Statistical Analysis Plan

1/2 - Dopaminergic Dysfunction in Late-Life Depression (The D3 Study)

IRB #7976

NCT #04493320

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C.11. DATA ANALYSES: We will examine variables for illegitimate values and outliers. The distribution of demographic variables and baseline characteristics will be examined across LLD (N=120) and never-depressed elder (NDE) subjects (N=60) as means, standard deviations, proportions, and 95% confidence intervals. As a precaution, indications of inequality between diagnostic groups (Aim 1) or the L-DOPA and placebo groups (Aim 2) in specific features (despite randomization) will trigger examination of whether differences in primary outcome measures may be attributed to group imbalances on background characteristics. For all analyses, significance tests will be reported after Benjamin-Hochberg adjustment controlling for FDR at level 0.05.

Analyses for Aim 1: By design the LLD and NDE subjects will be age and gender distribution matched. All analyses will control for site (2 sites). **Hyp 1**: The EEfRT analytic procedures will output data on the proportion of high-effort choices made, the relative influence of reward magnitude on making high-effort choices, and neural activations in the PFC and striatal ROIs. Depressed and never-depressed groups will be compared on these measures using linear regression models with group membership (LLD vs. NDE) as the primary predictor. In sensitivity analyses, NDE participants will be categorized as slowed (gait speed <1m/s) or non-slowed, and between-group comparisons will be performed to test LLD subjects vs. NDE-slow and NDE-non-slow groups. **Hyp 2:** Combining data from both LLD and NDE subjects, linear regression will assess associations between dopamine measures (specifically [^{18}F]-FDOPA relative influx rate [K_{occ} in striatal ROI], [^{18}F]-fallypride binding [BP_{ND} in midbrain and striatal ROIs], and mean NM-MRI signal intensity in the SNc) and primary RDoC outcome measures (behavioral/neural activation measures from the EEfRT, the processing speed latent factor, the NIH-EXAMINER Executive Composite score, and ST gait speed). Separate regressions will be fit for each of the RDoC outcome measures, including the different dopamine imaging measures as simultaneous predictors while controlling for demographics, site, and group status. Similar regression analyses will examine associations between the dopamine imaging measures and the first-level MIDT measures (i.e., neural activations on the anticipation and receipt of monetary reward contrasts in *a priori* ROIs), secondary cognitive outcomes, and secondary physical performance outcomes. **Hyp 3:** To further assess the degree to which slowing is a key pathway leading to the LLD phenotype, linear regression will test associations between the processing speed latent factor, NIH-EXAMINER Executive Composite score, ST gait speed, and the probability of choosing the HC/HR option on the EEfRT.

Analyses for Aim 2: Randomization in Aim 2 will be stratified by site, and analyses will adjust for site effects. Analyses will occur on an intention-to-treat basis. **Dropouts and Missing Data/Imputation:** Based on the preliminary studies, we expect that missingness will be minimum. Nonetheless, missing data will be imputed using multiple imputation. We will conduct sensitivity analyses to explore the impact of missing data via pattern mixture models (e.g., by investigating robustness of results to perturbations of assumed values for missing data within implausible clinical ranges). **Hyp 1**: ANCOVA models will test for treatment group differences in the change in each outcome between baseline and Week 3. Outcomes include behavioral data and neural activations from fMRI tasks as above, cognitive measures, and motor function tests. **Hyp 2:** We will use linear regression to estimate and test the effect modification of baseline PET/NM-MRI measurements ([^{18}F]-FDOPA relative influx rate, [^{18}F]-fallypride binding, and NM-MRI CNR in SNc) on L-DOPA's effect on each outcome. Specifically, the change in each outcome measure will be regressed on treatment group, baseline value of the outcome, each baseline PET/NM-MRI

measurement, and the interaction of treatment and each PET/NM-MRI measurement. The modification effect will be tested by the significance of the interaction effect.