# Glutamatergic changes detected upon functional activation with a Stroop Task in healthy controls and in subjects with Schizophrenia

Reggie Taylor[1,2], Betsy Schaefer[3], Richard Neufeld[3], Peter Williamson[1,3], and Jean Theberge[1,2]

[1]*Medical Biophysics, Western University, London, ON, Canada,* [2]*Lawson Health Research Institute, London, ON, Canada,* [3]*Psychiatry, Western University, London, ON, Canada*

**Introduction:** Single voxel proton magnetic resonance spectroscopy ($^1$H-MRS) is a useful technique to non-invasively determine metabolic concentrations over a small, localized area in the human brain. The metabolic concentrations often infer valuable information concerning the health of the tissue within the $^1$H-MRS voxel, making it a desired tool when studying neuropsychiatric disorders. Schizophrenia (SZ) is a particularly debilitating neuropsychiatric disorder in which $^1$H-MRS studies have previously implicated a role for glutamate (Glu), the main excitatory neurotransmitter in the brain, and its precursor glutamine (Gln)[1]. Most of these studies assume a somewhat constant metabolic concentration over the duration of the acquisition, however, recent studies have demonstrated that certain metabolites, including Glu, will have significantly altered concentrations when the tissue contained within the $^1$H-MRS voxel is in a state of functional activation [2,3,4]. It makes sense that an abnormality in Glu or Glu could manifest itself via a concentration change during functional activation. It is therefore of interest to quantitatively examine the dynamic regulation of Glu in SZ upon localized functional $^1$H-MRS (fMRS) activation. The Anterior Cingulate Cortex (ACC) has previously been implicated in SZ through both $^1$H-MRS studies [1] and fMRI studies involving the Stroop Task [5], making it a prime area to observe fMRS in SZ.

**Methods:** The Stroop Task is a common assessment in neuropsychiatry which involves differentiating conflicting word and colour stimuli in congruent (i.e. "RED" written in red ink), incongruent (i.e. "BLUE" written in red ink), word only (i.e. "red" in white ink) and colour only (i.e. "XXXX" written in red ink) conditions. In all cases except the word only condition, the subject is asked to respond on a keypad with the colour of the ink within a two second interval. In the word only condition, they are asked to respond with the word. Subjects were given practice prior to entering the MRI and were required to respond correctly on at least 80% of their responses. Prior to beginning the fMRS study, fMRI datasets were acquired for 8 subjects performing the Stroop Task in order to locate the consistent site of activation within the ACC to place the fMRS voxel. Spectra were acquired individually using a STEAM [6] sequence with TE/TM/TR 10ms/32ms/3seconds. The fMRS protocol consisted of five, 4 minute blocks, alternating resting and Stroop conditions, for a total of 20 minutes, so each 4 minute block consists of 80 averages. Frequency correction, phase correction, and averaging were performed offline. Macromolecules were removed by subtracting a metabolite nulled spectrum from the full spectrum [7]. In addition, 16 averages of water unsuppressed data were acquired for QUECC correction [8] and to determine metabolite concentration. Spectra were quantified using fitMAN, a time-domain fitting algorithm previously described in the literature [9]. Acquisition is ongoing, but currently 14 healthy controls, 14 subjects with SZ within their first two years of symptom onset, and another 10 subjects with unipolar mood disorder to be used as a psychiatric control group have been scanned. All scans were performed on an Agilent/Magnex 7T head-only MRI located at the Center for Functional and Metabolic Mapping (CFMM) in London, Ontario using a 10/23 Transmit/Receive coil with B1 shimming. Paired two-tailed student t-tests were employed to test significance ($p<0.05$).

**Results and Discussion**: The Glu responses to activation in the different subject groups can be seen in Fig.1. The healthy controls and the SZ groups both increased significantly during the first block of activation relative to the resting condition (2.1% and 1.4% for the healthy controls and the SZ group, respectively), which is consistent with what has been observed in the occipital cortex with a visual stimuli[2] in healthy controls. The mood group's Glu response did not reach significance yet, but their numbers are still low. No significance was reported on the second block of activation in any of the groups, however in all groups there seems to be a decrease in Glu during the second activation. This is surprising given the significant increases observed in the first activation block. With enough practice, the Stroop task becomes easier and will induce relatively less activation in the ACC. Although it is possible this is a reason for the lack of increase in Glu during the second functional activation, it would not explain the decreases observed. It may be that not enough resting time was provided in the second resting period to fully allow Glu to recover from the initial response. Each fMRS block is an average of 4 minutes of activation, so it is possible that the Glu response in the first Stroop block increased initially then decreased, but still resulted in an average net increase. Correlating the Glu responses with symptom severity and the response time data may provide more insight into the reasons for the observed decreases in Glu in the second Stroop block. Between group comparisons of other metabolites in the first resting block showed significantly decreased Gln concentrations in SZ relative to the mood and healthy control groups, which is in agreement with previously published results in SZ[1].

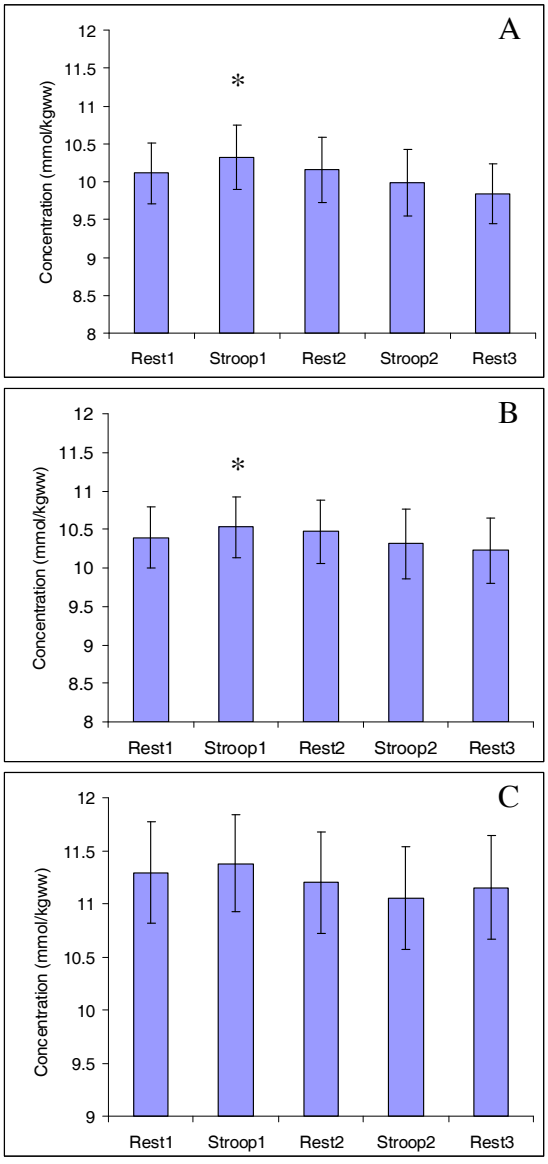


Figure 1. Glu time courses for the healthy control group (n=14) (A), the schizophrenic group (n=14) (B) and the mood group (n=10) (C). There are significant ($p<0.05$) increases in Glu between the first resting block and the first activation block in the healthy control group and the schizophrenic group, but not the mood group. Error bars represent the standard error of the mean.

**Conclusion:** Increases in Glu have been observed in the ACC upon functional activation using the Stroop Task in subjects with SZ and in healthy controls. This ongoing study is the first to report on the ability of patients with SZ to dynamically regulate their levels of ACC Glu.

**References**: [1] Theberge et al. *Am J Psychiatry 160:2231-2233* (2003). [2] Mangia et al. *J Cereb Blood Flow Metab* 27: 1055-1063 (2007). [3] Mullins et al. *NeuroImage* 26: 642-646 (2005). [4] Gussew et al. *NeuroImage 49:1895-1902 (2010).* [5] Ungar et al. *Psychiatry Res* 181:24-29 (2010) [6] I. Tkáč and R. Gruetter. *Appl Magn Reson.* 2005 March; 29(1): 139–157.*).* [7] Penner et al. *Proc. Intl. Soc. Mag. Reson. Med.* 18 (2010) [8] Bartha et al. *Magn Reson Med* 44:641-645(2000). [9] Bartha et al. *NMR Biomed* 12:205-216(1999