Cortical disorganization in Brodmann areas 9, 46 and 32 in schizophrenia: Evidence from Brodmann-based MRI morphometry.

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Introduction. The ratio of gray to white matter (GM/WM) is a measure of cortical organization (1) and reductions in total brain GM/WM in young schizophrenia (SCZ) patients compared to age-matched healthy controls have been observed (2). These reductions suggest a loss of global brain organization resulting from neuropathological processes associated with the illness. However, several lines of work suggest that certain regions of the brain may be particularly vulnerable in SCZ and therefore important for further exploration. Brodmann areas 9 & 46 (prefrontal cortex) and 32 (anterior cingulate) have been particularly implicated (3). These areas are associated with working memory and attentional regulation; fMRI and other studies suggest that both functions are compromised in SCZ (4,5). The assessment of structural disorganization in these areas in young SCZ patients is a question of central interest. Furthermore, Brodmann areas are defined based on the cytoarchitecture of the cortex (6) which is determined by several processes including: a) the complement of neurons and glia that originally migrate to the region, b) the ways in which those neurons differentiate and survive under the influence of intrinsic genetic programs, c) a myriad of trophic factors during development and maturation, and d) the degree to which afferent fibers and other neuronal and glial processes push cells apart. Abnormalities in these processes have been associated with SCZ, and would manifest in disturbed cytoarchitectural appearance and development. The result could be disorganized morphology of key Brodmann areas (7). Thus, assessing structural changes in *a priori* defined Brodmann regions (as opposed to sulcal or gyral based regions of interest) is an important endeavor (8), but one which presents many challenges. Unlike sulcii or gyrii, Brodmann areas cannot be observed in *in vivo* MRI images, therefore their locations must be estimated. We present an attempt to achieve this using stereotactic estimation of Brodmann areas 9, 46 and 32 using a Brodmann-Talairach atlas (9,10). These areas of interest (and a control region BA 19 in the secondary visual cortex) were estimated and volumetric information was extracted from normalized and volume-modulated MRI images of young SCZ patients and healthy controls (HC).

Methods. T_1-weighted SPGR images (124 contigual coronal slices; .9375 x .9375 x 1.5 mm; 1.5T G.E. system) were acquired for HC (n=80, mean age=18.1 yrs, 46 males) and unmedicated first-episode SCZ patients (n=55, mean age=19.5 years, 40 males; all subjects <25 yrs). MRI images were reoriented, normalized, segmented and modulated by volume using SPM2's optimized protocol (11). Areas were estimated by identifying their boundaries (on the anterior-posterior, inferior-superior and lateral-medial dimensions; see Fig 1) on successive slices in a Talairach-Brodmann atlas (9). Talairach coordinates were converted to MNI and the estimated regions were imposed on each subject's normalized and volume-modulated gray and white matter images. Regional gray and white matter volumetric information was extracted for each subject, area and hemisphere and GM/WM was computed. All scripts were executed in MATLAB (12). GM/WM data for each hemisphere were analyzed in separate analyses of covariance with group (SCZ vs. HC) and gender as factors, and age as covariate.

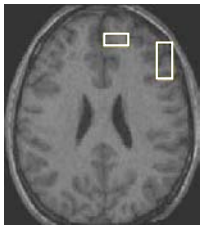

Figure 1. Definitions of BA 9 (medial aspect) and BA 46 (lateral aspect) are depicted as insets on a single slice (z=25 mm, MNI brain) of a normalized T_1-weighted image.

Results. Significant bilateral reductions in GM/WM were observed in SCZ in all the hypothesized areas of interest (BA 9, 46 and 32) except left BA 9 ($F_{1,130}$>4.14, p<.05). No significant differences were observed in the control region BA 19. The most statistically robust reductions (BA 32) are depicted in Figure 2.

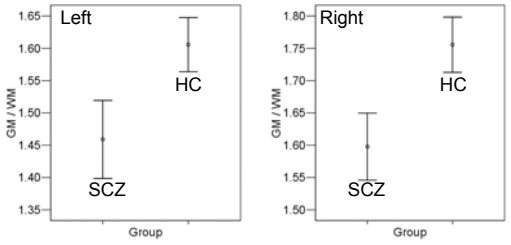

Figure 2. Bilateral reductions (p<.002) in GM/WM in SCZ compared to HC are shown for BA 32 (anterior cingulate). Error bars are 95% confidence intervals. Similar reductions were observed in BA 9 & 46 but not BA 19 (not shown).

Discussion. The specificity of these results to BA 9, 46 and 32 (in the heteromodal association cortex) but not BA 19 (unimodal cortex) suggest: a) disordered cortical organization in early schizophrenia may be particularly observed in key regions of the heteromodal association cortex and may be a structural basis for impaired performance of these areas as seen in fMRI studies, and b) tentative validation for the employed methodology of estimating cytoarchitectonic regions on an *a priori* basis in stereotactic space. Convergent histopathological and MRI analyses have noted that the spatial mapping of Brodmann areas into stereotactic space can be highly variable and that the spatial variability is complex and difficult to quantify (13). It may be possible to achieve better estimations of Brodmann areas in stereotactic space using spatial probability maps (14). Accounting for these factors, the present results must be treated as tentative, yet provide support for an approach toward assessing disordered cortical organization within a stereotactic framework that may be closer to the relevant cytoarchitecture of the cortex, than sulcal and gyral based region of interest schemes.

References. (1) S. B. Laughlin, T. J. Sejnowski, *Science* **301**, 1870 (Sep 26, 2003). (2) V. A. Diwadkar *et al*., International Society for Magnetic Resonance in Medicine, Miami, FL 2005. (3) D. Lewis, *Schizophr Bull* **23**, 529 (1997). (4) P. S. Goldman-Rakic, *Biol Psychiatry* **46**, 650 (1999). (5) K. R. Laurens, K. A. Kiehl, E. T. Ngan, P. F. Liddle, *Schizophr Res* **75**, 159 (Jun 15, 2005). (6) K. Brodmann, *Vergleichende Lokalisationslehre der Großhirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues.* (Barth, Leipzig, 1909). (7) S. E. Arnold, *Dev Psychopathol* **11**, 439 (Summer, 1999). (8) K. Amunts, K. Zilles, *Neuroimaging Clin N Am* **11**, 151 (May, 2001). (9) http://neurologie.uni-muenster.de. (10) J. Talairach, P. Tournoux, *Co-planar stereotactic atlas of the human brain.* (Thieme Medical Publishers, Inc., New York, 1988). (11) C. D. Good *et al.*, *Neuroimage* **14**, 21 (2001). (12) www.mathworks.com (13) K. Amunts *et al.*, *J Comp Neurol* **412**, 319 (Sep 20, 1999). (14) S. B. Eickhoff *et al.*, *Neuroimage* **25**, 1325 (May 1, 2005).