An investigation of intrinsic, task-interim resting state BOLD signal correlations with Broca's and Wernicke's areas in schizophrenics and in subjects at high genetic risk

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INTRODUCTION: Structural abnormalities in language areas [1,2] and linguistic processing deficits [3-8] have been reported in schizophrenia, but few studies have examined the non-task-correlated, or intrinsic, functional MRI (fMRI) BOLD signal correlation within the language areas of normative control or schizophrenic patients. Following our previously reported finding [7, 8], in this report we employed BOLD fMRI times series data, obtained at 1.5 Tesla, to extract, via spectral and correlation analysis, the resting-state connectivity of language processing areas in normal control subjects and schizophrenic subjects as well as their unaffected siblings, using "seed" vectors obtained from the subjects' mean Broca's and Wernicke's areas BOLD signals.

METHODS: BOLD fMRI data was acquired during application of a visual word/non-word discrimination task, which has been described in detail in Li et al. (Li et al., 2007), implemented on a Siemens 1.5T MRI magnet (Siemens Vision Systems, Erlangen, Germany). Control (NC, N=25), high-risk (HR, N=18), and schizophrenic (SZ, N=19) subjects completed four runs of 5 word/non-word discrimination blocks interspersed with 3 control task blocks, and 3 rest blocks each (169 T2*-weighted EPI volumes per run, TR/TE = 2000/50 msec, 64^2 matrix, FOV = 224 cm, 22 5 mm axial slices interleaved, no gap). A structural dataset (T2-weighted fast spin echo) was also acquired. Preprocessing steps consisted of (1) correction for temporal offsets, (2) time-domain lowpass filtering, and (3) rigid-body motion correction and (4) within-run registration to a fiducial volume (*AFNI* utilities). Residual data for resting state connectivity analysis was extracted using deconvolution of the task-correlated BOLD responses beginning with derivation of the baseline model, which was derived from deconvolution of mean white matter, cerebrospinal fluid, a polynomial trend, and subject motion vectors (roll, pitch, yaw, and volume translations) [9]. The residual datasets for each subject were then co-registered with the subject's structural T2 volume (in *AFNI)* and matched the Talairach-Tourneaux template. Residual signal vectors, averaged across each subject's left hemisphere (LH) Brodmann area 22 (Wernicke's area) and LH 44/45 (Broca's area) and used as seeds for voxelwise Pearson correlation analysis across the rest of the residual dataset. A 4 mm filter (FWHM) Gaussian kernel was applied to compensate for intersubject spatial variability, and the seed-based residual correlation results were subjected to t-test (*3dttest*) in Talairach space, using group (NC, HR, or SZ) as the grouping variable.

RESULTS: Schizophrenic patients' t-tests ($p \leq 0.01$) consistently exhibited stronger positive correlations with Wernicke's area (BA 22) than the NC or HR subjects in the right hemisphere (RH) superior parietal lobule (Brodmann area/BA 7), frontopolar BA 10, insular, supplementary motor, and inferotemporal cortices, and left hemisphere (LH) lingual (BA 18) and calcarine (BA 17) gyri and stronger positive correlations with Broca's area (BA 44/45) in LH BA 40, angular area 39, lingual (BA 18) and calcarine (BA 17) gyri, and the insula, as well as the RH superior parietal lobule.

In contrast, HR subjects displayed greater widespread correlations with the two language areas studied compared to the SZ patients or NC subjects. HR subjects exhibited stronger positive correlations with Wernicke's area than did SZ patients in RH motor (BA 4) and premotor (BA 6), precuneate (BA 19), and inferofrontal cortices and LH medial temporal, mid-temporal, and insular cortices and the hippocampus, and stronger positive correlations with Broca's area in cingulate areas (BA 24/31/33), and the LH superior parietal lobule. Both HR and SZ subjects tended to exhibit greater correlations with Broca's and Wernicke's areas versus NC subjects in infero- and medial frontal cortices, RH insula, and cingulate areas.

Interestingly, however, the strongest differences in Broca/Wernicke correlations were consistently observed in the cerebellar pyramids, culmen, tonsils, and inferior semilunar lobule, in both SZ versus NC ($3.405 \leq t \leq 6.348$) and HR versus NC subjects ($3.167 \leq t \leq 5.086$). These findings suggest substantial hyperconnectivity of the cerebellum and isocortical regions with respect to Broca's and Wernicke's areas in SZ patients and HR subjects.

DISCUSSION: This study demonstrates the utility of examining resting state information extracted from properly designed task-based BOLD fMRI data sets. In such data sets, resting and task-based noise is uncorrelated, providing a window into not simply the cognitive response to the task, but information relevant to the underlying brain network responsible for information processing.

Our results provided evidence for two important findings. First, high-risk subjects appear to display *more diffuse* language-area connectivity than schizophrenic or normative subjects, particularly in medial temporal, occipital, pericentral, and prefrontal regions. Conversely, the present study's patient population exhibited a degree of diffuse connectivity *between* that of the high-risk and normative subjects. These findings may indicate that the schizophrenic and HR (prodromal?) resting-state networks differ, within a single individual, only in that the latter is a more constrained version of the former. This finding would be consistent with the breakdown of the "multiple constraint organization" hypothesis of presenting schizophrenics [10] which suggests that SZ cortical networks exhibit excessive connectivity and are thus "effectively random".

Our second finding – that patients appear to effect greater cerebellocortical connectivity in the resting state, compared to high-risk and normative subjects – also supports prior studies that suggest rhombencephalic involvement in the motor coordination, sensory integration, and affective symptoms of schizophrenia [11, 12]. However, the correlation between cerebellar recruitment and symptomatology was not investigated in the present study, and further investigation is required to substantiate or refute such a link.

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