eMethods

DESCRIPTION OF OVERLAP WITH OTHER PUBLISHED SAMPLES:

This sample represents a pooling of participants studied in several different projects over a period of a decade. These projects were supported by grants MH40695, MH62185, MH074813, and MH48514 from the US Public Health Service awarded to Dr. Mann, Oquendo, Parsey, and Sullivan. Portions of this sample have been included in the following previous publications:

Miller JM, Hesselgrave N, Ogden RT, et al. Positron emission tomography quantification of serotonin transporter in suicide attempters with major depressive disorder. *Biol Psychiatry*. 2013;74 (4):287-295.

Sullivan G M, Oquendo M A, Milak M, et al. Positron emission tomography quantification of serotonin(1A) receptor binding in suicide attempters with major depressive disorder. *JAMA Psychiatry*. 2015;72(2):169-178.

Miller J M, Hesselgrave N, Ogden R T, et al. Brain serotonin 1A receptor binding as a predictor of treatment outcome in major depressive disorder. *Biol Psychiatry*. 2013;74(10):760-767.

Parsey R V, Ogden R T, Miller J M, et al. Higher serotonin 1A binding in a second major depression cohort: modeling and reference region considerations. *Biol Psychiatry*. 2010;68(2):170-178.

Parsey R V, Oquendo M A, Ogden R T, et al. Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study. *Biol Psychiatry*. 2006;59(2): 106-113.

IMAGING DATA ACQUISITION AND PROCESSING DETAILS:

BRAIN IMAGING ACQUISITION:

MRI Acquisition for Co-Registration:

MRIs were acquired on a GE 3 T Signa Advantage system. A sagittal scout (localizer) was performed to identify the AC-PC plane (1 min). A transaxial T1 weighted sequence with 1.5 mm slice thickness was acquired in a coronal plane orthogonal to the AC-PC plane over the whole brain with the following parameters: 3-dimensional SPGR (Spoiled Gradient Recalled Acquisition in the Steady State); TR 34 msec; TE 5 msec; flip angle of 45 degrees; zero gap; 124 slices; field of view of 22 x 16 cm; with 256 x 192 matrix, reformatted to 256 x 256, yielding a voxel size of 1.5 mm x 0.9 mm x 0.9 mm; time of acquisition of 11 min.

Pet Imaging Data Acquisition:

Radial arterial catheterization was applied for drawing blood samples to construct tracer input curves. A local anesthetic was given to reduce discomfort. Lines were inserted by physicians trained and credentialed by our Department of Anesthesia for this procedure.

Blood samples were drawn according to a detailed protocol through the arterial line to avoid repeated needle sticks and patients with a low hemoglobin were excluded. These samples were processed and results used to generate time activity curves (TACs).

Complications resulting from such catheterizations include bleeding, occlusion or clotting. The rate of complications increases with the duration of catheterization and is very low when the catheter is in place for fewer than 4 days. For example, sixteen investigators followed 106 subjects who had arterial lines placed in the context of a PET study. Abnormalities were reported in 8 of 106 (7.5%) cases. Of these eight cases, three (37.5%) were inpatients diagnosed with anorexia nervosa, a condition that may represent a risk factor. All abnormalities were benign, did not affect motor function, and did not require medical intervention. In this study, arterial catheters were in place less than 8 hours.

The exposure after a single injection of [^{11}C]WAY 100635 and [^{11}C]DASB is 2.637 rad, well below the single dose limit under the FDA 21 361 dose limits for research subjects of 5 rad. Total exposure resulting from the study was well below the FDA 21 361.1 dose limits for yearly cumulative exposure to research subjects (dose limits of 5 rads per year for whole body, active blood forming organs, lens of the eye and gonads; 15 rads per year for other organs). As well, we used tracer doses of radioligands that are without pharmacological effect.

BRAIN IMAGING DATA PROCESSING

PET images and MRI sequences, including anatomical MRI, were acquired and transferred to our lab using a secure ftp connection. These images were stored within a predefined directory structure that is automatically backed up once a week. For PET image analysis, the following broad steps were implemented. We first correct for motion. The motion corrected PET images were then coregistered to the MRI to transfer detailed anatomical labeling of regions of interest (ROIs), performed automatically on the MRI, to the PET images. The activity within each ROI was then calculated as a function of time, resulting in time activity curves (TACs). These steps were performed using a custom-built software pipeline known as the Brain Analysis Toolset (BAT), developed by our group in 2001 and continually expanded. This system allows the user to choose from approximately 20 different image-processing modules (steps), which are written in Matlab code.

In the second stage of the pipeline, quantitative estimates of binding were calculated from the TACs, with or without accompanying blood radioactivity measures. This was performed in the custom-built Matlab-based brain- processing tool known as BrainFit, which has been in use since 2000. BrainFit contains some commonly used algorithms as well as those developed in-house. BrainFit is able to handle all steps from the fitting of the metabolite and plasma radioligand concentration curves, and the modeling of the TACs, to the estimation of the outcomes parameters of interest (e.g. radioligand volume of distribution and binding potential) at

both the ROI and voxel level. BrainFit outputs are written to an SQL database, in which they can be stored, queried, reviewed (through a web interface), and locked to prevent further changes. A python-based system called MindBurst is capable of organizing both data and processing outputs as the images proceed through the image-processing pipeline. Mindburst keeps track of processing stages, the users who started them, the start and completion times, the machine platform, and software versions. MindBurst achieves this goal by wrapping the processing stages as separate Python scripts (called from the Unix command line) and by using the SQL database for keeping record both of data and execution of processing stages.

Each individual datum was independently commented, approved, disapproved, locked (secured) and unlocked by users who have been given prior permission based on data piece type. In the case of data pieces based on actual files, locking ensures that the file permissions are changed to be read-only. Data pieces can be queried from a web interface based on type, metadata (key-value pairs associated with the data) and generating process.

Image Analysis:

We used MEDX software (Sensor Systems, Inc., Sterling, Virginia) for drawing and storing regions of interest as previously described. All PET images were co-registered within a dynamic study to the previous frame using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Linear Image Registration Tool (FLIRT). The dynamic scans were reviewed in a cine or ‘movie’ mode with overlaid grids to verify the accuracy of the motion correction. No correction for transmission - emission mismatch was attempted. PET frames were then co-registered to the MRI using FLIRT. This co-registration step was verified by loading all MRI drawn regions of interest on the co-registered PET image. Partial volume correction was implemented using a three-tissue classification scheme as well as an ROI based approach.

Structural MRI Processing and Analysis:

Raw coronal MRI images were cropped to remove non-brain material utilizing the exbrain v.2 utility. On the rare occasion where exbrain was unable to process a MRI, the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Brain Extraction Tool (BET) v1.2 was used along with manual removal of non-brain matter left after utilizing BET. The FMRIB’s Automated Segmentation Tool (FAST) v3.3 was then used to segment MRI images into three classes, gray matter, white matter, and cerebrospinal fluid. The segmentation routine we employed does not correctly classify tissue types in subcortical regions or the cerebellum and hence is not used in these regions.