

论著·基础研究

谷氨酸通路基因多态性交互作用与快感缺失的关联研究

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[摘要] 目的·探究谷氨酸通路基因-基因交互作用与快感缺失的关联。方法·纳入2017年1月—2020年8月在上海交通大学医学院附属精神卫生中心门诊及病房招募的279例精神分裂症 (schizophrenia, SZ) 患者、236例重型抑郁障碍 (major depression disorder, MDD) 患者, 以及在社区招募的236例健康对照 (healthy control, HC) 为研究对象。收集并比较3组被试的一般人口学资料及临床特征。采用时间性愉快体验量表 (Temporal Experience of Pleasure Scale, TEPS) 中文版评估3组的愉快体验能力。采用广义多因子降维 (generalized multifactor dimensionality reduction, GMDR) 法建立谷氨酸通路基因 (NOS1AP、GSK3 β 、DAOA、DISC1及GRIN2A) 单核苷酸多态性 (single nucleotide polymorphism, SNP) 交互作用模型, 依据该模型将SZ及MDD患者分为高风险组和低风险组, 并对其愉快体验能力的差异进行组间比较, 以分析基因-基因交互作用对快感缺失的影响。结果·年龄、受教育年限在3组间的差异具有统计学意义, 首发年龄、病程在SZ、MDD组间的差异具有统计学意义 (均 $P=0.000$)。3组被试在总体愉快体验、期待性愉快体验及即时性愉快体验间差异均具有统计学意义 (均 $P=0.000$); SZ、MDD组患者的总体愉快体验、期待性及即时性愉快体验均低于HC组 (均 $P_{校正}=0.000$), 且SZ与MDD组在期待性愉快体验上具有边缘性统计学差异 ($P_{校正}=0.051$)。通过GMDR建模发现, 由DAOA-rs3916965与DISC1-rs821577组成的2位点交互作用模型对SZ患者总体愉快体验能力具有预测作用 ($P=0.003$), 由NOS1AP-rs1858232和GRIN2A-rs1014531组成的2位点交互作用模型对MDD患者期待性愉快体验能力具有预测作用 ($P=0.037$); 且SZ高风险组患者的总体愉快体验能力、MDD高风险组患者的期待性愉快体验能力均分别低于其低风险组 ($t=3.443$, $P=0.000$; $t=3.471$, $P=0.001$)。结论·谷氨酸通路基因多态性交互作用可能参与了快感缺失的发生。

[关键词] 快感缺失; 谷氨酸通路; 广义多因子降维; 交互作用

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Relationship between polymorphic interaction of glutamate pathway genes and anhedonia

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[Abstract] Objective·To explore the association between gene-gene interaction of glutamate pathway and anhedonia. **Methods**·A total of 279 patients with schizophrenia (SZ) and 236 patients with major depression disorder (MDD) recruited in the outpatient department and ward of Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, and 236 healthy controls (HC) recruited in the community from January 2017 to August 2020 were included in the study. General demographic data and clinical characteristics of the three groups were collected and compared. The Chinese version of Temporal Experience of Pleasure Scale (TEPS) was used to evaluate the pleasure experience ability of the three groups. Generalized multifactor dimensionality reduction (GMDR) method was used to establish the interaction model of the single nucleotide polymorphism (SNP) in glutamate pathway genes (*NOS1AP*, *GSK3 β* , *DAOA*, *DISC1* and *GRIN2A*). According to the interaction model, SZ and MDD patients were divided into high-risk group and low-risk group, and the differences in pleasure experience ability were compared between the two groups, so as to analyze the effect of gene-gene interaction on anhedonia. **Results**·There were significant differences in age and years of education among the three groups, and in age of onset and duration of illness between SZ and MDD groups (all $P=0.000$). There were significant differences among the three groups of participants in terms of overall pleasure experience, anticipatory pleasure experience and consummatory pleasure experience (all $P=0.000$); the overall pleasure experience, anticipatory pleasure experience and consummatory pleasure experience in the SZ and MDD group were lower than those in the HC group (all $P_{corr}=0.000$), and there was marginal statistical difference in anticipatory pleasure experience between the SZ and MDD groups ($P_{corr}=0.051$). Through GMDR modeling, it was found that the 2-loci interaction model composed of *DAOA*-rs3916965 and *DISC1*-rs821577 had a predictive effect on the overall pleasure experience ability of SZ patients ($P=0.003$), and the 2-loci interaction model composed of *NOS1AP*-rs1858232 and *GRIN2A*-rs1014531 had a predictive effect on the anticipatory pleasure experience ability of MDD patients ($P=0.037$); moreover, the overall pleasure experience ability of patients in the SZ high-risk group and anticipatory pleasure experience ability of patients in MDD high-risk groups were lower than those in their low-risk groups ($t=3.443$, $P=0.000$; $t=3.471$, $P=0.001$). **Conclusion**·The interaction of glutamate pathway gene polymorphisms may be involved in the occurrence of anhedonia.

[Key words] anhedonia; glutamate pathway; generalized multifactor dimensionality reduction (GMDR); interaction effect

快感缺失 (anhedonia) 指个体对愉快的体验能力降低, 并导致其社会功能和生活质量下降; 快感缺失是精神分裂症 (schizophrenia, SZ) 阴性症状的主要症状, 也是重型抑郁障碍 (major depression disorders, MDD) 的核心症状之一^[1]。有研究^[2]根据时间序列的不同, 将愉快体验分为2个维度: 即时性愉快体验和期待性愉快体验; 前者与满足感紧密联系, 是一种“当下”的快感体验, 而后者与动机、目标导向性行为和“欲望”的体验关系更为紧密。目前, 抗精神病药物及抗抑郁药物对快感缺失的治疗效果均不理想, 其主要是针对多巴胺、5-羟色胺等受体发挥作用, 继而提示快感缺失的发病机制可能与其他神经递质系统有关。

基于N-甲基-D-天冬氨酸受体 (N-methyl-D-aspartate receptor, NMDAR) 拮抗剂氯胺酮对MDD患者的抑郁症状具有快速缓解作用, 有学者提出了快感缺失的谷氨酸假说; 同时, LEE等^[3]发现小鼠大脑皮层谷氨酸水平下降可导致其抑郁样行为的发生、临床研究^[4]发现MDD患者的脑内存在较高水平的谷氨酸表达等均支持上述假说。而中枢神经系统NMDAR功能减退是谷氨酸假说的重要部分^[5], 如动物研究^[6]发现敲除小鼠大脑皮质和海马中间神经元的谷氨酸离子型受体NMDA亚基1 (glutamate ionotropic receptor NMDA type subunit 1, *Grin1*) 可

使该小鼠出现快感缺失症状, ZHANG等^[7]发现敲除谷氨酸离子型受体NMDA亚基3A (glutamate ionotropic receptor NMDA type subunit 3A, *Grin3a*) 的小鼠也表现出了快感缺失症状, 因此, 谷氨酸通路中与NMDAR相关的基因可能参与了快感缺失的发生。

有研究^[8]表明遗传因素在快感缺失的发生中具有一定的作用, 快感缺失被认为是一种“内表型”, 具有特异神经生物学基础。谷氨酸通路上有5个重要的候选基因, 包括D-氨基酸氧化酶激活剂 (D-amino acid oxidase activator, *DAOA*)、一氧化氮合酶1接头蛋白 (nitric oxide synthase 1 adaptor protein, *NOS1AP*)、精神分裂症断裂基因1 (disrupted in schizophrenia 1, *DISC1*)、糖原合成酶激酶-3 β (glycogen synthase kinase 3 beta, *GSK3 β*) 和谷氨酸离子型受体NMDA亚基2A (glutamate ionotropic receptor NMDA type subunit 2A, *GRIN2A*)。在该通路中, *DAOA*可影响D-氨基酸氧化酶的活性, 后者可降解NMDAR调节剂D-丝氨酸, 从而参与NMDAR的调控^[9]。*NOS1AP*可与突触后密度蛋白-95 (postsynaptic density protein-95, PSD-95) 竞争性地与神经元型一氧化氮合酶 (neuronal nitric oxide synthase, nNOS) 结合, 以抑制由NMDAR激活引起的一氧化氮 (nitric oxide, NO) 产生^[10]。*DISC1*通

过调控磷酸二酯酶4/蛋白激酶A/环腺苷单磷酸反应元件结合蛋白对NMDAR的表达和功能产生重要影响,进而调节NMDAR依赖的认知和情绪过程^[11]。GSK3 β 是一种丝氨酸/苏氨酸激酶,在神经发生、发育和学习记忆中起关键作用;有研究发现NMDAR是GSK3 β 的激活剂,GSK3 β -NMDAR信号通路参与了大脑的奖赏过程^[12]。*GRIN2A*是SZ和MDD的易感基因,研究发现该基因多态性与氯胺酮快速和持续的抗抑郁作用、血清氯胺酮和去甲氯胺酮的表达水平相关^[13]。同时,本课题组的前期研究^[14]发现*NOS1AP*、*DISC1*、*DAOA*和*GSK3 β* 的基因多态性位点的交互作用与早发精神分裂症易感性有关。

基于此,本研究采用广义多因子降维(generalized multifactor dimensionality reduction, GMDR)法分析谷氨酸通路基因多态性交互作用对快感缺失的预测能力,以期寻找快感缺失的神经生物学标志物,从而为快感缺失的干预及药物研发提供科学依据。

1 对象与方法

1.1 研究对象

选择2017年1月—2020年8月在上海交通大学医学院附属精神卫生中心精神科门诊及病房招募的279例SZ患者、236例MDD患者,以及医院周边社区招募的236例健康对照(healthy control, HC)为研究对象。

SZ患者的纳入标准:①符合《精神障碍诊断及统计手册(第五版)》[*Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)*, DSM-5]中SZ的诊断标准。②汉族。③年龄<70岁。MDD患者的纳入标准:①符合DSM-5中MDD的诊断标准。②汉族。③年龄<70岁。HC的纳入标准:①汉族。②年龄<70岁。③与患者无血缘关系。④无精神疾病及精神疾病家族史。所有被试的排除标准:①入组前8周内使用无抽搐电休克治疗。②处于怀孕或哺乳期。③存在物质滥用。④存在神经系统疾病及严重躯体疾病史。

1.2 研究方法

1.2.1 临床资料的收集及比较 收集并比较3组被试的临床资料,包括一般人口学资料(性别、年龄和受教育年限)和临床特征(首发年龄、病程和发作

次数)。

1.2.2 快感缺失水平评估 采用时间性愉快体验量表(Temporal Experience of Pleasure Scale, TEPS)中文版对3组被试的快感缺失水平进行评估。TEPS是一种自评量表,主要从时间进程的角度将愉快体验区分为2个因子,即期待性愉快体验与即时性愉快体验。英文版TEPS共18道题目^[15],中文版TEPS在英文版的基础上增加了2题,并将其2个因子细分为4个因子,即抽象期待和具体期待性愉快体验、抽象即时和具体即时性愉快体验。同时,该量表为6级评分(1根本不像我~6非常像我),得分越高则愉快体验越好。中文版TEPS信效度较高,总体内部一致性较好^[16-17]。

1.2.3 SNP位点的选择 从dbSNP数据库(<http://www.ncbi.nlm.nih.gov/snp/>)和Ensembl数据库(<http://asia.ensembl.org/index.html/>)中查询并下载谷氨酸通路上5个候选基因(*NOS1AP*、*GSK3 β* 、*DAOA*、*DISC1*及*GRIN2A*)的相关数据,并对其SNP位点进行选择,筛选条件为:在东亚人群中该位点的最小等位基因频率(minor allele frequency, MAF)>0.1,且既往文献^[13,18-20]报道其具有疾病易感性、与抑郁症状或SZ阴性症状相关。

1.2.4 DNA提取及基因型检测 分别采集3组被试的外周静脉血,并将其置于含2% EDTA的抗凝管中。使用血液基因组DNA提取试剂盒(天根生化科技有限公司)抽提全血中的基因组DNA,并使用Nanodrop 2000分光光度计对DNA样本的浓度和纯度进行检测,冻存于-80 $^{\circ}$ C,具体操作参照试剂盒说明书进行。而后,将DNA样本送至上海天昊生物科技有限公司进行分析,即采用改进的多重连接酶检测反应(improved multiple ligase detection reaction, iMLDR)对3组样本进行基因型检测。

1.2.5 交互作用模型的建立及愉快体验能力比较 利用GMDR 1.0软件^[21]建立对SZ及MDD患者快感缺失有预测作用的SNP位点交互作用模型,最佳模型的筛选条件为:①交叉验证(cross validation, CV)一致性最大且大于8。②预测准确率最高。而后,通过1 000次置换检验(permutation test)对模型的预测准确率进行统计检验^[22],选择性别、年龄和受教育年限作为协变量。同时,依据交互作用模型将SZ及MDD患者分为高风险组及低风险组,并对其愉快体验能力开展组间比较。

1.3 样本量计算

应用 Quanto 1.2.4 软件对样本量进行计算。在本研究筛选的 SNP 位点中 rs778294 的 MAF 最小 (0.22), 因此计算条件设置如下: MAF=0.22、OR=1.5、加性模式、统计效能为 0.75, 同时参考相关文献^[23] SZ 的一般人群患病率为 0.6%、MDD 的一般人群患病率为 3.4%, 最终 SZ 组、MDD 组和 HC 组的样本数量至少分别为 225 例、227 例、227 例。

1.4 统计效能检验

应用 Quanto 1.2.4 软件对统计效能进行计算。本研究筛选的 SNP 位点的 MAF 范围为 0.22~0.49, 因此条件设置为: MAF=0.22~0.49、OR=1.5、加性模式, 参考相关文献^[23] SZ 一般人群患病率为 0.6%、MDD 一般人群患病率为 3.4%, 以及本研究纳入的 3 组被试的样本量, 最终计算统计效能为 0.77~0.90。

1.5 统计学方法

利用 SPSS 23.0 软件进行统计分析。定性资料用 n (%) 表示, 采用 χ^2 检验进行分析。通过 Kolmogorov-Smirnov 对定量资料进行检验, 符合正态分布的定量资料用 $\bar{x}\pm s$ 表述, 采用独立样本 t 检验和单因素方差分析 (One-way ANOVA) 进行组间比较; 不符合正态分布的定量资料用 $M(Q_1, Q_3)$ 表示, 采

用 Mann-Whitney U 检验和 Kruskal-Wallis H 检验进行组间比较。两两比较选用邦费罗尼 (Bonferroni) 检验进行多重比较校正。采用广义线性模型 (generalized linear model, GLM) 对 GMDR 建立的交互作用模型进行验证。统计检验均为双侧检验, $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 3 组被试的一般人口学资料、临床特征及快感缺失水平的比较

对 3 组被试的一般人口学资料、临床特征及快感缺失水平进行比较分析, 结果 (表 1) 显示: ① 一般人口学资料方面, 年龄、受教育年限的组间差异具有统计学意义 (均 $P=0.000$)。② 临床特征方面, 首发年龄、病程在 SZ、MDD 组之间的差异具有统计学意义 (均 $P=0.000$)。③ 快感缺失水平方面, TEPS 总分、期待性愉快体验、即时性愉快体验以及其细分后的 4 因子的组间差异均具有统计学意义 (均 $P < 0.05$)。同时, 两两比较的结果 (表 1) 显示, 相比于 HC 组, SZ、MDD 组患者的 TEPS 总分、期待性及即时性愉快体验较低 (均 $P_{校正}=0.000$); 且 MDD 与 SZ 组在期待性愉快体验上具有边缘性统计学差异 ($P_{校正}=0.051$), 而该两组在即时性愉悦体验上无显著性差异。

表 1 3 组被试的一般人口学资料、临床特征及快感缺失水平的比较

Tab 1 Comparison of general demographic data, clinical characteristics and anhedonia levels among the three groups of participants

Item	SZ group ($n=279$)	MDD group ($n=236$)	HC group ($n=236$)	$\chi^2/Z/F$ value	P value
Gender/ n (%)				4.757	0.093
Male	146 (52.3)	104 (44.1)	125 (53.0)		
Female	133 (47.7)	132 (55.9)	111 (47.0)		
Age/year	24.5 (19.0, 31.0) ^{①,④}	27.0 (22.0, 33.0) ^②	32.0 (24.0, 57.3)	76.941	0.000
Years of education/year	12.0 (9.4, 15.0) ^{①,④}	15.0 (12.0, 15.0) ^②	16.0 (12.6, 17.0)	78.504	0.000
Age of onset/year	19.0 (16.0, 24.0)	25.0 (20.0, 31.0)	—	-7.125	0.000
Duration of illness/month	23.0 (7.5, 60.0)	6.0 (2.0, 24.0)	—	-6.712	0.000
Number of episodes	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	—	-0.309	0.757
TEPS total score/score	72.3 \pm 13.3 ^①	66.8 \pm 16.0 ^{②,③}	81.7 \pm 12.9	26.028	0.000
Anticipatory	34.0 (30.0, 38.0) ^①	30.0 (24.0, 37.0) ^②	37.0 (33.0, 43.0)	34.729	0.000
Abstract anticipatory	18.0 (14.0, 20.0) ^①	15.0 (11.5, 19.0) ^{②,③}	20.0 (18.0, 22.0)	51.744	0.000
Contextual anticipatory	16.0 (14.0, 19.0)	15.0 (13.0, 19.0) ^②	18.0 (14.8, 21.0)	9.606	0.008
Consummatory	39.0 (34.0, 44.0) ^①	38.0 (30.5, 42.5) ^②	44.0 (38.8, 50.0)	34.277	0.000
Abstract consummatory	24.5 \pm 5.3 ^①	22.5 \pm 6.3 ^{②,③}	27.7 \pm 4.6	20.481	0.000
Contextual consummatory	14.0 (11.5, 17.0) ^①	15.0 (11.5, 16.5) ^②	17.0 (14.0, 19.0)	22.299	0.000

Note: ①SZ<HC, ②MDD<HC, ③MDD<SZ, ④SZ<MDD, all $P < 0.05$.

2.2 SNP位点的选择结果

在5个候选基因中本研究共挑选出17个SNP位

点, 具体信息(名称、染色体位置、等位基因、MAF值、特征等)如表2所示。

表2 5个候选基因的17个SNPs的信息

Tab 2 Information on the 17 SNPs for the five candidate genes

Candidate gene	SNP	Chromosome	Position	Alleles	MAF	Feature
NOS1AP	rs12742393	1q23.3	162224586	C/A	0.32	Intron2
	rs1415259		162085309	C/T	0.42	Intron1
	rs1415263		162166043	C/T	0.48	Intron2
	rs1858232		162303838	G/A	0.33	Intron5
	rs348624		162335256	C/T	0.25	Synonymous_exon9
GSK3β	rs6680461	3q13.33	162255286	G/T	0.39	Intron2
	rs334558		119813282	G/A	0.40	5'-flanking
DAOA	rs6779828	13q33.2	119775147	C/T	0.28	Intron1
	rs3916965		106103360	C/T	0.36	Intergenic region
	rs778294		106142235	C/T	0.22	Synonymous_exon4
DISC1	rs947267	1q42.2	106139662	G/T	0.49	Intron3
	rs1538979		231896868	C/T	0.24	Intron4
	rs821577		232067057	G/T	0.38	Intron9
	rs821633		232148933	C/T	0.41	Intron11
GRIN2A	rs999710	16p13.2	232010943	G/A	0.40	Intron9
	rs1014531		9855794	G/A	0.27	3'-UTR
	rs1420040		9850397	G/A	0.42	3'-UTR

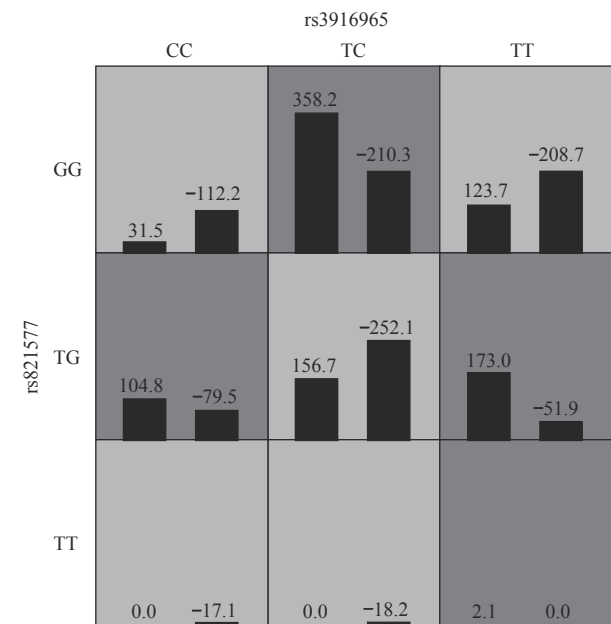
Note: UTR—untranslated region.

2.3 谷氨酸通路基因-基因交互作用对SZ患者快感缺失的预测作用

本研究利用GMDR建立对SZ患者愉快体验有预测作用的SNP位点交互作用模型, 结果(图1)显示, 由DAOA的rs3916965与DISC1的rs821577组成的2位点交互作用模型对SZ患者总体愉快体验能力(即TEPS总分)预测的CV一致性最大(即CV一致性=8), 且预测准确率最高(65.19%, $P=0.003$)。而后, 依据此交互作用模型将SZ患者分为高风险组和低风险组, 并对其总体愉快体验能力进行组间比较, 结果(图2)显示SZ高风险组患者的总体愉快体验能力低于其低风险组($t=3.443$, $P=0.000$)。在调整了性别、年龄和受教育年限作为协变量后, 采用GLM对GMDR建立的上述交互作用模型进行验证, 结果显示rs3916965与rs821577交互作用对SZ患者的总体愉快体验能力具有预测作用(Wald $\chi^2=12.671$, $P=0.013$)。

2.4 谷氨酸通路基因-基因交互作用对MDD快感缺失的预测作用

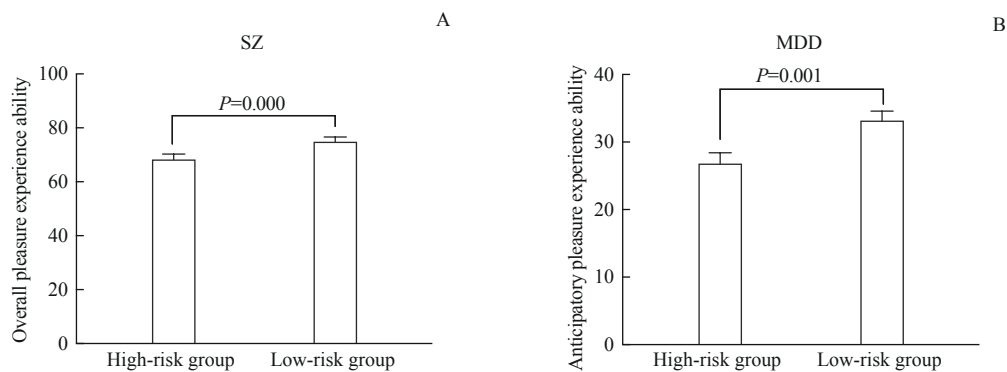
本研究采用GMDR建立对MDD患者愉快体验有



Note: The best identified model. In each cell, the left bar represents a positive score, and the right bar represents a negative score. High-risk cells are indicated by dark shading, and low-risk cells are indicated by light shading. Cells (representing genotype combinations) are categorized into 'high' and 'low' risk when the sum of the score is above and below zero, respectively.

图1 GMDR分析预测SZ患者总体愉快体验能力的最优2位点交互作用模型

Fig 1 The best 2-loci interaction model for predicting the overall pleasure experience ability of SZ patients by GMDR analysis



Note: A. Comparison of the overall pleasure experience ability of SZ patients between the high-risk group and low-risk group. B. Comparison of the anticipatory pleasure experience ability of MDD patients between the high-risk group and low-risk group.

图2 SZ和MDD患者高、低风险组总体、期待性愉快体验能力比较

Fig 2 Comparison of the overall and anticipatory pleasure experience ability between high-risk and low-risk group of the SZ and MDD patients

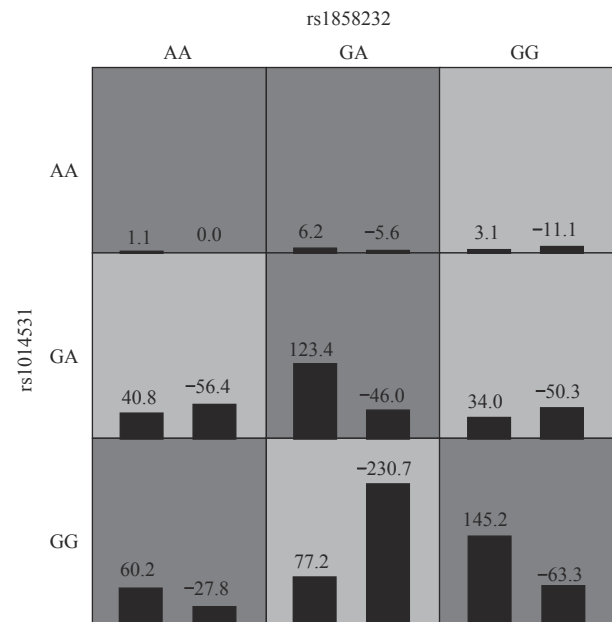
预测作用的SNP位点交互作用模型，结果（图3）显示，由 *NOS1AP* 的 rs1858232 和 *GRIN2A* 的 rs1014531 组成的2位点交互作用模型对MDD患者的期待性愉快体验能力预测的CV一致性最大（即CV一致性=9），且预测准确率最高（61.73%， $P=0.037$ ）。进一步依据此交互作用模型将MDD患者分为高风险组和低风险组，并对其期待性愉快体验能力进行组间比较，结果（图2）显示MDD高风险组患者期待性愉快体验能力低于其低风险组（ $t=3.471$ ， $P=0.001$ ）。在调整

了性别、年龄和受教育年限作为协变量，采用GLM对GMDR建立的上述交互作用模型进行验证，结果显示rs1858232与rs1014531交互作用对MDD患者的期待性愉快体验能力存在预测作用（Wald $\chi^2=11.853$ ， $P=0.008$ ）。

3 讨论

本研究发现SZ与MDD患者的期待性和即时性愉快体验均低于健康对照者，与LI等^[24]研究结论相一致。同时，该研究还发现MDD患者的期待性及即时性愉快体验与其抑郁症状严重程度、病程和住院次数显著相关，快感缺失在MDD患者中被认为是一种“状态”；而SZ患者的即时性愉快体验与临床症状相关，期待性愉快体验与临床特征无相关性，期待性快感缺失在SZ患者中则可能是一种“特质”。继而推测，期待性快感缺失在SZ患者中比在MDD患者中更稳定，这或可为本研究的结果（即SZ和MDD患者在期待性愉快体验上有边缘性统计学差异、在即时性愉快体验间差异无统计学意义）进行解释。

SZ及MDD是复杂且遗传模式不明确的多基因疾病，其表型均是由一个基因或多个基因的数个不同变异引起，且基因-基因交互作用在其发生中发挥了重要作用^[25]。研究^[26]发现 *DAOA* 的 rs3916965 位点与中国汉族人群SZ相关，系统评价^[27]显示D-丝氨酸和甘氨酸作为抗精神病药物的辅助药物在一定程度上可改善阴性症状，提示 *DAOA* 基因可能与SZ患者的阴性症状存在一定的关联。TOMPP0等^[19]报道，*DISC1* 的 rs821577 次要等位基因的携带者在社交快感缺失方面的得分显著高于对照组，提示 *DISC1* 基因与



Note: The best identified model. In each cell, the left bar represents a positive score, and the right bar represents a negative score. High-risk cells are indicated by dark shading, and low-risk cells are indicated by light shading. Cells (representing genotype combinations) are categorized into ‘high’ and ‘low’ risk when the sum of the score is above and below zero, respectively.

图3 GMDR分析预测MDD患者期待性愉快体验能力的最优2位点交互作用模型

Fig 3 The best 2-loci interaction model for predicting the anticipatory pleasure experience ability of MDD patients by GMDR analysis

快感缺失亦存在相关性。在本研究中我们也发现, *DAOA* 和 *DISC1* 基因变异位点的相互作用可能参与了 SZ 患者快感缺失的发生; 推测其原因, 可能与 *DAOA* 和 *DISC1* 相互作用共同调节 NMDAR 以影响谷氨酸通路信号传导有关, 但两者相互作用的具体机制仍需进一步探索。

NO 与多种行为、认知和情绪过程的调节有关, 如学习、运动、焦虑和抑郁等。动物研究^[28-29] 发现内源性 NO 参与了慢性非预期温和应激诱导的抑郁, 而靶向 PSD-95/nNOS 接头的小分子抑制剂则可在小鼠中发挥抗抑郁作用。由于 *NOS1AP* 能够改变神经系统 NO 的产生活性, 继而提示 *NOS1AP* 可能与抑郁症状的发生密切相关。同时, 本研究发现 *NOS1AP* 和 *GRIN2A* 基因的变异位点交互作用可影响 MDD 患者的期待性愉快体验; 推测其原因, 可能是 *NOS1AP* 和 *GRIN2A* 相互作用影响 NO 的产生进而参与快感缺失的发生, 但其中具体的神经生物学机制需进一步研究阐明。

此外, 本研究尚存在一定的局限性: ① 样本量偏小, 后续需扩大样本量进行验证。② 研究未控制药物的使用, 而药物对快感缺失具有一定影响, 未来需纳入未服药患者进行分析。③ 不同亚型的 SZ、MDD 患者的快感缺失的严重程度有所不同, 后续需按照疾病亚型开展分层分析。④ 仅针对基因交互作用与快感缺失的关联进行研究, 且其具体作用机制仍需进一步探索。⑤ 未纳入环境因素如压力、应激或童年创伤事件等, 后续需进一步研究基因-环境交互作用在快感缺失发生中的作用。

综上所述, 本研究发现谷氨酸通路基因-基因交互作用可影响 SZ、MDD 患者的愉快体验能力, 提示谷氨酸系统在快感缺失的发生中具有重要的作用, 这将为快感缺失的临床治疗及药物开发提供新的方向。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclose no relevant conflict of interests.

伦理批准和知情同意/Ethics Approval and Patient Consent

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All protocols in this study were reviewed and approved by Ethics Committee of Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine (Approval Letter No. 2017-19R), and all protocols were carried out by following the guidelines of *Declaration of Helsinki*. Consent letters have been signed by the research participants or their relatives.

作者贡献/Authors' Contributions

易正辉负责研究设计, 黄欣欣、吕钦谕、胡国芹、鲍晨曦参与数据收集, 黄欣欣、刘超、张瑶参与数据分析, 黄欣欣、刘超参与论文写作与修改。所有作者均阅读并同意了最终稿件的提交。

The research design was conducted by YI Zhenghui. Data collection were conducted by HUANG Xinxin, LÜ Qinyu, HU Guoqin and BAO Chenxi. Data analysis were performed by HUANG Xinxin, LIU Chao and ZHANG Yao. The manuscript was drafted and revised by HUANG Xinxin and LIU Chao. All the authors have read the last version of paper and consented for submission.

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