



# Gadolinium deposition in the brain: summary of evidence and recommendations

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See [Comment](#) page 495

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Emerging evidence has linked MRI signal changes in deep nuclei of the brain with repeated administration of gadolinium-based contrast agents. Gadolinium deposits have been confirmed in brain tissue, most notably in the dentate nuclei and globus pallidus. Although some linear contrast agents appear to cause greater MRI signal changes than some macrocyclic agents, deposition of gadolinium has also been observed with macrocyclic agents. However, the extent of gadolinium deposition varies between agents. Furthermore, the clinical significance of the retained gadolinium in the brain, if any, remains unknown. No data are available in human beings or animals to show adverse clinical effects due to the gadolinium deposition in the brain. On behalf of the International Society for Magnetic Resonance in Medicine, we present recommendations for the clinical and research use of gadolinium-based contrast agents. These recommendations might evolve as new evidence becomes available.

## Introduction

Gadolinium-based contrast agents (GBCAs) are widely used in research and clinical settings, for diagnosis and monitoring of many diseases. The signal intensity of an MR image is affected by T1 and T2 relaxation times, which are characteristic physical properties of each tissue related to its behaviour in a magnetic field. GBCAs shorten the T1 relaxation time of water protons near the agent, and this phenomenon produces images in which tissues with a high concentration of contrast agent are brighter than those with lower concentrations.

Over 30 million doses of GBCA are administered worldwide annually, and over 300 million doses have been administered since their introduction in 1987.<sup>1</sup> The risks associated with the use of GBCAs include allergic and adverse reactions (which are infrequent, but can be serious),<sup>2,3</sup> and nephrogenic systemic fibrosis in patients with renal failure. Nephrogenic systemic fibrosis is a rare scleroderma-like illness that occurs in patients with severe renal disease and after exposure to certain GBCAs. Its incidence has been effectively eliminated by restricting the administration of the GBCAs most closely associated with nephrogenic systemic fibrosis in high-risk populations, and by lowering of GBCA dosage.

Multiple studies have shown evidence of residual brightness of tissue in the deep nuclei of the brain, particularly the globus pallidus and the dentate nucleus, in people who have received a GBCA; additional evidence shows that these regional signal changes are directly associated with the deposition of the contrast agent. These findings raise concerns about the context in which gadolinium deposits in the brain, and pose the question as to whether this deposition might cause any harm.

On behalf of the International Society for Magnetic Resonance in Medicine (ISMRM), we summarise the evidence on gadolinium deposition in the brain, contextualise this evidence according to knowledge obtained from cases of nephrogenic systemic fibrosis, and provide recommendations for future use of GBCAs in research and clinical practice.

## Gadolinium deposition in the brain

The presence of high MRI signal intensity on unenhanced T1-weighted images of the dentate nucleus and the globus pallidus of patients who had undergone multiple GBCA-enhanced MRI examinations was first described in 2014.<sup>4</sup> Increased relative signal intensity correlated with the number of contrast-agent administrations. A comparison of signal intensities in a subgroup of patients who had undergone at least six contrast-enhanced MRI examinations, with either gadopentetate dimeglumine or gadodiamide, showed that these patients had higher signal intensities in these nuclei than did patients who had undergone only non-contrast MRI.<sup>4</sup> These results were confirmed in a similar study involving gadodiamide<sup>5</sup> and in numerous subsequent studies.<sup>6–8</sup> Emerging case-report evidence suggests that gadolinium deposition also occurs in children, with a similar deposition pattern to that observed in adults.<sup>9,10</sup>

Given the association of nephrogenic systemic fibrosis with renal failure, a relevant question is whether gadolinium deposition in the brain is also associated with renal failure. Signal intensities and post-mortem evaluation of the brains from 13 patients who had at least four gadodiamide-enhanced MRI examinations were compared with those from ten patients who did not receive GBCA.<sup>7</sup> Gadolinium deposition was confirmed in deep brain nuclei in patients who had undergone GBCA-enhanced MRI examinations, by use of inductively coupled plasma mass spectroscopy (ICP-MS). The signal intensity ratios were positively correlated with the tissue concentration of gadolinium, definitively linking increased signal intensity ratios with gadolinium deposition and relative gadolinium concentration. X-ray microanalysis also demonstrated gadolinium deposition in neuronal tissue. Gadolinium was observed in endothelial walls, but the authors stated: “gadolinium appears to have crossed the blood-brain barrier and been deposited into the neural tissue interstitium”.<sup>7</sup> Since all patients had normal renal function, gadolinium

deposition (in healthy and non-irradiated brain tissue) appears to be unrelated to renal function. In another study, brain specimens obtained at autopsy from five individuals without severe renal dysfunction who had at least two administrations of linear GBCAs were compared with those from individuals who had not received GBCAs by use of ICP-MS.<sup>11</sup> Two patients also had a history of gadoteridol administration, one of whom had additionally received a dose of gadodiamide. Gadolinium deposition was detected in all brain specimens from the GBCA group, with the highest concentration in the dentate nucleus and the globus pallidus, and at much lower concentrations in some brain specimens from the non-GBCA group. Gadolinium deposition in the brain was again confirmed in individuals with normal or near-normal renal function in this study.

Quantitative analyses were done as part of an industry-sponsored study<sup>12</sup> that examined rat brains after repeated administration of gadodiamide. This study showed gadolinium retention of 0.00019% of the administered dose at 1 week after deposition and, interestingly, clearance of 45% of the deposited gadolinium 20 weeks after deposition. No neurotoxicity was observed.

**Does gadolinium deposition depend on the GBCA class?**

An important question is whether the contrast agent or agent class affects gadolinium deposition. GBCAs can be classified as ionic and non-ionic; ionic agents have greater thermodynamic stability, but an association between stability and gadolinium deposition has not been established. Whereas thermodynamic stability and

pH-corrected conditional stability are sometimes used to predict dissociation rates, kinetic stability, which reflects the dissociation half-life of the GBCA from its ligand, might be a better predictor.<sup>13</sup> GBCAs are also commonly classified as linear or macrocyclic on the basis of the chemical structure of the chelating agent bound to the gadolinium ion. The table<sup>14</sup> summarises the characteristics of various contrast agents and lists studies comparing gadolinium deposition associated with particular agents.

Several studies have compared the effect of some linear and macrocyclic agents on gadolinium deposition. In one study, patients who underwent six or more examinations with gadopentetate dimeglumine (a linear GBCA) were compared with patients given gadoterate meglumine (a macrocyclic GBCA); the study showed that increases in signal intensity ratios in the dentate nucleus relative to the pons and in the globus pallidus relative to the thalamus were higher after exposure to the linear agent than the macrocyclic agent; no significant increase in signal intensity ratio was detected in participants who received the macrocyclic agent.<sup>6</sup> Another study compared the effects of exposure to gadobenate dimeglumine, a linear agent, with those of gadopentetate dimeglumine, another linear agent.<sup>26</sup> This study reported an increase in the signal intensity ratio of dentate nucleus to pons, and dentate nucleus to CSF with gadobenate dimeglumine exposure, but the change in dentate nucleus-to-CSF ratio was smaller after exposure to gadobenate dimeglumine than to gadopentetate, suggesting lower gadolinium deposition with this linear agent. A study by Radbruch and colleagues<sup>28</sup> of signal intensity ratios in the dentate

	Chemical structure	Ionic vs non-ionic	ACR NSF safety group	References reporting gadolinium deposition		
				Signal intensity changes	T1 changes	Gadolinium detection*
Gadopentetate dimeglumine	Linear	Ionic	1	Kanda et al, <sup>4,16</sup> Radbruch et al, <sup>6</sup> Roberts et al, <sup>9</sup> Robert et al, <sup>17</sup> Cao et al, <sup>18</sup> Schlemm et al <sup>19</sup>	Robert et al, <sup>17</sup> Tedeschi et al <sup>†20</sup>	Kanda et al, <sup>11</sup> Smith et al, <sup>12</sup> Robert et al <sup>17</sup>
Gadoversetamide	Linear	Non-ionic	1	..	..	..
Gadodiamide	Linear	Non-ionic	1	Kanda et al, <sup>4</sup> Errante et al, <sup>5</sup> McDonald et al, <sup>7</sup> Ramalho et al, <sup>8</sup> Robert et al, <sup>17,21</sup> Quattrocchi et al <sup>22</sup>	Robert et al <sup>17</sup>	McDonald et al, <sup>7</sup> Kanda et al, <sup>11</sup> Smith et al, <sup>12</sup> Robert et al <sup>17,21</sup>
Gadoteridol	Macrocyclic	Non-ionic	2	..	..	Kanda et al, <sup>11</sup> Murata et al <sup>23</sup>
Gadoterate meglumine	Macrocyclic	Ionic	2	..	Tedeschi et al <sup>†20</sup>	Robert et al <sup>17,21</sup>
Gadobutrol	Macrocyclic	Non-ionic	2	Stojanov et al <sup>24</sup>	Tedeschi et al <sup>†20</sup>	Murata et al <sup>23</sup>
Gadobenate dimeglumine	Linear	Ionic	2	Ramalho et al, <sup>8,25</sup> Weberling et al, <sup>26</sup> Robert et al <sup>17</sup>	Robert et al <sup>17</sup>	Robert et al, <sup>17</sup> Murata et al <sup>23</sup>
Gadoxetate disodium	Linear	Ionic	3	Kahn et al <sup>27</sup>	..	Murata et al <sup>23</sup>
Gadofosveset trisodium	Linear	Ionic	3	..	..	..

The ACR designates three categories of contrast agent groupings by risk of NSF.<sup>14</sup> Group 1 agents are associated with the greatest number of NSF cases. Group 2 agents are associated with few, if any, cases of NSF. Group 3 agents have only recently been commercially available and therefore evidence on NSF is not available yet. ACR=American College of Radiology. NSF=nephrogenic systemic fibrosis. \*One study<sup>15</sup> shows direct evidence of gadolinium deposition, after the patient received two doses of gadopentetate dimeglumine and two doses of either gadopentetate dimeglumine or gadodiamide; since these findings might be confounded, this reference is not included. †A study by Tedeschi and colleagues<sup>20</sup> reported T1 changes, but patients received combinations of three agents, and thus the results are confounded. ‡Patients receiving gadodiamide and gadoteridol in a study by Kanda and colleagues<sup>11</sup> also received gadopentetate, and thus results are confounded. For comparisons between agents, please see the appendix.

**Table: Contrast agents and gadolinium deposition**

See Online for appendix

nucleus to pons and dentate nucleus to middle cerebellar peduncle included 33 patients who had received 20 consecutive administrations of macrocyclic agents (gadoterate meglumine and gadobutrol); the study showed no significant increase in signal intensities in the dentate nucleus pertaining to either agent. Radbruch and colleagues<sup>28</sup> hypothesised that the differences in signal intensity ratios after linear versus macrocyclic agent exposure were probably due to the different chemical stabilities of the two agent classes, thus contributing different amounts of unchelated gadolinium. This hypothesis was based on the observation that gadolinium deposits, as measured in autopsy studies, correlated with signal intensity changes,<sup>7</sup> and that some linear agents have lower thermodynamic stability than macrocyclic agents currently in use. Thus, linear agents might release more gadolinium. Subsequently, another study showed increased brain signal intensity ratio changes in a subset of individuals given gadopentetate dimeglumine, but not in those given gadoteridol (a macrocyclic GBCA).<sup>16</sup>

An industry-sponsored study<sup>21</sup> investigated gadolinium deposition in rats imaged serially while receiving over 20 injections of various GBCAs. Three groups of rats were studied, including animals administered gadodiamide (linear GBCA), gadoterate meglumine (macrocyclic GBCA), or hyperosmolar saline. Repeated injections of gadodiamide resulted in a progressively increased signal intensity ratio, before reaching a plateau. The investigators also measured post-mortem gadolinium concentrations in the brain, and found that rats exposed to gadodiamide had higher gadolinium deposition than rats exposed to gadoterate meglumine. However, gadolinium concentration in the subcortical brain was also significantly higher in the macrocyclic group than in control rats receiving saline. Notably, repeated behavioural examinations found no abnormalities suggestive of neurological toxicity. The same industry group<sup>17</sup> studied gadoterate meglumine, gadopentetate dimeglumine, gadobenate dimeglumine, and gadodiamide, and control animals injected with saline, using their previous method<sup>21</sup> with the addition of T1 mapping. Signal intensity changes in the deep cerebellar nuclei were seen in the gadodiamide and gadopentetate dimeglumine groups, but not the gadoterate meglumine group. Quantitative measurements of gadolinium were highest for gadodiamide, followed by gadopentetate dimeglumine, gadobenate dimeglumine, and gadoterate meglumine, followed by saline. Concentrations of deposited gadolinium in brains of rats exposed to all three linear agents were significantly higher than in rats receiving either saline or gadoterate meglumine. No significant difference was observed between gadoterate meglumine and saline. The fact that the concentrations of deposited gadolinium were higher after exposure to less thermodynamically and kinetically stable agents supports the hypothesis that de-chelation

might play a role in gadolinium deposition. The investigators also concluded that “no obvious behavioural abnormalities were detected in rats, regardless of the GBCA administered”.

Studies in human beings show considerable variation in signal changes among agents, with inconsistent data reported even for the same agent. For example, gadobenate dimeglumine has been associated with signal intensity changes in deep brain nuclei.<sup>26</sup> However, a study<sup>8</sup> comparing the effects of gadodiamide and gadobenate dimeglumine indicated that gadodiamide was associated with signal intensity changes, whereas gadobenate dimeglumine was not. However, these patients received fewer doses of gadobenate dimeglumine on average than gadodiamide. Another study<sup>25</sup> compared individuals who had at least three gadobenate dimeglumine enhanced MRI examinations, and previous exposures to gadodiamide, with a group who had repeated gadobenate dimeglumine enhanced MRI examinations without previous gadodiamide exposure. The investigators hypothesised a potentiating effect by gadodiamide, but this mechanism is not yet understood.

Direct measurements of gadolinium deposition have been obtained from autopsy-derived brain samples from patients who had received various combinations of gadoteridol (macrocyclic GBCA), gadobutrol (macrocyclic GBCA), gadobenate dimeglumine (linear), and gadoxetate disodium (linear).<sup>23</sup> Gadolinium was found in all brain regions sampled, with exposure to each agent. This study showed that gadolinium from macrocyclic agents, and from linear agents considered to be associated with a low risk of nephrogenic systemic fibrosis, can deposit in the brain—this deposition was documented after the administration of even a single dose. Although the number of participants in this study was small, the findings suggested potential differences in deposition between the macrocyclic agents investigated, with a higher rate of deposition after gadobutrol administration than with gadoteridol. Furthermore, the extent of deposition observed for the two linear agents studied was less than that observed for agents previously thought to be associated with a high risk of nephrogenic systemic fibrosis.<sup>14</sup> These findings indicate that agent-specific characteristics, such as protein interactions and chelate stability, might play a role in the degree of gadolinium deposition.

Direct measurements showed gadolinium deposition in a patient who had received four doses of GBCAs (linear agents) over a lifetime but no measurable signal intensity change.<sup>15</sup> This finding raises the questions of whether the signal changes were absent simply because of low gadolinium concentration (although observed concentrations were similar to those in other studies), and if the chemical form of deposited gadolinium plays a role in the signal change. It is plausible that the chemical form of the deposited agent might be different for linear and macrocyclic agents.

On the basis of all this evidence, we conclude that the simple classification of agents into linear or macrocyclic does not take into consideration the pharmacokinetic complexity of GBCAs with regard to gadolinium deposition, and fails to consider their clinically significant differences in relaxivity.<sup>29</sup> Relaxivity refers to the amount of T1 shortening produced by an agent for a given concentration of that agent. The relaxivity depends heavily on the chelator for different GBCAs and can lead to clinically important differences in the detection of a variety of diseases.

### Potential confounding variables

Damage to the blood–brain barrier caused by disease processes or treatment (eg, radiation, chemotherapy) or both, is a potential confounding variable, since most patients undergoing repeated brain MRIs would have a known or suspected neurological disease. Signal intensity changes in the dentate nucleus and the globus pallidus have been reported in patients with relapsing-remitting multiple sclerosis who had repeated injections of gadobutrol.<sup>24</sup> Repeated injections over a shorter time period resulted in greater signal intensity changes than did repeated injections over a longer time period. Interestingly, a study published in 2009<sup>30</sup> showed dentate nucleus signal intensity increases with disease progression in patients with secondary progressive multiple sclerosis. This report raises the questions of whether disease progression is a confounding variable for, or potentiates, gadolinium deposition,<sup>31</sup> and if the disease subtype was relevant for the observed findings. A study<sup>20</sup> in patients with relapsing-remitting multiple sclerosis indicated that the observed phenomenon (ie, increased signal intensity changes) is independent of disease activity; relaxation times in the dentate nuclei were shortened even when disease-related factors were controlled for—eg, exclusion of patients with multiple sclerosis lesions near the dentate nucleus. Stojanov<sup>32</sup> contends that changes in signal intensity persist even after disease progression is controlled for, and that gadolinium deposition from macrocyclic agents contributed to the observed signal changes.<sup>32</sup> However, two studies<sup>18,19</sup> reported an increase in T1-weighted signal ratio between dentate nuclei and pons with gadopentetate dimeglumine (a linear agent), but not with gadobutrol (a macrocyclic agent). Another study also found no significant increase in signal intensity in general patients who had repeated examinations with gadobutrol,<sup>33</sup> contradicting the findings from Stojanov and colleagues mentioned above.<sup>24</sup>

### Gadolinium clearance

An industry-sponsored research group<sup>34</sup> studied whether gadolinium deposited in the brain can be cleared, using a rat model. The rat brain was analysed approximately at 1 week and 20 weeks after at least 20 doses of gadodiamide or gadopentetate dimeglumine were administered. The results showed the deposition of

gadolinium (as was expected) and that gadodiamide deposited more gadolinium than gadopentetate dimeglumine (0·00019% of the injected dose of

### Panel 1: Recommendations

Based on available evidence, as described in this Personal View, the recommendations for the clinical and research use of GBCAs from the International Society of Magnetic Resonance in Medicine (ISMRM) Safety Committee are as follows:

- 1 The ISMRM urges caution in the use of any medical compound, including gadolinium-based contrast agents (GBCAs). Per standard practice, use of GBCAs should be avoided when not necessary. The evidence on gadolinium deposition emphasises but does not alter this practice, and GBCAs should not be withheld from patients with a clinical indication for gadolinium-enhanced MRI. The physician responsible for the administration of a contrast agent should understand the benefits and risks of the agent.
- 2 The clinical indication for which a GBCA is administered, the specific contrast agent used, its dosage, and other pertinent information should be documented in the patient's medical record.
- 3 Some commercially available macrocyclic agents might deposit less gadolinium than some linear agents; however, evidence shows that gadolinium deposition in the brain can also occur after the administration of macrocyclic agents. Evidence suggests differences in gadolinium deposition rates among macrocyclic agents and among linear agents, although some data are discordant. Relaxivity differences between contrast agents and between the potentially deposited chemical species can complicate the interpretation of differences in signal intensity. No evidence shows any harmful effects from the deposition of gadolinium, and therefore whether use of macrocyclic agents should be favoured over linear agents is unclear. When choosing a contrast agent, many factors should be considered, including pharmacokinetics, relaxivity, efficacy, potential side-effects (such as allergic reactions), patient age, probability of the need for repeated examinations, and cost. Institutions should weigh these factors and consider that some agents might have a greater propensity for deposition than others.
- 4 Given the importance of GBCAs for advancing scientific discovery and improving clinical care, the ISMRM Safety Committee supports the views of the National Institutes of Health,<sup>42</sup> in that administration of GBCAs is appropriate in research settings under the guidance of protocols approved by an Institutional Review Board, and that must include patient's informed consent. Because no risks are known to be associated with gadolinium deposition in the brain, the ISMRM is unable to make an overarching recommendation regarding disclosure of gadolinium deposition to research participants. Therefore, each institution must decide whether inclusion of information on the deposition of gadolinium in the brain is necessary and should be included as part of the consent form; if so, the institution must decide on the description to use. The circumstances under which the GBCA is administered, the unknown risks of gadolinium deposition, and the need to explain the deposition to participants in appropriate language should be taken into account. In the event that new data are available describing adverse biological or clinical effects associated with gadolinium deposition subsequent to this Personal View, it might be appropriate to include that information as part of the consent process.
- 5 Investigators reporting studies on gadolinium deposition in the brain should exercise meticulous disclosure of financial, consulting, and advising relationships with industries as potential conflicts of interest. Although proper disclosure of conflicts of interest must be done for all academic publications, transparency is particularly relevant for studies of gadolinium deposition.
- 6 Due to the potential confounding of disease-related signal intensity changes with gadolinium deposition, future studies should explicitly describe all relevant clinical history of participants, including treatment of the patients in the study.

gadodiamide was detected 1 week after dosing). The deposition of gadolinium by gadodiamide decreased by approximately 43% from 1 week to 20 weeks, indicating the possibility of a clearing mechanism, with no indication of a saturation point. Furthermore, histopathological studies showed no neurotoxicity. Whether these results can be translated to human beings is unclear, but the potential clearance of gadolinium would be an important consideration in which GBCA to use if they have different clearances.

### Is there any evidence of harm?

The clinical and biological significance of retained gadolinium in the brain, if any, remains unknown. No harm from gadolinium exposure has been seen in animal models and no behavioural changes were reported in animals undergoing repeated examinations with

gadolinium agents over a very short time period.<sup>21</sup> Burke and colleagues<sup>35</sup> have reported a list of non-specific symptoms from a survey of patients who believed that they suffered from gadolinium toxicity, though no evidence is available from any well-controlled studies. Other than anecdotal reports, no data exist linking adverse biological or neurological effects to gadolinium deposition in the brain. The major physiological roles of the dentate nucleus—the site of deposition most often noted—include planning, initiation, and control of voluntary movements. No clinical conditions related to dysfunction of these roles have ever been associated with MRI in the retrospective studies published to date.<sup>6–8,11,16,18,20,22,24–26,33,36</sup> Specifically, no neurological symptoms have been reported that could be caused by damage to the dentate nucleus or other brain structures; prospective controlled studies would help to draw more definitive conclusions, although long-term studies might be required to conclude whether gadolinium deposition in the brain causes subtle neurological deficits.

#### Panel 2: Research priorities and unresolved questions regarding gadolinium deposition

- 1 Does the deposition of gadolinium in the brain cause any adverse effects, and are these effects dose dependent? What is the incidence and severity of adverse events (or perceived adverse events)?
- 2 What is the chemical state and structure of the deposited gadolinium?
- 3 What are the relative rates of deposition with each gadolinium chelate? Do dose and relaxivity play a role in the extent of observed signal intensity changes?
- 4 Are the observed differences in gadolinium deposition between gadolinium-based contrast agents dependent on the agent's class? How do field strength, sequences, and MRI settings used, and agent-dependent differences in T1 relaxivity affect our ability to pool large datasets?
- 5 Which groups of patients are more or less susceptible to gadolinium deposition?
- 6 How do treatments such as radiation or chemotherapy affect gadolinium deposition?
- 7 What is the mechanism of gadolinium deposition in the brain?

#### Search strategy and selection criteria

A literature search was done for this Personal View, consisting of PubMed, Google Scholar, and ISI Web of Science searches for the terms “gadolinium deposition”, “brain gadolinium”, “gd deposition”, and “deposition MRI” between September, 2015, and March, 2017. Because of the large number of published reports on this topic, those deemed most relevant for the aims of this Personal View were selected. Excluded from our selection were research articles that provided only anecdotal evidence. Papers with quantitative data were prioritised for inclusion, as were reports that sought to provide comparisons between agents.

#### Limitations of the available evidence

All clinical studies have been retrospective single-centre studies.<sup>6–8,11,16,18,20,22,24–26,33,36</sup> Participants were selected from hospital databases with various selection criteria, and thus selection and information bias are likely. Some studies included participants who had previous scans with other GBCAs than the GBCA under investigation.<sup>6,26,33</sup> A hypothesised potentiation effect of gadodiamide on gadobenate dimeglumine highlights the need for careful assessment of exposure history to various agents.<sup>25</sup>

With some exceptions,<sup>20</sup> investigators have used signal intensity ratios between target and reference areas of the brain for quantitative analysis. The value of this ratio depends on a variety of physical and acquisition variables that are system and site dependent. Use of quantitative T1 mapping techniques instead of signal intensity ratios might be helpful to reduce variability between sites.

Free elemental gadolinium is toxic, whereas chelated gadolinium is regarded as relatively safe. Many investigators assume that gadolinium is deposited in its unchelated form, because some linear agents with low thermodynamic stability are more strongly associated with gadolinium deposition than those with higher thermodynamic stability. However, the chemical form of the gadolinium that is deposited in the brain remains unknown, and post-mortem studies have been unable to address this issue.<sup>7,11,15,23</sup> Moreover, the presence and concentration of other substances with T1-shortening properties (eg, iron) has yet to be determined. A recently developed method to determine speciation of gadolinium has not yet been applied to brain tissue.<sup>37</sup>

#### Regulatory statements

The US Food and Drug Administration (FDA) is evaluating the potential risk of deposits of gadolinium in

the brain with repeated GBCA use.<sup>14</sup> The FDA stated that to “reduce the potential for gadolinium accumulation, health care professionals should consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary. Health care professionals are also urged to reassess the necessity of repetitive GBCA MRIs in established treatment protocols.”<sup>38</sup> The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency has recommended precautionary suspension of marketing authorisations for four linear agents—gadobenate dimeglumine, gadodiamide, gadopentetate dimeglumine, and gadoversetamide—citing the fact that their linear structure makes these agents more likely to release gadolinium.<sup>39</sup> After the final submission of this manuscript, the American College of Radiology independently issued a statement in response to the PRAC recommendations,<sup>40</sup> which is in agreement with the ISMRM recommendations above. Similarly the FDA updated their statement from July, 2015, recommending no change and reaffirming that no adverse effects have been identified from these agents.<sup>41</sup>

### Conclusions and future directions

Convincing evidence is available for the deposition of gadolinium in the deep nuclei of the brain, particularly after repeated exposure to GBCAs. Although differences in gadolinium deposition are apparent among the agents and between agents' class, some data are contradictory. Additionally, no data are available regarding gadolinium deposition for some contrast agents. The detection of gadolinium deposition in the brain is concerning; however, there are no reliable data regarding its clinical or biological significance, if any. On the basis of the available data, the ISMRM recommendations (panel 1) attempt to balance the potential (yet unknown) harm of gadolinium deposition with the proven clinical and research utility of GBCAs. Further research is needed to elucidate the mechanisms and relevance of gadolinium deposition. As such data emerge, our recommendations on the clinical and research use of GBCAs are expected to evolve.

The ISMRM supports rigorous research in all aspects of MRI, and will continue to urge and promote research and discussion on this subject at scientific meetings, workshops, academic journals, and through pilot grant funding opportunities. As shown in this Personal View, several issues remain unresolved (panel 2), which should be addressed in future studies.

#### Contributors

VG, FC, and SBR wrote an initial draft. All authors contributed to literature search, writing of the manuscript, and the generation of recommendations. The ISMRM Safety Committee reviewed a longer version of the manuscript and, after their comments were incorporated, the Board of Trustees of the ISMRM Safety Committee reviewed the revised manuscript, provided additional feedback, and approved the submitted manuscript. The manuscript was further revised during the peer review and editing process.

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