Synopsis. The dopamine hypothesis of schizophrenia holds that the positive symptoms of the illness are related to excess dopamine function. $^1$H MRSI and $^{[123]}$IIBZM SPECT were used to investigate the relationship between regional cortical deficits in neuronal functional integrity and baseline striatal dopamine hyperfunction in schizophrenia. Low NAA/Cr in several forebrain regions was found to correlate with abnormally elevated striatal dopamine activity. These findings suggest that cortical dysregulation of subcortical dopamine function may play a role in schizophrenia.

Background. Neuroreceptor imaging with SPECT and PET has recently provided in vivo evidence of excessive striatal dopamine function in schizophrenia, both under pharmacological stimulation with d-amphetamine and under resting, baseline conditions. These findings strongly support the classical dopamine hypothesis of schizophrenia. However, since abnormalities of dopaminergic projections to striatum have not been found in schizophrenia, the mechanism of this hyperactivity remains to be elucidated, and one hypothesis holds that dysregulation of the dopamine system by faulty cortical control plays a role. We sought to test this idea by measuring cortical NAA/Cr, a marker of neuronal functional integrity, and baseline striatal dopamine function within the same subjects. Prior studies of NAA/Cr in schizophrenia have generated a mixed literature, with the two largest studies in prefrontal cortex reporting no effect or a trend toward reduction in schizophrenia.

Methods. We combined proton magnetic resonance spectroscopic imaging ($^1$H MRSI) and single photon emission computed tomography (SPECT) imaging with the dopamine D$_2$ receptor radioligand $^{[123]}$IIBZM in an $\alpha$-methyl-para-tyrosine (AMPT)-induced dopamine depletion paradigm within the same study subjects. With the AMPT paradigm, baseline dopamine activity can be evaluated as the percent increase in binding potential (BP) between the baseline and post-depletion SPECT scans. Forty-three patients with schizophrenia and 38 healthy control subjects underwent MRSI studies, and 16 subjects from each group underwent the SPECT AMPT paradigm. All patients were unmedicated at the time of SPECT, while 5 of the 16 patients were unmedicated at the time of MRSI. Multislice $^1$H MRSI studies were performed on a 1.5T GE Signa MR unit, using the method of Duyn et al. with TE/TR 280/2300 ms, FOV 240 mm, four 15-mm slices oriented parallel to the Sylvian fissure, 3.5 mm inter-slice gap, 32 x32 phase-encoding steps with circular k-space sampling, and 256 points along the signal acquisition domain. The NAA/Cr ratio, a measure of neuronal functional integrity, was evaluated in multiple regions of interest (ROIs). Repeated measures ANOVA and post hoc t-tests were used to perform group comparisons of the MRS data and regression analysis was used for SPECT/MRS comparisons.

Results. No group differences in NAA/Cr across ROIs were found, while baseline striatal dopamine function measured by SPECT was elevated in the patients as previously reported. In the 5 patients unmedicated at the time of MRSI examination, low NAA/Cr in several forebrain regions (dorsolateral PFC gray and white matter, ventral PFC white matter, and superior temporal gyrus) correlated significantly with elevated baseline synaptic DA concentration in the striatum (see Figure); this correlation was not found in the medicated patients or healthy control subjects.

Conclusions. The absence of group differences in NAA/Cr suggests a small effect size of this deficit in schizophrenia, consistent with other reports on prefrontal cortex with comparable large sample sizes. The relationship found between low NAA/Cr and abnormally high baseline dopamine activity suggests that deficits of NAA/Cr in key brain regions may be related to dysregulation of baseline subcortical dopamine function in unmedicated patients with schizophrenia.

Supported by NARSAD and NIMH.