# Lateral prefrontal cortex activity during cognitive control of emotion predicts response to social stress in schizophrenia

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## Supplemental Methods

*Laboratory Assessments of Social Functioning*

We administered the Social Adjustment Scale - Self-Report (SAS-SR; Weissman, Prusoff, & Thompson, 1978) and Global Functioning: Social scale (Auther, Smith, & Cornblatt, 2006) (GF:S), two standard laboratory based measures of social functioning. The SAS-SR consists of 54 questions assessing six major areas of functioning: work, social and leisure activities, relationships with extended family, role as marital partner, parental role, and role within the family unit. Areas of functioning are assessed across four categories: performance at expected tasks, level of conflict with people, interpersonal relations, and feelings and satisfactions. Area scores can be averaged to create a single composite score of social functioning. Higher scores on the SAS-SR represent greater social impairment. The GF:S is a clinician rated assessment of social functioning using a 1 to 10 scale based on information gathered during clinical interviews; higher scores on the GFS and GFR reflect better functioning.

***MSIT-Emotion Affective Picture Stimuli***

Neutral pictures typically portrayed household objects including tables, chairs, and textiles; negative pictures included pictures of snakes, spiders, weapons, and interpersonal assault. Population means of valence and arousal ratings for these pictures, as reported in the IAPS manual, were as follows: the mean valence of negative pictures was 3.00 (SD = 0.91) and mean arousal was 6.29 (SD=0.58); the mean valence of neutral pictures was 4.96 (SD = 0.30) and mean arousal was 2.89 (SD= 0.57). Negative pictures were significantly more unpleasant ($t(94) = 14.297$, $p < 0.001$) and arousing ($t(94) = 29.030$, $p < 0.001$) than neutral pictures.

After the scan, 22 healthy participants and 20 schizophrenia participants rated the valence of each neutral and negative picture on a 7-point scale: -3 (extremely unpleasant) to extremely pleasant. Mean valence ratings for healthy participants: neutral pictures = 0.17 (SD=0.77); negative pictures = -1.80(SD=0.93). Mean valence ratings for schizophrenia participants: neutral pictures = 0.55 (SD=0.51); negative pictures = -1.77 (SD=0.61). There were no group differences in valence ratings of the neutral ($t(39) = -1.84$, $p = 0.73$) or negative pictures ($t(39)=-0.16$, $p=0.88$) indicating that schizophrenia and healthy participants experienced the affective stimuli as equally unpleasant.

*fMRI Image Acquisition*

Functional images were acquired with a 32 channel whole-head coil using a gradient echo $T_2$*-weighted echo planar sequence with parallel imaging (acceleration factor of 2; repetition time (TR), 2560ms; echo time (TE), 30ms; flip angle, 85 degrees). Each volume consisted of 47 contiguous slices acquired in the axial plane sequentially, in descending order (thickness, 3mm; gap, 0; field of view (FOV), 216mm x 216mm; matrix size, 72 x 72; voxel size, 3mm x 3mm x 3mm). Following functional image acquisition, a high resolution anatomical image was acquired for each subject using a 3-dimensional T1-weighted multi-echo magnetization-prepared rapid acquisition of gradient-echo (MEMPRAGE) sequence with parallel imaging (176 contiguous 1mm anterior commissure - posterior commissure slices; acceleration factor of 2; voxel size, 1 mm x 1 mm x 1 mm;

flip angle, 7 degrees; TR, 2530 ms; TE, 7.22 ms; FOV, 256 mm x 256mm; matrix size, 256 x 256). Head movement was minimized using foam padding in the head coil and subjects wore earplugs to muffle scanner noise.

*fMRI Image Processing*

Images were acquired on a Siemens 3T Tim Trio scanner (Siemens Sonata, Erlangen, Germany) and analyzed using SPM8 within the general linear model (GLM) framework. (Wellcome Department of Cognitive Neurology, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Image preprocessing included realignment to the first volume acquired, coregistration of anatomical and functional scans and transformation to standardized stereotaxic space (Montreal Neurological Institute template). Images were then smoothed with an 8mm full-width-half-maximum Gaussian kernel. All images were visually inspected for quality assurance by experienced neuroimaging analysts (LMT & CIH). Subjects with artifacts or abnormally low signal-to-noise ratio were excluded (1 HC; 1 SZ). When necessary, manual coregistration was conducted and preprocessing re-run. Artifact detection and movement correction was conducted using the Artifact detection tools software package (ART; Whitfield-Gabrieli, 2009). Regressors were created to exclude volumes with gross motion (>3mm relative to previous time frame) or spiking artifacts (global mean image intensity greater than 3SD from the mean of the entire time series within a scan) from analysis. Descriptives per group were as follows: HC mean = 10.54; SD = 7.71; range = 0 - 28; SZ mean = 10.52; SD = 8.11; range = 1 - 30.There were no group differences in number of outliers identified ($t(45) = 0.009$, $p = 0.993$).

**References:**

Auther, A., Smith, C., & Cornblatt, B. (2006). Global Functioning: Social Scale (GF: Social). *Glen Oaks, NY: Zucker Hillside Hospital*.

Weissman, M. M., Prusoff, B. A., & Thompson, W. D. (1978). Social adjustment by self-report in a community sample and in psychiatric outpatients. *Journal of Nervous and Mental Disease, 166*(5), 317-326.

Whitfield-Gabrieli, S. (2009). Artifact Detection Tools.

**Supplement8al Tables**

**S1: MSIT-Emotion Neutral Interference effect related fMRI BOLD responses within groups.**

| Region | Brodmann Areas | Peak MNI Coordinates | | | t value | Cluster Extent (voxels/mm) |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| NeuInt vs. NeuCon - HC Group | | | | | | |
| R vermis* | NA | 3 | -67 | -35 | 7.45 | 3932/106164 |
| L cerebellum | NA | -18 | -67 | -44 | 5.76 | 36/972 |
| R precentral gyrus | 44 | 48 | 5 | 28 | 5.28 | 81/2187 |
| *R inferior frontal gyrus* † | 48 | 36 | 14 | 19 | 4.45 | |
| R supplementary motor area | 6 | 6 | 11 | 52 | 4.63 | 83/2241 |
| L anterior cingulate | 32 | -6 | 11 | 46 | 4.26 | |
| L precentral gyrus | 44 | -42 | 2 | 31 | 4.42 | 23/621 |
| L cerebellum | NA | -27 | -49 | -50 | 4.28 | 19/513 |
| *L superior frontal gyrus* | 6 | -21 | -7 | 52 | 4.24 | 46/1242 |
| *R anterior cingulate* | 24 | 12 | 11 | 31 | 4.22 | 13/351 |
| R posterior cingulate | 23 | 6 | -28 | 28 | 4.20 | 18/486 |
| L precentral gyrus | 4 | -36 | -19 | 64 | 4.12 | 15/405 |
| R inferior occipital gyrus | 19 | 39 | -88 | -8 | 4.03 | 15/405 |
| L insula | 48 | -36 | 17 | 4 | 3.89 | 15/405 |
| NeuInt vs. NeuCon - SZ Group | | | | | | |
| R insula* | 48 | 33 | 20 | 7 | 7.87 | 215/5805 |
| L superior parietal lobule | 7 | -24 | -61 | 49 | 6.27 | 1643/44361 |
| L cerebellum | NA | -21 | -49 | -32 | 6.21 | 418/11286 |
| *R superior frontal gyrus* | 6 | 24 | 2 | 70 | 6.05 | 162/4374 |
| R fusiform gyrus | 37 | 24 | -52 | -20 | 5.92 | 335/9045 |
| L inferior occipital gyrus | 18 | -30 | -88 | -11 | 5.91 | 93/2511 |
| R cerebellum | NA | 24 | -61 | -47 | 5.70 | 38/1026 |
| R postcentral gyrus | 2 | 45 | -40 | 61 | 5.04 | 143/3861 |
| R superior parietal lobule | 7 | 24 | -64 | 52 | 4.92 | 254/6858 |
| *L inferior frontal gyrus* | 44 | -54 | 8 | 28 | 4.90 | 37/999 |
| R middle temporal gyrus | 21 | 48 | -46 | -2 | 4.69 | 12/324 |
| *L middle frontal gyrus* | 46 | -39 | 41 | 34 | 4.63 | 17/459 |
| L thalamus | NA | -12 | -16 | 10 | 4.57 | 27/729 |
| *R inferior frontal gyrus* † | 6 | 51 | 5 | 34 | 4.54 | 68/1836 |
| L insula | 48 | -33 | 17 | 10 | 4.50 | 27/729 |
| *R middle frontal gyrus* | 10 | 33 | 59 | 22 | 4.29 | 21/567 |
| R lingual gyrus | 19 | 21 | -64 | 4 | 4.24 | 36/972 |

Neural activity clusters are based on one-sample t-tests (NeuInt>NeuCon) within each group with a significance threshold of p<0.001 uncorrected and cluster threshold of 10 voxels/270mm. Clusters that in our LPFC region of interest mask are italicized. Neuroanatomical labels, MNI coordinates, and t-values are listed for the peak voxel of each cluster. Regions indicated with an asterisk survived whole brain correction for multiple comparisons at the peak level (FWE, $p < 0.05$). Regions indicated with superscript † survived small volume correction (FWE, $p < 0.05$) using our LPFC region of interest mask.

## S2: MSIT-Emotion negative Interference effect related fMRI BOLD responses within groups.

| Region | Brodmann Areas | Peak MNI Coordinates | | | t value | Cluster Extent (voxels/mm) |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| NegInt vs. NegCon - HC Group | | | | | | |
| L inferior parietal lobule* | 6 | -27 | -7 | 43 | 7.64 | 4673/126171 |
| R lateral orbital gyrus* | 47 | 42 | 20 | -8 | 6.73 | 332/8964 |
| L superior temporal gyrus | 22 | -39 | -46 | 10 | 6.43 | 130/3510 |
| R inferior parietal lobule | 7 | 21 | -46 | 46 | 6.22 | 304/8208 |
| L inferior temporal gyrus | 37 | -42 | -34 | -14 | 5.81 | 10/270 |
| R cerebellum | NA | 6 | -61 | -35 | 5.78 | 27/729 |
| L calcerine fissure | 19 | -21 | -70 | 7 | 4.70 | 95/2565 |
| L cerebellum | NA | -15 | -70 | -38 | 4.60 | 46/1242 |
| *R middle frontal gyrus* | 6 | 33 | -1 | 55 | 4.53 | 59/1593 |
| R calcerine fissure | 17 | 21 | -64 | 7 | 4.21 | 37/999 |
| R thalamus | NA | 12 | -10 | 13 | 4.06 | 14/378 |
| R precentral gyrus | 4 | 12 | -25 | 73 | 3.93 | 16/432 |
| NegInt vs. NegCon - SZ Group | | | | | | |
| *L inferior frontal gyrus* † | 9 | -57 | 5 | 31 | 5.56 | 84/2268 |
| R superior temporal gyrus | 48 | 69 | -34 | 22 | 5.04 | 10/270 |
| *L middle frontal gyrus* | 6 | -21 | -7 | 49 | 4.71 | |
| L inferior parietal lobule | 40 | -39 | -43 | 64 | 4.50 | 63/1701 |
| L precentral gyrus | 6 | -33 | -16 | 64 | 4.09 | 44/1188 |

Neural activity clusters are based on one-sample t-tests (NegInt>NegCon) within each group with a significance threshold of p<0.001 uncorrected and cluster threshold of 10 voxels/270mm. Clusters that in our LPFC region of interest mask are italicized. Neuroanatomical labels, MNI coordinates, and t-values are listed for the peak voxel of each cluster. Regions indicated with an asterisk survived whole brain correction for multiple comparisons at the peak level (FWE, p < 0.05). Region Regions indicated with superscript † survived small volume correction (FWE, p<0.05) using our LPFC region of interest mask.

## S3: Regions of Neural Activation During Cognitive Control of Negative Emotional Information in the MSIT-Emotion

| Region | Brodmann Area | Peak MNI Coordinates | | | t value | Cluster Extent (voxels/mm) |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| Group (HC > SZ) x condition (NegInt vs. NegCon > NeuInt vs. NeuCon) interactions | | | | | | |
| *R superior frontal gyrus (DLPFC)* † | 9 | 27 | 53 | 40 | 4.25 | 50/1350 |
| L dorsal Anterior Cingulate | 32 | -15 | 14 | 34 | 3.58 | 14/378 |
| R lateral orbital gyrus/LOFC | 11 | 48 | 26 | -17 | 3.83 | 77/2079 |
| Group (SZ > HC) x condition (NegInt vs. NegCon > NeuInt vs. NeuCon) interactions | | | | | | |
| No suprathreshold activity | | | | | | |

BOLD fMRI results from 2x2x2 Full Factorial ANOVA implemented in SPM8. Neural activity clusters are areas where NegInt-NegCon>NeuInt-NeuCon at $p < 0.001$ uncorrected with a cluster threshold of 10 voxels/270mm. Neuroanatomical labels, MNI coordinates, and t-values are provided for the peak voxel of each cluster.
†Only the cluster in the right superior frontal gyrus survived small volume correction (SVC) (FWE, $p < 0.05$) within our LPFC region of interest mask.