Methods Dynamic PET and MRI scans were performed on three baboons (2M/1F, 14.1±2.1 kg). Animals were anesthetized with isoflurane (1%) and mechanically ventilated. Physiological parameters were monitored continuously and maintained within normal ranges. All images were acquired on a 3T Siemens TIM-Trio with a BrainPET insert and a custom PET-compatible 8-channel array coil. About 5 mCi of [18F]FDG was continuously infused at a rate of 0.01 mL/sec intravenously for each study. PET data were stored in list mode and binned into 1-min frames. Dual echo pseudo-continuous arterial spin labeling (pCASL) data was acquired simultaneously (TR/TE1/TE2 = 4000/12/30ms, 2.2 x 2.2 x 4 mm)4. During an 100 min of dynamic PET/MRI scan, a hypercapnic challenge (7% CO2) was given for 10 min and two varying concentrations of isoflurane (1.5% and 2.0%) were also given for 15 min each. Break time was provided (10-20 min) between challenges to allow animal physiology to return to baseline condition. All data was motion and slice-time corrected, skull stripped, spatially smoothed and registered to a standard NHP atlas5. Percent changes in BOLD/CBF and quantitative CBF maps were calculated6. Because an irreversible two-tissue compartmental model best describes FDG update and utilization, therefore, the slope of the PET time activity curve (TAC) is proportional to cerebral metabolic rate of glucose (CMRglu). By performing a pair-wise subtraction on dynamic PET data, changes in slopes of the PET TACs can be derived into a time-series reflecting dynamic changes in CMRglu throughout the imaging session.

Results and Discussion Fig 1a shows our experimental design and imaging protocols. Mild hypercapnia induced an ~8 mmHg increase in ETCO2, but different levels of anesthesia did not modulate physiology significantly. Fig 1b represents the PET TAC from the grey matter. Increases in the level of isoflurane will decrease glucose metabolism. As expected, the slope of the PET TAC during the period of 2% isoflurane decreased when compare to baseline (1% isoflurane) condition (Fig 1b, red dash lines), suggesting a decrease in glucose metabolism. PET standard uptake value (SUV) maps also show a global decrease in FDG uptakes when comparing 2% and 1% isoflurane (Fig 1b, brain color insets). SUV changes are larger in the subcortical areas than cortical regions and cerebellum. Simultaneously obtained BOLD/ASL data (Fig 1c) demonstrated robust signal changes in responses to hypercapnia (~2.5-3% BOLD and ~90% CBF), 1.5% (~<1% BOLD and ~8% CBF), and 2.0% (~0.8-1.2% BOLD and ~20% CBF) isoflurane. It is important to note that change in CBF during hypercapnia did not affect FDG uptake, indicating that our radiotracer infusion protocol is not compromised by flow effects. This is important for future potential functional neuroimaging studies. Group results showed a graded decrease of glucose metabolism when isoflurane concentration was increased (Fig 2). Glucose consumptions decreased about 35% and 70% under 1.5% and 2% isoflurane from baseline (1%), respectively.

Our novel methodology confers multiple advantages. First and most important is the ability to investigate hemodynamic responses and metabolic changes simultaneously and dynamically in one scan. The reinvented use of FDG PET transforms it into a more attractive technique for functional neuroimaging. Our imaging protocol also allows estimation of changes in cerebral metabolic rate of oxygen using calibrated fMRI7. In addition, a similar GLM analysis approach commonly used for fMRI can also be applied for fPET. Since fMRI has been used extensively in neuroscience research, a fundamental understanding of how neurovascular and neurometabolic coupling results in fMRI signal will benefit the neuroimaging community.

Conclusions In this study, we demonstrated the feasibility of performing dynamic fPET and fMRI studies to reveal changes in neurovascular and neurometabolic coupling in response to physiological challenges in one scan. Our novel approaches enable a new tool for neuroscience research. Work is ongoing to validate CMRglu quantification using fPET and to examine neurovascular and neurometabolic coupling in response to physiological and pharmacological challenges.