

**Do gadolinium-based contrast agents affect the 18F-FDG PET/CT uptake in the dentate nucleus and the globus pallidus? A pilot study.**

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Running Title: Gadolinium deposits assessed by 18F-FDG PET/CT uptake in the dentate nucleus and the globus pallidus.

**Objectives** Gadolinium (Gd) is toxic and to avoid its deposition in the tissues, it must be chemically bonded with nonmetal ions to facilitate its excretion by the kidneys. High signal intensity in the dentate nucleus (DN) and globus pallidus (GP) on unenhanced T1-weighted MR images has been both morphologically and pathologically linked to gadolinium-based contrast agent (GBCA) retention in the brain. The purpose of this study is to determine if repeated administrations of GBCA would affect the uptake of  $^{18}\text{F}$ -FDG in the DN and GP on PET/CT.

**Methods** 376 patients who had both contrast enhanced MR (CE MR) of the brain and PET/CT from Jan 2004-Oct 2015 were identified. Patients with a history of brain irradiation, hepatic or renal disease were excluded. The maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ) was measured in the DN and GP on the PET/CT in patients who had 3 to 6 successive CE MR brain studies. The  $\text{SUV}_{\text{max}}$  of the corresponding areas in the control group of patients who had no prior CE MR, and a normal, unenhanced MR of the brain was also measured. A Wilcoxon two-sample test was used for statistical analysis. **Results** 15/376 (4%) cases [mean age  $54 \pm 18$ , M:F = 10:5] were included in the subject group, and 15 cases [mean age  $36 \pm 9$ , M:F = 11:4] were included in the control group. The median DN  $\text{SUV}_{\text{max}}$  was significantly lower in the subject group than in the control group (5.4 vs. 6.4, respectively;  $p=0.021$ ). Similarly, the median GP  $\text{SUV}_{\text{max}}$  was significantly lower in the subject group than in the control group (8.8 vs. 12.1, respectively;  $p=0.003$ ). **Conclusions** The median  $\text{SUV}_{\text{max}}$  in the DN and GP were 16% and 27% lower respectively in patients who received GBCAs compared to those who had not received GBCAs. This could be related to Gd deposition in these areas.

Key words: gadolinium, dentate nucleus, globus pallidus

## Background

Magnetic resonance imaging (MRI) utilizes non-ionizing electromagnetic radiation to diagnose and monitor disease. A major component of MRI is the use of Gadolinium-based contrast agents (GBCAs). It is estimated that over 200 million doses of GBCAs have been administered worldwide (1). Gadolinium (Gd) is a toxic element and to avoid its deposition in tissues it is chemically bonded with nonmetal ions to create GBCAs in an effort to facilitate its excretion by the kidneys (2). GBCAs are used at relatively low concentrations (0.1-0.3 mmol/kg) with serious adverse reactions only occurring in about 0.03% of administrations, usually in patients with compromised renal function. One of the more serious complications associated with GBCAs is nephrogenic systemic fibrosis (NSF), a potentially life-threatening complication resulting in widespread tissue fibrosis. NSF is widely attributed to Gd ions dissociating from their chelating agents and depositing in tissues (3). It has been believed that Gd agents were completely expelled from the body in patients with normal renal function; however, recent studies have shown that high signal intensity in the dentate nucleus (DN) and globus pallidus (GP) on unenhanced T1-weighted MR images have been linked to Gd retention in the brain (4). Originally it was thought that damage to the blood brain barrier, renal dysfunction, liver disease, or metabolic disorders were the cause of contrast deposition in the brain; however, recent studies have shown that Gd deposits in the brain of patients who have normal renal function and intact blood brain barriers following multiple contrast administrations (2).

Positron emission tomography (PET) coupled with computed tomography (CT) is a radiological modality that utilizes the administration of radiopharmaceuticals to diagnose and monitor physiological pathologies. <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) is a radioactive glucose analog that is commonly used in PET procedures to analyze the metabolic activity of tissue in the body.

There are very few studies showing a relationship between Gd deposition in the brain and the health of the surrounding tissue. The use of PET/CT allows for a comparison of the anatomical regions of Gd deposition with the metabolic activity of the same region. Given that intact GBCAs do not cross intact blood brain barriers of normal patients, it is not clear if Gd deposition may result in metabolic changes in the brain. The purpose of this pilot study is to determine if repeated administration of GBCAs affect the uptake of  $^{18}\text{F}$ -FDG in the DN and GP on PET/CT.

## **Methods**

All patients records included in this study were obtained from our institution. The Saint Louis University Hospital Institutional Review Board approved this retrospective study, and the requirement to obtain informed consent was waived. All data were handled in compliance with the Health Insurance Portability and Accountability Act of 1996.

### ***Magnetic Resonance Imaging***

Patients who had at least one contrast-enhanced MR (CE MR) and one PET/CT from January 2004 to October 2015 were identified. Patients who underwent three to six CE MR (of which at least 2 were brain studies) were then selected for the subject pool. The first CE MR of the brain was used to establish a baseline and the last CE MR of the brain was used for comparison. The brain MR acquisitions were performed according to the institution's protocol. The images were acquired on either a 1.5T Siemens MAGNETOM Aera or a 3T Philips Achieva. The brand of GBCA administered was not a factor in patient selection or exclusion. Patients with a history of brain irradiation or hepatic or renal disease were excluded from the study as these conditions can affect Gd deposition. Patients with known brain tumors or lesions were also excluded. The

control group consisted of patients who had never received a CE MR and had a normal unenhanced MR of the brain.

### ***Positron Emission Tomography/Computed Tomography***

For the patient to qualify for the study, the PET/CT used for analysis had to be completed after the last CE MR used for analysis. Following the administration of  $^{18}\text{F}$ -FDG, the PET/CT study was performed on a Philips Gemini Time of Flight system. Images for patients in the subject group were acquired using the institution's protocol for whole body acquisitions, while images for those in the control group were acquired as part of a dedicated brain acquisition.  $^{18}\text{F}$ -FDG doses were calculated based on weight at 5.18 MBq/kg (0.14 mCi/kg) with a maximum dose of 555 MBq (15 mCi), and administered intravenously using a butterfly needle; imaging was performed after an uptake time of 60 minutes. A fasting blood glucose level <150 mg/dL was required prior to injection. Regions of interest (ROIs) were drawn on the PET images around the DN and GP for each patient and the maximum standardized uptake values ( $\text{SUV}_{\text{max}}$ ) were recorded. ROIs were first drawn by a certified nuclear medicine technologist from the research team and then verified by a board-certified nuclear medicine physician who also holds certification as a neuroradiologist (fellowship-trained). The CT portion of the PET/CT was used to locate the anatomical regions in the brain (Fig. 1).

### ***Data Analysis***

Due to the small sample size in the subject and control groups, and an assumption of a non-normal distribution of data, Wilcoxon two-sample non-parametric test was chosen to compare the median  $\text{SUV}_{\text{max}}$  values from the DN and GP between each group. All statistical analyses

were conducted using the Statistical Analysis System (SAS) software, v. 9.4.

## Results

Three hundred and seventy six patients who had both a CE MR and a PET/CT from January 2004 to October 2015 were identified. 15/376 (4%) cases [mean age  $54\pm 18$ , M:F = 10:5] were included in the subject group, and 15 cases [mean age  $36\pm 9$ , M:F = 11:4] were included in the control group.

The results of the Wilcoxon two-sample test indicate that the median DN  $SUV_{max}$  was significantly lower in the subject group than in the control group (5.4 vs. 6.4, respectively;  $z=2.035$ , one-tailed  $p=0.021$ ). Similarly, the median GP  $SUV_{max}$  was significantly lower in the subject group than in the control group (8.8 vs. 12.1, respectively;  $z=2.717$ ,  $p=0.003$ ).

Additional analysis was performed to investigate an interaction effect from age or gender, but no significant interaction effect was found. A summary of the findings is presented in Table 1 and group median comparisons are presented in Figures 2 and 3.

## Discussion

GBCAs are a crucial element in diagnosing disease in MRI. Other studies have proven that Gd is dissociating from GBCAs and depositing in the DN and GP. Our study intended to evaluate the potential impact of Gd deposits on brain metabolic activity as detected by  $^{18}F$ -FDG PET/CT. Since FDG uptake corresponds to the metabolism of tissue, decreased uptake could imply decreased metabolism.

The DN and GP are separate regions of the motor cortices of the brain. The DN is part of the deep cerebellar nucleus and is located most laterally. The lateral hemispheres of the cerebellar cortex are connected to the cerebellum through the DN. The DN also has a connection through the superior peduncle to the ventral lateral nucleus of the thalamus which relays to the cerebral motor cortex(5). If the DN is exhibiting reduced FDG uptake, the deposited Gd could be reducing the function of the cells in the DN. This could lead to reduced cerebral motor output, as the DN connects regions of motor function in the brain. The GP is part of the basal ganglia and is included in the extrapyramidal system. The extrapyramidal system is considered part of the motor system and is thought to affect muscle tone, posture, and voluntary movement(6). If the GP exhibits decreased FDG uptake as a result of Gd deposition, this could lead to decreased control of muscle tone and voluntary movement. Compared to our control group, our subject group showed decreases in metabolic activity (as measured by  $SUV_{max}$ ) of 16% and 27% in the DN and GP, respectively.

When comparing  $^{18}F$ -FDG uptake in the DN and GP between subject and control groups, we measured and reported  $SUV_{max}$  rather than  $SUV_{mean}$  values. Previous research has indicated that  $SUV_{max}$  is becoming the more commonly reported measurement of radiopharmaceutical uptake on PET studies(7). This is due to the significant reproducibility of the  $SUV_{max}$  measurement, as well as the negligible effect that small spatial shifts in ROI placement have on the maximum value within the ROI.

Our study is not without limitations. Firstly, this study has a limited sample size. Although we started with over 350 patients, we were only able to utilize 15 patients for our subject group due to our extensive exclusionary criteria. In order to eliminate as many extraneous factors as possible, our patients had to be free of renal disease, liver disease, brain lesions or tumors, and

brain irradiation. They also had to have multiple GBCA administrations and brain MR acquisitions, and an  $^{18}\text{F}$ -FDG PET/CT after their CE MR studies. Secondly, a limitation of the control group is that the patients were not age-matched to the subject group. The mean age of the subject group ( $59 \pm 18$  years) was older than the median age of the control group ( $36 \pm 9$  years). Future studies would be both gender- and age-matched to control for these variables. As for other differences between the patient groups, the control group patients had no history of cancer while the subject group consisted of some patients who had cancer and some who did not; however, those patients who had brain tumors or lesions were excluded from the subject group in an attempt to control for that factor.

Thirdly, the PET/CT acquisition protocol differed between groups. The subject group received a whole body PET/CT as per standard protocol at our institution. The control group received a dedicated brain PET/CT as per another research protocol. As a result, the PET scan time per bed position for the brain differed between groups. A final limitation of this study is that we could only qualitatively state that our subjects had Gd deposition in the DN and GP, using evidence stated by peer-reviewed research that Gd has been shown to deposit in these regions of the brain. In future studies, the amount of Gd deposition could be quantitatively measured.

While our study suggests that Gd may cross intact blood brain barriers and affect FDG uptake in the DN and GP, our study does not evaluate or limit itself to a specific type (linear, macrocyclic, ionic, and nonionic) or brand of contrast. All of our patients received multiple types and brands of GBCA for their exams. Further studies need to be done to explore the types and brands of GBCAs individually to determine varying rates of Gd deposition. In an ideal setting, a useful approach would be to use the same patient for the control and subject group. The subject would have an  $^{18}\text{F}$ -FDG PET/CT before any GBCA administration, followed by a



series of brain MR studies and GBCA administrations, and finally another  $^{18}\text{F}$ -FDG PET/CT at the end. In this approach, the patient could serve as their own baseline and we could better track progression of Gd deposition and its effects on brain metabolism.

### **Conclusion**

The median  $\text{SUV}_{\text{max}}$  in the DN and GP were 16% and 27% lower respectively in patients who received GBCAs when compared to patients who did not receive GBCAs. This could be related to Gd deposition in these areas. Future research should focus on prospectively validating these results using appropriate age- and gender-matched controls.

### **Disclosure**

No potential conflict of interest relevant to this article was reported.

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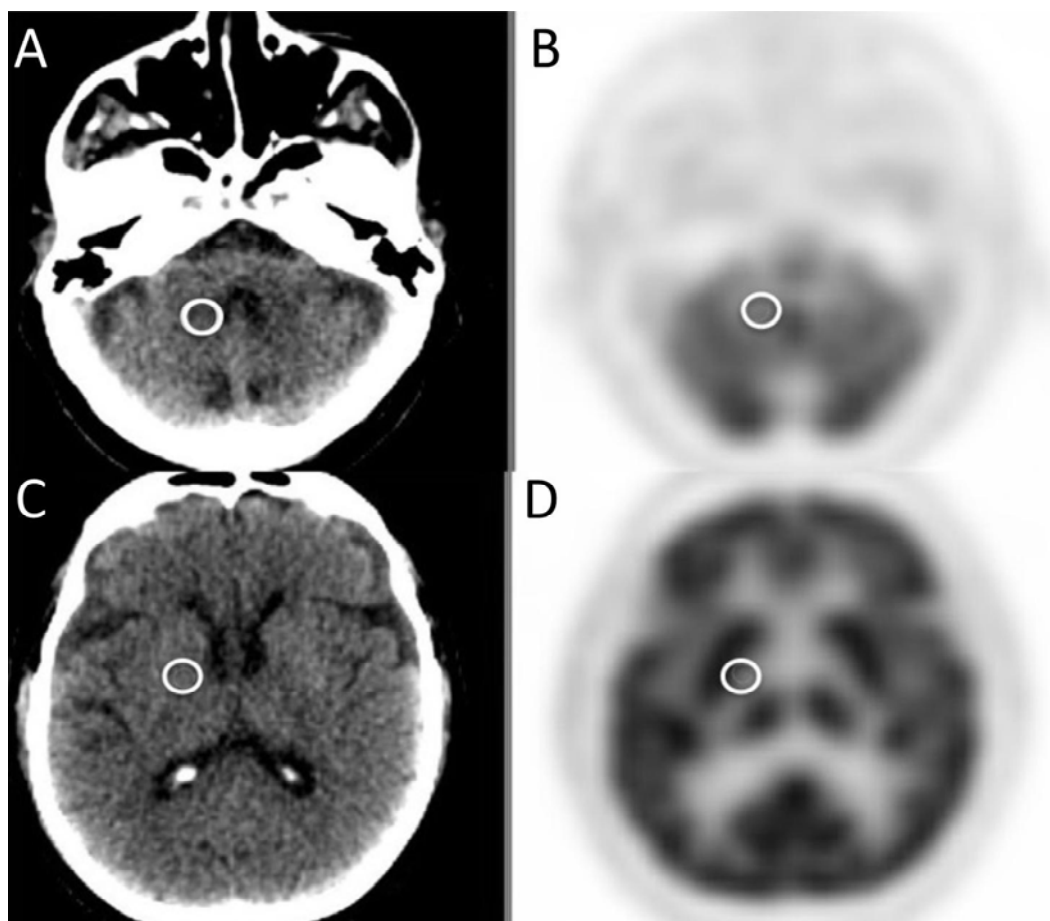


Figure 1. CT (A, C) and PET (B, D) images of 84 y/o male with a history of scalp melanoma.

White circles represent ROI analyses drawn around the DN (A & B) and GP (C & D).

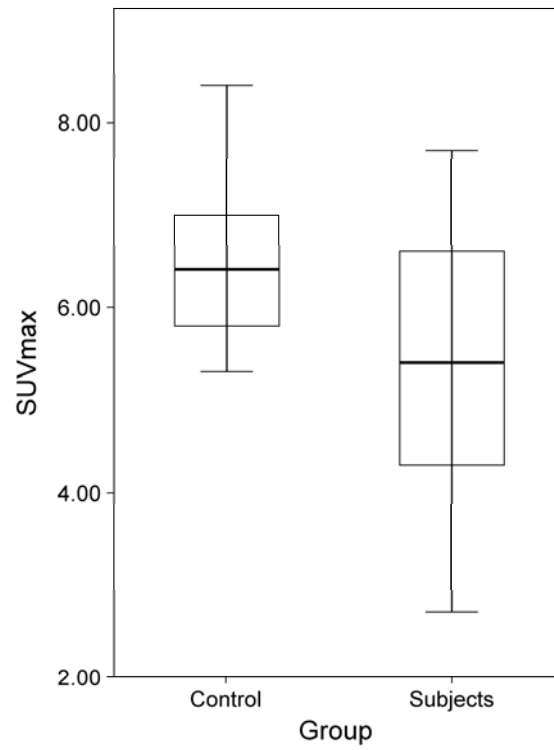


Figure 2. Boxplot of SUV<sub>max</sub> in the DN for controls and subjects. Median difference between groups is significant (p=0.021).

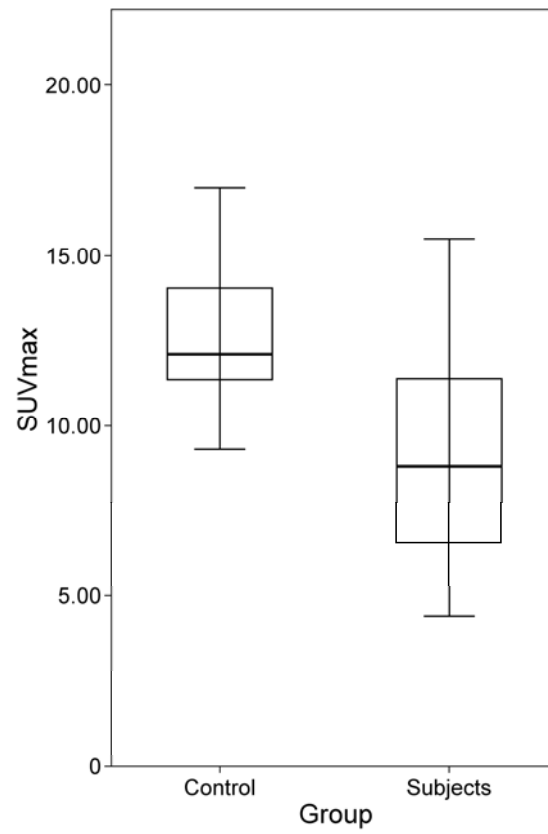


Figure 3. Boxplot of SUV<sub>max</sub> in the GP for controls and subjects. Median difference between groups is significant (p=0.003).

		25%	Median	75%	p-value <sup>1</sup>
DN	Controls	5.6	6.4	7	p = 0.021
	Subjects	3.7	5.4	6.7	
GP	Controls	11.2	12.1	14.4	p = 0.003
	Subjects	6.2	8.8	11.5	

<sup>1</sup> Wilcoxon Two-Sample Test

Table 1. Comparison of 25<sup>th</sup> percentile, median, 75<sup>th</sup> percentile, and one-tailed p-values from DN and GP for control and subject groups.