Association of Neuregulin 1 with Schizophrenia and Bipolar disorder in Anterior Cingulum: Diffusion Tensor Imaging Evidence

Myelination abnormalities and genes regulating white matter (WM) development and plasticity have been implicated in the development of schizophrenia and bipolar disorder (BP). Previous histology studies have also highlighted the involvement of WM anomalies by reduced oligodendrocyte density in the prefrontal cortex and amygdala in schizophrenia and mood disorders. In addition, postmortem studies have shown the down regulation of oligodendrocyte and myelin related genes such as ERBB3, OLIG2, SOX10, PLP1, MAG, CLDN11, and MOG in the prefrontal cortex in schizophrenia and BP. Increasing evidence has also suggested a pivotal role in WM connectivity between prefrontal cortex and the anterior cingulum (AC) in schizophrenia and BP.

Given the similar WM related abnormalities in schizophrenia and BP, we hypothesized an overlapping underlying mechanism of WM connectivity of the prefrontal cortex (PFC) and AC. More specifically, we postulated the involvement of the ventral part of the PCF - AC bundle in BP and involvement of the dorsal part of the PFC-AC bundle in schizophrenia. To test our hypothesis diffusion tensor imaging (DTI) was used to examine WM integrity in different subregions of the cingulum bundle with association of genomic background. This method is based on water diffusion principles. The diffusion changes usually mean the disturbance of white matter integrity as described by fractional anisotropy (FA). FA has been associated with the of myelin, axonal, microtubular and microfilamental architecture. In the studies, we used several DTI methodologies, such as region of interest (ROI) based DTI, fiber tracking DTI and voxel based DTI to determine differences between schizophrenia, BP and healthy subjects. Our findings showed deficits in the structural integrity of AC in both schizophrenia and BP. Furthermore, we found significantly decreased FA in the dorsal AC in schizophrenia and in the ventral AC in BP compared to healthy subjects suggesting a pivotal role for WM abnormalities in these disorders. These findings are consistent with previous reports. In
addition, to support our WM hypothesis, we investigated the association between neuregulin 1 (SNP8NRG221533) variation and susceptibility to schizophrenia and BP. This gene variation has been associated with schizophrenia in the Chinese population. In our study we showed that the T carrier exhibits lower FA values particularly in the dorsal part of the AC in schizophrenic patients. The NRG1 implication in BP is still under investigation.

In summary, we found NRG1 genetic variation is associated with more pronounced abnormalities in the structural integrity of the AC in schizophrenia. Our goal is to further investigate the connection between NRG 1 and AC abnormalities and the influence of variation of genes on the structure and function of brain circuitry.