# COVARIATE EFFECTS IN VERBAL WORKING MEMORY FMRI USING SCHIZOPHRENIA AND CONTROL PARTICIPANTS

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## Introduction:

In task-activated fMRI, one of the inherent challenges in interpreting functional activation differences seen in quasi-experimental designs between clinical groups and healthy controls is dealing with subject characteristics and task performance variables such as reaction time (RT). These variables may contribute significantly to the variance and confound the functional differences in the resulting activation. They are usually controlled by including them as nuisance covariates in the image analyses. However, the effectiveness of the inclusion of these covariates has not been systematically studied. In the present study, we investigated influences of various covariates on a verbal working memory (VWM) fMRI employing schizophrenia people and control participants. Working memory dysfunction has been considered to be a core cognitive symptom in schizophrenia [1-2], which employs the cortico-cerebellar-thalamo-cortico-circuit (CCTCC) [3-5]. We specifically investigated the following factors that may affect fMRI results: age, gender, handedness score, education year, RT and accuracy.

## Materials and Methods:

Eighteen patients diagnosed with schizophrenia (duration of illness >=1) and 18 age- and gender-matched healthy controls (volunteered with written informed consent) were studied using a 3T MR scanner with a 32-channel phased array coil (Trio Tim, Siemens, Erlangen, Germany). In addition to the age and gender, other "covariates", i.e. RT and accuracy rate in the scanner, handedness score [6] and years of education were not significantly different between the groups. A GE-EPI sequence was employed for fMRI using the following parameters: TR/TE = 2500 ms/24 ms, flip angle = 90 deg, 43 slices, 3.5 mm thick with no gap interleaved, FOV 240 mm, matrix size 64 x 64, voxel size of 3.75 x 3.75 x 3.5 mm3, and 191 volumes per run (total 2 runs). E-Prime software (Psychology Software Tools, Inc., PA, USA) was used for the paradigm generation and the response collection. Subjects viewed an array of 6 uppercase consonant letters followed by a 5.55 s delay and a consonant letter probe in lowercase. Subjects decided if the probe was present in the array of letters presented previously by pressing a button. Sixteen 27.5 s-epochs of either high (6 letters) or low (1 letter and 5 '#' signs) load in alternation for eight cycles were employed (2 sessions of about 8 min each). SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) was used for image analyses. Conventional preprocessing using DARTEL options were performed to ensure better image transformation. First level GLM analysis was conducted on each subject to contrast the working memory load. Two kinds of random-effects analyses were performed to obtain overall group activation: with and without 6 covariates of age, handedness score, education year, RT, accuracy, and gender included in the design matrix. We computed the high>low load VWM contrast as well as the low>high load default mode network (DMN) contrast (p<0.001, uncorrected). We also performed a conjunction analysis [7] to examine common neural procedures shared between the main contrasts and the covariates; a conjunction of patient, control and one covariate was computed for each of VWM and DMN contrasts (p<0.05, uncorrected).

## Results and Discussion

With- and without-covariate analyses yielded almost identical activation maps for each of the VWM and DMN (Fig. 1). However, peak t-values were different between with- and without-covariate analyses (Fig. 2). The peak location itself was different in schizophrenia group (VWM contrast); the location with the greatest t-value was in the left inferior/middle frontal cortex in the without-covariate analysis, but that was in the right intraparietal cortex in the with-covariate analysis (Fig. 2, lower left). The difference between schizophrenia and control might reflect the difference by the effect of covariates in addition to the difference caused by the disease. The conjunction analysis demonstrated overlaps between the contrast effects and covariates in both VWM and DMN contrasts (Fig. 3). Of note were the conjunctions in the intraparietal cortex in the VWM contrast, as well as, those in the posterior cingulate cortex, medial prefrontal cortex and the lateral parietal cortex in the DMN contrast (Fig. 3). The behavioral data covariates (RT and accuracy) specifically showed positive correlations with the DMN activation (Fig. 3, right); the results might reflect the self-regulating mechanism because the DMN has a relationship with the internal "self" cognition processes.

## Conclusions

The above demonstration suggests that the behavioral covariates contributed to the variance of the contrast despite the fact that the groups were matched (i.e. no significant difference) a priori on these measures.

**References**. [1] Honey et al., 2006. Neuroscience 139, 59-71. [2] Manoach, 2003. Schizophr Res 60, 285-298. [3] Andreasen, N., 2008, Biological Psychiatry 64, 81-88. [4] Chen et al., 2005. Neuroimage 24, 332-338. [5] Desmond et al., 1997. J Neurosci 17, 9675-9685. [6] Oldfield, 1971, Neuropsychologia 9, 97-113. [7] Price et al. 1997, Neuroimage 5, 261-270.

**Fig. 1 Section maps.** Cont: contro;. Schi: schizophrenia; no-c: no covariates in the design matrix (without-covariate analysis); 6-c: 6 covariates were included in the design matrix (with-covariate analysis); Red: VWM contrast; Blue: DMN contrast. Left is left of subjects. N=18 for each group.
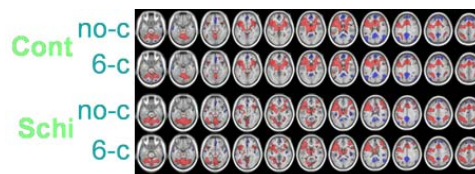


**Fig. 2 Orthogonal activation maps.** Cont: control; Schi: schizophrenia; no-c: no covariates in the design matrix (without-covariate analysis); 6-c: 6 covariates were included in the design matrix (with-covariate analysis).
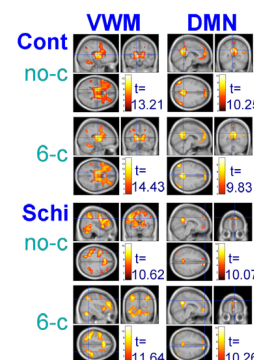
**Fig. 3 Conjunction analysis maps.** VWM: VWM contrasts of patients and controls; DMN: DMN contrasts of patients and controls; Hand: handedness score; edu: education year; Acc: accuracy; m>f: male larger female; Red: positive effect by the covariate; Blue: negative effect by the covariate. Left is left of subjects.