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Reproducibility of a parkinsonism-related metabolic brain network in non-human primates: A descriptive pilot study with FDG PET

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Abstract

Background—We have previously defined a parkinsonism-related metabolic brain network in rhesus macaques using a high-resolution research PET camera. This brief article reports a descriptive pilot study to assess the reproducibility of network activity and regional glucose metabolism in independent parkinsonian macaques using a clinical PET/CT camera.

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  C. Execution: CZ, YG, THJ, YM

2) Statistical Analysis

  A. Design: YM, DE

  B. Execution: YM, SP

  C. Review and Critique: YM, DE, JMB

3) Manuscript

  A. Writing of the first draft: YM, SP, CZ, YG

  B. Review and Critique: DE, JMB, THJ, JBK, SHF

Methods—[^{18}F]fluorodeoxyglucose PET scans were acquired longitudinally over three months in three drug-naïve parkinsonian and three normal cynomolgus macaques. Group difference and test-retest stability in network activity and regional glucose metabolism were evaluated graphically using all brain images from these macaques.

Results—Comparing the parkinsonian macaques to the controls, network activity was elevated and remained stable over three months. Normalized glucose metabolism increased in putamen/globus pallidus and sensorimotor regions, but decreased in posterior parietal cortices.

Conclusions—Parkinsonism-related network activity can be reliably quantified in different macaques with a clinical PET/CT scanner and is reproducible over a time period typically employed in preclinical intervention studies. This measure can be a useful biomarker of disease process or drug effects in primate models of Parkinson's disease.

Introduction

PET imaging of functional brain network activity may provide a valuable biomarker applicable to both preclinical studies in animals and translational research in humans. This methodology can potentially identify novel mechanisms of disease process and define mechanisms and extent of drug action. Using high resolution PET with [^{18}F]fluorodeoxyglucose (FDG) and brain network analysis, we have previously reported spatial covariance patterns of abnormal regional glucose metabolism in patients with Parkinson's disease (PD)[1] and in non-human primates (NHPs) following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration[2]. In both PD patients and MPTP-lesioned rhesus macaques, this parkinsonism-related pattern (PRP) was characterized by hypermetabolism in the putamen/globus pallidus, thalamus, pons and sensorimotor cortex, covarying with hypometabolism in the posterior parietal-occipital cortices. PRP network expression in individual subjects was found to be abnormally elevated in PD patients or parkinsonian macaques, correlated with the severity of motor symptoms and sensitive for assessing treatment responses to novel experimental therapies in clinical trials[3] and in a preclinical setting[4].

PRP networks have been defined consistently using FDG images acquired in multiple cohorts of PD patients on different PET scanners[5–8]. Although PRP network was found to be reproducible in two separate cohorts of MPTP-lesioned rhesus macaques (*Macaca mulatta*) imaged on the same high resolution research tomography (HRRT)[2], it is currently unknown whether this network can be reliably quantified in a different species of parkinsonian macaques scanned on a lower resolution clinical tomography. Moreover, the test-retest reliability of PRP expression demonstrated in PD patients[1] has not been evaluated in NHP models of PD.

In this descriptive pilot study we assessed (1) the network activity with a clinical PET/CT scanner in a previously untreated cohort of cynomolgus macaques undergoing systemic

MPTP administration; (2) the test-retest reproducibility of network activity in individual macaques over a time interval typically used in experimental therapeutic research with NHPs; (3) the effect of altered regional glucose metabolism on the stability of network activity in parkinsonian macaques. Our primary goal was to establish a viable methodology for accelerating biomedical advances in drug discovery based on common imaging biomarkers across both animals and humans.

Methods

Animal Preparation and Characteristics

This pilot study included six adult female cynomolgus macaques matched in age and weight (*Macaca fascicularis*, age 6.9 ± 0.5 [mean $\pm$ SD], range 6.2–7.5 years; weight 3.0 ± 0.2, range 2.7–3.3 kg). Three macaques exhibited stable MPTP-induced parkinsonism with moderate to marked levels of disability. Three others served as normal controls. Procedures of animal preparation, MPTP injection and behavioral testing have been fully described elsewhere[9]. All studies were performed with the regulatory approval (Suzhou IACUC, Jiangsu Province, China) and in accordance with the Guide for the Care and Use of Laboratory Animals (NIH, USA).

PET Imaging and Processing

FDG PET was performed at Huashan Hospital PET Center using a Siemens Biograph 64 PET/CT camera with a resolution of 4~6 mm[10]. The animal was awake during uptake and rapidly anesthetized at 30 min following intravenous injection of 5 mCi of FDG. Three MPTP animals were scanned two weeks in advance as an initial trial. The three MPTP and three normal animals were then scanned at baseline and after three months. One normal animal did not complete the follow-up imaging because of the failure of anesthesia. All animals were scanned between 40–80 min post-injection using the same imaging protocol (Supplementary Table 1).

Image preprocessing was performed using the procedures described previously[2]. PET images were spatially normalized into a macaque brain template[11] and smoothed with a 4 mm Gaussian filter. This produced fourteen usable PET images of cerebral glucose metabolism: nine for the parkinsonian animals and five for the normal controls.

Measurement of PRP Expression and Regional Glucose Metabolism

PRP expression was assessed for the parkinsonism-related brain network (Fig. 1A) derived previously in a derivation sample of rhesus macaques[2], using FDG PET images acquired on a HRRT human scanner with a superior 3D resolution of 2~3 mm[12]. Network scores were computed prospectively in multiple PET images from all cynomolgus macaques (i.e. validation sample) and converted into z-scores with respect to those in the derivation sample.

Normalized regional metabolic values were measured in the validation sample with a spherical volume of interest (3 mm in radius) centered in brain regions showing abnormal

metabolic activity in the PRP (Fig. 1A). The volumes were placed anatomically over all FDG PET scans in reference to a macaque brain atlas[13].

Graphic Procedures

Because the sample size of the animals was small in this pilot study we could not perform any statistical analysis such as repeated-measures analysis of variance. Instead, we used a graphical approach to visualize group differences in network score or regional metabolism and their longitudinal changes over time. Measures from the repeat scans in each animal were combined and clearly marked in the corresponding graphs.

Results

Reproducibility of PRP Expression in Independent Macaques

PRP scores were elevated in the MPTP-lesioned animals compared to the normal controls in both the derivation sample and the validation sample (Fig. 1B; Supplementary Fig. 1). PRP scores were similar between the normal controls but mostly lower in the parkinsonian animals in the validation sample than those in the derivation sample.

Test-retest Reliability of PRP Expression

PRP scores in the validation sample showed excellent stability over a short period of two weeks in the three MPTP-lesioned animals and in the five test-retest animals over a longer period of three months (Fig. 1C).

Metabolic Differences between Parkinsonian and Normal Macaques

FDG PET images revealed relative metabolic differences between the MPTP-lesioned and the normal animals (Fig. 2; Supplementary Table 2). Normalized metabolism increased bilaterally in the putamen/globus pallidus (18–19%) and sensorimotor cortex (20–25%) with smaller increases in the right supplementary motor area (15%), but decreased bilaterally in the posterior parietal cortex with a smaller magnitude (11–13%). These measures were also stable over time in all animals (Supplementary Fig. 2).

Discussion

This descriptive pilot study compared brain network activity between two independent cohorts of MPTP-lesioned and normal macaques using FDG PET imaging. We found that PRP scores were elevated in parkinsonian macaques in both cohorts imaged on two different PET scanners (Fig. 1). Lower PRP scores in the validation sample reflected milder motor symptoms in the drug-naïve parkinsonian animals. These levels of reproducibility across the animal cohorts, species and the imaging instruments paralleled several previous reports in patients with PD[5–8]. Moreover, we demonstrated high test-retest reliability of network expression in the parkinsonian animals, also very similar to that obtained in PD patients scanned with FDG PET over an interval of two months[1].

It is worth noting that the same PRP network previously identified in rhesus macaques can be detected in bilateral models of experimental parkinsonism produced in a different species

of NHPs, cynomolgus macaques. This is a major advantage given that both cynomolgus and rhesus macaques are commonly used in translational biomedical research. Furthermore, PRP expression can be determined on a prospective single-case basis using lower resolution clinical PET cameras that are more widely available.

We have also explored abnormal glucose metabolism in the parkinsonian cynomolgus macaques graphically (Fig. 2). Normalized metabolism was found to increase mainly in the key relay stations within the basal ganglia and the sensorimotor cortices, but decrease in the posterior parietal regions in the parkinsonian animals. The metabolic differences in these subcortical and cortical regions were more or less symmetrical in terms of anatomical distribution and magnitude, consistent with the predominantly bilateral motor symptoms seen in these macaques following MPTP administration.

It is this alteration in regional glucose metabolism that accounts for the observed differences in PRP scores between the parkinsonian and control cynomolgus macaques described above. Notably, the relative metabolic values in each brain region also exhibited high stability in support of the excellent test-retest reproducibility in the corresponding PRP scores. These results agreed with the key brain regions in the PRP (c.f., Fig. 1A) and those reported by others in early to advanced PD patients[14–18]. Moreover, pallidal hypermetabolism has consistently been seen in parkinsonian macaques with FDG PET[19, 20] and 2-deoxyglucose autoradiography[21, 22], lending the credence to the pathophysiological models of PD[23, 24]. In this study we did not observe metabolic changes in thalamus and distal regions in the pons as reported in our previous study[2], owing most likely to the small sample size, species difference or both.

In this study the macaques were awake during tracer uptake to reduce the potential effect of anesthesia on physiological state of the animal, unlike many other metabolic imaging studies in which tracer injection and uptake took place in anesthetized animals[19, 20, 25]. This novel procedure can minimize large variability in local and global brain function due to the varied metabolic responses of individual animals to anesthesia. It also ensures that PET imaging accurately measures the metabolic activity in conscious animals to match that measured in human subjects. This approach can be adopted as part of a viable protocol for PET imaging studies in animal models.

Because of the small sample size of the animals in this pilot study we had relied on a graphic approach to describe group differences in imaging measures by combining data from multiple time points in each animal. Although empirical this pragmatic approach was valuable in producing novel findings that were consistent by themselves and in comparison to previous reports. Imaging studies in larger samples, with both cross-sectional and longitudinal designs, are still needed to confirm these findings and to perform network or regional correlations with independent measures of clinical symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

References

1. Ma Y, Tang C, Spetsieris PG, Dhawan V, Eidelberg D. Abnormal metabolic network activity in Parkinson's disease: test-retest reproducibility. J Cereb Blood Flow Metab. 2007; 27(3):597–605. [PubMed: 16804550]

2. Ma Y, Peng S, Spetsieris PG, Sossi V, Eidelberg D, Doudet DJ. Abnormal metabolic brain networks in a nonhuman primate model of parkinsonism. J Cereb Blood Flow Metab. 2012; 32(4):633–642. [PubMed: 22126913]

3. Poston KL, Eidelberg D. Network biomarkers for the diagnosis and treatment of movement disorders. Neurobiol Dis. 2009; 35(2):141–147. [PubMed: 19013242]

4. Ma Y, Peng S, Flores J, et al. Abnormal metabolic brain network in parkinsonian macaques: Modulation by retinal pigment epithelial (RPE) cell implantation. Neurology. 2008; 71:154–155.

5. Niethammer M, Eidelberg D. Metabolic brain networks in translational neurology: concepts and applications. Ann Neurol. 2012; 72(5):635–647. [PubMed: 22941893]

6. Wu P, Wang J, Peng S, et al. Metabolic brain network in the Chinese patients with Parkinson's disease based on 18F-FDG PET imaging. Parkinsonism & related disorders. 2013; 19(6):622–627. [PubMed: 23529021]

7. Teune LK, Renken RJ, Mudali D, et al. Validation of parkinsonian disease-related metabolic brain patterns. Mov Disord. 2013; 28(4):547–551. [PubMed: 23483593]

8. Peng S, Ma Y, Spetsieris PG, et al. Characterization of disease-related covariance topographies with SSMPCA toolbox: effects of spatial normalization and PET scanners. Hum Brain Mapp. 2014; 35(5):1801–1814. [PubMed: 23671030]

9. Johnston TH, Fox SH, Piggott MJ, Savola JM, Brotchie JM. The alpha adrenergic antagonist fipamezole improves quality of levodopa action in Parkinsonian primates. Mov Disord. 2010; 25(13):2084–2093. [PubMed: 20824735]

10. Brambilla M, Secco C, Dominietto M, Matheoud R, Sacchetti G, Inglese E. Performance characteristics obtained for a new 3-dimensional lutetium oxyorthosilicate-based whole-body PET/CT scanner with the National Electrical Manufacturers Association NU 2-2001 standard. J Nucl Med. 2005; 46(12):2083–2091. [PubMed: 16330574]

11. Black KJ, Koller JM, Snyder AZ, Perlmutter JS. Template images for nonhuman primate neuroimaging: 2. Macaque. Neuroimage. 2001; 14(3):744–748. [PubMed: 11506546]

12. de Jong HW, van Velden FH, Kloet RW, Buijs FL, Boellaard R, Lammertsma AA. Performance evaluation of the ECAT HRRT: an LSO-LYSO double layer high resolution, high sensitivity scanner. Phys Med Biol. 2007; 52(5):1505–1526. [PubMed: 17301468]

13. Martin, R.; Browden, D. Primate Brain Maps: Structure of the Macaque Brain. Amsterdam, The Netherlands: Elsevier; 2000.

14. Ma Y, Tang C, Moeller JR, Eidelberg D. Abnormal regional brain function in Parkinson's disease: truth or fiction? Neuroimage. 2009; 45(2):260–266. [PubMed: 18992824]

15. Eggers C, Hilker R, Burghaus L, Schumacher B, Heiss WD. High resolution positron emission tomography demonstrates basal ganglia dysfunction in early Parkinson's disease. J Neurol Sci. 2009; 276(1–2):27–30. [PubMed: 18835490]

16. Huang C, Tang C, Feigin A, et al. Changes in network activity with the progression of Parkinson's disease. Brain. 2007; 130(Pt 7):1834–1846. [PubMed: 17470495]

17. Eckert T, Barnes A, Dhawan V, et al. FDG PET in the differential diagnosis of parkinsonian disorders. Neuroimage. 2005; 26(3):912–921. [PubMed: 15955501]

18. Tripathi M, Dhawan V, Peng S, et al. Differential diagnosis of parkinsonian syndromes using F-18 fluorodeoxyglucose positron emission tomography. Neuroradiology. 2013; 55(4):483–492. [PubMed: 23314836]

19. Brownell AL, Canales K, Chen YI, et al. Mapping of brain function after MPTP-induced neurotoxicity in a primate Parkinson's disease model. Neuroimage. 2003; 20(2):1064–1075. [PubMed: 14568476]

20. Emborg ME, Carbon M, Holden JE, et al. Subthalamic glutamic acid decarboxylase gene therapy: changes in motor function and cortical metabolism. J Cereb Blood Flow Metab. 2007; 27(3):501–509. [PubMed: 16835631]

21. Mitchell IJ, Clarke CE, Boyce S, et al. Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Neuroscience. 1989; 32(1):213–226. [PubMed: 2586750]

22. Guigoni C, Li Q, Aubert I, et al. Involvement of sensorimotor, limbic, and associative basal ganglia domains in L-3,4-dihydroxyphenylalanine-induced dyskinesia. J Neurosci. 2005; 25(8):2102–2107. [PubMed: 15728850]

23. Obeso JA, Marin C, Rodriguez-Oroz C, et al. The basal ganglia in Parkinson's disease: current concepts and unexplained observations. Annals of neurology. 2008; 64(Suppl 2):S30–S46. [PubMed: 19127584]

24. Eidelberg D. Metabolic brain networks in neurodegenerative disorders: a functional imaging approach. Trends Neurosci. 2009; 32(10):548–557. [PubMed: 19765835]

25. Kuge Y, Yokota C, Tagaya M, et al. Serial changes in cerebral blood flow and flow-metabolism uncoupling in primates with acute thromboembolic stroke. J Cereb Blood Flow Metab. 2001; 21(3):202–210. [PubMed: 11295874]
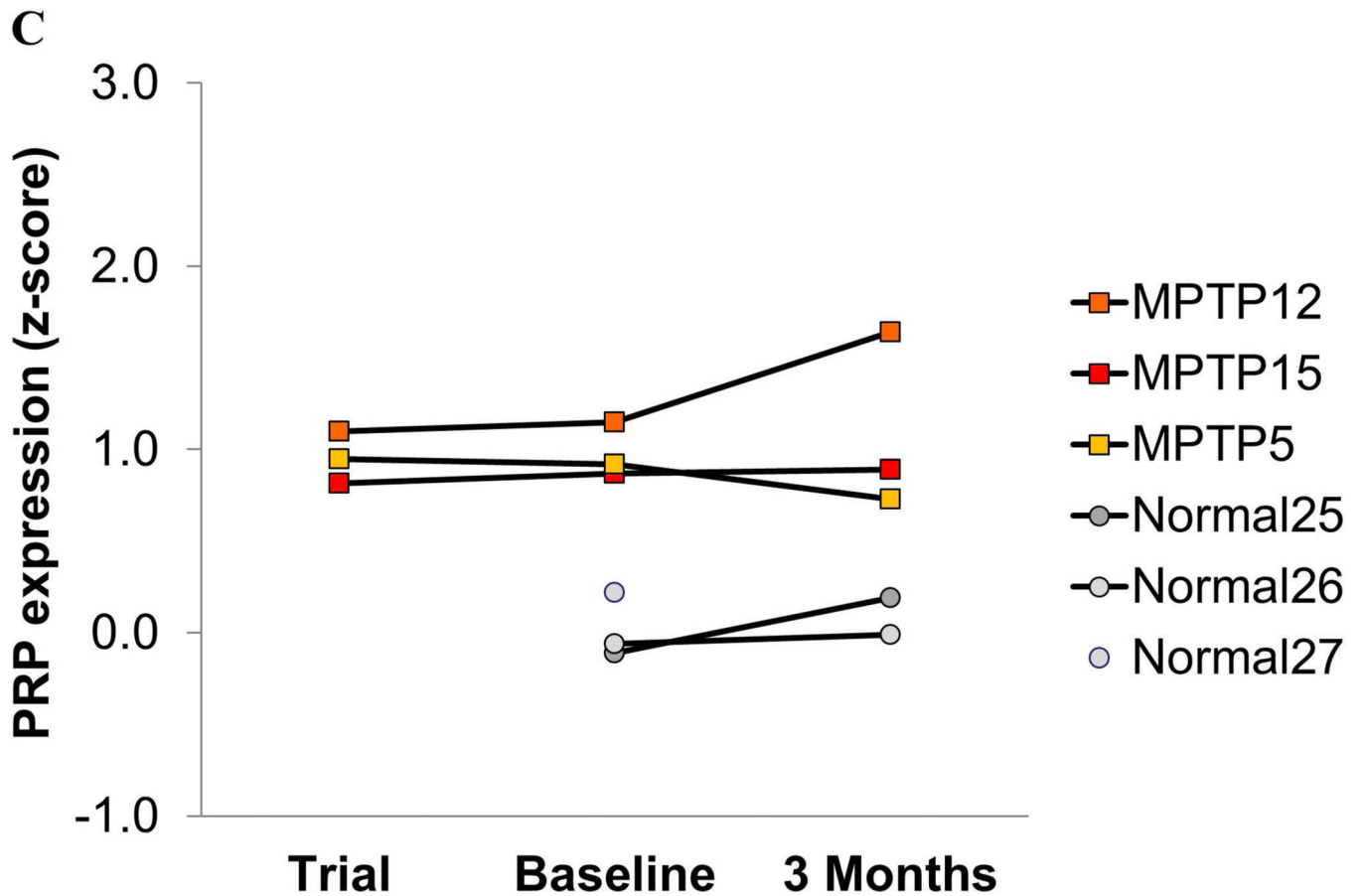
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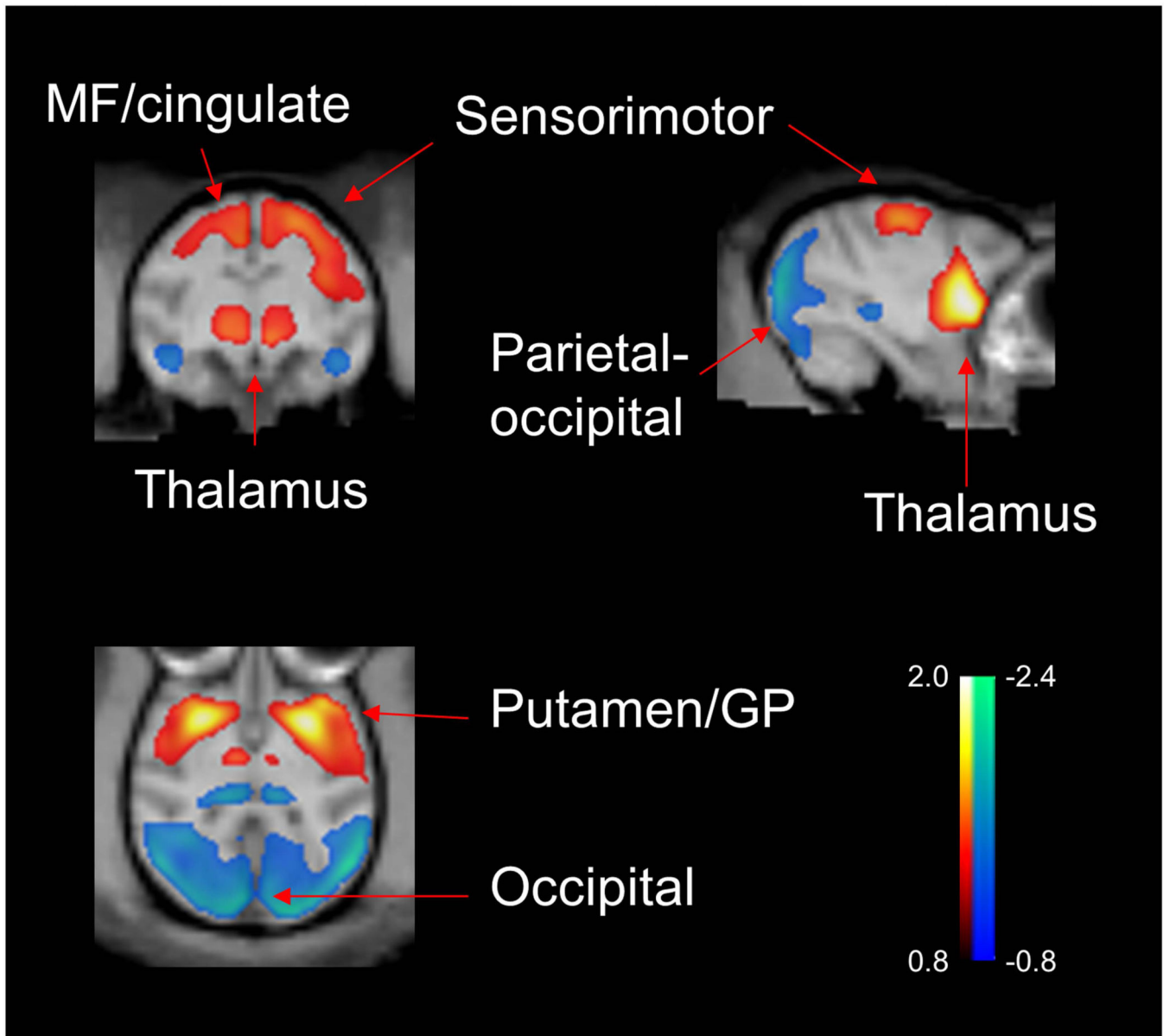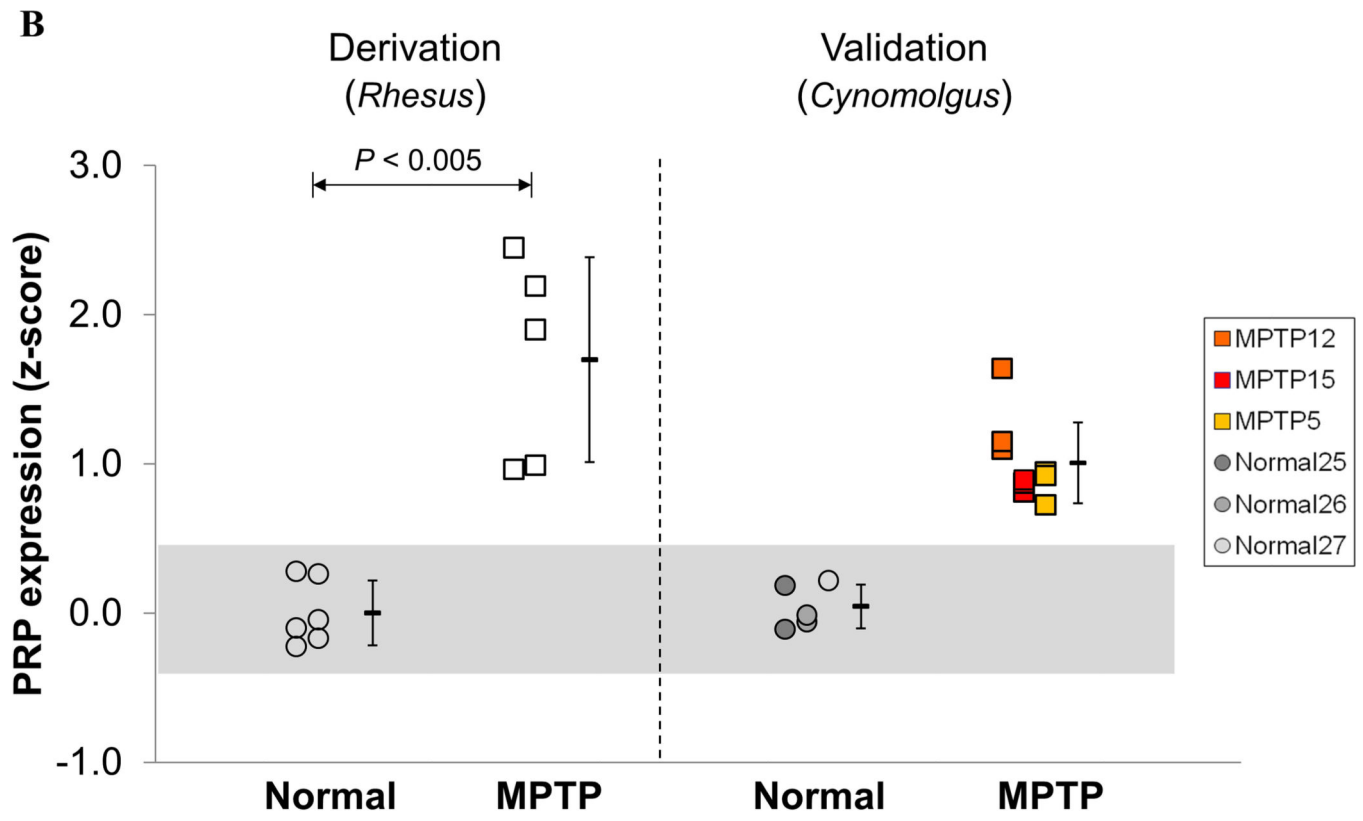
Fig. 1.
Reproducibility of a parkinsonism-related pattern (PRP) in non-human primates. A. PRP topography in parkinsonian macaques characterized by relatively increased (*red-yellow*) metabolic activity in the putamen, globus pallidus (GP), ventral thalamus, pons, and in the medial frontal (MF)/cingulate and sensorimotor (SMC) cortical regions, associated with relatively decreased (*blue-purple*) activity in the parietal-occipital cortex. This pattern was originally identified on a whole-brain basis using FDG PET images in the five MPTP-lesioned and six age-matched healthy rhesus macaques acquired with a HRRT scanner[2]. B. Group discrimination by PRP expressions in the original derivation sample imaged with the HRRT PET scanner and a prospective validation sample of nine parkinsonian and five normal control scans in cynomolgus macaques obtained with a clinical PET/CT scanner. C: Longitudinal changes in metabolic network expression between different time points in the prospective validation sample of parkinsonian and control animals. [The overlays represent the maps of PRP voxel weights from the network analysis, superimposed on a standard macaque MRI brain template[11]. Error bars in the graph refer to the standard deviations. The shaded area denotes the range of two standard deviations above and below the control mean in the derivation sample.]

A

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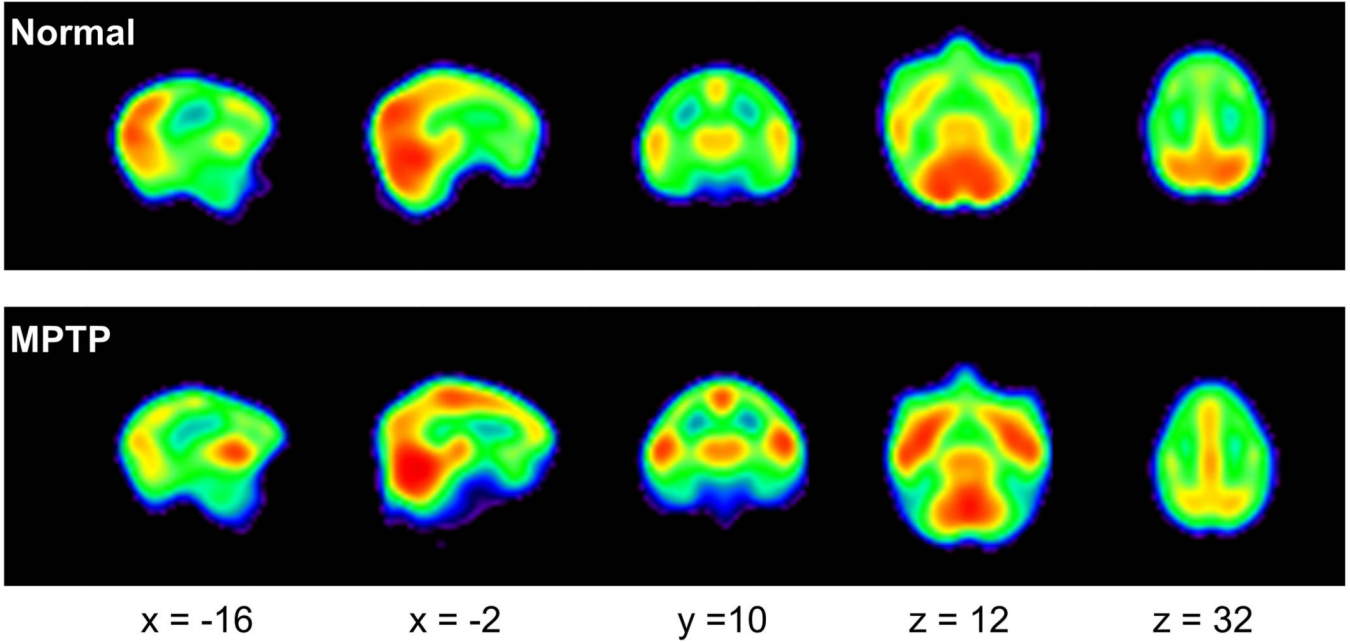
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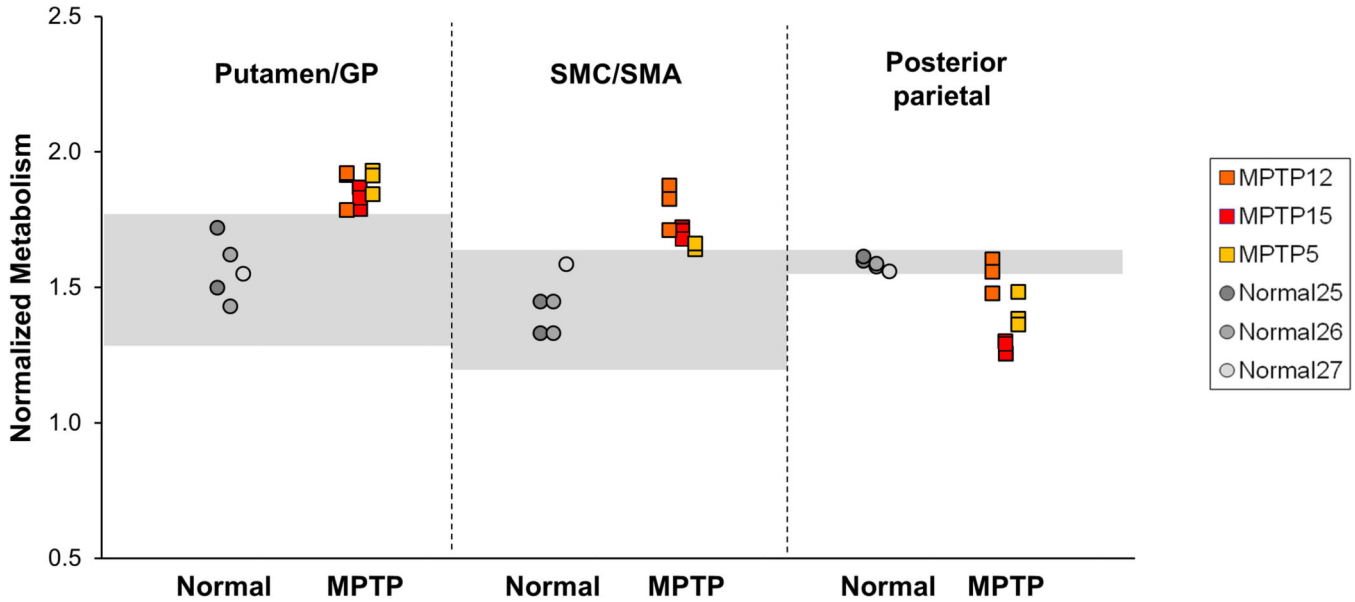
Fig. 2.
The distribution of abnormal regional glucose metabolism in non-human primates following MPTP administration. A. Mean images of relative cerebral glucose metabolism in normal (*top*) and MPTP-lesioned (*bottom*) cynomolgus macaques acquired with FDG using a clinical PET/CT scanner. The regional distribution of radiotracer uptake was highly symmetrical in both normal and parkinsonian macaques. B. Differences in relative regional glucose metabolism between the two animal groups comparing the nine parkinsonian and five normal control scans. Normalized metabolism increased in the putamen/globus pallidus

(GP) and sensorimotor (SMC)/supplementary motor area (SMA) regions, but decreased in the bilateral posterior parietal cortex. [The shaded areas in each panel denote the ranges of two standard deviations above and below the control mean values in the validation sample.]