Reductions in the ratio of total brain gray and white matter in schizophrenia measured using MRI: Evidence for altered neurodevelopment

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Introduction. Brain organization results from a complex schedule of genetically programmed neurodevelopment and environmental interaction (1). Healthy development results in an "optimal" balance in gray and white matter designed to minimize energy consumption and maximize connective efficiency. A characteristic of neurodevelopment is programmed loss of metabolically expensive cortical gray matter (synaptic pruning) during adolescence in conjunction with an expansion of white matter, simultaneous processes that reduce the metabolic load while enhancing inter-regional connectivity (2). This global organization of the cortical neural network is reflected in measures such as the ratio of brain gray matter to white matter (GM/WM) which can be estimated using *in vivo* high-resolution MRI images. GM/WM is a metric of interest in schizophrenia which is an illness mediated by epigenetic and neurodevelopmental factors (3). Early morphometric studies have suggested that schizophrenia is marked by focal abnormalities in grey matter volumes in heteromodal structures in the brain (4). However, several lines of work suggest that the illness is characterized by widespread cortico-cortical dysconnectivity (5), suggesting a more global neurodevelopmental abnormality. GM/WM may provide such a global metric of altered brain organization. We analyzed the GM/WM in a cohort of first episode patients, healthy controls and offspring of patients, an important group in which to investigate abnormalities associated with the pre-morbid phase of the illness. The analyses was restricted to young subjects (age<=25) in order to capture abnormal neurodevelopment, as opposed to neurodegenerative processes.

Methods. T_1-weighted SPGR images (124 contigual coronal slices; .9375 x .9375 x 1.5 mm) were acquired on a 1.5T G.E. system for all subjects: healthy controls (HC; n=86, mean age=18.4 yrs, 43 males), offspring of schizophrenia patients (HR; n=45, mean age=15.0 yrs; 24 males), and unmedicated first-episode schizophrenia patients (FE; n=61, mean age=19.4 years, 42 males; all subjects aged 8-25). The T_1-weighted images were segmented using SPM2b's iterative segmentation algorithm (6). Total brain gray and white matter volume was computed from the estimated voxel-wise concentrations across each subject's gray and white matter segment. Figure 1 depicts coronal sections of a single subject's gray and white matter segments. GM/WM values were entered into an analysis of covariance with group (FE, HR and HC) as a fixed factor and age and gender as covariates.

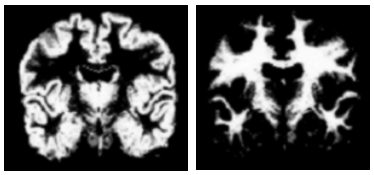

Figure 1. Mid-coronal sections of gray and white matter segments derived from segmented T_1 images.

Results. Mean GM/WM across the three groups are depicted in Figure 2. As can be seen FE showed a reduced ratio of gray to white matter in the brain, $F_{2,188}$=10.68, p<.001. The data suggest a linear decrease in GM/WM as a function of group (though contrasts were not significant). Trend analyses were conducted to explore non-linear relationships between age and GM/WM in each group separately. In HC, a decrease in GM/WM in HC in childhood and adolescence was observed, followed by a plateauing in young adulthood. HR showed a marked decrease in GM/WM with age. An articulated developmental trend was absent in FE.

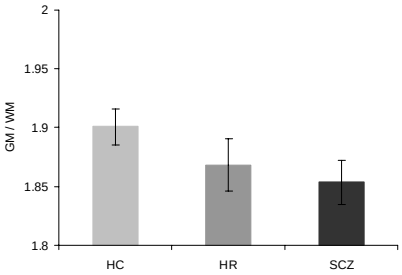

Figure 2. Reductions in the mean gray to white matter ratios from HC to SCZ are depicted. Error bars=±SEM.

Discussion. The results suggest schizophrenia is marked by a significant reduction in GM/WM, consistent with documented reductions in heteromodal gray matter in the illness and suggesting a plausible global brain deficit. These results expand upon previous findings in older, chronic male schizophrenia samples (7) by suggesting that the global deficit may be present at the earliest stages of the illness. Further, although the linear trend (HC -> SCZ) was not significant, the data suggest that the HR group may show a pattern of intermediate deficit, suggesting the possibility of emerging premorbid alterations in the brain's organization in these individuals. Increasingly MRI and fMRI evidence is demonstrating that schizophrenia is not associated with focal brain deficits, but is a disorder of the brain and its interconnections. The key to unraveling the neural basis of the illness may lie in understanding its developmental course and the crucial stages at which brain organization and function begins to diverge from a normative path.

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