·睡眠障碍·

慢性失眠合并阻塞性睡眠呼吸暂停患者睡眠结构和自主神经功能特征及其与神经心理特征相关分析

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【摘要】 **目的** 探讨慢性失眠合并阻塞性睡眠呼吸暂停患者睡眠结构和自主神经功能特征及其与神经心理特征的相关性。**方法** 纳入2019年9月至2021年6月天津医科大学总医院和空港医院收治的91例慢性失眠患者，根据是否合并阻塞性睡眠呼吸暂停分为单纯慢性失眠组（失眠组，46例）和慢性失眠合并阻塞性睡眠呼吸暂停组（共病组，45例），同时招募性别、年龄、受教育程度相匹配的22例对照者，采用PSM-100A睡眠呼吸监测设备分析睡眠结构和自主神经功能特征，匹兹堡睡眠质量指数、Epworth嗜睡量表和失眠严重程度指数评价主观睡眠质量，并行神经心理学测验。**结果** （1）睡眠结构：共病组总睡眠时间（$P=0.003,0.002$）、睡眠效率（$P=0.000,0.019$）、快速眼动睡眠期（REM）占比（$P=0.000,0.015$）、平均动脉血氧饱和度（SaO_2；$P=0.000,0.000$）、最低SaO_2（$P=0.000,0.000$）低于对照组和失眠组，觉醒次数（$P=0.028,0.033$）和睡眠呼吸暂停低通气指数（AHI；$P=0.000,0.000$）高于对照组和失眠组。（2）自主神经功能：共病组和失眠组低频耦合（LFC；$P=0.000,0.006$）和LFC/高频耦合（HFC）比值（$P=0.000,0.009$）高于对照组，HFC（$P=0.000,0.006$）和PNN50（$P=0.000,0.047$）低于对照组。（3）神经心理学测验：整体认知功能方面，共病组简易智能状态检查量表（MMSE）评分低于对照组（$P=0.000$）和失眠组（$P=0.002$），失眠组MMSE评分低于对照组（$P=0.008$）。记忆力方面，共病组听觉词语学习测验（AVLT）-短延迟回忆、长延迟回忆、再认评分低于对照组（$P=0.004,0.000,0.000$）和失眠组（$P=0.017,0.000,0.000$），共病组AVLT-即刻回忆评分低于对照组（$P=0.000$），失眠组AVLT-即刻回忆、长延迟回忆、再认评分低于对照组（$P=0.035,0.005,0.020$）。视空间能力方面，共病组本顿线方向测验（JLO）正确个数少于对照组（$P=0.000$）和失眠组（$P=0.000$），失眠组JLO正确个数少于对照组（$P=0.017$）。注意力方面，共病组数字广度测验（DST）顺背和倒背、符号数字转换测验（SDMT）正确个数少于对照组（$P=0.000,0.000,0.000$）和失眠组（$P=0.000,0.000,0.003$），失眠组DST倒背和SDMT正确个数少于对照组（$P=0.003,0.003$）。执行功能方面，共病组Stroop色词测验（SCWT）-A、SCWT-B、SCWT-C正确个数少于对照组（$P=0.000,0.000,0.000$）和失眠组（$P=0.004,0.025,0.044$），失眠组亦少于对照组（$P=0.003,0.007,0.011$）。焦虑和抑郁情绪方面，共病组汉密尔顿焦虑量表（HAMA）、汉密尔顿抑郁量表（HAMD）评分高于对照组（$P=0.000,0.000$）和失眠组（$P=0.000,0.000$），失眠组亦高于对照组（$P=0.000,0.000$）。（4）睡眠结构和自主神经功能与神经心理特征的相关性：慢性失眠合并阻塞性睡眠呼吸暂停患者总睡眠时间与DST顺背正确个数呈正相关（$r=0.325$，$P=0.031$）；REM占比与AVLT-即刻回忆（$r=0.302$，$P=0.047$）、短延迟回忆（$r=0.299$，$P=0.049$）、长延迟回忆（$r=0.480$，$P=0.001$）评分和SCWT-A正确个数（$r=0.311$，$P=0.040$）呈正相关；AHI与JLO（$r=-0.432$，$P=0.003$）、DST顺背（$r=-0.370$，$P=0.013$）、SDMT（$r=-0.449$，$P=0.002$）正确个数呈负相关，与HAMA（$r=0.407$，$P=0.006$）、HAMD（$r=0.446$，$P=0.002$）评分呈正相关；平均SaO_2与DST顺背正确个数呈正相关（$r=0.397$，$P=0.008$），与HAMA（$r=-0.370$，$P=0.013$）、HAMD（$r=-0.351$，$P=0.020$）

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评分呈负相关；最低SaO_2与JLO正确个数呈正相关（$r=0.473$，$P=0.001$）；LFC与HAMA（$r=0.428$，$P=0.004$）和HAMD（$r=0.337$，$P=0.025$）评分呈正相关关系；HFC与HAMA（$r=-0.428$，$P=0.004$）和HAMD（$r=-0.337$，$P=0.025$）评分呈负相关；LFC/HFC比值与HAMA（$r=0.415$，$P=0.005$）和HAMD（$r=0.308$，$P=0.042$）评分呈正相关。**结论** 慢性失眠合并阻塞性睡眠呼吸暂停患者存在睡眠结构紊乱、自主神经功能障碍、认知功能障碍和情绪障碍，睡眠结构紊乱和自主神经功能障碍可能是认知功能障碍和焦虑、抑郁情绪的潜在作用机制。

【关键词】 入睡和睡眠障碍； 睡眠呼吸暂停，阻塞性； 共病现象； 认知障碍； 神经心理学测验

Sleep structure and autonomic nervous function in patients with chronic insomnia combined with obstructive sleep apnea and their correlation with neuropsychological characteristics

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【Abstract】 Objective To investigate the sleep structure and autonomic nervous function of patients with chronic insomnia combined with obstructive sleep apnea (OSA) and analyze their correlation with neuropsychological characteristics. **Methods** A total of 91 patients with chronic insomnia admitted to Tianjin Medical University General Hospital and Airpot Hospital from September 2019 to June 2021 were included. They were divided into simple chronic insomnia group (insomnia group, n = 46) and chronic insomnia combined with OSA group (comorbidity group, n = 45) according to whether combined with OSA. And 22 volunteers matched in sex, age and education were recruited as the control group. Sleep structure and autonomic nervous function were analyzed by PSM-100A sleep breathing monitoring. Subjective sleep quality was assessed by Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and Insomnia Severity Index (ISI). Meanwhile, neuropsychological tests were performed. **Results** 1) Sleep structure: total sleep time (TST; $P=0.003$, 0.002), sleep efficiency ($P=0.000$, 0.019), proportion of rapid eye movement (REM; $P=0.000$, 0.015), mean arterial oxygen saturation (SaO_2; $P=0.000$, 0.000), minimum SaO_2 ($P=0.000$, 0.019) in the comorbidity group were lower than those in control group and insomnia group; while the wake times ($P=0.028$, 0.033) and sleep apnea hypopnea index (AHI; $P=0.000$, 0.000) were higher than those in control group and insomnia group. 2) Autonomic nervous function: the low frequency coupling (LFC; $P=0.000$, 0.006) and LFC/high frequency coupling (HFC) ratio ($P=0.000$, 0.009) in comorbidity group and insomnia group were higher than those in control group, while HFC ($P=0.000$, 0.006) and PNN50 ($P=0.000$, 0.047) were lower than those in control group. 3) Neuropsychological test: the comorbidity group had a lower Mini-Mental State Examination (MMSE) score than the control group ($P=0.000$) and insomnia group ($P=0.002$), and the insomnia group had a lower MMSE score than the control group ($P=0.008$). In terms of memory, Auditory Verbal Learning Test (AVLT)-short delayed recall, long delayed recall and recognition score were lower in the comorbidity group than those in the control group ($P=0.004$, 0.000, 0.000) and insomnia group ($P=0.017$, 0.000, 0.000). The AVLT-immediate recall score in comorbidity group was lower than that in control group ($P=0.000$), and the AVLT-immediate recall, long delayed recall and recognition score in insomnia group was lower than those in control group ($P=0.035$, 0.005, 0.020). In terms of visuospatial ability, the correct number of Benton′s Judgment of Line Orientation (JLO) was less in comorbidity group than in control group ($P=0.000$) and insomnia group ($P=0.000$), and the correct number of JLO in insomnia group was less than that in control group ($P=0.017$). In terms of attention, the number of correct number of Digit Span Test (DST) backward, DST downback and Symbol Digit Modalities Test (SDMT) in comorbidity group was less than that in control group ($P=0.000$, 0.000, 0.000) and insomnia group ($P=0.000$, 0.000, 0.003). The correct number of DST backward and SDMT in insomnia group was less than those in control group ($P=0.003$, 0.003). In terms of executive function, the correct numbers of Stroop Color-Word Test (SCWT)-A, SCWT-B and SCWT-C in the comorbidity group were less than those in the control group ($P=0.000$, 0.000, 0.000) and insomnia group ($P=0.004$, 0.025, 0.044). The correct numbers of SCWT-A, SCWT-B and SCWT-C in insomnia group were less than those in control

group (P = 0.003, 0.007, 0.011). In terms of anxiety and depression, the scores of Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) in the comorbidity group were higher than those in control group (P = 0.000, 0.000) and insomnia group (P = 0.000, 0.000), and the scores of HAMA and HAMD in insomnia group were also higher than those in control group (P = 0.000, 0.000). 4) The correlation of sleep structure and autonomic nervous function with neuropsychological characteristics: the TST in comorborbity group was positively correlated with the correct number of DST downback (r = 0.325, P = 0.031); the proportion of REM was positively correlated with AVLT-immediate recall (r = 0.302, P = 0.047), short delayed recall (r = 0.299, P = 0.049), long delayed recall (r = 0.480, P = 0.001) score, and the correct number of SCWT-A (r = 0.311, P = 0.040). AHI was negatively correlated with JLO (r = -0.432, P = 0.003), the correct number of DST downback (r = -0.370, P = 0.013), SDMT (r = -0.449, P = 0.002), and positively correlated with HAMA (r = 0.407, P = 0.006) and HAMD (r = 0.446, P = 0.013) score. The average SaO_2 was positively correlated with the correct number of DST (r = 0.397, P = 0.008), and negatively correlated with HAMA (r = -0.370, P = 0.013) and HAMD (r = -0.351, P = 0.020) score. The minimum SaO_2 was positively correlated with the correct number of JLO (r = 0.473, P = 0.001). LFC was positively correlated with HAMA (r = 0.428, P = 0.004) and HAMD (r = 0.337, P = 0.025) score. HFC was negatively correlated with HAMA (r = -0.428, P = 0.004) and HAMD (r = -0.337, P = 0.025) score. The LFC/HFC ratio was positively correlated with HAMA (r = 0.415, P = 0.005) and HAMD (r = 0.308, P = 0.042) score. **Conclusions** Patients with chronic insomnia combined with OSA have disturbed sleep structure, autonomic imbalance and cognitive decompensation, and disturbed sleep structure and autonomic nervous function may be potential mechanisms for cognitive decompensation and mood abnormalities.

【Key words】 Sleep initiation and maintenance disorders; Sleep apnea, obstructive; Comorbidity; Cognition disorders; Neuropsychological tests

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慢性失眠和阻塞性睡眠呼吸暂停(OSA)是临床最常见的睡眠障碍[1-2],二者可共病[3-7],39%～58%的阻塞性睡眠呼吸暂停患者自述存在失眠症状,29%～67%的慢性失眠患者合并阻塞性睡眠呼吸暂停[5-6],二者共病称为阻塞性睡眠呼吸暂停与慢性失眠共病(COMISA)[7]。长期睡眠不足可以导致情绪障碍、躯体化疾病和认知损害,慢性失眠患者记忆力、执行功能、注意力等认知功能明显减退[8-9];阻塞性睡眠呼吸暂停患者夜间间断性低氧和呼吸暂停使非快速眼动睡眠期(NREM)3期和快速眼动期睡眠期(REM)缩短,睡眠结构紊乱,导致日间过度思睡(EDS)、注意力下降、焦虑或抑郁情绪等,引起认知损害[10-12],且慢性失眠合并阻塞性睡眠呼吸暂停患者可能出现更严重的认知损害。鉴于此,本研究采用基于心肺耦合技术的睡眠监测设备监测慢性失眠合并阻塞性睡眠呼吸暂停患者的睡眠结构、自主神经功能,并采用神经心理学测验评价其认知功能、主观睡眠质量和情绪,初步探讨睡眠结构和自主神经功能与认知功能、焦虑和抑郁情绪之间的相关性。

对象与方法

一、研究对象

1.诊断标准 (1)慢性失眠:符合睡眠障碍国际分类第3版(ICSD-3)[13]的诊断标准,①存在睡眠紊乱,如入睡困难、睡眠维持困难、早醒。②存在日间功能受损,如疲乏感、注意力及记忆力减退、情绪障碍、工作或学习能力减退、日间思睡、冲动行为等。③失眠症状无法单纯以不恰当的睡眠环境和睡眠时间解释。④睡眠紊乱和日间功能受损每周发作≥3次且症状持续≥3个月。⑤睡眠紊乱和日常功能受损症状无法以其他类型的睡眠障碍解释。(2)阻塞性睡眠呼吸暂停:符合《成人阻塞性睡眠呼吸暂停基层诊疗指南(2018年)》[14]的诊断标准,①临床表现为以下症状中至少1项,白天思睡、醒后精力未恢复、疲劳或失眠;夜间憋气、喘息或窒息致觉醒;习惯性打鼾、呼吸中断;高血压、冠心病、脑卒中、心力衰竭、房颤、2型糖尿病、情绪障碍和认知功能障碍。②多导睡眠图(PSG)监测睡眠呼吸暂停低通气指数(AHI)≥5次/h,以阻塞性事件为主。③无临床

表1 3组受试者一般资料的比较
Table 1. Comparison of general data among 3 groups

观察指标	对照组(n=22)	失眠组(n=46)	共病组(n=45)	χ^2或F值	P值
性别[例(%)]				1.185	0.553
男性	7(31.82)	21(45.65)	19(42.22)		
女性	15(68.18)	25(54.35)	26(57.78)		
年龄($\bar{x}\pm s$,岁)	51.78±11.80	54.65±11.43	57.09±7.25	2.194	0.122
受教育程度($\bar{x}\pm s$,年)	13.96± 2.01	12.87± 3.32	12.58±3.46	2.473	0.092
高血压[例(%)]	3(13.64)	8(17.39)	15(33.33)	4.618	0.099
糖尿病[例(%)]	1(4.55)	7(15.22)	7(15.56)	1.810	0.404
高脂血症[例(%)]	4(18.18)	3(6.52)	6(13.33)	2.233	0.327
吸烟史[例(%)]	3(13.64)	6(13.04)	11(24.44)	2.339	0.310

One-way ANOVA for comparison of age and education, and χ^2 test for comparison of others,年龄和受教育程度的比较采用单因素方差分析,其余指标的比较采用χ^2检验

症状,PSG监测AHI≥15次/h,以阻塞性事件为主。同时符合①和②,或仅符合③,即可明确诊断。

2.纳入与排除标准 (1)年龄18~75岁。(2)受教育程度≥6年。(3)慢性失眠患者匹兹堡睡眠质量指数(PSQI)评分≥7分。(4)汉密尔顿抑郁量表(HAMD)评分<24分[15]。(5)汉密尔顿焦虑量表(HAMA)评分<21分[16]。(6)凡存在以下情况者不纳入本研究范畴:合并快速眼动睡眠期行为障碍(RBD)、周期性肢体运动障碍(PLMD)、发作性睡病等其他类型睡眠障碍;合并神经精神疾病;合并严重心、肺、肝、肾功能障碍;需行持续气道正压通气(CPAP);既往有酒精和药物滥用史;无法配合完成神经心理学测验。

3.一般资料 选择2019年9月至2021年6月就诊于天津医科大学总医院和空港医院神经内科门诊的慢性失眠患者共91例,根据是否合并阻塞性睡眠呼吸暂停分为慢性失眠组(失眠组,46例)和慢性失眠合并阻塞性睡眠呼吸暂停组(共病组,45例)。(1)失眠组:共46例,男性21例,女性25例;年龄为28~70岁,平均为(54.65±11.43)岁;受教育程度6~19年,平均(12.87±3.32)年;既往合并高血压占17.39%(8/46)、糖尿病占15.22%(7/46)、高脂血症占6.52%(3/46),吸烟占13.04%(6/46)。(2)共病组:共45例,男性19例,女性26例;年龄35~70岁,平均(57.09±7.25)岁,受教育程度6~19年,平均为(12.58±3.46)年;既往合并高血压占33.33%(15/45)、糖尿病占15.56%(7/45)、高脂血症占13.33%(6/45),吸烟占24.44%(11/45)。(3)无慢性失眠且无阻塞性睡眠呼吸暂停组(对照组):同期从我院健康体检中心招募22例无慢性失眠且无阻塞性睡眠呼吸暂停的受试者作为对照,无其他睡眠障碍病史,无认知功能减退主诉,能够配合完成神经心理学测验。男性7例,女性15例;年龄26~68岁,平均(51.78±11.80)岁,受教育程度为6~19年,平均(13.96±2.01)年;既往合并高血压占13.64%(3/22)、糖尿病占4.55%(1/22)、高脂血症占18.18%(4/22),吸烟占13.64%(3/22)。3组受试者一般资料比较,差异无统计学意义(均$P>0.05$,表1),均衡可比。

二、研究方法

1.睡眠结构和自主神经功能评价 失眠组和共病组患者药物治疗方案均为服用褪黑素受体激动剂(阿戈美拉汀25 mg/d)、选择性5-羟色胺再摄取抑制剂(草酸艾司西酞普兰10 mg/d)、非苯二氮䓬类药物(佐匹克隆7.50 mg/d或唑吡坦5 mg/d)。睡眠监测当晚停用催眠药物,于安静、舒适环境中采用便携式睡眠呼吸监测设备PSM-100A(思澜科技成都有限公司)和中国食品药物监督管理局(CFDA)批准的专利算法(专利号:20,162,210 145)评价睡眠结构以及自主神经功能。(1)睡眠结构:将心电记录仪贴于患者左侧胸骨旁或左侧锁骨中线上第3肋(男性)或第2~3肋(女性)处,同时佩戴鼻氧管和动脉血氧监测指套,于22:00至次日6:30连续记录8.50 h,由同一位经过睡眠监测技术培训的医师进行数据导入并处理分析心电信号和呼吸信号,计算机辅助生成各项睡眠结构参数,包括总睡眠时间(TST),入睡时间,睡眠效率(SE),REM、稳定睡眠期(NREM 1期和部分NREM 2期)、不稳定睡眠期(部分NREM 2期和NREM 3期)所占比例,觉醒次数,

AHI，平均动脉血氧饱和度（SaO_2），最低SaO_2。（2）自主神经功能：传统标准心电法测量心律之后，计算机自动生成频域指标和时域指标，频域指标主要包括校正后RR间期低频耦合（LFC）、高频耦合（HFC）占总睡眠时间比例，LFC/HFC比值；时域指标主要包括睡眠过程中相邻窦性心搏RR间期标准差（SDNN），睡眠过程中相邻窦性心搏RR间期差值平方和的均方根（RMSSD），PNN50（睡眠过程中相邻窦性心搏RR间期差值＞50 ms次数占心动周期次数的百分比）。

2.主观睡眠质量评价　由同一位经过睡眠相关量表培训的神经内科医师进行主观睡眠质量评价。（1）PSQI量表[17]：评价近1个月睡眠质量，包含睡眠质量、入睡时间、总睡眠时间、睡眠效率、睡眠障碍、催眠药物应用、日间功能障碍共7项内容，每项评分为0～3分，总评分为21分，评分越高、睡眠质量越差。（2）Epworth嗜睡量表（ESS）[18]：评价主观思睡程度，包括坐位阅读、看电视、公共场所静坐不动、乘车旅行持续1 h不休息、条件允许情况下下午卧床休息、静坐与他人谈话时、午餐不喝酒情况下餐后静坐、堵车情况下停车数分钟共8项内容，每项评分0～3分，总评分24分，评分越高、思睡倾向越严重，评分＞10分为存在白天过度思睡。（3）失眠严重程度指数（ISI）[19]：评价失眠严重程度，包括入睡困难程度、早醒程度、睡眠维持困难程度、睡眠满意度、对失眠症状的焦虑程度、对日间生活的影响程度、失眠对生活质量的影响程度共7项内容，每项评分0～4分，总评分为28分，评分越高、失眠越严重，评分0～7分为无意义的失眠、8～14分为亚临床失眠、15～21分为中度失眠、22～28分为重度失眠。

3.神经心理学测验　由同一位经过神经心理学测验量表培训的神经内科医师进行认知功能评价。（1）简易智能状态检查量表（MMSE）[20]：评价整体认知功能，包括定向力（10分）、记忆力（3分）、注意力和计算力（5分）、回忆功能（3分）、语言功能（8分）、视空间能力（1分）共7项内容，总评分30分，评分越低、认知功能越差，评分＜27分为存在认知功能障碍。（2）听觉词汇学习测验（AVLT）[21]：评价记忆力，包括即刻回忆、短延迟回忆、长延迟回忆和再认。嘱受试者对15个词汇进行5次重复学习并进行5次即刻回忆，每个词汇回忆正确计1分、回忆错误或无法回忆计为零，即刻回忆总评分75分；即刻回忆结束后，嘱受试者对另15个完全不同的词汇学习后进行即刻回忆，即短延迟回忆，总评分15分；短延迟回忆30 min后再次进行回忆，即长延迟回忆，总评分15分；长延迟回忆结束后即刻进行词汇再认，包括15个目标词汇和15个干扰词汇，正确识别目标词汇计1分，将干扰词汇识别为目标词汇减1分，回忆错误或无法回忆计为零，再认总评分15分；评分越低、记忆力越差。（3）数字广度测验（DST）[22]：评价即刻记忆和注意力，分为顺背（DSF）和倒背（DSB）两部分，顺背测验为测试者以1字/s速度连续说出数个无规律数字后，嘱受试者复述，测验难度随数字的增大而增加，自数字“2”增大难度至9位数字，记录正确复述个数，总评分16分，；倒背测验为测试者以1字/s速度连续说出数个无规律数字后，嘱受试者倒叙复述，自数字“2”增大难度至8位数字，记录正确复述个数，总评分14分；评分越低、即刻记忆和注意力越差。（4）本顿线方向测验（JLO）[23]：评价视空间能力，嘱受试者观察对照卡片上以扇形排列代表不同线段方向的数字1～11，说出每张测试卡片上两条不同长度、不同方向线段所对应的数字，两条均正确计1分，共30张测试卡片，总评分30分，评分越低、视空间能力越差，评分＜23分为视空间能力障碍。（5）Stroop色词测验（SCWT）[24]：评价执行功能，包括卡片A、B和C，卡片A由50个黑色印刷的“红”、“黄”、“蓝”、“绿”汉字组成，要求受试者快速且准确读出汉字；卡片B由50个红色、黄色、蓝色、绿色圆点随机排列组成，要求受试者快速且准确读出圆点颜色；卡片C由50个字体颜色与汉字意义不一致的汉字组成，要求受试者快速且准确说出汉字颜色；记录45 s内正确个数，正确数越少、执行功能越差。（6）符号数字转换测验（SDMT）[25]：评价注意力和信息处理速度，要求受试者将无意义的符号转化为相应符号所对应的数字，记录90 s内正确个数，正确数越少、注意力和信息处理速度越差，正确数≤21个为注意力和信息处理障碍。（7）HAMD量表[15]：评价抑郁情绪，包括躯体化障碍（6项）、认知功能障碍（3项）、睡眠障碍（3项）、抑郁障碍（4项）、体重变化（1项）、自知力（1项）共6方面计17项内容，每项评分0～2或0～4分，总评分54分，评分≤7分为无抑郁、8～16分为轻度抑郁、17～23分为中度抑郁、≥24分为重度抑郁。（8）HAMA量表[16]：评价焦虑情绪，包括躯体性焦虑（7项）和精神性焦虑（7项）两方面共14项内容，每项评分0～4分，总评分56分，评分≤7分为无焦虑、8～13分为轻度焦虑、14～20分

为中度焦虑、≥21分为重度焦虑。

4.统计分析方法 采用SPSS 23.0统计软件进行数据处理与分析。计数资料以相对数构成比(%)或率(%)表示,采用χ^2检验。正态性检验采用Kolmogorov-Smirnov检验,呈正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,采用单因素方差分析,两两比较行LSD-t检验;呈非正态分布的计量资料以中位数和四分位数间距[$M(P_{25},P_{75})$]表示,采用Kruskal-Wallis H检验,两两比较采用Mann-Whitney U检验。为进一步探究睡眠结构、自主神经功能与认知功能、情绪的相关性,并排除混杂因素,将本研究数据看作近似正态分布,睡眠结构、自主神经功能与认知功能、焦虑和抑郁情绪之间的相关性采用Pearson相关分析和偏相关分析。以$P\leqslant0.05$为差异具有统计学意义。

结 果

睡眠结构参数和主观睡眠质量比较,3组受试者各项睡眠结构参数差异具有统计学意义(均$P<0.05$,表2)。其中,共病组总睡眠时间($P=0.003$,0.002)、睡眠效率($P=0.000$,0.019)、REM占比($P=0.000$,0.015)、平均SaO_2($P=0.000$,0.000)、最低SaO_2($P=0.000$,0.000)低于对照组和失眠组,失眠组平均SaO_2亦低于对照组($P=0.000$);不稳定睡眠期占比($P=0.000$,0.014)、觉醒次数($P=0.028$,0.033)、AHI($P=0.000$,0.000)高于对照组和失眠组,失眠组不稳定睡眠期占比亦高于对照组($P=0.001$);失眠组和共病组入睡时间长于($P=0.000$,0.001)、稳定睡眠期占比低于($P=0.004$,0.000)对照组(表3)。共病组PSQI、ESS、ISI评分高于对照组($P=0.000$,0.000,0.000),仅ESS评分高于失眠组($P=0.000$);失眠组PSQI、ISI评分高于对照组($P=0.000$,0.000;表4)。

自主神经功能比较,3组受试者LFC($P=0.000$)、HFC($P=0.000$)、LFC/HFC比值($P=0.000$)、RMSSD($P=0.046$)和PNN50($P=0.000$)差异具有统计学意义(表5)。其中,共病组和失眠组LFC($P=0.000$,0.006)和LFC/HFC比值($P=0.000$,0.009)高于对照组、HFC($P=0.000$,0.006)和PNN50($P=0.000$,0.047)低于对照组,共病组RMSSD高于对照组($P=0.042$,表6)。

神经心理学测验比较,3组受试者各项评分差异具有统计学意义(均$P=0.000$,表7)。整体认知功能方面,共病组MMSE评分低于对照组($P=0.000$)和失眠组($P=0.002$),失眠组MMSE评分亦低于对照组($P=0.008$);记忆力方面,共病组AVLT-短延迟回忆、长延迟回忆和再认评分低于对照组($P=0.004$, 0.000, 0.000)和失眠组($P=0.017$, 0.000, 0.000),共病组AVLT-即刻回忆评分低于对照组($P=0.000$),失眠组AVLT-即刻回忆($P=0.035$)、长延迟回忆($P=0.005$)和再认($P=0.020$)评分低于对照组;视空间能力方面,共病组JLO正确个数少于对照组($P=0.000$)和失眠组($P=0.000$),失眠组JLO正确个数少于对照组($P=0.017$,表8)。注意力方面,共病组DST顺背、DST倒背、SDMT正确个数少于对照组($P=0.000$,0.000,0.000)和失眠组($P=0.000$,0.000,0.003),失眠组DST倒背($P=0.003$)和SDMT($P=0.003$)正确个数少于对照组;执行功能方面,共病组SCWT-A、SCWT-B、SCWT-C正确个数少于对照组($P=0.000$, 0.000, 0.000)和失眠组($P=0.004$, 0.025, 0.044),失眠组亦少于对照组($P=0.003$, 0.007, 0.011);焦虑和抑郁情绪方面,共病组HAMA、HAMD评分高于对照组($P=0.000$,0.000)和失眠组($P=0.000$, 0.000),失眠组亦高于对照组($P=0.000$,0.000;表9)。

睡眠结构与认知功能、情绪的Pearson相关分析结果显示,慢性失眠合并阻塞性睡眠呼吸暂停患者总睡眠时间与DST顺背正确个数呈正相关($r=0.332$,$P=0.026$);REM占比与AVLT-即刻回忆($r=0.302$,$P=0.044$)、短延迟回忆($r=0.562$,$P=0.000$)、长延迟回忆($r=0.506$,$P=0.000$)评分以及SCWT-A($r=0.311$,$P=0.038$)、SCWT-B($r=0.295$,$P=0.049$)正确个数呈正相关;AHI与JLO($r=-0.469$,$P=0.001$)、DST顺背($r=-0.344$,$P=0.021$)、SCWT-A($r=-0.433$, $P=0.003$)、SCWT-B($r=-0.388$, $P=0.008$)、SDMT($r=-0.450$,$P=0.002$)正确个数呈负相关,与HAMA($r=0.408$,$P=0.005$)和HAMD($r=0.447$,$P=0.002$)评分呈正相关;平均SaO_2与DST顺背正确个数呈正相关($r=0.465$, $P=0.001$),与HAMA($r=-0.367$,$P=0.013$)和HAMD($r=-0.335$, $P=0.024$)评分呈负相关,最低SaO_2与JLO正确个数呈正相关($r=0.472$,$P=0.001$;表10,11)。进一步行偏相关分析显示,慢性失眠合并阻塞性睡眠呼吸暂停患者总睡眠时间与DST顺背正确个数呈正相关($r=0.325$,$P=0.031$);REM占比与AVLT-即刻回忆($r=0.302$, $P=0.047$)、短延迟回忆($r=0.299$, $P=$

表2 3组受试者睡眠结构参数和主观睡眠质量的比较

Table 2. Comparison of sleep structure parameters and subjective sleep quality among 3 groups

观察指标	对照组(n=22)	失眠组(n=46)	共病组(n=45)	F或χ^2值	P值
TST($\bar{x}\pm s$,min)	382.72±65.42	373.85±75.43	321.69±65.50	8.557	0.000
入睡时间($\bar{x}\pm s$,min)	21.16± 9.59	42.13±19.77	41.58±27.25	21.865	0.000
睡眠效率($\bar{x}\pm s$,%)	80.53± 5.54	76.13± 8.01	71.23±10.06	9.443	0.000
REM占比($\bar{x}\pm s$,%)	24.31± 2.22	22.91± 2.74	21.43± 2.35	10.499	0.000
稳定睡眠期占比($\bar{x}\pm s$,%)	32.06±12.89	21.86±12.80	15.95±10.48	13.472	0.000
不稳定睡眠期占比($\bar{x}\pm s$,%)	43.64±13.30	55.23±13.03	62.62±11.05	17.638	0.000
觉醒次数($\bar{x}\pm s$,次)	21.14± 8.14	22.48± 7.73	27.40±11.01	4.102	0.022
平均SaO_2($\bar{x}\pm s$,%)	96.77± 0.53	96.02± 0.58	94.80± 0.89	63.337	0.000
最低SaO_2($\bar{x}\pm s$,%)	89.68± 2.98	88.57± 3.05	80.49± 8.19	22.741	0.000
AHI[$M(P_{25},P_{75})$,次/h]	1.80(0.40,3.20)	1.70(0.80, 3.03)	12.30(6.85,15.50)	80.076	0.000
PSQI($\bar{x}\pm s$,评分)	4.00± 1.95	12.72± 3.62	12.13± 3.27	115.808	0.000
ESS[$M(P_{25},P_{75})$,评分]	0.00(0.00,0.00)	0.00(0.00, 1.00)	2.00(0.00, 4.00)	21.361	0.000
ISI[$M(P_{25},P_{75})$,评分]	0.00(0.00,4.25)	12.00(10.00,15.50)	12.00(10.00,15.50)	49.087	0.000

Kruskal-Wallis H test for comparison of AHI, ESS and ISI, and one-way ANOVA for comparison of others, AHI、ESS和ISI的比较采用Kruskal-Wallis H检验,其余指标的比较采用单因素方差分析。TST, total sleep time, 总睡眠时间; REM, rapid eye movement, 快速眼动睡眠期; SaO_2, arterial oxygen saturation, 动脉血氧饱和度; AHI, apnea hypopnea index, 呼吸暂停低通气指数; PSQI, Pittsburgh Sleep Quality Index, 匹兹堡睡眠质量指数; ESS, Epworth Sleepiness Scale, Epworth嗜睡量表; ISI, Insomnia Severity Index, 失眠严重程度指数

表3 3组受试者睡眠结构参数的两两比较

Table 3. Pairwise comparison of sleep structure parameters among 3 groups

组间两两比	TST		入睡时间		睡眠效率		REM占比		稳定睡眠期占比	
	t值	P值	t值	P值	t值	P值	t值	P值	t值	P值
对照组:失眠组	0.695	0.876	5.252	0.000	2.817	0.119	3.053	0.083	4.659	0.004
对照组:共病组	4.759	0.003	5.096	0.001	5.933	0.000	6.280	0.000	7.331	0.000
失眠组:共病组	5.046	0.002	0.171	0.992	3.880	0.019	4.018	0.015	3.336	0.052
组间两两比	不稳定睡眠期占比		觉醒次数		平均SaO_2		最低SaO_2		AHI	
	t值	P值	t值	P值	t值	P值	t值	P值	Z值	P值
对照组:失眠组	5.128	0.001	0.792	0.842	5.740	0.000	1.072	0.730	0.452	0.945
对照组:共病组	8.371	0.000	3.682	0.028	15.020	0.000	8.790	0.000	7.800	0.000
失眠组:共病组	4.045	0.014	3.590	0.033	11.550	0.000	9.582	0.000	10.240	0.000

TST, total sleep time, 总睡眠时间; REM, rapid eye movement, 快速眼动睡眠期; SaO_2, arterial oxygen saturation, 动脉血氧饱和度; AHI, apnea hypopnea index, 呼吸暂停低通气指数

0.049)、长延迟回忆($r=0.480$, $P=0.001$)评分以及SCWT-A正确个数($r=-0.311$, $P=0.040$)呈正相关关系;AHI与JLO($r=-0.432$, $P=0.003$)、DST顺背($r=-0.370$, $P=0.013$)、SDMT($r=-0.449$, $P=0.002$)正确个数呈负相关,与HAMA($r=0.407$, $P=0.006$)和HAMD($r=0.446$, $P=0.002$)评分呈正相关;平均SaO_2与DST正确个数呈正相关($r=0.397$, $P=0.008$),与HAMA($r=-0.370$, $P=0.013$)和HAMD($r=-0.351$, $P=0.020$)评分呈负相关;最低SaO_2与JLO正确个数呈正相关($r=0.473$, $P=0.001$;表12,13)。慢性失眠合并阻塞性睡眠呼吸暂停患者自主神经功能与情绪的Pearson相关分析显示,LFC与HAMA($r=0.321$, $P=0.031$)和HAMD($r=0.449$, $P=0.002$)评分呈正相关;HFC与HAMA($r=-0.321$, $P=0.031$)和HAMD($r=-0.449$, $P=0.002$)评分呈负相关;LFC/HFC比值与HAMA($r=0.297$, $P=0.047$)和HAMD($r=0.434$, $P=0.003$)评分呈正相关(表14)。进一步行偏相关分析结果显示,慢性失眠合并阻塞性睡眠呼吸暂停患者LFC与HAMA($r=0.428$, $P=0.004$)和HAMD($r=0.337$, $P=0.025$)评分呈正相关关系;HFC与HAMA($r=-0.428$, $P=0.004$)和HAMD($r=-0.337$, $P=0.025$)评分呈负相关;LFC/HFC比值

表4 3组受试者主观睡眠质量的两两比较

Table 4. Pairwise comparison of subjective sleep quality among 3 groups

组间两两比	PSQI		ESS		ISI	
	*t*值	*P*值	*Z*值	*P*值	*Z*值	*P*值
对照组：失眠组	14.780	0.000	-6.176	0.401	-54.829	0.000
对照组：共病组	13.740	0.000	-28.957	0.000	-53.985	0.000
失眠组：共病组	1.225	0.663	-22.781	0.000	0.844	0.902

PSQI，Pittsburgh Sleep Quality Index，匹兹堡睡眠质量指数；ESS，Epworth Sleepiness Scale，Epworth 嗜睡量表；ISI，Insomnia Severity Index，失眠严重程度指数

与HAMA（$r = 0.415$，$P = 0.005$）和HAMD（$r = 0.308$，$P = 0.042$）评分呈正相关（表15）。

讨　论

慢性失眠是最常见的睡眠障碍类型，患病率为5%～40%，尤以老年女性多见，农村地区高于城市地区[26-27]。我国失眠患病率为2.6%～60.3%，50岁以下人群约38.8%，老年人群约42%[28]。自1973年首例慢性失眠合并阻塞性睡眠呼吸暂停病例被报道以来[6-7]，逐渐发现慢性失眠合并阻塞性睡眠呼吸暂停发生率高于单纯慢性失眠或阻塞性睡眠呼吸暂停[7,29-30]，考虑可能与共病患者症状复杂严重致就诊率较高有关。与慢性失眠或阻塞性睡眠呼吸暂停相比，慢性失眠合并阻塞性睡眠呼吸暂停患者更易出现睡眠质量、日间工作效率、生活质量下降，情绪和认知功能障碍，甚至出现明显躯体化症状如头晕、眩晕、心慌、气短、烧灼感等[31-33]。

PSM-100A睡眠呼吸监测设备对睡眠结构的评价标准与PSG不同，该设备基于心肺耦合（CPC）原理对睡眠结构进行分期，即利用心电信号标准窦性心搏RR间期的标记获得RR间期心率时序并推导QRS间期在每次搏动的呼吸调节时序，再通过两个时序的互补交叉光谱功率和相干度乘积的Fourier算法，获得心肺耦合睡眠光谱特征图，从而将睡眠分为极低频（< 0.01 Hz）、低频（< 0.10 Hz）和高频（< 0.40 Hz）耦合带，其中，极低频耦合带为REM；低频耦合带为不稳定睡眠期，对应NREM 1期和部分NREM 2期；高频耦合带为稳定睡眠期，对应部分NREM 2期和NREM 3期[34]。本研究以PSM-100A睡眠呼吸监测设备评价睡眠结构，其结果显示，慢性失眠合并阻塞性睡眠呼吸暂停患者存在更严重的睡眠结构紊乱，如总睡眠时间缩短，睡眠效率、REM占比减少，觉醒次数增加；此外，主观睡眠质量评价提示日间思睡程度加重，与既往基于PSG监测的临床研究结果基本一致[35-36]。慢性失眠与阻塞性睡眠呼吸暂停相互独立又相互影响，后者夜间发生呼吸暂停和低氧血症可引起胸腔压力剧烈变化，使左心室后负荷增加，心房牵张释放心房利钠肽，进而抑制肾素-血管紧张素-醛固酮系统，导致肾小管重吸收障碍，夜尿增多；此外，低氧血症引起的频繁觉醒还可激活下丘脑-垂体-肾上腺（HPA）轴，增强交感神经兴奋，夜尿增多，最终导致觉醒次数增多，睡眠维持困难和睡眠质量下降[37]，这可能是慢性失眠合并阻塞性睡眠呼吸暂停患者睡眠结构紊乱加重的主要原因。本研究结果显示，共病组REM占比低于对照组和失眠组。REM是机体呈高度活跃状态的睡眠时相，表现为眼球快速运动、肌肉完全松弛和做梦，与清醒期和其他睡眠时相相比，REM对低氧血症和高碳酸血症的敏感性最低[38]。有13.5%～36.7%的阻塞性睡眠呼吸暂停患者低通气和呼吸暂停事件主要发生于REM，从而引起频繁觉醒，导致REM缩短[39]。睡眠时间缩短、睡眠质量降低和频繁觉醒可使5-羟色胺（5-HT）水平降低，导致细胞外与突触后5-HT受体结合减少，进一步加重慢性失眠合并阻塞性睡眠呼吸暂停患者的焦虑和抑郁情绪，且易出现日间功能障碍如乏力、日间思睡、反应迟钝和精神紊乱等。

心率变异性（HRV）是最常用的自主神经功能评价指标[40-42]，是窦房结对交感神经和副交感神经系统相互作用、相互影响所产生的特征性反应，可引起连续RR间期细微变化，是交感神经与副交感神经相互平衡拮抗的产物，与副交感神经张力活性呈正相关，同时与昼夜节律密切相关[41]。研究发现，健康人群日间工作活动时交感神经兴奋性增高，副交感神经兴奋性降低，表现为心率变异性降低；而夜间睡眠时副交感神经兴奋性增高，交感神经兴奋性降低，则表现为心率变异性升高。本研究采用PSM-100A睡眠呼吸监测设备对心率变异性进行分析以反映睡眠期自主神经功能变化，其中时域参数SDNN、RMSSD、PNN50主要反映副交感神经兴奋性，三者均与心率变异性呈正相关关系[40-42]；频域参数LFC反映交感神经兴奋性，HFC反映副交感神经兴奋性，LFC/HFC比值反映交感神经与副交感神经兴奋性的均衡[40]。本研究结果显示，慢性失眠合并阻塞性睡眠呼吸暂停患者LFC和LFC/HFC比值

表5 3组受试者自主神经功能的比较

Table 5. Comparison of autonomic nervous function among 3 groups

观察指标	对照组(n=22)	失眠组(n=46)	共病组(n=45)	F或χ^2值	P值
LFC($\bar{x}\pm s$,%)	54.45±11.66	64.06±13.53	69.81± 9.94	12.465	0.000
HFC($\bar{x}\pm s$,%)	45.55±11.66	35.94±13.53	30.19± 9.94	12.465	0.000
LFC/HFC比值($\bar{x}\pm s$)	1.33± 0.55	2.18± 1.20	2.67± 1.19	10.985	0.000
SDNN($\bar{x}\pm s$,s)	78.28±19.55	74.50±25.38	72.92±21.16	0.412	0.663
RMSSD[$M(P_{25},P_{75})$,s]	33.25(26.68,44.78)	28.25(22.15,40.63)	27.00(23.60,33.75)	6.159	0.046
PNN50[$M(P_{25},P_{75})$,%]	11.18(5.51,23.09)	5.67(3.39,14.06)	3.90(1.87, 7.53)	16.324	0.000

Kruskal-Wallis H test for comparison of RMSSD and PNN50, and one-way ANOVA for comparison of others, RMSSD和PNN50的比较采用Kruskal-Wallis H检验,其余指标的比较采用单因素方差分析。LFC, low frequency coupling, 低频耦合;HFC, high frequency coupling, 高频耦合;SDNN, standard deviation of normal-to-normal intervals, 窦性心搏RR间期标准差;RMSSD, the square root of the mean squared differences of successive normal-to-normal intervals, 窦性心搏RR间期差值平方和的均方根

表6 3组受试者自主神经功能的两两比较

Table 6. Pairwise comparison of autonomic nervous function among 3 groups

组间两两比	LFC		HFC		LFC/HFC比值		RMSSD		PNN50	
	t值	P值	t值	P值	t值	P值	Z值	P值	Z值	P值
对照组:失眠组	4.427	0.006	4.427	0.006	4.238	0.009	-1.913	0.167	3.397	0.047
对照组:共病组	7.047	0.000	7.047	0.000	6.622	0.000	2.457	0.042	5.829	0.000
失眠组:共病组	3.271	0.058	3.271	0.058	2.976	0.094	0.684	1.000	3.032	0.086

LFC, low frequency coupling, 低频耦合;HFC, high frequency coupling, 高频耦合;RMSSD, the square root of the mean squared differences of successive normal-to-normal intervals, 窦性心搏RR间期差值平方和的均方根

升高,HFC和PNN50降低,提示存在明显的自主神经功能紊乱。不同睡眠时相自主神经功能呈现生理性变化,NREM副交感神经兴奋性增高、交感神经兴奋性降低,REM交感神经兴奋性增高、副交感神经兴奋性降低[43]。本研究还发现,慢性失眠合并阻塞性睡眠呼吸暂停患者稳定睡眠期占比减少,使交感神经张力抑制作用减弱,出现自主神经功能障碍。阻塞性睡眠呼吸暂停患者呼吸暂停可引起二氧化碳潴留,刺激化学感受器激活副交感神经,呼吸恢复后机体仍处于缺氧状态,使交感神经长期处于亢奋状态,导致自主神经功能紊乱[44]。此外,阻塞性睡眠呼吸暂停患者夜间频繁觉醒,激活大脑皮质唤醒机制,使其处于高度生理唤醒状态,同样可激活交感神经[37]。然而,本研究仅对慢性失眠合并阻塞性睡眠呼吸暂停患者整体睡眠过程中自主神经功能变化进行分析,尚待今后研究进一步对各睡眠时相心率变异性动态变化及日间心率变异性进行监测分析,以更全面地评价慢性失眠合并阻塞性睡眠呼吸暂停患者自主神经功能变化。

既往研究显示,慢性失眠合并阻塞性睡眠呼吸暂停患者较单纯慢性失眠或阻塞性睡眠呼吸暂停患者表现为更严重的认知功能减退,多采用MMSE量表和蒙特利尔认知评价量表(MoCA)等整体认知功能评价量表,但是对高级认知功能的评价鲜有报道[45]。本研究采用各认知域特征性量表对各项认知功能进行针对性评价,发现共病组整体认知功能、记忆力、视空间能力、注意力和执行功能较对照组和失眠组明显降低。慢性失眠和阻塞性睡眠呼吸暂停均可引起认知功能减退,睡眠片段化和低氧血症是主要原因。研究显示,间断性低氧血症通过诱导炎症和氧化应激,引起海马等与认知功能密切相关脑区神经细胞凋亡、结构破坏;同时还可升高缺氧诱导因子1α(HIF-1α)水平,导致*BACE-1*基因表达上调、β-淀粉样蛋白(Aβ)生成途径激活,引起Aβ沉积,最终导致认知功能减退[46-47]。睡眠结构紊乱通过影响昼夜节律系统和睡眠稳态系统引起认知功能减退[48]。动物模型显示,睡眠剥夺(SD)可抑制大脑对代谢产物的清除、海马发育、学习能力、记忆力[49],睡眠时间越少、大脑皮质Aβ沉积越多[50]。深睡眠时间减少,尤其1~2 Hz的NREM 3期睡眠减少与脑脊液tau蛋白、Aβ升高有关[51]。fMRI研究发现,失眠患者背侧注意网络与默认网络之间联系失衡,阻塞性睡眠呼吸暂停患者扣带回、岛叶皮质、腹内侧前额皮质等脑区损害,这些改变均可导致神经

表7 3组受试者神经心理学测验的比较($\bar{x} \pm s$)

Table 7. Comparison of neuropsychological tests among 3 groups ($\bar{x} \pm s$)

观察指标	对照组(n=22)	失眠组(n=46)	共病组(n=45)	*F*值	*P*值
MMSE(评分)	29.73± 0.63	28.48± 1.64	27.36± 1.81	34.721	0.000
AVLT-即刻回忆(评分)	44.41± 7.03	39.96± 9.29	34.71± 7.35	11.346	0.000
AVLT-短延迟回忆(评分)	11.05± 1.29	8.66± 2.00	6.84± 1.02	91.370	0.000
AVLT-长延迟回忆(评分)	9.68± 1.52	8.20± 2.27	6.49± 1.24	39.200	0.000
AVLT-再认(评分)	14.23± 0.69	13.13± 1.45	11.89± 1.91	29.385	0.000
DST顺背正确个数(个)	15.18± 1.22	13.85± 2.50	11.78± 2.68	25.546	0.000
DST倒背正确个数(个)	9.41± 2.09	7.72± 2.25	6.04± 1.36	27.454	0.000
JLO正确个数(个)	26.59± 1.87	24.63± 2.64	22.27± 3.10	24.894	0.000
SCWT-A正确个数(个)	85.00±15.33	71.11±17.59	60.38±13.63	20.997	0.000
SCWT-B正确个数(个)	66.77±15.48	55.09±16.09	47.04±12.02	13.887	0.000
SCWT-C正确个数(个)	48.78±14.03	39.22±13.06	32.84±11.12	12.067	0.000
SDMT正确个数(个)	42.64±13.06	33.09±13.00	25.49± 6.41	20.422	0.000
HAMA(评分)	3.82± 2.44	9.15± 3.82	11.91± 2.75	73.826	0.000
HAMD(评分)	3.73± 2.35	8.98± 2.95	11.56± 2.88	57.084	0.000

MMSE, Mini-Mental State Examination, 简易智能状态检查量表; AVLT, Auditory Verbal Learning Test, 听觉词汇学习测验; DST, Digit Span Test, 数字广度测验; JLO, Benton's Judgment of Line Orientation, 本顿线方向测验; SCWT, Stroop Colour-Word Test, Stroop色词测验; SDMT, Symbol Digit Modalities Test, 符号数字转换测验; HAMA, Hamilton Anxiety Scale, 汉密尔顿焦虑量表; HAMD, Hamilton Depression Scale, 汉密尔顿抑郁量表

表8 3组受试者整体认知功能、记忆力和视空间能力的两两比较

Table 8. Pairwise comparison of overall cognitive function, memory and visuospatial function among 3 groups

组间两两比	MMSE		AVLT-即刻回忆		AVLT-短延迟回忆		AVLT-长延迟回忆		AVLT-再认		JLO正确个数	
	*t*值	*P*值	*t*值	*P*值	*t*值	*P*值	*t*值	*P*值	*t*值	*P*值	*t*值	*P*值
对照组：失眠组	4.335	0.008	3.560	0.035	1.445	0.565	4.563	0.005	3.852	0.020	3.940	0.017
对照组：共病组	8.278	0.000	5.501	0.000	4.629	0.004	9.769	0.000	8.182	0.000	8.658	0.000
失眠组：共病组	4.912	0.002	2.424	0.204	3.957	0.017	6.479	0.000	5.390	0.000	5.872	0.000

MMSE, Mini-Mental State Examination, 简易智能状态检查量表; AVLT, Auditory Verbal Learning Test, 听觉词汇学习测验; JLO, Benton's Judgment of Line Orientation, 本顿线方向测验

表9 3组受试者注意力、执行功能和情绪的两两比较

Table 9. Pairwise comparison of attention, execution ability and emotion among 3 groups

组间两两比	DST顺背正确个数		DST倒背正确个数		SDMT正确个数		SCWT-A正确个数	
	*t*值	*P*值	*t*值	*P*值	*t*值	*P*值	*t*值	*P*值
对照组：失眠组	3.044	0.084	4.837	0.003	4.794	0.003	4.834	0.003
对照组：共病组	7.739	0.000	9.585	0.000	8.578	0.000	8.538	0.000
失眠组：共病组	5.839	0.000	5.913	0.000	4.716	0.003	4.617	0.004
组间两两比	SCWT-B正确个数		SCWT-C正确个数		HAMA		HAMD	
	*t*值	*P*值	*t*值	*P*值	*t*值	*P*值	*t*值	*P*值
对照组：失眠组	4.405	0.007	4.163	0.011	9.141	0.000	10.170	0.000
对照组：共病组	7.410	0.000	6.915	0.000	13.820	0.000	15.110	0.000
失眠组：共病组	3.748	0.025	3.433	0.044	5.845	0.000	6.173	0.000

DST, Digit Span Test, 数字广度测验; SDMT, Symbol Digit Modalities Test, 符号数字转换测验; SCWT, Stroop Color-Word Test, Stroop色词测验; HAMA, Hamilton Anxiety Scale, 汉密尔顿焦虑量表; HAMD, Hamilton Depression Scale, 汉密尔顿抑郁量表

轴突变性，进而影响认知功能[52-53]。

本研究还发现，慢性失眠合并阻塞性睡眠呼吸暂停患者睡眠结构与多项神经心理学测验评分存在相关性。REM占比与AVLT-即刻回忆、延迟回忆

表10 慢性失眠合并阻塞性睡眠呼吸暂停患者睡眠结构与整体认知功能、记忆力和视空间能力的Pearson相关分析

Table 10. Pearson correlation analysis of sleep structure and overall cognitive function, memory and visuospatial function in comorbidity group

观察指标	MMSE		AVLT-即刻回忆		AVLT-短延迟回忆		AVLT-长延迟回忆		AVLT-再认		JLO正确个数	
	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值
TST	0.081	0.596	-0.045	0.768	-0.039	0.801	0.027	0.860	0.077	0.615	0.069	0.654
入睡时间	0.056	0.717	-0.043	0.781	-0.016	0.915	-0.113	0.461	0.025	0.868	0.129	0.397
睡眠效率	0.058	0.704	-0.111	0.464	-0.039	0.798	-0.026	0.868	-0.057	0.711	-0.078	0.610
REM占比	0.254	0.096	0.302	0.044	0.562	0.000	0.506	0.000	-0.176	0.249	0.073	0.633
稳定睡眠期占比	0.061	0.689	-0.109	0.475	0.086	0.575	-0.005	0.975	0.011	0.945	0.016	0.918
不稳定睡眠期占比	0.054	0.726	0.039	0.798	-0.201	0.186	-0.103	0.501	0.027	0.858	-0.031	0.842
觉醒次数	-0.033	0.828	0.039	0.802	-0.245	0.134	-0.031	0.841	0.147	0.335	0.133	0.385
AHI	-0.162	0.288	-0.162	0.289	-0.160	0.293	-0.283	0.059	-0.147	0.335	-0.469	0.001
平均SaO_2	0.184	0.227	0.233	0.124	0.164	0.281	0.189	0.213	0.186	0.220	0.290	0.053
最低SaO_2	-0.088	0.570	0.097	0.525	0.042	0.785	0.015	0.921	0.017	0.914	0.472	0.001

TST, total sleep time, 总睡眠时间; REM, rapid eye movement, 快速眼动睡眠期; AHI, apnea hypopnea index, 呼吸暂停低通气指数; SaO_2, arterial oxygen saturation, 动脉血氧饱和度; MMSE, Mini-Mental State Examination, 简易智能状态检查量表; AVLT, Auditory Verbal Learning Test, 听觉词汇学习测验; JLO, Benton's Judgment of Line Orientation, 本顿线方向测验

表11 慢性失眠合并阻塞性睡眠呼吸暂停患者睡眠结构与注意力、执行功能和情绪的Pearson相关分析

Table 11. Pearson correlation analysis of sleep structure and attention, execution ability and emotion in comorbidity group

观察指标	DST顺背正确个数		DST倒背正确个数		SCWT-A正确个数		SCWT-B正确个数	
	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值
TST	0.332	0.026	-0.033	0.829	0.029	0.848	0.029	0.848
入睡时间	-0.071	0.643	0.002	0.990	-0.140	0.359	-0.139	0.363
睡眠效率	0.095	0.533	0.064	0.675	0.044	0.775	0.092	0.548
REM占比	-0.209	0.167	0.107	0.483	0.311	0.038	0.295	0.049
稳定睡眠期占比	0.120	0.431	0.109	0.477	0.091	0.551	-0.003	0.985
不稳定睡眠期占比	-0.070	0.650	-0.126	0.410	-0.153	0.317	-0.060	0.695
觉醒次数	0.233	0.124	0.209	0.168	-0.147	0.336	-0.052	0.734
AHI	-0.344	0.021	-0.146	0.337	-0.433	0.003	-0.388	0.008
平均SaO_2	0.465	0.001	0.082	0.593	0.236	0.119	0.284	0.059
最低SaO_2	0.067	0.661	-0.041	0.791	0.176	0.247	0.156	0.306

观察指标	SCWT-C正确个数		SDMT正确个数		HAMA		HAMD	
	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值
TST	-0.078	0.609	0.102	0.505	-0.060	0.699	-0.017	0.913
入睡时间	0.090	0.556	0.177	0.244	0.011	0.942	-0.032	0.837
睡眠效率	-0.000	0.998	-0.242	0.109	-0.147	0.335	-0.064	0.674
REM占比	0.176	0.247	-0.002	0.988	-0.219	0.154	-0.261	0.087
稳定睡眠期占比	0.031	0.839	0.100	0.512	-0.236	0.119	-0.254	0.092
不稳定睡眠期占比	-0.067	0.663	-0.095	0.535	0.234	0.123	0.251	0.097
觉醒次数	-0.055	0.721	0.001	0.996	-0.095	0.535	-0.009	0.955
AHI	-0.276	0.067	-0.450	0.002	0.408	0.005	0.447	0.002
平均SaO_2	0.113	0.458	0.291	0.052	-0.367	0.013	-0.335	0.024
最低SaO_2	0.095	0.534	0.030	0.843	0.038	0.803	0.017	0.911

TST, total sleep time, 总睡眠时间; REM, rapid eye movement, 快速眼动睡眠期; AHI, apnea hypopnea index, 呼吸暂停低通气指数; SaO_2, arterial oxygen saturation, 动脉血氧饱和度; DST, Digit Span Test, 数字广度测验; SCWT, Stroop Color-Word Test, Stroop色词测验; SDMT, Symbol Digit Modalities Test, 符号数字转换测验; HAMA, Hamilton Anxiety Scale, 汉密尔顿焦虑量表; HAMD, Hamilton Depression Scale, 汉密尔顿抑郁量表

表12 慢性失眠合并阻塞性睡眠呼吸暂停患者睡眠结构与整体认知功能、记忆力和视空间能力的偏相关分析

Table 12. Partial correlation analysis of sleep structure and overall cognitive function, memory and visuospatial function in comorbidity group

观察指标	MMSE		AVLT-即刻回忆		AVLT-短延迟回忆		AVLT-长延迟回忆		AVLT-再认		JLO正确个数	
	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值
TST	0.100	0.519	-0.045	0.773	-0.059	0.704	-0.003	0.984	0.087	0.574	0.108	0.485
入睡时间	0.081	0.603	-0.028	0.858	-0.057	0.714	-0.109	0.480	0.048	0.757	0.154	0.309
睡眠效率	0.020	0.898	-0.023	0.883	-0.103	0.505	-0.045	0.770	-0.111	0.473	-0.131	0.397
REM占比	-0.020	0.897	0.302	0.047	0.299	0.049	0.480	0.001	-0.175	0.255	0.074	0.632
稳定睡眠期占比	0.051	0.741	-0.105	0.498	-0.159	0.302	-0.011	0.943	0.000	0.999	0.007	0.965
不稳定睡眠期占比	-0.044	0.776	0.035	0.823	0.807	0.575	-0.092	0.551	0.037	0.810	-0.022	0.886
觉醒次数	-0.037	0.810	0.040	0.795	-0.046	0.767	-0.013	0.935	0.144	0.351	0.130	0.400
AHI	-0.159	0.301	-0.062	0.690	-0.017	0.914	-0.049	0.754	-0.289	0.057	-0.432	0.003
平均SaO_2	0.167	0.280	0.097	0.530	-0.004	0.980	0.196	0.203	0.171	0.268	0.284	0.061
最低SaO_2	-0.087	0.573	0.262	0.086	0.226	0.140	-0.017	0.911	0.017	0.915	0.473	0.001

TST, total sleep time, 总睡眠时间; REM, rapid eye movement, 快速眼动睡眠期; AHI, apnea hypopnea index, 呼吸暂停低通气指数; SaO_2, arterial oxygen saturation, 动脉血氧饱和度; MMSE, Mini-Mental State Examination, 简易智能状态检查量表; AVLT, Auditory Verbal Learning Test, 听觉词汇学习测验; JLO, Benton's Judgment of Line Orientation, 本顿线方向测验

表13 慢性失眠合并阻塞性睡眠呼吸暂停患者睡眠结构与注意力、执行功能和情绪的偏相关分析

Table 13. Partial correlation analysis of sleep structure and attention, execution ability and emotion in comorbidity group

观察指标	DST顺背正确个数		DST倒背正确个数		SCWT-A正确个数		SCWT-B正确个数	
	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值
TST	0.325	0.031	-0.034	0.827	-0.008	0.957	-0.008	0.958
入睡时间	0.019	0.901	-0.007	0.963	-0.137	0.375	-0.136	0.378
睡眠效率	-0.088	0.569	0.904	0.545	0.034	0.828	0.089	0.564
REM占比	-0.218	0.155	0.107	0.489	0.311	0.040	0.296	0.051
稳定睡眠期占比	0.082	0.598	0.114	0.461	0.088	0.570	-0.007	0.965
不稳定睡眠期占比	-0.031	0.844	0.131	0.396	-0.150	0.331	-0.057	0.713
觉醒次数	0.231	0.132	0.211	0.169	-0.148	0.337	-0.054	0.073
AHI	-0.370	0.013	-0.170	0.269	-0.236	0.124	-0.182	0.238
平均SaO_2	0.397	0.008	0.099	0.521	0.240	0.116	0.292	0.055
最低SaO_2	0.071	0.646	-0.041	0.793	0.176	0.253	0.156	0.311

观察指标	SCWT-C正确个数		SDMT正确个数		HAMA		HAMD	
	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值	*r*值	*P*值
TST	-0.056	0.716	0.158	0.307	-0.058	0.707	-0.026	0.866
入睡时间	0.072	0.642	0.213	0.164	-0.005	0.975	-0.037	0.809
睡眠效率	0.045	0.770	-0.342	0.023	-0.136	0.379	-0.065	0.675
REM占比	0.176	0.254	-0.001	0.994	-0.050	0.748	-0.046	0.766
稳定睡眠期占比	0.042	0.786	0.088	0.570	-0.230	0.133	-0.254	0.096
不稳定睡眠期占比	-0.077	0.618	-0.083	0.591	0.228	0.136	0.251	0.101
觉醒次数	-0.051	0.740	-0.004	0.980	0.098	0.527	-0.008	0.960
AHI	-0.089	0.567	-0.449	0.002	0.407	0.006	0.446	0.002
平均SaO_2	0.149	0.333	0.274	0.072	-0.370	0.013	-0.351	0.020
最低SaO_2	0.096	0.537	0.031	0.844	0.038	0.805	0.017	0.912

TST, total sleep time, 总睡眠时间; REM, rapid eye movement, 快速眼动睡眠期; AHI, apnea hypopnea index, 呼吸暂停低通气指数; SaO_2, arterial oxygen saturation, 动脉血氧饱和度; DST, Digit Span Test, 数字广度测验; SCWT, Stroop Color-Word Test, Stroop色词测验; SDMT, Symbol Digit Modalities Test, 符号数字转换测验; HAMA, Hamilton Anxiety Scale, 汉密尔顿焦虑量表; HAMD, Hamilton Depression Scale, 汉密尔顿抑郁量表

表14 慢性失眠合并阻塞性睡眠呼吸暂停患者自主神经功能与情绪的Pearson相关分析

Table 14. Pearson correlation analysis of autonomic nervous function and emotion in comorbidity group

观察指标	HAMA		HAMD	
	*r*值	*P*值	*r*值	*P*值
LFC	0.321	0.031	0.449	0.002
HFC	-0.321	0.031	-0.449	0.002
LFC/HFC比值	0.297	0.047	0.434	0.003
SDNN	-0.026	0.868	0.011	0.945
RMSSD	0.049	0.750	-0.022	0.888
PNN50	-0.047	0.761	-0.142	0.352

LFC, low frequency coupling, 低频耦合; HFC, high frequency coupling, 高频耦合; SDNN, standard deviation of all normal-to-normal intervals, 窦性心搏RR间期标准差; RMSSD, the square root of the mean squared differences of successive normal-to normal intervals, 窦性心搏RR间期差值平方和的均方根; HAMA, Hamilton Anxiety Scale, 汉密尔顿焦虑量表; HAMD, Hamilton Depression Scale, 汉密尔顿抑郁量表。The same for Table 15

表15 慢性失眠合并阻塞性睡眠呼吸暂停患者自主神经功能与情绪的偏相关分析

Table 15. Partial correlation analysis of autonomic nervous function and emotion in comorbidity group

观察指标	HAMA		HAMD	
	*r*值	*P*值	*r*值	*P*值
LFC	0.428	0.004	0.337	0.025
HFC	-0.428	0.004	-0.337	0.025
LFC/HFC比值	0.415	0.005	0.308	0.042
SDNN	0.072	0.643	-0.001	0.994
RMSSD	-0.174	0.258	0.019	0.902
PNN50	-0.155	0.314	-0.273	0.073

评分呈正相关，提示REM缩短与语言记忆功能减退密切相关。语言记忆主要与大脑左侧内侧颞叶杏仁-海马区相关，睡眠减少可通过神经炎症改变引起海马区神经退行性变，出现灰质体积减少[54]。θ振荡是REM的主要脑电波，尤以海马最显著，皮质和皮质下结构也可记录到θ振荡，对空间记忆编码和后续巩固至关重要[55]。通过光遗传干扰内侧隔核以干扰REM θ波可损伤海马相关场景相关记忆，REM抑制可引起新生神经元轻微突触结构改变，使突触功能降低，影响记忆力[56]。本研究结果显示，慢性失眠合并阻塞性睡眠呼吸暂停患者AHI与视空间能力、注意力和执行功能障碍存在负相关，与焦虑和抑郁情绪存在正相关关系。皮质、皮质下结构和皮质-皮质下连接在认知功能方面发挥重要作用[57]，前额皮质是调节情绪、注意力和记忆力等认知功能的高级联合皮质，背外侧前额叶与执行功能相关，丘脑是感觉和运动的中继站，背侧丘脑-正中前额叶回路与执行功能相关，背外侧丘脑损伤时也可出现前额叶损伤症状[58]。间歇性低氧血症与脑血流量和血压快速波动有关，导致氧化应激、炎症和内皮功能障碍。局部一致性(ReHo)研究显示，严重阻塞性睡眠呼吸暂停患者右侧颞叶、顶叶和额叶脑区局部一致性明显降低[59]。基于体素的形态学分析(VBM)显示，慢性失眠和阻塞性睡眠呼吸暂停患者背外侧前额皮质[60]、右侧顶下小叶、颞上回后部、前额叶下部皮质、腹内侧前额皮质体积减少，尤以右侧显著[61]，这些脑区损伤是视空间能力、注意力、执行功能、工作记忆力减退以及焦虑、抑郁情绪的可能作用机制。

本研究结果显示，慢性失眠合并阻塞性睡眠呼吸暂停患者交感神经兴奋性与焦虑、抑郁情绪呈正相关，副交感神经兴奋性与焦虑、抑郁情绪存在负相关关系，提示自主神经功能越差、焦虑和抑郁情绪越明显。交感神经兴奋性增高易出现明显的情绪波动，出现心率加快、易激惹和易疲劳感，而副交感神经兴奋性增高则主要表现为心态更平和[62]。间断性低氧和频繁觉醒可以激活HPA轴，促进皮质醇和去甲肾上腺素释放，使交感神经兴奋性增高，交感神经与副交感神经失衡，从而增加焦虑、抑郁易感性[63]。交感神经过度兴奋可以引起焦虑、抑郁情绪，反之，焦虑、抑郁情绪又可加重自主神经功能紊乱。

本研究尚存一定的局限性：(1)以神经内科就诊患者为研究对象，样本量较小且相对局限，可能存在选择偏倚。(2)未对慢性失眠合并阻塞性睡眠呼吸暂停患者进行阻塞性睡眠呼吸暂停亚型分类。(3)为单中心横断面研究，未对研究对象进行长期随访。未来尚待进一步扩大样本量，多中心合作，对慢性失眠合并阻塞性睡眠呼吸暂停进行亚型分类，结合影学检查结果，进行长期纵向随访以明确睡眠结构与认知功能之间的具体作用机制及相互作用关系。

综上所述，慢性失眠合并阻塞性睡眠呼吸暂停患者存在明显的睡眠结构紊乱、自主神经功能障碍、认知功能障碍和情绪障碍，睡眠结构紊乱可加重认知功能障碍，自主神经功能障碍可加重焦虑、抑郁情绪，临床医师应注重慢性失眠合并阻塞性睡眠呼吸暂停的筛查，积极干预，改善患者睡眠结构

和认知功能。

利益冲突 无

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·小词典·

中英文对照名词词汇（四）

简明认知行为疗法
brief cognitive behavioral therapy for insomnia（BBT-I）
简易智能状态检查量表
Mini-Mental State Examination（MMSE）
焦虑自评量表 Self-Rating Anxiety Scale（SAS）
脚桥被盖核 pedunculopontine tegmental nucleus（PPT）
结节乳头体核 tuberomammillary nucleus（TMN）
解耦联蛋白 uncoupling protein（UCP）
经颅多普勒超声 transcranial Doppler ultrasonography（TCD）
惊恐障碍 panic disorder（PD）
静态脑血流自动调节 static cerebral autoregulation（sCA）
局部一致性 regional homogeneity（ReHo）
聚偏二氟乙烯 polyvinylidene fluoride（PVDF）
抗核抗体 anti-nuclear antibody（ANA）
抗溶血性链球菌素O anti-streptolysin O（ASO）
抗原呈递细胞 antigen-presenting cell（APC）
快速傅里叶变换 fast Fourier transform（FFT）
快速眼动睡眠期 rapid eye movement（REM）
快速眼动睡眠期肌肉失弛缓
rapid eye movement sleep without atonia（RSWA）
快速眼动睡眠期行为障碍
rapid eye movement sleep behavior disorder（RBD）
快速眼动睡眠期行为障碍问卷香港版
Rapid Eye Movement Sleep Behavior Disorder Questionnaire-Hong Kong（RBDQ-HK）
快速眼动睡眠潜伏期
rapid eye movement sleep latency（RSL）
辣根过氧化物酶 horseradish peroxidase（HRP）
类风湿因子 rheumatoid factor（RF）
连线测验 Trail Making Test（TMT）
磷酸盐缓冲液 phosphate-buffered saline（PBS）
磷脂酰肌醇-3激酶 phosphatidylinositol 3-kinase（PI3K）
路易体痴呆 dementia with Lewy bodies（DLB）
卵圆孔未闭 patent foramen ovale（PFO）
绿色荧光蛋白 green fluorescent protein（GFP）
脉冲电磁场 pulsed electromagnetic fields（PEMFs）
慢波睡眠 slow wave sleep（SWS）
慢性低度炎症 chronic low-grade inflammation（CLGI）
慢性脑低灌注 chronic cerebral hypoperfusion（CCH）
3米步行测验 3 Meter Walk Test（3MWT）
美国精神障碍诊断与统计手册第5版
Diagnostic and Statistical Manual of Mental Disorders Fifth Edition（DSM-5）
美国食品与药品管理局
Food and Drug Administration（FDA）
美国睡眠医学会
American Academy of Sleep Medicine（AASM）
蒙特利尔认知评价量表
Montreal Cognitive Assessment（MoCA）
模式识别受体 pattern recognition receptors（PRRs）
脑白质高信号 white matter hyperintensity（WMH）
脑淀粉样血管病 cerebral amyloid angiopathy（CAA）
脑灌注压 cerebral perfusion pressure（CPP）
脑过度灌注综合征 cerebral hyperperfusion syndrome（CHS）
脑血管反应性 cerebrovascular reactivity（CVR）
脑血流量 cerebral blood flow（CBF）
脑血流速度 cerebral blood flow velocity（CBFV）
脑血流自动调节 cerebral autoregulation（CA）
脑源性神经营养因子
brain-derived neurotrophic factor（BDNF）
帕金森病 Parkinson's disease（PD）
帕金森病预后量表-自主神经功能部分
Scales for Outcomes in Parkinson's Disease-Autonomic（SCOPA-AUT）
匹兹堡睡眠质量指数 Pittsburgh Sleep Quality Index（PSQI）
平均动脉压 mean arterial pressure（MAP）
前列腺素D2 prostaglandin D2（PGD2）
6-羟基多巴胺 6-hydroxydopamine（6-OHDA）
25-羟基维生素D 25-hydroxy vitamin D[25（OH）D]
5-羟色胺 5-hydroxytryptamine（5-HT）