Age-related metabolite alterations in adolescents with high functioning autism, an 1H-MRS study

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Target audience

Clinical neuroscientists

Purpose

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopment syndrome in the category of pervasive developmental disorders. Due to the atypical behavioral development in ASD, the existence of atypical brain development has been suggested [1]. The cellular and metabolic pathophysiology underlying this abnormal brain development in autism is unclear [2]. Potential abnormalities in brain neurochemistry can be assessed using proton magnetic resonance spectroscopy (^{1}H-MRS). In this cross-sectional study, we investigate the effect of age and intelligence on occipital metabolite concentrations in adolescents (aged 13-19y) with high functioning autism (HFA) and healthy controls.

Methods

Subjects 17 adolescents with clinically diagnosed HFA according to DSM-IV (1F, age 16.2±1.4 y) and 15 matched control adolescents (1F, age 15.2±1.4 y), all attending regular secondary school were included. All subjects underwent an intelligence test (Wechsler Intelligence Scale for Children third edition (WISC-III). **MRI** MRI/^{1}H-MRS was performed on a 3.0 Tesla (Philips Achieva) scanner. For anatomic reference, first T1-weigthed three-dimensional (3D) turbo field echo (TFE) images were acquired with the following parameters: repetition time (TR) 8.2 ms, echo time (TE) 3.7 ms, flip angle 8°, matrix 240x240, field of view (FOV) 256x256x180 mm^3, 1 mm adjacent coronal slices. During ^{1}H-MRS, spectra were acquired from a 3x3x3 cm^3 voxel (27 ml) located in the occipital lobe (Figure 1A). The occipital lobe was chosen as i) it is known to be involved in altered visual processing in ASD [3] and ii) it yields high quality spectra, due to the remoteness to the oral region, where adolescents typically wear braces (Figure 1A). Single voxel spectroscopy data (PRESS, TR/TE=2000/35 ms, 128 averages, VAPOR water suppression) was obtained. Additionally, a spectrum (16 averages) was recorded of unsuppressed water. **Analysis** ^{1}H-MRS spectra were analyzed using LCModel (Version 6.2-2B). The metabolite basis set (PRESS, TE 35 ms, 3.0 T) including simulated macromolecule peaks was kindly provided by Dr. Provencher. Metabolites include total creatine (tCr), total choline (tCho), total NAA (tNAA), glutamate / glutamine (Glx), and myo-inositol (Ins). tCr concentrations are calculated in arbitrary units, relative to water, all other metabolites are calculates as ratios relative to tCr. Metabolite estimates were excluded from analysis, if the Cramer-Rao lower bounds (CRLB) exceeded the 20% range. **Statistics** Linear regression was performed, with each metabolite concentration as dependent, and group, age, intelligence, and group*age as independent variables (IBM SPSS, v20).
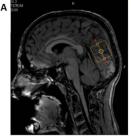
Results

The WISC-III intelligence test did not yield significant differences between adolescents with HFA and the controls (116±5 vs 112±5, p = 0.06). For ^{1}H-MRS the range of SNR was 25-54, indicative of excellent spectral quality (Figure 1B). Linear regression revealed significant group (β= 5.2, p = 0.010) and autism specific age (β= -2.6, p = 0.016) effects for tCho/tCr (Figure 1C). For Glx/tCr concentration, a trend was found for intelligence (β= -0.4, p = 0.072). No other significant results were found.
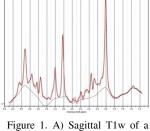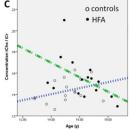
Discussion

In this study we observed a significant higher concentration of tCho, and a significant decrease of tCho with age in HFA. Choline can be considered as a measure of phosphate membrane turnover, and alterations in Cho concentrations have been reported previously in younger ASD populations [4,5]. However, the current study is the first to report a significantly abnormal membrane metabolism [i.e. Cho] development. The data also suggest that in ASD, the concentration of glutamine/glutamate decreases with IQ (trend, not significant). This is in line with previous reports of suggested impaired glutamergic transmission [6].

Figure 1. A) Sagittal T1w of a healthy control (male, 16y) indicating the 1H-MRS voxel (yellow) in occipital lobe, B) corresponding spectrum & LCModel fit, C) tCho concentration as function of age (blue and green dashed lines indicate linear trends for controls and HFA, respectively).

Conclusion

^{1}H-MRS provides evidence of atypical membrane metabolism development in HFA, which potentially underlies the observed atypical behavioral development in ASD.

References

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