《心理学报》审稿意见与作者回应

题目：NR3C1 基因多态性及单倍型、父母教养方式对青少年焦虑障碍的影响
作者：周雅，范方，彭婷，龙可，梁颖欣，周洁莹

第一轮

审稿人 1 意见：
该研究选题较新颖，研究目的明确，思路较清晰，然而其存在的问题也不少：

意见 1：题目表述不规范，“交互作用”是影响的表现形式之一，所以，可以说 A 和 B 对 C 的交互作用，但不能说 A 和 B 的交互作用对 C 的影响。

回应：感谢审稿专家的指正。我们已对标题进行修改。

意见 2：焦虑障碍的界定和表述不够科学，从现有字面的意义来看，焦虑障碍包括躯体化障碍，实际上，应该是焦虑障碍的症状表现常包括躯体化障碍。

回应：感谢审稿专家的指正。文中已对焦虑障碍界定做出修改，改动部分用红色字体标出。

意见 3：在筛选病例组和对照组被试时，该研究使用了“平均分以上 1 个 SD 和平均分以下 1.5 个 SD 作为标准”，作者的解释是为了防止焦虑障碍自我报告的虚高现象的影响，所以使用了较严格的标准。那么既然如此，为什么不使用正负 1.5 个标准差作为筛选标准呢？目前的标准仅是提高了对照组的入选标准，而非病例组。

回应：感谢审稿专家的意见。文中已对采用不同标准筛选疑似病例组与疑似对照组的原因作了详细说明。“因为以往有研究指出个体自评的焦虑症状通常存在虚高现象，大部分人尤其具有焦虑相关人格特质的人往往倾向于主观夸大自己的焦虑症状及其他心理困扰(Derakshan & Eysenck, 1997)。这提示某些被试实际的焦虑症状可能不如自评那么严重，因此出于节约研究资源的考虑，我们采用更为严格的 1.5 个 SD 标准来筛选疑似对照组，控制纳入此组人数、减少后续诊断访谈的工作量。而为了尽可能不遗漏样本中的焦虑障碍阳性病例，我们采用 1 个 SD 标准来筛选疑似病例组。”

意见 4：研究工具的介绍中需要补充计分的具体含义，譬如 0-2 计分，0、1 和 2 分别代表什么。

回应：修改稿已补充所用工具的分数含义，改动部分用红色字体标出。

意见 5：尚存在格式问题，譬如 2.3 部分的标题字体与其他部分不一致

回应：感谢审稿专家的细心指正。我们已对文章格式作了检查与调整。

意见 6：目前的统计分析没有考虑基因型分布是否与父母教养类型存在显著关联，即是否存在基因-环境的相关问题，性别与基因型分布是否显著关联的问题，以及不同基因位点基因型的分布是否相关的问题。

回应：按照审稿专家的意见，我们做了主要研究变量的相关矩阵，在修改稿中列为表 2。

意见 7：数据处理分析部分写道："由于焦虑组与对照组的性别构成以及自评地震暴露达到显著差异（参见表 1），所有 Logistic 模型均将性别与地震暴露作为协变量"，然而后面的结果部分却将性别作为自变量，且考察了性别与基因、教养方式对焦虑障碍的交互作用。

回应：感谢审稿专家的细心指正。Logistic 模型的协变量确实只有地震暴露，上述语句将性别作为协变量为表述失误，文中已经更正。

意见 8：表 2 和表 3 中基因型的呈现不够规范。

回应：修改稿新增了两个表格，一个呈现研究变量的相关矩阵（编为表 2），一个呈现单倍型在病例组与对照组的分布频率（编为表 4），故将原文中表 2 和表 3 的内容合并在一个表格呈现（编为表 3），其中基因型的呈现方式已做修改。

意见 9：该研究进行了多次回归分析，为保证研究结果的可靠性，应进行显著性水平的矫正。

回应：感谢审稿专家的指正。修改稿已进行显著性水平矫正。经矫正仍显著的交互作用项

仅有 rs41423247 与母亲温暖关怀。

意见 10：NR3C1 基因的 3 个位点可能存在连锁不平衡，而该研究没有考虑这种效应，会影响研究结果的可信度。

回应：修改稿已进行 3 个位点 rs6191-rs6196-rs41423247 的单倍型分析，在样本总体中得出频率>5%的单倍型有 3 种，即 GAG、TAC、TGC。由于前面分析得出 rs41423247 与母亲温暖关怀的交互作用显著，我们将母亲温暖关怀区分高低两种水平，也分别进行了单倍型分析。具体结果请参见修改稿。

意见 11：对于交互作用的结果，作者认为支持了优势敏感性模型，然而事实上，没有发现消极教养条件下的效应，可能与这些所谓的消极教养得分不能真正反映消极教养有关，即与消极教养的得分范围有关。

回应：感谢审稿专家的意见。文中已对交互作用结果的可能解释作了重新讨论。"本研究仅报告rs41423247 GG基因型与母亲较多的温暖关怀可降低青少年的焦虑障碍风险，而未发现rs41423247多态性与消极教养的交互作用，这种结果提示rs41423274与教养方式的交互作用可能符合"优势敏感性模型"，即rs41423247仅对积极教养环境易感。而以往有研究报告rs41423247基因型可调节某些负性环境变量对焦虑相关障碍的影响，例如，Lian等人(2014) 以460名PTSD患者和1158名健康对照为被试，发现携带rs41423247 G等位基因与较高的创伤暴露程度、较多的负性生活事件、较少的社会支持可使个体罹患PTSD的风险增加3倍多。据此推断rs41423247还是可能对消极教养环境易感的。这也表明本研究结果有另一种解释的可能，即rs41423247与教养的交互作用其实符合"不同易感性模型"，但在本研究中由于被试报告的消极教养的分数变异范围有限，不足以揭示出rs41423247与消极教养的交互作用。"

审稿人 2 意见：

This study investigated the effects of NR3C1 polymorphism, parenting styles, and the interaction of the two on anxiety disorders among 238 adolescents (high school students). Clinical scales were used to screen students with psychopathology and a neuropsychiatric interview was utilized to diagnose the screened students. Students filled in parenting questionnaire. They found significant interaction effects of NR3C1 polymorphism (rs6196, and rs41423247) and parenting styles (paternal autonomy and maternal warmth).

This investigation tried to examine parenting styles among adolescent samples in testing gene-environment interaction as parenting styles have never been examined and adolescent samples have never been used in such studies. However, there are many theoretical and methodological issues of the current form of manuscript.

Response: Thanks for the reviewer' invaluable comments. We have carefully responded to these comments point-by-point, and revised the manuscript accordingly. Changes are marked in red in the text. Please find as follows our specific responses to the comments in red italics.

Introduction

Generally, the Introduction is fairly short and lacks a lot of necessary details.

Comment 1: When they talk about anxiety disorders, they need to provide citations. More importantly, they need to point out what types of anxiety disorder(s) they want to focus on in the current study and define it.

Response: Citations pertinent to the definition and epidemiology of anxiety disorders were provided. In this study, we were concerned with adolescents diagnosed with any anxiety-related disorders rather than a specific type of anxiety disorder. Among the total 117 cases, there were 6 cases of panic disorder, 17 of agoraphobia, 10 of social phobia, 18 of specific phobia, 4 of obsessive compulsive disorder, 12 of generalized anxiety disorder, 13 of PTSD, and 37 of mixed anxiety disorders. This has been specified in the Participants and Procedure section.

Comment 2: The second paragraph starts with the mechanisms of anxiety disorder, which needs more details. The remaining sentences talks about HPA functioning, which doesn't follow the mechanisms of anxiety disorder logically. I would suggest to talk more about the physiological mechanisms of how NR3C1 modulates the HPA functioning, then lead to anxiety disorders.

Response: As the reviewer suggested, we rewrote most part of the Introduction section. A more detailed description on how NR3C1 modulates the HPA functioning has been added.

Comment 3: The last but one paragraph starts with the discussion of the need to examine gene-environment interaction effects on anxiety disorder. However, not the entire paragraph is about this theme. I would suggest reorganize this section. They need to provide evidences of both main effects of each focal variables as well as interaction effects.

Response: As the reviewer suggested, the revised Introduction used separate subsections to talk about the relationship between NR3C1 and anxiety, the relationship between parenting and anxiety, and possible interaction effects between NR3C1(and other genes) and parenting.

Comment 4: They need to provide rationales (a) why investigating the interaction effects is important? (b) why extending from adult samples to adolescent sample is important? Would they expect any differences? (c) why extending from other environmental factors to parenting factors? (d) why do they need to distinguish paternal and maternal parenting?

Response: These have been specified in the revised Introduction. For rationales of (a) and (c), please refer to the first paragraph of 1.3. For the rationale of (b), please refer to the last paragraph of 1.1. For the rationale of (d), please refer to the last paragraph of 1.2.

Comment 5: Are there any studies done among other countries rather than China regarding the interaction between NR3C1 polymorphisms and parenting styles?

Response: To our knowledge, no existing studies concerning adolescent anxiety have looked into the interaction between NR3C1 polymorphisms and parenting. However, there are some studies that have examined the interacting effects of some other candidate genes and parenting on adolescent anxiety. These studies were cited in the revised Introduction.

Comment 6: The literature review mentioned some NR3C1 polymorphisms but the current study focused on a different set of polymorphisms. They need to provide the reasons.
Response: As can be noted from the literature review, the rs41423247 polymorphism of NR3C1 is commonly investigated in anxiety studies. Apart from rs41423247, different studies usually examined different polymorphisms of this gene, and there were no conclusive findings so far. As such, our study detected rs41423247 and two other polymorphisms that have been found to be associated with HPA axis regulation and stress-related illnesses (Koper, van Rossum, & van den Akker, 2014).

Koper, J. W., van Rossum, E. F., & van den Akker, E. L. T. (2014). Glucocorticoid receptor polymorphisms and haplotypes and their expression in health and disease. Steroids, 92(92), 62–73.

Comment 7: What are the specific research questions? What are the hypotheses?
Response: These have been addressed in the last paragraph of the revised Introduction.

Method and Results
Generally, the methodology of the current study suffers from many critical flaws.
Comment 8: Screening procedure: it seems a stricter rule has been applied to the control group (1.5 SD below the average) which ends with fewer people in this group (152). The corresponding statements are misleading.
Response: This has been addressed as we responded to Comment 3 of the first reviewer.

Comment 9: It seems that the authors kept adolescents who not only shows anxiety disorder, but also depression and PTSD from both the screening scales and the psychiatric interview. However, the title and literature review only deal with anxiety disorder. This is very problematic.
Response: We used self-reporting measures on anxiety, PTSD and depression in the screening survey, in order to detect as many as possible adolescents with probable mental problems and include them in the MINI interview. Through the interview, there were actually 139 adolescents diagnosed with depression in addition to the 117 diagnosed anxiety cases. However, in the current manuscript, we chose to focus on anxiety, primarily due to the manuscript word limits.

Comment 10: They need to provide citations for the original screening scales.
Response: This has been addressed in the revised text.

Comment 11: The age, sex, qualification, background information of the 4 psychologists is missing. Similar information for the 10 pilot participants is also missing. How were the 4 psychologists trained?
Response: The 4 interviewers were graduate students in clinical psychology in our team. Demographic information of the interviewers and 10 pilot participants, as well as the MINI training procedure, were specified in the revised text.

Comment 12: How the parenting questionnaires were distributed and collected? Citation for the questionnaire?
Response: As stated in the Participants and Procedure section, the parenting questionnaire was completed by each participant upon the completion of his/her MINI interview. The citation for

the questionnaire was provided in the revised text.

Comment 13: Why not using continuous anxiety disorder scores? When categorization approach is being adopted, you lose all the advantages of using multiple steps of identifying anxiety disorder individuals and using psychiatric interviews. I believe the screening scale results should be the same as the psychiatric interview. They could simply use a stricter cutting point after screening. Statistically, instead of logistic regression, regular multiple regression is going to provide more information and more robust for the interaction effects.
Response: Thank you for the suggestion. Previous studies concerning candidate gene polymorphisms and adolescent anxiety usually used self-reporting scales to assess anxiety symptoms. Using psychiatric interviews to make positive diagnosis of anxiety disorders was then considered as a major strength of our study. As such, we still used the presence/absence of diagnosed anxiety as the dependent variable.

Comment 14: In Table 1, why did they conduct ANOVA when they only compared two groups?
Response: t tests were used to compare differences between case and control groups. Results of the comparison between sexes were also added in Table 1.

Comment 15: All the regression tables lack information about one or two parenting factors, exposure to earthquake although it is control variable.
Response: The backward stepwise method was used to run the logistic regressions. Only variables or interaction items included in the final models were presented in the table (Table 3).

Comment 16: A correlation table is desirable in reporting results.
Response: A correlation table was added as Table 2 in the revised article.

Comment 17: The interpretation of paternal autonomy, rs6196, and adolescent sex interaction is problematic. It is also possible that adolescents carrying GG allele showed significant higher risk for anxiety disorder.
Response: We changed the procedure of building logistic models in the revised article. As no significant interactions between sex and genotype/parenting were found, the three-way interaction items were not examined in the logistic models.

Comment 18: It is better to plot the three-way interaction in the same graph.
Response: As stated above, the three-way interaction was not examined.

Discussion
Generally, the Discussion is not a discussion rather than a literature review. A lot of discussion should go to the Introduction section.
Comment 19: The second paragraph discussing how NR3C1 polymorphism modulate HPA functioning should go to Introduction. The third paragraph discussing parenting styles and its relations to mental health should also go up. This discussion of the diathesis-stress model, differential susceptibility model, and the vantage sensitivity model should also go to the Introduction section.
Response: As the reviewer suggested, the second and third paragraphs were moved to Introduction. The discussion of the gene-environment interaction models was not moved, as the

manuscript did not intend to testify and compare these models and this discussion seemed redundant in the Introduction.

Comment 20: Some statements of interpretation are quite misleading, consider rewording.
Response: We rephrased some sentences to avoid inaccuracy or vagueness.

Comment 21: The Discussion section needs to be rewritten. Basically, they need to discuss (a) why the interactions only happened on this particular polymorphism not others? (b) why the interaction only limited in father-son relationship? (c) why the interactions only evident on positive parenting styles not negative ones?
Response: Results of the main effects of genotypes and parenting and the interaction between them were discussed more thoroughly in the revised text.

第二轮

审稿人 1 意见：

总体而言，作者根据审稿专家的意见和建议对文稿进行了认真修改，文稿质量有了较大提高。需要作者进一步修改或者做出解释的几点如下：

意见 1：对于病例组和对照组被试的筛选标准问题，作者的解释是“过往研究表明个体自评的焦虑症状通常存在虚高现象，大部分人尤其具有焦虑相关人格特质的人往往倾向于主观夸大自己的焦虑症状及其他心理困扰”，既然如此，无论病例组和对照组，被试都会存在虚高现象，那么，为了科学筛选被试，二者都应采用较为严格的标准，但作者接下来的做法以及相应解释是：为了节约资源，对照组采用 1.5SD，为了不遗漏样本，病例组采用 1SD。两组筛选的依据不一致，且与前面的表述也不能呼应。若作者仍然坚持使用此标准，就需要提出足以令人信服的解释或者依据。

回应：感谢审稿专家的意见。我们原本是用统一标准 1.5SD 来筛选疑似的病例组与对照组，但经临床访谈过后确诊的焦虑障碍病例不足百人，因此“为了增加病例组样本量、尽可能不遗漏样本中的焦虑障碍阳性病例，我们最终采用 1 个 SD 标准来筛选疑似病例组”。文稿先前对此的表述不是很清楚，修改稿已进行明确说明，改动部分用蓝色字体标出。

意见 2：该文没有考察抑郁和创伤后应急障碍，但研究工具部分作者呈现了《儿童抑郁障

碍自评量表》和《创伤后应激障碍清单》的详细介绍，不知是如何考虑的。

回应：我们在筛查疑似病例与对照时用到了《儿童抑郁障碍自评量表》和《创伤后应激障碍清单》，因此在工具部分作了介绍。而之所以在被试筛查时除了《儿童焦虑性情绪筛查量表》，还用到这两个量表，是因为 PTSD 本就是焦虑障碍的一种，抑郁与焦虑也有较高的共患，施测 PTSD 与抑郁的量表是为了尽可能有效地筛选出可能有焦虑与可能正常的被试。筛选出的疑似病例与对照，都经过一对一的访谈诊断，最终病例组与对照组的入组是以诊断结果为准，这确保了本研究的严谨性。

意见 3：根据连锁不平衡分析的结果，作者增加了单倍型的相关分析，但在考察单倍型与环境的交互作用时，作者仅根据单位点分析的结果考察了单倍型与母亲温暖关怀的交互作用，似乎欠妥。譬如单位点与父亲温暖关怀不存在交互作用，并非意味着单倍型与父亲温暖关怀也不存在交互作用。

回应：按照审稿专家的建议，我们考察了单倍型与父母四类教养方式的交互作用，主要结果呈现在表 4 和表 5 中，“结果”和“讨论”的文字部分也做了相应修改，改动部分用蓝色字体标出。

审稿人 3 意见：

该研究采用病例 NR3C1 多态性、单倍型以及父母教养方式对青少年焦虑障碍的影响。选题新颖，思路明晰，讨论较为深入。但是，尚存在一些问题值得商榷。

意见 1：文字表述的逻辑性需进一步提升。如，在问题提出 1.2 父母教养方式与青少年焦虑部分第二自然段，“然而，既有研究大多关注母亲教养方式。针对父亲教养方式与孩子焦虑的研究数量较少且结果不一。例如，Beato 等人(2015)采用问卷评估 309 名学龄儿童的焦虑症状及其父母的控制型、冷漠型、支持型教养方式，数据分析仅得出母亲的冷漠教养与孩子的高焦虑相关显著，并未发现父亲教养方式与孩子焦虑的相关关系；Hudson 与 Rapee (2002)在实验（注：什么意思？）观察 57 名孩子（37 名检出焦虑障碍，20 名正常对照）与其父母的互动模式，发现焦虑障碍孩子的父亲相比母亲表现得更有控制性；杨智

辉、王瑞敏与王建平(2010)调查我国 1056 名初中生，结果报告父亲的过度保护、苛刻要求、情感疏离与初中生自评的焦虑症状有显著的正相关。以往研究结果的不一致（该句表达的意思不清晰，是指关于父亲教养与儿童焦虑的研究结果不一致吧？因为该自然段的第二句“父亲教养方式与孩子焦虑的研究数量较少且结果不一”是该自然段的核心句 ），一方面可能是由于样本特征（比如，孩子的焦虑是否达到临床诊断水平）、教养方式测评手段（比如，问卷评估或实验室观察）等方法学层面的差异，另一方面也提示了父亲与母亲教养对于孩子焦虑的作用模式可能不同（注：以往关于父亲教养与儿童焦虑的研究结果不一致，并不能说明父亲与母亲教养对于孩子焦虑的作用模式可能不同）。”

回应：感谢审稿专家的细心指正。我们已对此段结尾处表述不明的部分进行了修改，“以往研究结果的不一致”的确是指关于父亲教养与儿童焦虑的研究结果不一致，而列举的 Beato 等人（2015）、Hudson 等人(2002)的研究同时考察了父母的教养，其结果提示“父亲与母亲教养对于孩子焦虑的作用模式可能不同”。

意见 2：本研究在研究方法 2.2.4 父母教养方式部分把父母教养方式划分为关怀、自主、冷漠拒绝、过度保护四个维度，但是在后面的文稿部分经常使用“温暖关怀”来代替“关怀”，建议作者注意用词的一致性。

回应：感谢审稿专家的细心指正。修改稿已统一教养方式的用词。

意见 3：本研究以青少年为被试探讨了 NR3C1 基因与父母教养方式对焦虑障碍的影响，作者在问题提出部分也特别强调在探讨心理病理的遗传及心理社会机制时应考虑个体发展阶段在其中的作用，但是作者在讨论部分并没有很好地呼应这一问题，例如本研究以青少年为被试所得研究结论是否能够推广到其他年龄阶段。

回应：感谢审稿专家的意见。修改稿在本研究局限部分讨论了被试的年龄问题和结果的可推广性，改动部分用蓝色字体标出。

意见 4：讨论部分，作者在讨论单个位点多态性与青少年焦虑障碍的效应时，没有把本研究的研究结果与已有研究的研究结果进行比较。

回应：按照审稿专家的意见，修改稿在讨论单个位点多态性与青少年焦虑障碍的关系时，已将本研究结果与以往研究结果进行比较，改动部分用蓝色字体标出。

第三轮

意见：作者对二审中的问题作出了较恰当的说明或者修改。建议发表前进一步修色语言，譬如“3.4 部分”，语言流畅性仍有待提高。

回应：感谢审稿专家的意见。我们已对全文进行反复通读，并对个别段落的文字表达加以润色（如 3.4 部分，改动用绿色字体标出），以确保全文语言的通顺连贯。