Developmental changes of neurochemical profile in rat retrosplenial cortex measured by in vivo ^{1}H-MRS

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Introduction In vivo ^{1}H-MRS has been used to assess development-related cerebral metabolic changes in human [1] and animals [2]. The human study demonstrated that posteromedial cortex (i.e., including posterior cingulate, retrosplenial cortex (RSC), and medial parietal cortex/precuneus) had increasing N-acetyl aspartate (NAA), glutamate (Glu) and total creatine (tCr) levels and decreasing myo-inositol (Ins) and glycerophosphocholine + phosphocholine (tPC) levels from 3.5 to 24.1 years of age [1]. Rats were shown to have a rather similar trend of metabolic changes in the striatum from postnatal 7d to 60d, except for decreasing Ins and taurine (Tau) levels with age [2]. In this study, we measured metabolic profile of RSC in Sprague-Dawley (SD) rats at preadolescence, adolescence and adulthood with in vivo ^{1}H-MRS. Development-related metabolic changes in this brain region were assessed.

Materials and methods Three groups of rats at different developmental stages were used: the preadolescence group (25-26d, n=7, 78± 11 g), adolescence group (37-39d, n=13, 189±16 g) and adulthood group (108-110d, n=10, 528±32 g). All spectra were acquired on a 7 T/20 cm Bruker Biospec scanner with a volume coil for RF transmission and a quadrature surface coil for detection. The animals were anesthetized with 1.8-2.5% isoflurane. Localized spectra were acquired from bilateral RSC (2.0 mm×2.0 mm×2.5 mm, Fig. 1) of each animal with a PRESS sequence, VAPOR water suppression, TR/TE 4000/15 ms, spectral bandwidth 4 kHz, 2048 data points and 512 averages. A water spectrum from the same voxel was acquired for eddy current correction and absolute quantification. LCModel was used for absolute metabolic quantification. All spectra had a signal-to-noise ratio greater than 8. Only the results with fitting CRLBs less than 30% were reported. Analysis of variance (ANOVA) with Bonferroni *post hoc* tests was used for statistical analysis. A $p<0.05$ was considered to be statistically significant.

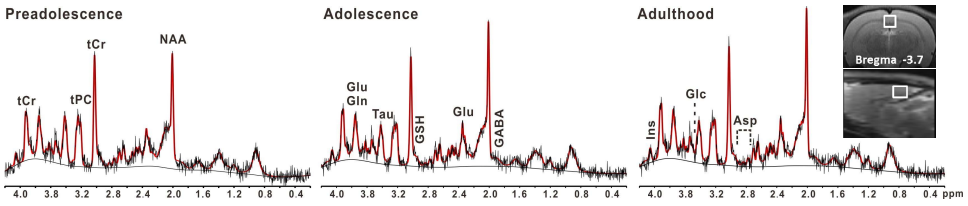

Figure 1. Representative localized spectra from RSC at different age. The raw spectra are shown in black, while the LCModel fits to the raw spectra are shown in red. The gray curves underneath the spectra are fitted baselines. GABA: γ-Aminobutyric Acid, Gln: glutamine, Asp: aspartate, Glc: glucose, GSH: glutathione. From left to right, the spectra are displayed in such a scale that the tCr peak height ratio is 1:1:1.3.

Results Figure 1 shows the location of the voxel for RSC, representative spectra for different age and the corresponding LCModel fits. Figure 2 plots development-related changes in absolute metabolite concentration in the RSC. The Gln, Asp, Glc and GSH levels did not show any significant changes with development. In contrast, the changes for NAA, Tau, Ins and tPC levels were statistically significant across all three developmental ages. More interestingly, the development-related changes of GABA, Glu and tCr levels were statistically significant only between adulthood and adolescence, but not between adolescence and preadolescence.

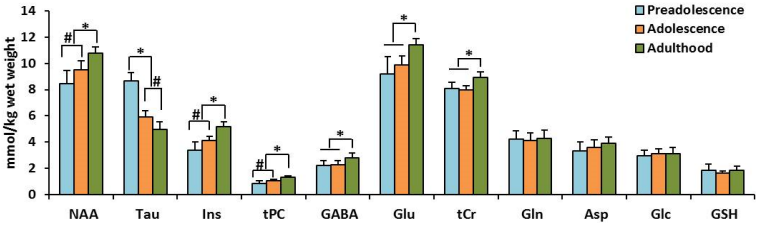

Figure 2. Development-related changes in absolute metabolite concentrations in the RSC. #: significantly different from the preadolescence group; *: significantly different from the preadolescence and adolescence groups.

Discussion RSC plays an important role in cognitive functions including episodic memory, navigation, imagination and planning for the future in human, and is known for underpinning spatial memory and navigation function in rodent [3]. Much has been learned about the adult structure and functions of the RSC, little is known about their development [4]. The results showed that the development-related metabolic changes in the RSC are more or less similar to those observed in rat striatum from adolescence to adulthood, except for tCr whose level increased significantly in the RSC, but not in the striatum [2]. In human, tCr increases consistently with age only within the PMC, but not in parietal white matter and thalamus [1]. It has been suggested that the distinctive pattern of tCr changes in the PMC may indicate more significant changes in energy metabolism in this part of the brain during development [1]. In addition, we found significant increase in Glu and GABA levels from adolescence to adulthood, suggestive of that this developmental stage may be the critical period for the maturation of glutamatergic/GABAergic neurotransmission and/or dendritic stabilization in rat RSC [5, 6].

References [1] Degnan AJ et al, J Comp Neurol, 522: 3717-32, 2014. [2] Morgan JJ et al, NMR Biomed, 26: 683-91, 2013. [3] Le Magueresse C et al, Neuron, 77: 388-405, 2013. [4] Zgraggen E et al, Cereb Cortex, 22: 144-57, 2012. [5] Kilb W, Neuroscientist, 18: 613-30, 2012. [6] Ichinohe N et al, Eur J Neurosci, 18: 1764-74, 2003.