Functional MRI of Choice Reaction Time in Chronic Schizophrenia and First-Degree Relatives

D. P. McAllindon[1,2], A. H. Wilman[1], S. E. Purdon[2,3], and P. G. Tibbo[2,3]

[1]Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada, [2]Bebensee Schizophrenia Research Unit, Edmonton, Alberta, Canada, [3]Psychiatry, University of Alberta, Edmonton, Alberta, Canada

Introduction – Schizophrenia is a psychiatric illness with diverse symptoms and course that has resisted attempts to determine a biological marker. Among the many cognitive limitations associated with schizophrenia, slow and variable reaction time may represent a specific deficit. Our group has previously investigated procedural learning in schizophrenia using a serial reaction time task [1, 2] and identified regions with lesser activation, which may indicate cerebral dysfunction, and regions with greater activation, which may indicate a compensation. Functional neuroimaging with electroencephalography (EEG) during an auditory choice RT task suggested a relative lack of activation in the anterior cingulate cortex (ACC) motor areas in a sample of patients with schizophrenia compared to a sample of healthy volunteers [3]. We used functional magnetic resonance imaging (fMRI) with a visual choice RT paradigm to better locate the lack of activation identified with EEG as well as to examine asymptomatic first-degree relatives of people with schizophrenia to investigate whether the deficit is familial.

Methods –

Subjects: The subjects were recruited from outpatient populations and the general population. All subjects were interviewed using the Structured Clinical Interview for Diagnosis (SCID) to ensure their suitability for the study and were given the Peabody Picture Vocabulary Test, 3rd ed, as an estimate of IQ since IQ has been reported as correlated with reaction time [4].

Paradigm: We used a 2-choice visual RT task with two conditions. In one condition, called choice, the subject presses the left or right button in response to a large black target circle that appears in one of two large boxes aligned horizontally. For the second condition, called watch, the subjects only watch the stimuli. The boxes' outlines change color to indicate the condition - red for the choice condition and black for the watch condition. The inclusion of a watch condition is unique and serves to remove visual area activations. The block design used 6 blocks of each condition, 32s long, separated by 24s of fixation cross. The task was presented using EPRIME v1.1 software (Psychology Software Tools, Pittsburgh, USA) and RTs are recorded.

Imaging and Analysis: Gradient echo echo planar imaging (EPI) scans were acquired at 1.5T (TR 2 s, TE 50ms) and cover the whole brain with 23 slices of thickness 4 mm and 1 mm gap between slices and 3.75x3.75mm inplane resolution. A fat inversion pulse was used to minimize artifact from fat. A structural scan was done in the same scanning session using MPRAGE with 1mm slice thickness, 144 slices, and 0.5x0.5mm inplane resolution. Data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK) and BrainVoyager QX v1.9 (Brain Innovation, Netherlands). Preprocessing consisted of realignment (motion correction), coregistration to the structural image, normalization to MNI template and spatial smoothing with a 6mm FWHM Gaussian kernel. Statistics were estimated both individually and in groups to generate statistical maps. Differences in activations between groups were determined using one-way ANOVA in SPM5, followed by 2-sample t-tests. Coordinates in tables generated from SPM5 were converted from MNI to Talairach coordinates by the MATLAB function mni2tal (M.Brett, 1999).

Results – Demographic and RT data for the groups are summarized in Table 1. The behavioural performance is comparable among the groups. There is no correlation between median RT and IQ or Age for the entire subject group. A group map for the HV group is shown in Figure 1. The group map accords well with results reported for similar protocols using EEG, PET, fMRI and event-related fMRI [3, 5, 6, 7]. Strong activations include bilateral cingulate motor areas (CMA), primary motor cortex (PMC) and cerebellum. Regression of the entire subject group SPM with median RT did not reveal any significant correlations, as had been reported in previous studies with healthy volunteers only [6, 7]. Comparison of the groups currently do not reveal any statistically significant differences ($p<0.05$, corrected for multiple comparisons) but non-significant trends are reported in Table 2. First-degree relatives have a trend to a larger activation than other groups in right and left cerebellum, left cingulate gyrus and right medial frontal gyrus.

Conclusion – We are seeing activations in CMA, PMC and cerebellum that correspond with earlier studies. Although we have limited group sizes, we already see some trends toward differences between groups. Specifically, first-degree relatives trend to greater activation than healthy volunteers or chronic schizophrenia patients in right cerebellum, left cingulate gyrus and right medial frontal gyrus. With further subjects, we hope to identify statistically significant differences in brain activations between groups and increase our understanding of the effects of schizophrenia on brain function.

References –

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Table 1 Summary of Demographics and RT of Subjects by Group

Group	N	Mean Age	Mean IQ	Median RT (ms) (Range)	Mean Errors
Healthy Volunteers (HV)	5	31 ±10.7	112 ± 7.1	300.5 (34)	0.6
First-Degree Relatives (FR)	5	38 ± 9.3	113 ± 5.3	307 (16.5)	2.6
Chronic Schizophrenia (CH)	5	39 ± 8.8	107 ± 6.7	302 (49)	2.8

Table 2 Trend Differences in Group Activations

Anatomical Region	Center of Gravity (Talairach Coordinates)	Peak F Value	Likely Group Difference
R Cerebellum (2 centers)	(24, -60, -25) (6, -50, -15)	45.41/33.01	FR > HV/CH
L Cerebellum	(-3, -60, -25)	26.48	FR > CH
L Cingulate Gyrus BA 24/23	(-3, -16, 34)	22.32	FR > HV/CH
R Medial Frontal Gyrus BA 8	(24, 31, 40)	18.36	FR > HV/CH
R MFG BA 9/10, ACG BA32	(9, 44, 14)	16.95	FR > CH

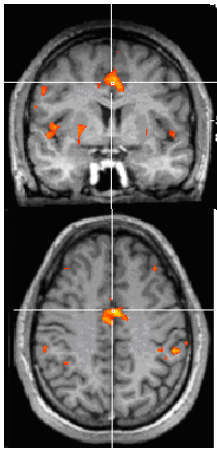

Figure 1. Group Map of Healthy Volunteers with sections along the mid-line. t-value is shown by color with yellow higher than orange. Areas of strong activation in CMA extending to SMA, and cerebellum are apparent, as are weaker activations. (R is L in diagrams)