FUNCTIONAL CHANGES IN THE CEREBRO-CEREBELLAR VERBAL WORKING MEMORY NETWORK IN SCHIZOPHRENIA

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Introduction:

Working memory dysfunction has been considered to be a core cognitive symptom in schizophrenia [1-2]. More recently, a cortico-cerebellar-thalamo-cortico-circuit (CCTCC) has been proposed to be disrupted in schizophrenia [3] and schizophrenia has been described as a disconnection syndrome [4]. To further investigate this, we applied a Sternberg Verbal Working Memory (VWM) Task to compare patients with schizophrenia and healthy controls using functional magnetic resonance imaging (fMRI). This VWM task has been shown to robustly activate the cerebro-cerebellar circuitry involved in verbal working memory [5]. We identified nine regions of interest (ROIs) based on an established cerebro-cerebellar model of verbal working memory [5-6], as well as, according to the activation peaks in the healthy controls. We computed the numbers of activated voxels with positive t-values within each ROI, computed the summations of t-values for those voxels to represent the magnitude of activation within the ROI and calculated the laterality indices for the ROIs. We hypothesized that patients with schizophrenia would show decreased activity and t-values in this network, as well as, differences in laterality indices from healthy controls.

Materials and Methods:

Seventeen patients diagnosed with schizophrenia and 17 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 mm^3, 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 GLM analysis was conducted on each subject to contrast high vs. low working memory load. A random-effects analysis was applied to obtain overall group activation. ROIs were identified based on the cerebro-cerebellar VWM model [6] for both hemispheres using the WFU PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas) as follows: (1) pars triangularis and pars opercularis of the inferior frontal gyrus (IFG), (2) inferior parietal lobule including the intraparietal cortex (IPL), (3) insula, (4) supplementary motor area (SMA), (5) pons, (6) thalamus, (7) dentate nucleus (dilated), (8) cerebellum lobule VI (Cbl6) and (9) cerebellum lobule VIII (Cbl8). All these areas contained activation peaks in either or both hemispheres of the control subjects ($p<0.001$, uncorrected, FDR<0.05 at cluster-level). Within each ROI, number of voxels with positive t-values ($t > 0$) was computed, and their t-values were aggregated. A laterality index (LI) was obtained by the following formula: $LI = \sum[tn\{(L-R)/(L+R)\}]/VN$, where L=left, R=right, tn=summation of positive t-values of voxels surviving at a given t-value threshold, VN=number of voxels with positive t-values in the pair of ROIs [7]. This laterality index technique does not rely on conventional thresholding methods and represents how lateralized the subject's performance is at every t-value threshold (index of '1' represents activation is left lateralized at all t-value thresholds with no activation in the right, and '-1' represents right lateralization with no activation on the left). Two-sample t-tests were applied to compare the ROI activations, summation of t-values and laterality indices between patients and controls.

Table 1 Summary of participants

	Gender	Handedness	Age	Education (year)	RT (ms)	accuracy (%)
Patients	total 17	96.35	25.12	13.87	943.54	89.61
	F/M: 9/8	*6.20*	*6.60*	*2.10*	*141.28*	*6.85*
Controls	total 17	94.51	25.06	15.53	853.05	93.29
	F/M: 9/8	*15.22*	*6.58*	*1.81*	*123.45*	*4.55*

Notes. F/M=female/male. Edinburgh handedness score was used. Age showed no significant differences between the two groups, whereas years of education were less in patients ($p<0.05$). Italic indicates standard deviation.

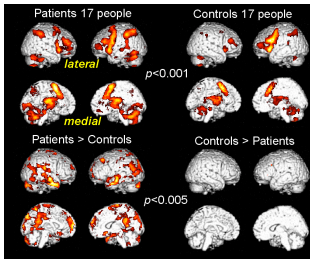

Fig. 1 Rendered activation maps from random-effects group analyses. The schizophrenia patients' maps (upper left) apparently show extensive activation specifically in the right hemisphere. The comparison shows augmented activation in patients (lower left), although the areas shown do not overlap much with activated regions in high vs. low contrast.

Results and Discussion

The random-effects group comparison showed overall increased activation in the patients (Fig. 1, lower left). The activated areas, however, did not overlap much with the contrast of high vs. low load (Fig. 1, upper), and appeared to be more consistent with the default mode network [8]. Increased activation was observed specifically in bilateral hemispheres of patients as compared with the controls where activations were predominantly left lateralized (Fig. 1, upper). Number of voxels with positive t-values was significantly greater in the SMA, IPL, insula and IFG for patients than for controls (Table 2). These findings were contrary to our hypothesis of decreased activity within the VWM network in patients, however, consistent with our prediction of differing laterality. Previous studies also reported not only hypo activation but also hyper activation in schizophrenia compared to healthy controls such as in the prefrontal cortex [2] as well as in the medial temporal lobe [9]. The summations of the positive t-values derived from the high vs. low load comparison were not significantly different between the two groups except for the left SMA. That is, although the extent of activation within the respective ROIs were significantly greater in the patients, the t-values were not higher, possibly suggesting a compensation system for cortical inefficiency. Differences in the laterality index demonstrated shifts to a bilateral activation pattern in patients (Table 2). There are controversies for the existence of the reduction of the left asymmetry in the brain anatomy of schizophrenia [10]. Our data demonstrated a possibility of a degenerative change in the asymmetry in VWM function that might represent a compensatory involvement of the opposite hemisphere that is normally not recruited during VWM, and a disruption in the cerebro-cerebellar circuitry.

Table 2 Two-sample t-tests for voxels in ROIs

	IFG	IPL	Insula	SMA	Pons	Thalamus	Dentate	Cbl6	Cbl8
left voxel N	-	P > C *	P > C †	P > C **	-	-	-	-	-
right voxel N	P > C †	P > C **	-	P > C **	-	-	-	-	-
left sum of T	-	-	-	P > C †	-	-	-	-	-
right sum of T	-	-	-		-	-	-	-	-
LI	C(+) > P(+) †	-	P(-) > C(-) †	P(-) > C(-) †	P(+) > C(-) *	C(+) > P(+) *	-	C(+) > P(+) *	C(+) > P(+) †

Notes. **: $p<0.01$, *: $p<0.05$, †: $p<0.1$. P: patients, C: controls. (+): the mean of the group was positive value, (-): negative value.

Conclusions

Hyperactivity in ROIs involved in a cerebro-cerebellar VWM circuitry and the decrease in laterality in our schizophrenia patients within the context of "normal" behavioral data, suggested a compensatory system to cope with a functionally weakened verbal working memory network.

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] Friston et al., 1995. Clin Neurosci 3, 89-97. [5] Chen et al., 2005. Neuroimage 24, 332-338. [6] Desmond et al., 1997. J Neurosci 17, 9675-9685. [7] Matsuo et al., in preparation. [8] Pomarol-Clotet et al., 2008. Psychol Med 38, 1185-1193. [9] Ragland et al., 2009. Am J Psychiatry 166, 863-874. [10] Deep-Soboslay et al., 2010. Brain 133, 3113-3122.