Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage:www.elsevier.com/locate/apjtm

Document heading doi:

Study of the hippocampus and the anterior cingulate gyrus by proton MR spectroscopy in patients with post-traumatic stress disorder

Min Guo[1], Feng Chen[1*], Jun-Cheng Guo[1], Chuan-Zhu Lu[2], Xiang-Ling Jiang[1], Tao Liu[1], Min Li[1], Wei Song[1]

[1]*Psychological Research Center, Hainan Provincial People's Hospital 570311, China*
[2]*Hainan Medical College, Haikou 571101, China*

ARTICLE INFO

Article history:
Received 10 November 2011
Received in revised form 15 December 2011
Accepted 15 January 2012
Available online 20 February 2012

Keywords:
Late-life depression
Magnetic resonance spectroscopy
Hippocampus
Anterior cingulate gyrus

ABSTRACT

Objective: To explore the characteristics of metabolic changes in patients with post-traumatic stress disorder through 1H-MRS in neuroanatomical circuit comparing with age-matches controls. **Methods:** Fifty patients with post-traumatic stress disorder and 50 gender-and age-matched normal controls were involved. The neurochemical abnormalities including the levels of choline (Cho)/ creatine(Cr) and N-acetylaspartate (NAA)/Cr were measured respectively in hippocampus and the anterior cingulate gyrus with three-dimension 1H-proton spectroscopy(3D 1H-MRS). **Results:** The values of NAA/Cr ratios in hippocampus and the anterior cingulate gyrus were significant lower in patients with post-traumatic stress disorder(1.71±0.32, left 1.58±0.29, right 1.55±0.31) than that in controls(2.24±0.41, left 1.98±0.27, right 2.02±0.36) (P<0.05), but the values of Cho/Cr in hippocampus(left 1.64±0.23, right 1.66±0.34) were no significant with that of controls (left 1.48±0.29, right 1.54±0.38). Values of Cho/Cr in cingulate gyrus were significant higher in post-traumatic stress disorder patients (1.88±0.44) than that in controls (1.37.±0.32) (P<0.05). **Conclusions:** The results indicate some special neurochemical and histological structure changes in post-traumatic stress disorder patients, which might occurre earlier in anterior cingulate gyrusthe than in hippocampus.

1. Introduction

Nowadays with increasing traumatic events like war, social violence, natural disaster, domestic violence, child abuse, etc, there is an increasing morbidity for posttraumatic stress disorders (PTSD). Research on PTSD is more concentrated on the exploration of neurobiology mechanism and it is found that damage associated with the stress is focused on the bilateral limbic system of the brain, particularly with hippocampal damage being prominent. These research did not perform the clinical grouping for the PTSD patients and the study area is limited, so it can not explain the full view of PTSD. Magnetic resonance spectroscopy (MRS) is a non-invasive and functional imaging test procedure used to detect *in vivo* celluar metabolic changes and it is also a unique zero damage technique utilized to determine chemical composition in a particular area *in vivo*. Three-dimension ^{1}H-proton spectroscopy (3D ^{1}H-MRS) can simutaneously detect the metabolic abnormalities of mutiple brain regions to provide study clew to reveal biological basis. The study utilized 3D ^{1}H-MRS to do research on type Ⅰ PTSD patients and metabolic changes in prefrontal cortex cingulate gyrus and bilateral hippocampus, thus providing new non-invasive methods to reveal the pathogenesis of PTSD.

2. Materials and methods

2.1. Study population

2.1.1. PTSD group

A total of 50 type I PTSD patients including 29 males and 21 females, attending Psychological Counseling and Treatment Centre Outpatient Clinic of People's Hospital of Hainan Province from January 2010 to October 2011, were included in the study. The inclusion criteria were as follows: 1) it was

*Corresponding author: Feng Chen, Psychological Research Center, Hainan Provincial People's Hospital 570311, China.
Tel: 13876901502
E-mail: fenger0802@163.com
Foundation project: This paper was funded by the National Natural Science Foundation (Grant No. 30860082,81060160) and key technology projects in Hainan Province (Grant No. 090209, zdxm2010043).

coinciding with the diagnostic standards of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IVTR), PTSD17 screening questionnaire [PTSDChecklist Civilian Version (PCL-C)] score was ≥44, and clinician administered PTSD scale (CAPS) was >60; 2) aged between 18-50 years old; 3) first attack with less than 1 year duration of the disease; 4) righ-handed; 5) having no history of taking antipsychotic, antimanic, antidepressant and benzodiazepines drugs; 6) having more than junior high school education and Wechsler Adult Intelligence Scale Revised (WAIS-R) >80. The exclusion criteria were: 1) having a history of disturbance of consciousness more than 5 min; 2) having a clear diagnosis of neurological disease history or serious body disease of heart, liver and kidney history and endocrine disorder history; 3) having a clear diagnosis of other mental diseases; 4) having a history of abusing alcohol and morphine and a history of childhood abuse.

2.1.2. Normal control group

A total of 50 volunteers including 26 males and 24 females, aged between 18-50 years old, attending our hospital for normal check-up, having no history of mental diseases, craniocerebra trauma and organic disease of brain, righ-handed, were included in the study and served as control. There was no significant difference for sex and age of the two groups (P>0.05). An informed consent was obtained from each patient before the examination.

2.2. Methods

GE Signa 1.5 T Twinspeed/ExciteII superconductive magnetic resonance scanner was used to collect ^{1}H-MRS data. All the patients were performed routine cerebral magnatic resonance imaging (MRI) examination, including sequences of T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) of fluid attenuated inversion recover (FLAIR) from the transverse view and sequences of fast recovery fast spin echo (FRFSE) from the sagittal view, using 8 channel head phased array coils in order to exclude unknown lesions of the brain and it also used scanning to locate ^{1}H-MRS. Anterior cingulate gyrus and bilateral hippocampus were selected as regions of interest in routine T2 weighted images using MRS special coil. The sampling point of ^{1}H-MRS was zygomorphic with an volume of 40 cm^{3}. No significant difference was observed between the two groups. The scanning time was13 min 24 s, and the measuring voxel was 1 cm^{3}. Point resolved selective spectroscopy sequence (PRESS) was used to collect spectrum. The imaging parameters were as follows: frequency (10), phase (10), thickness (10 mm); space (10 mm), field of vision (FOV) (16), repetition time (TR)/echo time (TE) (1 000 ms/144 ms). FLAIR was averaged to be 98.6%.

2.3. Data analysis

Functool 2 analyzing software (GE Company, US) and ACD 4.0 version software were used to determine N-acetylaspartate (NAA) of regions of interest of anterior cingulate gyrus and bilateral hippocampus, and choline(Cho)/creatine(Cr) ratio, respectively.

2.4. Statistical analysis

The SPSS for windows 11.5 version statistical software package was used for the statistical analysis. Data were expressed as mean±SD. The mean data of the two groups were subjected to normality test. If it obeyed the normal distribution, "t" test would be used, otherwise nonparametric test and Rank sum test were used. P<0.05 was considered to be significant and P<0.01 was considered to be highly significant.

3. Results

The values of NAA/Cr ratios in hippocampus and the anterior cingulate gyrus were significantly lower in PTSD group than that in controls (P<0.05). The difference of the values of Cho/Cr ratios in hippocampus as not significant (P>0.05). The values of Cho/Cr ratios in PTSD group was significantly increased (P<0.05) (Table 1).

Table 1

Comparison of NAA/Cr and Cho/Cr in different brain regions in PTSD group and control group (mmol/L, mean±SD).

Parameters		PTSD group	Control group
NAA/Cr	Anterior cingulate gyrus	1.71±0.32*	2.24±0.41
	Left hippocampus	1.58±0.29*	1.98±0.27
	Right hippocampus	1.55±0.31*	2.02±0.36
Cho/Cr	Anterior cingulate gyrus	1.88±0.44*	1.37±0.32
	Left hippocampus	1.64±0.23	1.48±0.29
	Right hippocampus	1.66±0.34	1.54±0.38

*: P<0.05 when compared with control group.

4. Discussion

The age, type and the duration of time of traumatic events suffered by each individual were different, so the PTSD manifestations were different. Internationally, Terr taxonomy is more frequently used to classify PTSD which can be divided into two groups: one-time trauma occurring in the adult stage was considered as type I trauma; slightly more complicated, long-term recurred trauma occurring in the childhood stage was regarded as type II trauma, i.e. complex trauma. About 1/3 PTSD patients can not recover throughout their lives and 1/2 patients will be accompanied by drug abusing and other metal disorders, whose suicide rate is 6 times than that of the normal individuals[1]. Therefore, how to reduce the damage to human health and the huge consumption of social resources caused by PTSD is becoming a scientific cutting-edge issue primarily focused by the government and scientific community. Over the past 10 years, rapidly developed medical imaging technology, especially brain imaging technique, have provided new methods to study the brain structure and function of PTSD patients. Domestic and overseases authors used advanced functional imaging technology to study PTSD and acquired great achievement.

Hippocampus is located in the medial temporal lobe of the brain. It is essential to the formation of stable declarative memory in humans and spatial memory in rodents and is the brain functional domain closely associated with learning and memory, and cognitive function. Not only hippocampus

is a neural structure associated with the process of memory, but also its electrical activity and biochemical metabolism are closely related with memory. Bremner reviewed some similar researches and found that the volume of the left hippocampus in PTSD patients who got the trauma in their early lives was significantly reduced; however, in PTSD patients who suffered trauma in their later lives, the volume of bilateral and right hippocampus was reduced. It may be due to the fact that postnatal hippocampus will continue to develop. Damages occurring in different stages have different effects on hippocampus[2]. Yang *et al*[3] and Li *et al*[4] found that the values of NAA/Cr ratios of the left hippocampus in PTSD patients were significantly reduced compared to normal control and no change was observed in the right hippocampus. Type I PTSD patients were included in the present study and the results revealed that the values of NAA/Cr ratios in bilateral hippocampus were significantly reduced and no obvious change was observed in the values of Cho/Cr ratios, which was in agreement with the above research result. Reduction of the values of NAA/Cr ratios suggests that a series of biological change occurring in the PTSD patients caused damage to the metabolism of hippocampal neuron or neuron loss. Cho signals include phosphorylcholine, glycerophosphocholine, phosphatidylcholine and sphingomyelin. Cho is a precusor of acetylcholine (Ach), a neurotransmitter, closely associated with memory and emotion and is the pathophysiological basis for emotional disturbance. It is also a component of phospholipid metabolism of neural diolame to participate the process of cell membrane synthesis and degradation and is considered as a reflect for metabolism of glial cells and functional change. The duration of type I PTSD is relatively short, the loss of hippocampal neurons is a slow process, and generally no large amounts of cell membrane disintegration and excessive hyperplasia of glial cells will occur; therefore, no obvious change was observed in the concentration of Cho. The hippocampal metabolites levels can more reflect the pathological changes in the hippocampus as compared with its volume.

Prefrontal lobe is an important brain domain to guide working memory, inhibit inappropriate cognition and emotional response or scattered stimulation, and promote the plan and execution of effective organizational behavior. Evidences demonstrate that interior prefrontal lobe can inhibit the activity of amygdala to modulate emotional response associated with specific memory. Researches reveal that the volume of right anterior cingulate gyrus in PTSD associated with maltreat patients was significantly reduced compared to non PTSD patients[6]. A MRS research demonstrated that the values of cerebral ACC NAA/Cr ratios in 11 PTSD associated with maltreat children were significantly decreased compared to normal control group[7]. Mahmutyazicio *et al*[8] found that the values of NAA/Cr ratios of bilateral hippocampus and anterior cingulate gyrus in PTSD patients were significantly reduced, the values of Cho/Cr ratios of bilateral hippocampus were significantly increased, and no obvious change was observed in the values of Cho/Cr ratios of anterior cingulate gyrus compared to normal control group. The present study reveals that no obvious change was observed in the values of Cho/Cr ratios of bilateral hippocampus and the values of Cho/Cr ratios of anterior cingulate gyrus were significantly increased. Prefrontal lobe is a main centre to modulate amygdala and hippocampus, and its biological changes happened earlier than that in hippocampus. The above study reveals that PTSD is associated with neural loss and viability reduction of bilateral hippocampus and CAA. It can be speculated that bilateral hippocampus and anterior cingulate gyrus possibly play an important role in the pathological change of PTSD. Particularly, it should be pointed that PTSD is a reexperienced symptom for traumatic events.

The imbalance of declarative memory and non-declarative memory in PTSD patients mainly involves the three brain domains of hippocampus, anterior cingulate gyrus and prefrontal lobe. Therefore, we argue that PTSD is not a lesion occurring in a certain nerve cell or brain sturcture, but a lesion occurring in multiple brain domains or abnormality occurring in the interconnection between those multiple brain domains, so there is a strong need to carry out multipoint research on PTSD. It's a pity that due to technology limitation, it's very difficult to locate MRS because the position of amygdala is near hippocampus and inferior horn of lateral ventricle, and there exists local heterogeneity and flow artifact. Hopefully, with advanced development of imaging technology, research on PTSD damage to cranial nerve circuit will be completed.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Li LJ, Yu X. *Prevention guide to posttraumatic stress disorder*. Beijing: People's Medical Publishing House; 2010, p. 1-2.

[2] Brenmcr JD. Does stress damage the brain? *Biol Psychiatry* 1999; **45**(7): 797-805.

[3] Yang B, Zhou YC, Xia J, Xia LM, Wang CY. The study of the volume and 1H MRS of the hippocampus in posttraumatic stress disorder. *Chin J Radiol* 2006; **40**: 36-40.

[4] Li LJ, Chen SL, Liu J, Zhang JL, He Z, Lin X. Magnetic resonance imaging and magnetic resonance spectroscopy study of deficits in hippocampal structure in five victims with recent-onset posttraumatic stress disorder. *Can J Psychiatry* 2006; **51**: 431-437.

[5] Schuff N, Neylan TC, Lenoci MA, Du AT, Weiss DS, Marmar CR, et a1. Decreased hippocampal N-acety-laspartate in the absence of atrophy in posttranmatic stress disorder. *Biol Psychiatry* 2001; **50**: 952-959.

[6] Kitayama N, Quinn S, Bremner JD. Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. *J Affect Disord* 2006; **90**(2-3): 171-174.

[7] De Bellis MD, Keshavan MS, Spencer S, Hall J. N-Acetylaspartate concentration in the anterior cingulate of maltreated children and adolescentswith PTSD. *Am J Psychiatry* 2000; **157**(7): 1175-1177.

[8] Ham BJ, Chey J, Yoon SJ, Sung Y, Jeong DU, Ju Kim S, et al. Decreased N-acctylaspartate levels in anterior cingulate and hippocampus in subjects with post-traumatic stress disorder: a proton magnetic resonance spectroscopy study. *Eur J Neurosci* 2007; **25**(l): 324-329.