Proton magnetic resonance spectroscopy (^{1}H-MRS) of the cerebellum in men with schizophrenia

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Objective: To investigate whether there are cerebellar vermis abnormalities in schizophrenia. **Design:** Prospective imaging study with proton magnetic resonance spectroscopy (^{1}H-MRS). **Setting:** Schizophrenia clinic at a large urban hospital. **Patients and controls:** Twelve right-handed male patients with schizophrenia, and 12 control subjects with no psychiatric history. **Interventions:** MRS data were acquired from a 2.0 × 2.0 × 2.0 cm volume of interest that included the entire cerebellar vermis. **Outcome measures:** Spectral peak arising from *N*-acetylaspartate (NAA), phosphocreatine/creatine (Cr) and choline (Cho). **Results:** There were no significant differences between the patients with schizophrenia and the controls in cerebellar vermis ratios of NAA to Cr (p = 0.71) or Cho to Cr (p = 0.50). **Conclusions:** This study does not support earlier structural studies that found abnormalities of the cerebellar vermis in schizophrenia, although it does support reported neurochemical studies. It does not rule out cerebellar involvement in schizophrenia through mechanisms such as aberrant circuitry. Larger in vivo structural/neurochemical and functional imaging studies in other parts of the cerebellum are needed.

Objectif : Déterminer s'il existe des anomalies du vermis dans la schizophrénie. **Conception :** Étude prospective d'imagerie par spectroscopie à résonance magnétique protonique (SRM-^{1}H). **Contexte :** Clinique de traitement de la schizophrénie d'un grand hôpital urbain. **Patients et témoins :** Douze patients droitiers de sexe masculin atteints de schizophrénie et 12 sujets témoins sans antécédent psychiatrique. **Interventions :** On a tiré des données SRM d'un volume de 2,0 × 2,0 × 2,0 cm d'intérêt qui incluait le vermis au complet. **Mesures de résultats :** Pic spectral provoqué par le *N*-acétylaspartate (NAA), la phosphocréatine/créatine (Cr) et la choline (Cho). **Résultats :** On n'a enregistré aucune différence significative entre les patients atteints de schizophrénie et les témoins en ce qui concerne les ratios de NAA sur Cr (p = 0,71) ou de Cho sur Cr (p = 0,50). **Conclusions :** Cette étude n'appuie pas des études structurelles antérieures qui ont découvert la présence d'anomalies du vermis de sujets atteints de schizophrénie, même si elle appuie des études neurochimiques qui ont fait l'objet de rapports. Elle n'exclut pas l'atteinte du cervelet, dans des cas de schizophrénie, par des mécanismes comme des circuits aberrants. Des études structurelles–neurochimiques et d'imagerie fonctionnelle in vivo de plus grande envergure dans d'autres régions du cervelet s'imposent.

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The cerebellum's contribution to higher cognitive function and its possible role in schizophrenia are of current interest. Post mortem macroscopic and microscopic analyses have shown cerebellar abnormalities in schizophrenia, specifically loss of Purkinje cells and thinning of the granular and molecular layers of the vermis.[1,2] Structural neuroimaging studies using computed tomography (CT) and magnetic resonance imaging (MRI) have been inconsistent in showing cerebellar atrophy. Global cerebellar atrophy[3,4] and vermal atrophy[5,6] in schizophrenia have been reported, but other studies show no differences[7] when compared with controls. However, only a limited number of neuroimaging studies have examined the cerebellum, rather than the temporal and frontal lobes, in this illness.

Proton magnetic resonance spectroscopy (^{1}H-MRS) allows the noninvasive study of metabolism in the brains of individuals with schizophrenia. The spectral peak arising from *N*-acetylaspartate (NAA) has been compared with those arising from phosphocreatine/creatine (Cr) and choline (Cho). NAA is of considerable interest in schizophrenia research, as it is thought to be located mainly within the neurons and provides an index of neuronal mass and integrity. Reported NAA reductions in cortical areas in schizophrenia could therefore represent the volume loss that has been reported in other structural studies. Such reductions have been reported for the hippocampus, prefrontal and frontal cortex, cingulate region, thalamus, and temporal cortex in schizophrenia.

We studied the cerebellum in schizophrenia using ^{1}H-MRS. To our knowledge, this is the first in vivo ^{1}H-MRS study primarily involving the cerebellar vermis in schizophrenia.

Methods

Subjects

All subjects were right-handed to control for laterality confounders (handedness determined by hand preference for most skilled and unskilled activities) and male to control for sex effects. Subjects with a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (n = 12, mean age 34.1, standard deviation [SD] 10.24 years) and able to give informed consent were either referred or recruited from the Schizophrenia Clinic at the University of Alberta Hospitals. Only patients who were considered stable while receiving a current dosage of atypical/novel antipsychotics for at least 2 months were recruited. Control subjects with no previous psychiatric history (n = 12, mean age 27.9, SD 8.1 years) were recruited through an advertisement. Subjects with a history of head injury, medical or neurological illness, chronic alcoholism or drug dependence were excluded. Written informed consent was obtained from all subjects following full explanation of the research protocol.

Proton magnetic resonance spectroscopic studies

All MRS data were acquired at 3 T using a magnet (Magnex Scientific PCL, Abingdon, UK) equipped with actively shielded gradients and a nuclear magnetic resonance spectrometer (Surrey Medical Imaging Systems PCL, Guilford, IK) equipped with a quadrature birdcage resonator. MR images were acquired using a multislice gradient echo imaging sequence (echo time [TE] = 20 ms, typically with 5-mm slices). An initial series of transverse, sagittal and coronal images was acquired to select the appropriate cerebellum volume. A 2.0 × 2.0 × 2.0 cm volume of interest (VOI) was registered on the middle-most sagittal slice with the medial edge parallel to the floor of the fourth ventricle and the fastigium transecting the half-way point of the medial edge. This placement allowed for inclusion of the entire cerebellar vermis; however, the size of the voxel required to optimize the signal-to-noise ratio resulted inclusion of small portions of the cerebellar hemispheres as well. This volume was then reviewed in all 3 planes to ensure that the VOI was entirely contained in the cerebellum (Fig. 1). Water-suppressed MRS data were acquired from this VOI using an inversion null, PRESS pulse sequence with inversion time (TI) = 600 ms, TE = 120 ms, repetition time (TR) = 2 s, and gradient strength = 0.6 mTm^{-1} (0.2 ppm mm^{-1}). Each spectrum was the average of 128 acquisitions. Three spectra were acquired, with each one spatially optimized for either NAA, Cr or Cho, according to our previously reported methodology.[8] A representative spectrum is shown in Fig. 2.

After filtering of the free induction decay with a 3-Hz exponential multiplication factor, the peak area of the appropriate metabolite from each spectrum was determined using the PERCH spectrum analysis package (PERCH Project, Department of Chemistry, University of Kuopio, Finland). Metabolite ratios were compared using 2-way independent Student's t-tests.

Results

There were no significant differences between the groups in age or parental socioeconomic status (as derived from the modified Hollingshead scale). There was a significant difference in years of education (t = –2.71, p = 0.02). The mean length of illness for the patients was 8.8 (SD 8.3) years, and mean scores on the following scales were: Positive and Negative Syndrome Scale total 71.8 (SD 11.9), positive 19.2 (SD 5.2), negative 17.6 (SD 6.4), and Global Assessment of Functioning Scale 66.1 (SD 9.0).

There were no significant differences between the patients with schizophrenia and the controls in terms of the following rations in the cerebellar vermis: NAA/Cr (patients, mean 1.18 SD 0.13 v. controls mean 1.17 SD 0.07, t = –0.373, p = 0.71) and Cho/Cr (patients, mean 0.97 SD 0.13 v. controls, mean 1.00 SD 0.07, t = 0.681, p = 0.50).

Discussion

This study does not support previous structural studies reporting abnormalities of the cerebellar vermis in schizophrenia, although it does support reported neurochemical studies. These results are in agreement with the one other reported in vitro ^{1}H-MRS study of the cerebellar vermis[9] and the only other in vivo ^{1}H-MRS study of the cerebellum (although the study involved the cerebellar hemispheres rather than vermis).[10] This is a preliminary study; however, we were able to keep confounding variables to a minimum, and we used methodology to ensured that each peak was derived from exactly the same cerebellar volume to maximize the validity of the metabolite ratios. The size of the mean difference between the groups that can be detected with 80% power is 0.41 (a 65% change) with our sample size and average standard deviation. A generous estimate of change needed to be detected by MRS is 30%, and thus we feel our sample size had the power to detect differences in metabolite ratios.

We also feel that reporting results as a ratio, rather than absolute concentrations, of metabolites was appropriate for this study. This allowed us to compare our preliminary results with those already reported. In addition, absolute quantification of the metabolites relies on acquiring several additional data sets both from a reference peak (e.g., water), and in taking into account the effects of T_1 and T_2 relaxation on the metabolite peaks, as well as on the reference. The primary value of this approach is that, if both the numerator and denominator are changing approximately equally and in the same direction, then a ratio will not reveal any pathologic process that may be occurring. The main disadvantage of using water as a reference is related to dynamic range. In brain, water occupies ~70% to 80% of the space, equivalent to a concentration of ~40 mol/L, compared with the metabolites, which are 5 to 10 mmol/L (a 10 000-fold concentration differ-

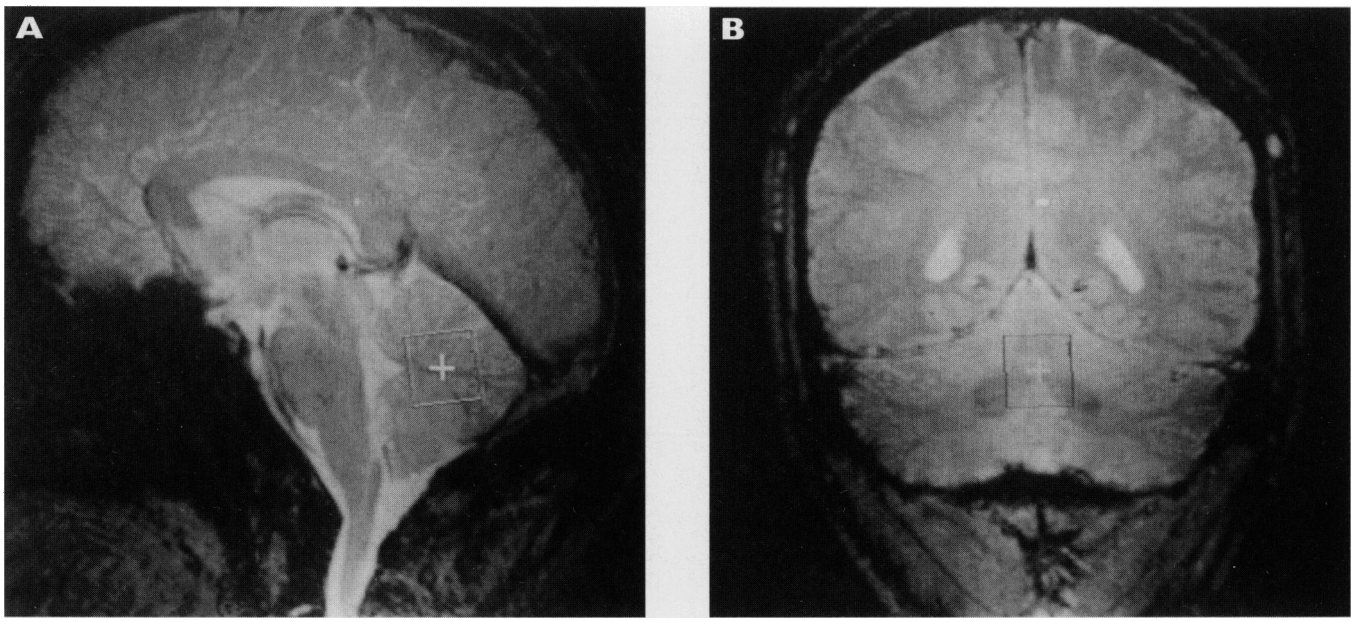

Fig. 1: Voxel placement for ^{1}H-MRS spectra. (A) Sagittal view. (B) Coronal view.

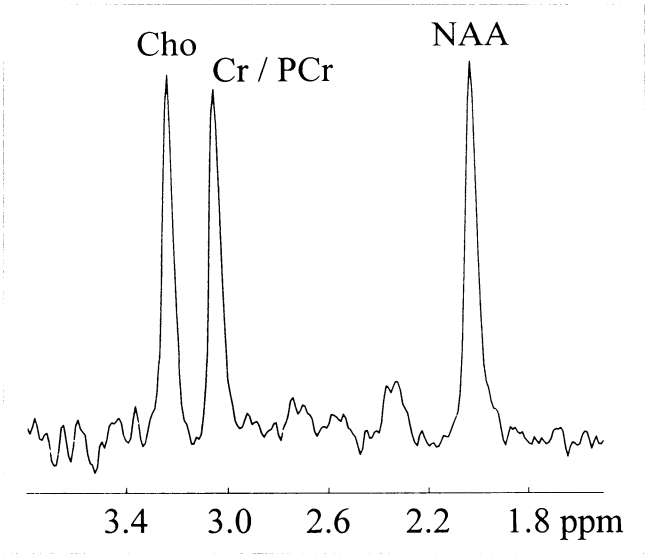

Fig. 2. Representative ^{1}H-MRS spectra of the volume of interest.

ence). Therefore, a small error in measuring the absolute water peak for comparison with the metabolites could produce a substantial error. On the other hand, a ratio compares peak areas of metabolites with equivalent concentrations and therefore reduces this dynamic range error.

These results do not rule out the possibility of cerebellum involvement in schizophrenia. It is possible that aberrant circuitry between the cerebellum and cortex may not be reflected in structural/neurochemical pathology. Larger in vivo studies of other parts of the cerebellum, including both structural/neurochemical and functional imaging, are required to answer these questions.

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