Statistical Analysis Plan
Biomarker Strategies for Medication-Enhanced Cognitive Training in Schizophrenia
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The primary statistical considerations for these data are those required to test the primary hypothesis that memantine (MEM) would enhance sensorimotor gating and neurocognition in schizophrenia (SZ) patients. The operational measure of sensorimotor gating was prepulse inhibition of startle (PPI). The primary hypothesis was tested by a 2-way repeated-measure ANOVA of PPI with MEM dose and prepulse interval (10, 20, 30, 60 or 120 ms) as within-subject factors. The key dependent measure was %PPI, calculated according to common practices in the literature. The hypothesis that MEM will increase PPI in SZ patients was to be confirmed by a significant main effect of drug (active > PBO) or significant interaction among the variables of drug, dose (10 or 20 mg), diagnosis (healthy subject (HS) or SZ) or prepulse interval, and informative post-hoc comparisons. The assumptions behind these analyses range from the standard assumptions underlying the use of parametric analyses, to those specific to prepulse inhibition, e.g. related to the potential confounding effects of drug or diagnosis effects on startle magnitude. Data were demonstrated to be normally distributed and drug effects on PPI were shown to be independent of changes in startle magnitude. Analyses confirmed the hypothesis for the 20 mg dose of MEM in SZ patients.

The same general analytic approach was applied towards MEM effects on neurocognition, assessed via the MATRICS Comprehensive Cognitive Battery (MCCB). Here, neurocognitive domain (7 domains) was a within-subject variable along with drug (active vs. PBO), and diagnosis and dose were between-subject factors. The dependent measure was MCCB T-score for each of the 7 domains, as well as a single comprehensive T-score. The hypothesis that MEM will increase MCCB scores in SZ patients was to be confirmed by a significant main effect of drug (active > PBO) or significant interaction among the variables of drug, dose (10 or 20 mg), diagnosis (healthy subject (HS) or SZ) or MCCB domain, and informative post-hoc comparisons. Again, the assumptions behind these analyses range from the standard assumptions underlying the use of parametric analyses, to those specific to neurocognitive performance, e.g. related to the potential confounding effects on levels of consciousness (i.e. increasing or decreasing alertness). Data were demonstrated to be normally distributed and drug effects on MCCB were shown to be independent of changes in self-assessed drowsiness. Analyses failed to confirm the hypothesis that MEM acutely enhanced neurocognition, in either HS or SZ patients.