Abstract

Neuroreceptor Imaging of the Awake Nonhuman Primate

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Measuring dynamic changes in neurotransmitter systems with positron emission tomography (PET) can provide insight on dysfunction in neurotransmission that gives rise to central nervous system disorders. Studies in the nonhuman primate (NHP) are valuable for guiding translational research approaches for human studies. Thus, the scope of this dissertation was to develop methods for neuroreceptor imaging in awake and anesthetized NHP studies.

The first aim was to develop an automated algorithm that optimizes PET-MR NHP registrations. Accurate spatial alignment between PET and MR images is necessary for kinetic analysis of dynamic PET data. With our previous registration method, registering the first 10 min of the PET acquisition to the MR, failures became more frequent as the range in types of tracer experiments increased. Therefore, the Multi-Transform Method (MTM) algorithms were developed to create multiple transformations by registering PET images of different time intervals from a dynamic study, to a single reference (i.e., MR images, MTM-I) or multiple reference images (i.e., MR and PET images pre-registered to the MR, MTM-II). Mutual information was used to compute similarity between the transformed PET images and the reference image(s) to choose the optimal transformation, evaluated via visual rating scores to assess spatial alignment. MTM proved to be robust for a wide variety of tracer studies, performed under different

conditions (e.g., blocking studies) and with scanners having different resolutions.

The second aim was to develop an algorithm for attenuation correction (AC) of awake emission data using transmission datasets acquired under anesthesia, for the same animal. Acquiring transmission scans was not feasible for awake, unrestrained NHPs in the Focus-220 due to the noise and proximity of the transmission point source. The algorithm was tested using pairs of emission data with aligned attenuation images from anesthetized scans performed on different days. MTM was used to register the non-attenuation corrected images to the MR image. Multiplying both transforms brought the transmission image into the space of the other emission dataset for AC. TACs in regions-of-interest (ROIs) were compared between emission images corrected for attenuation with a realigned transmission image and the original aligned transmission image for different tracers. Error analyses were performed for incorrect AC due to misregistrations, data loss, and an attenuating object in the field-of-view. The results suggest that transmission data from alternate scan days be used to synthesize a transmission scan for AC of awake emission data.

The third aim was to develop methods for awake NHP PET imaging. The majority of NHP studies are conducted under anesthesia, shown to affect the interpretability of receptor binding measures. The aims of this study were 1) to develop awake NHP imaging with minimal head restraint, and 2) to test this methodology by comparing $GABA_A$-benzodiazepine [^{11}C]flumazenil binding in anesthetized and awake conditions. For awake imaging, the Focus-220 scanner was fitted to mechanical device that raised and tilted the scanner 45º while the awake NHP was tilted back 35º in a custom chair for optimal brain positioning. To reduce scan time, bolus plus constant

infusion methods were used for tracer delivery. The Vicra infrared camera tracked the NHPs head motion during the awake emission acquisition. Cortisol measurements were acquired during awake and anesthetized scans to assess stress. Equilibrium analysis was used to compute binding potential (BP_{ND}) for anesthetized and awake datasets. We hypothesized that [^{11}C]flumazenil BP_{ND} would be higher in the anesthetized condition. We successfully performed awake NHP imaging with minimal head restraint, where there was close agreement in [^{11}C]flumazenil BP_{ND} values between awake and anesthetized conditions.

The fourth aim was to detect acute fluctuations in glutamate transmission at the metabotropic glutamate receptor 5 (mGluR5) with allosteric antagonist, [^{11}C]ABP688. A recent pilot study in baboons showed a significant global reduction in [^{11}C]ABP688 binding after increasing glutamate levels with *N*-acetylcysteine (NAC), with no change from test to retest. This study was designed to replicate and extend their finding in anesthetized rhesus monkeys with [^{11}C]ABP688 test-retest studies and NAC challenge studies with the same dose and a higher dose. Different modeling methods were evaluated for kinetic analysis to estimate distribution volume and BP_{ND}. We hypothesized a dose-dependent decrease in [^{11}C]ABP688 BP_{ND}. Although we did not strictly replicate the baboon study based on BP_{ND}, components of our study supported their findings. As anesthetic induction with ketamine may have influenced our results, it would be beneficial to investigate this study in awake animals.

These studies provide a framework for awake NHP PET to correlate behavioral imaging paradigms with PET radioligand measurements with the overall goal of guiding translational research approaches for human studies.