ACTIVATION AND DEACTIVATION IN THE CEREBELLUM IN SCHIZOPHRENIA STUDIED USING VERBAL WORKING MEMORY FMRI

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Introduction:

The cerebellum plays an important role for symptoms in the schizophrenia disease [1]. However, detailed functional roles in various cerebellum regions have not been fully understood. We applied a Sternberg verbal working memory (VWM) fMRI to compare patients with schizophrenia and healthy controls specifically focusing on the cerebellum [2-3]. Working memory dysfunction has been considered to be a core cognitive symptom in schizophrenia [4-5]. We designed high and low working memory load conditions to investigate two contrasts: high load > low load contrast for the VWM activation, and low load > high load contrast for the default mode network (DMN) "deactivation". Specifically, schizophrenia subjects showed a "failure of deactivation in the DMN" [6], which may indicate a less distinctiveness between an attention to the outside world and that to the internally directed cognition [7].

Materials and Methods:

Eighteen patients diagnosed with schizophrenia and 18 age- and gender-matched healthy controls (volunteered with written informed consent, Table 1) were studied using a 3T MR scanner with a 32-channel phased array coil (Trio Tim, Siemens, Erlangen, Germany). 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. 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. The differences in upper and lower case were to decrease visual recognition and maximize phonological storage retrieval. 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 minutes 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 statistics was conducted on each subject to obtain two kinds of contrast images: high>low loads and low>high loads. A random-effects statistics was applied to obtain overall group activation with covariates of age, gender, response time and accuracy rate in the scanner, handedness score [8] and years of education to minimize the confounding effects. According to the group results, we created binary masks for each of left and right sides of the following 4 cerebellum regions: Cerebellum VI, Crus I and Vermis for the VWM contrast, and Crus II for the DMN contrast. The former 3 masks were generated from the intersections of the Automated Anatomy Template masks [9] and the "global" contrast of controls and patients (i.e., activation shown by either or both of the subject groups computed using the conjunction analysis function in SPM8). The Crus II mask was created from the "global" activation, partly showing an overlap with the Crus I anatomy. Using these binary masks, we performed an ROI analysis computing number of voxels (VN) with positive t-values (t > 0), summation of the positive t-values (sumT), and the average (aveT, i.e. sumT/VN) for the corresponding contrasts (i.e., VWM or DMN). Two-sample t-tests were applied to compare these ROI parameters between patients and controls.
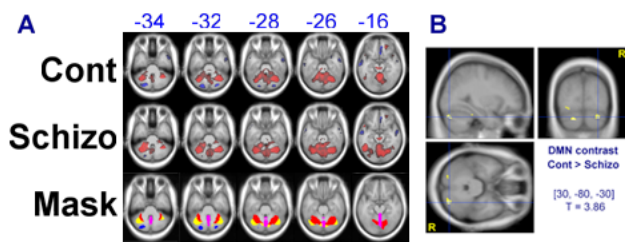

Fig. 1 Activation maps in the cerebellum. A: Slice views from each subject group. N=18 each, p<0.001, uncorrected. Cont: control. Schizo: schizophrenia. Mask: ROI masks. Numbers on the top indicate z coordinates of the MNI. For activation in Cont and Schizo, red indicates High>Low VWM contrast, and blue indicates Low>High DMN contrast. For masks, red is for CerebellumVI, yellow for Crus I, magenta is for Vermis, and blue for Crus II. B: Orthogonal view of activation differences in the cerebellum for the DMN contrast (control>schizophrenia, p<0.005, uncorrected). The hairline cross indicates a local maximum, which coordinates and peak t-value are shown in the right lower side.

Results and Discussion:

The VWM contrast yielded a wide range of the cerebellum (Fig. 1A), which was consistent with the cortico-cerebellar-thalamo-cortico-circuit (CCTCC) model of the working memory [3-4]. The activation overlapped with the Cerebellum VI, Crus I and Vermis [10]. In contrast, the DMN contrast yielded activation in the Crus II of the cerebellum. The group analysis showed the difference between control and schizophrenia for the cerebellum only in the DMN contrast (Fig. 1B). The ROI analysis indicated significantly larger VN in the Cerebellum VI in schizophrenia at the VWM contrast (Fig. 2); however, the sumT and aveT did not yield significant differences. The results suggested that even though the activation was wider in the schizophrenia, the intensity was not extensive. In contrast, the ROI analysis for the Crus II at the DMN contrast yielded significant differences in the VN, sumT and aveT, indicating extensive "deactivation" in the control group (Fig. 2). The results suggested a "failure in deactivation" in schizophrenia, which is frequently demonstrated in the DMN [6]. The Crus II structure might be involved in the DMN, which typically consists of the posterior cingulate cortex, medial prefrontal cortex and a lateral parietal portion around angular gyrus [7]. The less "deactivation" in the DMN contrast in schizophrenia may indicate an alteration in the internally directed cognition [7], which would affect stimuli-oriented cognitive functions such as VWM.

Conclusions:

The study demonstrated functional segregations in the cerebellum structures in the verbal working memory and the default mode network; the former involved the Cerebellum VI, Crus I and Vermis, and the latter involved the Crus II. Less "deactivation" in the Crus II observed in the schizophrenia group in contrast with an extensive "deactivation" in the control group might be an indicator of the disease.

References:

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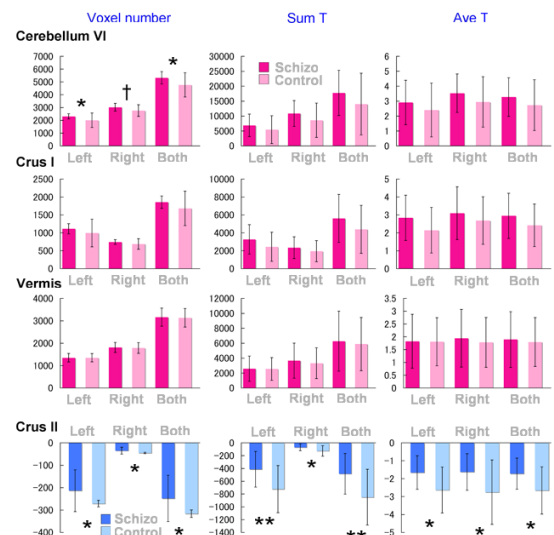
Fig. 2 ROI analysis for the cerebellum. Schizo, schizophrenia. Voxel number, number of voxels with positive t-values in the ROI. Sum T, summation of t-values within the ROI. Ave T, averaged t-value in the ROI. Error bars indicate the standard deviation. **, p<0.01. *, p<0.05. †, p<0.10.