

双相障碍与吸烟导致的脑区活动动态性改变

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[摘要] 目的: 双相障碍(bipolar disorder, BD)患者吸烟率较高, 吸烟状态可能协同疾病相关脑功能异常, 共同影响静息态脑活动。为探究BD诊断与吸烟状态对脑区动态活动不稳定性的独立及交互效应, 本研究基于静息态功能磁共振成像(functional magnetic resonance imaging, fMRI)数据, 综合动态低频振幅(dynamic amplitude of low-frequency fluctuation, dALFF)、动态分数低频振幅(dynamic fractional amplitude of low-frequency fluctuation, dfALFF)、动态局部一致性(dynamic regional homogeneity, dReHo)评估局部脑活动动态波动, 并分析异常脑区与临床症状及每日吸烟量的关系。方法: 纳入2022年7月至2025年11月中南大学湘雅二医院招募的113名研究对象, 包括25名吸烟的BD患者(BDsm组)、33名不吸烟的BD患者(BDnsm组)、23名吸烟的健康对照者(HCsm组)及32名不吸烟的健康对照者(HCnsm组)。BDsm组和BDnsm组合并为BD组, HCsm组和HCnsm组合并为HC组。采集静息态fMRI数据并完成预处理后, 采用滑动窗口方法计算dALFF、dfALFF和dReHo。3项动态指标经标准化后进行主成分分析, 提取第一主成分作为综合动态脑区活动指标。构建全脑双因素协方差分析模型, 分析BD诊断与吸烟状态的主效应及其交互效应, 协变量包括年龄、性别、受教育年限和数据集来源; 对显著脑区进一步事后比较及Pearson相关分析。结果: 全脑分析显示, BD诊断与吸烟状态在右侧丘脑存在显著交互效应。事后分析显示, BDsm组的右侧丘脑动态活动不稳定性显著高于HCsm组($t=3.955$, $P<0.001$)和BDnsm组($t=5.987$, $P<0.001$), BDnsm组的右侧丘脑动态活动不稳定性低于HCnsm组($t=-6.681$, $P<0.001$), HCsm组低于HCnsm组($t=-4.530$, $P<0.001$)。控制数据集来源后, 该交互效应仍显著, 且仅在男性样本中重复分析时结果一致。BD诊断主效应出现在腹内侧前额叶皮层和左侧背外侧前额叶皮层。事后分析显示, BDsm的腹内侧前额叶皮层和左侧背外侧前额叶皮层的动态活动不稳定性均显著高于HCsm组(腹内侧前额叶皮层: $t=5.046$, $P<0.001$; 左侧背外侧前额叶皮层: $t=3.152$, $P=0.003$), BDnsm的腹内侧前额叶皮层和左侧背外侧前额叶皮层的动态活动不稳定性亦均显著高于HCnsm组(腹内侧前额叶皮层: $t=3.440$, $P=0.001$; 左侧背外侧前额叶皮层: $t=4.684$, $P<0.001$)。未观察到吸烟状态的主效应。全部吸烟者中, 每日吸烟量与右侧丘脑动态活动不稳定性呈正相关($r=0.335$, $P=0.026$); 吸烟BD患者左侧背外侧前额叶皮层动态活动不稳定性与焦虑症状呈正相关($r=0.451$, $P=0.031$)。结论: BD诊断与吸烟状态对右侧丘脑动态活动存在交互影响。非吸烟状态下, BD患者表现为丘脑动态活动不稳定性降低; 在吸烟状态下, BD相关丘脑动态活动降低的表现减弱, 并与吸烟暴露强度存在一定关联。BD患者前额叶脑区动态活动不稳定性升高, 提示情绪调节和认知控制相关脑区存在动态活动异常。

[关键词] 双相障碍; 神经影像; 吸烟; 丘脑; 前额叶皮层

Dynamic alterations in regional brain activity associated with bipolar disorder and smoking status

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ABSTRACT

Objective: Patients with bipolar disorder (BD) have a high prevalence of smoking. Smoking status may interact with disease-related brain functional abnormalities and jointly influence resting-state brain activity. This study aims to investigate the independent and interactive effects of BD diagnosis and smoking status on the dynamic instability of regional brain activity. Based on resting-state functional magnetic resonance imaging (fMRI) data, dynamic amplitude of low-frequency fluctuation (dALFF), dynamic fractional amplitude of low-frequency fluctuation (dfALFF), and dynamic regional homogeneity (dReHo) were integrated to evaluate fluctuations in regional brain activity. Furthermore, associations between abnormal brain regions, clinical symptoms, and daily cigarette consumption were analyzed.

Methods: From July 2022 to November 2025, a total of 113 participants were recruited at the Second Xiangya Hospital of Central South University, including 25 smoking patients with BD (BDsm group), 33 non-smoking patients with BD (BDnsm group), 23 smoking healthy controls (HCsm group), and 32 non-smoking healthy controls (HCnsm group). The BDsm and BDnsm groups were combined as the BD group, while the HCsm and HCnsm groups were combined as the healthy control (HC) group. Resting-state fMRI data were collected and preprocessed, followed by calculation of dALFF, dfALFF, and dReHo using a sliding-window approach. The 3 dynamic indices were standardized and subjected to principal component analysis, with the first principal component extracted as a composite measure of dynamic regional brain activity. Whole-brain two-way analysis of covariance (ANCOVA) was performed to examine the interaction effects and main effects of BD diagnosis and smoking status, with age, sex, years of education, and dataset source included as covariates. Brain regions showing significant effects were further analyzed using post hoc comparisons and Pearson correlation analyses.

Results: Whole-brain analysis revealed a significant interaction effect between BD diagnosis and smoking status in the right thalamus. Post hoc analyses showed that dynamic activity instability in the right thalamus was significantly higher in the BDsm group than in the HCsm group ($t=3.955$, $P<0.001$) and the BDnsm group ($t=5.987$, $P<0.001$). The BDnsm group exhibited lower right thalamic dynamic activity instability than the HCnsm group ($t=-6.681$, $P<0.001$), and the HCsm group showed lower instability than the HCnsm group ($t=-4.530$, $P<0.001$). After controlling for dataset source, the interaction effect remained significant, and the results were replicated only in the male subgroup. A main effect of BD diagnosis was identified in the ventromedial prefrontal cortex and left dorsolateral prefrontal cortex. Post hoc analyses showed that dynamic activity instability in the ventromedial prefrontal cortex and left dorsolateral prefrontal cortex was significantly higher in the BDsm group than in the HCsm group (ventromedial prefrontal cortex: $t=5.046$, $P<0.001$; left dorsolateral prefrontal cortex: $t=3.152$, $P=0.003$). Similarly, the BDnsm group exhibited significantly higher dynamic activity instability in these regions than the HCnsm group (ventromedial prefrontal cortex: $t=3.440$, $P=0.001$; left dorsolateral prefrontal cortex: $t=4.684$, $P<0.001$). No significant main effect of smoking status was

observed. Among all smokers, daily cigarette consumption was positively correlated with dynamic activity instability in the right thalamus ($r=0.335$, $P=0.026$). Among smoking patients with BD, dynamic activity instability in the left dorsolateral prefrontal cortex was positively correlated with anxiety symptoms ($r=0.451$, $P=0.031$).

Conclusion: BD diagnosis and smoking status exert interactive effects on dynamic activity in the right thalamus. Under non-smoking conditions, patients with BD exhibited reduced thalamic dynamic activity instability; however, this BD-associated reduction was attenuated among smokers and showed an association with smoking exposure intensity. Patients with BD demonstrated increased dynamic activity instability in prefrontal regions, suggesting abnormalities in brain regions involved in emotional regulation and cognitive control.

KEY WORDS bipolar disorder; neuroimaging; smoking; thalamus; prefrontal cortex

双相障碍(bipolar disorder, BD)与吸烟之间的关系一直备受关注。根据最新的世界精神卫生调查数据^[1], BD的终身患病率男性为2.5%, 女性为2.3%。此外, BD患者人群的吸烟率明显高于普通人群^[2]。BD症状可能促使个体开始吸烟, 或以“补偿性行为”的形式增加烟草使用^[3]。精神分裂症研究中常被引用的自我药疗假说^[4-5]提出, 尼古丁可能有助于缓解认知受损、抵消抗精神病药物的不良反应, 并减轻快感缺失等阴性症状。因此, 在BD中也可能存在类似机制: 尽管吸烟总体上有害健康, 但其或许能带来某些特定的神经生物学“收益”。一项研究^[6]在探讨BD患者吸烟与认知功能的关系时发现, 吸烟患者在主观认知表现评估中得分更高。

虽然, 已有大量关于吸烟与BD关联的研究^[7-8], 但大部分仍停留在行为或症状层面, 对于二者在神经生物学层面的共同影响关注不足。2项神经影像学研究^[9-10]探讨了BD与吸烟的共同作用。Jørgensen等^[9]的研究指出吸烟患者(包括BD与精神分裂症患者)相较于不吸烟患者, 前扣带皮层和岛叶的皮层更薄。Ohi等^[10]发现, 吸烟状态与BD诊断均与左侧岛叶皮层厚度减少相关, 并且二者呈叠加效应。但这些研究尚未进一步考察吸烟与BD对脑区活动的联合作用。BD与吸烟可能对大脑产生协同影响, 而目前该领域的功能磁共振成像(functional magnetic resonance imaging, fMRI)研究仍然缺乏。静息态fMRI衍生的低频振幅(amplitude of low-frequency fluctuation, ALFF)、分数低频振幅(fractional amplitude of low-frequency fluctuation, fALFF)和局部一致性(regional homogeneity, ReHo)常用于表征脑区活动^[11]。同时, 脑区活动具有动态特征, 会随时间发生变化^[12-13]。因

此, 动态低频振幅(dynamic ALFF, dALFF)、动态分数低频振幅(dynamic fALFF, dfALFF)、动态局部一致性(dynamic ReHo, dReHo)被认为能够捕捉脑区活动的不稳定性, 并越来越多地应用于精神障碍的研究^[14-15]。本课题组此前关于BD的研究^[16-18]发现, 多个脑区(如海马旁回、中扣带回、尾状核、下颞回)的dfALFF、dALFF或dReHo存在异常。另有研究^[19-21]表明, 吸烟也会使健康人群多个脑区(如下额回、扣带回、楔前叶)的dReHo与dALFF发生改变。值得注意的是, 本课题组还曾研究抑郁与吸烟的联合作用, 发现二者交互会使中央前回与楔前叶的动态脑区活动增加^[22]。因此, 有必要结合dALFF、dfALFF与dReHo来探讨BD与吸烟对脑区活动的交互影响。本研究旨在探讨BD与吸烟对脑区活动的交互效应, 从而为BD人群中吸烟率偏高提供神经影像学证据。

1 对象与方法

1.1 伦理声明

本研究已获得中南大学湘雅二医院医学伦理委员会批准[审批号: (2022)国伦审第(K024)号]。所有研究对象均为汉语母语者、右利手, 并签署了书面知情同意书。

1.2 对象

共招募113名研究对象, 均来自中南大学湘雅二医院, 招募时间为2022年7月至2025年11月, 包括25名吸烟的BD患者(BDsm组)、33名不吸烟的BD患者(BDnsm组)、23名吸烟的健康对照者(HCsm组)及32名不吸烟的健康对照者(HCnsm组)。BDsm组和BDnsm组合并为BD组, HCsm组和HCnsm组合并为

HC组。

所有BD患者均由执业精神科医师诊断, 纳入标准为: 1)符合精神障碍诊断与统计手册第四版(Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, DSM-IV)中双相I型或双相II型障碍诊断标准; 2)年龄16~55岁; 3)受教育年限 ≥ 9 年; 4)汉语母语者; 5)右利手; 6)签署书面知情同意书。BD患者的排除标准为: 1)由药物或精神活性物质引起精神障碍; 2)神经系统疾病; 3)严重躯体疾病; 4)存在磁共振扫描禁忌证; 5)曾有持续超过5 min的意识丧失史; 6)接受过电休克治疗和经颅磁刺激治疗; 7)孕产妇; 8)共病其他精神障碍。临床症状采用17项汉密尔顿抑郁量表(Hamilton Depression Rating Scale, HAMD)^[23]、汉密尔顿焦虑量表(Hamilton Anxiety Rating Scale, HAMA)^[24]、杨氏躁狂量表(Young Mania Rating Scale, YMRS)^[25]及简明精神病评定量表(Brief Psychiatric Rating Scale, BPRS)^[26]进行评估。

吸烟者定义为: 1)至少连续1年、每日吸烟 ≥ 1 支; 2)戒烟时间不超过3个月; 3)年龄16~55岁^[27]。

健康对照者从当地社区招募, 在年龄、性别和受教育程度方面尽量与BD患者匹配, 并使用精神障碍诊断与统计手册定式临床检查(Structured Clinical Interview for DSM, SCID)非患者版进行筛查。健康对照者需不符合DSM-IV任何精神障碍诊断标准, 且一级亲属无精神障碍病史; 其余纳入和排除标准与患者组一致。

本研究为探索性横断面研究, 样本量未进行正式先验计算, 主要依据研究期间连续招募的符合纳入标准的研究对象数量确定, 并参考既往同类BD、吸烟及静息态fMRI研究^[17, 19, 28]的样本规模。

1.3 影像数据采集与预处理

本研究的数据分别在2台磁共振成像扫描仪上采集, 其中数据集1使用Siemens Allegra 3.0T扫描仪, 数据集2使用Philips Gyroscan Achieva 3.0T扫描仪。

2套数据的影像采集参数及研究对象分布如下。1)数据集1: 重复时间(repetition time, TR)为2 000 ms, 回波时间(echo time, TE)为30 ms, 层厚4 mm, 层间距5 mm, 采集矩阵 64×64 , 视野为 $250 \text{ mm} \times 250 \text{ mm}$, 翻转角 80° , 体素大小 $4 \text{ mm} \times 4 \text{ mm} \times 5 \text{ mm}$ 。每个脑体积包含32层, 功能扫描共采集216个图像体积。2)数据集2: TR为2 000 ms, TE为30 ms, 层厚4 mm, 层间距4 mm, 采集矩阵 64×64 , 视野为 $240 \text{ mm} \times 240 \text{ mm}$, 翻转角 90° , 体素大小 $4 \text{ mm} \times 4 \text{ mm} \times 4 \text{ mm}$ 。每个脑体积包含36层, 功能扫描共采集250个图像体积。

2套数据分别根据各自扫描参数进行预处理, 使用的软件为统计参数映射软件12(Statistical Parametric Mapping 12, SPM12)与静息态功能磁共振数据处理助手(Data Processing Assistant for Resting-State fMRI, DPABI)^[29]。为使研究对象适应扫描环境并保证扫描仪稳定性, 首先剔除最初10个时间点的图像体积。随后, 对剩余体积进行切片时序校正, 以修正不同切片之间的采集延迟, 并将所有图像配准至中间体积。配准后, 将图像空间归一化至蒙特利尔神经学研究所(Montreal Neurological Institute, MNI)标准空间, 并重采样为 $3 \text{ mm} \times 3 \text{ mm} \times 3 \text{ mm}$ 体素。再采用高斯核进行空间平滑处理, 半高全宽(full width at half maximum, FWHM)为8 mm。接着, 进行线性去趋势处理, 并回归去除干扰协变量, 包括脑脊液信号、白质信号、6个刚体头动校正参数及全脑平均信号。与此同时, 还进行了头动擦除(scrubbing)回归, 以减少细微头动带来的混杂影响。最后, 将逐帧位移(frame-wise displacement, FD) > 0.5 的“坏帧”及其相邻帧(前1帧、后2帧)进行标记, 并纳入回归处理。

剔除标准为: 头动在任一方向平移超过2.5 mm或旋转超过 2.5° , 以及fMRI数据无法归一化至MNI空间者。最终8名研究对象因头动超过预设阈值被排除, 纳入105名研究对象进入后续分析, 其中吸烟BD患者23名、不吸烟BD患者30名、吸烟HCs 23名、不吸烟HCs 29名。数据集1包含48名研究对象, 其中吸烟BD患者4名、不吸烟BD患者10名、吸烟HCs 17名、不吸烟HCs 17名。数据集2共包含57名研究对象, 其中吸烟BD患者19名、不吸烟BD患者20名、吸烟HCs 6名、不吸烟HCs 12名。

1.4 dALFF、dfALFF、dReHo的计算

采用动态脑连接组(dynamic brain connectome, DynamicBC)v2.2工具箱中的滑动窗口方法计算动态指标^[30]。为降低窗口过短导致的虚假波动风险, 窗口长度(以时间计)不宜小于 $1/f_{\min}$, 其中 $f_{\min}$ 为时间序列的最低频率^[31]。本研究 $f_{\min}$ 设定为0.01 Hz, 对应 $1/f_{\min}=100 \text{ s}$; 结合 $\text{TR}=2 \text{ s}$, 窗口长度设为50个TR, 即100 s。在数据集1中, 时间序列共206个TR(412 s), 窗口以1个TR(2 s)为步长滑动, 将全长序列划分为每名研究对象157个窗口。数据集2中, 时间序列为240个TR(480 s), 同样以1个TR(2 s)为步长滑动, 划分为191个窗口。随后获得每个窗口对应的ALFF、fALFF和ReHo图, 并计算跨窗口的变异系数, 以反映脑区活动的不稳定性。

1.5 主成分分析

将3种动态指标(dALFF、dfALFF、dReHo)堆叠为矩阵,并在主成分分析前进行标准化处理。使用

Matlab中的pca()函数提取第一主成分,作为脑区活动不稳定性的表征。具体计算步骤见图1。

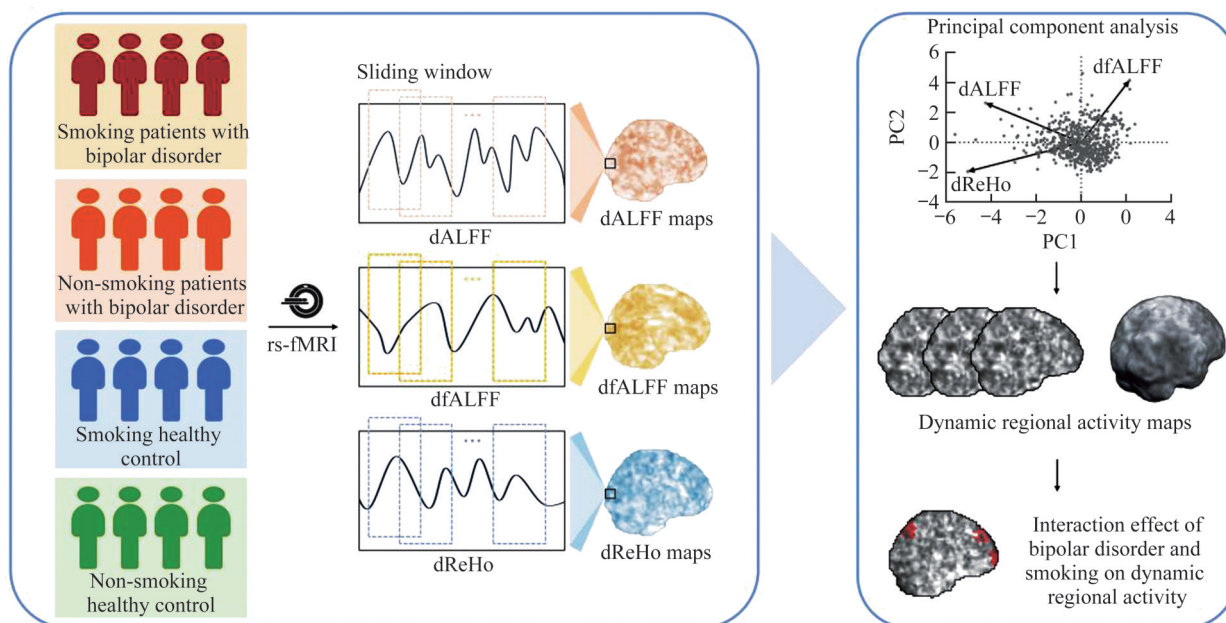


图1 研究方法流程图

Figure 1 Flowchart of this study

rs-fMRI: Resting-state functional magnetic resonance imaging; dALFF: Dynamic amplitude of low-frequency fluctuation; dfALFF: Dynamic fractional amplitude of low-frequency fluctuation; dReHo: Dynamic regional homogeneity; PC: Principal component.

1.6 统计学处理

采用SPSS 19.0对人口学和临床数据进行分析,显著性水平设定为 $P<0.05$ 。年龄、受教育年限及量表评分等连续变量采用均数 $\pm$ 标准差表示,组间比较采用 t 检验;性别、治疗阶段、用药情况及双相心境状态以例表示,组间比较采用 χ^2 检验。

采用SPM12对fMRI数据进行分析。构建全脑双因素协方差分析(analysis of covariance, ANCOVA)模型,分析BD诊断(BD vs HCs)与吸烟状态(吸烟 vs 不吸烟)的主效应及其交互效应。模型中纳入性别、年龄、受教育年限及数据集来源作为协变量,其中数据集来源为二分类变量,以哑变量形式纳入统计模型。统计推断采用体素水平阈值 $P<0.001$,簇大小 ≥ 23 个体素(AlphaSim校正)。

为排除不同扫描仪及采集参数对主效应的潜在干扰,进一步进行敏感性分析:1)比较4组研究对象在2个数据集分布中的分布差异,确保亚组间数据来源均衡;2)提取上述全脑分析中显著交互效应脑区的平均信号值,建立以诊断、吸烟状态及其交互项为主要

效应,并控制年龄、性别、受教育年限和数据集来源的ANCOVA模型;3)检验数据集来源与诊断、吸烟状态之间的交互项,以评估主要结果是否受数据集来源调节。

提取存在组间差异脑区的平均不稳定性数值后,进一步进行事后比较,并采用Bonferroni校正,显著性水平为 $P<0.05$ /比较次数。同时,采用Pearson相关分析检验相关脑区与症状严重程度和每日吸烟量之间的关系。

2 结果

2.1 研究对象的特征

BD组的年龄、男女性别比及受教育年限分别为(25.04 $\pm$ 6.40)岁、33/20、(13.02 $\pm$ 3.02)年,HC组的年龄、男女性别比及受教育年限分别为(24.63 $\pm$ 6.83)岁、41/11、(12.90 $\pm$ 3.57)年,2组在年龄($t=0.312$, $P=0.756$)、性别($\chi^2=3.469$, $P=0.063$)和受教育年限($t=0.178$, $P=0.859$)方面的差异均无统计学意义。BDsm

组每日吸烟量显著高于HCsm组[(15.26±12.37)支 vs (9.24±4.73)支, $t=2.094$, $P=0.042$]。

BDsm组和BDnsm组在年龄、受教育年限、发病年龄、病程、用药状态、服药时间、药物使用情况、双相心境状态及各临床症状量表评分方面差异均无统计学意义(均 $P>0.05$), 与BDnsm组相比, BDsm组男性比例较高($\chi^2=4.430$, $P=0.035$; 表1)。

HCsm组年龄为(23.91±8.24)岁, 受教育年限为

(12.48±3.47)年, 每日吸烟量为(9.24±4.73)支; HCnsm组年龄为(25.21±5.56)岁, 受教育年限为(13.24±3.68)年。

4组在年龄和受教育年限方面差异均无统计学意义(分别为 $F=0.479$, $P=0.697$; $F=0.236$, $P=0.871$), 但性别构成存在显著差异($\chi^2=17.335$, $P=0.001$), 吸烟组男性比例较高。

表1 BD患者的一般临床资料

Table 1 General clinical data of BD patients

Characteristic	BDsm group (n=23)	BDnsm group (n=30)	χ^2/t	P
Age/Years	26.00±6.02	24.30±6.68	0.958	0.343
Male/female	18/5	15/15	4.430	0.035
Education/Years	13.00±2.94	13.03±3.12	-0.039	0.969
Age at onset/Years	21.32±5.13	21.69±5.43	-0.248	0.805
Duration of illness/Months	67.05±76.49	42.85±49.69	1.382	0.173
Cigarettes smoked per day	15.26±12.37	—	—	—
Medication status (drug-naïve/on medication)	3/20	9/21	2.137	0.144
Duration of medication treatment/Months	8.35±18.29	9.69±19.76	-0.250	0.804
Medication use				
Lithium	10	13	0.000	0.992
Antiepileptic mood stabilizers	9	11	0.034	0.854
Antipsychotics	11	14	0.007	0.933
Antidepressants	8	12	0.151	0.698
Bipolar mood state			1.004	0.800
Depressive episode	8	12	—	—
Manic/hypomanic episode	4	5	—	—
Mixed episode	1	3	—	—
Euthymic state	10	10	—	—
Clinical symptom scale scores				
HAMD total score	10.74±9.65	14.34±8.04	-1.470	0.148
HAMA total score	8.48±7.41	11.28±8.40	-1.256	0.215
YMRS total score	6.83±10.13	8.69±9.95	0.666	0.509
BPRS total score	29.45±8.19	33.45±8.86	-1.646	0.102

Continuous variables are presented as mean±standard deviation and are compared using independent-samples t tests. Categorical variables are presented as frequencies (percentages) and are compared using χ^2 tests. All tests are 2-sided, and $P<0.05$ is considered statistically significant. BD: Bipolar disorder; BDsm: Smoking patients with BD; BDnsm: Non-smoking patients with BD; HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; YMRS: Young Mania Rating Scale; BPRS: Brief Psychiatric Rating Scale.

2.2 交互效应

全脑分析(图2、表2)显示, BD诊断与吸烟在右侧丘脑[MNI: (18, -27, 3), 簇大小=38]存在显著的交互效应。事后分析(图2、表2)显示: BDsm组的右

侧丘脑动态活动不稳定性显著高于HCsm组($t=3.955$, $P<0.001$)和BDnsm组($t=5.987$, $P<0.001$), BDnsm组的右侧动态丘脑活动不稳定性低于HCnsm组($t=-6.681$, $P<0.001$), HCsm组低于HCnsm组($t=-4.530$,

$P<0.001$)。4组的右侧丘脑动态活动均值数据见附表1(<https://doi.org/10.57760/sciencedb.xbyxb.0005x>)。考虑到吸烟组与不吸烟组性别比例差异可能影响结果,本研究仅在男性样本中重复分析。验证后结果与主分析(男女合并)一致,丘脑同样出现交互效应(表3),均值数据见附表2(<https://doi.org/10.57760/sciencedb.xbyxb.0005x>)。

敏感性分析表明,BDsm组、BDnsm组、HCsm组及HCnsm组研究对象在2个数据集的分布存在统计学差异($\chi^2=18.604$, $P<0.001$),提示需控制数据集来源的潜在影响。在右侧丘脑感兴趣区(region of interest, ROI)水平上,纳入年龄、性别、受教育年限及数据集来源后,诊断×吸烟的交互效应仍显著[F

(1, 95)=41.474, $P<0.001$],吸烟×数据集[$F(1, 95)=0.472$, $P=0.494$]及诊断×数据集[$F(1, 95)=0.288$, $P=0.593$]的交互效应均不显著。上述结果支持右侧丘脑所观察到的交互效应具有稳健性,并非主要由数据集差异驱动。

此外,无论整体BD患者还是吸烟BD患者,丘脑动态活动不稳定性与临床症状均无显著相关性(均 $P>0.05$,表4)。进一步在全部吸烟者中分析每日吸烟量与右侧丘脑动态活动不稳定性的关系,发现二者呈显著正相关($r=0.335$, $P=0.026$);在BD吸烟者亚组中,相关方向一致但未达显著($r=0.327$, $P=0.128$)。

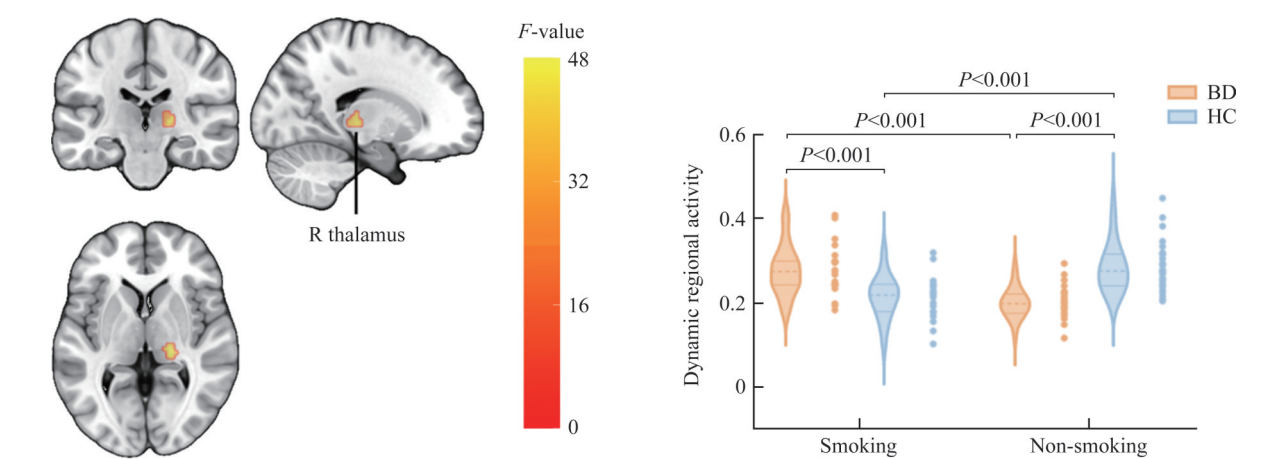


图2 BD与吸烟之间的交互效应

Figure 2 Interaction effects between bipolar disorder and smoking

A significant interaction effect is shown in the thalamus using 2-way ANCOVA. The statistical significance level is set at $P_{\text{voxel}}<0.001$ and cluster size ≥ 23 voxels (AlphaSim corrected). Bonferroni correction with 4 planned comparisons. HC: Healthy control.

表 2 受吸烟、BD 交互作用及主效应影响的动态活动不稳定性脑区						
Table 2 Brain regions with dynamic activity instability due to main effects of smoking, BD, or their interaction						
Brain regions	CM LR	CM PA	CM SI	<i>k</i>	BDsm vs BDnsm	
					<i>t</i>	<i>P</i>
Interaction between BD and smoking						
R thalamus	18	−27	3	38	5.987	<0.001
Main effects of BD						
Ventromedial prefrontal cortex	−6	33	−15	107	—	—
L dorsolateral prefrontal cortex	−33	45	39	23	—	—
Main effects of smoking						
Not available						

表 2(续)

Brain regions	BDsm vs HCsm		BDnsm vs HCnsm		HCsm vs HCnsm	
	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>
Interaction between BD and smoking						
R thalamus	3.955	<0.001	-6.681	<0.001	-4.530	<0.001
Main effects of BD						
Ventromedial prefrontal cortex	5.046	<0.001	3.440	0.001	—	—
L dorsolateral prefrontal cortex	3.152	0.003	4.684	<0.001	—	—
Main effects of smoking						
Not available						

Cluster centroid coordinates are reported in MNI space (mm). Whole-brain effects are examined using a 2×2 analysis of covariance (ANCOVA), with diagnosis (BD/HC), smoking status (smoker/non-smoker), and their interaction as fixed effects; age, sex, years of education, and dataset source are included as covariates. The whole-brain threshold is set at voxel-wise $P<0.001$ with a cluster extent of ≥ 23 voxels, corrected using AlphaSim. Post hoc pairwise comparisons of extracted regional values are conducted using independent-samples t tests, with Bonferroni-adjusted P values. All tests are 2-sided. k : Number of voxels in cluster; CM: Center of mass of cluster; LR: Left-right; PA: Posterior-anterior; SI: Superior-inferior; HCsm: Smoking healthy control; HCnsm: Non-smoking healthy control.

表 3 受吸烟、BD 主效应及其交互作用影响的脑区(仅在男性样本中重复分析)

Table 3 Brain areas affected by the main effects of smoking, BD, or their interaction (a repeated analysis conducted on males)

Brain regions	CM LR	CM PA	CM SI	<i>k</i>	BDsm vs BDnsm	
					<i>t</i>	<i>P</i>
Interaction between BD and smoking						
R thalamus	18	−24	0	24	3.992	<0.001
Main effects of BD						
Ventromedial prefrontal cortex	−6	36	−15	40	—	—
Main effects of smoking						
Not available						

Brain regions	BDsm vs HCsm		BDnsm vs HCnsm		HCsm vs HCnsm	
	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>
Interaction between BD and smoking						
R thalamus	3.036	0.004	-5.943	<0.001	-4.793	<0.001
Main effects of BD						
Ventromedial prefrontal cortex	4.673	<0.001	3.819	<0.001	—	—
Main effects of smoking						
Not available						

Cluster centroid coordinates are reported in MNI space (mm). Whole-brain effects are examined using a 2×2 analysis of covariance (ANCOVA), with diagnosis (BD/HC), smoking status (smoker/non-smoker), and their interaction as fixed effects; age, sex, years of education, and dataset source are included as covariates. The whole-brain threshold is set at voxel-wise $P<0.001$ with a cluster extent of ≥ 23 voxels, corrected using AlphaSim. Post hoc pairwise comparisons of extracted regional values are conducted using independent-samples t tests, with Bonferroni-adjusted P values. All tests are 2-sided.

表4 BD患者丘脑动态活动与临床症状相关性分析
Table 4 Correlation analysis between thalamic dynamic activity and clinical symptoms in patients with BD

Statistical indicators		BD group (n=53)	BDsm group (n=23)
HAMD	<i>r</i>	-0.047	0.159
	<i>P</i>	0.740	0.468
HAMA	<i>r</i>	0.008	0.133
	<i>P</i>	0.953	0.545
YMRS	<i>r</i>	-0.126	-0.210
	<i>P</i>	0.372	0.336
BPRS	<i>r</i>	-0.073	0.058
	<i>P</i>	0.613	0.797

Values are presented as Pearson correlation coefficients (*r*) and 2-sided *P* values. Correlations between dynamic activity instability in the right thalamus and clinical symptom scale scores are examined separately in all patients with BD (*n*=53) and smoking patients with BD (*n*=23). *P*<0.05 is considered statistically significant.

2.3 主效应

BD诊断的主效应(图3、表2)出现在腹内侧前额叶皮层(ventromedial prefrontal cortex, vmPFC)[MNI: (-6, 33, -15), 簇大小=107]与左侧背外侧前额叶皮层(dorsolateral prefrontal cortex, dlPFC)[MNI: (-33, 45, 39), 簇大小=23]。事后分析(图3、表2)显示, BDsm组的vmPFC和左侧dlPFC的动态活动不稳定性均显著高于HCsm组(vmPFC: *t*=5.046, *P*<0.001; 左侧dlPFC: *t*=3.152, *P*=0.003), BDnsm组的vmPFC和左侧dlPFC的动态活动不稳定性亦均显著高于HCnsm组(vmPFC: *t*=3.440, *P*=0.001; 左侧dlPFC: *t*=4.684, *P*<0.001)。4组的vmPFC和左侧dlPFC动态活动均值数据见附表1(<https://doi.org/10.57760/sciencedb.xbyxb.0005x>)。未观察到吸烟的主效应。

对吸烟BD患者进行相关分析发现, 左侧dlPFC的动态活动不稳定性与焦虑症状呈正相关(*r*=0.451, *P*=0.031)。在全体BD患者中未见显著相关性(表5)。

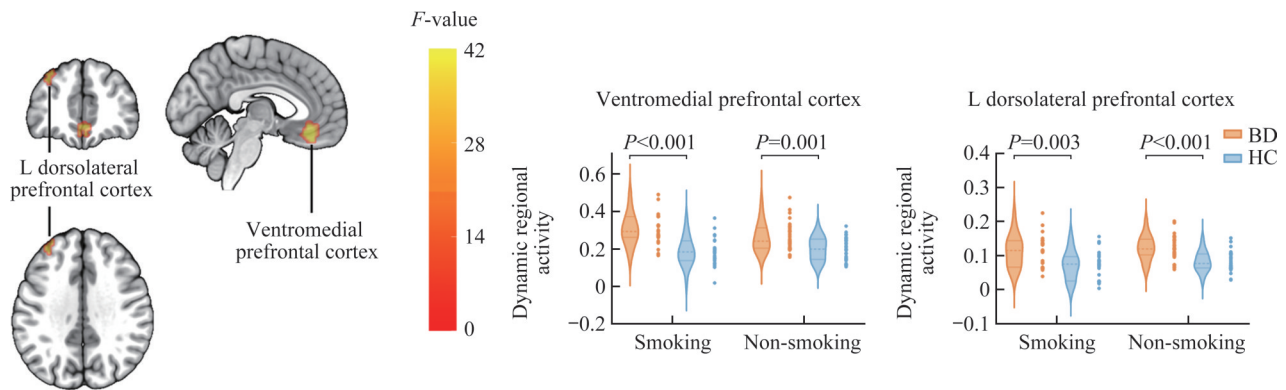


图3 BD的主效应

Figure 3 Main effects of BD

Significant main effects of disease in the vmPFC and dlPFC. The statistical significance level is set at *P*_{voxel}<0.001 and cluster size ≥ 23 voxels (AlphaSim corrected). Bonferroni correction with 2 planned comparisons. vmPFC: Ventromedial prefrontal cortex; dlPFC: Dorsolateral prefrontal cortex.

表5 BD患者vmPFC和dlPFC动态活动与临床症状相关性分析

Table 5 Correlation analysis between dynamic activity in the vmPFC and dlPFC and clinical symptoms in patients with BD

Statistical indicators		BD group (n=53)		BDsm group (n=23)	
		vmPFC	L dlPFC	vmPFC	L dlPFC
HAMD	<i>r</i>	-0.120	0.128	0.150	0.268
	<i>P</i>	0.396	0.365	0.494	0.216
HAMA	<i>r</i>	-0.179	0.192	0.152	0.451
	<i>P</i>	0.204	0.172	0.489	0.031

表 5(续)

Statistical indicators		BD group (<i>n</i> =53)		BDsm group (<i>n</i> =23)	
		vmPFC	L dlPFC	vmPFC	L dlPFC
YMRS	<i>r</i>	-0.131	0.142	-0.341	-0.006
	<i>P</i>	0.355	0.314	0.111	0.980
BPRS	<i>r</i>	-0.223	0.143	-0.229	0.190
	<i>P</i>	0.115	0.317	0.304	0.397

Values are presented as Pearson correlation coefficients (*r*) and 2-sided *P* values. Correlations of dynamic activity instability in the vmPFC and L dlPFC with clinical symptom scale scores are examined separately in all patients with BD (*n*=53) and smoking patients with BD (*n*=23). *P*<0.05 is considered statistically significant. vmPFC: Ventromedial prefrontal cortex; L dlPFC: Left dorsolateral prefrontal cortex.

3 讨 论

本研究提取3种动态指标并进行主成分分析,以考察BD与吸烟对大脑动态脑区活动的影响。结果显示,BD与吸烟的交互效应出现在丘脑:与不吸烟健康对照者(HCs)相比,不吸烟BD患者的丘脑动态活动不稳定性降低;而与吸烟HCs相比,吸烟BD患者的丘脑动态活动不稳定性升高。与此同时,BD的主效应表现为vmPFC与dlPFC动态活动不稳定性增加;相反,未观察到吸烟的主效应。

本研究最主要的发现是,吸烟可减缓BD患者丘脑动态活动异常降低的幅度,为理解BD人群较高的吸烟率提供了神经影像学线索。从动态角度来看,常用于解释精神分裂症吸烟风险升高的自我药疗假说^[2]也可能适用于BD:吸烟相关的丘脑调节可能是BD人群吸烟率偏高的潜在机制之一。相反,在健康人群中,吸烟可能诱发丘脑异常,这与既往研究^[32-33]中“吸烟可降低谷氨酸水平并导致丘脑激活异常”的结果一致。因此,本研究对BD与吸烟在脑区活动不稳定性上的交互效应进行了检验,为BD吸烟率高提供了神经生物学层面的参考。

从解剖学上看,丘脑位于中脑与大脑皮层之间,主要参与感觉信息加工、注意调控、决策以及记忆巩固等过程^[34]。有研究^[35]指出,丘脑是脑内烟碱型乙酰胆碱受体(nicotinic acetylcholine receptors, nAChRs)密度最高的脑区,并在与尼古丁成瘾相关的丘脑-皮层环路中发挥核心作用。尼古丁作为烟草中的主要神经活性成分,主要通过nAChRs通路增强中枢神经系统的多巴胺能神经传递^[36-37]。研究^[38-39]表明,吸烟者相较于不吸烟者在丘脑的形态和功能上的改变,主要由尼古丁对nAChRs的调节所介导。近期研究^[40]进一步显示,尼古丁相关信念本身也可诱发丘脑活动及丘脑-vmPFC功能连接的剂量样反应,提示丘

脑不仅参与尼古丁的药理效应,也可能参与吸烟相关认知和奖赏加工。此外,戒烟治疗相关fMRI综述指出,丘脑体积及丘脑-楔前叶功能连接可能与复吸风险和戒烟治疗反应有关^[41]。

与此同时,不断有研究^[42-44]报道BD患者存在丘脑异常,包括体积减小、脑血流灌注模式改变以及功能连接异常。近年的静息态fMRI研究^[45]进一步提示,BD患者存在丘脑-皮层环路异常,且部分丘脑连接异常可能具有特质样特征,而部分则与当前心境状态有关。因此,本研究从动态视角提示丘脑可能在BD与吸烟的关联中发挥关键作用。不过,这一结果与本研究此前在抑郁吸烟者中观察到的结论不同:在抑郁症患者中,吸烟似乎会进一步加重与抑郁相关脑区的异常^[22]。本研究认为,这种差异可能与BD和抑郁症在神经病理机制上的不同有关^[42]。与导致抑郁患者吸烟率升高的因素不同,吸烟状态与BD患者丘脑动态脑区活动异常减弱之间的关联,可能反映了BD人群吸烟率偏高背后更为独特的神经生理过程。

值得注意的是,在全部吸烟者中,每日吸烟量与右侧丘脑动态活动呈显著正相关;在BD吸烟者中,二者相关方向一致,但该相关性无统计学意义。既往研究^[40]提示,丘脑是尼古丁依赖相关神经环路中的重要节点。尼古丁可通过烟碱型乙酰胆碱受体影响丘脑-皮层环路,并进一步参与奖赏加工、注意调节、反应抑制和显著性归因等过程。此外,丘脑结构和功能连接已被发现与尼古丁依赖严重程度、吸烟渴求及复吸风险相关^[41];也有研究^[46]显示,丘脑体积和功能连接性与尼古丁依赖的严重程度和渴求有关,提示丘脑不仅参与尼古丁的药理效应,也可能参与吸烟相关的认知和奖赏加工。因此,本研究中每日吸烟量与右侧丘脑动态活动的正相关结果,可能反映了吸烟暴露强度与丘脑动态调节之间的关系。

虽然BD吸烟者中该相关性无统计学意义,但其方向与全部吸烟者一致,提示丘脑可能是连接吸烟暴露与BD相关脑功能异常的重要脑区。考虑到BD患者本身存在丘脑-皮层环路异常^[45],吸烟相关丘脑调节可能与疾病相关丘脑异常发生交互,从而形成不同于健康吸烟者的动态脑活动模式。本研究未发现BD患者丘脑动态活动与HAMD、HAMA、YMRS和BPRS评分之间存在显著相关性。这一阴性结果可能提示,丘脑动态活动异常并不简单反映当前横断面症状严重程度,而更可能与BD的疾病特征、神经环路易感性或吸烟相关调节有关。此外,本研究样本量较小,且患者处于不同心境状态,症状异质性和用药差异可能降低了相关分析的统计效能。

本研究还发现,与HCs相比,BD患者在vmPFC与dlPFC的脑区活动不稳定性升高。vmPFC和dlPFC与BD的关联在文献中已被多次报道,二者均是BD精神病理的重要脑区^[47-50]。其中,vmPFC与价值加工、决策、情绪调节和社会认知等功能密切相关^[51],也是默认模式网络(default mode network, DMN)的关键组成部分^[49]。与本研究一致,既往研究^[48, 52-53]也在BD患者的vmPFC或DMN中报告了ALFF、fALFF与ReHo异常。此外,dlPFC在认知功能中具有核心地位,尤其与工作记忆和认知控制相关^[54-55];也有研究^[56-57]报告了BD患者dlPFC的ALFF与fALFF异常。总体而言,本研究从动态角度为BD患者vmPFC与dlPFC的共同异常提供了证据。

本研究亦存在一定局限。第一,样本量较小可能导致统计效能不足,未来有必要进一步扩大样本量。第二,吸烟组男性显著多于女性,导致吸烟组与不吸烟组之间性别比例不均,因此本研究在男性样本中进行了重复分析,结果与主分析一致。第三,本研究的吸烟信息主要基于自报记录,且原始记录中仅采集了吸烟状态判定指标和每日吸烟量,未系统记录具体吸烟年限,因此无法计算吸烟时长及累积吸烟量/包年数。第四,本研究未测量血液或唾液中尼古丁、可替宁等客观生物标志物,因此无法进一步区分自报吸烟量、实际尼古丁暴露及尼古丁代谢差异对丘脑动态活动的影响。第五,本研究中多数BD患者处于药物治疗阶段。尽管BD吸烟组与BD非吸烟组在未用药/用药中比例、服药时间、锂盐、抗癫痫心境稳定剂、抗精神病药及抗抑郁药使用方面均无显著差异,但既往研究^[58]提示锂盐、抗精神病药和抗癫痫心境稳定剂等药物可能影响BD患者的脑功能活动和功能连接模式,因此仍不能完全排除药物种类、剂量及疗程对丘脑-前额叶环路的潜在影响。

综上,本研究首次从动态脑区活动角度观察到

BD与吸烟状态在丘脑中的交互效应,提示吸烟可减缓BD患者丘脑动态活动异常降低的幅度。丘脑相关动态活动异常可能参与BD人群较高吸烟率背后的神经生物学机制。同时,本研究还观察到BD在vmPFC与dlPFC的主效应,为这些脑区动态活动不稳定性的异常提供了证据。未来仍需纵向研究、戒烟或尼古丁干预研究及更精确的尼古丁暴露测量,以进一步验证其因果关系和机制。

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