Published in final edited form as:

Schizophr Res. 2015 October ; 168(0): 338–344. doi:10.1016/j.schres.2015.08.022.

Abnormal GABAergic Function and Face Processing in Schizophrenia: A Pharmacologic-fMRI Study

Ivy F. Tso^{a,*}, Yu Fang^a, K. Luan Phan^b, Robert C. Welsh^{a,c}, and Stephan F. Taylor^a

^a Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA.

^b Department of Psychiatry, University of Illinois at Chicago, IL, USA.

^c Department of Radiology, University of Michigan, Ann Arbor, MI, USA.

Abstract

The involvement of the gamma-aminobutyric acid (GABA) system in schizophrenia is suggested by postmortem studies and the common use of GABA receptor-potentiating agents in treatment. In a recent study, we used a benzodiazepine challenge to demonstrate abnormal GABAergic function during processing of negative visual stimuli in schizophrenia. This study extended this investigation by mapping GABAergic mechanisms associated with face processing and social appraisal in schizophrenia using a benzodiazepine challenge. Fourteen stable, medicated schizophrenia/schizoaffective patients (SZ) and 13 healthy controls (HC) underwent functional MRI using the blood oxygenation level-dependent (BOLD) technique while they performed the Socio-emotional Preference Task (SePT) on emotional face stimuli (“Do you like this face?”). Participants received single-blinded intravenous saline and lorazepam (LRZ) in two separate sessions separated by 1-3 weeks. Both SZ and HC recruited medial prefrontal cortex/anterior cingulate during the SePT, relative to gender identification. A significant drug by group interaction was observed in the medial occipital cortex, such that SZ showed increased BOLD signal to LRZ challenge, while HC showed an expected decrease of signal; the interaction did not vary by task. The altered BOLD response to LRZ challenge in SZ was significantly correlated with increased negative affect across multiple measures. The altered response to LRZ challenge suggests that abnormal face processing and negative affect in SZ are associated with altered

* Correspondence concerning this article should be addressed to Ivy Tso, Department of Psychiatry, University of Michigan, Rachel Upjohn Building, 4250 Plymouth Road, Ann Arbor, Michigan 48109, U.S.A. ivyts@umich.edu. Tel: 1-(734)-232-0373. Fax: 1-(734)-936-7868..

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

CONFLICTS OF INTEREST

S.F.T has a research contract with St Jude Medical and research support from Neuronetics. The authors declare no conflict of interest pertinent to this study.

CONTRIBUTORS

Ivy Tso, Ph.D., undertook the statistical analyses, interpreted the data, and wrote the first draft and revised the manuscript; she has approved the final version of the manuscript. Yu Fang, M.S.E., undertook the fMRI data processing and analyses, and provided feedback on the manuscript; she has approved the final version of the manuscript. K. Luan Phan, M.D., advised on the study design and data collection strategies, and provided feedback on the manuscript; he has approved the final version of the manuscript. Robert Welsh, Ph.D., advised on the fMRI data analysis strategies, wrote the fMRI data processing scripts, and provided feedback on the manuscript; he has approved the final version of the manuscript. Stephan Taylor, M.D., designed the study, wrote the protocol, interpreted the data, and provided feedback on the manuscript; he has approved the final version of the manuscript.

GABAergic function in the visual cortex, underscoring the role of impaired visual processing in socio-emotional deficits in schizophrenia.

Keywords

fMRI; psychosis; social cognition; emotion; benzodiazepine

1. Introduction

The role of the gamma-aminobutyric acid (GABA) system in the pathophysiology of schizophrenia has gained increasing attention. Post-mortem studies have provided strong evidence for an altered GABA system in the disorder. One of the most consistent finding has been the reductions of glutamic acid decarboxylase-67 (Akbarian and Huang, 2006; Benes, 2010; Lewis et al., 2012; Nakazawa et al., 2012), a synthetic enzyme for GABA, observed in multiple brain regions associated with critical cognitive functions, including the dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), motor cortex, visual cortex, and hippocampus. Few studies have examined *in vivo* GABA function in schizophrenia, and while the results have been somewhat mixed (Taylor and Tso, 2014), it remains an important goal to show how GABAergic abnormalities observed in post-mortem studies may be related to the behavioral phenotype of schizophrenia.

GABAergic interneurons are the major machinery of inhibition in the human brain, central to the synchronization and oscillations of neuronal activity that are critical to perception, memory, and cognition (Cobb et al., 1995; Osipova et al., 2006; Wang and Buzsaki, 1996). Clinical observations suggest that altered socio-emotional deficits in schizophrenia may be closely related to GABAergic dysfunction. For example, GABA-manipulating agents such as benzodiazepine and valproate are frequently used to augment antipsychotics and treat negative affect (e.g., anxiety, dysphoria) in schizophrenia (Wassef et al., 1999). Further, these drugs are used to facilitate mood regulation in bipolar disorder (Cousins and Young, 2007), in which glutamic acid decarboxylase-67 abnormalities are also observed in postmortem studies (Guidotti et al., 2000). While increased trait negative affect (Horan et al., 2008) and socio-emotional deficits (Tso et al., 2010) are well-documented phenomena in schizophrenia and have been shown to be important determinants of functional outcome, their association with GABAergic dysfunction has been rarely explored but could advance our understanding of the disease mechanisms of schizophrenia.

In a recent study, we paired a benzodiazepine challenge and blood-oxygen-level dependent (BOLD) fMRI to map GABAergic mechanisms associated with affect processing in schizophrenia (Taylor et al., 2014). We used lorazepam (LRZ), a non-subtype selective benzodiazepine and an allosteric modulator of GABA receptors that potentiates GABA function (Olsen and Tobin, 1990), to probe GABAergic activity during passive viewing of emotionally salient images. Schizophrenia patients showed increased BOLD signal in the dorsomedial PFC (dmPFC) and occipital regions in the LRZ condition, instead of decreased BOLD signal found in the healthy controls. This abnormal response was correlated with

increased negative affect, providing the first evidence for the involvement of GABAergic dysfunction in affect processing and negative affect in schizophrenia.

In this study, we used the same pharmacologic-fMRI design to investigate the involvement of GABAergic dysfunction in abnormal face processing and its relationship to negative affect in schizophrenia. Face processing is impaired in schizophrenia, although it is unclear whether the impairment is specific to the processing of the socio-emotional aspects of faces or represents a general visual processing deficit (Darke et al., 2013). In previous work, we used a face appraisal task and showed reduced co-modulation between ACC, dmPFC and occipital cortex in schizophrenia, which was correlated with poor social functioning (Taylor et al., 2011). In the current study, we employed this socio-emotional preferential task (SePT), to investigate face processing as a whole, as well as isolate the effect of social appraisal in the dmPFC. We hypothesized that abnormal BOLD response (reduced inhibition or increased activation) to LRZ challenge during face processing would be observed in the dmPFC and occipital cortex in schizophrenia, and these abnormalities would be more pronounced during social relative to non-social appraisal. In addition, we hypothesized that these abnormal fMRI findings would be correlated with increased negative affect in schizophrenia.

2. Methods

2.1. Participants

Seventeen stable, medicated outpatients with DSM-IV schizophrenia or schizoaffective disorder, established by a Structured Clinical Interview for Diagnosis (First et al., 1995), were recruited. Fourteen completed the study and provided usable data. Thirteen healthy control participants were recruited from community advertisements and selected to match the basic demographics (age, sex, and parental education level) of the SZ group. All participants were provided information on the purpose and risks of the study prior to giving written informed consent. The study was conducted in accordance to a protocol approved by the University of Michigan Medical School Institutional Review Board for adherence to ethical standards of research. See Supplementary materials for more details about the participants.

2.2. Assessments

Clinical symptoms of the SZ participants were assessed by an experienced clinician (S.F.T.) using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Calgary Depression Scale (Addington et al., 1993), and the Scale for the Assessment of Negative Symptoms (Andreasen, 1983). All participants completed the Wide Range Achievement Test, revised, Reading subtest (WRAT3-R) (Jastak and Wilkinson, 1984) for general intellectual achievement and the Brief Assessment of Cognition for Schizophrenia (BACS) for general neurocognition (Keefe et al., 2004).

Prior to each scanning session, participants completed self-report measures of emotional state, including the Perceived Stress Scale (PSS) (Cohen et al., 1983), Spielberger State-Trait Anxiety Inventory (state; STAI) (Spielberger CD et al., 1993), and the Differential

Emotions Scale (DES) (Fredrickson et al., 2003). Participant characteristics are summarized in Table 1.

2.3. Task Design

The Socio-emotional Preferential Task (SePT) is a simple social judgment task that has been applied in schizophrenia research previously (Taylor et al., 2011). Participants were shown happy, neutral, and fearful faces. Each face was presented for 3 seconds, and participants were required to press a button to indicate whether the face is male or female (GenderID; “Gender? Male/Female”) or whether they like the face or not (“Like? Yes/No”). They were instructed to respond quickly based on their first impression. Faces were displayed in blocks, and each block consisted of four faces of the same valence and task (Like or GenderID), separated by rest periods of 4 – 8 seconds where a fixation cross appeared in the center of the screen. Task alternated between blocks, and the order of valence was pseudorandomized. The task consisted of 72 blocks in total over 4 runs, each 368 seconds of duration (3 valence $\times$ 3 blocks $\times$ 2 tasks $\times$ 4 runs). Prior to the first scanning session, all participants experienced a desensitization run in a mock scanner, in which they viewed stimuli and responded on a button apparatus similar to the actual scanner.

2.4. Scanning Sessions

Participants underwent two fMRI scanning sessions in a single-blinded, cross-over design (Figure 1). All participants had negative urine toxicology screens for drugs of abuse prior to each scanning session. After placement of an intravenous line, they received bolus injections either of lorazepam 0.01 mg/kg, or an equivalent amount of saline solution. Participants were placed in the MRI scanner and the task began approximately 30 min after injection, when blood levels of intravenous LRZ were maximal (Wermeling et al., 2001). Each session consisted of the SePT and another activation task (reported elsewhere).

Prior to the intravenous line placement, before each task, and then again after the scanning session, participants completed 6 visual analogue scales (VAS) assessing their subjective feelings of drowsiness, anxiety, happiness, fear, sadness, and excitement.

2.5. Functional MRI Acquisition

MRI scanning occurred on a GE 3T Signa scanner (LX [8.3] release, General Electric Healthcare, Buckinghamshire, United Kingdom). A T1-weighted image was acquired in the same prescription as the functional images to facilitate co-registration. Functional images were acquired with a T2*-weighted, reverse spiral acquisition sequence (gradient recalled echo, TR=2000 msec, TE=30 msec, FA=90 degrees, field of view=22 cm, 40 slice, 3.0mm thick/0mm skip, equivalent to 64 x 64 voxel grid) sensitive to signal in ventral medial frontal regions (Yang et al., 2002). Subjects underwent 4 runs (18 blocks/runs), each consisting of 184 volumes, plus 4 initial, discarded volumes to allow for equilibration of scanner signal, with isotropic voxels 3 mm on edge. Total duration of the task was approximately 25 minutes. After acquisition of functional volumes, a high resolution T1 scan (3D SPGR, field of view=26 cm, T1=500 msec, TR=20 msec, TE=1.8 msec, 256 $\times$ 256 matrix, 124 slices, 1.2 mm interleaved with no skip) was obtained for anatomic normalization.

2.6. Behavioral Data Analysis

Behavioral data were analyzed using SPSS, version 22. For Gender ID accuracy and preferential response, separate mixed-model ANOVAs were performed, with group as a between-subjects factor and valence and drug as within-subjects factors. For reaction time, a mixed-model ANOVA was performed with group as a between-subjects factor and task, valence, and drug as within-subjects factors.

2.7. fMRI Data Analysis

fMRI data were processed with Statistical Parametric Mapping SPM8 package (Wellcome Institute of Cognitive Neurology, London) and standard routines. Slice time was corrected using sinc-interpolation, weighted by a Hanning kernel in time. Then all scans were realigned to the 10th volume acquired during each scan (“mcflirt”, Jenkinson et al. 2002). Subjects with movement exceeding either 1 voxel or 2 degree rotation within a scan were discarded (see Supplementary material for analysis of movement). Time series of functional volumes were then co-registered with high resolution T1 image, spatially normalized to the MNI152 brain, and then spatially smoothed with an 8 mm isotropic Gaussian kernel.

First-level analysis began with applying a high pass filter (128 s) to the anatomically normalized time series, and regressed on 12 regressors (2 tasks [Gender, Like] $\times$ 3 face valences [happy, neutral, fearful] $\times$ 2 sessions [LRZ, SAL]) convolved with a canonical hemodynamic response function, along with 6 movement regressors. Beta estimates of each participant at the first level were taken to a second-level analysis using a flexible factorial design, with task, valence, scan session as within-subject factors and group as between-subjects factor. Statistical inference was controlled by applying correction using Gaussian random field theory (Worsley and Friston, 1995). For peak results, a threshold of family-wise error (FWE) corrected $p < 0.05$ was used. For cluster sizes, 3dClustSim from the AFNI package was used to obtain a combination of uncorrected p threshold (0.005) and extent threshold, which provides an FWE-corrected inference significant at $p < 0.05$.

3. Results

3.1 Subjective Ratings

The full results of the VAS ratings are previously reported (Taylor et al., 2014). Critically, LRZ did not have an effect on drowsiness ratings. However, it reduced fearfulness ($F[1,23]=4.8$, $p=0.04$) and showed a trend to reducing anxiety ($F[1,23]=3.49$, $p=0.07$). See Supplementary material for additional analysis of VAS ratings.

3.2. Behavioral Results

Accuracy of Gender ID, rate of “liked” faces, and RT are presented in Figure 2. For Gender ID, participants were more accurate with happy and fearful faces than with neutral faces, $F(2,50)=9.41$, $p<0.001$. SZ were as accurate as HC, $F(1,25)=2.15$, $p=0.16$. No group interactions were observed.

For preference judgment, participants “liked” happy faces more frequently than neutral faces, which were in turn “liked” more often than fearful faces, $F(2,50)=66.07$, $p<0.001$.

Overall, SZ “liked” more of the faces than did HC, $F(1,25)=4.31$, $p=0.048$. No group interactions were observed.

As expected, LRZ slowed down responses compared with SAL, $F(1,25)=6.01$, $p=0.022$. RT was longer for preference than gender judgment, $F(1,25)=10.43$, $p=0.003$. Participants took the longest to respond to neutral faces, followed by fearful faces, then happy faces, $F(2,50)=32.49$, $p<0.001$. However, a Valence $\times$ Task interaction, $F(2,50)=22.33$, $p<0.001$, indicated that this valence effect on RT was specific to preference trials and absent for gender judgment, consistent with previous behavioral findings of this paradigm (Taylor et al., 2011). Again, no group interactions were observed.

3.3. fMRI Results

Results of the significant peaks and clusters are summarized in Supplementary Materials Table S1. A robust task effect (like>gender) was observed in dmPFC/ACC and bilateral inferior frontal/anterior insula cortex (Figure S1), and a robust group effect (HC>SZ) at baseline was observed in dmPFC/ACC and posterior cingulate (Figure S2), consistent with previous findings using the same paradigm (Taylor et al., 2011).

A significant Drug $\times$ Group interaction was observed in the medial occipital cortex (lingual gyrus/Brodmann area 18) (Figure 3a). Beta extraction (5 mm radius sphere) from this region revealed that SZ showed increased BOLD signal when processing faces (relative to the implicit baseline) under LRZ challenge, while HC showed an expected decrease of signal when under LRZ (Figure 3b). However, no significant Drug $\times$ Group interaction was found in the other *a priori* region, dmPFC.

No significant Drug $\times$ Task $\times$ Group interaction was observed, failing to support the hypothesis that abnormal BOLD response to LRZ challenge in SZ would be more pronounced in social than non-social appraisal.

No additional group by drug interactions (Drug $\times$ Valence $\times$ Group; and Drug $\times$ Task $\times$ Valence $\times$ Group) were observed in the *a priori* regions of dmPFC and visual cortex.

3.3. Correlations between LRZ-induced BOLD Changes and Negative Affect

To test the hypothesis of GABAergic involvement in negative affect in schizophrenia, planned correlations were run between LRZ-induced change at the medial occipital cortex focus (i.e., extracted parameter estimates of the SAL – LRZ contrast) and negative affect measures. Among SZ participants, increased BOLD response to LRZ challenge relative to SAL (i.e., LRZ > SAL) was correlated with more negative affect across multiple measures and greater relief of subjective anxiety following LRZ infusion (Figure 4). These correlations were absent or in the opposite direction among HC. Abnormal BOLD response to LRZ challenge was not correlated with positive/negative symptoms (BPRS, SANS) or antipsychotic dose.

4. Discussion

This study demonstrated an LRZ-induced increase in reactivity during face processing in the visual cortex in SZ, positively correlated with negative affect, thus supporting the involvement of GABAergic dysfunction in socio-emotional deficits in SZ. Although the increased BOLD response to LRZ challenge in SZ appears counterintuitive, it is consistent with two broad findings in postmortem studies. First, the finding of fewer postsynaptic GABA_A $\alpha 1$ receptors in SZ (Lewis et al., 2012) suggests that potentiating GABA receptors with LRZ would induce less inhibitory effect on pyramidal neurons in SZ compared with healthy participants. Second, upregulated GABA_A $\alpha 2$ receptors in chandelier neurons (Volk et al., 2002), which *excite* pyramidal neurons (Szabadics et al., 2006), suggests that GABA receptor potentiation could also lead to increased excitation in SZ. Although these postmortem findings were generally observed in PFC, there is evidence showing that GABAergic abnormalities in SZ are rather similar across cortical regions, including the visual cortex (Hashimoto et al., 2008).

Specifically, the abnormal response to LRZ in SZ was observed in secondary visual cortex (Brodmann area 18) in this study. V2 is an important visual association area, integrating output from V1 to form more complex visual representations. This finding is consistent with work documenting impairment in visual integration in SZ (Butler et al., 2008), which has been shown to be related to reduced BOLD signal in V2-V4 (Silverstein et al., 2009) and theorized as a result of reduced inhibitory activity of GABAergic interneurons (Silverstein and Keane, 2011). Studies have demonstrated abnormal visual cortical functions in SZ where GABA-related decreased cortical inhibition was inferred, such as weakened suppression and lateral connectivity in V1 (Dakin et al., 2005) and weakened center-surround interactions in motion perception in MT (Chen et al., 2008; Tadin et al., 2006). In addition, reduced *in vivo* GABA signal in V1 has been associated with deficits in early sensory processing in SZ (Yoon et al., 2010). Although it is unclear how reduced GABA concentration corresponds to aggregated neuronal activity and BOLD signal, these data broadly support that GABAergic dysfunctions in the visual cortex may underlie visual perception deficits in SZ. Since deficits have been observed in a wide range of visual areas in SZ, it is unlikely that GABAergic dysfunction is specific to V2. The current finding in V2 may simply reflect the fact that visual integration function associated with V2 was most relevant to task of face processing used in this study.

Our finding of altered GABAergic function in the visual cortex during face processing confirms the involvement of altered early visual processing in social cognitive deficits in previous behavioral (Sergi and Green, 2003; Sergi et al., 2006; Tso et al., 2014; Tso et al., 2012) and neuroimaging studies (Taylor et al., 2012). The correlation with increased negative affect, consistent across multiple measures, suggests that GABA abnormalities may underlie the “aversive drift” phenomenon in schizophrenia (Meehl, 1962, 1990). Interestingly, higher degree of GABAergic abnormality in SZ was associated with more subjective relief of anxiety following LRZ intake. This may explain why some patients with SZ seek out benzodiazepines. Future studies should investigate whether GABA-directed therapies (Stan and Lewis, 2012) may be therapeutic for SZ through normalizing social information processing, in addition to providing anxiety relief.

Contrary to our hypothesis, we did not find a Drug $\times$ Task $\times$ Group interaction, suggesting that the abnormal BOLD response to LRZ in SZ was not significantly different during social appraisal vs. non-social appraisal of faces. While one may conclude that altered social appraisal of faces in SZ may be unrelated to GABAergic dysfunctions, considering the modest sample size and low statistical power for detecting a three-way interaction, this negative finding should be interpreted with caution.

We did not find a Drug $\times$ Group interaction in the dmPFC as we hypothesized. Although a significant Drug $\times$ Group interaction was observed in mPFC/superior frontal gyrus in the same sample during a passive viewing task of emotionally salient pictures (Taylor et al., 2014), the SePT task in this study was different in terms of the contents of the stimuli and the cognitive processes involved. Thus, differential results are not entirely surprising. Further, BOLD responses in posterior regions generally show larger effect sizes of experimental manipulations compared with frontal regions and thus are more likely to reach statistical significance (Desmond and Glover, 2002). Therefore, the finding of abnormal BOLD response in the occipital cortex (but not dmPFC) during LRZ challenge in SZ should not be interpreted as an indication that GABAergic dysfunction was only present in the visual cortex. Rather, the finding suggests that GABAergic dysfunction may underlie observed social perceptual tasks (such as face processing) in SZ due to its recruitment of the visual cortex, a key association area in social cognitive processes.

This study was limited by the small sample size, although we carefully matched SZ and HC participants for major demographic characteristics. All but one of our SZ participants were medicated, making it impossible to isolate the effect of medications, although SZ's abnormal BOLD response to LRZ was not correlated with antipsychotic dose in this study. Since there are few dopamine D2 receptors in the visual cortex (Kantrowitz and Javitt, 2010), potential interactions between antipsychotic use and LRZ administration should be minimal. Lastly, the SZ sample of this study was mostly chronic patients, limiting the generalizability of our findings to patients in different stages of illness. Although there was no correlation with duration of illness, future studies with larger samples and a wider range of illness chronicity would help confirm the findings of this study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank Inga Brege for her assistance in subject recruitment, data acquisition, and initial data processing. This work was previously presented at the Biological Psychiatry Annual Meeting in New York in 2014.

FUNDING

This work was supported by the National Institute of Mental Health (R21MH086701 to S.F.T.), the Boledovich Schizophrenia Research Fund (to S.F.T.), University of Michigan Clinical Translational Science Award (UL1RR024986 to S.F.T.), and the National Institutes of Health (5KL2TR000434-08 to I.F.T.). None of the funding sources had a role in study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Role of the Funding Source

None of the funding sources had a role in study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

References

- Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. *Br J Psychiatry*. 1993; (Suppl(22)):39–44.
- Akbadian S, Huang HS. Molecular and cellular mechanisms of altered GAD1/GAD67 expression in schizophrenia and related disorders. *Brain Res Rev*. 2006; 52(2):293–304. [PubMed: 16759710]
- Andreasen, NC. The scale for the Assessment of Negative Symptoms. The University of Iowa; Iowa City: 1983.
- Benes FM. Amygdalocortical circuitry in schizophrenia: from circuits to molecules. *Neuropsychopharmacology*. 2010; 35(1):239–257. [PubMed: 19727065]
- Butler PD, Silverstein SM, Dakin SC. Visual perception and its impairment in schizophrenia. *Biological psychiatry*. 2008; 64(1):40–47. [PubMed: 18549875]
- Chen Y, Norton D, Ongur D. Altered center-surround motion inhibition in schizophrenia. *Biological psychiatry*. 2008; 64(1):74–77. [PubMed: 18206855]
- Cobb SR, Buhl EH, Halasy K, Paulsen O, Somogyi P. Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature*. 1995; 378(6552):75–78. [PubMed: 7477292]
- Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983; 24(4):385–396. [PubMed: 6668417]
- Cousins DA, Young AH. The armamentarium of treatments for bipolar disorder: a review of the literature. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2007; 10(3):411–431.
- Dakin S, Carlin P, Hemsley D. Weak suppression of visual cortex in chronic schizophrenia. *Curr. Biol*. 2005; 15(20):R822–R824. [PubMed: 16243017]
- Darke H, Peterman JS, Park S, Sundram S, Carter O. Are patients with schizophrenia impaired in processing non-emotional features of human faces? *Frontiers in psychology*. 2013; 4:529. [PubMed: 23970872]
- Desmond JE, Glover GH. Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *J Neurosci Methods*. 2002; 118(2):115–128. [PubMed: 12204303]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), version 2.0. Biometrics Research; New York: 1995.
- Fredrickson BL, Tugade MM, Waugh CE, Larkin GR. What good are positive emotions in crises? A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. *J Pers Soc Psychol*. 2003; 84(2):365–376. [PubMed: 12585810]
- Guidotti A, Auta J, Davis JM, Di-Giorgi-Gerevini V, Dwivedi Y, Grayson DR, Impagnatiello F, Pandey G, Pesold C, Sharma R, Uzunov D, Costa E. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. *Arch Gen Psychiatry*. 2000; 57(11):1061–1069. [PubMed: 11074872]
- Hashimoto T, Bazmi HH, Mirnics K, Wu Q, Sampson AR, Lewis DA. Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. *Am J Psychiatry*. 2008; 165(4):479–489. [PubMed: 18281411]
- Horan WP, Blanchard JJ, Clark LA, Green MF. Affective traits in schizophrenia and schizotypy. *Schizophrenia bulletin*. 2008; 34(5):856–874. [PubMed: 18667393]
- Jastak, S.; Wilkinson, GS. Wide Range Achievement Test -Revised. Jastak Associates, Inc.; Wilmington, DE.: 1984.
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002; 17(2):825–841. [PubMed: 12377157]
- Kantrowitz JT, Javitt DC. N-methyl-d-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? *Brain research bulletin*. 2010; 83(3-4):108–121. [PubMed: 20417696]

- Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res.* 2004; 68(2-3):283–297. [PubMed: 15099610]
- Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci.* 2012; 35(1):57–67. [PubMed: 22154068]
- Meehl PE. Schizotaxia, schizotypy, schizophrenia. *American Psychologist.* 1962; 17:827–838.
- Meehl PE. Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *Journal of Personality Disorders.* 1990; 4:1–99.
- Nakazawa K, Zsiros V, Jiang Z, Nakao K, Kolata S, Zhang S, Belforte JE. GABAergic interneuron origin of schizophrenia pathophysiology. *Neuropharmacology.* 2012; 62(3):1574–1583. [PubMed: 21277876]
- Olsen RW, Tobin AJ. Molecular biology of GABAA receptors. *FASEB J.* 1990; 4(5):1469–1480. [PubMed: 2155149]
- Osipova D, Takashima A, Oostenveld R, Fernandez G, Maris E, Jensen O. Theta and gamma oscillations predict encoding and retrieval of declarative memory. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2006; 26(28):7523–7531. [PubMed: 16837600]
- Overall JE, Gorham DR. Brief psychiatric rating scale. *Psychological Reports.* 1962; 10:799–812.
- Sergi MJ, Green MF. Social perception and early visual processing in schizophrenia. *Schizophr Res.* 2003; 59(2-3):233–241. [PubMed: 12414080]
- Sergi MJ, Rassovsky Y, Nuechterlein KH, Green MF. Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am J Psychiatry.* 2006; 163(3):448–454. [PubMed: 16513866]
- Silverstein SM, Berten S, Essex B, Kovacs I, Susmaras T, Little DM. An fMRI examination of visual integration in schizophrenia. *Journal of Integrative Neuroscience.* 2009; 8(2):175–202. [PubMed: 19618486]
- Silverstein SM, Keane BP. Perceptual organization impairment in schizophrenia and associated brain mechanisms: review of research from 2005 to 2010. *Schizophrenia bulletin.* 2011; 37(4):690–699. [PubMed: 21700589]
- Spielberger, CD.; G.R.; Lushene, R.; Vagg, PR.; Jacobs, GA. Manual for the State-Trait Anxiety Inventory (Form Y). Mind Garden; Palo Alto, CA.: 1993.
- Stan AD, Lewis DA. Altered cortical GABA neurotransmission in schizophrenia: insights into novel therapeutic strategies. *Curr Pharm Biotechnol.* 2012; 13(8):1557–1562. [PubMed: 22283765]
- Szabados J, Varga C, Molnar G, Olah S, Barzo P, Tamas G. Excitatory effect of GABAergic axo-axonic cells in cortical microcircuits. *Science.* 2006; 311(5758):233–235. [PubMed: 16410524]
- Tadin D, Kim J, Doop ML, Gibson C, Lappin JS, Blake R, Park S. Weakened center-surround interactions in visual motion processing in schizophrenia. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2006; 26(44):11403–11412. [PubMed: 17079669]
- Taylor SF, Chen AC, Tso IF, Liberzon I, Welsh RC. Social appraisal in chronic psychosis: role of medial frontal and occipital networks. *J Psychiatr Res.* 2011; 45(4):526–538. [PubMed: 20797730]
- Taylor SF, Demeter E, Phan KL, Tso IF, Welsh RC. Abnormal GABAergic function and negative affect in schizophrenia. *Neuropsychopharmacology.* 2014; 39(4):1000–1008. [PubMed: 24154667]
- Taylor SF, Kang J, Brege IS, Tso IF, Hosanagar A, Johnson TD. Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. *Biological psychiatry.* 2012; 71(2):136–145. [PubMed: 21993193]
- Taylor, SF.; Tso, IF. GABA abnormalities in schizophrenia: A methodological review of in vivo studies.. *Schizophr Res.* 2014. <http://dx.doi.org/10.1016/j.schres.2014.10.011>
- Tso IF, Carp J, Taylor SF, Deldin PJ. Role of visual integration in gaze perception and emotional intelligence in schizophrenia. *Schizophrenia bulletin.* 2014; 40(3):617–625. [PubMed: 23666503]
- Tso IF, Grove TB, Taylor SF. Emotional experience predicts social adjustment independent of neurocognition and social cognition in schizophrenia. *Schizophr Res.* 2010; 122(1-3):156–163. [PubMed: 20051314]

- Tso IF, Mui ML, Taylor SF, Deldin PJ. Eye-contact perception in schizophrenia: relationship with symptoms and socioemotional functioning. *J Abnorm Psychol.* 2012; 121(3):616–627. [PubMed: 22250658]
- Volk DW, Pierri JN, Fritschy JM, Auh S, Sampson AR, Lewis DA. Reciprocal alterations in pre- and postsynaptic inhibitory markers at chandelier cell inputs to pyramidal neurons in schizophrenia. *Cereb Cortex.* 2002; 12(10):1063–1070. [PubMed: 12217970]
- Wang XJ, Buzsaki G. Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 1996; 16(20):6402–6413. [PubMed: 8815919]
- Wassef AA, Dott SG, Harris A, Brown A, O'Boyle M, Meyer WJ 3rd, Rose RM. Critical review of GABA-ergic drugs in the treatment of schizophrenia. *J Clin Psychopharmacol.* 1999; 19(3):222–232. [PubMed: 10350028]
- Wermeling DP, Miller JL, Archer SM, Manaligod JM, Rudy AC. Bioavailability and pharmacokinetics of lorazepam after intranasal, intravenous, and intramuscular administration. *J Clin Pharmacol.* 2001; 41(11):1225–1231. [PubMed: 11697755]
- Worsley KJ, Friston KJ. Analysis of fMRI time-series revisited--again. *Neuroimage.* 1995; 2(3):173–181. [PubMed: 9343600]
- Yang Y, Gu H, Zhan W, Xu S, Silbersweig DA, Stern E. Simultaneous perfusion and BOLD imaging using reverse spiral scanning at 3T: characterization of functional contrast and susceptibility artifacts. *Magn Reson Med.* 2002; 48(2):278–289. [PubMed: 12210936]
- Yoon JH, Maddock RJ, Rokem A, Silver MA, Minzenberg MJ, Ragland JD, Carter CS. GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2010; 30(10):3777–3781. [PubMed: 20220012]

Figure 1.

Single-blinded, cross-over design. Participants were randomized to receive either saline or lorazepam (LRZ) in the first fMRI session. Six (out of 13) HC and 7 (out of 14) SZ received saline first and the rest of the participants received LRZ first. All participants underwent both sessions, occurred with a minimal separation of 3 days (12.1 ± 9.7 days). Participants were blinded to the drug condition throughout the study.

Figure 2.

Behavioral responses and reaction time to Gender ID and Preferential tasks. Error bars indicate standard errors of mean.

Figure 3.

Effect of lorazepam (LRZ) on blood oxygenation level-dependent (BOLD) signal during face processing. a) A significant Group $\times$ Drug interaction was observed at medial occipital cortex [0, -82, -8], $Z = 5.28$, FWE-corrected $p = 0.001$, cluster size = 468, FWE-corrected $p < 0.05$. Voxels rendered at uncorrected significance $p < 0.005$. b) Extraction of parameter estimate of peak focus for group by drug interaction at medial occipital cortex revealed that HC showed decreased BOLD signal in response to LRZ as expected, while SZ showed abnormally increased activity to LRZ.

Figure 4.

Pearson's (r) and non-parametric (ρ) correlations between LRZ-induced BOLD changes and negative affect measures. X-axis represents difference of extracted beta estimate at medial occipital cortex between the SAL and LRZ conditions; negative values indicate LRZ > SAL. mOcc: medial occipital cortex; SAL: saline; LRZ: lorazepam. * $p < 0.05$.

Table 1

Demographic and Clinical Characteristics of Participants

	SZ (n = 14) Mean ± SD	HC (n = 13) Mean ± SD	t / χ^2	p
<i>Demographics</i>				
Age	43.0 ± 12.6	41.5 ± 12.7	0.30	0.77
Sex (male/female)	9/5	8/5	0.22	0.88
Education, years	15.4 ± 2.7	16.3 ± 2.1	1.00	0.32
Parental education, years	16.5 ± 2.7	14.9 ± 2.8	1.49	0.15
Duration of illness	23.8 ± 14.3	--	--	--
CPZeq	398 ± 321	--	--	--
<i>Neurocognition</i>				
WRAT3-R	50.8 ± 7.0	53.5 ± 2.3	1.31	0.20
BACS	-1.5 ± 1.5	-0.1 ± 1.0	-3.00	0.006
<i>Emotion Assessments</i>				
PSS	14.7 ± 5.9	8.9 ± 5.0	2.73	0.011
STAI	33.0 ± 9.1	27.9 ± 4.6	1.81	0.083
DES-positive	2.69 ± 0.53	2.96 ± 0.77	-1.06	0.30
DES-negative	1.07 ± 0.50	0.44 ± 0.29	3.96	0.001
<i>Symptom Assessments</i>				
BPRS total	29.5 ± 4.5	--	--	--
BPRS positive	7.5 ± 2.5	--	--	--
BPRS negative	6.0 ± 1.9	--	--	--
CDS	2.1 ± 2.4	--	--	--
SANS global sum	4.9 ± 2.6	--	--	--

Note. CPZeq = antipsychotic dose in chlorpromazine equivalent mg daily. WRAT3-R = Wide Range Achievement Test, revised, Reading subtest. BACS = Brief Assessment of Cognition for Schizophrenia. PSS = Perceived Stress Scale. STAI = Spielberger State-Trait Anxiety Inventory. DES = Differential Emotion Scale. BPRS = Brief Psychiatric Rating Scale. CDS = Calgary Depression Scale. SANS = Scale for the Assessment of Negative Symptoms.