Relationship of Age and Paternal Age to Neuronal Functional Integrity in the Prefrontal Cortex in Schizophrenia determined by ^{1}H MRS

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Introduction:

Recent epidemiologic and genetic studies have shown that increasing paternal age is an independent risk factor for sporadic or nonfamilial schizophrenia [1]. A proton magnetic resonance spectroscopy (^{1}H MRS) measure of neuronal functional integrity, the ratio of N-acetylaspartate (NAA) to creatine-containing compounds (Cr), has been found in healthy subjects to decline with age [2]. In some but not all studies in schizophrenia, NAA/Cr has been reported to be in deficit in the dorsolateral prefrontal cortex (DLPFC), consistent with a possible deficit of glutamatergic function in that region. In this study, we investigated the effects of paternal age and subject age on this MRS measure in a group of hospitalized patients with schizophrenia.

Methods:

We studied 34 patients with DSM-IV schizophrenia and 34 group-matched healthy control subjects using MRS to determine NAA/Cr in the DLPFC. Twenty-five of the 34 patients had sporadic illness. The acquisition protocol consisted of a multislice spin-echo sequence with outer volume suppression [3] (see Figure). A DLPFC region of interest (ROI) was defined, and the ROI mean of the ratio of NAA/Cr was computed as outcome measure. We examined the effects of paternal age on this outcome measure, controlling for maternal age and subject age, using multiple regression analysis within the sporadic and familial patient groups separately. We used regression analysis to examine the effects on DLPFC NAA/Cr of subject age in the pooled sample of patients and control subjects, in the patient group alone, and in the subset of patients with sporadic illness.

Results:

In the patients with sporadic illness (n=25), there was a significant effect of paternal age on DLPFC NAA/Cr (df = (3,20), F=3.94, p=.017, after controlling for age (p=0.436) and maternal age (p=0.550)). The effect of paternal age was not significant among the familial cases of schizophrenia. Consistent with prior literature, the subjects showed a significant decline of NAA/Cr with age in this brain region (pooled controls and patients, n=68, r=0.30, p=0.013; patient group, n=34, r=0.45, p=.008), with the sporadic patients showing a trend in the same direction (n=25, r=0.38, p=.058). DLPFC NAA/Cr did not differ between the patients and control subjects by two-tailed t test.

Conclusions:

These data show that DLPFC NAA/Cr declines with age in patients with schizophrenia, as previously shown in healthy subjects. The possibility that age dependence may be confounded by age-related atrophy will be addressed by volumetric analysis of the ROI. This study also shows that among sporadic cases of schizophrenia, advancing paternal age is associated with decreased DLPFC NAA/Cr, even after accounting for the effects of subjects' age and maternal age. These data suggest that sporadic, paternal age-related schizophrenia may involve distinct neurochemical alterations.

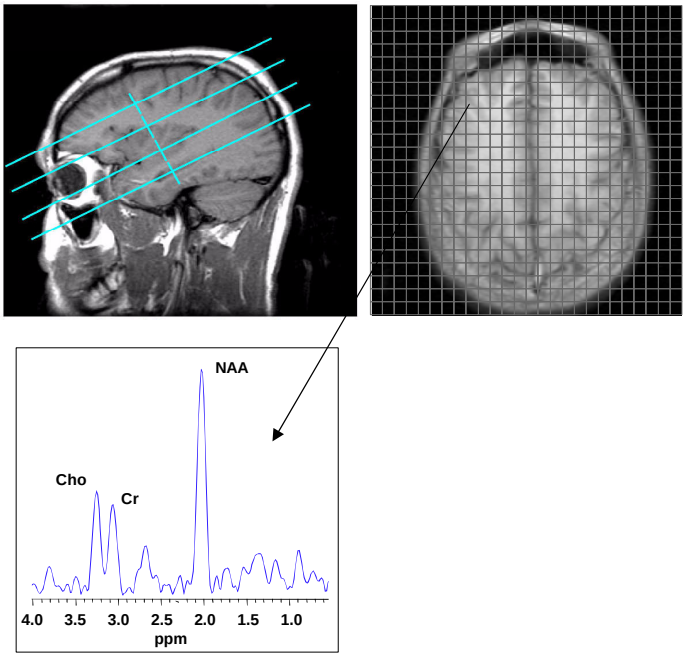

Figure. Upper left panel, sagittal scout image depicting 4 interleaved oblique axial slices. Upper right, most dorsal slice is shown with superimposed grid of .8 cm X .8 cm voxels. Lower left, 1H spectrum is shown from a typical voxel in the DLPFC.

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