

· 影像医学 ·

定量磁敏感图对终末期肾病患者脑铁沉积的定量研究

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[摘要] 目的:应用定量磁敏感图(quantitative susceptibility mapping, QSM)比较终末期肾病(end-stage renal disease, ESRD)患者和健康对照者大脑深部灰质核团的磁敏感值(magnetic susceptibility value, MSV),并分析ESRD患者MSV与蒙特利尔认知评估量表(montreal cognitive assessment, MoCA)评分的相关性,探讨QSM技术评估ESRD患者脑铁沉积的价值以及脑铁沉积对认知功能的影响。方法:招募南通大学附属医院25例ESRD患者及25例年龄性别相匹配的健康对照者,应用QSM技术测量每个人大脑深部灰质核团的MSV,应用Mann-Whitney *U* 检验比较各核团MSV的差异,应用受试者工作特征(receiver operating characteristic, ROC)曲线分析评价其诊断效能,应用Spearman相关性分析评估ESRD患者MSV与MoCA评分的相关性。结果:ESRD患者双侧红核(red nucleus, RN)、黑质(substantia nigra, SN)、尾状核头部(caudate head, CA)、壳核(putamen, PU)的MSV大于健康对照者(P 均 <0.05)。双侧RN、SN、PU及CA的MSV可以区分ESRD患者与健康对照者,当右侧PU的MSV为0.085时,曲线下面积(area under the curve, AUC)最大,敏感性为67%,特异性为91%。ESRD患者右侧RN的MSV与语言能力、抽象能力呈负相关,左侧CA的MSV与注意力、语言能力呈负相关,左侧苍白球(globus pallidus, GP)的MSV和视觉空间与执行能力呈负相关(P 均 <0.05)。结论:QSM技术不仅可以定量评估ESRD患者脑内铁沉积,还可以分析ESRD患者脑内铁沉积对认知功能的影响。

[关键词] 终末期肾病;脑;磁共振成像;铁;定量

[中图分类号] R816.7

[文献标志码] A

[文章编号] 1007-4368(2021)05-741-05

doi:10.7655/NYDXBNS20210519

Quantitative study of brain iron deposition in patients with end-stage renal disease by quantitative susceptibility mapping

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[Abstract] **Objective:** This study aims to explore the effect of quantitative susceptibility mapping (QSM) in evaluating brain iron deposition in the patients with end-stage renal disease (ESRD) and the impact of iron deposition on cognitive function by comparing the magnetic susceptibility value (MSV) of the deep gray matter nuclei between the patients with ESRD and healthy controls, and analyzed the correlations between the MSVs of the patients with ESRD and the scores of the Montreal Cognitive Assessment (MoCA). **Methods:** Twenty-five patients with ESRD and 25 healthy controls who are age and sex-matched were recruited in this study. The MSVs of the deep gray matter nuclei of all the patients with ESRD and healthy controls were measured with QSM. The differences of the MSVs of the nuclei between the patients and controls were analyzed by the Mann-Whitney *U* test. The diagnostic efficacy of the MSVs was analyzed by the receiver operating characteristic (ROC) curve. The correlations between the MSVs of the patients and the scores of the MoCA were analyzed by Spearman correlation analysis. **Results:** In the patients with ESRD, the MSVs of bilateral red nucleus (RN), substantia nigra (SN), caudate head (CA) and putamen (PU) were higher than those in the controls ($P < 0.05$ respectively). The MSVs of bilateral RN, SN, PU and CA can distinguish the patients from healthy controls. ROC analysis revealed that the cut-off values of PU MSV (0.085) provided the best combination of sensitivity (67%) and specificity (91%) to distinguish the ESRD patients from controls. In the patients with ESRD, the MSV of the right RN was negatively correlated with language ability and abstract ability, the left CA was negatively correlated with attention and language ability, and the left globus pallidus (GP) was negatively correlated with visuospatial

[基金项目] 江苏省卫生健康委科研项目(H2019089);南通市科技计划项目(MS12020044)

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and executive ability ($P < 0.05$ respectively). **Conclusion:** In patients with ESRD, QSM not only can evaluate brain iron deposition quantitatively, but contribute to analyze the impact of iron deposition on cognitive function.

[Key words] end-stage renal disease; brain; magnetic resonance imaging; iron; quantitative

[J Nanjing Med Univ, 2021, 41(05): 741-745]

终末期肾病(end-stage renal disease, ESRD)可导致中枢神经系统多种功能损伤,其中以认知功能障碍与急性脑血管病多见。到目前为止,其损伤机制尚不明确,可能与多种因素有关,ESRD患者脑内铁沉积过多可能是原因之一。有研究显示,脑内铁沉积过多可能引起认知功能下降^[1]。所以,无创性检测ESRD患者脑内铁沉积具有重要的临床价值。

磁共振成像(magnetic resonance imaging, MRI)是诊断中枢神经系统疾病最常用的影像方法。目前场强依赖弛豫成像法(field-dependent relaxometry imaging, FDRI)技术与磁敏感加权成像(susceptibility weighted imaging, SWI)技术可以评估脑内铁沉积。但是,FDRI技术扫描时间较长,空间分辨率较低,数据偏差较大;SWI技术可以定性检测铁沉积,但不能进行定量分析,所以临床上需要一种无创的MRI技术用于定量评估ESRD患者脑内铁沉积。

定量磁敏感图(quantitative susceptibility mapping, QSM)是在SWI基础上发展起来的可以定量测量人体组织磁化率的MRI技术^[2]。目前,QSM技术最常用于无创评估肝脏铁含量。QSM技术在中枢神经系统应用较少,现在主要用于帕金森病、阿尔兹海默症、多发性硬化等,在ESRD脑内铁沉积方面的应用很少^[3-5]。

本研究应用QSM技术测量ESRD患者大脑深部灰质核团的磁敏感值(magnetic susceptibility value, MSV),分析ESRD患者脑铁沉积的特点及脑铁沉积与认知障碍之间的相关性,探讨QSM技术评估ESRD患者脑铁沉积方面的价值。

1 对象和方法

1.1 对象

本研究以25例ESRD患者[男13例,女12例,年龄范围39~71岁,平均(57±12)岁]作为ESRD组,及25例年龄性别相匹配的健康对照者[男13例,女12例,年龄范围37~73岁,平均(57±10)岁]作为对照组。入组标准:ESRD患者的入组条件符合美国肾脏病基金会对ESRD患者的诊断标准^[6]。所有

ESRD组与对照组均为右利手。所有患者均为透析患者,并同时患有贫血及补铁治疗,平均透析时长7年8个月。排除标准:①其他各种与铁沉积相关的脑疾病;②其他可以引起脑铁异常沉积的各类疾病;③近期服用影响铁代谢食物或药物;④MRI检查禁忌证。本研究经本院医学审查委员会批准,患者均知情同意。

1.2 方法

1.2.1 MRI检查

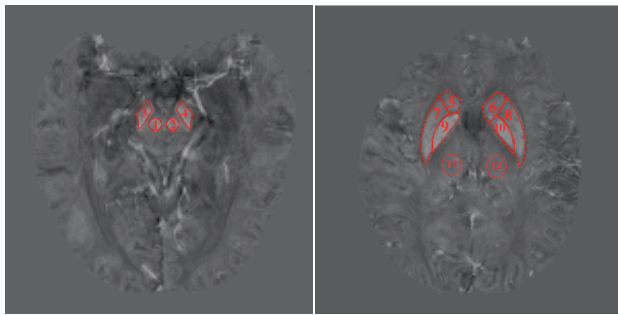
本研究应用3.0T MR扫描仪(GE Signal 750w),采用16通道头颈联合线圈。受试者头部用海绵衬垫固定,防止移位。QSM扫描以梯度回波序列为基础进行多体素横断面扫描,扫描参数如下:TR/TE 32.5 ms/3.3 ms,层厚1mm,翻转角20°,FOV 256 mm×256 mm,矩阵256×256,接受带宽62.50 HZ/PX。QSM扫描范围为中脑黑质区及基底节区,两侧对称,避免颅底鼻窦气体、颅骨、血管、脑脊液等影响。定位后先进行预扫描,当自动匀场达到半高线宽98%以上,方可开始扫描。另外,在QSM扫描前先进行T1WI、T2WI和T2FLAIR常规图像扫描用以筛查各类脑疾病。

1.2.2 图像的处理与分析

本研究的感兴趣区(region of interest, ROI)设置为双侧红核(red nucleus, RN)、黑质(substantia nigra, SN)、尾状核头部(caudate head, CA)、壳核(putamen, PU)、苍白球(globus pallidus, GP)、丘脑(thalamus, TH)。由2名经验丰富的神经影像医师测量每一个ROI的MSV,取平均MSV作为最后的计算值,测量时选取解剖层面清晰的最大层面,避开颅骨、大血管、脑脊液(图1)。

1.2.3 认知能力评估

本研究应用蒙特利尔认知评估量表(montreal cognitive assessment, MoCA)对ESRD患者的认知能力进行评分,包括视觉空间与执行力、命名能力、记忆力、注意力、语言能力、抽象能力、延迟记忆和定向力等7项。由1名经验丰富的神经内科医师以同一标准单独评分。



1: 右侧红核;2: 左侧红核;3: 右侧黑质;4: 左侧黑质;5: 右侧尾状核头部;6: 左侧尾状核头部;7: 右侧壳核;8: 左侧壳核;9: 右侧苍白球;10: 左侧苍白球;11: 右侧丘脑;12: 左侧丘脑。

图1 磁敏感图上不同的ROI

Figure 1 Susceptibility mapping images with different ROI

1.3 统计学方法

应用SPSS 22.0统计软件对数据进行统计分析,所有计量资料均以均数±标准差($\bar{x} \pm s$)表示。应用Mann-Whitney *U*检验分析ESRD组与对照组各部位的MSV差异;应用受试者工作特征(receiver operating characteristic, ROC)曲线分析诊断ESRD患者脑内铁沉积的切峰值、敏感性与特异性;应用Spearman相关性分析评估ESRD患者各部位MSV与MoCA评分亚项之间的相关性。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 ESRD组与对照组各部位MSV的比较

ESRD组双侧RN、SN、CA、PU的MSV均大于对照组,差异有统计学意义($P < 0.05$)。两组间的双侧GP及TH的MSV差异无统计学意义($P > 0.05$,表1,图2)。

2.2 ESRD组与对照组MSV的ROC曲线分析

双侧RN、SN、CA、PU的MSV可以鉴别诊断ESRD组与对照组(P 均 < 0.05),其中当右侧PU的MSV为0.085时,曲线下面积(area under the curve, AUC)最大,敏感性为67%,特异性为91%(表2,图3)。

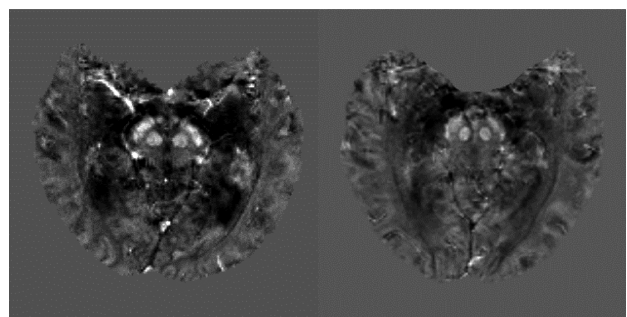
2.3 ESRD组各部位MSV与MoCA评分及其亚项的相关性分析

右侧RN的MSV与语言能力($P=0.023$, $r=-0.056$)、抽象能力($P=0.012$, $r=-0.608$)呈负相关,左侧CA的MSV与注意力($P=0.042$, $r=-0.513$)、语言能力($P=0.019$, $r=-0.579$)呈负相关,左侧GP的MSV与视觉空间与执行能力($P=0.037$, $r=-0.524$)呈负相关。ESRD组各部位MSV与MoCA评分总分无相关性($P > 0.05$)。

表1 ESRD组与对照组的MSV比较

Table 1 Comparison of the MSV between the ESRD and control group ($\bar{x} \pm s$)

| 部位 | ESRD组 | 对照组 | <i>P</i> 值 |
|------|---------------|---------------|------------|
| 右侧RN | 0.103 ± 0.032 | 0.076 ± 0.030 | 0.009 |
| 左侧RN | 0.097 ± 0.027 | 0.074 ± 0.024 | 0.004 |
| 右侧SN | 0.099 ± 0.042 | 0.067 ± 0.022 | 0.004 |
| 左侧SN | 0.093 ± 0.059 | 0.067 ± 0.023 | 0.016 |
| 右侧CA | 0.058 ± 0.034 | 0.040 ± 0.020 | 0.029 |
| 左侧CA | 0.062 ± 0.044 | 0.037 ± 0.017 | 0.007 |
| 右侧PU | 0.120 ± 0.151 | 0.063 ± 0.027 | 0.002 |
| 左侧PU | 0.123 ± 0.172 | 0.065 ± 0.025 | 0.008 |
| 右侧GP | 0.137 ± 0.040 | 0.126 ± 0.060 | 0.421 |
| 左侧GP | 0.129 ± 0.041 | 0.125 ± 0.040 | 0.421 |
| 右侧TH | 0.032 ± 0.016 | 0.024 ± 0.014 | 0.141 |
| 左侧TH | 0.033 ± 0.015 | 0.025 ± 0.017 | 0.107 |



左图:女,48岁,ESRD患者;RN及SN信号增高,提示铁沉积增多;右图:女,48岁,对照者。

图2 ESRD患者与对照者磁敏感图对比

Figure 2 Comparison in susceptibility mapping between the ESRD patient and control

表2 ESRD组与对照组MSV的ROC曲线分析

Table 2 The ROC curve analysis of MSV between ESRD and control group

| 部位 | 切峰值 | 敏感性(%) | 特异性(%) | AUC | <i>P</i> 值 |
|------|-------|--------|--------|-------|------------|
| 右侧RN | 0.094 | 67 | 81 | 0.736 | 0.009 |
| 左侧RN | 0.097 | 57 | 91 | 0.763 | 0.004 |
| 右侧SN | 0.074 | 71 | 76 | 0.760 | 0.004 |
| 左侧SN | 0.071 | 71 | 67 | 0.717 | 0.016 |
| 右侧CA | 0.053 | 52 | 81 | 0.690 | 0.029 |
| 左侧CA | 0.058 | 48 | 95 | 0.744 | 0.007 |
| 右侧PU | 0.085 | 67 | 91 | 0.778 | 0.002 |
| 左侧PU | 0.068 | 76 | 71 | 0.739 | 0.008 |

3 讨论

慢性肾病(chronic kidney disease, CKD)是全球性的健康问题,有研究显示,CKD1~5期患病率达

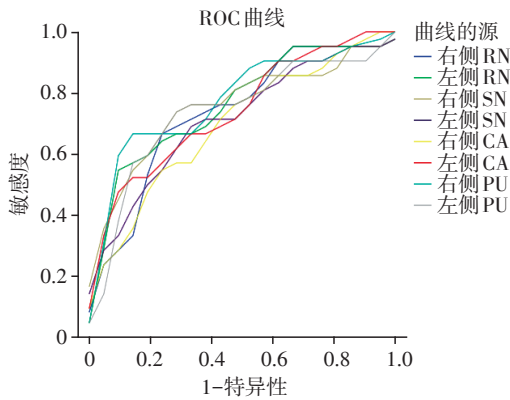


图3 ESRD组与对照组MSV的ROC曲线分析
Figure 3 The ROC curve analysis of MSV between ESRD and control group

16.8%，其中ESRD是CKD最严重的阶段，患病率达0.1%^[7]。ESRD患者常伴有贫血，所以常采用红细胞生成刺激药物加快造血速度，并通过输血、饮食等方面进行补充，但这容易引起ESRD患者的铁过载。铁过载的情况下，机体内游离的铁离子则通过复杂的跨膜转运机制通过血脑屏障，并在特定脑区过度沉积，而脑内铁过度沉积则会加速神经变性^[8-9]。因此，无创性地评估ESRD患者脑内铁沉积具有重要的临床价值。目前测量脑铁沉积的主要方法包括正电子发射计算机断层显像(positron emission tomography, PET)、CT、MRI等。相比于PET与CT，MRI不但无辐射损伤，而且具有较高的准确率。目前已有多种MRI技术用于无创性测量铁沉积，而QSM是目前研究脑铁沉积最有效的工具^[10]。

本研究应用QSM技术对ESRD患者脑内灰质核团铁沉积进行定量分析，发现ESRD组双侧RN、SN、CA、PU的MSV大于对照组，提示这些部位铁沉积增加。分析铁增加的原因可能是ESRD患者长期透析易导致铁缺失，需要定期进行补铁治疗，所以可能引起铁过载^[11]。肾脏的损伤通常伴随着脑血管的病变，尤其是脑内微小出血，从而引起铁沉积增加^[12-13]。Atay等^[14]应用SWI序列研究发现，ESRD患者脑内微出血灶的比例明显大于正常人，提示铁沉积增多，与本研究结果相似。但是SWI序列仅限于定性评估脑内铁沉积，而本研究可以对脑内铁沉积同时进行定性及定量测量。本研究结果与报道的研究结果一致，而且本研究进一步发现双侧RN、SN、PU及CA的MSV可以鉴别ESRD组与对照组，其中右侧PU的MSV表现出更高的组间区分能力，特异性为91%^[15-16]。因此，QSM技术可以定量评估ESDR患者脑内异常的铁沉积，有助于临床进

一步评估ESRD患者病情程度与治疗方案的调整。

认知功能障碍是CKD患者常见的临床症状，其中ESRD患者的认知功能障碍最严重^[12,17]。本研究应用MoCA评分量表评估ESRD患者认知功能发现，ESRD组右侧RN的MSV与语言能力、抽象能力呈负相关，左侧CA的MSV与注意力、语言能力呈负相关，左侧GP的MSV和视觉空间与执行能力呈负相关，提示右侧RN、左侧CA及左侧GP的铁沉积增多，导致相关核团微结构的改变，引起认知功能的障碍。这与Chai等^[16]发现双侧CA的MSV与简易智能精神状态检查量表(mini-mental state examination, MMSE)评分呈负相关的结论不一致。大量研究发现，MoCA评分量表对CKD患者认知障碍的监测较MMSE具有更高的敏感性，且MoCA评分已被指定用于CKD患者轻度认知障碍的筛查^[17-18]。认知功能测试包含多个评分亚项，大脑深部灰质核团也对应不同的功能区，本研究更加细化地探究了大脑深部灰质核团铁沉积与认知功能障碍的相关性。在一项帕金森病的研究中，发现包括GP在内的纹状体产生的纹状体多巴胺转运蛋白的丢失与认知功能障碍，尤其是视觉空间与执行力障碍密切相关，这与本研究结果相符合^[19]。铁异常沉积造成神经元中的DNA、蛋白质、脂质氧化损伤，引起衰老或肥大细胞死亡^[8]。有研究发现，Meynert基底核在胆碱能输入到皮层的神经通路的损伤导致语言功能、注意力及抽象能力的障碍^[20-21]，与本研究发现关于右侧RN的MSV与语言能力、抽象能力呈负相关，左侧CA的MSV与注意力、语言能力呈负相关一致。因此，本研究认为，ESRD患者的认知功能障碍可能是机体铁代谢异常，大脑深部灰质核团铁沉积过多导致其加速萎缩、神经变性，并且铁沉积越多，相关认知功能越差。

本研究还有一定的局限性。首先，大脑灰质核团ROI的勾画过程中，很难避免层面不同引起的误差。为了减少误差，选取解剖层面清晰的最大层面，2名经验丰富的神经影像医师每人测量3次，取平均值。其次，样本量较小，对于ESRD患者没有根据病程、透析方法进行再分类。在今后的研究中，将扩大样本量进行更详细的分析。

QSM作为一种无创的评估脑铁沉积的MRI方法，不仅可以定量分析ESRD患者脑铁沉积程度，而且有助于评估ESRD患者认知功能障碍。

[参考文献]

[1] YAWEN S, XIN G, XU H, et al. Characterizing brain iron

- deposition in patients with subcortical vascular mild cognitive impairment using quantitative susceptibility mapping: a potential biomarker [J]. *Front Aging Neurosci*, 2017,9:81
- [2] JUNG W, BOLLMANN S, LEE J. Overview of quantitative susceptibility mapping using deep learning: current status, challenges and opportunities [J]. *NMR Biomed*, 2020:e4292
- [3] EBANI E J, KAPLITT M G, WANG Y, et al. Improved targeting of the globus pallidus interna using quantitative susceptibility mapping prior to MR-guided focused ultrasound ablation in Parkinson's disease [J]. *Clin Imaging*, 2020,68:94-98
- [4] KIM H G, PARK S, RHEE H Y, et al. Evaluation and prediction of early alzheimer's disease using a machine learning-based optimized combination-feature set on gray matter volume and quantitative susceptibility mapping [J]. *Curr Alzheimer Res*, 2020,17(5):428-437
- [5] TOLAYMAT B, ZHANG W, CHEN H, et al. Sex-specific differences in rim appearance of multiple sclerosis lesions on quantitative susceptibility mapping [J]. *Mult Scler Relat Dis*, 2020,45:102317
- [6] GOOLSBY M J. National kidney foundation guidelines for chronic kidney disease: evaluation, classification, and stratification [J]. *J Am Acad Nurse Prac*, 2002,14(6):238-242
- [7] DUAN J Y, DUAN G C, WANG C J, et al. Prevalence and risk factors of chronic kidney disease and diabetic kidney disease in a central Chinese urban population: a cross-sectional survey [J]. *BMC Nephrol*, 2020,21(1):115
- [8] COZZI A, ORELLANA D I, SANTAMBROGIO P, et al. Stem cell modeling of neuroferritinopathy reveals iron as a determinant of senescence and ferroptosis during neuronal aging [J]. *Stem Cell Rep*, 2019,13(5):832-846
- [9] BURKHART A, SKJØRRINGE T, JOHNSEN K B, et al. Expression of iron-related proteins at the neurovascular unit supports reduction and reoxidation of iron for transport through the blood-brain barrier [J]. *Mol Neurobiol*, 2016,53(10):7237-7253
- [10] CHEN Y, JAKARY A, AVADIAPPAN S, et al. QSMGAN: improved quantitative susceptibility mapping using 3D generative adversarial networks with increased receptive field [J]. *Neuroimage*, 2020,207:116389
- [11] CHEN C H, SHU K H, YANG Y. Long-term effects of an oral iron chelator, deferasirox, in hemodialysis patients with iron overload [J]. *Hematology*, 2015,20(5):304-310
- [12] YEH Y, KUO Y, HUANG M, et al. Association of brain white matter lesions and atrophy with cognitive function in chronic kidney disease [J]. *Int J Geriatr Psych*, 2019,34(12):1826-1832
- [13] HAYASHI K, TAKAYAMA M, KANDA T, et al. Association of kidney dysfunction with asymptomatic cerebrovascular abnormalities in a Japanese population with health checkups [J]. *Circ J*, 2017,81(8):1191-1197
- [14] ATAY M, ALKAN A, TOPRAK H, et al. Effect of cerebral microhemorrhages on neurocognitive functions in patients with end-stage renal disease [J]. *Acta Radiol*, 2020:284185120946709
- [15] CHAI C, YAN S, CHU Z, et al. Quantitative measurement of brain iron deposition in patients with haemodialysis using susceptibility mapping [J]. *Metab Brain Dis*, 2015,30(2):563-571
- [16] CHAI C, ZHANG M, LONG M, et al. Increased brain iron deposition is a risk factor for brain atrophy in patients with haemodialysis: a combined study of quantitative susceptibility mapping and whole brain volume analysis [J]. *Metab Brain Dis*, 2015,30(4):1009-1016
- [17] ERKEN E, ALTUNOREN O, SENEL M E, et al. Impaired cognition in hemodialysis patients: the Montreal cognitive assessment (MoCA) and important clues for testing [J]. *Clin Nephrol*, 2019,91(5):275-283
- [18] LEE S H, CHO A, MIN Y K, et al. Comparison of the montreal cognitive assessment and the mini-mental state examination as screening tests in hemodialysis patients without symptoms [J]. *Ren Fail*, 2018,40(1):323-330
- [19] KIM H, OH M, OH J S, et al. Association of striatal dopaminergic neuronal integrity with cognitive dysfunction and cerebral cortical metabolism in Parkinson's disease with mild cognitive impairment [J]. *Nucl Med Commun*, 2019,40(12):1216-1223
- [20] HAMODAT H, FISK J D, DARVESH S. Cholinergic neurons in nucleus subputaminalis in primary progressive aphasia [J]. *Can J Neurol Sci*, 2019,46(2):174-183
- [21] ECK S R, XU S J, TELENSON A, et al. Stress regulation of sustained attention and the cholinergic attention system [J]. *Biol Psychiatry*, 2020,88(7):566-575

[收稿日期] 2020-10-23