Supplemental Data

Inclusion and Exclusion Criteria

Study criteria for subjects with schizophrenia were 1) diagnosis of schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual (DSM-IV); 2) no other DSM-IV axis I diagnosis; 3) no lifetime history of alcohol or substance abuse or dependence (nicotine dependence was allowed); 4) absence of any psychotropic medication for at least 21 days (six weeks for fluoxetine) before the study; 5) no concomitant or past severe medical conditions; 6) not pregnant; 7) no current suicidal or homicidal ideation. Study criteria for healthy comparison subjects included no past or present neurological or psychiatric illnesses including substance abuse. For both subjects and controls the absence of pregnancy, medical and neurological disorders was assessed by history, review of systems, physical and neurological examination, routine blood tests (including pregnancy test), urine toxicology and ECG.

Electroencephalogram induced gamma-band oscillations

Our previous results indicated that healthy individuals with greater capacity to increase extracellular GABA levels post-tiagabine (a “GABA reserve”) exhibit enhanced frontal gamma-band oscillatory activity in the context of a cognitive control task (1, 2). Consequently, a total of 34 subjects (19 healthy comparison subjects, 6 antipsychotic-naive schizophrenia patients and 9 antipsychotic-exposed schizophrenia patients) underwent EEG measurement of frontal lobe gamma-band oscillations during a cognitive task (3). In all subjects, the electrophysiology study was performed approximately one week prior to the PET scans. Subjects underwent the Preparing to Overcome Prepotency (POP) task, a cued stimulus-response reversal paradigm that requires increases in cognitive control to overcome prepotent response tendencies (3), while EEG data were acquired as described (1, 2), providing a summary measure of frontal gamma activity for each subject.

REFERENCES

1. Frankle WG, Cho RY, Mason NS, Chen CM, Himes M, Walker C, et al. [11C]flumazenil binding is increased in a dose-dependent manner with tiagabine-induced elevations in GABA levels. PLoS One. 2012;7(2):e32443.
2. Frankle WG, Cho RY, Narendran R, Mason NS, Vora S, Litschge M, et al. Tiagabine increases [11C]flumazenil binding in cortical brain regions in healthy control subjects. Neuropsychopharmacology. 2009;34(3):624-33.
3. Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. PNAS. 2006;103(52):19878-83.

FIGURE S1. Scatterplot of dorsolateral prefrontal cortex [^{11}C]flumazenil ΔV_T with plasma tiagabine levels in the healthy comparison group (CTR) (r=–0.41,p=0.27; black markers and line), the schizophrenia group as a whole (SCH) (r=0.37, p=0.33; green line), the antipsychotic-naive schizophrenia group (DN) (r=0.09, p=0.81; blue markers and line), and antipsychotic-exposed schizophrenia group (DF) (r=0.16, p=0.68; red markers and line).

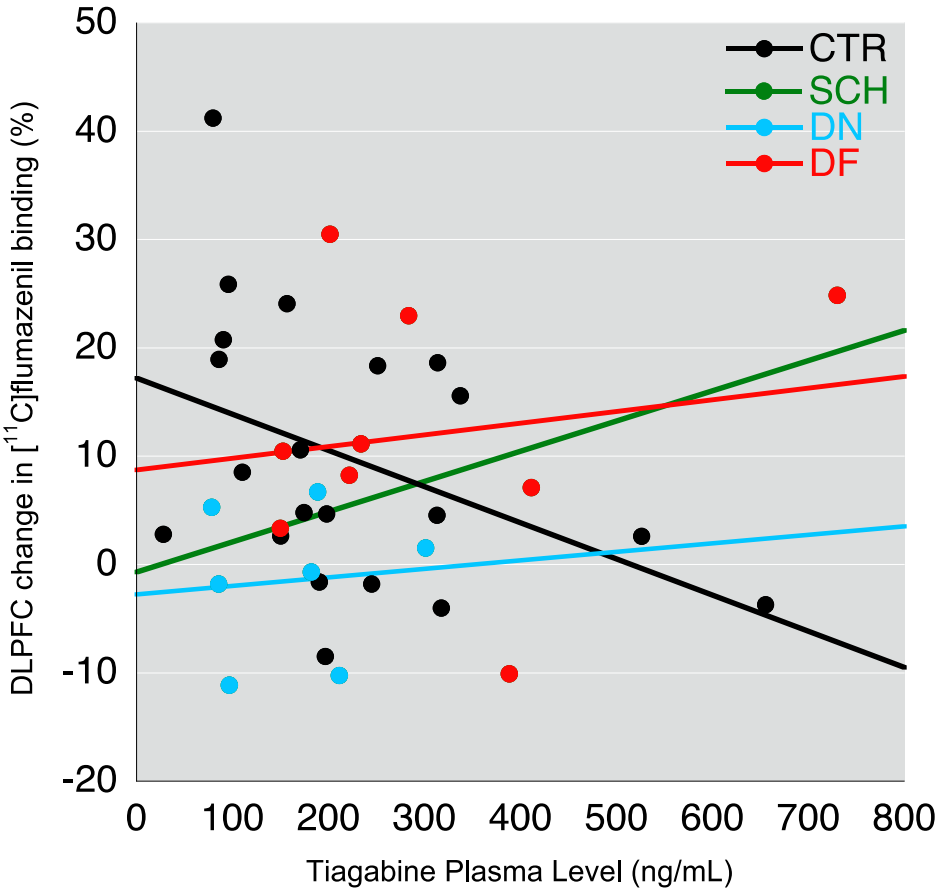

FIGURE S2. Scatterplot of [^{11}C]flumazenil ΔV_T in the amygdala with PANSS positive score in the antipsychotic-naive schizophrenia group (DN SCH) (r=0.88, p=0.002; blue) and antipsychotic-exposed schizophrenia group (DF SCH) (r=–0.07, p=0.86; red).

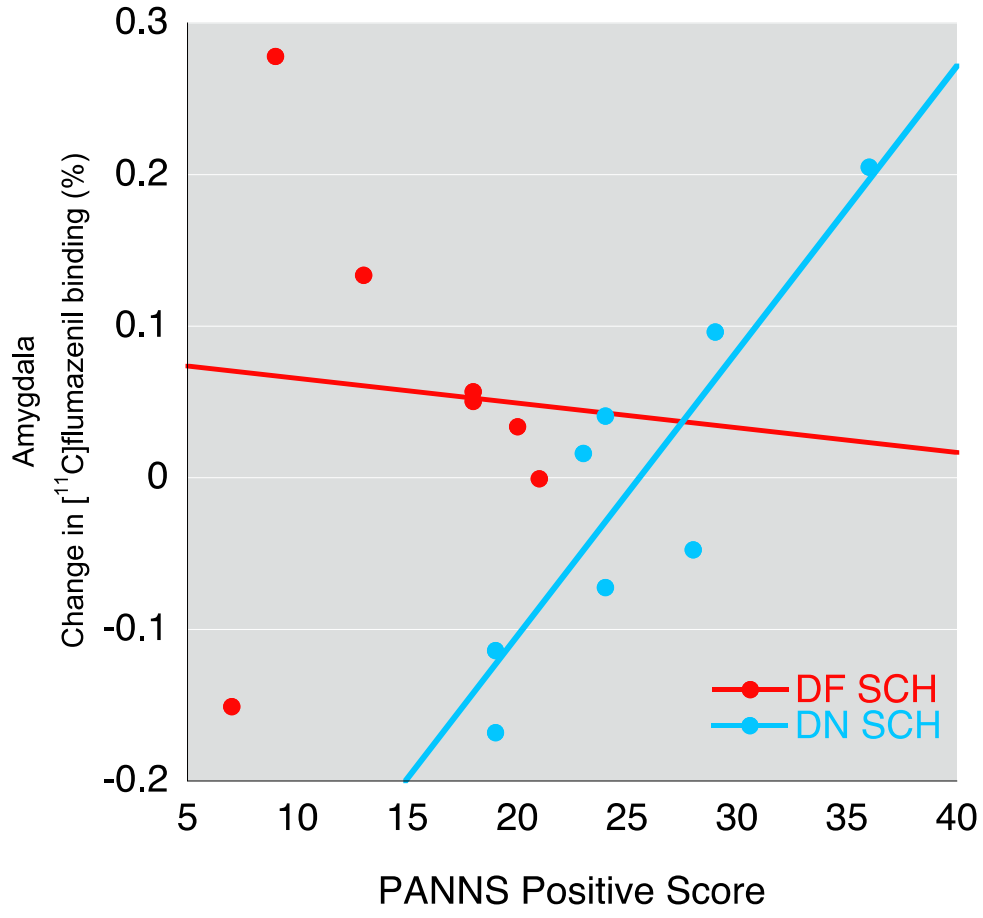

FIGURE S3. The ability to increase GABA levels in the association cortex, measured as the change in [^{11}C]flumazenil binding in response to GAT1 blockade, predicts (r=0.69, p=0.04) the ability to entrain cortical networks, measured via EEG gamma oscillations, in healthy ccomparison subjects (Panel A) but not in subjects with schizophrenia (Panels B and C, antipsychotic-exposed schizophrenia patients and antipsychotic-naive schizophrenia patients, respectively).

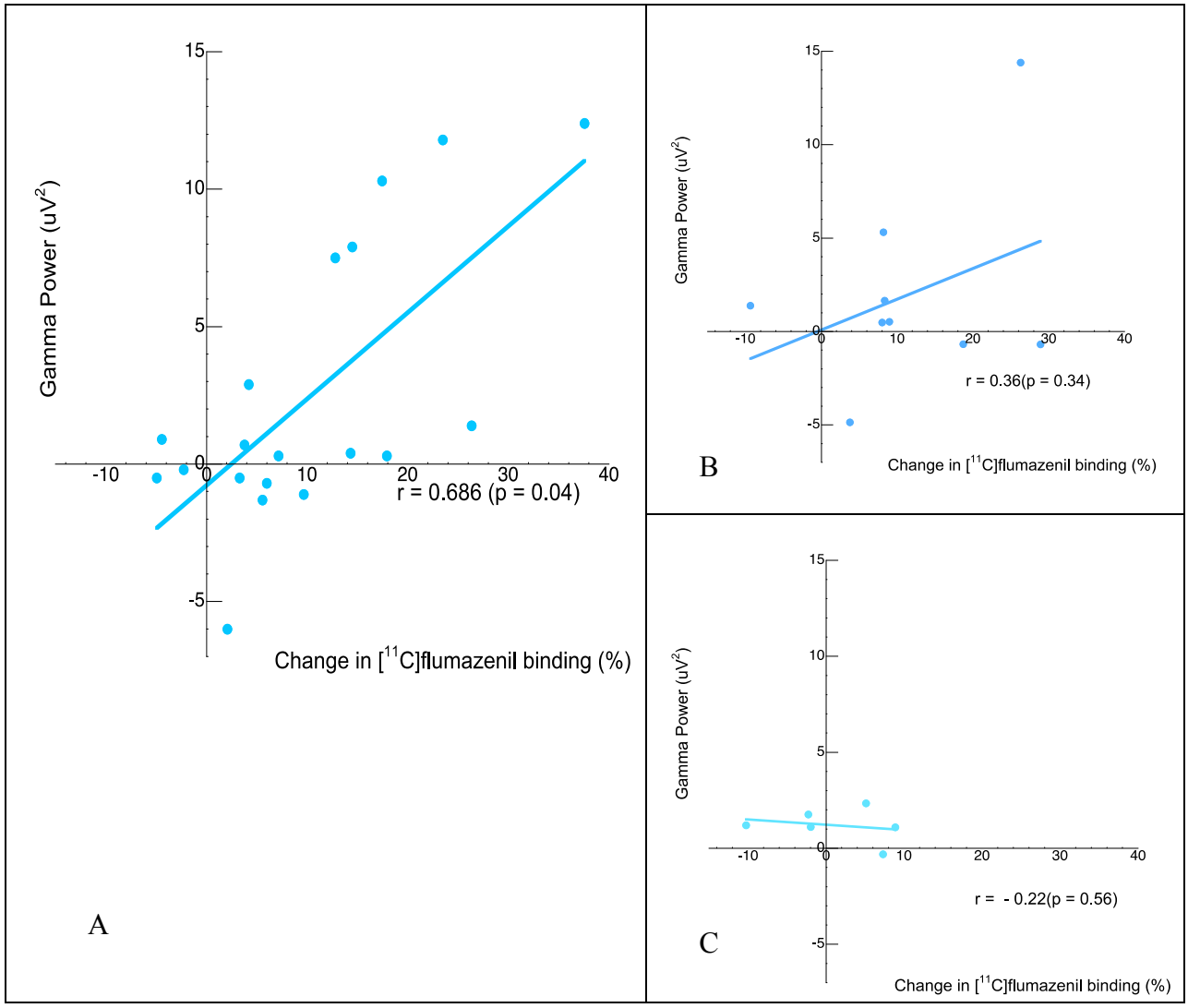

FIGURE S4. Scatterplot of medial temporal lobe [^{11}C]flumazenil baseline binding with gamma power in the healthy comparison group (CTR) (r=–0.42, p=0.26; black markers and line), the schizophrenia group as a whole (SCH) (r=–0.25, p=0.51; green line), the antipsychotic-naive schizophrenia group (DN) (r=0.95, p=0.0001; blue markers and line), and the antipsychotic-exposed schizophrenia group (DF) (r=–0.31, p=0.41; red markers and line).