Supplemental Methods

Sequenom/Agena iplex genotyping: Primer Design and PCR Amplification: Briefly, the protocol involves PCR amplification of DNA using SNP specific primers, followed by a base extension reaction using the iPLEX Gold chemistry (Agena San Diego, CA). SNP- specific PCR and extension primers were designed and organized into pools with the Assay Design Suite (Agena). PCR primers were pooled into 0.5 micro molar stock solutions. The concentration of extension primers within their respective pools depends on their mass and can range from 8 to 15 micromoles. All primers were purchased from Integrated DNA Technologies (Coralville, IA). A QC run was performed with Coriell and CEPH controls, and results were tested for mendelian inconsistencies. HotStar Taq Polymerase (Qiagen) was used for all PCRs. 15 ng of DNA was added to each 5-ul PCR reaction mixture a 384- well microtiter plate. The PCR condition was 94°C for 15 min for hot start, followed by 45 cycles of denaturing at 94°C for 20 sec, annealing at 56°C for 30 sec, extension at 72°C for 1 min for 45 cycles, and final incubation at 72°C for 3 min. The PCR products were then treated with SAP (shrimp alkaline phosphatase, Agena) for 40 min at 37°C then ramped to 85°C for 5 min to remove excess dNTPs, as described (Ding & Cantor 2003).

Base Extension: iPLEX enzyme (Agena) was used for the base extension reactions. Base extension was carried out whereby both alleles interrogated by the base extension primer were extended by adding a mixture of ddNTPs and dNTPs. Two microliters of primer extension mix was added to seven microliters of SAP treated PCR product to yield 9 ul reactions. The reaction condition was 94°C for 30 sec, followed by 40 cycles of 94°C for 5 sec, a five cycle run of 52°C for 5 sec, and 72°C for 5 sec for 200 cycles for multiplex reactions. All reactions were carried out in a C1000 touch (BioRAD, Inc.). The final base extension products were diluted in 18 ul of double distilled water and then treated with 6mg of SpectroCLEAN (Agena) resin per

well to remove contaminating salts. The samples are rotated for 15 minutes and centrifuged for 15 minutes at 3,000 x g.

Mass Spectrometry and Data Analysis: 10-18 nl of treated extension product was spotted to the appropriate location on a 384-pad SpectroCHIP II (Agena) using a Sequenom MassARRAY Nanodispenser (Agena, San Diego, CA). A MassARRAY Analyzer Compact MALDI-TOF MS (Agena) was used for data acquisitions from the SpectroCHIP. The expected molecular weights of all relevant peaks were calculated before the analysis and identified from the mass spectrum. Each spot was ionized 75x per second at five different rasters and all resultant genotyping calls were performed in real time by the MassARRAY Typer Analyzer v4.0.26.73 (Agena). The call cluster plot for each SNP was viewed, and calls were manually adjusted if needed. Data was exported into a Microsoft Excel spreadsheet. Mendelian inconsistency was tested, and inconsistent assays were failed.

Supplemental Figure Legend

S1. Effects of MEM on autonomic and subjective measures in HS and CPD subjects, assess prior to and after MCCB administration. Values represent change from baseline (pre-pill) measures for each subject. The SRS is a visual analog scale (VAS) designed to assess general somatic and psychological symptoms, and level of consciousness (Bond et al., 1974; Bunney et al., 1999; Norris 1971). Participants rated on each 100 mm VAS the levels of several subjective states: "happy," "drowsy," (shown here) "queasy," "dizzy" and "perceptual sensitivity" that included prompts such as "Normal sounds seem unusually intense or loud" (Swerdlow et al., 2002). No statistically significant effects of drug were detected on any measure in either subject group.

S2. Example of alternative strategies to understand MEM effects on neurocognitive domains:

effects of MEM on MCCB domains that incorporate a timing / speed demand (SP, AV, RP) vs.

those without such a demand (WM, VL, VisL, SC) significant main effect of drug. MCCB

domains were separated into those that do vs. do not include a demand for speeded response

(reaction time). Among SZ patients, 10 mg MEM had no significant effect on either grouping of

domains (F's<1), while 20 mg MEM significantly reduced performance in speed-dependent

(p<0.006) but not non-speed-dependent domains (F<1).

Table S1. Inclusion Criteria

For both CPD subjects and HS:
1. English speaking
2. 18-50 years of age
3. Able to provide written informed consent
4. No hearing deficits, color blindness, mental retardation or medical exclusion criteria (see text)
5. UTox negative for recreational drugs
6. Not pregnant; double barrier contraception

For HS:
1. No current or past DSM IV TR Axis I diagnosis on SCID-NP

For CPD subjects:
1. Axis I diagnosis of SZ or schizoaffective disorder, depressed type on M.I.N.I. plus 6
2. No psychiatric hospitalization in the past 2 months
3. No history of substance dependence/abuse OR in full remission for more than 6 months at the time of screening

UTox: urine toxicology screen

Table S2. Subjects excluded from final analyses (n=7)

CPD Subjects (n=4)
1. Past history of surgical excision of brain tumor discovered upon study completion
2. History of Hepatitis C discovered upon study completion
3. Quit smoking during study participation
4. Nausea and vomiting on test day 2

HS (n=3)
1. Diagnosed with SZ after study completion
2. History of dominant hand Injury restricted task performance
3. UTox was positive for cocaine on follow-up visit.

Table S3. Subject Characteristics (n=82)

MEM dose / Characteristics	10 mg		20 mg	
Diagnoses (n)	CPD (20)	SZ (19)	CPD (21)	SZ (20)
		SAD (1)		SAD (1)
	HS (19)		HS (22)	
Age in years [mean(SD)]	CPD – 35.4(8)		CPD – 37.38(7.2)	
	HS – 29(9)		HS – 26.2(5.5)	
Sex (M:F)	CPD -13:7		CPD – 16:5	
	HS – 16:3		HS – 15:7	
Smoker : non-smoker	CPD – 11:9		CPD – 9:12	
	HS – 0:19		HS – 3:19	
Ethnicity (% White)	CPD – 45%		CPD – 28.57%	
	HS – 52.63%		HS – 27.27%	
Daily Caffeine intake in mg [mean (SD)]	CPD – 235.95 (282.17)		CPD – 308.03 (393.91)	
	HS – 135.90 (219.86)		HS – 106.63 (143.21)	
In CPD Subjects Only				
Duration of illness in years [mean(SD)]	15.06 (8.6)		20.95 (8.98)	
Age of onset [mean (SD)]	20.63 (5.0)		17 (8.4)	
Anticholinergic activity pmol/ml [mean (SD)]	9.85 (16.01)		18.64 (56.22)	
Global assessment of functioning [mean (SD)]	59.6 (7.53)		56 (4.95)	
AP medications (n)	FGA[1] (1)/FGA +SGA[2] (4)		FGA[4] (1)/FGA +SGA[5] (6)	
	SGA[3] (11)		SGA[6] (13)	
	Clozapine (1)		Clozapine (0)	

SAD: Schizoaffective Disorder, Depressed; FGA: 1st generation AP; SGA: 2nd generation AP.
1: haloperidol (HAL; n=1)
2: HAL (n=2), fluphenazine (FLU; n=1), FLU decanoate (-D) (n=1), aripiprazole (ARI; n=3), risperidone (RIS; n=2), quetiapine (QTP; n=1)
3: Olanzapine (OLN; n=2), ziprasidone (n=1), QTP (n=2), paliperidone (PPN; n=1), RIS (n=5)
4: HAL and HAL-D(n=1)
5: HAL (n=2), HAL-D (n=2), FLU (n=1), chlorpromazine (n=1), RIS (n= 2), QTP (n=4), PPN (n=1)
6: OLN (n=2), OLN long acting (LA) (n=1), QTP (n=2), RIS (n=2), RIS LA (n=1), ARI (n= 1), ARI LA (n=1), lurasidone (n=3), PPN (n=1), ziprasidone (n=1)

Table S4. Timing of Test Day Procedures

Time (hours)	Procedure
0830	Check-in; UTox; check for medication/lifestyle changes; VS; SRS; Standardized breakfast
0900	Study pill administration (PBO vs MEM (10 mg or 20 mg)
0930	VS; SRS
1030	VS; SRS
1130	VS; SRS
1140	Lunch
1220	VS; SRS
1230	Startle testing
1250	VS; SRS
1300	MCCB testing
1435	VS; SRS
1445	ERP testing
1535	VS; SRS
1605	VS; SRS; Check-out

VS: Vital signs; SRS: Symptom rating scales; ERP: Event-related potential

Table S5A. Moderators (R) of OCME MCCB performance in CPD subjects.

Moderators / OCME variables	DOI (y)		Age of Onset (y)		GAF		PANSS total score	
	10 mg	20 mg	10 mg	20 mg	10 mg	20 mg	10 mg	20 mg
SP	0.30	0.23	0.52*	0.01	0.06	0.07	0.20	0.22
AV	0.55*	0.16	0.02	0.18	0.01	0.14	0.09	0.05
WM	0.09	0.01	0.27	0.03	0.22	0.02	0.35	0.09
VL	0.14	0.20	0.18	0.14	0.03	0.39	0.37	0.22
VsL	0.19	0.30	0.15	0.45*	0.00	0.25	0.42	0.05
RP	0.23	0.22	0.37	0.18	0.22	0.35	0.11	0.33
SC	0.42	0.23	0.08	0.00	0.25	0.14	0.28	0.00
Composite	0.16	0.00	0.34	0.15	0.00	0.25	0.30	0.18

* $p < 0.05$

DOI: Duration of illness; GAF: Global Assessment of Functioning Scale score; PANSS: Positive and Negative Symptom Scale score

Table S5B: Effect of age and post-PBO MCCB performance on OCME MCCB performance in all subjects grouped by dose

Moderators / OCME variables	Age (y)		PBO MCCB Composite T Score	
	10 mg	20 mg	10 mg	20 mg
SP	0.20	0.18	0.02	0.18
AV	0.38	0.26	0.15	0.30
WM	0.09	0.16	0.00	0.19
VL	0.16	0.34*	0.03	0.25
VsL	0.27	0.21	0.03	0.28
RP	0.03	0.09	0.05	0.10
SC	0.05	0.29	0.17	0.14
Composite	0.04	0.48**	0.21	0.36*

* $p < 0.025$

** $p < 0.001$

Table S6. PCR primer sequences for 4 SNPs

SNP ID	PCR Primer	PCR Primer	Extension Sequencing Primer
rs40184	ACGTTGGATGAACACACCCTTGACAGGTGC	ACGTTGGATGATCTGATCAATACGCCCCAG	ATGCCTCACTCAAACT
rs1394785	ACGTTGGATGCTGGGCCAGCAAAACATTTA	ACGTTGGATGATTTGTGGCTTTTCTTGGG	CCAGCAAAACATTTAACAGAT
rs1583337	ACGTTGGATGCACAGGCTCACAGGAAAATC	ACGTTGGATGCTTAGGTTAGGTGTTGGGTC	GGCTCACAGGAAAATCTAGTAT
rs1337697	ACGTTGGATGTAGCTCTTTCTAGCTGTACC	ACGTTGGATGGCTGAGTAATGGAAGATGGC	CTAGCTGTACCTTAAAGGAACTGTA

Table S7: Practice effects (Main effect: Day 2 vs Day 1) for Cognitive Domain T-Scores for each group

Dose / Diagnosis	10 mg	20 mg
HS	F=105.65, df (1,18), p<0.0001	F=8.57, df (1,20), p<0.01
CPD	F=17.33, df (1,19), p=0.0006	F=8.60, df (1,19), p<0.01

HS: Healthy subjects; CPD: Chronic psychotic disorder subjects

Figure S1

Figure S2.