# Gamma-Aminobutyric Acid Concentration is Reduced in Visual Cortex in Schizophrenia and Correlates with Orientation-Specific Surround Suppression

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## Abstract

The neural mechanisms underlying cognitive deficits in schizophrenia remain largely unknown. The gamma-aminobutyric acid (GABA) hypothesis proposes that reduced neuronal GABA concentration and neurotransmission results in cognitive impairments in schizophrenia. However, few *in vivo* studies have directly examined this hypothesis. We employed magnetic resonance spectroscopy (MRS) at high field to measure visual cortical GABA levels in 13 subjects with schizophrenia and 13 demographically matched healthy control subjects. We found that the schizophrenia group had an approximately 10% reduction in GABA concentration. We further tested the GABA hypothesis by examining the relationship between visual cortical GABA levels and orientation-specific surround suppression (OSSS), a behavioral measure of visual inhibition thought to be dependent on GABAergic synaptic transmission. Previous work has shown that subjects with schizophrenia exhibit reduced OSSS of contrast discrimination (Yoon et al., 2009). For subjects with both MRS and OSSS data (n=16), we found a highly significant positive correlation (r=0.76) between these variables. GABA concentration was not correlated with overall contrast discrimination performance for stimuli without a surround (r=-0.10). These results suggest that a neocortical GABA deficit in subjects with schizophrenia leads to impaired cortical inhibition and that GABAergic synaptic transmission in visual cortex plays a critical role in OSSS.

## Keywords

surround suppression; inhibition; schizophrenia; GABA; visual processing; cognitive deficits

## Introduction

Gamma-aminobutyric acid (GABA) has been the focus of significant interest in the search for neural mechanisms of cognitive deficits in schizophrenia. Converging evidence points to deficient GABA synthesis resulting from reduced transcription of the 67 kDa isoform of glutamic acid decarboxylase (GAD67) within parvalbumin-staining cortical neurons (PV) (Akbarian et al., 1995; Volk et al., 2000; Hashimoto et al., 2003; Hashimoto et al., 2008b). Animal studies showing decreased GABA in PV+ interneurons following deletion of the GAD67 gene (Asada et al., 1997; Chattopadhyaya et al., 2007) suggest that GABA

concentrations may be reduced in schizophrenia. However, there is a paucity of *in vivo* studies that have examined this prediction. One recent report described decreased GABA in the basal ganglia in schizophrenia but no difference in the parieto-occipital or frontal lobes (Goto et al., 2009). Furthermore, the GABA hypothesis predicts that abnormalities in GABAergic neurons should result in impairments in dependent cognitive processes in schizophrenia (Cho et al., 2006).

In the first part of our study, we measured *in vivo* GABA concentrations in the visual cortex of subjects with schizophrenia and healthy control subjects using high field magnetic resonance spectroscopy (MRS). Recent histological evidence suggests that GABA deficits in schizophrenia are pan-cortical and not restricted to a particular region (Hashimoto et al., 2008a). Specifically, reduced GAD67 mRNA has been reported in a number of neocortical regions, including visual cortex. Consequently, we hypothesized that GABA concentration in schizophrenia would be reduced in visual cortex.

Measurement of GABA concentrations allowed us to assess the functional significance of a GABA deficit for behavior. We examined the relationship between GABA concentrations and performance on orientation-specific surround suppression (OSSS), a process thought to rely on GABAergic neurotransmission in the visual cortex. Surround suppression is most pronounced for center and surround stimuli sharing the same stimulus orientation (Blakemore and Tobin, 1972; Xing and Heeger, 2001). Animal and human studies (Blakemore and Tobin, 1972; Cavanaugh et al., 2002a; Haynes et al., 2003; Zenger-Landolt and Heeger, 2003) have demonstrated neural correlates of surround suppression in primary visual cortex, an area known to contain many orientation-selective neurons. Current models of OSSS postulate a critical role for GABAergic inhibitory neurons in early visual cortex (Angelucci and Bressloff, 2006; Schwabe et al., 2006). However, there is currently little direct evidence supporting this role for GABA. We have previously reported that subjects with schizophrenia exhibit diminished OSSS compared to healthy control subjects (Yoon et al., 2009). In the present study, we correlated GABA levels obtained in the first part of the study with subjects' performance on the OSSS task. We hypothesized that there would be a positive correlation between visual cortical GABA levels and magnitude of OSSS.

## Materials and Methods

### Subjects

We studied 13 subjects with schizophrenia and 13 healthy control subjects matched on basic demographic factors (Table 1). All patients were clinically stable and recruited as outpatients. They consisted of a mixture of chronic and recent onset schizophrenia. Diagnosis was made by master or doctoral-level clinicians using SCID-I and confirmed by consensus conference. Exclusion criteria were: IQ<70, drug or alcohol dependence or abuse within three months of testing, a positive urine drug screen on day of testing, medical or neurological illness affecting brain function, or history of significant head trauma. Exclusion criteria for controls were lifetime diagnosis of Axis I disorder or first-degree relative with a psychotic disorder. Subscores from the Brief Psychiatric Rating Scale, Scale for the Assessment of Negative Symptoms, and Scale for the Assessment of Positive Symptoms were used to derive indices for the following three major domains of symptoms: reality distortion, disorganization, and negative symptoms (Barch et al., 2003). At time of testing, five patients had not been taking anti-psychotics for at least one month. Four of these subjects had minimal prior exposure to any anti-psychotic (less than two weeks of treatment). Among the medicated patients, one subject was on a typical anti-psychotic and seven were on atypical anti-psychotics. No control subject was taking any psychotropic medication. This study was approved by the IRB at UC Davis, and all subjects provided written informed consent for all procedures.

## Spectroscopy methods

GABA was measured with proton MRS using a Siemens Trio 3 Tesla MRI system. Paired surface coils (Nova Medical, Wilmington, MA) were positioned under the occiput. A 35×30×25mm voxel was centered on the calcarine sulci bilaterally, with its posterior border 7 mm anterior to the dura. A single volume MEGA-PRESS J-difference spectral editing sequence measured total GABA (Mescher et al., 1998). Alternating subspectra were obtained with and without a frequency-selective inversion pulse applied to the GABA C3 resonance. The subspectra were subtracted to generate a difference spectrum containing an upright total GABA signal at about 3.0ppm. The following scanning parameters were used: TR=1500 msec; TE=68 msec; edit frequency 1.9ppm; delta frequency=-1.7; edit pulse bandwidth 45 Hz; NEX 256; scan duration 6.5 minutes. Four consecutive scans were acquired for each subject from the same volume location.

Using jMRUI software (Stefan et al., 2009), all spectra were phase-aligned with reference to water, zero-filled from 1024 to 4096, apodized with a 4Hz Gaussian filter, and frequency aligned to creatine at 3.02ppm. Peak integration was used to quantify total GABA ($2.99 \pm 0.12$ppm) and Glx (glutamine + glutamate) ($3.76 \pm 0.11$ppm) in the difference spectra and creatine ($3.02 \pm 0.09$ppm) in the summed spectra. The ratio of total GABA/total creatine signal was used for hypothesis testing. Normalizing to creatine reduces intersubject variance due to differences in global signal strength and CSF fraction within the voxel and has been shown to yield reliable GABA concentration estimates (Bogner et al., 2009). Significant subject motion during acquisition causes residual creatine signal to obscure the GABA signal in the difference spectra. One of us (RJM) examined each scan for such artifacts while blinded to group membership. Out of a total of 52 scans for each group, 13 patient and 8 control scans were excluded.

## Visual psychophysics

For the present study, we used psychophysical results from 16 subjects (7 controls and 9 patients) who also participated in the MRS experiment. Data from 13 subjects are from a previously reported study (Yoon et al., 2009). The task was a contrast discrimination task (Figure 1) in which one segment within the annulus contained lower contrast than the other segments under three conditions: no surround (NS), vertically-oriented surround (parallel surround, PS), and horizontally-oriented surround (orthogonal surround, OS). The stimulus was a circular patch consisting of a contrast-reversing (4Hz), gray-scale sinusoidal grating with a spatial frequency of 1.1 cycles/degree. The stimulus was divided into annulus and surround regions (when present) by concentric black lines. The inner and outer radii of the annulus were 2.9 and 5.6 degrees respectively. The surround region contained the remainder of the stimulus: the central portion, extending from the central fixation point to the inner border of the annulus, and the outer portion, extending from the outer border of the annulus to an eccentricity of 9.2 degrees. In half the trials, a segment with lower contrast was present, and the location of this target within the annulus varied randomly. In the remaining trials, no target was present, i.e. all segments displayed the same contrast. Task difficulty was adjusted using an adaptive staircase. The ratio of contrast discrimination thresholds of the PS and OS conditions (PS/OS) provides the most direct measure of OSSS, because the these stimuli are identical except for the orientation of the surround relative to the annulus. Additionally, the PS/OS ratio is the measure most commonly used in the single-unit electrophysiology literature to characterize correlates of OSSS. For these reasons, the PS/OS ratio was used to correlate OSSS with GABA concentrations. All statistical comparisons were conducted using two-tailed tests of significance.

## Results

### MRS GABA Measurements

Clearly resolved MRS peaks for both total GABA and Glx (combined glutamate and glutamine) were observed in all participants. Group-averaged spectra for GABA and Glx and their means, normalized by the creatine (Cr) peak integration value for each subject, are displayed in Figure 2A. A significant difference between patients and controls in GABA/Cr variance was not present (Levene's Test for equality of variance, p=0.66). Patients displayed significantly smaller GABA/Cr ratios compared to healthy control subjects, C=0.105, SZ=0.094, p<0.05. Glx/Cr peaks were equivalent across groups, C=0.102, SZ=0.103, p=0.88 (Figure 2B). To examine the possible confound of anti-psychotic medications, we conducted two analyses. First, the correlation between daily chlorpromazine equivalents (CPZ) and GABA/Cr was r=0.003. Second, we performed an ANCOVA of GABA/Cr with CPZ as a covariate, with all subjects, including controls, not taking neuroleptics being assigned a value of zero CPZ. This analysis revealed non-significant covariance with medication dosage, $F_{1,23}<0.001$, p=0.988, and a trend towards main effect of group, $F_{1,23}=3.48$, p=0.075.

### Correlation of visual cortical GABA levels and OSSS

For the 16 subjects with both MRS and surround suppression data, we correlated visual cortical GABA/Cr values with behavioral measures of surround suppression. Previous work has shown that surround suppression is selective for stimulus orientation, with greater suppression in the PS relative to the OS condition (Yoon et al., 2009). The reduction in surround suppression in schizophrenia is also orientation-specific: it is present for the PS but not the OS condition (Yoon et al., 2009), indicating a deficit in neural circuits that are selective for stimulus orientation. In the present study, there was also a significant group difference in OSSS, as indexed by the ratio of PS and OS thresholds (PS/OS), p=0.003. We related GABA/Cr levels to PS/OS because this index is the most direct measure of the component of surround suppression that is orientation-specific (Figure 3A). This correlation was highly significant, r=0.76, p=0.001. In contrast, the correlation of GABA concentration and NS performance was not significant, r=-0.10, p=0.70, indicating that the correlation with OSSS was not due to contrast discrimination performance.

To test whether the significant correlations were driven by outliers, we performed a jack-knife analysis. The data were resampled *n* times (*n*=number of subjects) and in each resampling one subject was excluded and the correlation was then computed. The range of GABA-PS/OS correlations was 0.58-0.83, for all samples p<0.05. In contrast, the range of GABA-NS threshold correlations was -0.32-0.04, for all samples p>0.1.

To evaluate the possibility that the GABA-PS/OS correlation was the result of group differences in these variables, we conducted the following analyses. ANCOVA of the PS/OS ratio with GABA/Cr as a covariate and group as a factor assessed the effect of GABA concentration on surround suppression while taking into account group differences in GABA levels. The effect of the GABA covariate was significant, $F_{1,13}=8.50$, p=0.01, and there was a trend towards a main effect of group, $F_{1,13}=4.28$, p=0.059. The power of the GABA covariate was 0.77. We accounted for group differences in both GABA and PS/OS ratio by subtracting the group means from the subject's values, and then testing the association between the normalized data. This correlation was significant, r=0.62, p<0.05. Using r=0.62 as the estimate of the effect size, power=0.77. And finally, we conducted GABA-PS/OS correlations separately for each group: controls r=0.71, p=0.077; schizophrenia r=0.32, p=0.40. A power analysis showed that in control subjects, we would need N=12 to have power=0.80 at a significance level of p=0.05.

There were no significant correlations between GABA concentration and any clinical measure.

## Discussion

This is one of the first published studies examining *in vivo* brain GABA levels in schizophrenia. We found significantly reduced visual cortical GABA in the schizophrenia group. We also found a significant positive correlation between GABA levels and magnitude of OSSS. Taken together, these findings support the GABA deficit hypothesis of cognitive impairments in schizophrenia—that reduced neocortical GABA neurotransmission in schizophrenia leads to impairments in cognitive processes involving inhibition. These results also suggest that relatively simple behavioral tasks such as surround suppression may serve as behavioral assays of inhibitory dysfunction in schizophrenia.

Although our conclusions are derived from measurements of GABA in visual cortex and a task thought to involve visual cortical GABAergic transmission, it is likely that analogous abnormalities generalize to other cortical areas. Histological studies have documented similar deficits in GABAergic markers in a number of cortical regions in schizophrenia (Hashimoto et al., 2008a). In addition, there is substantial evidence that the morphological subtypes of cortical neurons and their basic laminar and tangential connectivity are conserved across cortical areas (Douglas and Martin, 2004).

Our group and others have previously demonstrated impaired visual inhibition in schizophrenia, (Must et al., 2004; Dakin et al., 2005; Tadin et al., 2006; Yoon et al., 2009). While these prior studies are consistent with the GABA deficit hypothesis, they did not measure GABA concentrations. The present study, by both demonstrating a deficit in GABA concentrations in schizophrenia and a strong association between GABA levels and a behavioral measure of visual inhibition, provides a direct link between GABA dysfunction and cognitive deficits in schizophrenia.

Our finding of reduced GABA is consistent with the animal and post-mortem literature. The GAD67 synthesizes the overwhelming majority of neural GABA (Asada et al., 1997; Chattopadhyaya et al., 2007). In schizophrenia, post-mortem studies have documented an approximately 50% reduction in the number of PV+ neurons with detectable levels of GAD67 mRNA in the DLPFC, where PV+ neurons constitute approximately 25% of all GABAergic neurons (Hashimoto et al., 2003). These results suggest that GAD67 deficits in schizophrenia should translate into measurable reductions in GABA concentration.

A number of studies have addressed issues of sensitivity and validity of MRS measurements of brain GABA. A recent study demonstrated high test-retest reliability of the MEGA-PRESS method, particularly when employing the creatine normalization procedure (Bogner et al., 2009). Other studies have demonstrated that the MEGA-PRESS method has sufficient sensitivity to detect changes in GABA levels resulting from interventions known to alter GABA concentrations (Verhoeff et al., 1999; Floyer-Lea et al., 2006).

We did not find a group difference in Glx values. Prior studies measuring glutamate or Glx in prefrontal regions have yielded inconsistent results (Theberge et al., 2002; van Elst et al., 2005; Ohrmann et al., 2007; Lutkenhoff et al., 2008; Galinska et al., 2009). We are not aware of any MRS studies of glutamate or Glx in visual cortex in schizophrenia. Our Glx results control for generalized measurement error because the potential sources of bias towards finding group differences for Glx are nearly identical to those for GABA, e.g. sensitivity to head movement and differences in the proportions of gray matter within the volume. Equivalent Glx measurements suggest that the group differences in GABA are specific.

Dopamine blocking agents have been shown to lower extracellular levels of GABA (Bourdelais and Deutch, 1994). While the specific mechanisms are likely complex, with D2 and D1 receptor activation promoting decreased and increased GABA release, respectively (Seamans et al., 2001), anti-psychotics could be contributing to the lower GABA MRS measurements in subjects with schizophrenia. Several lines of evidence, however, suggest that this may not be the case. Monkey and humans studies have shown similar patterns of GAD67 deficits in subjects with and without exposure to anti-psychotics (Volk et al., 2000; Hashimoto et al., 2008b). In our sample, the trend towards the persistence of the group difference in GABA concentration after covarying for medication dosage and the low correlation between anti-psychotic dosage and GABA concentration argue against a significant effect. Nonetheless, future studies testing a larger sample of medication naïve subjects is required to fully address this medication confound.

The fact that surround suppression exhibits selectivity for stimulus orientation for both behavior (Xing and Heeger, 2001; Yoon et al., 2009) and V1 neuron responses (Blakemore and Tobin, 1972; Cavanaugh et al., 2002b) suggests an early visual cortical locus. In addition, fMRI studies (Zenger-Landolt and Heeger, 2003) have demonstrated correlates of surround suppression in primary visual cortex. However, the spatial (Angelucci et al., 2002; Cavanaugh et al., 2002b) and temporal (Bair et al., 2003) properties of surround suppression suggest a critical role for feedback projections from extrastriate cortex (Angelucci and Bressloff, 2006). Because these feedback projections are excitatory, current models propose that they modulate surround suppression via inhibitory GABAergic interneurons (Cavanaugh et al., 2002b; Schwabe et al., 2006; Smith, 2006). These models receive support from intracellular recordings of V1 neurons, in which presentation of a surround stimulus elicited a transient increase in inhibitory conductance followed by a sustained reduction in both excitatory and inhibitory conductance, all of which were orientation-selective (Ozeki et al., 2009).

A previous study assessed the effects of local iontophoresis of the GABAA receptor antagonist bicuculline on surround suppression (Ozeki et al., 2004). Bicuculline reduced the magnitude of surround suppression of individual V1 neuronal responses approximately 12%. However, it is difficult to interpret the effects of local changes in inhibition, as surround suppression likely involves circuits outside the region of drug administration. In contrast, we measured global GABA concentrations in visual cortex and demonstrated its strong correlation with the magnitude of OSSS.

An important issue not addressed by this study is the primacy of GABA deficits in schizophrenia, particularly in reference to glutamatergic dysfunction. Some have proposed that GABA abnormalities are downstream effects of impaired NMDA receptor-mediated neurotransmission which results in reduced glutamatergic drive on activity-dependent GABA synthesis. (Lewis and Gonzalez-Burgos, 2006).

In summary, we found reduced GABA concentrations in the visual cortex of subjects with schizophrenia. GABA concentrations were highly correlated with a behavioral measure of visual inhibition, such that higher GABA concentration predicted greater OSSS. These findings provide the first *in vivo* evidence of a deficit in cortical GABA in schizophrenia and support the GABA deficit hypothesis of cognitive deficits in this disorder. Further study of the GABA system is likely to provide important insights into the neural mechanisms of these cognitive deficits.

## Acknowledgments

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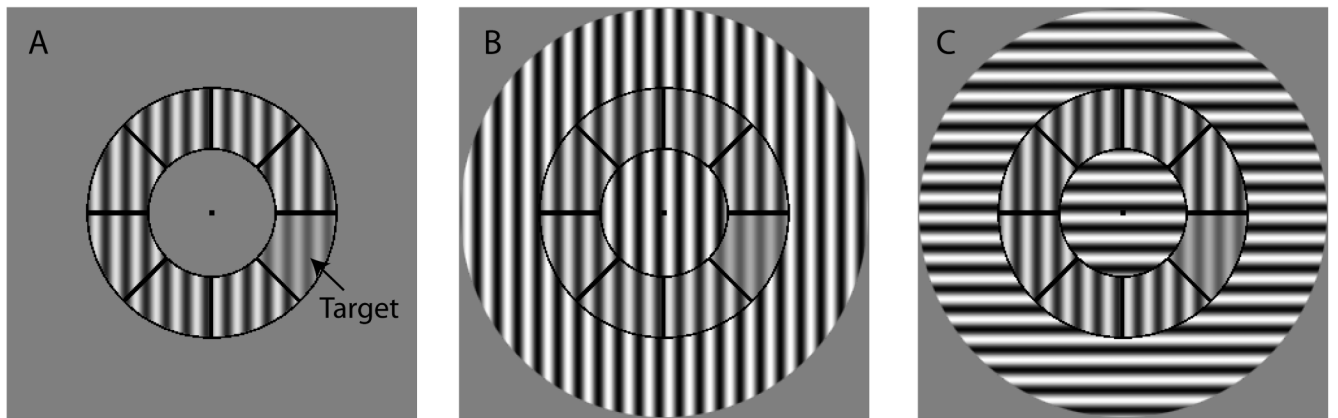
**Figure 1. Surround suppression stimuli**
Subjects indicated whether they perceived a difference in contrast between any one segment (target) and the other segments in the annulus under three conditions: A) no surround (NS), B) parallel surround (PS), and C) orthogonal surround (OS). The annulus is identical in all three conditions in this figure.
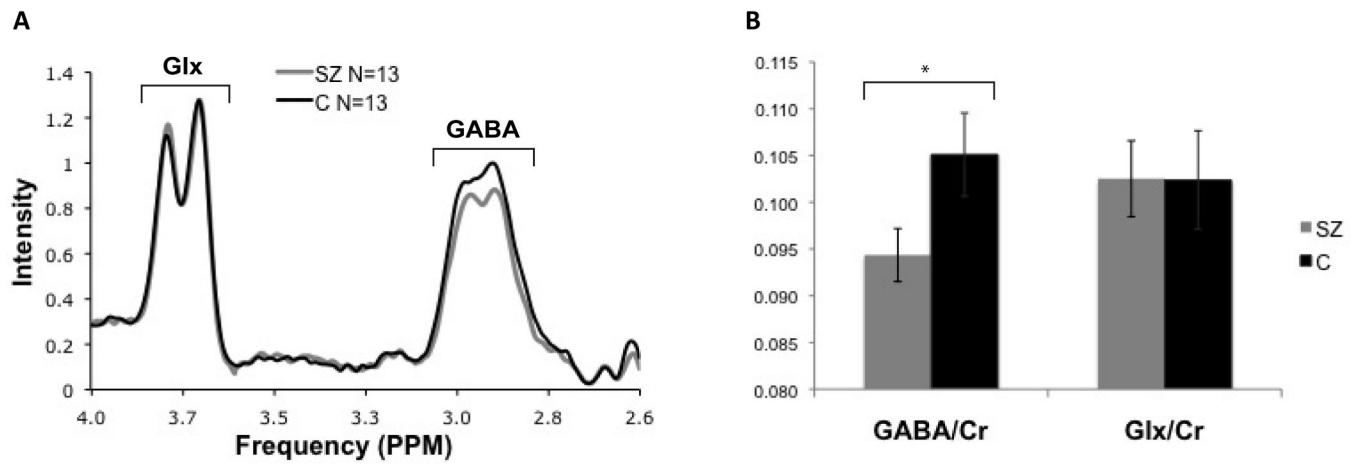
**Figure 2. NMR spectra results**
A) group averaged, creatine-normalized Glx (glutamine+glutamate) and total GABA spectra;
SZ (schizophrenia), C (controls). B) Integrals of the creatine-normalized GABA and Glx peaks.
* p<0.05. Error bars are denote standard deviations.
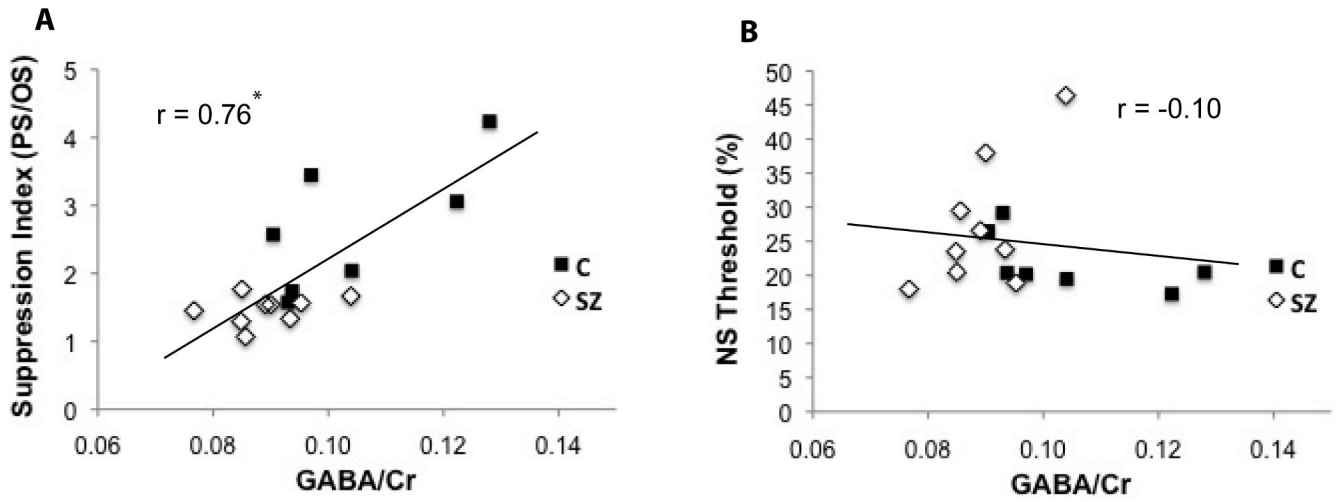
**Figure 3. Visual cortical GABA levels correlate with OSSS**
GABA/Cr plotted against: A) the contrast discrimination threshold in the PS condition
normalized by the OS threshold, * p=0.001; B) threshold in the NS condition.

**TABLE 1**

**Subject demographics and patient clinical characteristics**

| | Patient (N=13) | | Control (N=13) | | p-value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (years) | 27.5 | 8.8 | 28.1 | 8.2 | .87 |
| Gender (% male) | 85 | | 85 | | |
| Education (years) | 14.0 | 1.4 | 15.9 | 1.7 | .01 |
| Parental Education (years) | 14.5 | 2.4 | 15.0 | 3.4 | .69 |
| On medications (%) | 62 | | | | |
| CPZ equivalents (mg) | 433 | 228 | | | |
| GAF | 49.8 | 12.7 | | | |
| BPRS | 41.4 | 10.5 | | | |
| SAPS | 5.8 | 4.4 | | | |
| SANS | 10.2 | 3.3 | | | |