and B, Digit Symbol Substitution
- **Visuospatial** Picture Completion, Block Design
- **Language** Boston Naming Test, Category Fluency

Imaging Exams

- Unenhanced MRI
- PET/CT
- PiB

Laboratory Exams

- CBC/Chem 7
- ApoE4 Gene Testing

QUESTION: Are Gd Deposits Clinically Significant?

MCSA STUDY POPULATION

Variable (Mean (SD))	Control N = 2946	Gd-exposed N = 1315
Age @ Enrollment	71.1 (10.9)	72.2 (9.7)
Observation time (years)	4.9 (2.2)	5.5 (2.1)
Person Years of Observation	16,078	7,104
Person Years of Clinical Data	236,384	83,119
Female (%)	49.7%	51.1%
ApoE4 Allele (%)	26.5%	27.2%
Charlson Index	2.85	3.86
Years of Education	14.5 (2.7)	14 (12-16)
Mean Gd doses	-	3.0 (2.1)
Duration of Retained Gd	-	2240 (1379)
Person years of Gd Exposure	-	6704
MMSE score (initial)	28.1 (1.4)	28.1 (1.3)
Memory Z score (initial)	-0.14 (1.02)	-0.13 (0.99)
Language Z score (initial)	-0.10 (1.03)	-0.15 (1.03)
Visual Z score (initial)	-0.06 (1.04)	-0.14 (1.00)
Attention Z score (initial)	-0.12 (1.07)	-0.13 (1.08)
UDPRS score (initial)	1.57 (3.70)	1.72 (4.17)

Gd study comprised of cognitively normal patients at time of enrollment in MCSA between 2004-2012.

Among 4261 Cognitively Normal Patients

- N = 2946 Patients Never Exposed to GBCA (Control)
- N = 1315 Omniscan Exposed Patients (Gd-Exposed)

Omniscan-Exposed Cohort

- N = 742 had 4 or less doses
- N = 573 had 5 or more doses

Observation time (mean/person years)

- Control: 4.9 (2.2) years / 16,078 person years
- Gd-exposed: 5.5 (2.1) years / 7,104 person years

QUESTION: Are Gd Deposits Clinically Significant?

DOES GD EXPOSURE AFFECT COGNITION OR NEUROLOGIC FUNCTION?

Neurologic Outcomes	Odds Ratio (95% CI)	P-value
Mini-mental status exam:	0.95 (0.89-1.04)	.16
Memory Z score:	1.04 (0.97-1.12)	.58
Language Z score:	1.01 (0.98-1.05)	.96
Attention Z score:	0.97 (0.92-1.02)	.79
Visual Z score:	1.02 (0.98–1.05)	.80
Dementia (UPDRS) score:	1.01 (0.96-1.07)	.22

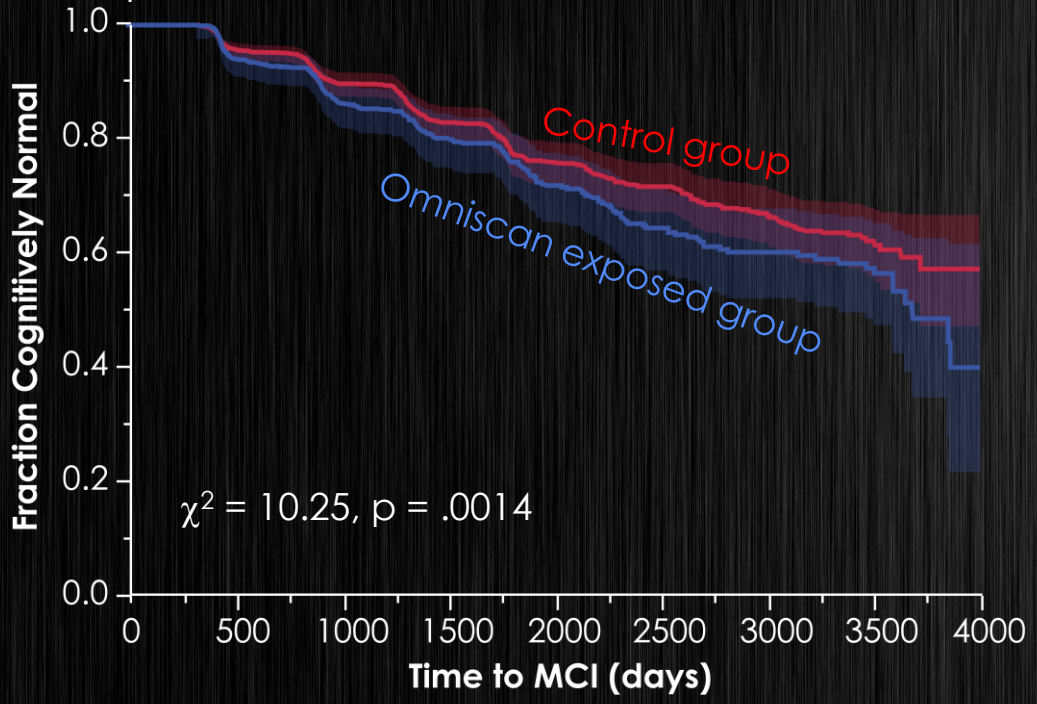
No effect of exposure or dose-response relationship

multivariate models adjusted for demographics (age, gender), comorbidities (Charlson score, CV disease, DM), clinical variables (BMI, ApoE4), social history (smoking, education level), and baseline test performance.

QUESTION: Are Gd Deposits Clinically Significant?

DOES GD EXPOSURE AFFECT NORMAL PROGRESSION RATE OF COGNITIVE DECLINE?

Kaplan-Meier Model



Cox Proportional Hazards Model

Variable	Hazard Ratio (95% CI)	P-value
Gadolinium Exposure	1.02 (0.95-1.20)	.77
# of Gadolinium doses	0.99 (0.95-1.08)	.85

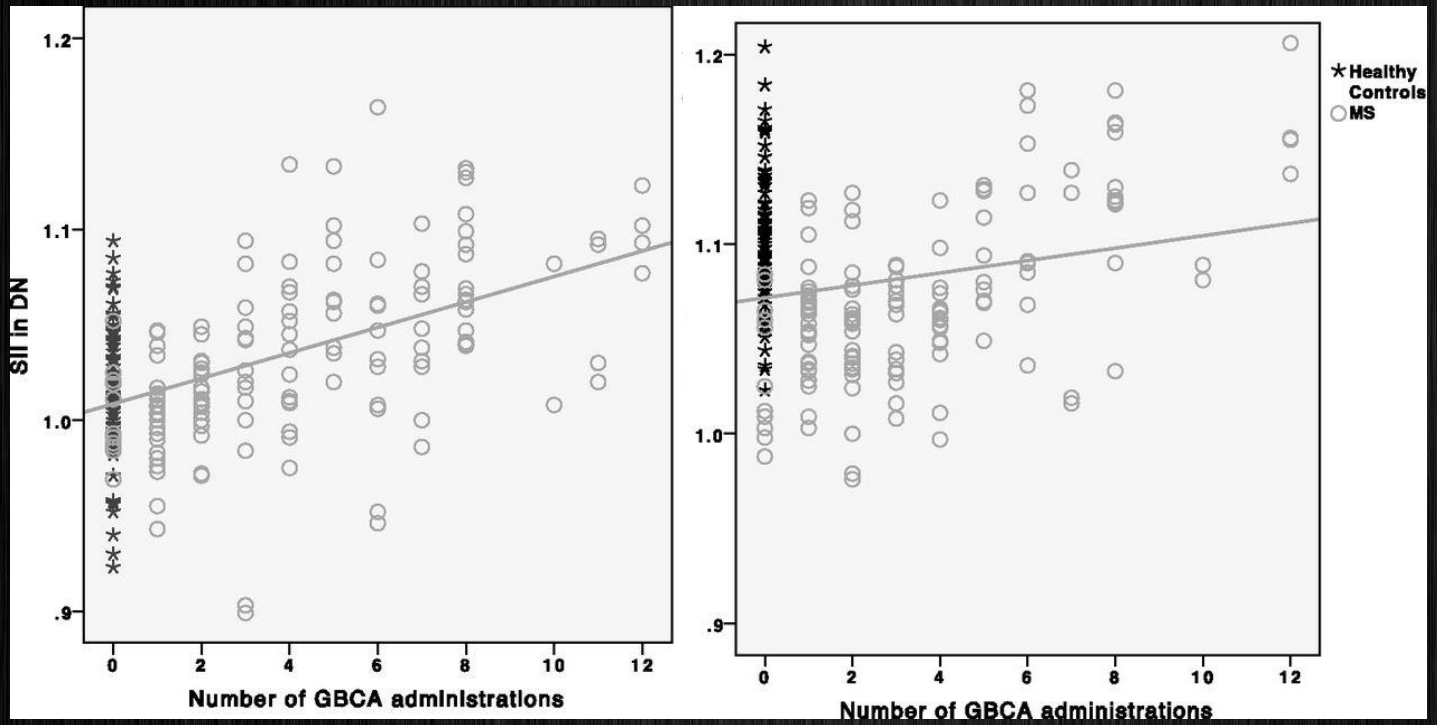
Markov Multiple Exposure Model (INCOMPLETE)

Variable	Hazard Ratio (95% CI)	P-value
Gadolinium Exposure	0.96 (0.88-1.04)	.32
# of Gadolinium doses	1.04 (0.98-1.09)	.59

- Neither Omniscan exposure nor cumulative Omniscan dose appears to have a significant effect on rate of initial cognitive decline (Normal → MCI).
- Markov model analysis needed to eliminate confounding from multiple exposures to Gd after initial enrollment. Early results corroborate with Cox model findings.

QUESTION: Are Gd Deposits Clinically Significant?

KAROLINSKA DATA



Increased Signal Intensity Index in the dentate nucleus among patients with MS was associated with lower verbal fluency scores, which remained significant after correction for several aspects of disease severity ($\beta = -0.40$ $P = .013$)

Forslin Y, et al. AJNR Am J Neuroradiol. 2017 Jul;38(7):1311-1316.

QUESTION: Are Gd Deposits Clinically Significant?

WHAT ABOUT GADOLINIUM DEPOSITION DISEASE?

Residents inRadiology

Gadolinium in Humans: A Family of Disorders

Richard C. Semelka[1]
Miguel Ramalho[1,2]
Mamdoh AlObaidy[1,3]
Joana Ramalho[1,4]

OBJECTIVE. The literature informs us that gadolinium can cause health issues. At least four major gadolinium disorders, including the two well-recognized nephrogenic systemic fibrosis and severe acute adverse event, have been identified.

CONCLUSION. We propose naming the histopathologically proven presence of gadolinium in brain tissue "gadolinium storage condition," and we describe a new entity that represents symptomatic deposition of gadolinium in individuals with normal renal function, for which we propose the designation "gadolinium deposition disease."

- Uncontrolled survey amongst patients who had ascribed symptoms from GBCA exposure
- To date, the FDA does not find sufficient causal evidence to support the existence of GDD
- Further research is needed to exclude the possibility of an extremely rare phenomenon
- If GDD is real, it appears to be associated with BOTH linear and macrocyclic GBCAs

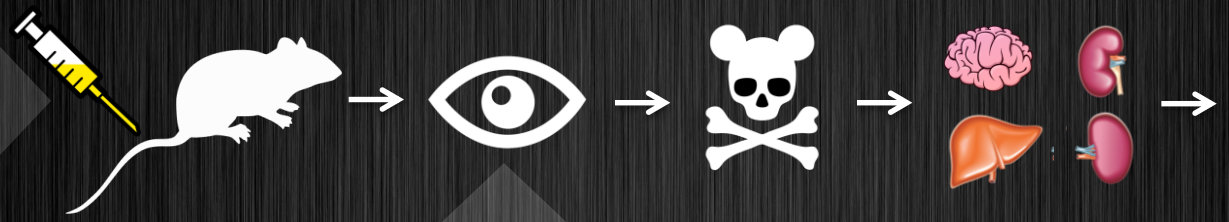
Semelka RC, et al AJR 2016;207:229-233

QUESTION: Are Gd Deposits Clinically Significant?

USING A PRECLINICAL RAT MODEL TO STUDY THE EFFECT OF GD ON LOCOMOTOR, COGNITIVE/MEMORY, MOOD & BALANCE/COORDINATION FUNCTION

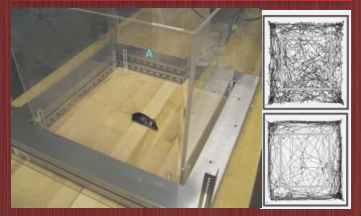
Study Groups

Group	Agent	Dose (mmol/kg)
1	Saline	-
2	Gadopentetate	2.5
3	Gadodiamide	2.5
4	Gadoversetamide	2.5
5	Gadobenate	2.5
6	Gadoteridol	2.5
7	Gadobutrol	2.5
8	Gadoterate	2.5
9	Gadoxetate	2.5
10	Gadodiamide	0.6
11	Gadoterate	0.6

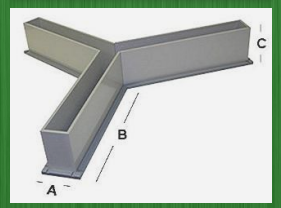


Mayo Clinic Rodent Behavioral Core Facility

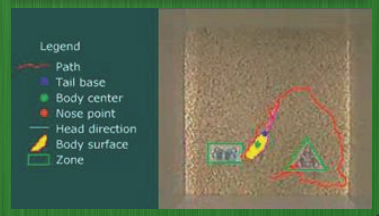
Open Field Arena



Y-maze

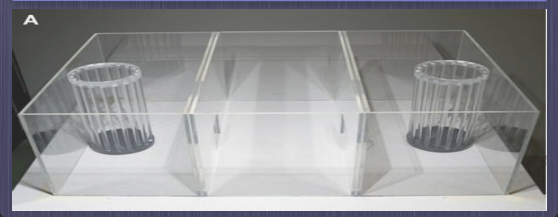


Novel Object Recognition

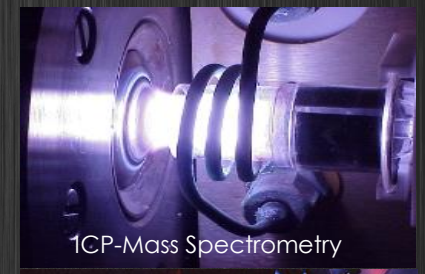


Ladder Rung Task

Social Anxiety Test



Tissue Analysis



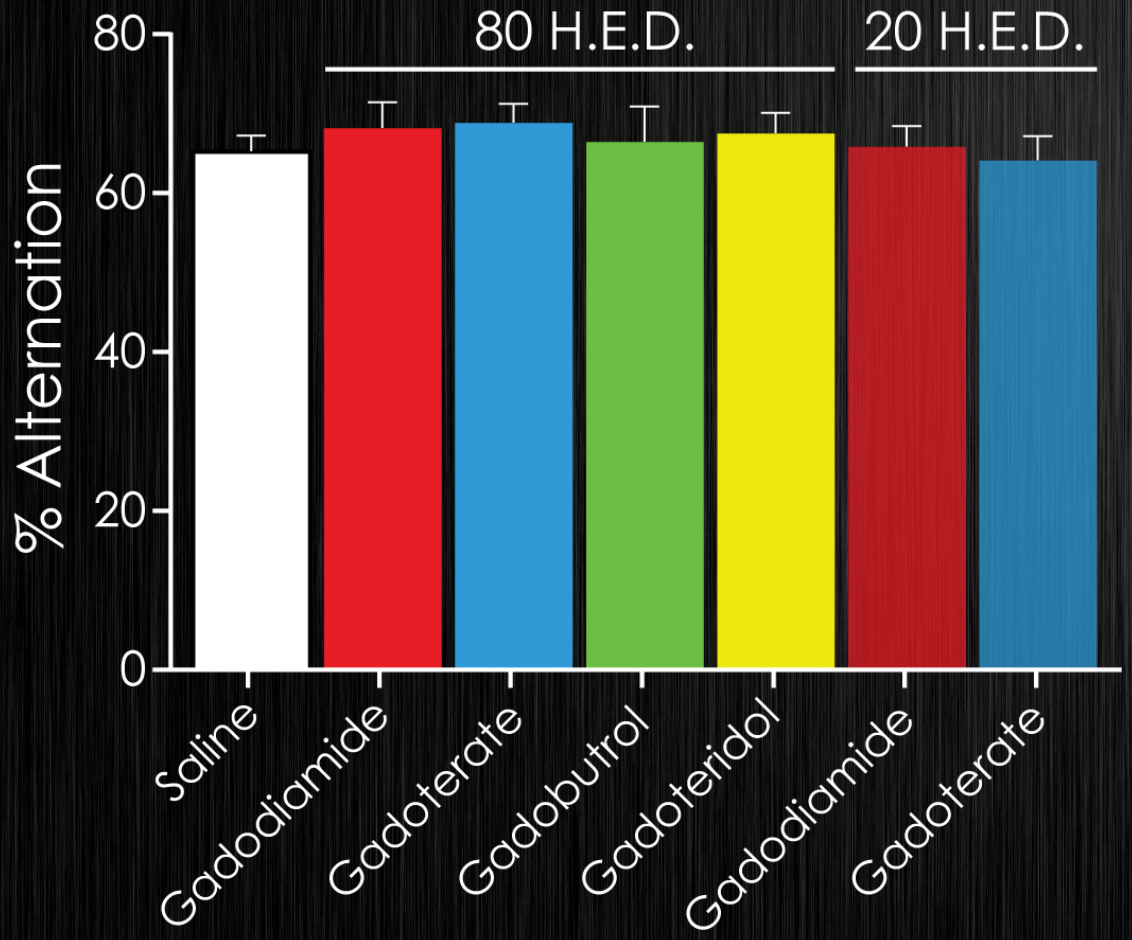
1CP-Mass Spectrometry

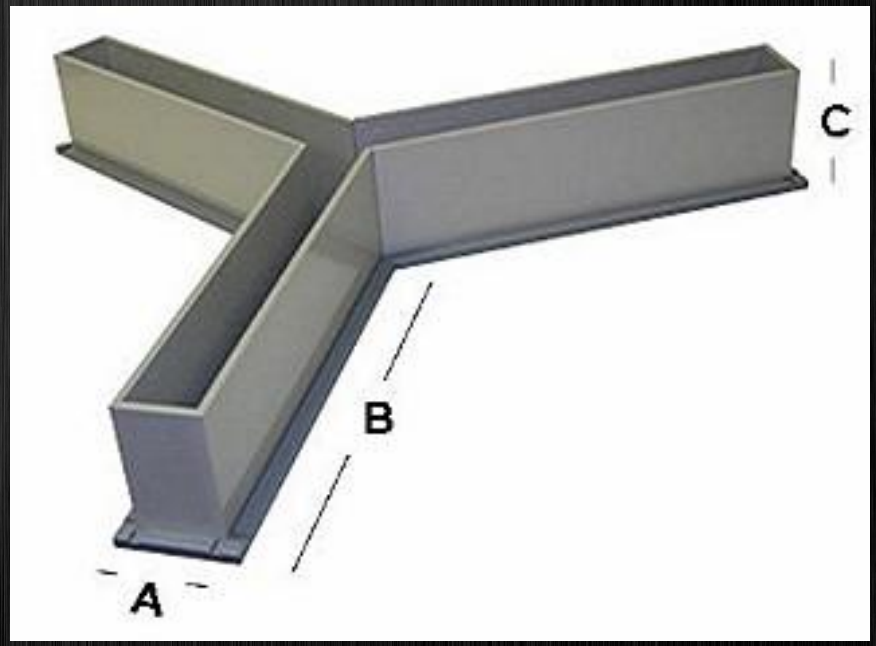
Transmission Electron Microscopy

Light Microscopy

QUESTION: Are Gd Deposits Clinically Significant?

Y MAZE SPONTANEOUS ALTERNATION TEST

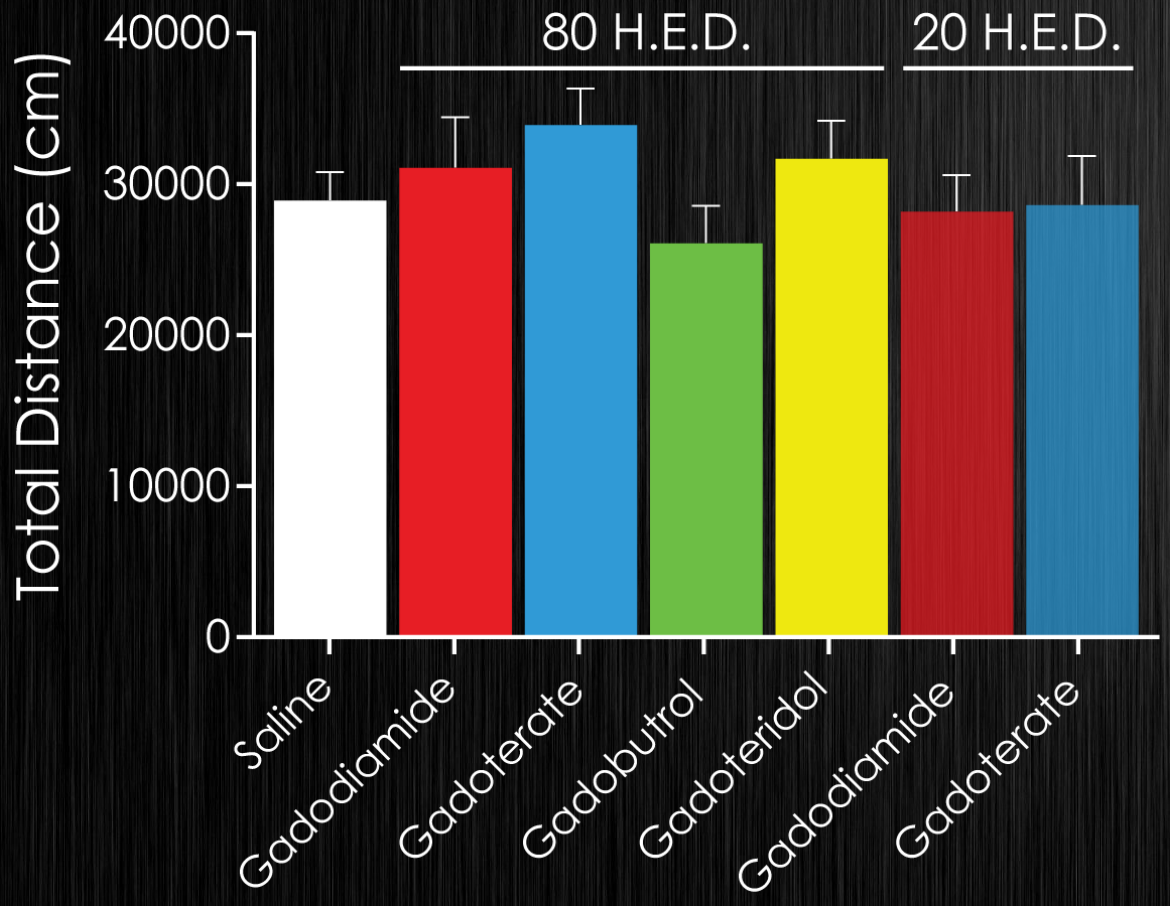


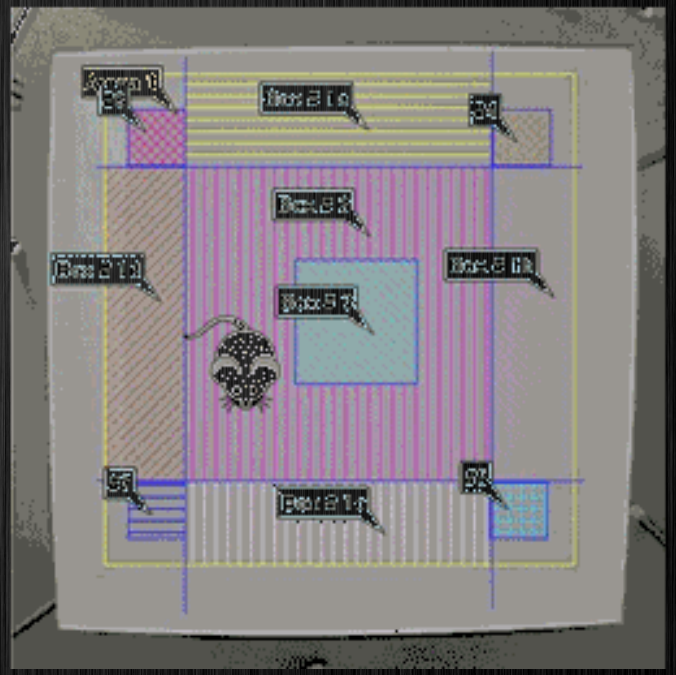


Using 1-way ANOVA there was no significant difference in alternation ($p > .05$)

QUESTION: Are Gd Deposits Clinically Significant?

OPEN FIELD ARENA

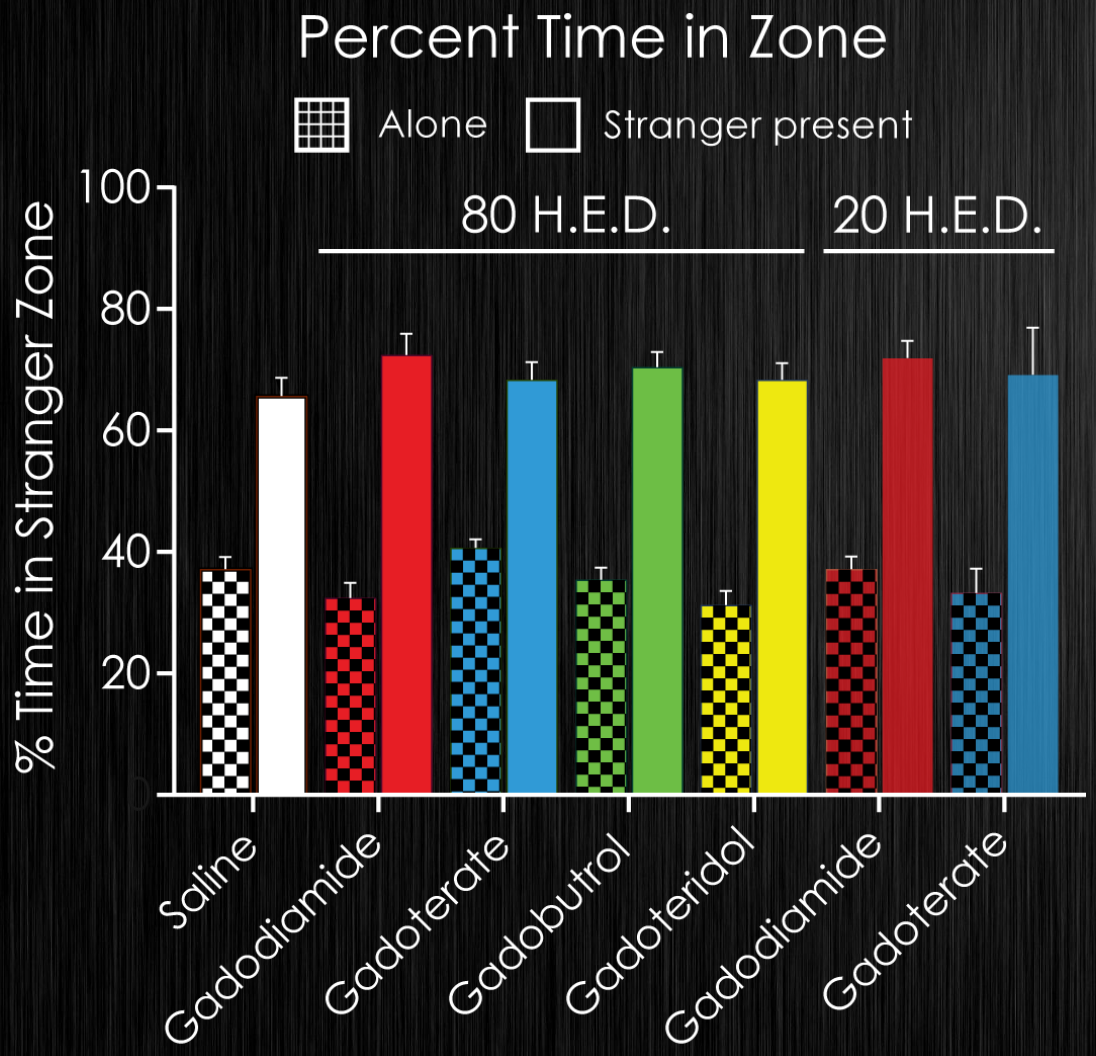




Using 1-way ANOVA there was no significant difference in distance traveled ($p > .05$)

QUESTION: Are Gd Deposits Clinically Significant?

SOCIAL ANXIETY TASK

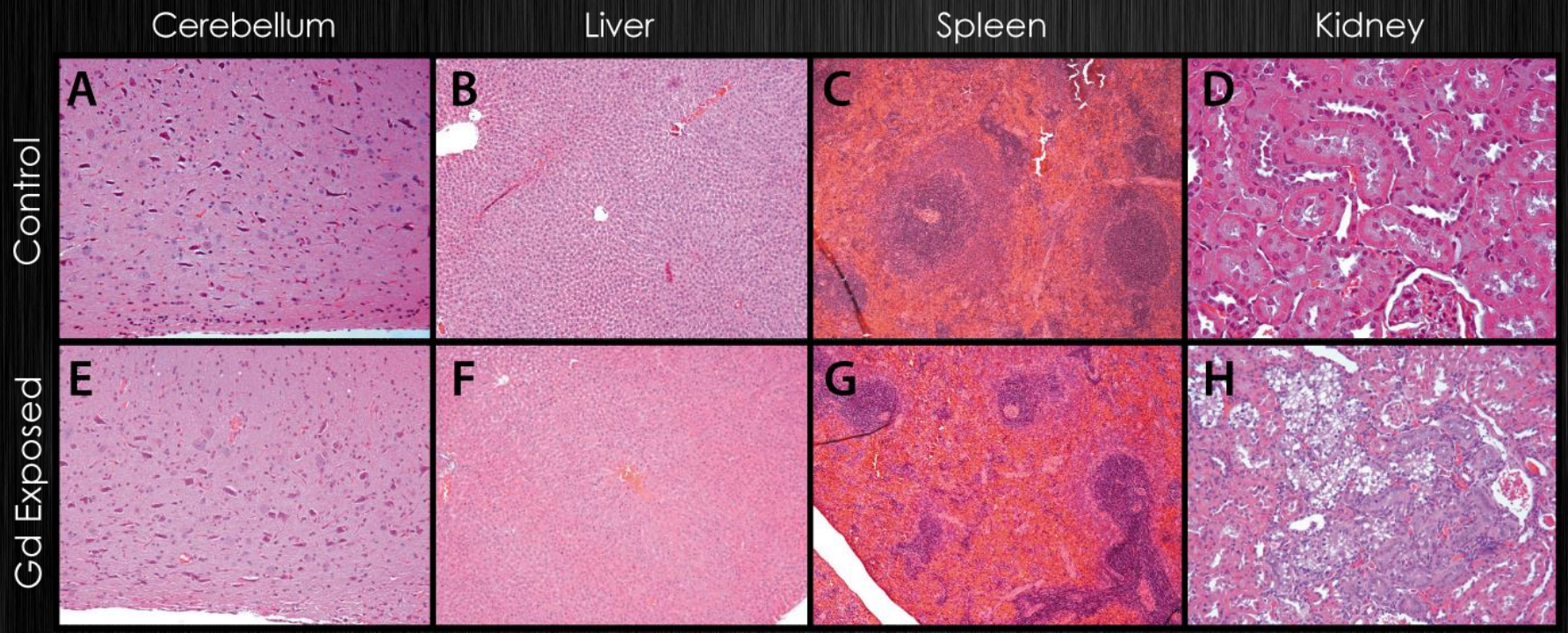


Two-way ANOVA showed a significant effect of stranger rat presence on time spent in the stranger zone all groups ($p < .0001$).

However, no significant differences were observed between control (saline) and GBCA exposed animals within either group (alone, stranger present) ($p > .05$).

QUESTION: Are Gd Deposits Toxic?

HISTOLOGIC RESULTS FROM PRECLINICAL RAT MODEL



- No Histologic changes noted in brain, liver, or spleen
- High dose Gd causes diffuse vacuolar degeneration of the proximal convoluted tubule in the renal cortex.

McDonald et al, in press, Radiology 2017

SUMMARY: GBCA CNS Toxicity/Clinical Significance?

NO EVIDENCE OF CNS INJURY OR CLINICAL SEQUELAE FROM GBCA EXPOSURE

	Study	# Subjects Total / Exposed	Endpoint	Dose range	Observation Time
Animal	Smith 2016	42 / 30	Histopathology + EM	10 or 20 HED	Up to 6 months
	Marino, in prep	42 / 30	Histopathology + EM	10 or 20 HED	Up to 1 year
	McDonald 2017 (a)	25 / 19	Histopathology + EM	80 HED	5 weeks
	Lohrke 2017	50 / 40	Histopathology + EM	80 HED	12 weeks
	McDonald, in prep	280/250	Histopathology + EM + Behavior	20 or 80 HED	40 weeks
Clinical	McDonald 2015	23 / 13	Histopathology	1 to 29 doses	Up to 9.7 years
	McDonald 2017 (b)	5 / 3	Histopathology - Pediatric	4 to 9 doses	Up to 9 months
	Cao 2016	76 / 25	Change in no. of clinical issues post-Gd	1 to 2 doses	1 month
	Welk 2016	246,557 / 99,739	Incidence of parkinsonism	97.5% <4 doses 2.5% ≥4 doses	Up to 10 years
	Mayo Aging Study	4261 / 1315	Neurological testing	1 to 28 doses	Median 5.5 years

SUMMARY: GBCA CNS Toxicity/Clinical Significe?

POSSIBLE EVIDENCE OF CNS INJURY OR CLINICAL SEQUELAE FROM GBCA EXPOSURE

	Study	# Subjects Total / Exposed	Endpoint	Dose range	Observation Time
Clinical	Semelka 2016	42 / 42	Survey	1 or more doses	4 months to 8 years*
	Forslin 2017 (b)	46 / 23	Verbal Fluency	X doses	Up to 18 years
	Quatrocci 2017	?	Change in fMRI signal	?	?

Intracranial Gadolinium Deposition

UNANSWERED SCIENTIFIC QUESTIONS

1. Is there scientific evidence of CNS toxicity from gadolinium deposits?
   - Clear evidence of acute CNS toxicity from intrathecal administration and animal models with disrupted BBB.
   - If yes, we must determine if there is dose dependency and toxicity threshold.
2. What mechanisms of CNS injury should be interrogated?
   - To date, there is no convincing histopathological or ultrastructural EM data to suggest Gd deposition is associated with cellular injury.
   - Are we not looking in the right place?
   - Should we focus more on gene expression, cellular function assays?

Intracranial Gadolinium Deposition

UNANSWERED CLINICAL QUESTIONS

1. Is there clinical evidence of CNS toxicity from gadolinium deposits?
   - Mixed results to date – a few studies may suggest the possibility of toxicity
   - We must be vigilant in study design to avoid confounding results with expected manifestations of disease.
2. Limitations with existing data
   - Studies may be confounded, too small, wrong target population, or may not be looking for appropriate symptoms.
   - We must be mindful that there are two groups of patients that need to be studied – the patient who receives 1-3 doses (majority) and the patient who receives 20+ doses due to a chronic condition (minority). The risk-benefit equation significantly differs between these two groups.
3. What are the most high yield future studies?
   - Should we focus on larger registry studies, RCTs, or more focused clinical studies?
   - Studies should be multicenter when possible to avoid confounding and increase reliability of data.