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ABSTRACT

The disorder of schizophrenia is defined by the presence of positive and negative clinical symptoms. One of the hallmark positive symptoms is the presence of auditory hallucinations which have previously been studied to involve bilateral temporal lobe anamolies. Our study seeks to further define and potentially quantify these anamolies in temporal lobe response by looking at the correlation of clinical symptoms with temporal lobe activation. To accomplish this task we have subjected 22 first episode and 64 chronic patients along with 104 matched healthy controls to a functional MRI scan while undergoing an auditory 'oddball' task. Analysis of this data is unique in the use of independent component analysis (ICA) via Matlab toolbox (GIFT). Results showed expected positive activation patterns for temporal lobe activity across all participants but revealed no statistically significant differences within patient populations (first episode (FE) vs. chronic) or between patients and matched healthy controls. We observed strong correlation coefficients for both patient groups as positive symptoms were negatively correlated to temporal lobe response (FE rho = -0.31, chronic rho = -0.20). Negative symptoms were positively correlated but only statistically significant for first episode patients (rho = +0.23). This data is consistent with other studies involving EEG recordings of P300 amplitude response. Finally, in analyzing frontoparietal (FP) lobe activation we showed statistically signficant activation differences between patients and controls. This result could potentially be used as a future diagnostic test. In addition, we uncovered another point of asymmetry in first episode patients whose right FP lobe showed a nearly two-fold correlation coefficient value versus the left FP lobe for negative symptoms. This unique asymmetry could offer a new area of focus for future researchers into the pathophysiology of schizophrenia.

INTRODUCTION

Schizophrenia is a psychotic disorder characterized by abnormal behaviors, incongruent thought processes and disrupted thought content (Liddle, 1987) which cross-culturally affects 1% of the population worldwide. Currently schizophrenia is a clinical diagnosis based upon the presence of positive and negative symptoms. As stated in the DSM-IV, positive symptoms include delusions, hallucinations (most commonly auditory), disorganized speech, and grossly disorganized or catatonic behavior. Negative symptoms include the presence of a flat affect, alogia, and avolition. The pathophysiology of this disease which create these psychological abnormalities remains an active area of research.

Since auditory hallucinations are a hallmark of the disorder, extensive research has been conducted on the auditory neural pathyways and its potential dysfunctional nature in patients. Although studies have uncovered structural analomies in temporal lobe shape and volume (Engelian) in schizophrenic patients, functional testing has provided more definitive differentiation amoung schizophrenia patients and healthy controls. Calhoun showed successful discrimination between healthy controls and schizophrenia patients based on auditory cortex testing and bilateral temporal lobe response (Calhoun, Kiehl 2004) . Studies by Engelien have show that schizophrenia is characterized by disturbed auditory processing which is suggestive of left temporal lobe abnormalities (Engelien). In addition, EEG testing in which an intermittent stimuli elicits an electrical event-related potential (ERP) 300 msec after onset, commonly known as P300 or P3, has shown a consistent amplitude reduction for schizophrenia patients (Ford et al. 1992, McCarley et al 1991). The P300 response is generated by multiple brain regions (including subsets of frontal and parietal cortex) but is also a function of temporal lobe response (Halgren et al). We will seek to further define and potentially quantify these anamolies in temporal lobe response by perfoming functional magnetic resonance imaging (fMRI) on patients and healthy controls while undergoing an auditory ‘oddball’ task.

By utilizing fMRI scans we can identify the neural networks across the whole brain as it engages in auditory processing. We used the auditory 'oddball' task both as a way to have more control over participant's behavior beyond just "resting" and also to stimulate the brain with a task that both patients and controls can perform accurately and which is known to elicit robust brain function differences between the two groups (Kiehl and Liddle, 2001, Kiehl et al 2005b, Salisbury, et. al 1998). Furthermore, our intent is to use independent component analysis (ICA) as a means of separating the complex mixed signals arising from the auditory 'oddball' task into individual components with both a spatial brainmap and its timecourse. The application of ICA analysis to fMRI data provides a means of measurement of both connectivity and task-relatedness. This allows for the identification of brain networks involving multiple brain regions as well as the ability to test for which of these networks are affected by schizophrenia (Calhoun, et al 2001a). By doing so, we can analyze the differences between patients and controls as well as between first episode and chronic schizophrenics. Finally, we seek to analyze the correlation of clinical symptoms (both positive and negative) on the temporal lobe response. Although there are studies looking at the relationship of clinical symptoms versus P300 amplitude response the correlation between symptoms and fMRI activation is a new area of research. Based on work by Debruille, et. al. which found a strong negative correlation between positive symptoms and P300 amplitude we should expect to uncover similar results. In addition, we hypothesize that a stronger correlation exists between clinical symptoms and chronic schizophrenia patients versus first episodes.

Below, we describe our study protocol and provide details on the data processing techniques used as well as the results and conclusions of our findings.

METHODS

Participants

A subset of study data from a total of 86 patients with schizophrenia and 104 matched healthy controls were taken from the larger the Mental Illness and Neuroscience Discovery

(MIND) Clinical Imaging Consortium (MCIC) research project. The MCIC's group members include the University of New Mexico in Albuquerque, University of Iowa in Iowa City, Massachusetts General Hospital in Boston, and the University of Minnesota in Minneapolis. All subjects were required to be at least age 18 and no older than 60, and to be fluent in English. The MCIC research protocol provided written informed consent for all study participants and outlined the criteria for classifying volunteers as either first episode (FE) or chronic schizophrenia patients or as matched healthy controls. Diagnoses were based on the American Psychiatric Association DSM IV during an initial interview. First episode patients included those diagnosed with either schizophrenia, schizophreniform disorder, or schizoaffective disorder. Chronic patients all carried a diagnosis of schizophrenia. A table outlining the entire critieria for both first episode and chronic schizophrenia patients is included in the Appendix. For FE subjects, an emphasis was placed on finding newly diagnosed schizophrenia patients who were neuroleptic naïve and fMRI measurements could be obtained prior to long term administration of any medication. Scoring of clinical symptoms (positive and negative) for schizophrenia patientswere based on the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1984). Below is a breakdown of demographic data of participants:

Table of Demographics

	First Episode Controls	First Episode Patients	Chronic Schiz Controls	Chronic Schiz Patients
Average Age / Std. Dev.	25.8 yrs / 6.7 SD	26.4 yrs / 7.7 SD	35.0 yrs / 12.0 SD	36.3 yrs / 11.1 SD
Gender	29 M / 23 F	25 M / 7 F	58 M / 35 F	68 M / 22F
Handedness	Right: 48 Left: 2 Ambi: 1 No Response: 1	Right: 27 Left: 2 Ambi: 2 No Response: 1	Right: 85 Left: 5 Ambi: 3 No Response: 0	Right: 78 Left: 2 Ambi: 6 No Response: 4
Parental SES	2.62	2.56	2.63	2.71
SAPS Average / Std. Dev.	N/A	5.5 / 2.2 SD	N/A	4.3 / 2.9 SD
SANS Average / Std. Dev.	N/A	8.5 / 3.9 SD	N/A	7.3 / 3.6 SD

Auditory 'Oddball' Task

For the auditory 'oddball' task participants wore sound-insulated earphones (Avotec, Stuart, FL) that presented the auditory stimuli while also shielding them from gradient amplifier noise. Subjects were expected to respond and press a button with their right index finger every time they heard a target stimulus and not to respond to a series of standard and novel sounds. The same auditory stimuli were used and found to be effective in differentiating healthy controls from schizophrenia subjects (Kiehl and Liddle, 2001; Kiehl et al., 2005). Standard stimuli occurred with a probability of p = 0.82 and were represented with 1 kHz tones. Target and novel stimuli were infrequent and each occurred with a probability of p = 0.09 (Fig. 1). Target stimuli were represented with 1.2 kHz tones and novel stimuli were computer generated complex sounds. Each stimulus was presented with a pseudorandom order and last for 200 ms. The interstimulus interval changed randomly in the interval 550-2050 ms and the mean was 1200 ms. A total of four runs were acquired per session and each run was comprised of 90 stimuli. The sequences for target and novel stimuli were exchanged between runs to balance their presentation and to ensure that the activity evoked by the stimuli were not because of the type of the stimulus used.

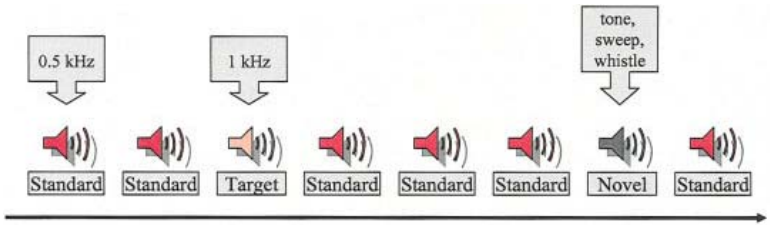

Figure 1.
Auditory oddball paradigm. Auditory oddball event-related fMRI task.

fMRI Imaging Parameters

FMRI data acquired through either 1.5T or 3T MRI scanners. The University of New Mexico used at 1.5T scanner, Massachusetts General Hospital, the University of Iowa and the University of Minnesota used 3.0T scanners. Parameters for these functional scans are as indicated below:

Pulse sequence = PACE-enabled (on Siemens scanners), Single shot, single echo EPI
Scan plane = oblique axial, AC-PC, copy T2 in-plane prescription

FOV = 22 cm
27 slices, slice thickness = 4mm, 1 mm skip
TR = 2000 ms
TE = 30ms (3T); 40ms (1.5T - 39ms is ok)

FA = 90 degrees
BW = ±100 kHz =3126 Hz/Px
64.64 matrix, 1 shot

Data Analysis

Data was preprocessed using the software package SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Images were motion-corrected using INRIalign – a motion correction algorithm unbiased by local signal changes (Freire and Mangin 2001; Freire, et al. 2002). Data were spatially normalized into the standard Montreal Neurological Institute space (Friston, 1995) and slightly sub-sampled to 3x3x3 mm, resulting in 53x63x46 voxels. Next the data was spatially smoothed with a 10x10x10 mm full width at half-maximum Gaussian kernel. The resulting coordinates were converted to the Talairach and Tournoux standard space for anatomical mapping (Talairach and Tournoux 1988).

Independent Component Analysis

After the preprocessing was completed, a group ICA was performed on the data (Calhoun, et. al 2001). A Matlab toolbox known as GIFT, (http://icatb.sourceforge.net version 1.3c), was used to accomplish this task. ICA is a data-driven multivariate analysis method that identifies distinct groups of brain regions with the same temporal pattern of hemodynamic signal change. FMRI time series data for all participants were first compressed through principal component analysis (PCA). There were 3 data reduction stages in our PCA, in which data were temporally concatenated for further dimension reduction at each stage. This is a method that has been shown to be a practical approach to group ICA and was done in order to make the estimation computationally tractable (Calhoun, et al. 2001, Schmithorst and Holland 2004). The final dimensionality of the data was estimated to be 20 maximally independent components using the modified minimal description length (MDL) criteria tool built into GIFT (Li, et al. 2007). The data reduction was followed by a group spatial ICA, performed on the participants' aggregate data, resulting in the final estimation of our independent components. The algorithm used in this

process was the Infomax algorithm, which attempts to minimize the mutual information of network outputs (Bell and Sejnowski, 1995).

Statistical Analysis of ICA Results

From the group spatial ICA, we reconstructed spatial maps and their corresponding ICA time courses that represented both the spatial and temporal characteristics of each component, subject, and session. These characteristics are able to depict component and subject group variability existent in the data. In all, this resulted in 7,600 independent component spatial maps (190 subjects x 2 sessions x 20 independent components), each with an associated ICA time course. These maps and time courses were then subjected to a second level analysis to determine whether the resultant components were task-related or simply noise or artifacts.

We then performed statistical analysis of the spatial components. We averaged the spatial maps produced during the ICA across the 2 sessions. The spatial maps were then converted to z-score maps and then entered into a second level one-sample t-test to identify voxels which contributed significantly to a given component for the group. Next these components were analyzed statistically and compared with group-specific thresholds to observe regional neural activations and any potential trends amoung participant groups.

We also statistically analyzed the ICA time courses of each component. We performed a temporal sorting of the ICA time courses using an SPM5 design matrix containing one regressor corresponding to the auditory sensorimotor stimuli. Temporal sorting is a method by which we compare the model's time course with the ICA generated time course. Using a multiple linear regression sorting criteria, the concatenated ICA time courses were fit to the model time course. Upon completion of this step, components were then sorted according to the r-square statistic. This resulted in a set of beta-weights for each regressor associated with a particular subject and independent component. The purpose of this temporal regression was to illustrate the significance of a particular component with respect to certain characteristics of the experiment that it represented. In other words, the value of the beta weight indicated the degree to which

the component was modulated by the auditory task. Next, we calculated the event-related averages of the time courses for all the components. Each plot of the event-related average depicts the level of neural activation for that particular component over the course of the experimental period.

For each independent component in the study, we performed one and two-sample t-tests as well as averaged the beta weights across particular subject and site subgroups. The voxel-wise one and two-sample t-tests were performed on the beta values obtained for each component to detect statistically significant brain or neural network activation amoung first episode, chronic or healthy controls. Two-sample t-tests were used to compare the differences in activation or response between experimental groups as follows:

i. chronic patients vs. matched healthy controls,
ii. first episode patients vs. matched healthy controls,
iii. chronics vs. first episode
iv. all schizophrenia patients vs. all matched healthy controls.

Correlation of Task-related Activation with Clinical Symptoms

The final step in our analysis involved identifying any potential correlations between positive and negative clinical symptoms and ICA component activation. This was done by conducting Pearson correlations for each independent component across participant groups (first episode and chronic patients) versus clinical symptoms (positive and negative). These comparisons were then statistically thresholded and corrected for multiple comparisons based on the false discovery rate.

RESULTS

Results of the analysis as outlined previously we identified a large number of independent components (ICs) which exhibited statistically significant differences between patients and their matched healthy controls. These ICs included the primary motor cortex (20), the occipital or visual cortex (12 & 19) and the default mode (4 & 5). For the purposes of this study we will

focus on the results for the temporal lobes (IC# 13 and 17) and the frontoparietal lobes (IC# 7 and 9).

Temporal Lobe Results

For the temporal lobe, one-sample t-tests revealed positive direction activation for all participant groups (see figure 1 below).

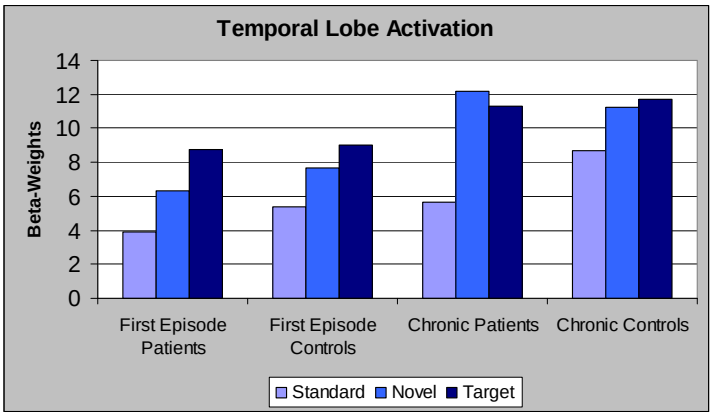

Figure 1. Temporal Lobe Activation under Auditory 'Oddball' Task

However, based on the results of two-sample t-tests there was no statistically significant difference in activation between patients (first episode or chronic) and their matched healthy controls. In addition, no difference in temporal lobe response existed within the patient populations (first episode versus chronic).

Correlation coefficients between temporal lobe response and clinical symptoms were calculated and then thresholded at a p-value of <0.05 (FDR corrected) using a nonparametric permutation approach. For the temporal lobe areas, chronic and first episode patients, showed statistically significant correlation with positive and negative symptoms:

	First Episode Patients	Chronic Patients
Positive Symptoms	rho = -0.31	rho = -.20
Negative Symptoms	rho = 0.23	n/a

Frontoparietal (FP) Lobes

For the left frontoparietal lobe, one-sample t-tests revealed positive activation for all participant groups (see figure 2 below). For the right frontoparietal lobe, activation was mixed and was shown to be significant only for target tones during the auditory task by first episode patients (target, t=2.23 df=21) and matched healthy chronic controls (target t=3.33 df=73).

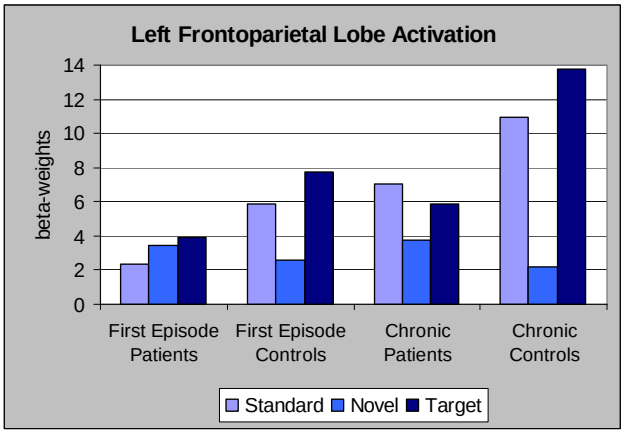

Figure 2. Frontoparietal Lobe Activation under Auditory 'Oddball' Task.

Two-sample t-tests revealed statistically significant differences in FP lobe activation between patients and controls. The table below outlines the statistically significant response differences between patient and control groups for both left and right lobes.

Two-Sample T-test			
Left Fronto-Parietal Lobe	FE Patients vs FE Controls	Chronic Patients vs Chronic Controls	All Patients vs All Controls
Novel	2.41	3.29	4.07
Target	2.83	4.60	5.42
Right Fronto-Parietal Lobe	FE Patients vs FE Controls	FE vs. Chronic Patients	
Standard	2.38	2.39	

The calculated correlation coefficients between chronic patients and right FP lobe activation only showed significance for positive symptoms (+0.19). For first episode patients, the table below highlights the correlation values across both lobes.

First Episode Patients	Frontoparietal Lobe	
	Left	Right
Positive Symptoms	-0.21	-
Negative Symptoms	0.22	0.43

DISCUSSION

Looking at the results for temporal lobe activation, our analysis is consistent with other similar studies involving fMRI data and P300 amplitude response. The lack of statistically significant differences in temporal lobe response between patients and healthy controls was previously highlighted in a study by Kiehl, et. al (2001). Debruille found the same negative relationship existed between the degree of temporal lobe activation and positive clinical symptoms. However our data did uncover a larger negative correlation amoung first episode versus chronic patients with respect to positive symptoms. The explanation for this difference would require more analysis as it may simply be a function of age difference between patient populations or it could be the effects of long term drug treatment. A study by Jones looking at quetiapine in first episode patients showed that "During auditory stimulation, the healthy control group and stably treated group produced significantly greater activation in the superior temporal gyrus than the drug naïve sample." Looking at our one sample t-test data, we would tend to support this statement. However, further work would need to be done to highlight the average dose years of our chronic schizophrenia patients to confirm this secondary finding.

Although our original focus was on the temporal lobe we offer up the results of the bilateral frontoparietal regions as this area was consistently activated in other studies (in particular P300 measurements) during auditory cortex stimulation. Our results show that patient stimulation of left frontoparietal regions was consistently and statistically larger in response as compared to matched heathly controls when exposed to both novel and target stimuli during the auditory oddball task. This differentiation between patients and controls could represent a future

diagnostic test to diagnose patients. Of course, more extensive research and study would be required to confirm this data and to begin to quantify the sensitivity and specificity of such a diagnostic test. What's intriguing about this possibility is that fact that the results also showed a statistically significant difference in the right FP lobe within the patient population (FE vs. chronic for Standard tones) which could potentially be exploited to track disease progression.

Finally, we see the same pattern in correlation coefficients for first episode patients for FP lobes as for temporal lobes; namely positive symptoms were negatively correlated as negative symptoms were positively correlated. These correlation relationships seem reasonable since increased severity of positive symptoms suggest increased psychosis which would tend to further impair attention to task performance and decrease brain activation.

Another interesting finding of our results is the asymmetry in correlation values for negative symptoms for FE patients. The data shows a nearly two-fold larger correlation coefficient for right versus left FP lobe activation. Previous studies have highlighted a consistently larger negative correlation in left temporal lobe response as measured in P300 amplitude (McCarley). This new asymmetry may suggest a new area of focus for future researchers and given that it is statistically significant only for FE patients could suggest a point of origin for the pathophysiology of schizophrenia. Clearly, this results needs more investigation.

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M. Benavidez, M. Juarez, and V. Calhoun performed the data analysis and interpretation as well as contributed to writing of this research paper. V. P. Clark, B. Ho, G. Kuperberg, T. White helped design and implement the experiment, collect the data and faciliated the imaging and behavioral data-sharing to make this analysis possible.

REFERENCES

Andreasen, NC (1982): Negative symptoms in schizophrenia: Definition and reliability. Archives of General Psychiatry 39:784-788.

Andreasen NC. 1984. The Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, IA: The University of Iowa.

Bell A.J., Sejnowski T.J., (1995): "An information-maximization approach to blind separation and blind deconvolution." Neural Comput. 7(6):1129-59.

Bruder, Gerard E., et. al. (2001): "Event-related potentials in schizophrenia during tonal and phonetic oddball tasks: Relations to diagnostic subtype, symptom features and verbal memory" Biol Psychiatry 50:447-452.

Calhoun V.D., et. al. (2001): "A method for making group inferences from functional MRI data using Independent Component Analysis." Human Brain Map. 14(3):140-151.

Calhoun V.D., Kiehl K.A., Liddle P.F., Pearlson G.D. (2004): "Aberrant Localization of Synchronous Hemodynamic Activity in Auditory Cortex Reliably Characterizes Schizophrenia." Biological Psychiatry 55:842-849.

Debruille, J. Bruno, et. al, "The correlation between positive symptoms and left temporal event-related potentials in the P300 time window is auditory specific and training sensitive." Schizophrenia Research, 78: 117-125.

Engelien, Almut Stern, E., Silbersweig, D., "Functional Neuroimaging of Human Central Auditory Processing in Normal Subjects and Patients with Neurological and Neuropsychiatric Disorders.", Journal of Clinical and Experimental Neuropsychology, Vol 23. No. 01, 94-120.

Ford, J.M., Pfefferbaum, A., Roth, W., 1992. "P3 and Schizophrenia." Ann. N.Y. Acad. Sci. 658, 146-162.

Freire L, Mangin JF, (2001): "Motion correction algorithms may create spurious brain activations in the absence of subject motion." NeuroImage 14(3):709-722.

Freire L, Roche A, Mangin JF. (2002): "What is the best similarity measure for motion correction in fMRI time series?" IEEE Trans. Med. Imaging 21(5):470-484.

Friston K., et. al. (1995): "Spatial registration and normalization of images.", Human Brain Mapping, 3(3): 165 – 189.

Halgren E, Marinkovic K, Chauvel P. (1998): "Generators of the late cognitive potentials in auditory and visual oddball tasks." Electroencephalogr Clin Neurophysiol. 106(2):156-64.

Kiehl KA, Liddle PF. (2001): "An event-related functional magnetic resonance imaging study of an auditory oddball task in schizophrenia." Schizophr.Res. 48(2-3):159-171.

Kiehl KA, Stevens MC, Celone K, Kurtz M, Krystal JH. (2005b): “Abnormal hemodynamics in schizophrenia during an auditory oddball task.” Biological Psychiatry 57(9):1029-1040.

Li, Y., Adali T., Calhoun V.D. (2007): “Estimating the number of independent components for fMRI data.” Human Brain Map. 28(11):1251-1266.

Liddle PF. (1987): “The symptoms of chronic schizophrenia. A re-examination of the positive negative dichotomy.”, Br.J.Psychiatry 151:145-151.

McCarley, R.W., et. al. “Event-related potentials in schizophrenia: their biological and clinical correlates and a new model of schizophrenic pathophysiology.” Schizophr. Res. 4, 209–231.

Renoult, Louis, et. al. “P300 asymmetry and positive symptom severity: A study in the early stage of a first episode of psychosis.” Schizophr. Res. 93 (2007): 366-373.

Salisbury DF, et. al. (1998): “First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe.” Arch. Gen. Psychiatry 55(2):173-180.

Schmithorst V.J., Holland S.K., (2004):”Comparison of three mehtods for generating group statistical inferences from independent component analysis of functional magnetic resonance imaging data.” J. Magn. Reson. Imaging 19(3):365-368.

Talairach J, Tournoux P. (1998):Co-planar stereotaxic atlas of the human brain: 3-Dimensional Proportional System – An Approach to Cerebral Imaging. New York: Thieme Medical Publishers. pp132.

APPENDIX

From the MCIC Protocol:

All Subjects must meet be the following inclusion / exclusion critieria:

All subjects will be fluent in English. If a subject agrees to participate, informed consent will be obtained following consideration of the following exclusion criteria based on current recommendations for fMRI studies:

- History of neurologic or psychiatric disease other than schizophrenia
- History of head injury resulting in prolonged loss of consciousness and/or neurological sequelae
- History of skull fracture
- History of epilepsy, except for childhood febrile seizures
- History of prior neurosurgical procedure
- Substance abuse or dependence within the past month
- Use of inhalants
- Metal in the head, metal injury to the eyes
- Implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, or ventriculo-peritoneal shunt
- Pregnancy (If the patient cannot rule out the possibility of pregnancy, a pregnancy test will be conducted prior to study)
- IQ less than or equal to 70, based on a standard IQ test or the ANART

All First Episode (FE) subjects will be between 18-60 years of age.

Additionally, all FE subjects will be defined and categorized into the following:

1. Psychotic symptoms of any duration with a lifetime exposure of 10mg or less of haloperidol equivalents.
2. Psychotic symptoms <5 years with a lifetime exposure of 10mg or less of haloperidol equivalents.
3. Psychotic symptoms of <5 years with a lifetime exposure of 12 weeks of antipsychotic exposure but none in the last 3 weeks.
4. Psychotic symptoms of <5 years with a lifetime exposure of 12 weeks of antipsychotic exposure with some in the last 3 weeks.
5. Psychotic symptoms of <2 years duration, combined with no more than 6 months of antipsychotic exposure.

Chronic Patients Definition:

The chronic patients will meet the inclusion/exclusion criteria and be 18-60 years of age and will be limited to patients with a DSM diagnosis of schizophrenia who do not fit the FE categories above.

Healthy Matched Contols:

The healthy volunteer subjects will also be recruited from the community through newspaper advertising. They will be carefully screened using a structured interview to rule out medical, neurological, and psychiatric illnesses, including substance abuse. They will be assessed at intake and followed longitudinally.

Healthy normal volunteers who have not been diagnosed with any psychiatric disorders, but who have been medicated with antidepressants, antianxiety medication and medication for sleep deprivation, can be included in the study, provided that the duration of the medication does not exceed 2 months of continuous use at any time and they have not been used at least 6 months prior to the scan.