A NRG1 GENETIC VARIANT ASSOCIATED WITH DECREASED ACTIVATION IN VERBAL WORKING MEMORY IN PATIENTS WITH SCHIZOPHRENIA

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Introduction:

A dysfunction in working memory (WM) has been suggested to be a core cognitive impairment in schizophrenia [1-3]. NRG1 has been identified as a candidate vulnerability gene for schizophrenia [4-5] and has been associated with WM functions [6]. We examined the impact of the NRG1-P3 (rs56228203) on activation during verbal working memory (VWM) using functional magnetic resonance imaging (fMRI) in both schizophrenia patients and normal controls. We also analyzed the "failure of deactivation", which is often reported in schizophrenia; signal decrease in a "default mode network (DMN)" during task performances has been often found to be smaller in patients than in controls. We applied a Sternberg VWM task [7-9] with high- and low-load WM conditions during a block-design fMRI. We examined two types of contrasts derived from the WM loads: "high-load>low-load" and "low-load>high-load" to represent the VWM and DMN contrast, respectively.

Materials and Methods:

Forty outpatients diagnosed with schizophrenia (SZ) and 40 healthy controls (CT) who gave written informed consent were examined. The protocol was approved by the National Taiwan University Hospital institutional review board in adherence to the Declaration of Helsinki. Four groups were classified (20 participants each, female/male=10/10): SZ Risk, SZ No Risk, CT Risk and CT No Risk. Risk indicates subjects carried the NRG1-P3 risk allele (TC/CC), whereas No Risk indicates subjects with no risk (TT). A 2-by-2 analysis of variance (ANOVA) for the four groups indicated no significant differences in age, reaction time (RT) and accuracy during the VWM performance in the scanner. A Welch t-test for Risk vs. No Risk for each of SZ and CT demonstrated no significant differences in age, handedness scores, years of education, RT and accuracy. No significant differences were indicated between the Risk and No Risk in the SZ for age onset, duration of illness and chlorpromazine equivalent dose [10]. All scanning was performed using a 3T MR scanner with a 32-channel phased array coil (Trio Tim, Siemens, Erlangen, Germany). A GRE-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 (about 8 min). Two runs were administered to each subject. Subjects were presented with 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. SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) was used for image analyses. First level statistics was conducted on each subject to obtain two kinds of contrast images: high>low and low>high loads. A random-effects statistics using a 2-by-2 ANOVA was applied to compare overall group activation ($p<0.005$, extent threshold of k=20; [11]).

Results and Discussion:

All four groups demonstrated typical VWM and DMN maps for within group analyses. A comparison analysis between the SZ and CT replicated our previous findings [12]: a decrease in the VWM network specifically in the thalamus and cerebellum vermis in the SZ (Fig. 1A, yellow rectangle; Fig. 2A) and smaller differences in DMN in the SZ, which is often remarked as "failure of deactivation". In contrast, the comparison of "Risk vs. No Risk" demonstrated surprisingly different maps; specifically, the DMN was increased in the Risk groups, the opposite of the "SZ > CT" results (Figs. 1B&2B). When we divided the SZ and CT, the SZ Risk revealed a marked decrease in the VWM as compared with SZ No Risk, specifically in the thalamus, cerebellum and around the hippocampus, in addition to the increase in the DMN. The CT Risk group demonstrated only an increase in the DMN as compared with the CT No Risk group (Figs. 1C&2C). Moreover, when we compared the SZ and CT by separating the Risk and No Risk groups, we confirmed a marked decrease in VWM for SZ only in the risk carriers (Figs. 1D&2D). To summarize, only the SZ Risk group had decreased activation in the VWM (thalamus and cerebellum), and both SZ Risk and CT Risk groups showed increased activation in the DMN.

Conclusions:

To our knowledge, the current study is the first to show a clear interaction of NRG1-P3 (rs56228203) expressed as an imaging endophenotype in WM between SZ and CT. Schizophrenia patients who are risk carriers of NRG1-P3 showed markedly decreased activation in the thalamus and cerebellum, which are crucial in working memory [13-14].

References:

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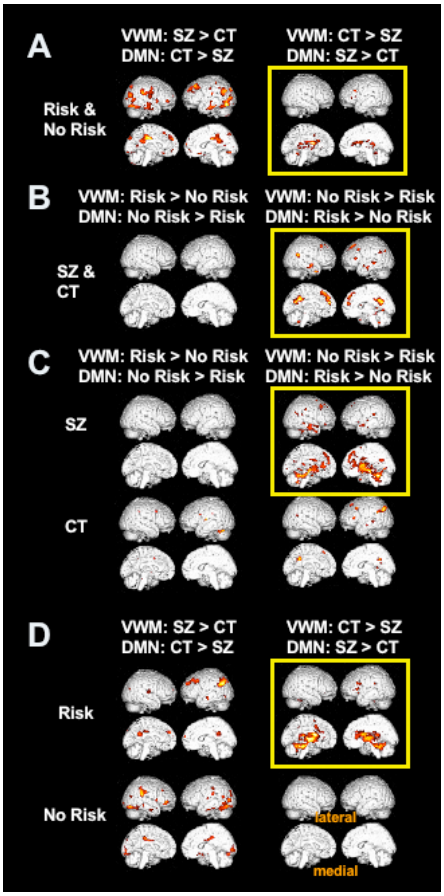

Fig. 1. 3D rendered maps from ANOVA. N=80 (in total). P<0.005 with extent threshold of k=20. Yellow rectangles indicate contrasts shown in Fig. 2.

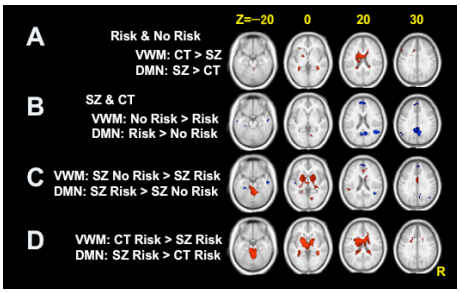

Fig. 2. Axial section views. N=80 (in total). P<0.005, extent threshold of k=20. Red color indicates regions inclusively masked with results from the VWM contrast (high>low) of all subjects (p<0.001, uncorrected), whereas blue color indicates those with the DMN contrast (low>high). Z coordinates are of the MNI. R: right.