Alterations of the regional low-frequency fluctuation and peculiarities of the brain metabolism in autistic children: fMRI and in-vivo $^1$H MRS study

Poster No.: C-0207
Congress: ECR 2014
Type: Scientific Exhibit
Authors: Z. Rozhkova, O. Omelchenko; Kiev/UA
Keywords: CNS, Head and neck, Neuroradiology brain, MR, MR-Functional imaging, MR-Spectroscopy, Diagnostic procedure, Molecular imaging, Imaging sequences, Developmental disease, Image registration, Metabolic disorders
DOI: 10.1594/ecr2014/C-0207

Any information contained in this pdf file is automatically generated from digital material submitted to EPOS by third parties in the form of scientific presentations. References to any names, marks, products, or services of third parties or hypertext links to third-party sites or information are provided solely as a convenience to you and do not in any way constitute or imply ECR's endorsement, sponsorship or recommendation of the third party, information, product or service. ECR is not responsible for the content of these pages and does not make any representations regarding the content or accuracy of material in this file.

As per copyright regulations, any unauthorised use of the material or parts thereof as well as commercial reproduction or multiple distribution by any traditional or electronically based reproduction/publication method is strictly prohibited.

You agree to defend, indemnify, and hold ECR harmless from and against any and all claims, damages, costs, and expenses, including attorneys' fees, arising from or related to your use of these pages.

Please note: Links to movies, ppt slide shows and any other multimedia files are not available in the pdf version of presentations.

www.myESR.org
Aims and objectives

Autism is a neurodevelopment disorder that characterized by the three core features: impairments in social functioning, difficulties in communication, and restricted and repetitive behaviours. Autism spectrum disorder is a heterogeneous neurodevelopment syndrome in the category of pervasive developmental disorders. Due to the atypical behavioural development in the patients with autism spectrum disorder, the existence of atypical brain development has been suggested. The cellular and metabolic pathophysiology underlying this abnormal brain development in autism is unclear. Potential abnormalities in brain neurochemistry can be assessed using 1H MRS in-vivo. Functional Magnetic Resonance Imaging (fMRI) has been widely applied to detect the functional abnormalities of autism spectrum disorder.

In the recent studies [1-4] are shown that fMRI technique has revealed multiple brain regions and networks that are likely responsible for social cognitive deficits of autism. However, the vast majority of autism-related studies with fMRI are mainly conducted by recruiting autistic patients from high-functioning adult/adolescent subjects. So far, it remains largely unknown how the regional functional patterns are altered in very young autistic children at very young stage, as compared to normally developing children. In vivo $^1$H MRS investigation of the foetal, neonatal and adolescent human brain gives us a unique possibility for monitoring of the neurodevelopment and provides a baseline for age related differences in the normal human brain and in the brain under pathology.

In this study fMRI and $^1$H MRS were applied to examine the brain functional activities in treatment-naive autistic children and healthy children. We propose amplitude of low-frequency fluctuations ALFF, and values of the fractional ALFF ($f$ALFF), and also the ratios of the main cerebral metabolites for the characteristics of functional and metabolic abnormalities of autism.
Methods and materials

26 sedated (i/v Propofol) children are examined by fMRI and $^1$H MRS using 1.5T Signa EXCITE HD (GE). All subjects are divided into two groups. The 1\textsuperscript{st} group (NG) consists of 8 healthy children (3-16yo). The 2\textsuperscript{nd} group (PG) includes 18 (3-14yo) autistic children are diagnosed according to the ADI-R and DSM-IV. The subjects of both groups are divided into 3 age groups: from 3 to 6y, from 6 to 8y, and older than 8y. For all subjects T2*W-GE-EPI (TR/TE = 3000/71ms, FA = 90, NEX = 8, FoV = 25.6, 160x160 matrix, sl.thikn. = 6mm), 140 time point fMR-images were obtained. Data processing using FEAT, Version 5.98, part of FSL was carried out. Single subject ICA, and group ICA analysis using MELODIC, Version 3.10, 3.12, respectively, were carried out. The frequency fluctuations of the BOLD signal in the range 0.0024-0.167 were measured. To quantify the functional activity across the brain, amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) were used [5, 6]. Specifically, the first five volumes were discarded for each subject, leaving 195 images for further analysis. ALFF and fALFF were calculated using REST software [7], and analyzed in two different frequency bands (slow-5: 0.01 - 0.027Hz, slow-4: 0.027 - 0.073Hz) [8]. To detect the group differences of ALFF or fALFF between autistic children and normally developing children, a General Linear Model (GLM) were applied to all voxels in the gray matter (GM). Statistical significance were determined by a cluster extent threshold of p<0.05 (FEW-corrected), with a height threshold of p<0.01 (uncorrected) at a voxel-level. $^1$H spectra are recorded with STEAM-sequence with following parameters: TR/TE = 1500/144ms in both hemispheres in the white and gray matter (WM, GM).
Fig. 6 on page 10 Regional differences of frequency-dependent ALFF/fALFF in NG and PG were obtained. In PG decreasing ALFF of both frequency bands and fALFF of slow-5 band, including left inferior/middle/superior temporal gyrus, left inferior parietal gyrus, left supramarginal gyrus, left angular gyrus, left fusiform gyrus, left middle occipital gyrus are found.

In PG in slow-4 band fALFF decreased in right inferior/middle/superior temporal gyrus, right supramarginal gyrus, right angular gyrus, right fusiform gyrus, and right lateral cerebellum.

Fig. 1 on page 6
Fig. 2 on page 6
Fig. 3 on page 7

In PG in slow-4 band fALFF decreased in right inferior/middle/superior temporal gyrus, right supramarginal gyrus, right angular gyrus, right fusiform gyrus, and right lateral cerebellum.

In contrast, ALFF of slow-5 band increased in bilateral brainstem, cerebellar vermis, media cerebellum, and left parahippocampal gyrus.

Our analysis revealed frequency-specific ALFF/fALFF abnormalities in PG in multiple regions that are associated with deficit of social cognition. The affected regions such as bilateral angular gyrus, bilateral supramarginal gyrus, and the left parahippocampal gyrus have been repeatedly reported as components of default mode networks, which were putatively associated with core symptoms in autistic adolescents and adults [1, 3]. Other observed regions such as posterior superior temporal sulcus (pSTS) and temporoparietal junction (TPJ) are among the brain areas consistently showing aberrant structure and function in autism [2, 8]. Particularly, autistic children showed significant decreases of ALFF/fALFF in the fusiform gyrus and the superior temporal gyrus, i.e. the main functional areas of the face perception, which could play a role in the deficits of social cognition related with the face processing [4]. On the other hand, the increased fALFF values in the brain steam, cerebellar vermis may be related with maldevelopment or compensation of functional abnormalities of autism [9].

In the PG (in all ageing group) decrease of NAA/Cr, increase of Cho/Cr, and mIns/Cr in anterior cingulate and left striatum in comparison with NG are obtain. In WM in the NG in the age from 3 to 6y the Glu/Cr increase rapidly from (0.23+0.02), reach maximum in 6y (0.34+0.02), and thereafter decreased moderately to adults level (0.30+0.02) for the age 8y. In GM in the NG in the age from 3 to 6y the Glu/Cr (0.28+0.02) increase rapidly
before values (0.36+/-0.03), characteristic for adult level. In PG in all ageing groups the Glu/Cr is higher than in NG, and in both regions (WM, GM) of the brain, no plateau is observed. In the neonates of the PG in WM the mean values of Glu/Cr are (0.35+/-0.03), and in GM (0.48+/-0.06). In the PG in children older than 3y the mean values of Glu/Cr are (0.40+/-0.03), and (0.53+/-0.03) in the WM and GM, respectively.

Fig. 4 on page 8

Fig. 5 on page 9

Fig. 6 on page 10

In WM in the NG in the age from 1 to 3 months the Glu content increase rapidly, reach maximum in 6 months, and thereafter decreased moderately to adults level for the age 1 year. In GM in the NG in the age from 1 to 3 months the Glu content increase rapidly before values, characteristic for adult level. These data have served as a basis for identification of epileptic foci with MRS. In children with the events of neurological disorders (PG) in all ageing groups the Glu content is higher than in NG, and in both regions (WM, GM) of the brain no plateau is observed. In all subjects of the PG the mean values of Glu concentration and Glu/Cr ratios are higher than in NG. In the neonates of the PG in WM the mean values of Glu/Cr = (0.35+/-0.03), and in GM Glu/Cr = (0.48+/-0.03). In the PG in children older than 3 years the mean Glu/Cr = (0.40+/-0.03), and (0.53+/-0.03) in WM and GM, respectively. In hypoxic, ischemic, or recovering brain, the amplitude of Glu signal is elevated. It is probably a reflection of the protective function of the astrocyte, where Gln-synthetase removes the potentially toxic excess of Glu to accumulate as the relatively harmless product Gln [10].
**Fig. 1:** The main effect for the two groups on ALFF slow-5 band. Hot areas represent higher ALFF in the PG in comparison with CG. Blue areas represent lower ALFF.

© Z.Rozhkova
Fig. 2: The main effect for the two groups on ALFF slow-5 band. Hot areas represent higher ALFF in the PG in comparison with CG.

© Z.Rozhkova
**Fig. 3:** The main effect for the PG on fALFF of slow-5 band. Areas with hot color represent higher fALFF in patients of the PG in comparison with patients of the CG.

© Z.Rozhkova
Fig. 4: Dependences of mean concentrations values of Glu (green), NAA (red), and Cr (blue) in the normal developing brain as a function of age $t$ (month)

© Z.Rozhkova
Fig. 5: The number of subjects P as a function of Glu and Cr concentrations in the brain of normal developing children

© Z. Rozhkova
**Fig. 6:** Dependences of mean concentrations values of Glu in various regions of the brain of the normal developing children, and children with seizure disorders as a function of the age $t$ (years): in WM, and in GM in the NG (red), in WM, and in GM in the PG without of epileptic foci on MRI (blue), and in WM, and GM in children of the PG with epileptic foci on MRI (green).

© Z.Rozhkova
Conclusion

fMRI and MRS give us a unique possibility for monitoring of the brain functional development in the norm and under pathology. Our study reveals the abnormalities of functional activity of very young autistic children in multiple brain regions, which possibly underlies core symptoms of autism. These results also suggest that the ALFF/fALFF analysis based on sedated state fMRI can be utilized as a potential method to evaluate brain functional development in very young children.
References