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Adolescence and risk of psychopathology: Understanding trajectories and early interventions

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Adolescence and risk of psychopathology: Understanding trajectories and early interventions

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Table of contents

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Early Detection of Temperament Risk Factors: A Comparison of Clinically Referred and General Population Children

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Despite an extensive literature on associations between early childhood temperament and behavior problems, most of this evidence is based on general population samples. Hence, relatively little is known about the temperament characteristics of children who have been referred for in- or outpatient treatment of emotional and/or behavioral problems. Whether temperament-to-behavior problems identified in community samples would also be found in samples of clinically referred children is poorly understood. To redress this limitation, we compared temperament attributes of a predominantly preschool-aged sample of children referred for treatment of emotional and/or behavioral disorders ($N = 87$) with those from a similarly-aged general population sample ($N = 85$) by using the Integrative Child Temperament Screener (ICTS)—a new nine-item scale to identify clinically significant temperament attributes. Behavioral symptoms in the clinical sample were assessed through diagnostic interviews in combination with the Child Behavior Checklist (CBCL), which was also administered to the general population children. Compared with general population children, referred children exhibited substantially higher scores on all ICTS subscales except behavioral inhibition. Furthermore, areas under the curve analyses showed that discrimination of both groups based on CBCL scales could be improved by adding the ICTS. Overall, the findings fill a long-standing gap in evidence regarding temperament characteristics of children with serious emotional and/or behavioral symptoms and suggest a useful role for the ICTS in assessment, screening, and prevention.

Keywords: preschool, child temperament, behavior problems, assessment, screening, clinically referred, externalizing behavior problems

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STATEMENT OF PUBLIC SIGNIFICANCE

This study provides one of the first demonstrations that temperament risk factors identified in general population studies are also exhibited by children referred for psychiatric treatment, albeit in more marked form. Furthermore, the findings indicate that these predisposing temperament factors can be accurately screened for by using a nine-item scale.

INTRODUCTION

Early childhood temperament is one of the few behavioral characteristics that has been found to predict clinically significant outcomes beyond childhood, sometimes up to adulthood (1). In general, studies suggest that certain attributes of preschool temperament shape risk for anxiety, depression, attention-deficit hyperactivity, and conduct problems (2–5). Most of the evidence for associations between early child temperament and later psychopathology so far, however, derives from general population studies. Less is known about the temperament attributes of preschool children who have been clinically referred for in- or outpatient treatment of emotional and/or behavioral problems (6). One reason for the limited number of studies of preschool temperament in clinically referred children may lie in the practical difficulties involved in studying special populations; another is the considerable length of well-established temperament questionnaires such as the Children's Behavior Questionnaire or the Junior Temperament and Character Inventory, which may overtax the temporal or attentional resources available in special population settings.

Examining temperament attributes in clinically referred preschool children is important for at least four reasons. First, a comparison of clinically referred children with general population children can provide insights as to whether the temperament attributes involved in mild behavior problems differ from those involved in more severe problems and, if so, whether they differ in magnitude or in kind. Second, young children referred for psychiatric treatment are those who need the most support and who would particularly benefit from an understanding of predisposing temperamental factors. Third, if temperament risk factors can be discerned early, when brain and behavioral plasticity is relatively high, this gives interventions a better chance to succeed. Fourth, the merits of temperament scales in detecting early appearing temperament risk factors remain limited as long as their capacity to discriminate normally developing children from children referred for social and emotional behavior disorders remains unknown.

Researchers interested in measuring temperament in children referred for mental health care face a large number of child temperament measures that often include age-specific variants for the infancy, toddler, preschool, and school periods (7). Such diversity can prove confusing and make results across instruments difficult to compare. However, if the interest of the researcher lies primarily in capturing key vulnerability factors for the development of behavior problems over the long term, it is possible to significantly reduce the vast number of traits and scales to a few characteristics that are represented across most models of temperament.

Indeed, most of the evidence for persistent, long-lasting effects of early childhood temperament crystallizes around three temperament components. Behavioral inhibition, which is related to harm avoidance, is a well-documented risk factor for the development of later anxiety and depressive symptoms [e.g., (8, 9)]. Anger/frustration, as well as low effortful control, have been found to predict various types of externalizing problems, including attention deficit hyperactivity disorder, substance dependence, and conduct and antisocial personality disorders [e.g., (10–13)]. The latter two dimensions often compound one another in putting children at risk for externalizing behavior problems. Thus, toddler inattention and impaired emotion regulation, as measured in response to a frustration task, were found to be powerful predictors of a chronic externalizing profile (14). They also coalesce in the construct of undercontrol—a clinically significant cluster defined by traits such as impulsivity, inattention, and emotional volatility (15). A similar cluster characterized by low attentional focusing, low approach tendencies, anger/frustration, and impulsivity was found to predict poor adaptive functioning in children with autism (16). It is also noteworthy that the combination of negative emotionality, notably anger, and low effortful control was more strongly associated with violent and non-violent delinquency than psychopathic traits and childhood traumatic events in a sample of juvenile offenders (5). Long-term behavior problems associated with these early childhood temperament attributes are summarized in **Tables 1A,B**.

A tool for measuring these attributes, the Integrative Child Temperament Screener (ICTS), was recently introduced (17). Derived from the 30-item Integrative Child Temperament Inventory [ICTI (18)], it assesses anger/frustration, behavioral inhibition, and attentional persistence as key temperamental vulnerability factors that are represented across models of child temperament (hence the instrument's designation as "integrative"). Because anger/frustration is a risk factor for developing externalizing problems especially when it co-occurs with low attentional persistence, the instrument also makes provision for computing a score that combines both scales. We termed this composite dimension impulsivity, since children with low frustration tolerance and difficulties focusing attention often appear to behave impulsively. However, we realize that terms such as "undercontrol," "low self-control" or "temperamental difficulty" could have been used instead, and that impulsivity has a more circumscribed meaning in certain temperament theories and inventories. **Table 2** provides a summary of the characteristics measured by the ICTS, along with related temperament dimensions.

An important consideration in designing the ICTS was that it should measure the vulnerability factors shown in **Table 2** in an economical, developmentally appropriate, and cross-nationally comparable way. Thus, each ICTS attribute is measured with three items only, resulting in a nine-item scale that can be administered in about 1 min (17). Items representing each component were specifically selected on the basis of their developmental suitability and measurement invariance across the period from 2 to 8 years of age. For example, attentional persistence was included as the facet of effortful control with the greatest likelihood of exhibiting measurement invariance from infancy to school age. The items have also shown measurement invariance across several nations (17). Demonstration of measurement invariance is important because it ensures that items retain the same meaning across different age or national groups, thus allowing for unbiased cross-temporal or cross-national comparisons.

TABLE 1A | Infant-to-preschool temperament predictors of adolescent and adult personality and psychopathology: undercontrol/inattention.

Longitudinal study	Early childhood temperament	Adolescent/adult outcomes	Predictive range
Dunedin Health and Development Study	Undercontrol/impulsivity	Elevated suicide risk Criminal offending Substance dependence	3–18 years 3–26 years 3–32 years
Mauritius Child Health Project	Fearlessness, disinhibition	Psychopathy	3–28 years
Block & Block Longitudinal Project	Ego-undercontrol	Ego-undercontrol Narcissism	3–23 years 3–23 years
Colorado Longitudinal Twin Study	Impulse control	Executive functions	18–36 months to 16–17 years
Mannheim Longitudinal Study	Attentional deficits	Novelty seeking	3 months to 16 years
Fullerton Longitudinal Study	Temperamental difficulty	Externalizing and internalizing behaviors	18 months to 17 years

Tables 1A *and* ***1B*** *adapted from Zentner (1, 17).*

TABLE 1B | Infant-to-preschool temperamental predictors of adolescent and adult personality and psychopathology: inhibition/fearfulness.

Longitudinal study	Early childhood temperament	Adolescent/adult outcomes	Predictive range
Harvard Longitudinal Study	High reactivity	Trait anxiety Amygdala hyperresponsiveness	4 months to 15 years 4 months to 21 years
University of Maryland Longitudinal Study	Inhibition	Internalizing problems	14 months to 26 years
Dunedin Health and Development Study	Inhibition	Depression Harm avoidance	3–18 years 3–26 years
LOGIC Study	Inhibition	Internalizing problems	4–23 years
Uppsala Longitudinal Study	Shyness	Social anxiety Depressive symptoms	20 months to 21 years 20 months to 21 years
Bernese Longitudinal Study	Infant reactivity Irritability	Shyness	3–4 months to 15 years

TABLE 2 | Summary and capsule definitions of temperament dimensions included in the ICTS.

ICTS dimension (number of items)	Capsule definitions	Examples of related dimensions
Behavioral inhibition (3)	Inhibition of behavior in response to novel unfamiliar people and situations	Harm avoidance (JTCI)[a]; shyness (CBQ, EAS); social fearfulness (TBAQ)
Anger/frustration (3)	Aggressive or irritated behavior in response to painful and/or frustrating input	Anger/frustration (CBQ); anger (TBAQ); distress to limitations (ICQ)
Attentional persistence (3)	Capacity for attentional focusing and control as the basis for voluntary behavior, including persistence	Effortful control (CBQ), persistence (JTCI); interest (TBAQ); distractibility (BSQ)
Impulsivity[b]	Low tolerance for frustration combined with low self-regulatory abilities	Negative emotionality (CBQ), difficultness (ICQ), undercontrol (15)

[a]*Initials refer to questionnaires that include the listed scales. BSQ, Behavioral Style Questionnaire (19); CBQ, Child Behavior Questionnaire (20); EAS, EAS Temperament Survey for Children (21); ICQ, Infant Characteristics Questionnaire (22); JTCI Junior Temperament and Character Inventory (23); TBAQ, Toddler Behavior Assessment Questionnaire (24).*
[b]*Composite variable composed of anger/frustration and attentional persistence.*

As would be expected from previous research, in a community sample of preschoolers, ICTS anger/frustration has been found to be distinctively associated with mother-reported conduct problems, lack of attentional persistence with hyperactivity symptoms, and inhibition with emotional symptoms (17). Interestingly, the specific ICTS scales explained considerably more variance in problem behaviors than did broad, higher order factors such as effortful control or negative emotionality (25). However, as is the case for the vast majority of studies, these temperament-to-behavior problem associations were found in general population samples. What little is known about such associations in referred children seems

to point to a similar pattern of temperament-to-behavior problem associations (6). However, the scant evidence leaves several questions unanswered. For example, whether the pattern generalizes across nations and assessment instruments and, most notably, which tools may offer sufficient utility to be used in child mental health settings for the identification of an at-risk temperament profile.

To fill this gap, in the current study, we examined temperament characteristics in young children referred for treatment of emotional and/or behavioral disorders and compared them with those from an age- and gender-matched general population sample by using the ICTS. We reasoned that, since the ICTS scales were specifically designed to identify temperament characteristics associated with risk for behavioral problems, the scales should differentiate referred from non-referred children by standard discrimination metrics, such as area under the receiver operating characteristic (AUROC) curve analyses. We were also interested in examining whether the ICTS would add to the prediction of diagnostic status above and beyond the Child Behavior Checklist (CBCL) scales. Finally, to see whether the ICTS could predict, in addition to binary diagnostic status, specific symptom profiles, we formed subgroups that exhibited an internalizing and externalizing symptom profile and repeated the AUROC analyses in relation to these more specific symptom groups.

METHOD

Participants

The clinically referred sample comprised all in- and outpatients treated at the Department of Child and Adolescent Psychiatry and Psychotherapy in Hall in Tirol, Austria between August 2017 and January 2020, for whom temperament ratings were available. This was the case for 87 children aged 2–11 years ($M = 4.96$, $SD = 1.86$), 67.8% of whom were boys. The vast majority of children (87%) were preschoolers (aged 6.5 years or less). This sample was compared with a general population sample assessed as part of a longitudinal study on temperament and development conducted at the University of Heidelberg, comprising 85 children aged 5–6 years ($M = 5.02$, SD = 0.15), 54.1% of whom were boys. Sample characteristics are displayed in **Table 3**.[1]

To determine the adequacy of the sample size, we conducted a power analysis by using G*Power 3.1 (26) for *t*-tests on two independent groups, and for a multiple regression with 10 predictors. The expected effect size was based on a previous study using the ICTS (17), in which problem behaviors correlated with the relevant ICTS dimensions between $r = 0.43$ and $r = 0.46$, averaging $r = 0.44$ ($d = 0.98$; AUC = 0.76). From these criteria G*Power estimated a minimum sample size of 72 participants to achieve a power of $1–\beta = 0.95$ and $\alpha = 0.05$.

TABLE 3 | Descriptive statistics of clinically referred and general population children.

	Clinical sample (Hall) *N = 87*	Population sample (Heidelberg) *N = 85*	*p*
Clinical treatment			
Inpatient	32 (36.8%)	NA	
Outpatient	55 (63.2%)	NA	
Sex			0.092
Male	59 (67.8%)	46 (54.1%)	
Female	28 (32.2%)	39 (45.9%)	
Age			0.003
(at time of assessment or initial admission)	4.92 (1.81)	5.51 (0.08)	
Relationship status of biological parents			<0.001
Living together	36 (62.1%)	85 (100%)	
Separated/Divorced	20 (34.5%)	0 (0.00%)	
Separated by death	1 (1.72%)	0 (0.00%)	
Never lived together	1 (1.72%)	0 (0.00%)	

Measures

Child Temperament

The ICTI is a 30-item measure that assesses the temperament dimensions of anger/frustration, behavioral inhibition, attention/persistence, activity level, and sensory sensitivity in preschool and early school-age children (18). The nine items of the ICTS are embedded in the ICTI and capture the three clinically most significant scales of the ICTI with three items each (17): anger/frustration (e.g., "cries or yells when asked to stop favorite occupation"); behavioral inhibition (e.g., "is shy when meeting unfamiliar children"); and attentional persistence (e.g., "when looking at a book or painting, is quickly bored and changes activity"). For the sake of brevity, the ICTS dimensions are sometimes simply referred to as frustration (for anger/frustration), inhibition (for behavioral inhibition), and attention (for attentional persistence). A composite trait termed "impulsivity" is defined by low frustration tolerance in combination with poor attentional control. It is computed by adding the anger/frustration and the (reverse-scored) attentional persistence scale items (17). The items are presented on a six-point scale ranging from 1 (*behavior occurs never or hardly ever*) to 6 (*behavior occurs always or close to always*). The complete scale can be found in (7).

Child Problem Behavior

Upon admission, children were assessed with a routine diagnostic battery comprising expert ratings and parental reports.

[1]Because there were some differences in age and sex between the clinical and general population sample (see **Table 3**), we ran two types of analyses to examine whether these differences could have been a source of bias. First, we re-ran the analyses with a "trimmed" sample, in which children older than 7 years and younger than 3 years were removed. This age-restricted sample ($N = 69$) was characterized by a much lower spread ($SD = 1.14$, down from $SD = 1.81$ in the full sample), all while remaining broadly comparable in regard to the average age ($M = 4.85$ vs. 5.51, for the clinically referred and the general population sample, respectively). Second, we recomputed the analyses controlling for sex and age. Both types of analyses left the results reported in **Tables 4–6** effectively unchanged. When changes occurred, they were minimal and did not change the results substantially nor any of our conclusions. The respective analyses are available on request.

Standardized clinical interviews provided essential information for diagnostic classification. Although children aged 6 years and older were assessed with the Kinder-DIPS—a diagnostic interview for assessing mental disorders in children and adolescents (27)—there are no generally accepted, standardized measures for assessing preschool mental disorders in German-speaking countries. Thus, diagnoses for children aged 5 years and younger were primarily based on developmental and disorder-specific measures, as well as behavioral observations.

Clinical diagnoses for all children were determined according to the Multiaxial System (MAS) of the 10th revision of the *International Classification of Diseases* (ICD-10) in combination with criteria from the DC: 0–5 in multidisciplinary classification meetings, in which child and adolescent psychiatrists, clinical psychologists, and psychotherapists evaluated children's symptoms based on anamnestic information, behavioral observations, and questionnaire data. An overview of the diagnoses can be found in **Supplementary Table 1**. A total of 20 children did not meet the criteria of a specific axis 1-MAS diagnosis but were non etheless referred for treatment at the clinic because of elevated strain. Of the other behavioral and emotional disorders (F98), the majority of children ($n = 32$, 76.2%) were diagnosed with unspecified behavioral or emotional disorders (F98.9), five (11.9%) with non-organic encopresis (F98.1), four (9.5%) with other specified behavioral and emotional disorders (F98.8) and four with eating disorder (F98.2), and two (4.8%) with non-organic enuresis (F98.0). This distribution of behavior disorders is broadly reflective of the prevalence of preschool behavior disorders as identified in large-scale epidemiological studies [e.g., (28–30)]. According to these, the majority of problems fall into the externalizing class (DSM-VI: ADD, ODD, CD; ICD-10: F90-98); followed by internalizing problems (DSM-VI: Depression, SAD, GAD, social phobia; ICD-10: F40-48), and disorders of psychological development (ICD-10: F8).

To assess internalizing and externalizing problem behavior, we asked the caregivers of the clinically referred children to complete the CBCL for ages 1.5–5 (31) or for ages 6–18 (32), depending on the child's age. Caregivers of the children recruited in the population study completed the CBCL for ages 4–18 (33), since this study was conducted before the new CBCL versions became available. Caregivers were asked to rate items on a three-point scale (0 = not at all true, 1 = somewhat true, 2 = very true). Scores for internalizing and total problems were computed in accordance with scoring instructions described in the respective manuals (31–33). In the case of the externalizing scale, we proceeded by following the manual instructions for the CBCL/1.5–5, whereas we added the attention problems subscale to the externalizing composite for CBCL/4–18 and CBCL/6–18. This was done to ensure comparability with the results obtained in an earlier study with the Strengths and Difficulties Questionnaire (17), which includes hyperactivity in the externalizing broadband symptom scale. To make the scores of the different CBCL versions comparable, we computed *T*-scores for the subscales and the broadband syndrome scales according to gender-specific norms reported in the respective manuals. Internal consistency reliabilities for internalizing and externalizing scales of the CBCL ranged from $\alpha = 0.89$ to $\alpha = 0.93$. From continuous scores, children can be allocated to normal, borderline, and clinical ranges regarding externalizing, internalizing, and total problems in reference to the respective manuals (31–33). Allocation to the corresponding categorical CBCL risk groups was used for certain types of analyses.

To ensure that parental CBCL ratings were reflective of symptoms as identified in the clinical diagnoses, we compared parental CBCL ratings to the ICD-10 diagnoses and symptoms. The comparisons were carried out on externalizing symptoms because of the ICTS' particular relevance to this symptom class. Agreement was in the moderate range, $\kappa = 0.562$ (95% confidence interval 0.384 to 0.740; $p < 0.001$; $n = 83$), for dichotomous ratings (0 = no externalizing symptoms, 1 = externalizing symptoms).

Procedure

Parents completed the ICTI and the CBCL. The questionnaires in the referred group were mostly completed by the mothers, who were the primary caregivers, and partially by the fathers. For three children of the clinical sample (3.45%), no mother ratings on the CBCL were available and so they were substituted with father ratings. For four children (4.60%), no CBCL ratings were available at all. For eight children (9.20%), no mother ICTI ratings were available, but only father ratings; therefore, the latter were used. In the general population sample, ratings were available by fathers and mothers for the ICTI and by mothers only for the CBCL. To make the ratings comparable with the sample of referred children, we used only maternal ICTI ratings, except for four cases in which missing mother ratings were substituted with the father ratings. For one child (1.18%), neither mother nor father ratings of the ICTI were available. CBCL ratings in the general population sample were available for all but one child (1.18%). Caregivers of the clinically referred children signed informed consents for using data for scientific research and knew that participation in the study would not influence treatment. The study involving the clinically referred group was approved by the medical ethical committee of Innsbruck Medical University.

RESULTS

Temperament Traits in Clinically Referred Children Compared With General Population Children

Means, standard deviations, and scale intercorrelations of the combined samples are shown in **Table 4**. As can be seen, all CBCL subscales and all ICTS scales except inhibition were significantly associated with the clinical status of children. The three significant ICTS-to-diagnostic status correlations were comparable to the CBCL-to-diagnostic status correlations in magnitude, which is somewhat surprising given that the ICTS scales were not designed to directly assess problem behaviors. The ICTS and CBCL scales were plausibly intercorrelated. For example, the highest correlation of ICTS Frustration was with CBCL Aggressive Behavior ($r = 0.64$, $p < 0.001$), the highest

TABLE 4 | Means, standard deviations, and Pearson zero-order correlations.

	Variable	*M*	*SD*	1	2	3	4	5	6	7	8	9	10	11	12
1	Clinical treatment (0 = no, 1 = yes)	0.51	0.50												
2	Sex (0 = boys, 1 = girls)	0.39	0.49	−0.14											
3	Age (years)	4.86	1.32	−0.13	0.11										
4	ICTS frustration	10.02	3.90	0.44**	−0.21**	−0.02									
5	ICTS inhibition	8.05	3.79	0.09	0.01	−0.05	0.28**								
6	ICTS attention	12.23	3.87	−0.60**	0.04	−0.06	−0.45**	−0.15							
7	ICTS impulsivity	18.80	6.61	0.61**	−0.15	0.02	0.85**	0.25**	−0.85**						
8	CBCL aggressive behavior	60.20	10.09	0.31**	−0.09	0.13	0.64**	0.20*	−0.38**	0.61**					
9	CBCL attention problems	57.46	9.08	0.50**	−0.13	0.25**	0.53**	0.13	−0.67**	0.70**	0.63**				
10	CBCL anxious/depressive	57.04	8.99	0.38**	−0.06	0.12	0.46**	0.41**	−0.44**	0.53**	0.56**	0.56**			
11	CBCL withdrawn	58.44	8.05	0.33**	−0.15	−0.06	0.39**	0.45**	−0.31*	0.41**	0.44*	0.42**	0.59**		
12	CBCL somatic complaints	57.11	8.36	0.37**	0.09	0.07	0.37**	0.16*	−0.37**	0.44**	0.45**	0.44**	0.52**	0.38**	
13	CBCL total problems	58.90	10.89	0.34**	−0.11	0.17*	0.64**	0.34**	−0.49*	0.67**	0.83**	0.73**	0.77**	0.66**	0.61**

*ICTS, Integrative Child Temperament Screener; CBCL, Child Behavior Checklist. ICTS scores represent total scores, CBCL scores represent T-scores. *p < 0.05, **p < 0.01.*

TABLE 5 | *t*-Test comparisons and area under the curve of the ICTS and ICTI scales for the referred and non-referred samples.

	Referred (*n* = 87) *M* (*SD*)	Non-referred (*n* = 85) *M* (*SD*)	*t*-Test	*p*-Value	d (95% CI)	AUC (95% CI)
ICTS						
Frustration	11.68 (3.96)	8.29 (2.98)	6.42	<0.001	0.98 (0.66–1.30)	0.76 (0.68–0.83)
Inhibition	8.37 (3.89)	7.72 (3.68)	1.02	0.31	0.16 (−0.14–0.46)	0.55 (0.46–0.64)
Attention	9.90 (3.68)	14.56 (2.34)	−9.62	<0.001	1.46 (1.12–1.79)	0.84 (0.78–0.90)[a]
Impulsivity	22.70 (6.09)	14.73 (4.16)	9.98	<0.001	1.52 (1.18–1.86)	0.86 (0.81–0.92)
ICTI						
Frustration	22.14 (7.41)	16.34 (5.12)	5.92	<0.001	0.91 (0.60–1.23)	0.74 (0.66–0.82)
Inhibition	17.96 (7.05)	16.20 (6.64)	1.68	0.10	−0.25 (−0.05–0.56)	0.57 (0.49–0.66)
Attention	19.88 (6.02)	27.19 (4.68)	−8.85	<0.001	1.36 (1.03–1.69)	0.83 (0.77–0.89)[a]
Activity	23.32 (7.05)	20.39 (6.58)	2.80	<0.01	0.43 (0.13–0.74)	0.62 (0.54–0.71)
Sensory Sensitivity	19.15 (6.80)	16.00 (5.73)	3.28	<0.01	0.51 (0.20–0.81)	0.65 (0.56–0.73)

ICTS, Integrative Child Temperament Screener; ICTI, Integrative Child Temperament Inventory; CI, confidence interval; d, Cohen's d; AUC, area under the curve. Ranges in parentheses.
[a]AUC value was computed from reverse-scored Attention to make high scores indicate more risk (Inattention).

correlation of ICTS Inhibition was with CBCL Withdrawn ($r = 0.45$, $p < 0.001$), and the highest negative correlation of ICTS Attention was with CBCL Attention Problems ($r = -0.67$, $p < 0.001$). In line with previously reported findings (17), all ICTS scales exhibited satisfactory internal consistency reliability (Frustration: $\alpha = 0.75$; Inhibition: $\alpha = 0.73$; Attention: $\alpha = 0.80$; Impulsivity: $\alpha = 0.80$).

Table 5 shows the mean level differences in temperament traits between the referred and the non-referred children, along with effect size estimates and AUROC curves for both the ICTS and the ICTI. The AUROC is a measure for the diagnostic efficiency of a measurement. An AUROC of 0.50 indicates that the measurement performs at chance levels, and an AUROC of 1.0 indicates that the measurement performs perfectly. The following AUROC benchmarks have often been used in the literature: 0.90 is "excellent," 0.80 is "good," 0.70 is "fair," and below 0.70 is "poor." In practice, AUROCs in the range of 0.70 to 0.80 are considered to be realistic of a good test (34). As can be seen from **Table 5**, ICTS Frustration, ICTS Inattention (reverse-scored ICTS Attention), and the composite variable Impulsivity performed within this range, as did the corresponding ICTI scales. The ICTI scales not included in the ICTS, Activity and Sensory Sensitivity, did not discriminate between the clinically referred and non-referred children.

To examine whether the longer and more comprehensive ICTI scales added to the prediction of diagnostic status relative to the shorter and more clinically focused ICTS, we ran a multivariate binary logistic regression. Adding the ICTI scales

TABLE 6 | *t*-Test comparisons and area under the curve of ICTS scales for children at risk and at no risk for externalizing, internalizing, and total problems according to the CBCL.

ICTS Scales	Externalizing ($n = 42$) *M* (*SD*)	No externalizing[a] ($n = 98$) *M* (*SD*)	*t*-Test	*p*-Value	AUC (95% CI)
Frustration	13.55 (3.31)	8.39 (3.41)	−8.48	<0.001	0.86 (0.79–0.92)
Inhibition	8.62 (4.06)	7.51 (3.70)	−1.58	0.117	0.58 (0.48–0.69)
Inattention[b]	9.69 (4.03)	13.41 (3.14)	5.08	<0.001	0.75 (0.66–0.84)
Impulsivity	24.69 (6.02)	15.98 (5.20)	−8.83	<0.001	0.86 (0.79–0.93)
	Internalizing ($n = 41$)	**No internalizing ($n = 102$)**			
Frustration	12.29 (4.01)	8.52 (3.49)	−5.77	<0.001	0.77 (0.68–0.86)
Inhibition	10.00 (4.10)	7.08 (3.40)	−4.37	<0.001	0.72 (0.62–0.81)
Inttention[b]	10.07 (4.19)	13.41 (3.23)	4.66	<0.001	0.73 (64–0.82)
Impulsivity	23.22 (6.50)	16.04 (5.61)	−6.60	<0.001	0.80 (0.71–0.88)
	Overall problem behavior ($n = 51$)	**No overall problem behavior ($n = 98$)**			
Frustration	12.92 (3.55)	8.22 (3.21)	−8.34	<0.001	0.84 (0.77–0.91)
Inhibition	9.29 (4.00)	7.05 (3.40)	−3.60	<0.001	0.67 (0.58–0.76)
Inattention[a]	9.84 (4.03)	13.76 (3.08)	5.85	<0.001	0.77 (0.69–0.85)
Impulsivity	23.94 (5.76)	15.47 (5.12)	−9.31	<0.001	0.87 (0.81–0.93)

CBCL, Child Behavior Checklist; ICTS, Integrative Child Temperament Screener; AUC, area under the curve; CI, confidence interval.
[a]*Children showing borderline externalizing problems (n = 27), internalizing problems (n = 24), and total problems (n = 18) were excluded from analyses.*
[b]*Attention was reverse scored and labeled "Inattention" here to make high scores indicate more risk.*

to the ICTS scales resulted only in marginal incremental utility ($\Delta\chi^2 = 9.7$; $\Delta R^2 = 0.04$, $p = 0.088$), suggesting that most of the clinically relevant temperament information is captured by the ICTS scales. **Table 6** shows the mean level differences in temperament traits, along with effect size estimates and AUROC curves, for children of both samples combined, who were categorized as being at risk and not at risk for externalizing, internalizing, and total problems according to CBCL categorical scoring guidelines (see Method). The results remained effectively unchanged when age and sex differences between the clinically referred and the general population sample were accounted for (See footnote 1). The results both corroborate and extend those found for prediction of general clinical status. Specifically, externalizing risk status was accurately predicted by ICTS Frustration, Inattention, and Impulsivity. Internalizing risk status was predicted by ICTS Inhibition, though with less accuracy compared with the ICTS predictors for externalizing problems.

PREDICTION OF CLINICAL STATUS FROM ICTS AND CBCL SCALES

Lastly, we conducted a hierarchical binary logistic regression that predicted diagnostic status from CBCL Externalizing and CBCL Internalizing problem scores, gender, and age in a first step, adding the ICTS scales in a second step. As shown in **Table 7**, the results indicated that, after prediction of diagnostic status by the two broadband CBCL scales, gender and age, the ICTS still added substantially to prediction of diagnostic status, confirming its incremental utility. When using the three specific CBCL subscales that are most closely related to the ICTS scales (aggressive behavior, attention problems, and withdrawn), the amount of incremental variance explained by the ICTS was smaller but still significant (see **Table 8**). On the whole, the results of the logistic regression converged with the AUROC analyses in showing that anger/frustration and attentional persistence (reverse scored) were the ICTS scales with the best ability to discriminate clinically referred children from general population children.

DISCUSSION

Temperament and Psychopathology

The results of this study extend previous research on temperament and psychopathology by showing that children referred for psychiatric treatment exhibit temperament attributes that are similar to those that have been found to relate to behavior problems in general population studies. In line with previous research that found negative emotionality, particularly anger, in combination with poor self-regulation to have a special role in predicting externalizing disorders (1–3, 5, 17), we found anger-frustration and low

TABLE 7 | Summary of a multivariate binary logistic regression analysis predicting clinical treatment from ICTS and CBCL-broadband scales.

	Model 1				Model 2			
Predictor	***OR***	***SE***	***z***	***p***	***OR***	***SE***	***z***	***p***
Constant	0.05	1.21	5.96	0.02	0.08	1.64	2.42	0.12
Age	0.76	0.15	3.57	0.06	0.70	0.19	3.43	0.06
Sex	0.56	0.37	2.48	0.12	0.55	0.50	1.48	0.22
CBCL Externalizing	0.99	0.02	0.15	0.70	0.90	0.03	9.69	<0.01
CBCL Internalizing	1.09	0.02	13.84	<0.01	1.09	0.04	5.96	0.02
ICTS Frustration					1.33	0.09	9.99	<0.01
ICTS Inhibition					1.62	0.07	4.26	0.04
ICTS Inattention[a]					1.59	0.09	28.68	<0.01
Model Summary		$\chi^2 = 28.26$	$R^2 = 0.22$	<0.001	$\chi^2 = 97.41$		$R^2 = 0.61$	<0.001
Model Comparison (1 vs. 2)		$\chi^2 = 69.15$	$\Delta R^2 = 0.39$	<0.001				

N = 160. CBCL, Child Behavior Checklist; ICTS, Integrative Child Temperament Screener.
[a]*Attention was reverse-scored and labeled "Inattention" to make high scores indicate more risk.*

TABLE 8 | Summary of a multivariate binary logistic regression analysis predicting clinical treatment from ICTS and specific CBCL scales.

	Model 1				Model 2			
Predictor	***OR***	***SE***	***z***	***P***	***OR***	***SE***	***z***	***P***
Constant	0.00	2.17	17.62	<0.01	0.00	2.33	10.48	<0.01
Age	0.53	0.22	8.49	<0.01	0.58	0.23	5.90	0.02
Sex	0.70	0.42	0.70	0.40	0.79	0.48	0.25	0.62
CBCL Aggressive Behavior	0.99	0.03	0.10	0.75	0.97	0.04	0.76	0.38
CBCL Withdrawn	1.03	0.03	0.98	0.32	1.06	0.04	2.55	0.11
CBCL Attention Problems	1.22	0.04	23.36	<0.01	1.10	0.05	3.60	0.06
ICTS Frustration					1.18	0.09	3.71	0.05
ICTS Inhibition					0.88	0.08	2.74	0.10
ICTS Inattention[a]					1.45	0.10	14.90	<0.01
Model Summary		$\chi^2 = 66.99$	$R^2 = 0.46$	<0.001	$\chi^2 = 93.21$		$R^2 = 0.59$	<0.001
Model Comparison (1 vs. 2)		$\chi^2 = 26.22$	$\Delta R^2 = 0.16$	<0.001				

N = 160. CBCL, Child Behavior Checklist; ICTS, Integrative Child Temperament Screener. [a]*Attention was reverse-scored and labeled "Inattention" to make high scores indicate more risk.*

attentional persistence to be the factors most distinctively associated with referral status and with an externalizing problem behavior profile in particular. In turn, behavioral inhibition was found to be elevated only in children with an internalizing problem profile. Overall, this pattern suggests that predisposing temperamental factors previously identified in general population samples differ from those present in children referred for psychiatric treatment by degree rather than type.

If children's referral status is taken as a reference, the attributes deviating most strongly from levels found in general population children were low attentional persistence and the composite variable impulsivity. This finding is consistent with CBCL "Attention Problem Scale"-items having shown to have the greatest efficacy in discriminating between referred and non-referred children (35) as well as with the crucial role of low effortful control and low self-control in predicting a broad range of social-emotional problems throughout childhood and up to adulthood (3, 5, 11). That behavioral inhibition did not discriminate between referred and non-referred children may be related to the lower prevalence of internalizing relative to externalizing symptoms in clinically referred preschoolers as well as to the lesser visibility of internalizing compared to externalizing difficulties for parents and professionals in children of this age group (29, 36, 37).

Screening Utility of the ICTS

Diagnostic status could be well-predicted by the ICTS, thus corroborating its clinical validity and showing promise as a potential screening tool. Somewhat surprisingly, the ICTS predicted children's diagnostic status as accurately as the 100-plus-item CBCL, and even added significantly to the prediction of diagnostic status above and beyond the CBCL. It is also worth noting that clinically relevant temperament information was captured by the nine-item ICTS scales as effectively as by the 30-item ICTI. Three factors may help explain the somewhat

unsuspected sensitivity of the ICTS in identifying clinically referred children.

First, a growing body of research points to frustration proneness and low attentional control as core features of the externalizing problem cluster and to behavioral inhibition as a core component of the internalizing cluster. By directly capturing the temperamental core components of externalizing and internalizing psychopathology, the ICTS may achieve a relatively high level of diagnostic accuracy despite its brevity. This notion is supported by the finding that of the 11 CBCL items that have been found to discriminate most powerfully between referred and non-referred children in a large-scale German study (35), many resemble the ICTS items in their focus on deficits in attentional and emotional regulation. Second, the CBCL covers a broad range of problem behaviors, some of which were not exhibited by the clinically referred children. It is possible that the CBCL's diagnostic acuity was weakened by the lack of relevance of some CBCL scales in the present context. This is suggested by the smaller incremental prediction of clinical status by the ICTS over the CBCL, when the CBCL scales that are most closely related to the ICTS were used. A third possible reason is that, because the wording of ICTS items implies less serious behavior problems compared to the wording of many CBCL items, parents might be inclined to answer more truthfully when asked about their children's behaviors. All while providing plausible reasons for the relatively good performance of the ICTS vis-à-vis the CBCL, we should emphasize that the goal of the ICTS is not to serve as a diagnostic tool, but as potential screening device among others. Also, future studies are necessary to determine whether the findings will replicate in other samples.

Limitations

Results from the current research should be interpreted within its limitations. First, the data was cross-sectional. Therefore, it is difficult to draw conclusions regarding the causal role of the ICTS temperament attributes in the onset of the disorders. Second, although assignment of children to externalizing and internalizing problem status based on the CBCL was consistent with the information used for the ICD-10 classification, and seemed useful in light of the difficulties of ascertaining specific mental disorders during the preschool years (38), the distinction between actual and implied diagnosis needs to be kept in mind in interpreting the CBCL-related findings. Third, and in regard to the prediction of clinical status more generally, it needs to be kept in mind that the clinical significance of the ICTS dimensions was established on the basis of the distribution of disorders in the current clinical sample. Although this distribution seems broadly reflective of the prevalence of preschool disorders as identified in epidemiological studies, additional studies are necessary to particularize the clinal significance of the ICTS scales. Fourth, because of the relatively small sample sizes, it would be premature to draw strong conclusions as to the generalizability of the findings. Finally, the temperament components included in the ICTS were selected on the basis of their early developmental appearance, their predictive validity for behavior disorders over the long term and their measurement-invariant properties. We do not suggest that the ICTS provides an exhaustive assessment of all child temperament dimensions that could potentially place a child at risk for behavior problems. For instance, attentional focusing is a key facet of effortful control that is included in the ICTS (via the attentional persistence scale) because it can be assessed in very young children with items that are both reliable and measurement-invariant over time. However, as children grow older, inhibitory control might also be considered for inclusion in a scale of temperament risk factors.

OUTLOOK AND CONCLUSIONS

These limitations notwithstanding, the current research provides one of the first demonstrations that temperament risk factors identified in general population studies are also exhibited by children referred for psychiatric treatment, albeit in more marked form. The finding that these factors can be quickly and accurately assessed by the ICTS substantiates the instrument's clinical validity, thereby commending consideration by child mental health professionals. Indeed, beyond their scientific merits, the current results could also be of value in making prevention and interventions more viable and effective. Specifically, several recent studies have demonstrated the importance of adequate parenting in reducing adverse consequences of child temperament attributes that are similar to those assessed by the ICTS (39–41). Parallel to these research developments, the last decade has also seen the advent of several temperament-based prevention and intervention programs that use parent and teacher guidance (42), behavioral skills training (43), and computer exercises aimed at promoting self-regulation [e.g., (44)] or reducing behavioral inhibition [e.g., (45)].

Promising though these programs are, they will be difficult to put into widespread practice, such as through primary pediatric care or preschool service systems, without a measure that allows for a quick and valid assessment of a child's temperament. In virtue of its brevity and promising screening effectiveness for a relatively broad range of behavioral or emotional problems, the ICTS helps to remove an important barrier to the implementation of programs designed to reduce risks associated with particular temperament attributes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical University of Innsbruck Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MZ developed the research idea. Data collection and processing was done by EM, KS, and CT. MZ, VB, and HS analyzed the data with input from CT. MZ and VB drafted the manuscript with input from all authors. The study design was developed collaboratively by all authors. All authors provided feedback and contributed to critical revisions of the manuscript's draft and approved the final version of the manuscript for submission.

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SUPPLEMENTARY MATERIAL

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frontiers in Psychiatry

ORIGINAL RESEARCH
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What Contributes to the Development and Maintenance of School Refusal in Chinese Adolescents: A Qualitative Study

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Objective: Although, there has been a growing number of studies on school refusal in Western cultures, the underlying factors that contribute to school refusal in Chinese adolescents remain unclear. This study aimed to better understand why Chinese adolescents refuse to go to school and to further interpret what they want to express through their school refusal behaviors.

Methods: We performed a qualitative study using an interpretative phenomenological analysis. Twenty adolescents with school refusal experiences were recruited from the clinical psychology department of two mental health hospitals in Shanghai, China. They participated in semistructured, face-to-face in-depth interviews. The interviews were transcribed verbatim and analyzed according to the guidelines of interpretative phenomenological analysis.

Findings: Five main superordinate themes emerged from data analysis: (a) competition-oriented social environment; (b) family living space dominated by conflicts; (c) personal living space lacking meaningful support; (d) conflict between the pros and cons of being labeled with a psychiatric diagnosis; and (e) reintegration in school life.

Conclusions: Our analysis emphasized the complex interacting effects of the social environment, family interpersonal conflicts, personal psychological factors and mental health complaints on the development and maintenance of Chinese adolescents' school refusal. These factors contributed to school refusal at each level and influenced each other's effects on school refusal behaviors. Therefore, interventions for Chinese teenagers with school refusal may need to integrate strategies that inspire reorganization and changes in different ecosystems, such as strategies related to government policy, peer relationships, family systems and individual inner dynamics.

Keywords: adolescents, school refusal, interview, interpretative phenomenological analysis, qualitative study

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INTRODUCTION

School refusal behavior refers to a child's refusal to go to school and/or persistent difficulty remaining in class for the entire school day (1). A student who is reluctant or refuses to attend school usually experiences emotional distress that is temporal and indicative of aversion to attendance (e.g., excessive fearfulness, temper tantrums, unhappiness, unexplained physical symptoms) or emotional distress that is chronic and hindering attendance (e.g., depressive affect; sleep problems), usually but not necessarily manifest in absence (e.g., late arrivals; missing whole school days; missing consecutive weeks, months, or years) (2). School refusal can be a source of considerable distress for young people and their families and affects ∼1% of pupils; children with school refusal behavior account for 5% of the children seeking psychiatric consultation (3). Previous investigations have indicated that boys and girls are nearly equally likely to show school refusal (4).

Adolescence is a sensitive period during which the risks of serious consequences of school refusal are highest (5). For youth, school plays an important role in their acquisition of knowledge and development of socialization skills. Sustained school absenteeism can lead to negative consequences, including poor social functioning, unemployment in adulthood, impaired social performance, and school dropout (6). Hence, research exploring the factors contributing to school refusal in adolescents can promote the design of more effective treatment, which might lead to a more positive prognosis.

One of the features of school refusal is the heterogeneity of the affected population at a causal level, that is, in terms of both the reasons for individuals' behavior and their response behavior (7). Moreover, previous research from Western culture has suggested that there are many factors contributing to school refusal and that the interaction mechanisms among these factors might be complex. Therefore, it is difficult for researchers to establish a single classification model to determine the causal relationships between school refusal and the correlated contributors based on a certain study (7). To date, the results from prior studies have suggested that the factors contributing to the development and maintenance of school refusal involve individual psychological variables, the family interpersonal environment, the institutional climate and the socioeconomic environment and culture.

Individual Psychological Variables

Previous research has implied links between children's school refusal and various individual psychological factors, such as emotional distress, feelings of burnout, dysfunctional emotion regulation and childhood trauma. For example, Devenney and O'Toole's (8) study found that children's school refusal could be predicted by adverse childhood experience, anxiety, depression, conduct disorder, and attention deficit hyperactivity disorder. A study on 1,842 Spanish adolescents suggested that students who rejected school were at a higher risk of developing social anxiety problems (9). Meanwhile, school burnout, understood as emotional, physical and mental exhaustion due to education, was found to cause students to refuse to go to school (10). Moreover, an investigation of 184 adolescents demonstrated that children's expressive suppression was linked to their school refusal (11).

Familial Interpersonal Environment

Prior studies have suggested that the development of school refusal is correlated with a dysfunctional family environment and parenting style (12). For example, children with school refusal behaviors reported more interpersonal conflicts and enmeshment with their parents (9, 13, 14). Meanwhile, other factors demonstrated to impact school refusal in adolescents include parental psychopathology, familial psychiatric disorders, poor family cohesion, considerable conflicts or isolation, parental overprotectiveness, ineffective parental control, separation and divorce, poverty, and parental psychological control (11, 15, 16).

Institutional Climate

A previous research has suggested that there are correlations between school absenteeism and school factors such as interpersonal conflicts with peers, teacher-student relations and class climate (13, 14). For example, a study on Norwegian students from the 6th to 10th grades suggested that poor relationships with classmates and perceived poor support from teachers increased the risk of school refusal (6). Similarly, Hendron and Kearney (17) study revealed significant links between school absenteeism severity and poor interclassmate and student-teacher relationships.

Socioeconomic Status and Culture

Socioeconomic status and culture are important macro factors that affect students' schooling. An investigation in Spain indicated that among students with school refusal problems, 37% were raised in economically disadvantaged environments, while only 19% came from advantageous environments (16). An investigation of 600 Indian adolescent girls indicated that school absenteeism was associated with physical pain and culture-related embarrassment during menstruation. The subjects reported that menstruation restricted their daily activities at school and that they chose to be absent from school due to the lack of privacy at school (18). Additionally, Kearney's study identified four potential conditions and causes of school refusal behavior in English-speaking areas, including *escape from aversive social and/or evaluative situations*, *pursuit of attention from significant others*, and *pursuit of tangible reinforcement outside of school*. The validity and reliability of this model has been proven in non-English-speaking countries such as Germany and Ecuador (19, 20). Devenney and O'Toole explored education professionals' views and experiences of school refusal within second-level schools in Ireland. Key themes included the influence of family socioeconomic status, unequal access to support services and pressures for academic achievement (8).

Additionally, socioeconomic status also affect the screening of students with school absenteeism and their access to care. For example, Martin et al.'s study showed that migrant school refusers were less likely to be identified with school refusal by school professionals, and more likely to be considered as truants. Therefore, they were less likely to be offered appropriate mental health care (21).

Background and Aims of Current Study

Although there has been a growing number of studies on school refusal in Western culture, the underlying factors that contribute to school refusal in Chinese adolescents and the mechanism by which these potential factors interact with each other remain unclear. The impact of Chinese sociocultural factors on this phenomenon has not been investigated. In psychological and psychiatric clinics in China, children's school refusal has become the most concerning problem in need of solutions (22). Chinese culture is deeply influenced by Confucianism, and the advocacy of education has a long history (23). Due to the large population and limited qualified education resources, academic performance has become the main means of identifying educational talent and socially stratifying Chinese students. This implies that Chinese adolescents may experience greater academic stress than their Western counterparts and that long school absence may have more serious impacts on young Chinese people's mental health and occupational development (23, 24).

Hence, the aims of this study are (1) to better understand why adolescents refuse to go to school in Chinese culture and (2) to further describe what they want to express through their school refusal behaviors. Because this was an exploratory study on Chinese adolescents' subjective experiences of school refusal, a qualitative research approach was adopted to explore the participants' opinions (25). Moreover, according to the results of previous Western studies, the development of school refusal is inseparable from the intertwined effects of the social environment, the school education environment, the family environment and personal emotional disorders. This is consistent with ecological system theory (EST), which emphasizes that "individual development is nested in a series of environmental systems that influence each other" (26, 27). Thus, EST was adopted as the framework of reference for the current study.

METHODS

Study Design and Methodology

Interpretative phenomenological analysis (IPA) was performed in this study because it has emerged as an increasingly popular methodological tool that enables the in-depth exploration of the meaning of specific issues that are pertinent to participants (28). The use of this methodology allowed us to examine the participant's subjective experiences in all their diversity and frame questions about the participants' cognitive and affective processes (29).

Participants

Twenty adolescents (10 boys and 10 girls) aged 13–18 years old were recruited through purposive sampling between May 2020 and April 2021 from the outpatient clinical psychology departments of two mental health hospitals in Shanghai, China. Contact was made *via* psychiatrists and psychotherapists working with the adolescents. The sample size was determined based on data saturation—e.g., at the point when no new themes emerged from the participants' experiences. All the participants fulfilled Berg's criteria for school refusal: (1) an unwillingness or refusal to attend school, which often leads to excessive and prolonged school absence, by children who (2) stay home during school hours with their parents' knowledge rather than concealing the problem; (3) experience physical symptoms or emotional distress such as anxiety, depression, and unhappiness at the prospect of attending school; (4) do not show severe antisocial behavior; and (5) whose parents have made reasonable efforts to guarantee the child's safety at school (30). Meanwhile, youth with intellectual disability were excluded. Eight adolescents were also diagnosed with mental health disorders, such as major depressive disorder, bipolar disorder and generalized anxiety disorder. Five participants had been receiving medication, and 12 were accepting psychotherapy when they were enrolled in this study. The participants' demographic characteristics are listed in **Table 1**.

Ethical Standards

Ethics approval for this research was received from the ethics committee of Tongji University as well as the Shanghai Pudong New Area Mental Health Center (No. PWRd2020–01). Participants were informed of the purpose of the research, after which written informed consent was obtained from the adolescents and their parents for their child's participation in this study. Written informed consent was also obtained from the parents of the adolescents for the publication of their research data. Confidentiality was ensuring by using numbers instead of names (e.g., P1, P2) and removing identifying information from the transcripts.

Data Collection

Semistructured interviews were performed with every participant in a private interview room. The interviews were conducted by three researchers who had conducted qualitative research for at least 1 year. The duration of each interview was ∼60 min. With participant permission, all interviews were audio-recorded. A broad data-generating question was first asked: "Please tell me about your experiences after school refusal." Open-ended follow-up questions were used to obtain detailed descriptions. Probing questions, such as "Please tell me more about that," were used to enhance the depth of discussion. The guiding questions that were loosely followed in the interviews were as follows:

1. Can you talk about your experience with studying in school before? What is your opinion on the meaning of going to school?
2. How were the relationships between you and your classmates and teachers before?
3. When did you decided not to go school? Can you talk about how this idea came about?
4. What do you think would be the reasons that led to your school absence? How did you and your families make this decision at that time?
5. How did the people around you react when you stopped going to school? How did you respond to their reactions?
6. Do you have any plans for your future life?
7. Do you have any worries about going back to school in the future? Have you or people around you tried to help you back

TABLE 1 | Characteristics of the participants.

IP	Age	Grade	Gender	Number of siblings	Birth order	Parents' marital status	Length of SR (month)	Psychiatric diagnosis
P1	13	JHS	M	1	2nd	Divorced	0.5	None
P2	15	JHS	F	0	1st	Married	1	MDD
P3	12	JHS	M	0	1st	Married	15	None
P4	14	JHS	M	0	1st	Divorced	7	None
P5	16	JHS	M	1	1st	Divorced	8	None
P6	14	JHS	F	0	1st	Married	3	None
P7	17	HS	F	1	1st	Married	5	GAD
P8	18	HS	F	0	1st	Remarried	10	MDD
P9	18	HS	F	0	1st	Married	13	None
P10	15	JHS	M	0	1st	Married	9	None
P11	16	HS	M	0	1st	Married	16	None
P12	17	HS	F	0	1st	Married	5	MDD
P13	13	JHS	M	0	1st	Married	14	None
P14	14	JHS	M	0	1st	Divorced	6	None
P15	16	HS	F	0	1st	Married	10	BD
P16	18	HS	M	0	1st	Married	8	BD
P17	17	HS	F	1	1st	Married	7	MDD
P18	15	JHS	F	0	1st	Married	9	MDD
P19	17	HS	M	0	1st	Married	9	None
P20	12	JHS	F	0	1st	Married	4	None

M, male; F, female; MDD, major depressive disorder; BD, bipolar disorder; GAD, Generalized anxiety Disorder; HS, high school; JHS, junior high school.

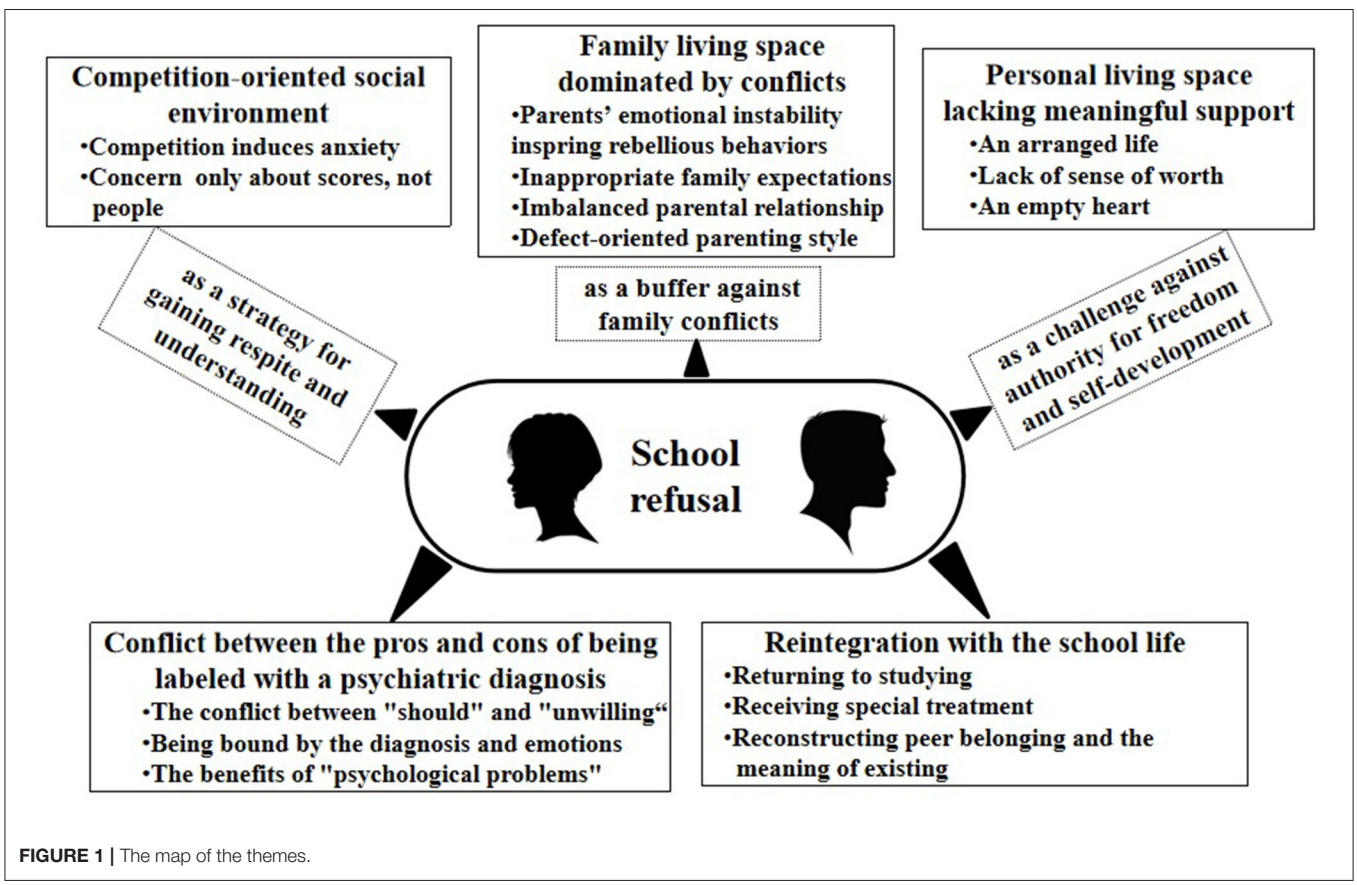

FIGURE 1 | The map of the themes.

to school? If you have, what methods have you tried? Did those methods work well or not? Why?

Data Analysis

The transcribed interviews were analyzed following Smith et al.'s (28) guidelines. The transcripts were read several times, and the left-hand margin was used to annotate what was interesting or significant about what the respondent said. The second step was initial noting, in which the semantic content and language use were examined in a very exploratory manner. The process of initial coding included descriptive, linguistic, and conceptual comments. The third step was developing emergent themes. The main task in this process was to reduce the volume of detail while maintaining complexity in terms of mapping the interrelationships, connections, and patterns among the exploratory notes. The fourth step consisted of further reducing the data by establishing connections between the preliminary themes and clustering them appropriately. Finally, a table was produced that showed each higher-order theme and the subthemes that composed them. After the analysis of each interview separately, connections among the superordinate themes across the interviews were identified.

Several strategies were used to ensure trustworthiness and credibility. Two coauthors (LL and YW) analyzed the transcripts independently by bracketing their preconceived ideas and strictly following the adapted method from Smith et al. described above. The findings were then compared and discussed by two authors until consensus on themes, theme clusters, and superordinate themes was achieved. Meanwhile, an audit trail was maintained to ensure that all analysis steps could be traced back to the original interviews. After completing the analysis, we chose three analytic texts to return to the participants and asked them to evaluate whether the text analysis was in line with their real-life experiences.

RESULTS

Five interconnected and relatively independent superordinate themes emerged from the data analysis: (1) competition-oriented social environment, (2) family living environment dominated by conflicts, (3) personal living space lacking meaningful support, (4) conflict between the pros and cons of being labeled with a psychiatric diagnosis, and (5) reintegration in school life. Eighteen subthemes were identified in relation to these 5 master themes. The main results are shown in **Figure 1**.

Competition-Oriented Social Environment

Almost every adolescent in our study experienced pressure caused by academic competition. Adolescents' academic performance was considered the most important criterion for evaluating their excellence and for subsequent talent selection. However, the significance of other aspects of their existence was ignored to some extent.

Competition Induces Anxiety

Eighteen teenagers reported that they felt great pressure due to the fierce competition with their classmates in terms of scores. In daily conversations, parents and teachers often compared their children's academic performance with that of their peers. They also created an atmosphere in which the following idea was communicated: "if you get poor scores, you will be eliminated, and no one will like you." Teenagers felt exhausted due to bearing this pressure. They became depressed, anxious and self-critical.

> "My dad himself is very anxious; he always tells me that if I sleep more than 5 h a day, I'll be washed out. Because when I am sleeping, all my classmates are studying hard. School teachers also compare their classmates with each other frequently. Students who can get high scores are always popular with their teachers and classmates. This made me feel nervous, angry and helpless"—P19.

Some teenagers even said that this competitive atmosphere had existed since kindergarten. They felt deeply drained.

> "Just like most of my classmates, we have been taking various training courses since kindergarten. The purpose of all these is to win the competition with my peers so we can get into good primary and middle schools and universities. I have hated going to school from the time I was little. It is very boring and tiring for me"—P15.

This kind of competitive environment also triggered anxiety among teachers. The students' scores were regarded as indicators of the teachers' work performance, which could affect teachers' career development.

> "At the end of every semester, our teachers are ranked according to the scores of the students in their classes. If the students do not perform well-enough, the teacher will be replaced. So, our teachers are also under pressure. They transfer their stress to us and push us to learn much harder"—P7.

Concern Only About Scores, Not People

All teenagers in our study complained that their parents and teachers used test scores as the only criterion to judge their value. They felt that the adults did not care about them and their pain and did not see their value aside from their academic performance. This made them angry, stressed and frustrated.

> "For my parents, scores are everything. It doesn't matter to them if I live happily or if am I having a tough time or not. They either don't care about what skills and advantages I have besides studying. They don't care about me"—P3.
> "Our headteacher only cares if we can get high scores or not. Many classmates of mine became depressed due to academic pressure. Some even hurt themselves or committed suicide. However, to my surprise, he (the headteacher) said that the students who were depressed were malingering. He asked them to do more math papers to cure themselves"—P5.

Six participants reported that teachers treated students differently based on their test scores, which they perceived as unfair and which made them feel helpless.

> "Our teachers treat the students unfairly. It doesn't matter if you don't follow school rules as long as you get good scores. But if you

are not good at this, you are just a good for nothing. I feel very disgusted with this"—P7.

School Refusal as a Strategy for Gaining Respite and Understanding

All 17 participants in the study stated that when the stress of academic competition became unbearable, they refused to go to school so that they could have a break and rest. In addition, most parents would have a dramatic change in their attitudes toward their children. They began to care about their children's feelings and needs instead of pushing them to learn.

"I told my parents that my school and the students around me were too good for me to catch up with. I wanted to take a year off. I could take a rest and make up for my lessons. Then, I could have a repeat year in school with less pressure"—P19.

"Now, my mom dares not to push me to finish all my homework or get high scores. She said she would accept each of my requirements as long as I go back to school. To be honest, I feel very relaxed, just go back to school sometimes to have fun with my classmates when I want to"—P3.

Family Living Space Dominated by Conflicts

Our analysis indicated that from the adolescents' view, their family atmosphere was filled with criticism, unstable emotions, high expectations from their parents and marital conflicts between their parents.

Parents' Emotional Instability Inspiring Rebellious Behaviors

In addition to the teenagers, most parents were also influenced by career competition and survival stress. Many were unable to properly manage their expression of emotions in front of the adolescents. They became anxious, depressed or angry. Some parents were overcontrolling of their children. This would trigger more negative emotions of the adolescents, as well as rebellious behaviors such as school refusal. All 17 teenagers in the study emphasized the negative effects of their parents' emotional instability.

"It's my mom who needs psychotherapy. Her mood is very unstable; she will be super nervous if she finds me with a slightly poor score. Sometimes, she gets into a temper like a hysterical psychosis. Every time I see her like this, I feel very tired of living. I have to deal with my studies while dealing with her, which makes me more reluctant to study"—P8.

Inappropriate Family Expectations

In addition, 12 adolescents reported that their families had overly high expectations for their academic performance. For them, these expectations were far beyond their ability. When adolescents failed to meet expectations, their families criticized, judged or attacked them and continued to push them to study. This made them anxious, helpless, self-critical and angry. Many adolescents resisted satisfying the expectations of their families and refused to go to school.

"My father asked me to enter Fudan University, but this is far, far beyond my ability. I am not a 'straight A student.' I told him I could not do it, but he morally attacked me, saying I am not filial, not considerate of his hard work to make money. I just realized no matter how hard I tried, I couldn't make it, and he always felt bad. In this case, I'd rather not to go to school"—P7.

Imbalanced Parental Relationship

In some adolescents' families, there were unresolved marital conflicts between their parents, which led to dull, tense and unstable interpersonal relationships in the family. Many parents transferred their negative emotions caused by marital conflicts onto their children. The adolescents had to spend energy comforting their parents and responding to their emotions, which eliminated their enthusiasm for learning.

"My parents should never have gotten married. They have never had peace. They (my parents) quarrel almost every day; sometimes they even fight with each other. There was a time, as long as I was home, I got so annoyed, because I was always worried if they were going to fight. This distracted me from my homework and my papers"—P13.

"They (the parents) have been fighting with each other for many years. My dad does not care about my mom anymore. So, every time my mom gets frustrated, I have to take over my dad's responsibility to take care of his wife. To draw an analogy, if I have 100% energy, I have to spend at least 70% comforting my mom every day. I barely have the energy to deal with my studies"—P11.

From some teenagers' views, their parents translated their marital disappointment into high expectations of the children's academic performance, which made the adolescents anxious.

"My mother has always been disappointed with my father. She thinks she married the wrong man. She always nags me, 'Study hard; don't become a useless man like your father'; she has always pushed me to study. I feel like a scapegoat for her unhappy marriage, like the last hope for her life. When I think about all of this, I feel angry and anxious. It is not fair!"—P14.

Defect-Oriented Parenting Style

Many anxious parents focused on their children's shortcomings but rarely offered praise, appreciation or encouragement. This made the teenagers feel worthless and engage in self-denial. Therefore, they lacked confidence and motivation in dealing with learning challenges and were more likely to give up when frustrated in their studies. Our analysis suggested that most of these parents were dissatisfied with their own lives or their marriages and had high expectations of their adolescents' academic performance.

"My parents don't have self-recognition. Nor can they gain recognition from each other, which leads them to only see my flaws. Normally, they say other children are excellent but never praise me. After a while I was like, 'Well, I'm crap; I can't make anything right, then what's the meaning of my studying?'"—P17.

School Refusal as a Buffer Against Family Conflicts

After the adolescents refused to go to school, family conflicts were temporarily relieved. It seemed that the school refusal forced the parents to acknowledge their family conflicts, took responsibility, and tried to solve them with different manners. Some parents temporarily stopped quarreling and tried to help their children through cooperative parental work. Some of them tried to control the excessive expression of their emotions. They had to lower their expectations of their children and began to praise their children. Consequently, some children were empowered and regained some confidence. In other words, many parents were forced to change because they had no other choice if they wanted their children to resume going to school.

> "After I stopped going to school, my parents stopped quarreling and began to cooperate. They discuss how they can let me go back to school every day. Now we are much more 'peaceful.' Sometimes I think it's good, better than when they were fighting all the time before"—P13.
>
> "My parents were much gentler with me after I got depressed and refuse to go to school. Especially my father, he now rarely loses his temper, has no requirements regarding my scores. I have a slight idea that I don't want to be recovered now actually, or they will make demands on me again"—P17.

Personal Living Space Lacking Meaningful Support

The third superordinate theme explored the motivation for school refusal from the perspective of the adolescents' individual autonomy and existential experience.

An Arranged Life

Fifteen teenagers reported that their lives were excessively controlled by their families and teachers from an early age, including their living habits, time schedules, school choice, friend selection and hobbies. They did not have the right to manage their own lives. They lacked the opportunity to make their own plans and choices so that they did not experience the joy and satisfaction of growing, learning, and overcoming adversity.

> "I feel like I've been living like a zombie since I was a baby. Everything has been arranged by my parents, including my education, so I feel like life has been boring since I was a child. I can almost see what I'll be like when I am 70 or 80 years old based on now. If everything is predetermined, why should I study so hard?"—P10.

For some adolescents, the experience of being excessively controlled in childhood made them even more resistant to their parents' demands, including to study at school.

> "My life is like a precise instrument preprogrammed by my parents from the day I was born. I could not make any decisions about my life, from what clothes to wear and what food to eat, to what schools to enter and what friends to choose. Now I do not want to obey them anymore. I want to be myself"—P16.

Lack of Sense of Worth

Fourteen adolescents complained that long-term parental excessive control and negative judgment made their self-esteem extremely low. They felt they were neither worthy of living nor appreciated by others. Some adolescents did not believe they could be in charge of their own lives. As a result, they were more likely to give up when confronted with academic setbacks.

> "To be honest, I do not feel I have any advantages really. I have no other skills to be proud of or any other life values. Getting high scores is my only ability to make my parents feel great. However, I failed this exam; I was deprived of the only capital that I had, good scores. I surrendered to life, didn't want to study anymore"—P15.

In some families, the reason why parents paid close attention to their children's shortcomings was closely related to the traditional Chinese culture, which advocates individual modesty. The adolescents' parents thought that even if their children have advantages, they should not give them too much praise; otherwise, it would make their children too proud to study hard.

> "My dad always says, 'Be humble.' He is always worried that if he praises me, I'll self-aggrandize, so he never says anything nice about me. He always praises other children in front of me. After a time, I really felt very badly about myself that I was not good at anything compared to others"—P6.

An Empty Heart

Sixteen teenagers generally reported a strong feeling of emptiness in their hearts. Life was confusing and meaningless to them. They felt they had nothing to pursue, no expectations for life and no idea of the meaning to go to school.

> "I was asked what I wanted to do with my life. To be honest, I really do not know what I want to do in the future; I do not even know what people are living for. My daily life is just going to school, doing exercises and taking exams. This kind of life... well, how to say, not painful, but very boring, a feeling that my heart is empty"—P2.

Eleven teenagers even claimed that studying was a meaningless job assigned to them by society and their families. They did not want to go to school. Nevertheless, they understood that school refusal was not accepted by society. This dilemma made them feel torn.

> "Going to school was just a job assigned to me by the adults. I don't want to do it, but I can't give it up, or I'll be seen as a monster. Well... in fact, I study only to complete the task. Although I can get high scores and often get praise, my heart is always empty, feeling no sense of achievement"—P1.

School Refusal as a Challenge Against Authority for Freedom and Self-Development

Fourteen teenagers reported that school refusal became a way to revolt against parental authority. After they firmly refused to go to school, their parents' behavior pattern changed significantly,

including their parents not overcontrolling their lives, starting to care about their feelings, and starting to praise them.

> "Now I'm blackmailing my parents by not going to school, because I know that is what matters most to them. If I said I wouldn't go to school, my father would not dare to scold me, my mother would not dare to scream at me. They do not dare to come into my room without my permission. I'm free if I don't go to school"—P16.

Ten teenagers even developed new interests, hobbies and abilities during their absence from school. They made new friends through the internet, expanded their horizons, and improved their self-confidence.

> "This semester, I didn't go to school; I found a new hobby, rap music. I record my own music with home devices and post it on Weibo and Bilibili. Many people give me thumbs-up and tell me that I have talent. I feel very happy, as I never have been recognized like this before"—P12.
> "My favorite thing right now is to go to the comics club and draw comics with my friends and to do cosplay. Lots of people praise my painting or come to take photos with me, saying 'Little sister, you are so good at cosplay.' I feel very satisfied from my heart"—P18.

Conflict Between the Pros and Cons of Being Labeled With a Psychiatric Diagnosis

Almost all teenagers in the study developed anxiety or depression due to school-related fatigue. Several were diagnosed by psychiatrists. The fourth superordinate theme captured the conflict between the pros and cons of being diagnosed with a mental disorder.

The Conflict Between "Should" and "Unwilling"

Fifteen teenagers reported that they were ambivalent about school. On the one hand, they thought they should go to school or they would not have a bright future. On the other hand, they were unwilling to study. They became trapped in such emotional dilemmas, becoming anxious, depressed and angry. Eight adolescents even met the diagnostic criteria for one type of mental disorder and claimed to be "mentally ill."

> "I'm on edge right now. I think I should go back to school, but it's too hard for me. But, I, I can't allow myself to give up school either. I'm so anxious, angry and helpless. The doctor said I had depression, and I agreed. I think I do have a 'psychological problem'"—P17.

Being Bound by the Diagnosis and Emotions

Some adolescents considered themselves to be "psychotic patients." They thought that psychiatric diagnoses such as depression prevented them from continuing school study. They believed that the precondition of resuming school was to eliminate "mental illness."

> "After the doctor diagnosed me with bipolar disorder, I understood why I couldn't go to school. It was not that I didn't want to go to school, but I couldn't. I need to recuperate, get more rest and adjust my emotions better"—P15.

The Benefits of "Psychological Problems"

Meanwhile, 10 teenagers reported that a diagnosis and emotional disturbance provided them with some "benefits," that is, gave them a legitimate reason to stay out of school and thus avoid high expectations from families and intense academic competition from their peers. However, some teenagers had a sense of stigma and wished that others would not regard them as patients with mental disorders.

> "To be honest, I dare not get well now, because if I recover from my illness, my parents will certainly revert to their high requirements of me. Hence, sometimes I think it's good to be a psychiatric patient"—P15.
> "How to say it? The fact that I've been diagnosed with a mental illness is, in some ways, a good thing. Because my teachers and parents stopped pushing me to study after I got sick. But I also noticed that my classmates were looking at me strangely, as if I were a patient with a mental disorder. I don't like it"—P2.

Reintegration in School Life

The last superordinate theme concerned the participants' experiences of returning to school. Eighteen adolescents in the study had attempted to return to school and experienced the following challenges and resources.

Returning to Studying

When adolescents tried to restart their studies after a period of school absenteeism, they faced fierce academic competition among classmates again and needed time to adjust to the learning intensity of the school. With their families' support, some adolescents in our study used their resources to develop resilience strategies to cope with the challenge. However, some failed and asked for suspension from school again.

> "I tried several times to regain any course, but it didn't work. The pace of teaching in our school is too fast that if I just miss half a day, there will be a stack of papers waiting for me. I missed classes for such a long time that I couldn't keep up with my classmates now. I'm confused about this; I have no idea what to do"—P16.
> "During the half year of rest time, my father helped me to find two tutors and a social training class to make up my English and math, and it's kind of worked out. Now I'm trying to go back to school, and I feel a bit relaxed in these two subjects"—P20.

Receiving Special Treatment

Nine teenagers reported that when they returned to school, some teachers and classmates treated them with special attitudes, including giving them excessive attention and inquiring about their situation. Some teenagers felt that they were treated as "abnormal" psychiatric patients. This made them uncomfortable, offended and frustrated. They wished they could be treated equally as the other students.

> "When I went back to school a while ago, I was constantly being asked by my classmates, 'What happened to you? Why have you

been away from school for so long? Are you alright?' I knew they meant no harm, but it just made me uncomfortable, feeling like I was being treated as a different monster"—P11.

"Our head teacher is very nervous now. Whenever she sees me with no smile on my face, she comes to me and asks if I am OK or do I need to see a doctor. It makes me very uncomfortable. I feel like she is paying too much attention to me, as I if I were a patient. Actually, all she needs to do is just treat me like the others"—P18.

Reconstructing Peer Belonging and the Meaning of Existing

Fifteen participants reported that after being absent from school for a time, they felt estranged from their classmates due to a lack of connection with them and lagging behind in their studies. This made them feel confused, lonely, and frustrated.

"Although, I wanted to go back to school now, I'm afraid to do so. Since I haven't seen my classmates for a long time, I feel like I don't have common topics with them. I don't understand their discussion about academic points either. Some students even tease me as if I were silly. I feel quite lonely, have nobody to talk to"—P11.

With assistance from their families and schools, some adolescents reconnected with their classmates using several strategies, such as talking with peers about common hobbies and participating in group activities in the class. Six participants reported that the above approaches began to take effect.

"To increase my contact with my classmates, my dad came up with the idea of inviting the boys in my class to visit his game design company together with me, and it worked! I finally had a chance to talk with those classmates I was unfamiliar with—P20.

"I think it's a virtuous circle. The more attached I am to the school, the more I want to participate in group activities, and then the more my classmates and teachers like me, and then, hmm... In fact, although I still dislike to do homework right now, I am willing to play with my classmates"—P20.

However, some participants failed to receive support from their families, peers and teachers. They still found themselves disagreeing with their classmates and had little sense of belonging. Then, they had to suspend their schooling again.

"I don't know, anyway... I've tried to talk to my classmates, but I just thought they were too immature to talk to. My parents seem to have given up on me. They hardly talk to me now, only take care of my younger brother. I don't want to go back to studying any more. Maybe I can start a small business in the future to feed myself, that's enough"—P5.

DISCUSSION

This is the first qualitative study to explore Chinese adolescents' experiences with school refusal. The first theme that emerged from the data concerned the Chinese social environment characterized by strong competition. Our results indicated that the anxiety and helplessness caused by high societal expectations were important factors that contributed to the adolescents' school refusal. This finding is consistent with reports from previous research showing that anxiety related to social expectations and school burnout were correlated with children's school absenteeism (8–10). Our analysis suggested that the emergence of this phenomenon may be related to fierce occupational competition and survival stress within the adult system. Parental anxiety about life might have been transmitted to their children. Moreover, it seems that the influence of parental anxiety on the children in this study may have existed since they were in kindergarten and have become more serious after they entered middle school (23). Meanwhile, the anxiety of adolescents and their families was reinforced and magnified by the teaching system. Finally, adolescents, parents and schools co-constructed an educational atmosphere that promoted anxiety.

Accordingly, school refusal may have unconsciously become a strategy adopted by the adolescents to obtain temporary relief from academic stress. This made their parents and teachers realize the adolescents' suffering and care more about the children' needs. They lowered their expectations of the children and stopped pushing them to study. Then the children's anxiety about academic performance was temporarily eased. This result partially coincides with previous findings that school refusal helps adolescents escape aversive social evaluative situations and supports them in pursuing attention from significant others (19, 20).

Regarding **the second theme**, *family living environment dominated by conflicts*, our analysis first suggested that parents' unstable emotions were closely related to adolescents' emotional stress such as anxiety. The latter may, in turn, have triggered or reinforced school refusal among the adolescents. This finding coincides with Bowen's systems theory that emotional stress among the parental subsystem is contagious in the family and might be transmitted to the children's subsystem through mechanism of low differentiation. Then, the children may develop emotional and behavioral problems including depression, anxiety and school refusal in response to the parents' unstable emotions (31). Meanwhile, it is partially consistent with the opinions of attachment theory that the emotional instability of caregivers is correlated with children's uncertainty and insecure attachment experience and related to more psychosomatic complaints among children (32). As implied by Li et al.'s (33) study, school refusers often display somatic symptoms including headache, abdominal pain, vomiting, nausea, dizziness, diarrhea, muscular ache, fatigue and palpitation, and anxiety was found to be the most recurrent etiology of those somatic complains. Moreover, prior studies have also suggested that children's school refusal is correlated with their interpersonal conflicts, their enmeshment with their parents and parental psychopathology (9, 13, 14, 16). Hence, a clinical implication of this finding is that psychotherapy for adolescents with school refusal may integrate interventions for the caregiver's emotional stress simultaneously.

Second, the findings that parents' marital conflicts contributed to adolescents' school refusal coincided with Bowen's triangulation theory (31). This result suggested that Chinese teenagers' school absenteeism may be triangulated with the marital conflicts of parents (34). The emergence of

this subtheme also partially verified the conclusions of previous research that children involved in parental marital conflicts have poorer academic performance (35).

In terms of *inappropriate family expectations* and *defect-oriented parenting styles*, the findings on the former were consistent with Stierlin's delegation theory, which states that when family expectations are beyond the ability of the offspring, offspring may restrict their self-development and experience psychosomatic symptoms (36). Many parents in our study had overly high expectations for the adolescents' academic performance (high delegation). For the children, the delegation was overwhelming and made them anxious. It seems that they resisted satisfying their families' expectation, and develop school refusal as a challenge against the parental authority for freedom. Meanwhile, at the individual level, a defect-oriented parenting style may cause adolescents to *lack self-worth*, which makes them lack motivation to pursue academic achievements and have less confidence to deal with academic challenges (37).

Interestingly, we found that for the participants, school refusal acted as a buffer against family stress. The parents' attitudes toward their children changed, and their expectations decreased accordingly. This is partially consistent with the perspectives of systemic theory that symptoms such as school refusal may have functions including setting side family conflicts, controlling interpersonal relationships and expressing needs (38).

In the summary of the second theme, our analysis implied that the mechanisms reflected by the four subthemes not only jointly caused teenagers' school refusal but also each promoted the development of the other. In addition, these four subthemes may be linked with the first theme of *competition-oriented social living space*. For example, parents who were anxious about social competition and who were not satisfied with their marriages seemed more likely to delegate excessive expectations to their children and were more inclined to focus on the defects of their children. This may in turn have frustrated the learning motivation of teenagers.

Our third theme concerned the *lack of support for adolescents' personal living*. This theme reflected the youths' sense of emptiness in relation to the value and meaning of life. It has some similarity with the symptoms of *developmental depression*. Developmental depression has been proposed as sub-type of moderate depression that is a common and potentially normative developmental process of spiritual individuation in the pathway of late adolescent (39). The clinical presentation of developmental depression may include adolescents' frustration and anger in not finding meaning of their lives, a hunger for more connection and the struggle for existential value in a perceived valueless word (39). Our finding suggested that Chinese adolescents with school refusal might have also experienced the existential despair and struggle as their Western counterparts do during the process of developmental depression.

Meanwhile, our analysis implied that this phenomenon might be related to Chinese culture. Chinese tradition emphasizes filial piety and children's obedience to the family (40). In most families in our study, the adolescents might have experienced more excessive control from their families than their Western counterparts would experience (24). Additionally, Chinese culture emphasizes individual modesty. Thus, Chinese parents may be more reserved than Western parents in praising their children. Hence, the adolescents might have received less recognition from their families. These factors may together contribute to lower self-esteem, less intrinsic motivation and poorer mental resilience of adolescents (41). The adolescents might thus have become more vulnerable to academic stress and school absenteeism (11). Correspondingly, our analysis suggested that school refusal may have become a way for the adolescents to confront the authoritative education system and culture, balance their self-development with family expectations, and explore their new life goals.

The fourth theme regarded mental health diagnoses that both benefited and limited the adolescents. Our analysis verified the findings from previous research that mental health complaints such as depression were barriers preventing teenagers from going back to school (8, 14). Additionally, our analysis suggested that adolescents might have secondary gains from a psychiatric diagnosis. Mental health symptoms gave them a temporary respite from academic competition, overly high family expectations, and parental criticism. This is consistent with the symptomatic function emphasized in the theory of family therapy (38), suggesting that there may be some value in discussing the functions of psychiatric symptoms such as depression in psychotherapy for Chinese adolescents with school refusal.

The last factor concerned adolescents' experience of *reintegration into school*. The emergence of this theme implied that adolescents benefited from sincere acceptance from their teachers and classmates during their return to school. This finding coincides with the findings of previous research showing that a lack of interpersonal support from peers is an important contributor to children's school refusal (6, 14, 17, 42). Meanwhile, our analysis suggested that excessive attention from and special treatment from teachers and classmates hindered the adolescents' reintegration in school. Such treatment might be correlated with adolescents' stigma (43). It also implied that for adolescents with school refusal, a balance between being properly supported and being overprotected by people around them may be critical for their return to school.

In summary, our analysis emphasized the complex interacting effects of the social environment, family interpersonal conflicts, personal psychological factors and mental health complaints on the development and maintenance of adolescents' school refusal behaviors. These factors contributed to school refusal at each level. Meanwhile, these factors may interact and influence each other's effects on school refusal. This is consistent with EST (26, 27). In this study, teenagers who refused to go to school were placed at the center of their families, peers, school, and social contexts. The first ecological system, the microsystem, could include the adolescents' immediate interpersonal environmental surroundings with which they interacted, such as families and peers. The second layer was the meso-system. It could include the school and educational environments. The macrosystem could refer to the social and cultural environment characterized by high levels of anxiety in which all the other systems were nested. Our analysis implied that stress and dysfunctions occurring in the three systems

co-contributed to adolescents' school refusal in an interactive manner. Therefore, interventions for Chinese teenagers with school refusal may need to integrate strategies that inspire reorganization and changes in different ecosystems, such as the release of new policies, improvement of peer relationships, restructuring of family systems and reconstruction of individual inner dynamics (39, 44).

Limitations

There are several limitations to our study. The first limitation is that we only analyzed adolescents' experiences without interviewing their family members, such as their parents. This may have led to some deviation in the thematic structure achieved from our analysis. Future research could include the opinions of adolescents' families in the analysis and compare their experience with those of children. Second, some participants were diagnosed with mental health disorders. Their experience with school absenteeism might be different from those of adolescents without psychiatric diagnoses. Hence, it is suggested that future studies distinguish these two heterogeneous groups to obtain more specific conclusions. Third, although our findings implied some potential interventions for adolescents' school refusal, we did not focus on the exploration of effective treatment for school absenteeism. Future studies analyzing what children with school refusal identify as helpful in psychotherapy are suggested. Forth, it seems that some participants (e.g., P20) in our study had more supportive parents than the others. With a bigger sample, it might have been possible to describe different profiles of adolescents depending on their parents' parenting strategies (e.g., supported, pressurized, ignored, etc.), and the impact of these parenting strategies on the course of school refusal. Hence, future research related with this topic are also suggested. Fifth, although the current study took EST as the theoretical framework of reference, we also found other theories, such as Stierlin's family therapy and Bowen's systemic theory could be used to explain part of the themes and their interactions. However, the detailed connections between adolescents' school refusal and these theories have not been fully discussed. Thus, future studies analyzing the relationships of school refusal with other theoretical frameworks are strongly suggested.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Tongji University as well as the Shanghai Pudong New Area Mental Health Center (No. PWRd2020-01). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LL and XZ designed this study. LL, HG, and YW made substantial contributions to the participants' interviews, data transcriptions and manuscript draft, ensuring that the work was appropriately investigated and resolved. LL and YW conducted the data coding and analysis. All authors read and approved the final manuscript.

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The Mediating Effect of Self-Control on Depression and Tendencies of Eating Disorders in Adolescents

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Self-control is very important for the adaptation among adolescents. It is associated with depression and tendencies of eating disorders. This study aimed to investigate the relationship between the two and the mediating role of self-control for adolescents. In total, 1,231 adolescents (11–18 years) participated in this study. Self-control, depression, and tendencies of eating disorders were evaluated using the Dual-Mode of Self-Control Scale (DMSC-S), 11-item Kutcher Adolescent Depression Scale (KADS-11), and Eating Attitudes Test (EAT-26). The correlations among these factors were analyzed using mediating effect models. Girls had higher scores on the both subscales (impulse system and control system) of DMSC-S ($P < 0.001$). Those between 15–18 years had higher scores on impulse system than those between 11–14 years ($P < 0.001$). A significant mediating effect (12.8%) of the impulse system was observed between depression and tendencies of eating disorders in adolescents.

Keywords: self-control, depression, eating disorder, mediating effect, adolescents

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INTRODUCTION

Depression is the leading cause of illness and disability among adolescents (1). Adolescent depressive disorder, which is a group of mental illnesses mainly characterized by negative feelings, may be accompanied by varying degrees of cognitive and behavioral changes, psychotic symptoms, impulsive non-suicidal self-injury (NSSI), and impulsive suicide, among others (2–5). The 2014 Ontario Child Health Study reported that the 6 month prevalence of possible major depressive disorder (MDD) was 7.5% for adolescents (12–17 years old) (6). The overall prevalence of depressive symptoms among Chinese adolescents was 14.81% (7). Based on these findings, adolescent depressive disorder can considered to be a common social problem and should be paid more attention.

Eating disorder (ED) symptoms are highly prevalent in adolescents and are regarded as one of the most important ED precursors clinically (8). An ED, which includes anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) (9), is characterized by impulsive eating or following diets compulsively, and is the result of the interaction between specific cultural and psychosocial factors. In adolescents, the lifetime prevalence of AN, BN, and BED was 0.3, 0.9, and 1.6%, respectively (10).

Depression comorbid with ED is common and can increase both conditions' severity and chronicity (11). Studies have shown 80% of patients with ED have emotional disorders (12), with depression being the most common (12). Compared with ED patients

without other mental disorders or with anxiety, the symptoms of ED patients with depression are more complex (13). There have been some studies on the relationship between depression and ED; however, the mechanism of the comorbidity remains unknown.

Depression may put the patient at a risk of developing a chronic ED (14, 15). MDD frequently co-occurs with BED or BN, and there is evidence that depression predicts the onset of ED and loss of controlled eating in adolescent girls (16). But how do comorbidities affect patients remain unknown. Impulsivity has been found to be a significant contributing factor for depression and ED (17), and has been long associated with the former (18)—patients with MDD show poor impulse control (19). A study of mood disorders and impulsivity reported that people with depression had significantly higher impulsivity scores than healthy individuals (20). Several studies have shown that people with BED are characterized by increased impulsivity (21, 22), and it has been associated with an increased risk of ED development (23). Individuals with ED have many impulsive behaviors, including substance abuse (24), NSSI (25), and shoplifting (26).

The Dual Modes of Self Control scale (DMSC-S) includes impulse and control systems (27). Hofmann et al. (28) first proposed DMSC-S, believing that DMSC-S includes: ① impulse system, which is the cause of impulsive behavior. When faced with temptation, it will automatically arouse a corresponding impulsive behavior, supporting individuals to choose instant gratification; ②The control system is the cause of higher order psychological activities in the face of temptation, including thoughtful evaluation and inhibition criteria, encouraging individuals to choose to wait to achieve the predetermined goal. The individual's final choice depend on which system plays a greater role in achieving a predetermined goal. The level of self-control was assessed in this study. Strong impulses or weak controls can lead to impulsivity (28), and weak controls may lead to antisocial outcomes during youth (29). Recent evidence has indicated that the control and impulse systems are different and there is only a moderate negative correlation between them (30). Several studies have shown that the dual-systems model fits the data significantly better than a one-dimension alone (30, 31).

While few studies have explored the relationship between depression and ED, the effects of depression on ED through self-control systems have not been studied. Therefore, the relationship among depression, ED, and self-control needs to be further studied. This study has two hypotheses— first, depression is a predictor of ED; and second, depression can directly predict the severity of ED and also indirectly affect ED through self-control.

MATERIALS AND METHODS

Participants

This cross-sectional study was conducted between February 15 and May 15 2017, in three middle schools in Rizhao, Shandong Province, China. To obtain a representative sample, we randomly selected four schools. From each school, ninth grade classes were randomly chosen, and all students in the selected classes were asked to participate. These students' parents also agreed to participate in the study and signed informed consents. A total of 1,300 students participated in this survey, and 1,231 (94.7%) completed the questionnaire. Participation was voluntary, and participants were asked to do so anonymously. This study was approved by the Institutional Review Board of Beijing Huilongguan Hospital.

Procedure

Our research team completed the assessment during school hours, and it lasted about 45 min. Questionnaires were collected on the spot. We designed a general questionnaire to investigate the age, grade, height, ideal weight, actual weight, and other general information of the participants and used the above information to calculate the ideal body mass index (BMI) and the actual BMI. BMI was calculated as weight in kilograms divided by height in meters squared.

The 11-item Kutcher Adolescent Depression Scale (KADS-11), a self-reported instrument, was initially applied to a Canadian population (32) to investigate depression. The language of this scale is easy to understand and it can quickly identify patients with depression (32). The items of the KADS-11 are constructed according to the frequency of depressive symptoms and core symptoms of depression. The severity levels are 0 (almost none), 1 (most of the time), 2 (most of the time), and 3 (all the time). The total score is the sum of the scores for each item, ranging from 0 to 33, and a score of $\geq$9 indicates that the respondent has depressive symptoms (validity and reliability of the Chinese version of the Kutcher Adolescent Depression Scale). The Cronbach's coefficient of the KADS-11 was 0.84 (32).

The DMSC-S was used to investigate a participant's self-control levels (28). It has 21 items, and each answer is measured on a five-point scale, from 1 = "Not at all true" to 5 = "Very true." The DMSC-S includes the impulse system (12 items) and control system subscales (nine items). They contain three (impulsivity, easy distraction, and delay gratification) and two factors (problem-solving and future time view), respectively. The total score of each dimension was calculated, and the higher the score, the higher was the level of individual impulse system/control system. The Cronbach's coefficient of the scale was 0.82.

The Eating Attitudes Test (EAT-26) was used to assess cognitive, emotional, and behavioral predispositions in eating (33). The EAT-26 is a 26-item self-report instrument, with each item having a six-point scale, based on the severity of symptoms: from 1 ("never") to 6 ("always"). The total score is the sum of the scores for each item. A total score $\geq$20 indicates abnormal eating behavior (34), and the higher the score, the higher are the risk of tendencies of ED (35, 36). Kang et al. confirmed the reliability of rechecking and the factorial validity of the Chinese version of the EAT-26 (36). The Cronbach's coefficient of the EAT-26 was 0.80 (37).

Data Analysis

Data were analyzed using SPSS version 24.0. Descriptive statistics were used to calculate the frequency of sample characteristics of the study population, and the results were presented as mean, standard deviation (SD), or percentage (%). The differences in

socio-demographic characteristics, clinical characteristics, and self-control among the different groups were analyzed. For the data of normal distribution and non-normal distribution, the chi-square test was used for the classified variables, and the *T*-test and Mann-Whitney U test were used for continuous variables. The correlation among the each factor of DMSC-S, depression, and attitudes of disordered eating was evaluated using Spearman's correlation coefficient. Significance was based Bonferroni correction for 6 models $p < 0.05/6 = 0.0083$. Finally, we used the PROCESS v3.4 (by Andrew F. Hayes) macro (38) for SPSS to perform the mediation analysis. Random sampling was set 5,000 times. Under the 95% confidence interval, the sampling method selected the non-parametric percentile method of deviation correction. A *P*-value of <0.05 indicated a significant difference.

RESULTS

The average age of the 1,231 participants was 14.53 ± 1.38 years old, and 679 (55.2%) were aged 11–14 years, while 552 (44.8%) were aged 15–18 years. The sample consisted of 587 (47.6%) males and 644 (52.3%) females. Of these, 523 (42.5%) met the criteria for depression and 106 (8.6%) were at a risk of developing ED. In all, 62 (11.9%) patients with depression met the criteria for ED. Relevant socio-demographic and clinical data of the participants are summarized in **Table 1**. This study found that girls had higher scores on the both subscales of DMSC-S than boys. Among all participants, the 15–18 years group had higher scores on the impulse system than the 11–14 years group. Participants residing in urban areas also had higher scores on the both subscales than those in rural areas. Compared with participants who had a normal perceived body weight, participants who were perceived to be underweight or overweight had higher scores on the both subscales. Participants with depressive symptoms had higher scores on the both subscales than participants who did not have depressive symptoms. Participants who met the ED criteria had higher scores on the impulse system than those who did not meet the ED criteria (see **Table 2**). In the correlation analysis,

TABLE 2 | Relationship between socio-demographic and clinical characteristics of DMSC-S (*N* = 1,231).

Variables	Impulse system		Control system	
	M, SD	*P*	Median (IQR)	*P*
Gender		**<0.001**		**<0.001**
Male	29.76, 8.78		29 (25, 33)	
Female	30.98, 8.30		30 (26, 33)	
Age group		**<0.001**		**0.001**
11–14 years	29.36, 8.24		29 (25, 33)	
15–18 years	31.63, 8.73		29 (25, 32)	
Region		**<0.001**		**<0.001**
Rural	30.54, 8.53		29 (25, 33)	
Urban	30.27, 8.57		29 (26, 33)	
Body weight perception		0.158		**<0.001**
Normal weight	30 (24, 36)		30 (26, 33)	
Underweight	29 (25, 35)	**<0.001**	28 (25, 32)	**<0.001**
Overweight	31 (25, 37)	**<0.001**	29 (25, 33)	**<0.001**
Depression		**<0.001**		**<0.001**
Yes	31.03, 9.03		30 (26, 33)	
No	29.95, 8.13		29 (25, 32)	
Disordered eating attitudes		**<0.001**		**<0.001**
Yes	36.55, 8.38		28 (24, 33)	
No	29.69, 8.27		29 (26, 33)	

P < 0.001 means the difference is statistically significant.

TABLE 1 | Socio-demographic characteristics and association with depression and risk of disordered eating attitudes (*N* = 1,231).

Variables	*n*	%	Depression			Disordered eating attitudes		
			n	%	*P*	*n*	%	*P*
Gender					0.872			**<0.001**
Male	587	47.6	248	42.2		32	5.5	
Female	644	52.3	275	42.7		74	11.5	
Age group					0.380			0.073
11–14 years	679	55.2	290	42.7		48	7.1	
15–18 years	552	44.8	228	41.3		56	10.1	
Region					0.089			**<0.001**
Rural	670	54.4	299	44.6		40	6.0	
Urban	561	45.6	223	39.8		66	11.8	
Body weight perception					0.908			**<0.001**
Normal weight	192	15.6	165	85.9		23	12.0	
Underweight	334	27.1	138	41.3		7	2.1	
Overweight	705	57.3	220	31.2		76	10.8	
Depression	523	42.5	–	–	–	62	11.9	**<0.001**
Disordered eating attitudes	106	8.6	62	11.9	**<0.001**	–	–	–

P < 0.001 means the difference is statistically significant.

the each factor of control system (future time perspective and problem solving) were positively correlated with sex in participants with depressive symptoms. Among participants with tendencies of ED, sex was positively correlated with each factor of impulse system (impulsivity, distractibility and poor delay of gratification) (see **Table 3**).

With X as the score of KADS-11, M as the score of the DMSC-S impulse system, and Y as the score of EAT-26, the mediating effect measured by Process Model 4 was $Y = -2.7937 + 0.37x + 0.2911M$. The equation was statistically significant ($P < 0.01$); partial regression coefficient B was 0.2911 and was significant ($P < 0.01$) with 95% CI (0.2435, 0.3387); partial regression coefficient C was 0.37 and significant ($P < 0.01$), with 95% CI (0.2738, 0.4665). The total effect was 0.4246, direct effect was 0.3701, and indirect effect was 0.0544. The intermediate effect accounted for 12.8%, bootstrap 95%CI (0.0116, 0.0999). The 95% confidence interval did not include 0, indicating that DMSC-S impulse system could predict ED directly and indirectly. The direct effect (0.3701) accounted for 87.2% of the total effect (0.4246), and the intermediate effect (0.0544) accounted for 12.8% of the total effect (0.4246) (**Table 4**). After controlling for age and sex, the median effect was 11.7%. The mediating effects of the DMSC-S impulse system on depression and ED are shown in **Figure 1**.

DISCUSSION

Our study found a high incidence of depression and ED among adolescents. Some studies showed that one in ten adolescents had suffered from depression during the previous 12 months, and 14–18% were estimated to suffer from it throughout their lifetimes (39, 40). A study on the prevalence of mental disorders in China showed that the weighted lifetime prevalence of depressive disorders was 6.8% (41). Our study found that 42.5% of the participates met the criteria for depression. This result was much higher than the 14.81%, which we mentioned at the beginning of this article. The possible reason is that there is great pressure on students to excel academically during their high school and college entrance examinations. Consistent with previous studies (42, 43), our study also indicated that depression was highly prevalent in adolescents with ED. Depression and ED seem to have a circular relationship, in which they reinforce one another over time (44). This may be related to the levels of 5-HT in our bodies. Recent studies have shown that 5-HT receptor-binding alterations may lead to depression and ED (45, 46).

This study found that depression was not correlated with sex, age, region, or body weight perception among adolescents. This conclusion differs from previous studies. Previous studies (10, 28, 47) had found that boys were more likely to be depressed before mid-puberty, while the prevalence of depression is doubled in girls between 15 and 19 years. The possible reason is that our sample size is relatively small, and the subjects in this study came from a specific region of China, which might have affected the sample's representativeness. Further research with larger sample is needed to test if depression is correlated with sex. Tendencies of ED were correlated with sex, region, and body weight perception, but not with age. Previous studies have shown that the prevalence of ED in female adolescents is higher than that in males (48, 49). Young Chinese people generally believe that the thinner they are, the better. Thinness and prevention of weight gain are thus widely promoted by the Chinese media, especially for young women (50), and they may adopt various methods to control their weight, including fitness, diet, purging, etc., to cater to societal expectations. Therefore, they are more likely to suffer from ED.

TABLE 3 | Correlation factor analysis of the each factor of DMSC-S.

Variables	Depression		Disordered eating attitudes	
	Male	Female	Male	Female
Future time perspective	0.121**	0.161**	−0.029	−0.109**
Problem solving	0.134**	0.165**	−0.103	0.049
Impulsivity	0.116**	0.058	0.290**	0.304**
Distractibility	0.036	0.027	0.206**	0.237**
Poor delay of gratification	0.080	0.012	0.199**	0.235**

***P < 0.0083.*

TABLE 4 | Analysis of total effect, direct effect, and indirect effect.

	Effect value	Boot SE	Boot CI lower	Boot CI upper	Relative effect value
Total effect	0.4246	0.0517	0.3232	0.5259	
Direct effect	0.3701	0.0491	0.2738	0.4665	87.2%
Indirect effect	0.0544	0.0224	0.0116	0.0999	12.8%

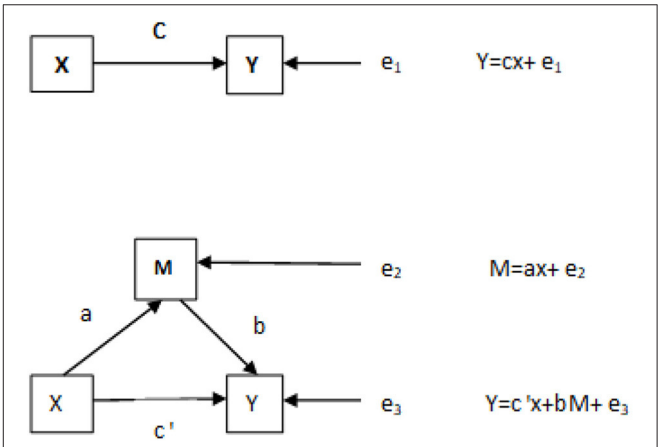

FIGURE 1 | The mediating effect of DMSC-S impulse system on depression and disordered eating attitudes. X, Depression; M, DMSC-S impulse system; Y, disordered eating attitudes; a, the regression coefficient of X to M; b, the regression coefficient of M to Y; c, the regression coefficient of X to Y; e1, e2, e3, the regression residual.

Depression was positively correlated with each factor of control system. This means the higher the level of individual control system, the higher the risk of depression. There were no relevant reports on relationship between depression and control system. The possible reason is that adolescents are more rebellious and have ambivalence toward many things. The higher the adolescents' control over their emotions and behaviors, the more obvious the inner rebellion. If they can't find a proper outlet, they will feel more and more depressed. Some studies had reported no association between impulsivity and depression (51, 52), while others seem to support an association (53). The result of this study was consistent with the former. The tendencies of ED were positively correlated with all factors of the impulse system. This means the higher the level of impulsivity, the higher the risk of ED. This is consistent with previous study (54). It showed that the higher the impulsivity, the greater the risk of developing ED. Another study (55) found that the impulsivity was associated with binge eating. It was found, by mediating effects, that the impulse system could directly predict tendencies of ED. The direct effect (0.3701) and intermediate effect (0.0544) accounted for 87.2 and 12.8% of the total effect (0.4246), respectively (**Table 4**). After controlling for age and sex, the median effect was 11.7%. The mediating effect of the impulse system on depression and tendencies of ED is shown in **Figure 1**. Previous studies (54) have demonstrated that depression can cause tendencies of ED. Spence and Courbasson's research showed that participants could take action and use food as a coping mechanism to alleviate negative emotions (56). Konttinen's study indicated that depression is associated with mood and eating (57). However, there is no relevant report (domestically or internationally) to indicate whether it is directly or indirectly related through intermediary factors. In this study, we found that impulse systems have a mediating effect between depression and tendencies of ED.

Our findings have clinical implications by stressing the potential role of self-control in the development of ED, and hence as potential preventative therapeutic targets. Furthermore, findings point to the importance of therapeutic interventions targeting emotional regulation across these disorders, for example, interventions aimed at learning healthier strategies for coping with distress. Previous studies (58) had shown that cognitive behavioral therapy (CBT) could improve impulsivity and thus reducing the incidence of ED. The essential interventions are food-related cue exposure with response prevention and the development of self-control strategies. We can also provide CBT interventions for adolescents who are screened to be prone to ED to prevent the occurrence of ED. The present study had some limitations. First, the subjects in this study came from a specific region of China, which might have affected the sample's representativeness. Second, this study used a self-measuring scale. Finally, we choosed cross-sectional study. We did not find a causal relationship among depression, self-control and tendencies of ED. Prospective cohort study should be considered in the future.

CONCLUSIONS

This study demonstrated that the impulse system might exert mediating effects between depression and tendencies of ED in adolescents. This indicates that guiding adolescents to control the degree of impulsivity and depression may be of great significance for preventing ED.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

H-JL and JL: conceptualization and investigation. JL, MQ, and T-HS: methodology. MQ and T-HS: validation. H-JL: formal analysis and writing—original draft preparation. H-JL, MQ, and T-HS: data curation. JL and J-XC: writing—review and editing. J-XC, MQ, and T-HS: supervision. J-XC: project administration and funding acquisition. All authors contributed to the article and approved the submitted version.

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The Association Between Suicide Attempts, Anxiety, and Childhood Maltreatment Among Adolescents and Young Adults With First Depressive Episodes

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Objective: Adolescents and young adults are susceptible to high-risk behaviors such as self-harm and suicide. However, the impact of childhood maltreatment on suicide attempts in adolescents and young adults with first episode of depression remains unclear. This study examined the association between suicide attempts and childhood maltreatment among adolescents and young adults with first depressive episodes.

Methods: A total of 181 adolescents and young adults with first depressive episodes were included. The Child Trauma Questionnaire (CTQ), Beck Anxiety Inventory (BAI), and Patient Health Questionnaire-2 (PHQ-2) were used to assess childhood maltreatment and the severity of anxiety and depressive symptoms, respectively. The suicide item in the MINI-International Neuropsychiatric Interview (M.I.N.I.) 5.0 was used to assess the suicide attempts. Logistic regression analyses were used to explore the associated factors of suicide attempts.

Results: The prevalence of SA in the total sample was 31.5% (95% CI = 24.9–38.1%). Multivariate logistic regression analyses revealed that the diagnosis of bipolar disorder (OR = 2.18, 95% CI = 1.07–4.40), smoking (OR = 2.64, 95% CI = 1.10–6.37), anxiety symptoms (OR = 1.05, 95% CI = 1.02–1.08), and childhood maltreatment (OR = 1.04, 95% CI = 1.01–1.07) were potential associated factors of SA. In addition, anxiety symptoms had a mediating effect on the relationship between childhood maltreatment and SA.

Conclusion: Adolescents and young adults with first depressive episodes and having experiences of childhood maltreatment are at a high risk of suicide. The severity of anxiety symptoms may mediate the relation between childhood maltreatment and suicide attempts in this group of patients.

Keywords: suicide attempt, first depressive episode, anxiety, adolescents, childhood maltreatment

INTRODUCTION

Suicide attempt (SA), one of the major suicidal behaviors, is defined as an act of self-injuring with the intention of ending one's own life (1). Around 703,000 people die from suicide worldwide, each year. Suicide is a leading cause of death among young people aged 15–24 years and suicide attempts are considerably high among children and adolescents aged 12–17 years (2, 3). The prevalence of SA among Chinese adolescents ranges from 0.94 to 9.01%, with an overall prevalence of 2.94% (95% CI = 2.53–3.41%) (4).

Mental disorders, such as major depressive disorder (MDD) and bipolar disorder (BP), could increase the risk of suicide behaviors in adolescents and young adults (5–7). A meta-analysis found that MDD and BP were the most common diagnoses among youths with SA (8, 9). The risk of SA is five times higher in adolescents with MDD than in the general population (10). The lifetime prevalence of SA in younger BP patients (14.7%, 95% CI = 5.9–20.0%) (11) was significantly higher than those without psychiatric disorders (0.8%, 95% CI = 0.7–0.9%) (12). For patients with BP, suicide behaviors were predominantly present during depressive episodes (13), especially during the first depressive episode (14).

Apart from the negative outcomes of physical injury and the increased risk of completed suicide, SA could worsen patients' general well-being and increase their utilization of health services and the economic burden (15). Understanding the associates of SA could benefit the development of effective prevention strategies for adolescents and young adults with MDD and BP.

Childhood maltreatment, including abuse (i.e., physical, sexual, and emotional abuse) and neglect (i.e., physical and emotional neglect), often has negative and long-term adverse effects on individuals' mental health (16–18). Increasing evidence shows that childhood maltreatment is closely related to the following self-harm and suicide behaviors including suicide attempts. Such phenomenon has also been confirmed among patients with MDD and BP (19, 20). For example, childhood maltreatment, such as physical abuse and emotional neglect, could increase the risk of subsequent SA among patients with MDD and BP (21, 22). Several theories have been raised to explain the path from childhood maltreatment to SA. For instance, childhood maltreatment can disturb developmental processes associated with strengthening of emotional regulation and relevant interpersonal skills and increased impulsivity and neuroticism. These disturbances may lower the threshold of suicidal behavior in individuals to experience stressful events. And the reduction in long-term social support associated with childhood maltreatment also increases the risk of suicide attempts (23). Previous studies majorly examined the association between SA and childhood maltreatment among adults with MDD and BP (22, 24). However, limited studies have discussed this relationship among adolescents and young adults. Besides, the existing studies are majorly conducted in Western populations, which may limit their generalization among other racial groups including China (20).

Considering that childhood maltreatment may lead to SA among patients with MDD and BP and suicide behaviors are most likely presented in their first depressive episode (14, 25), we conducted this study to examine the relationship between childhood maltreatment and SA among adolescents and young adults with first depressive episodes. Antidepressants, such as buprenorphine (26) and ketamine (27) and cognitive behavioral therapy (CBT) can reduce self-harming behaviors in depressed patients (28, 29). For antidepressants, which can increase 5-HT neurotransmission and 5-HT1A autoreceptor sensitivity, release hopelessness feelings and reduce depression, achieve the effect of reducing suicide-related behavior (30). For CBT, aims to change feelings of negativity and behaviors into positive thoughts and behaviors to redress adverse cognitive and decrease negative emotional affects (31). Therefore, we targeted on psychiatric treatment -naive patients first depressive episode in this study to avoid the impact of psychiatric medication and psychotherapy on suicide behaviors. For both patients and clinical practitioners, this study will try to verify the understanding on the impact of childhood maltreatment experience by using a purer sample and strengthen the evidence of intervening childhood maltreatment at an early age.

In addition, studies among healthy adults suggested that negative emotion, such as depression and anxiety, may mediate the association between childhood maltreatment and suicide behaviors (32–34). Such association is still under discussed among patients with depression. Therefore, we further explored the mediation effect of depressive and anxiety symptoms between childhood maltreatment and SA in our studied population.

MATERIALS AND METHODS

Participants

This cross-sectional study is part of Youth Depression Cohort (XiangyYa) study (YDC-XY), which was conducted from January 1, 2018, to December 31, 2019, at the outpatient department of the Second Xiangya Hospital of Central South University, China. Patients who visited the hospital because of their first depressive episode were consecutively recruited if they fulfilled the following criteria: (1) aged between 14 and 24, (2) experiencing their first depressive episode, (3) diagnosed with MDD or BP according to the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V), and (4) received no psychiatric treatment (including antipsychotic drugs and psychotherapy) in the past 3 months. The exclusion criteria were as follows: (1) comorbid with neurological conditions or substance dependence and (2) participating in other clinical trials.

Measurements

Sociodemographic and clinical data were collected, including age, gender, education year, marital status, nationality, occupation, history of smoking, drinking, drug use, family history of psychiatric disorders and parents' marital status. Drug use history was assessed using a dichotomous item: "In your lifetime, have you ever used any of the following drugs (according to the MINI-International Neuropsychiatric Interview, M.I.N.I)?." Smoking and drinking history was assessed using two dichotomous items: "Have you ever smoked?" and "Have you ever consumed

alcohol?." SA was assessed using the item of M.I.N. I: "In the past month did you attempt suicide?."

The Child Trauma Questionnaire (CTQ) (35), a 28-item self-report instrument, was used to assess the experience of abuse and neglect in childhood and adolescence. The scale was first developed by Bernstein in 1998 and has been widely used. Its Chinese version has been validated in both adolescents and adults (36). The CTQ assesses childhood maltreatment from five aspects, including emotional neglect, emotional abuse, physical neglect, physical abuse, and sexual abuse. Each subscale consists of five five-point items, with each item rated from "1" (not at all) to "5" (very often). The scores of each subscale were the summation of all loaded item scores and ranged from 5 to 25, while the total score of the CTQ was the summation of all subscale scores and ranged from 25 to 125.

The Beck Anxiety Inventory (BAI) (37) was used to assess the anxiety symptoms. It is a self-rating scale consisting of 21 four-point items with each item rated from "0" (not at all) to "3" (severely), and the total score of the scale ranged from 0 to 63, with a higher total score indicating more severe anxiety symptoms. The Chinese version of the BAI was found to have satisfactory reliability and validity in adolescents and adults (38).

The Chinese version of the Patient Health Questionnaire-9 has been widely used in research and clinical practice to screen depressive symptoms (39). The Patient Health Questionnaire-2 (PHQ-2) (40) is a short version of the PHQ-9 and has been found to have equal psychometric properties compared to the PHQ-9 for depressive symptom screening (41). The two items of the PHQ-2 were rated from "0" (none at all) to "3" (almost every day), and the total score of the scale ranged from 0 to 6.

Procedures

The continuous sampling method was applied. All patients who were first time visit the psychiatric outpatient services because of depression invited to participate in the survey. After obtaining written informed consent from the participants, a face-to-face interview was conducted to reconfirm the psychiatric diagnosis by a senior psychiatrist using a structured diagnostic tool, the M.I.N.I according to the DSM-V. Then all participants were asked complete all measurements mentioned above. According to patients' response to the item "In the past month did you attempt suicide?" in M.I.N.I, patients were recognized as having "suicide attempts" if they answer "yes" and as having "no suicide attempts" if "no."

Statistical Analysis

The SPSS 24.0 software was used for all statistical analyses. The two-independent sample *t*-tests and chi-square tests were used to compare the socio-demographic and clinical data between patients with and without SA, as appropriate. Multiple logistic regressions were performed to examine the independent variables associated with SA. Variables with $p < 0.10$ in univariate analyses were entered into the regression model as independent variables. In addition, the association between the total score of the BAI and CTQ was tested using Pearson's correlation coefficient. Mediation analysis was conducted using the PROCESS v3. 3 to examine the extent to which potential mediators may explain the relationship between childhood maltreatment and SA. Potential mediators were selected based on the results of the multiple logistic regression. The significance level was set as $p < 0.05$ (two sides).

Ethical Approval and Informed Consent

This study was approved by the ethics committee of The Second Xiangya Hospital of Central South University. All patients signed written informed consent.

RESULTS

A total of 181 adolescents and young adults with first depressive episodes met the eligibility criteria and were included. Among them, 31.5% (95% CI = 24.9–38.1%) ($n = 57$) reported SA. The sociodemographic and clinical data are shown in **Table 1**. The majority of the patients were female (75.1%). The mean age of the patients was 18.6 ± 2.3 years, while the mean years of education was 12.2 ± 2.3 years. A total of 115 (63.5%) patients were diagnosed with MDD, while the remaining 66 (36.5%) patients were diagnosed with BP.

Patients with SA were more likely to have a diagnosis of BP (52.6 vs. 29.0%, $p = 0.002$), drink (31.6 vs. 17.7%, $p < 0.050$), smoke (26.3 vs. 13.7%, $p < 0.050$), and present with more severe anxiety symptoms (30.9 ± 11.0 vs. 23.5 ± 10.9, $p < 0.001$) than those without. Compared to patients without SA, patients with SA experienced significantly more severe emotional abuse (12.7 ± 4.7 vs. 10.3 ± 4.0, $p < 0.001$), physical abuse (8.1 ± 3.9 vs. 6.9 ± 3.2, $p = 0.033$), emotional neglect (18.4 ± 5.7 vs. 16.2 ± 5.0, $p < 0.001$), physical neglect (11.5 ± 3.8 vs. 9.5 ± 3.0, $p < 0.001$), and overall childhood maltreatment (57.1 ± 14.8 vs. 48.5 ± 12.1, $p < 0.001$). There was no significant difference in the PHQ-2 total score between patients with and without SA (3.3 ± 1.2 vs. 3.1 ± 1.1, $p = 0.405$) (**Table 1**).

A multiple logistic regression model revealed that the diagnosis of BP [odds ratio (OR) =2.18, 95% CI = 1.07–4.40], smoking (OR = 2.63, 95% CI = 1.10–6.37), severity of anxiety symptoms (OR = 1.05, 95% CI = 1.02–1.08), and childhood maltreatment (OR = 1.04, 95% CI = 1.01–1.07) were significantly and positively associated with SA (**Table 2**). There was a significant positive association between the severity of anxiety symptoms and overall childhood maltreatment ($r = 0.201$, $p < 0.001$).

The mediation analysis revealed that anxiety symptoms mediated the relationship between childhood maltreatment and SA [coefficient (indirect) =0.01, standard error (SE) =0.005, 95% CI = 0.004–0.023] and explained 24.40% of the total effect (**Figure 1**, **Table 3**).

DISCUSSION

This study found that 31.5% of treatment-naïve adolescents and young adults with first depressive episodes had SA, which was higher than one previous study about the first-episode and drug naïve patients with MDD with a prevalence of 19.9% (42). Several possible reasons may contribute to this

TABLE 1 | Sociodemographic and clinical characteristics among adolescents and young adults with first depressive episode.

Variables	Total sample		Non-SA		SA		Statistics	
	Mean	SD	Mean	SD	Mean	SD	*t*	*P*
Age (year)	18.6	2.3	18.9	2.2	18.2	2.4	0.134	0.055
Education year	12.2	2.3	12.2	2.3	12.1	2.3	0.010	0.661
The PHQ-2 total score	3.2	1.1	3.1	1.1	3.3	1.2	1.840	0.405
The BAI total score	25.8	11.5	23.5	10.9	30.9	11.0	0.023	<0.001
The CTQ total score	51.2	13.6	48.5	12.1	57.1	14.8	3.677	<0.001
The CTQ subscale score								
Emotional abuse	10.9	4.4	10.3	4.0	12.7	4.7	1.668	<0.001
Physical abuse	7.2	3.5	6.9	3.2	8.1	3.9	5.017	0.033
Sexual abuse	6.0	2.1	5.9	2.0	6.4	2.3	2.585	0.118
Emotional neglect	16.9	5.3	16.2	5.0	18.4	5.7	1.733	0.007
Physical neglect	10.1	3.3	9.5	3.0	11.5	3.8	3.656	<0.001
	N	%	N	%	N	%	X^2	*P*
Diagnosis							9.387	0.002
MDD	115	63.5	88	71.0	27	47.4		
BP	66	36.5	36	29.0	30	52.6		
Gender								
Male	45	24.9	34	27.4	11	19.3	1.379	0.240
Female	136	75.1	90	72.6	46	80.7		
Nationality								
Ethnic Han	167	92.7	113	91.1	54	94.7	0.712	0.399
Others	14	7.7	11	8.9	3	5.3		
Occupation							0.137	0.711
Students	155	85.6	107	86.3	48	84.2		
Others	26	14.4	17	13.7	9	15.8		
Drinking							4.342	0.037
No	141	77.9	102	82.3	39	68.4		
Yes	40	22.1	17	17.7	18	31.6		
Smoking							4.264	0.039
No	149	82.3	107	86.3	42	73.7		
Yes	32	17.7	17	13.7	15	26.3		
Family history							1.264	0.261
No	154	85.1	103	83.1	51	89.5		
Yes	27	14.9	21	16.9	6	10.5		
Marital relationship of parents				2.911	0.406			
Good	103	56.9	72	58.1	31	54.4		
Bad	37	20.4	28	14.5	9	15.8		
Divorced	32	17.7	19	15.3	13	22.8		
Widow	9	5.0	5	4.0	4	7.0		

SA, suicide attempt; SD, standard deviation; BP, bipolar disorder; MDD, major depressive disorder; BAI, Beck Anxiety Inventory; CTQ, Child Trauma Questionnaire; PHQ-2, Patient Health Questionnaire-2.

discrepancy. On the one hand, the patients in this study were untreated adolescents and young adults in the first episode of depression and acute episode, those who had severe depressive symptoms. On the other hand, our study recruited clinical psychiatric outpatients, those who had more severe depressive symptoms than those surveyed in the community. Adolescents and young adults are the most common age groups for first mood disorders (43, 44), such as MDD and BP. These people are not mature in terms of cognitive structure, emotional structure and rationality. When an adverse stressful event or major environmental change cannot be dealt with, it is possible they may decide to commit suicide to end the current pain and escape the existing situation (45).

One of the important findings of this study is that patients with SA experienced more childhood maltreatment than those without SA. Previous studies also found a similar association

between childhood maltreatment and SA among general adolescents and adults (21, 46). Patients experiencing childhood maltreatment often have negative family environments, such as a lack of shelter and safe living conditions, which can prevent the patients from developing appropriate emotional regulation and stress coping skills (47). As a result, they may impulsively react to stressful life events and even present suicidal behaviors. Emotional trauma may negatively affect the development of the hypothalamus-pituitary-adrenal axis (HPA axis) in growth and progression, and alteration of the function of the HPA axis was found to have an impact on individuals' biological, emotional, behavioral, and cognitive responses to stressful events (48–52), which were related to suicidal behaviors.

Another important finding of this study is that anxiety symptoms were found to mediate the relationship between childhood maltreatment and SA among adolescents and young adults with first depressive episodes, which is consistent with previous studies (53). These results have been confirmed in previous studies (54–56), which found an independent association between SA and anxiety symptoms in adolescents. Anxiety can also predict the occurrence of SA (57). Behavioral avoidance, one clinical feature of anxiety, often leads to social isolation, reduced quality of life, and impaired functioning, all of which are related to an increased risk of suicide (58, 59). Relevant studies have shown that the influence of childhood maltreatment on SA is indirectly affected by psychological factors (34). This suggests that anxiety should be the treatment target in the prevention strategies of SA in depressed adolescents and young adults.

Furthermore, this study found that young patients with BP were more likely to have SA than those with MDD, which is consistent with previous findings (8, 60). For example, in a study of people hospitalized after SA, 28 percent were diagnosed with MDD and 39 percent with BP (61). In an 18-month follow-up cohort of patients with BP and MDD, 19.9% of those with BP and 9.5% of those with MDD attempted suicide (62). The possible reasons for the relatively higher risk of SA in patients with BP

TABLE 2 | Multiple logistic regression model assessing variables associated with SAs among adolescents and young adults with first depressive episode.

Variables	*P*	Odds ratio (OR)	95% Confidence interval (95% CI)	
Psychiatric diagnosis				
MDD	Ref			
BP	0.031	2.175	1.074	4.404
Smoking	0.005	2.644	1.098	6.365
Drinking	0.320	1.691	0.600	4.764
BAI total score	0.005	1.049	1.015	1.084
CTQ total score	0.006	1.039	1.011	1.067

SA, suicide attempt; BP, bipolar disorder; MDD, major depressive disorder; BAI, Beck Anxiety Inventory; CTQ, Child Trauma Questionnaire; Ref, reference group.

TABLE 3 | The mediation effect of anxiety symptoms between childhood maltreatment and SA.

	Effect	Boot SE	Boot LLCI	Boot ULCI	Proportion mediated %
Direct effect	0.0373	0.0132	0.0114	0.0632	75.60
Indirect effect	0.0121	0.0050	0.0040	0.0231	24.40
Total effect	0.0494	0.0025	0.0052	0.0148	100

SA, suicide attempt; LLCI, lower limit confidence interval; ULCI, upper limit confidence interval; SE, standard error.

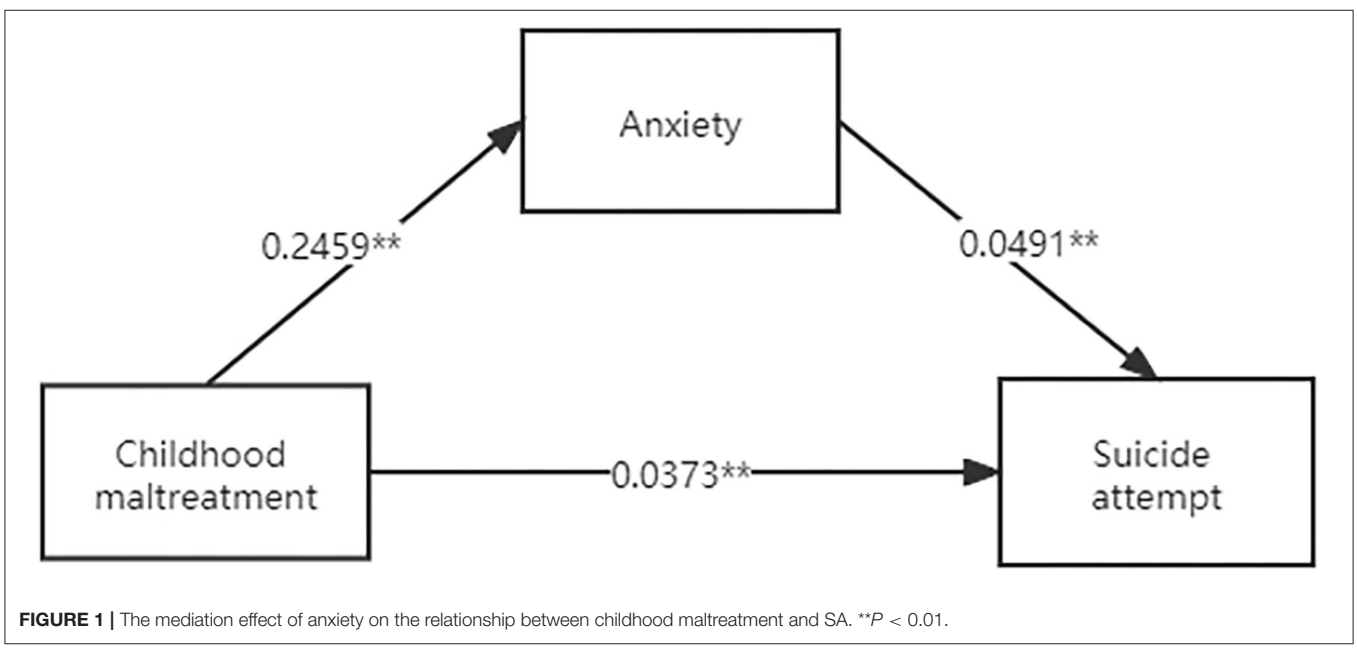

FIGURE 1 | The mediation effect of anxiety on the relationship between childhood maltreatment and SA. $^{**}P < 0.01$.

compared to their counterparts with MDD may be that they have more severe depressive symptoms during their depressive episodes (60), more difficulties of treatment, more impulsivity, and a higher risk of comorbidity of anxiety (63) than patients with MDD.

The strengths of the present study include the large sample size of treatment-naïve adolescents and young adults with first depressive episodes. In addition, the study examined the association between SA and childhood maltreatment among adolescents and young adults with MDD and BP, and discussed the association between childhood maltreatment and suicide behaviors among patients with depression. However, several methodological limitations should be considered. First, as a cross-sectional study, a causal relationship between SA and associated factors could not be generated. Second, some potential factors associated with SA, such as residential type and socioeconomic state (15, 64), were not examined. Third, the single-site study design could limit the generalization of the results. Forth, young patients with MDD may convert to BP during the progression of the disease, which may bias the estimation of the prevalence of SA in patients with each disorder. Fifth, although PHQ-2 has been proved to have equal psychometric properties compared to the PHQ-9 for depressive symptom screening, only using 2 items for depressive symptom screening may influence the identification of other depressive symptoms and the results of this study. Sixth, although we studied a pure sample that was treatment-naïve and with a first depressive episode, the acute illness phase may increase the risk of suicide behaviors in this population, which may potentially bias the results. Finally, some potential associated factors, such as smoking and drinking, were not included in the mediation model.

CONCLUSION

This study found that treatment-naive adolescents and young adults with first depressive episodes were at a high risk of SA. Patients with SA were more likely to have experiences of childhood maltreatment and present more severe anxiety symptoms than those without SA. Anxiety symptoms may mediate the relationship between childhood maltreatment and SAs. Considering the severe negative outcomes of SA, it is essential to develop prevention strategies for SA among depressed adolescents and young adults. Alleviating anxiety may be an effective way to reduce the risk of suicide in this group of patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HC, SZ, and JZ: conceived and designed the study. PL, JL, XCh, HG, CL, and XL: participated in the acquisition of data. HC: analyzed the data and drafted the manuscript. WL, XCa, JZ, and XW: revised the manuscript. All authors read and approved the final manuscript.

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The Effect of Abnormal Regional Homogeneity and Spontaneous Low-Frequency Brain Activity on Lower Cognitive Ability: A Cross-Sectional Study on Postoperative Children With Tetralogy of Fallot

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Despite intracardiac malformation correction, children with Tetralogy of Fallot (TOF) may still suffer from brain injury. This cross-sectional study was primarily designed to determine the relationship between blood oxygenation level-dependent (BOLD) signal changes after surgery and cognition in school-aged children with TOF. To evaluate the differences between TOF children (n = 9) and healthy children (n = 9), resting-state functional magnetic resonance imaging (rs-fMRI) and the Wechsler Intelligence Scale for Children–Chinese revised edition (WISC-CR) were conducted in this study. The results showed that TOF children had a lower full-scale intelligence quotient (FSIQ, 95.444 ± 5.354, p = 0.022) and verbal intelligence quotient (VIQ, 92.444 ± 4.708, p = 0.003) than healthy children (FSIQ = 118.500 ± 4.330;VIQ = 124.250 ± 4.404), and that significant differences in regional homogeneity (ReHo) and amplitude of low-frequency fluctuation (ALFF) existed between the two groups. Besides, VIQ had significantly positive correlations with the decreased ALFF value of the middle inferior occipital gyrus (MIOG, beta = 0.908, p = 0.012) after fully adjusting for all covariates. In addition, elevated ReHo values of the left and right precuneus were positively related to ALFF in the MIOG. This study revealed that brain injury substantially influences neural activity and cognition in postoperative TOF children, providing direct evidence of an association between BOLD signal changes and the VIQ and prompting further attention to language development in TOF children.

Keywords: Tetralogy of Fallot, ALFF, ReHo, cognition, VIQ, brain injury

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INTRODUCTION

Tetralogy of Fallot (TOF) is one of the most common cyanotic congenital cardiac malformations (Diaz-Frias and Guillaume, 2020), accounting for approximately 5% of all congenital heart diseases (CHDs) (Apitz et al., 2009). TOF is characterized as a ventricular septal defect (VSD), aortic overriding, right ventricular outflow tract obstruction, and right ventricular hypertrophy (Warnes et al., 2008), and patients with TOF exhibit a decrease in systemic vascular resistance and an increase in pulmonary resistance, which leads to a right-to-left shunt in combination with a VSD and an obvious decrease in saturation (Ho et al., 2018). Less than 1% of patients survive to 40 years old naturally (Ai et al., 2018), but nearly 90% of patients with early diagnosis and surgical treatment will go on to survive (Hickey et al., 2009); however, adverse outcomes can still occur many years after cardiac surgery, including heart failure, arrhythmia, and right ventricular outflow tract reobstruction (Apitz et al., 2009). Notably, brain injury is still a non-negligible issue that persistently negatively influences survivors (Gaynor et al., 2015).

Brain injury among repaired TOF cases has recently been reported, for which children with multiple cerebral domain injuries to areas such as the cortex, basal ganglia, thalamus, and cerebral white matter account for nearly a fifth of cases (Hovels-Gurich et al., 2006; Leonetti et al., 2019). Moreover, many studies have shown that children with cerebral injuries usually have neurodevelopmental disabilities, which may manifest as cognitive impairment, oral dyskinesia, language expression abnormalities, motor delays, or attention deficit/hyperactivity disorder (ADHD) (Marino et al., 2012; Mussatto et al., 2014; Wernovsky and Licht, 2016). Although it is thought that human neurodevelopment is almost complete at the end of the second or third trimester of pregnancy, recent studies have shown that cortical neurogenesis is still active after birth (Morton et al., 2017; Ortinau et al., 2018), and that children with CHDs have delayed brain development (Clouchoux et al., 2013). Thus, early detection and intervention could afford greater neurodevelopmental benefits for children with CHDs. Fortunately, functional magnetic resonance imaging (fMRI) has been applied to identify neurodevelopmental disabilities more accurately (Ma et al., 2020).

Two blood oxygenation level-dependent (BLOD) fMRI signals, regional homogeneity (ReHo) and the amplitude of low-frequency fluctuations (ALFFs) (Zang et al., 2004, 2007), have been widely used to investigate the pathophysiology, diagnosis, and treatment effectiveness of cognitive disorders (Ni et al., 2016; Bak et al., 2018; Gur et al., 2021) and neuropsychiatric disorders, such as depression (Liu et al., 2012), schizophrenia (Guo et al., 2014; Xu et al., 2015), epilepsy (Maneshi et al., 2014), Alzheimer's disease (Liu et al., 2014; Lyu et al., 2021), and Parkinson's disease (Helmich et al., 2010; Li et al., 2018; Yue et al., 2020). ReHo reflects regional functional connectivity or synchronization and indicates the regional integration of information processing (Zuo et al., 2013; Jiang et al., 2015). ALFF is a method of monitoring low-frequency brain spontaneous activity and blood oxygen levels, which indicates the spontaneous activity of brain regions (Zang et al., 2007).

However, there was no research on ReHo and ALFF changes in TOF or CHD and the influence of ReHo and ALFF changes on the cognitive abilities of children following TOF repair surgery remains to be elucidated. Our study explored ReHo and ALFF fMRI changes, evaluated the cognitive abilities of TOF children, and further identified the relationship between them. Interestingly, the results revealed that decreased ALFF values in the left middle inferior occipital gyrus are correlated with a lower verbal intelligence quotient (VIQ).

MATERIALS AND METHODS

Subjects

From November 2015 to June 2016, 9 school-aged children with TOF after repair surgery were validated as participants, and 9 healthy children (HC), identified as having no cardiovascular or nervous system diseases and matched with the TOF children by age, sex, and education, were enrolled as the control group. All TOF children underwent correction surgery at Children's Hospital of Nanjing Medical University and were identified to be free of central nervous system diseases or hereditary syndromes, such as craniocerebral trauma, cerebral tumors, or Down syndrome. Informed consent was obtained from all the participants' legal guardians. All children were right handed and had no known contraindications to MRI, including claustrophobia and implanted pacemakers. Finally, all 18 children underwent resting-state fMRI (rs-fMRI) examination. Additionally, all data met the standards for further analysis: All participants completed all testing tasks of Wechsler Intelligence Scale. The results need not to be calculated by alternative subtests. All children were requested to keep their eyes closed and avoid sleeping, thinking about anything, or any head motion as far as possible (less than 1 mm of translation or 1° of rotation) during the MRI scanning.

Cognitive Ability Evaluation

The Wechsler Intelligence Scale for Children–Chinese revised edition (WISC-CR) was used to evaluate the cognitive abilities of the subjects. The WISC is an authoritative intelligence scale to assess the cognitive ability of children (Marino et al., 2012). Based on the Chinese population, the WISC-CR was adaptive for Chinese children aged 6–16, and the test contains 12 domains, including analogies, common sense, arithmetic, comprehension, vocabulary, digit span, picture arrangement, missing picture completion, block design, decoding, object collocation, and mazes (of these, digit span and mazes are optional). According to the operating manual and adjusted for the subject's age, the subjects' scores were calculated. The VIQ depended on the first six items, and the performance intelligence quotient (PIQ) depended on the last six items. Finally, the full-scale intelligence quotient (FSIQ) was measured.

Functional Magnetic Resonance Imaging Data Acquisition and Preprocessing

Functional MRI scans were performed on all subjects using a 1.5T MRI scanner (Siemens MAGNETOM Trio, Erlangen,

Germany) at the Radiology Department of our hospital. Earplugs and foam were used to decrease scanning noise and head motion, respectively. All subjects were not anesthetized, and were required to keep their eyes closed and avoid sleeping, thinking about anything, or any head motion as far as possible during the scanning. In total, 176 high spatial resolution T1-weighted structural images were acquired using a magnetic prepared gradient echo (GE) sequence [repetition time (TR) = 1,940 ms, echo time (TE) = 3.08 ms, field of view (FOV) = 250 mm × 250 mm, matrix = 256 × 256, slice thickness = 1 mm; flip angle = 15°], and 180 functional images by using an echo-planar imaging sequence sensitive to BOLD contrast (TR = 2,000 ms, TE = 25 ms, FOV = 240 mm × 240 mm, matrix = 64 × 64, slice thickness = 4 mm, flip angle = 90°). Twenty-two fluid attenuated inversion recovery images were used to screen for structural brain lesions by two radiology chief physicians (TR = 8,000 ms, TE = 92 ms, FOV = 220 mm × 220 mm, matrix = 512 × 464, slice thickness = 5 mm).

Preprocessing was carried out by applying DPARSFA using SPM8.[1]

We underwent preprocessing as follows:

(1) We have collected 180 points by BOLD in this study and removed the first 10 time points to reduce the influence of MRI magnetic field instability and noise during the initial scan.
(2) Slice-timing correction: we carried out slice-timing correction for the remaining time points make different layers within a TR equivalent to the same time acquisition.
(3) Head movements correction: This included translation and rotation in 3D space. Considering the long scan time and the influence of magnetic resonance noise, the purpose of head movement correction was to eliminate the tiny head movement caused by respiration, heartbeat, and other physiological factors. Subjects would be removed from this study when their head movement of x, y, or z axis were more than 1 mm of translation or 1° of rotation.
(4) Spatial registration: All MRI images were standardized to the same reference space (standard anatomical template for the head, Montreal Neurological Institute, Canada) because of the differences in brain morphology among different subjects.
(5) Linear detrending: The standardized data were then processed to remove linear trends to remove physiological linear drift, noise caused by head movement, and instability of the machine.
(6) Low-frequency filtering. A frequency band of 0.01–0.08 Hz was considered valuable physiological signals and used to filter out low-frequency drift.
(7) Spatial smoothing. A Gaussian kernel function with a full width at half maximum (FWHM) of 4 × 4 × 4 mm^3 was used to perform spatial smoothing of fMRI images.

[1]www.fil.ion.ucl.ac.uk/spm

Regional Homogeneity and Amplitude of Low-Frequency Fluctuation Analysis

The preprocessed fMRI data were used for the ReHo analysis of all subjects. Kendall's coefficient concordance (KCC) was used as an indicator to measure the similarity between the time series of a voxel and those of its adjacent neighbors in the ReHo analysis. We considered 27 individual voxels as a whole and acquired ReHo maps for each participant by calculating the KCC value between each individual voxel and the other 26 adjacent voxels. ReHo images were smoothed with an isotropic Gaussian kernel of 4 mm full-width half-maximum (FWHM) to reduce space noise. The brain was divided into different regions of interest (ROI), and the mean ALFF value of each ROI was calculated with the Resting-State fMRI Data Analysis Toolkit (REST version 1.8)[2] (Song et al., 2011). ReHo and ALFF differences between the children with TOF and the HC were analyzed with a two-sample *t*-test in REST software. AlphaSim was calibrated with $P < 0.01$ and a cluster size = 23 voxels in the ReHo analysis. AlphaSim was calibrated with $P < 0.05$ and a voxel size > 65 in the ALFF analysis.

Statistics

SPSS 20.0 (IBM Corp., Armonk, NY, United States) was used to perform the statistical analyses in the study. We present continuous variable data as the mean ± SE in **Table 1**. Differences between the children with TOF and the HC were calculated by two-sample *t*-tests. Correlations between the ALFF value, ReHo value, intelligence quotient (IQ), and related covariates were investigated by using single and multiple linear regression analyses. Statistical significance was considered when $P < 0.05$.

RESULTS

The demographic characteristics of the TOF and HC groups are shown in **Table 1**. The summarized hospital information of the TOF children is also shown. No significant differences were observed for age, sex, education, or household income. Additionally, children with TOF had lower VIQ (92.444 ± 4.708, $P = 0.003$) and FSIQ (95.444 ± 5.354, $P = 0.022$) scores than the HC.

Differences in ReHo and ALFF are separately shown in **Tables 2**, **3**, respectively. Compared with the HC group, ReHo values were increased in the right brainstem, right middle occipital gyrus, right inferior parietal gyrus, right precuneus, and left precuneus of the TOF group, but reduced in the right posterior lobe of the cerebellum and right inferior temporal gyrus (**Table 2** and **Figure 1**). In addition, TOF children had higher ALFF values of the left medial prefrontal cortex, left cingulum and right parahippocampal gyrus, and lower ALFF values of the left cerebellum, left middle inferior occipital gyrus (MIOG.L), left inferior occipital gyrus, and right cerebellum (**Table 3** and **Figure 2**).

After analyzing the Pearson correlations between the demographic variables and ReHo or ALFF changes in TOF children, age at surgery, postoperative time, preoperative

[2]http://www.restfmri.net/forum/REST_V1.8

TABLE 1 | Characteristics of TOF and healthy children.

Variables	TOF	HC	*p*-value
	(*n* = 9)	(*n* = 9)	
Age (month)	121.547 ±7.811	117.560 ±3.687	0.651
Sex (male%)	66.667	55.556	0.653
Education (month)	29.427 ±4.931	28.227 ±4.412	0.858
Household income (Yuan per year)	82000.000 ±9327.379	84666.667 ± 6960.204	0.822
Age of surgery (month)	27.309 ± 7.880	NA	
Postoperative time (month)	86.674 ± 11.232	NA	
Hospital stays (day)	17.250 ± 1.943	NA	
Preoperative SpO_2 (%)	74.286 ± 5.830	NA	
Preoperative SBP (mmHg)	100.143 ± 3.622	NA	
Preoperative DBP (mmHg)	60.000 ± 2.104	NA	
Preoperative Ph	7.339 ± 0.012	NA	
CPB time (min)	62.750 ± 2.589	NA	
AO time (min)	38.063 ± 1.848	NA	
VIQ	92.444 ± 4.708	124.250 ± 4.404	**0.003**
PIQ	97.778 ± 6.302	108.000 ± 5.492	0.342
FSIQ	95.444 ± 5.354	118.500 ± 4.330	**0.022**

Mean ± SE.
TOF, Tetralogy of Fallot; HC, healthy children; SpO_2, saturation of pulse oxygen; SBP, systolic blood pressure; DBP, diastolic blood pressure; pH, potential of hydrogen; CPB, cardiopulmonary bypass; AO, aortic occlusion; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; FSIQ, full scale intelligence quotient; NA, not available.
Bold values represent that the results have statistical significance.

TABLE 2 | Cerebral ReHo changings in TOF group.

	Voxel	MNI coordinates			*T*-value
		X	Y	Z	
Right brainstem	25	12	−27	−39	4.3840
Right posterior lobe of cerebellum	23	18	−84	−39	−3.4583
Right inferior temporal gyrus	28	51	12	−42	−4.1134
Right middle occipital gyrus	26	36	−96	6	4.9977
Right inferior parietal gyrus	52	48	−45	42	5.6256
Right precuneus	24	12	−54	69	5.5039
Left precuneus	37	−15	−48	75	3.9901

Adjusted by AlphaSim, Cluster size = 23, $P < 0.01$.
ReHo, regional homogeneity; TOF, Tetralogy of Fallot; MNI, Montreal Neurological Institute.

saturation of pulse oxygen (SpO_2), preoperative systolic blood pressure (SBP), cardiopulmonary bypass (CBP) time, and aortic occlusion (AO) time were found to be related to ReHo changes (**Supplementary Table 1**), and preoperative SpO_2, CBP time, and AO time were related to ALFF changes (**Supplementary Table 2**).

The correlations between VIQ, FSIQ, and ReHo or ALFF changes were further determined by multiple linear regression (**Table 4** and **Supplementary Table 3**). The results showed that

TABLE 3 | Cerebral ALFF changings in TOF group.

	Voxel	BA	MNI coordinates			*T*-value
			X	*Y*	*Z*	
Left cerebellum	132	18	−30	−66	−21	−4.8936
Left middle inferior occipital gyrus	122	19	−51	−75	6	−5.2099
Left inferior occipital gyrus	132	18	−21	−93	6	−4.6053
Right cerebellum	87	18	6	−81	−30	−3.6358
Left medial prefrontal cortex	88	46	−39	30	30	4.6931
Left cingulum	106	23	3	−63	21	4.7138
Right parahippocampal gyrus	94	36	30	−30	−18	4.6963

Adjusted by AlphaSim, voxel > 65, $P < 0.05$.
ALFF, amplitude of low frequency fluctuations; TOF, Tetralogy of Fallot; MNI, Montreal Neurological Institute; BA, Brodmann area.

only ALFF changes in the MIOG.L were positively associated with VIQ (beta = 0.908, $P = 0.012$) after adjusting for all covariates (model 3). Additionally, **Table 5** shows that ReHo changes in the right precuneus (PCUN.R) and left precuneus (PCUN.L) were positively associated with ALFF changes in the MIOG.L.

DISCUSSION

Our cross-sectional study was the first to identify positive correlations between decreased ALFF values in the MIOG.L and a lower VIQ in postoperative TOF children at school age. In addition, abnormal ReHo values in the PCUN.L and PCUN.R were also positively related to ALFF values in the MIOG.L, which may compensate for the VIQ caused by low ALFF values in MIOG.L.

ALFF and ReHo, two BOLD signals, can indirectly reflect brain function (Golestani et al., 2017). Our previous study focused on the effects of structural alteration on the cognitive abilities of TOF children, indicating positive correlations between decreased cortical thickness and a low VIQ (Ma et al., 2020). Considering decreased oxygen consumption and oxygen delivery in the brain before surgery (Sun et al., 2015), close attention to neuronal activity changes should be paid in children with TOF. However, few studies have investigated the relationship between neuronal activity and cognition in TOF children. Herein, based on units of neurons, the association between neuronal activity and cognition was determined in this study, and combined with the existing research, the underlying mechanisms of a low VIQ induced by abnormal ReHo and ALFF values were also explored.

The results revealed that TOF children with lower ALFF values in the MIOG.L had a lower VIQ, indicating that the MIOG.L plays a critical role in language development. Generally, the MIOG.L is recognized as a visual processing region; however, it is also important to speech perception, including semantic and syntactic processing, language processing strategy, semantic representation, object identification, and generalization (Pigdon et al., 2019; Stroh et al., 2019; Victoria et al., 2019; Fairhall, 2020; Liu et al., 2020; Maffei et al., 2020). Different from the traditional understanding of visual regions, some studies have shown that visual processing also promotes early language development

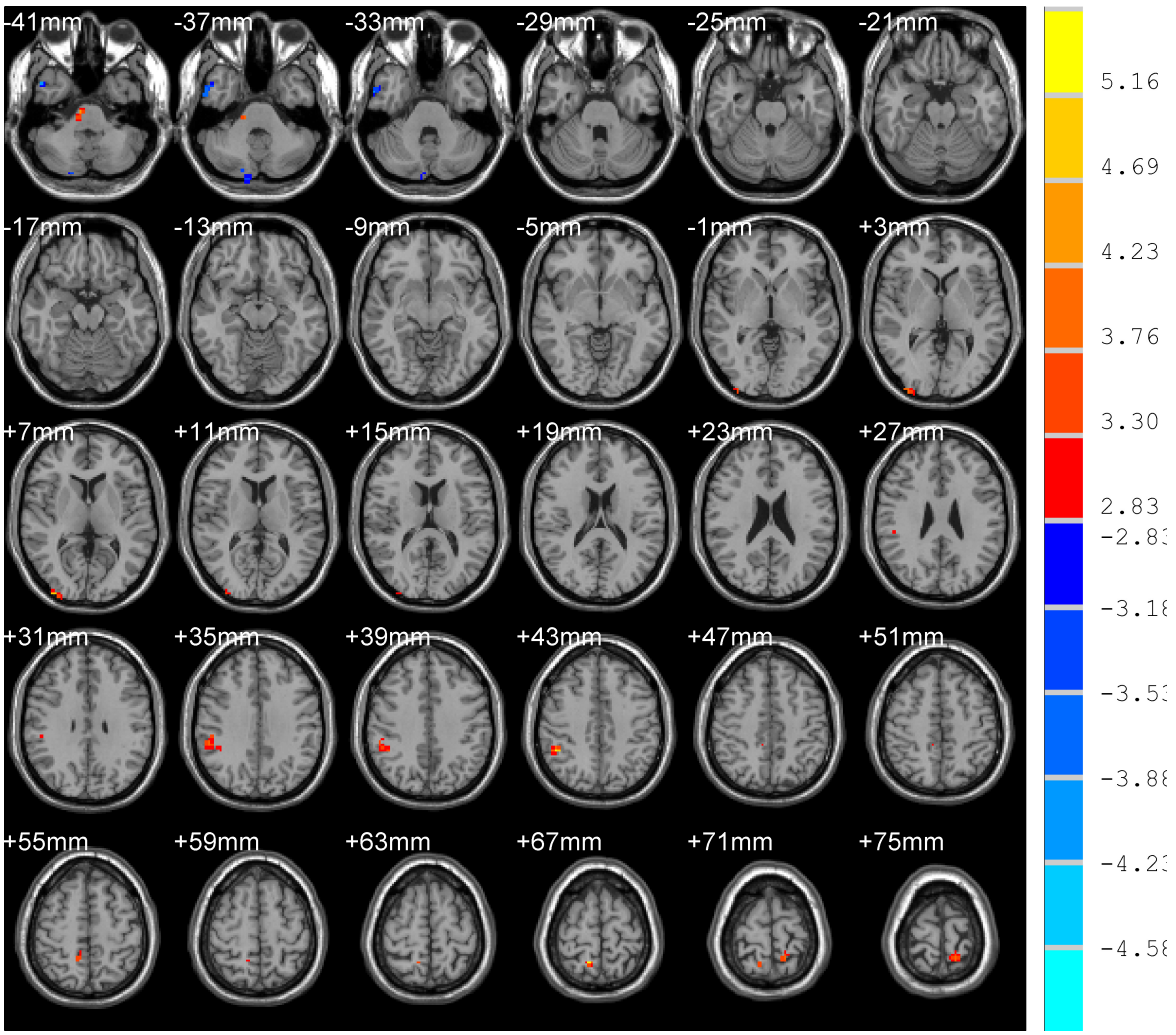

FIGURE 1 | Compared with HC, TOF children showed increased ReHo values in the right brainstem, right middle occipital gyrus, right inferior parietal gyrus, right precuneus, and left precuneus, and decreased ReHo values in the right posterior lobe of the cerebellum and right inferior temporal gyrus. AlphaSim correction with $P < 0.01$; cluster size > 23.

(Teinonen et al., 2008). Recently, left occipital regions were demonstrated as a visual input to language areas, which might manifest as pure alexia (without agraphia) when affected by ischemia (Sheetal et al., 2019). Additionally, a study on children with developmental language disorders showed that increased left inferior occipital volume may compensate for language regions (Pigdon et al., 2019). In addition, occipital regions can couple with other brain regions participating in many forms of verbal processing. When syntactic processing occurs, the left middle occipital regions along with the right supramarginal gyrus (SMG) are activated (Stroh et al., 2019). Moreover, population-based studies have shown that occipitotemporal (OT) regions play a crucial role in transforming visual symbols into meanings and sounds (Taylor et al., 2019; Zhou et al., 2019) and that semantic information strengthens the connection between OT regions and the left ventral inferior frontal gyrus (Wang J. et al., 2019).

Our results also showed that decreased ALFF values in the MIOG.L are positively correlated with increased ReHo values in the PCUN.L and PCUN.R, suggesting that elevated neuronal connections in the PCUN.L and PCUN.R may compensate for the low VIQ induced by inactive spontaneous activity in the MIOG.L. The PCUN, an associative region, is a part of the posteromedial parietal cortex, which engages in visuospatial imagery, episodic memory retrieval, self-processing, and consciousness by associating with many brain regions, including the thalamus, posterior cingulate, supplementary motor area, and dorsal premotor area (Cavanna and Trimble, 2006; Cunningham et al., 2017; Wang Z. et al., 2019). In addition, the parietal cortex, along with the temporal cortex and occipital cortex, connects to the temporoparietooccipital cortex (TPO), which is a highly associative cortical network and is involved in the integration of somatosensory, auditory, and visual information (Leichnetz,

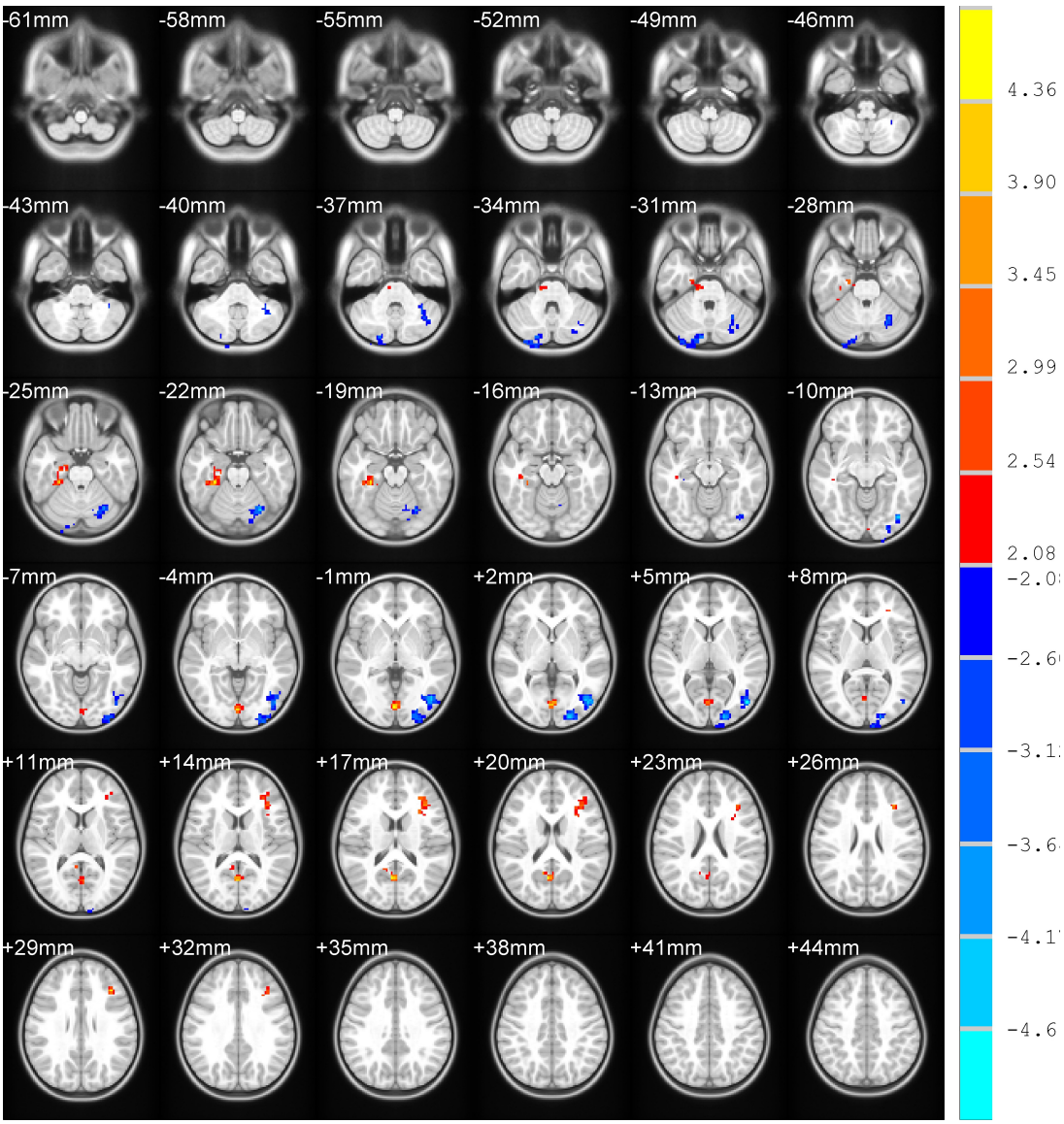

FIGURE 2 | Compared with HC, TOF children had higher ALFF values in the left medial prefrontal cortex, left cingulum, and right parahippocampal gyrus, but lower ALFF values in the bilateral cerebellum, left middle inferior occipital gyrus, and left inferior occipital gyrus. AlphaSim correction with $P < 0.05$; cluster size > 65.

2001). Additionally, many studies have reported that the PCUN is related to semantic processing and phonologic processing (Kjaer et al., 2001; Coslett and Schwartz, 2018). Similarly, our previous study suggested that the PCUN may connect with the temporal lobe *via* the temporoparietal junction (TPJ) and influence VIQ in TOF children (Ma et al., 2020). Thus, based on our results and those of previous studies, we speculate that increased neuronal connections in the PCUN.L and PCUN.R play a compensatory role in low VIQ induced by decreased ALFFs in the MIOG.L.

However, some limitations still exist in our study. First, our research should have recruited more participants to increase the reliability and generalizability of the results. Moreover, we evaluated the cognitive ability of TOF children after surgery at school age, and the specific timing of the start and maintenance of ReHo and ALFF changes is still unclear. Those children require continuous follow up. Furthermore, though recent study on 7–11 years old children who were conducted general anesthesia under 3 has shown that the exposure to general anesthesia in early childhood was not markedly related to the reduced intelligence in later stage (Schuttler et al., 2021), anesthesia was still demonstrated to be a non-negligible factor of cognitive levels in many studies (Pang et al., 2021; Shen et al., 2021; Wu and Zhu, 2021). However, we did not analyze the effect of anesthesia on cognition because of lots of anesthesia data missed. Additionally, children who were suspected of having neurodevelopmental disorders according to their guardians were more likely to be enrolled in this study, which may result in

TABLE 4 | Multivariable association of cerebral amplitude of low frequency fluctuations changings and cognitive abilities in TOF postoperative children.

	VIQ		FSIQ	
	Beta (95%CI)	***p*-value**	**Beta (95%CI)**	***p*-value**
Cb. L				
Model 1	−0.644 (−199.094, 30.801)	0.119	−0.482 (−262.708, 92.762)	0.274
Model 2	−0.644 (−199.094, 30.801)	0.119	−0.482 (−262.708, 92.762)	0.274
Model 3	−0.559 (−210.423, 72.949)	0.249	−0.453 (−319.912, 148.396)	0.367
MIOG. L				
Model 1	**0.847 (38.248, 236.593)**	**0.016**	**0.800 (24.405, 326.257)**	**0.031**
Model 2	**0.847 (38.248, 236.593)**	**0.016**	**0.800 (24.405, 326.257)**	**0.031**
Model 3	**0.908 (46.240, 210.637)**	**0.012**	0.796 (−9.657, 355.872)	0.058
IOG. L				
Model 1	−0.253 (−86.195, 54.243)	0.584	−0.133 (−108.428, 85.799)	0.777
Model 2	−0.253 (−86.195, 54.243)	0.584	−0.133 (−108.428, 85.799)	0.777
Model 3	−0.213 (−86.362, 62.957)	0.686	−0.110 (−126.076, 107.490)	0.836
Cb. R				
Model 1	0.062 (−32.278, 35.964)	0.895	0.248 (−34.730, 54.677)	0.591
Model 2	0.062 (−32.278, 35.964)	0.895	0.248 (−34.730, 54.677)	0.591
Model 3	0.261 (−29.052, 43.112)	0.617	0.324 (−40.944, 67.800)	0.531
MPFC. L				
Model 1	0.449 (−33.386, 85.252)	0.312	0.474 (−42.001, 115.858)	0.283
Model 2	0.449 (−33.386, 85.252)	0.312	0.474 (−42.001, 115.858)	0.283
Model 3	0.350 (−50.086, 86.926)	0.497	0.445 (−64.586, 136.754)	0.376
Cg. L				
Model 1	0.638 (−4.989, 30.853)	0.123	0.505 (−13.307, 40.942)	0.247
Model 2	0.638 (−4.989, 30.853)	0.123	0.505 (−13.307, 40.942)	0.247
Model 3	0.521 (−13.304, 34.144)	0.290	0.485 (−22.459, 52.292)	0.330
PHG. R				
Model 1	−0.387 (−119.600, 55.682)	0.392	−0.489 (−166.466, 57.361)	0.266
Model 2	−0.387 (−119.600, 55.682)	0.392	−0.489 (−166.466, 57.361)	0.266
Model 3	−0.295 (−120.564, 76.721)	0.571	−0.464 (−193.660, 87.659)	0.355

Model 1 adjusted for age, hospital stays, age of surgery and postoperative time.
Model 2 adjusted for model 1 plus CPB time and AO time.
Model 3 adjusted for model 2 plus preoperative SpO2, preoperative SBP, preoperative DBP and preoperative pH.
Cb. L, left cerebellum; MIOG. L, left middle inferior occipital gyrus; IOG. L, left inferior occipital gyrus; Cb. R, right cerebellum; MPFC. L, left medial prefrontal cortex; CG. L, left cingulum; PHG. R, right parahippocampal gyrus; VIQ, verbal intelligence quotient; FSIQ, full scale intelligence quotient.
Bold values represent that the results have statistical significance.

TABLE 5 | Pearson correlation between cerebral ReHo changings and cerebral ALFF changings in TOF group.

	Cb. L	**MIOG. L**	**IOG. L**	**Cb. R**	**MPFC. L**	**Cg. L**	**PHG. R**
BS. R	0.331	−0.144	0.666	0.170	−0.595	0.058	0.377
PLC. R	−0.114	0.272	−0.248	0.577	0.346	−0.062	0.381
ITG. R	−0.628	0.280	−0.586	−0.089	**0.758***	0.166	−0.080
MOG. R	**0.680***	−0.492	**0.679***	0.000	−0.656	0.254	−0.090
IPG. R	−0.274	0.031	**−0.817****	−0.343	0.283	0.226	−0.125
PCUN. R	**−0.807****	**0.750***	−0.348	0.036	0.280	0.101	0.174
PCUN. L	−0.633	**0.846****	−0.468	0.330	0.303	−0.235	0.218

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level.*
ReHo, regional homogeneity; ALFF, amplitude of low frequency fluctuations; TOF, Tetralogy of Fallot; Cb. L, left cerebellum; MIOG. L, left middle inferior occipital gyrus; IOG. L, left inferior occipital gyrus; Cb. R, right cerebellum; MPFC. L, left medial prefrontal cortex; CG. L, left cingulum; PHG. R, right parahippocampal gyrus; BS. R, right brainstem; PLC. R, right posterior lobe of cerebellum; ITG. R, right inferior temporal gyrus; MOG. R, right middle occipital gyrus; IPG. R, right inferior parietal gyrus; PCUN. R, right precuneus; PCUN. L, left precuneus; VIQ, verbal intelligence quotient.
Bold values represent that the results have statistical significance.

certain biases. Finally, this study was a cross-sectional study and cannot be used to determine the causal relationship between fMRI changes and cognition.

CONCLUSION

In summary, compared with HC, postoperative children with TOF had a lower VIQ at school age, which was positively related to decreased ALFF values of the MIOG.L. The results revealed that preoperative brain injury in TOF children, even at school age, have persistent negative effects on neurons, especially in the MIOG.L. The possible mechanisms may be delayed language development caused by inactive spontaneous neural activity in the MIOG.L. Fortunately, these changes might be compensated by increased neural connections in the PCUN.L and PCUN.R. Therefore, it is important to pay close attention to the language development of children with TOF. Cognitive ability evaluations, especially verbal cognition, should be included in conventional postoperative reviews and follow-ups.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Children's Hospital of Nanjing Medical University ethics committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

XM and MY designed the study protocol and proofread the manuscript. YH, YL, and SM collected the information and performed the data analysis under the close supervision of PZ, YP, ZY, FC, ZX, YC, and XL. SM drafted the manuscript. YP provided the help of technology. QH took charge of the modification of language. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2021.685372/full#supplementary-material

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REVIEW
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Hypospadias and Increased Risk for Psychiatric Symptoms in Both Childhood and Adolescence: A Literature Review

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Hypospadias is one of the most common congenital malformations in boys. Due to abnormal appearance in the penis with abnormal urination and erection, patients with hypospadias were vulnerable to suffering from stress and psychiatric difficulties. The present study aims to summarize all the current evidence of the association between hypospadias and the risk of psychiatric disorders by a comprehensive review. Seventeen clinical studies were identified in the four electronic databases. A total of 953,872 participants were involved, while 15,729 of them were hypospadiac patients and the remaining 938,143 were normal controls. The standard age for surgery for hypospadias ranged from 20.4 months to 21.5 years. Eight out of seventeen (8/17, 47%) included studies explicitly showed that patients with hypospadias had a significantly higher risk of psychosocial disorders (all $P < 0.05$). Specific types of psychiatric disorders included depression, anxiety, shyness, timidness, isolation, fear of ridicule, attention-deficit hyperactivity, autism spectrum, behavioral/emotional disorders, temper tantrums, emotionality, affective, psychosexual problems, and suicidal tendencies. Based on this review, psychiatric illnesses are frequently detected in hypospadiac patients' childhood, thus proper psychiatric guidance and early interventions from physicians, nurses, and parents may help these children to grow into less affected men.

Keywords: hypospadias, psychiatric disorder, risk, comprehensive review, depression

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INTRODUCTION

Hypospadias, one of the common diverse urologic anomalies among children, is characterized by a failure of urethral groove closure leading to an opening on the ventral aspect of the penis (1, 2). The severity of hypospadias depends on the failure timing of the incomplete fusion of the urethral folds. In hypospadias children, the urethra opens ventrally anywhere from the glans to as far back as the perineum, while distal hypospadias accounts for the majority of cases (3). Hypospadias occurs in 2–43 out of 10,000 live male births and exists along a spectrum of severity (4). The exact etiologies of hypospadias are still unclear, it is believed that genetic factors, endocrine hormones (i.e., androgens), environmental components contribute to the pathogenesis (5). There is no consensus on the timing of surgery (cognitive factors, risk of anesthesia, surgical considerations, psychological, developmental, and psychosexual considerations). Based on expert opinion, surgery is recommended between 6 and 18 months of age (6).

At present, debate persists whether hypospadias *per se* or surgical procedures have a negative influence on later psychiatric development. Mounting studies (7, 8) have examined psychiatric development and psychiatric symptomology in patients with hypospadias. Though a trend toward a potential association between hypospadias and psychiatric symptoms, the evidence has been controversial (9). The present study aims to summarize the published data related to this issue. Based on this review, it may be instructive to help the clinicians being conscious of the hazardous effect of hypospadias in the development of psychiatric disorders. Furthermore, it is meaningful to take some psychointervention from parents, doctors, and nurses to alleviate psychiatric ailments for the sufferers.

METHODS

To identify the eligible studies focusing on the relationship between hypospadias and psychiatric disorders, four electronic databases including MEDLINE, EMBASE, Cochrane Library, and PsychINFO were systemically retrieved up to date to August 01, 2021. The searching strategy used for screening the qualified publications in MEDLINE by the MeSH and terms was: (("Hypospadias"[Mesh]) OR (Hypospadia)) AND ((((((((((((((((((((((("Mental Disorders"[Mesh]) OR (Psychiatric disorder)) OR (Mental Disorder)) OR (Behavior Disorders)) OR (Depressions)) OR (Depressive Symptoms)) OR (Depressive Symptom)) OR (Symptom, Depressive)) OR (Symptoms, Depressive)) OR (Emotional Depression)) OR (Depression, Emotional)) OR (Depressions, Emotional)) OR (Emotional Depressions)) OR (Angst)) OR (Nervousness)) OR (Hypervigilance)) OR (Anxiousness)) OR (Social Anxiety)) OR (Anxieties, Social)) OR (Anxiety, Social)) OR (Social Anxieties)) OR (Stress)) OR (psychology)) OR (psychological)) OR (psychiatry)). Furthermore, we also reviewed the reference list to detect additional studies by a manual inspection. Duplicated data, review articles, letters/comments, case reports, meeting abstracts, and animal experiments were excluded in this study.

The process of study selection was conducted by two authors independently. Any ambiguities were resolved by the corresponding author. A standardized data collection table was used to extract the important data (e.g., the names of the first author, geographical distribution of the study, study design, publication year, mean age of the patients, the number of participants from the study group and the control group, the descriptions of psychological disorders in every single study, the age at criterion operation of hypospadias, and the assessment of psychiatric symptoms).

RESULTS

Literature Search and Eligible Study Characteristics

Figure 1 showed the search flowchart for screening eligible studies related to the topic of hypospadias and psychiatric disorders. During the initial search, 1,606 records were identified, of which 567 were from MEDLINE, 411 from EMBASE, 347 from Cochrane Library, and 281 from PsychINFO database. Finally, 17 eligible clinical studies (3, 10–25) containing with data met our predefined inclusion criteria. Six of these studies (13/17, 76%) had provided the data from both the hypospadias and the healthy control group. A total of 953,872 participants were involved, while 15,729 were hypospadiac patients and 938,143 were normal controls. Among the 17 studies included, eight were case-control designed, five for cohort designed, one for cross-sectional designed, one for randomized controlled trial (RCT), and one for prospective designed. The publication years of these selected studies ranged from 1982 to 2021.

The mean age of the hypospadiac patients ranged from 20.4 months to 34.2 years. The standard surgical age for hypospadias ranged from 20.4 months to 21.5 years. Types of psychiatric disorders reported in the 17 eligible studies included depression, anxiety, shyness, timidness, isolation, fear of ridicule, attention-deficit hyperactivity, autism spectrum, behavioral/emotional disorders, temper tantrums, emotionality, lack of vitality, esteem troubles, affective disorder, gender identity, psychosexual problem, gender-role behavior, and suicidal tendencies. The assessments of these psychiatric disorders among hypospadiac patients included the following methods, e.g., an interview by the psychiatrists or nurse specialists, child psychiatric symptoms list, standardized intelligence test, the Rorschach test, Spielberger anxiety questionnaire, Goldberg General Health Questionnaire, Beck Depression Inventory (BDI), Self-rating Depression Scale (SDS), Self-rating Anxiety Scale (SAS), Children's Fear Scale, Post-Hospitalization Behavioral Questionnaire, Modified Yale preoperative anxiety scale, Autism spectrum disorders, Attention deficit hyperactivity disorder, Behavioral/emotional disorders, Body-Esteem Scale for Adolescents and Adults; Psychological General Well-Being Index, Genital Examination Distress Scale, Ages and Stages Questionnaire and ASQ-Social Emotional Scale, Psychosexual milestones, Gender-Role Questionnaire, and the Mini International Neuropsychiatric Interview. The characteristics of the 17 included studies were summarized in **Table 1**. We had broken the hypospadias patients up by age with childhood, adolescence, and adulthood.

The evidence of psychological disorders in hypospadiac patients reported in the 17 included studies was illustrated in the Discussion Section.

DISCUSSION

Hypospadias, characterized by an opening of the urethra on the underside of the penis, is one of the most common congenital malformations in boys (26). Based on the published data of hypospadias, most of the studies have been focusing on the surgical techniques and the consequent functional, cosmetic, and sexual outcomes (18, 27, 28), but few studies have concerned the psychiatric symptoms in boys or adolescents with hypospadias. Actually, however, hypospadias alongside with the surgical procedures or surgical outcomes have all been postulated for leading to psychiatric disorders [e.g., depression, anxiety, and timidness; (25, 29)]. However, some studies actually failed to find a positive relationship between hypospadias and psychiatric

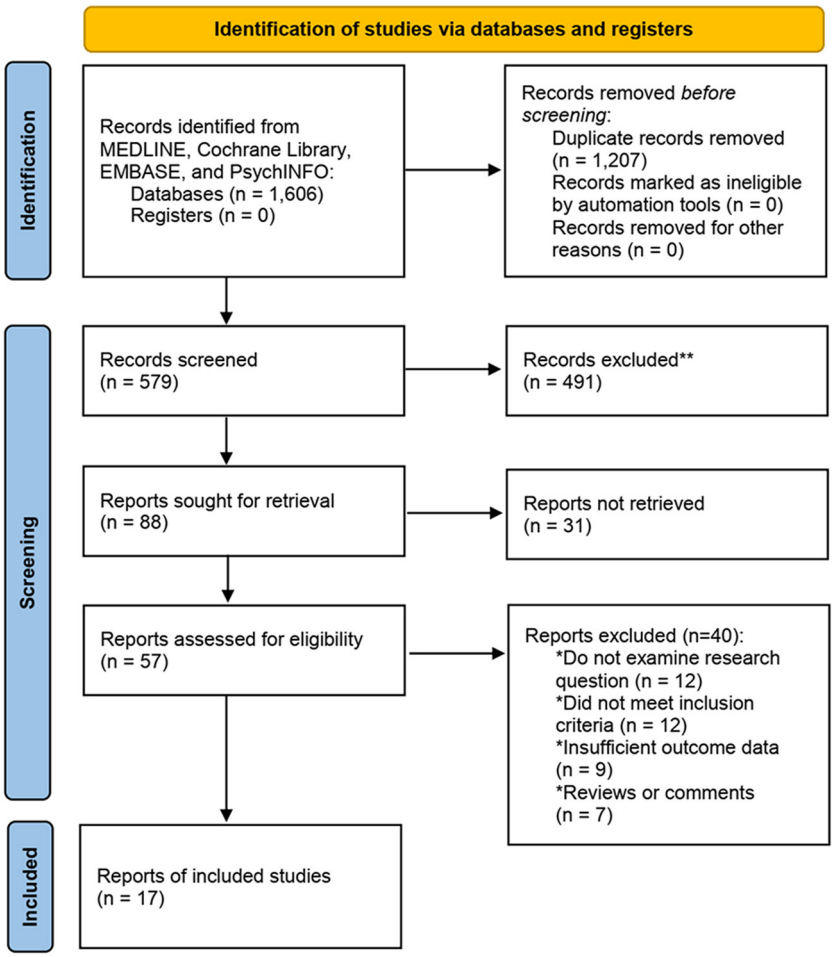

FIGURE 1 | Flow chart of study selection.

illness. For example, Mureau et al. conducted a comparative study investigating the psychosocial functioning between patients following hypospadias surgery and the healthy controls (30). The authors compared the differences between the two groups by performing the stratification analysis on the subject age, age at final surgery, penile appearance, the severity of hypospadias, number of operations, and type of surgical procedure, showing that children, adolescents, and adults following hypospadias surgery did not have a higher risk of poor psychosocial functioning as compared to general populations (30). At present, the evidence on the association between hypospadias and the risk of psychosocial disorders remains controversial among different studies.

Though hypospadias is one of the most common malformations, few studies focusing on its psychiatric comorbidity and the correlated data have been conflicting (31). Due to abnormal appearance in the penis with abnormal urination and erection (32), patients with hypospadias were vulnerable to suffering from stress and psychiatric difficulties on account of the negative effects on their social behaviors, school success, gender roles, and self-confidence (14). As illustrated in **Table 1**, nearly half of the included studies (6/14, 47%) suggested that patients with hypospadias were clearly more liable to suffer from psychosocial disorders than the controls. Berg et al. (11, 12) have conducted two clinical studies to investigate the association between hypospadias and psychosocial illnesses in the 1980s. The authors reported that hypospadias was correlated to more psychiatric symptoms (i.e., hostility, reduction of social relations and emotional relations, anxiety, less self-esteem, and less activity) than the controls in adult age ($P < 0.05$). The mean age of the participants in the study group was 27.2 years, and they received the criterion operation of hypospadias at their age at 3.0–9.5 years (mean: 5.6 years). A study developed in China showed that preoperative hypospadiac patients have significantly higher occurrences of depression and anxiety disorders than the control group ($P < 0.001$) (23). In addition, the authors also found that the postoperative SDS/SAS scores were significantly higher in

TABLE 1 | Characteristics of the 17 included studies.

Study	Study design	Mean age (years)	Number of patients	Types of psychiatric disorders	Descriptions of psychiatric disorder	Age at criterion operation of hypospadias (years)	Assessment of psychiatric disorder
Childhood							
Sanders (3) UK	RCT	20.4 months	20	Distress	NA	Mean: 20.4 months	Urology nurse specialist
Turk et al. (22) Turkey	Prospective study	5–12	30	Fear and anxiety	Imaging of micturition at home by using a video camera for outpatient visits following hypospadias surgery decrease the fear and anxiety of children.	5–12 years	The Children's Fear Scale
Duarsa et al. (15) Indonesia	Case-control	S: 5.9 ± 3.9 C: 5.5 ± 2.5	S: 10 C: 19	Distress	Poor Genital Examination Distress Scale score was detected more in the hypospadias group compared to the control group, but this was not statistically significant (30 vs. 15.8%, OR = 2.28, $P = 0.331$).	NA	Genital Examination Distress Scale
Luo et al. (16) China	Cohort	2–12	177	Temper tantrums, emotionality	Temperament emotionality: OR = 1.112 (1.011, 1.224), $P = 0.029$; Emotionality: OR = 1.148 (1.049–1.256), $P = 0.001$; there is an association between child anxiety upon entrance into the operation room and negative postoperative behavioral changes but not in the adjusted regression analysis.	2–12 years	Post-Hospitalization Behavioral Questionnaire and Modified yale preoperative anxiety scale
Adolescence							
Schonbucher et al. (20) Switzerland	Cross-sectional	S: 10.8 ± 3.2 C: 11.1 ± 3.2	S: 68 C: 68	Gender-role behavior	Patients with hypospadias did not significantly differ from the control subjects with regard to gender-role behavior. Gender-role behavior was significantly negatively correlated to the patients' age at last surgery and positively associated with follow-up since last surgery ($P < 0.05$).	Mean: 3.2 ± 2.5 years	Gender-Role Questionnaire
Butwicka et al. (13) Sweden	Case-control	13.2	S: 9,262 C: 463,100	Attention-deficit hyperactivity, autism spectrum, and behavioral/emotional disorders	The lifetime prevalence of any psychiatric disorders was 9.7% for cases with hypospadias and 7.6% for controls (OR 1.3, 95% CI: 1.2–1.4).	NA	Information on psychiatric disorders was extracted from the National Patient Register in Sweden
Adulthood							
Berg et al. (11) Sweden	Case-control	S: 27.2 C: 26.9	S: 34 C: 36	Depression, anxiety, shyness, timid, isolated	Hypospadias is associated with more psychiatric symptoms than controls in adult age ($P < 0.05$); The most marked difference is depressiveness (15/34 in hypospadias group and 5/36 in the control); more stress reactions are found in the hypospadias patients ($P < 0.01$).	3.0–9.5 years	An extensive interview was performed with each subject by an experienced psychiatrist; child psychiatric symptoms list
Berg and Berg (12) Sweden	Case-control	20–35	S: 33 C: 36	Depression, anxiety, shyness, timid, isolated	Patients with hypospadias have significant higher risk of hostility, reduction of social relations and emotional relations, anxiety, less self-esteem, and less activity ($P < 0.05$); but no significant differences on depression and authoritarian submission.	3.0–9.5, Mean: 5.6 years	A psychological test battery, including standardized intelligence test, the Rorschach test
Miller and Grant (17) UK	Cross-sectional	17.7–36.6	19	Depression	Four (4/19) patients reported marked impairment of psychological well-being.	2–8; median: 3 years	Spielberger Anxiety Questionnaire, Goldberg General Health Questionnaire, and BDI

(Continued)

TABLE 1 | Continued

Study	Study design	Mean age (years)	Number of patients	Types of psychiatric disorders	Descriptions of psychiatric disorder	Age at criterion operation of hypospadias (years)	Assessment of psychiatric disorder
Wang et al. (24) China	Case-control	S: 24.3–28.4 C: 24–35	S: 130 C: 50	Depression, anxiety, fear of ridicule	Depression and anxiety were significantly higher in the hypospadias group than in the control group ($P < 0.001$); the incidence of depression and anxiety were significant differ between groups A and B ($P < 0.01$), groups A and C ($P < 0.01$).	Median: Group A: 6.5, Group B: 13.0 Group C: 21.5	SDS, SAS
Schlomer et al. (19) USA	Case–control	S: 34 C: 33	S: 736 C: 684	Psychosexual problems	The mean number of mentally unhealthy days was significantly differed between severe untreated hypospadias and the controls (12.1 vs. 6.5 days, $P = 0.017$).	Untreated hypospadias (No surgery)	Psychosexual milestones
Ortqvist et al. (34) Sweden	Cohort	S: 34 C: 33	S: 167 C: 169	Core gender identity and gender role behavior	There was no association with core gender identity and gender role behavior between hypospadias patients and controls. However, patients with proximal hypospadias had a higher gender identity score ($P = 0.02$) and gender role behavior score ($P = 0.04$) compared with men with distal hypospadias.	Mean: 5 ± 4 years	A 12-item questionnaire
Andersson et al. (10) Sweden	Cohort	S: 14–35 C: 15–29	S: 64 C: 25	Anxiety, depressed mood, positive well-being, self-control, vitality, and esteem	No differences in anxiety, depressed mood, positive well-being, self-control, and vitality between hypospadias and control group (all $P > 0.05$).	NA	Body-Esteem Scale for Adolescents and Adults; Psychological General Well-Being Index
Ortqvist et al. (18) Sweden	Cohort	S: 34.2 ± 7.1 C: 27.2 ± 6.7	S: 33 C: 47	Affective, suicidal, and anxiety symptoms were more common in hypospadias patients than the controls, but this did not reach statistical significance	Psychiatric symptoms did not differ significantly between the hypospadias and control group, as well as between different severity or phenotype groups.	Median: 4 years	Mini International Neuropsychiatric Interview
No age information or the great age variation							
Wang et al. (23) China	Case-control	S: 3–26 C: 24–35	S: 130 C: 50	Depression and anxiety	Hypospadiac patients have significantly higher occurrences of depression/anxiety than the normal controls ($P < 0.001$); Also, the postoperative SDS/SAS scores were higher in patients with hypospadias; Patients with proximal hypospadias and multiple procedures have higher risk of sexual psychological problems.	Median: 16.5 years	SDS, SAS
Skarin et al. (21) Sweden	Cohort	NA	S: 4,738 C: 473,800	Autism, behavioral/emotional disorders, and attention deficit hyperactivity disorder	Patients with hypospadias did not differ from non-affected men regarding the majority of the investigated psychosocial outcomes (all $P > 0.05$).	NA	Autism spectrum disorders; Attention deficit hyperactivity disorder; Behavioral/emotional disorders
Cakmak et al. (14) Turkey	Case-control	NA	S: 78 C: 59	Communication, developmental and social-emotional problems	Multivariate logistic regression analysis showed that hypospadias was the independent predictive factor for the problems of the communication and personal-social skills (all $P < 0.05$).	NA	Ages and Stages Questionnaire and ASQ-Social Emotional Scale

SDS, Self-rating Depression Scale; SAS, Self-rating Anxiety Scale; BDI, Beck Depression Inventory; OR, Odds ratio; CI, Confidence Interval; S, Study group, patients with hypospadias; C, Control group, normal population; NA, Not Available.

patients with hypospadias. Furthermore, patients with proximal hypospadias and multiple procedures have a remarkably higher risk of sexual psychiatric problems.

Butwicka et al. (13) have conducted a large sample case-control study which was involving over 470,000 participants (mean age: 13.2 years), they found that the lifetime prevalence of any psychiatric disorders was 9.7% for cases with hypospadias and 7.6% for controls (OR = 1.3, 95% CI: 1.2–1.4). The common psychiatric disorders in hypospadias patients were attention-deficit hyperactivity, autism spectrum, and behavioral/emotional disorders. A previous study showed that boys aged 6–10 years with hypospadias had anxiety than the controls (33). Sandberg et al. had also confirmed the positive relationship between hypospadias and psychiatric morbidities, showing that emotional problems increased with the number of hospital-related experiences (29). Cakmak et al. (14) demonstrated that hypospadias was an independent predictive factor for impairment of communication (odds ratio = 4.06, 95%CI: 1.32–13.37, $P = 0.015$) and personal-social (odds ratio = 5.7, 95%CI: 1.23–26.34, $P = 0.026$) skills impairment. However, a cohort study developed by Ortqvist et al. (18) indicated that psychiatric symptoms (i.e., affective, suicidal, and anxiety symptoms) were more common in hypospadias patients than the healthy controls, but these psychiatric illnesses did not have e markedly difference between the two groups as well as between the severity or phenotype groups. Besides, no statistical significant difference was observed in the four included studies (10, 14, 15, 21). In line with these findings, Mureau et al. (30) demonstrated that psychiatric impairments did not differ obviously between patients with hypospadias surgery and those who underwent surgery for an inguinal hernia. Gender dysphoria and gender identity are two types of psychiatric illnesses. Two eligible studies (20, 34) suggested that patients with hypospadias did not significantly differ from the control subjects with regard to gender identity and gender-role behavior. However, Schönbucher et al. (20) reported that gender-role behavior was remarkably negatively associated with the patients' age at last surgery ($P < 0.05$). Further studies on gender issue in patients with hypospadias are warranted.

According to the above evidence, six included studies (10, 15, 18, 20, 21, 34) explicitly showed that there was a non-significant association between hypospadias and psychiatric illnesses, regardless of whether underwent the surgery or not, while eight included studies (11–14, 16, 19, 23, 24) suggested that patients with hypospadias had a significantly higher risk of psychiatric comorbidity than the controls. Since almost all the patients had received hypospadias surgery, when choosing the operative age, the psychiatric comorbidity should be considered comprehensively to achieve the optimal therapeutic effect. Wang et al. (24) observed a positive association between hypospadias and psychosocial disorders, they subsequently divided the hypospadiac patients into three groups based on age at last surgery, including group A (<10 years), group B (10–18 years), and group C (>18 years). The authors found that the SDS was 47.44 ± 5.88, 53.98 ± 7.23, and 54.25 ± 7.02 in Group A, Group B, and Group C, respectively. On the other hand, the SAS was 44.72 ± 8.44, 49.80 ± 7.25, and 50.66 ± 6.71 in Group A, Group B, and Group C, respectively. According to the statistical analyses, the authors revealed that the SDS, SAS, and the incidence of depression and anxiety differed significantly between Groups A and B ($P < 0.001$), groups A and C ($P < 0.001$), indicating that psychosocial disorders were even more obvious in patients who had completed surgery after 10 years old. However, some investigators indicated that a younger age might be more susceptible to some mental problems. Luo et al. (16) investigated the postoperative behavior changes in children undergoing hypospadias repair surgery and found that the incidence of the negative postoperative behavioral changes (i.e., temper tantrums and emotionality) was 1.5 times higher for children younger than 4 years old as compared to those older than 4 years old. Based on Wang et al. and Luo et al.'s studies, if solely minimizing the "psychiatric burden," the age for hypospadias repair surgery is recommended from 4 to 10 years.

Whether hypospadias *per se* or surgical procedures have a negative influence on later psychiatric development still needs further investigations. Among the 17 included studies, only Schlomer et al.'s study (19) pointed out that the hypospadias patients were untreated subjects. Notably, regardless of surgery or not, whether hypospadias was associated with psychological disorders was still controversial. Forty-seven percent of the included studies had confirmed the positive association between hypospadias and psychiatric comorbidity, while 35% of the included studies failed to find such an association. Among nine included studies supported this correlation, seven of them reported the hypospadias patients previously underwent surgery, one study reported non-surgery, and other one study did not explicitly the surgery issue. But we could not assess the exact roles of surgical procedures on later psychological development due to none of studies have provided the data of the psychiatric changes in pre- and post-operation.

As we know, this is the first study for summarizing all the evidence of the association between hypospadias and the risk of psychiatric disorders by a comprehensive review. However, several inherent limitations should be taken into account. First, only 17 studies were included for depth profiling. Second, this review could not demonstrate that which type of psychiatric illness is more common in patients with hypospadias due to a wide array of psychiatric disorders that have been described among these included studies. Third, we failed to conduct a meta-analysis due to the limited data, thus how risky psychiatric illness is among hypospadiac patients remains elusive.

CONCLUSION

Based on this review, hypospadiac patients' mental illnesses could be commonly detected in their childhood. Boys with hypospadias are recommended to be evaluated on their psychiatric status, which has crucial importance. Besides, proper psychiatric

guidance and early interventions from physicians, nurses, and patients may help these children to grow into less affected men.

AUTHOR CONTRIBUTIONS

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Risk Profiles of Korean Adolescents in Relations With Contextual Factors: Implications for Multi-Tiered Systems of Support

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Introduction: Although prior studies have supported the effectiveness of Multi-Tiered Systems of Support (MTSS) on addressing social, emotional, behavioral, and academic challenges faced by youth at-risk, educators using MTSS often do not consider contextual factors which may also influence youth at-risk and the interventions targeting them. This study thus aimed to identify youth at-risk who should be referred to targeted instructions within MTSS by examining the risk profiles of Korean adolescents. Based on the identified risk profiles, we also tried to investigate the effect of contextual factors on deciding youth at-risk and confirm whether and/or what contextual factors should be considered when implementing targeted interventions for them.

Method: To accomplish the research goal, a latent profile analysis on risk factors of Korean adolescents was performed, using the first year data of "Korean Children and Youth Panel Study (KCYPS) 2018."

Results: Four risk profiles were identified, using low academic motivation, low academic behavior, attention deficit, aggression, social withdrawal, and depression as indicators: the high risk, M-SEB (Moderate-social, emotional, & behavioral) risk, M-ACA (Moderate-academic) risk, and low risk group. The covariates of this study, home and school environmental variables, worked as predictors of adolescents included in the high group.

Conclusion: The results of this study suggest students in the high risk group (16.8%) should be given targeted instructions combining academic and SEB support within MTSS so as to prevent negative outcomes in the future among all adolescents. Those instructions need to be planned with consideration of contextual factors accompanied by teacher's careful understanding of social dynamics surrounding each student.

Keywords: youth at-risk, risk profiles, contextual factors, MTSS, KCYPS 2018

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INTRODUCTION

Adolescence involves dramatic social, psychological, and physical changes, which have great influences on social and career adjustment in adulthoods (1). This phase is also important since a great number of adolescents can face diverse risks that may prevent normal development and lead to academic failure, mental health problems, and maladjustment in society (2). Thus, it is highly necessary to monitor developmental trajectories of youth and identify whether they have

certain risk factors that may result in significant problems in the future. In other words, early identification and intervention to support youth at-risk should be one of the primary goals of secondary education.

Youth At-Risk

The concept "youth at-risk" has been defined in several ways. According to Resnick and Burt (3), youth at-risk is defined as adolescents with negative antecedent conditions creating vulnerabilities, combined with the presence of specific negative behaviors or experiences that are likely to lead to more serious long-term health consequences. Similarly, Evans (4) stated youth at-risk as adolescents who are unlikely to achieve independent adulthood due to maladjustment to school life, estimating about 16% of all adolescents as youth at-risk. Dryfoos (5) also identified adolescents (age between 10 and 17) at risk who have risk markers such as delinquency, substance abuse, or academic suspension, and 25% of all youths are designated to be at high risk. Although the definition and specific proportion deciding youth at risk were not exactly identical across researchers, it was agreed that youth at-risk experiences risks that may lead to other negative outcomes in the long run across social, emotional, behavioral, and academic domains.

For an academic domain, youth at-risk tend to experience significant distress and marginalization in classrooms because of push for testing outcomes and academic accountability (6). They are more likely to fail in academic achievement assessments and less likely to meet standards of general curriculum than their peers (6). In reciprocal relationships with academic skills, academic motivation is also one of the most typical characteristics of youth at-risk. Academic motivation is able to be generated by students having a goal of gaining a rich understanding of experiences through learning (7). However, it was frequently reported that students at-risk with the accumulated academic helplessness do not understand the value of studying (8). It is also important to note low academic motivation is strongly associated with low academic behavior which is defined as behaviors that promote one's ability to be prepared for, participate in, and benefit from an academic instruction (9). Since students with low academic motivation and behavior can develop serious problems such as academic failure and dropping out of school (7), supporting those students with effective intervention programs is highly recommended.

Youths at-risk also have been reported to experience attention deficits. Students having difficulties focusing on a certain task for an extended period of time predicts not only maladjustment to school-life but to drug use and addictive behavior in the future (10). If without appropriate educational intervention, these symptoms often result in difficulties from work and interpersonal relations, low self-esteem, anxiety, and emotional liability in adulthood (11). As students with attention deficit often have comorbidity with hyperactivity, aggression also presents similar patterns in developmental trajectories of youth. According to Sharma and Marimuthu (12), aggression in the age of 10–16 was highly related to hyperactivity, low academic performance, peer delinquency, and drug abuse. Therefore, aggression along with attention deficit can be important indicators for identifying adolescents at-risk in academic and behavioral domains.

Some youths-at-risk are characterized as socially withdrawn, spending most of their time alone and on the periphery of the social settings due to shyness or social anxiety (13). Social withdrawal has been shown to be stable from ages 5 to 11 years and so on (14), which can be a risk factor for psychosocial maladjustment since it is deeply interrelated with negative self-esteem, anxiety, depression, and peer rejection (15, 16). In addition, depression can also be the risk factor of the emotional domain, as adolescent depression has been highly correlated with adverse psychosocial and academic outcomes and increased incidence of substance abuse and suicide (17). According to Field et al. (18), depression in adolescence is deeply associated with relationships with parents, peers, lifestyle, and emotional wellbeing. Thus, depression is also qualified to be included in risk factors predicting adverse outcomes in the future as well as being affected by surrounding environments.

Throughout previous studies, the abovementioned externalizing (e.g., attention deficit, aggression) and internalizing (e.g., social anxiety, depression) risks are also highly correlated with effortful control, which refers to the ability to regulate cognition, emotion, and behavior (19). As this neurocognitive variable has been identified as a contributor to future outcomes across diverse domains, along with externalizing and internalizing challenges (19), a lack of this competency during adolescence would be able to predict adverse educational attainment of adulthood (20). Hence, neurocognitive difficulties may also deteriorate negative outcomes of youth at risk.

Previous studies have also supported that environmental factors significantly affect student's diverse risks across social, emotional, behavioral, and academic domains. According to Lim (21), home environments, including interaction with parents and school environments, including relationships with peers and teachers, had statistically significant influences on adolescent's level of mental health regardless of whether they experience low academic achievement. Specifically, students experiencing low-quality relationships with their parents, peers, and teachers tend to report higher risks in internalizing problems such as anxiety, depression, and suicidal impulse. Since adolescent's mental health problems predict school adjustment in the long term (22), it is reasonable to conclude that home and school environmental factors surrounding students are critical determinants of their school adjustment. Furthermore, Kim and Lim (23) also suggested that identical contextual factors are likely to affect adolescent's self-concept in various domains. Considering that the self-concept reflects one's own belief of oneself in social, familial, and academic contexts, which strongly affect life satisfaction and overall wellbeing, home and school environmental variables should be carefully examined and regulated in order for students to maintain healthier lives. Therefore, it is reasonable to assume that those * environmental factors are the vital contributors to the diverse challenges faced by adolescents.

MTSS to Support Youth At-Risk

Youth at-risk students need to be supported across academic, social, emotional, and behavioral domains in order not to experience adverse consequences in their adulthood adjustment. There were numerous attempts to support youth at-risk within school settings, and among them, the Multi-Tiered System of Support (MTSS) has been the representative model of early identification and systematic intervention targeting students at-risk. MTSS is a comprehensive framework designed to address the interplay of social, emotional, behavioral, and academic functioning and adaptation in the classroom (24, 25), which encompasses every kind of challenge students face. It emphasizes students' responsiveness to intervention and requires both universal and incrementally intensive strategies that encompass the students with diverse severity of difficulties (26) by providing more intensive strategies to students who do not respond to general instructions (24). To be specific, it is usually configured in pyramid-shaped three intervention levels: Tier 1 (universal instruction) is for the universal support providing strategies that are applied to all students as a foundation for specialized interventions; Tier 2 (selective instruction) consists of selective interventions to focus on individuals who can be classified as "students at-risk" and whose needs are not adequately met by Tier 1 approaches, which typically includes about 10–20% of all students; and Tier 3 (individualized instruction) indicates targeted strategies individualized to the needs of each student and generally for the 5–7% of students who do not respond to former interventions (27). Adopting a preventive approach that involves the early identification and provision of services before their problems are manifested and are identified as a disability in a student's functioning (28), MTSS is now widely accepted to initiate school-wide prevention and intervention model for students facing various risks.

Having lots of benefits, a significant limitation of MTSS widely agreed on is that its focus is primarily on intervention intensity and not tentative variables which contribute to student's add adoption (26, 29). In a traditional MTSS framework, the provision of educational services is solely determined by student's progress in targeted performances. It suggests the movement to the next level of intervention with a more intensive strategy if a student is not responsive to a less intensive level of instructions (30). However, as we have reviewed that risk factors of adolescents are significantly impacted by home and classroom environments surrounding each student (21–23), the response to intervention is also highly likely to be affected by identical contextual variables (26, 29). For example, according to Farmer et al. (27), teachers are familiar to conclude that the instruction was ineffective or the student is resistant to the instruction based on the lack of student progress after the instruction. In contrast, they often do not assume other contextual variables operated to prevent student's progress despite the high level of effectiveness of interventions, which leads them to subsume the educational services are sufficient even when instructional strategies are not fully adapted to the needs of each student (27). This does not indicate that MTSS is flawed or ineffective. Instead, it shows the necessity of educators considering contextual and ecological factors when planning instructions from the multi-tiered system since students' competencies in social, emotional, behavioral, and academic domains tend to develop as a whole in relation to those factors (31).

The Current Study

Although the abovementioned drawback of MTSS seems convincing, there was a lack of efforts to empirically demonstrate exactly what ecological factors significantly decide the challenges of youth at-risk. In this sense, the current study as supplementation of traditional MTSS was planned to confirm whether or what contextual factors can have significant impacts on deciding youth at risk. To accomplish this research goal, we conducted a latent profile analysis (LPA) to determine who are able to be identified as youth at-risk and should be referred to more intensive instructions within MTSS. The indicators for the LPA encompass social, emotional, behavioral, and academic challenges due to the aim of MTSS dealing with all kinds of problems faced by students (24). After deciding youth at-risk through LPA, we verified the effect of contextual variables on the decision of youth at-risk, compared to other latent profiles. As Kim and Lim (23) stated that the primary contexts surrounding adolescents could be signified as home and school environments, and Farmer et al. (32) suggested that dynamic relationships with significant others surrounding each student affect the effectiveness of interventions, home environmental variables (e.g., parenting attitudes) and school environmental variables (e.g., relationships with peers and teachers) were included as contextual factors.

In reviewing related research, Cho et al. (33) attempted to address the latent profiles based on diverse risk factors of Korean adolescents. However, the data originated from the teachers' perception of the characteristics of youth at-risk, not from the self-report of challenges. Furthermore, there were no studies identifying the relationships of risk profiles with contextual factors. Therefore, the present study is highly valuable as we successfully identified youth at-risk based on nationwide data [in this case, data from Korean Children and Youth Panel Survey (KCYPS) 2018] reported by students themselves and verified environmental variables that predict those youths. Through the findings of this research, we anticipate that the overall effectiveness of tiered instructions within MTSS can be enhanced by informing clinicians and educators of the most appropriate services as well as that the proportion of students inadvertently placed in a more intensive tier without receiving adaptive interventions in a lower tier may decrease.

To sum up, using the KCYPS data, this study was designed to identify the risk profiles of Korean adolescents across diverse domains and the impact of contextual factors on those profiles. In addressing the study purpose, the following research questions are raised:

RQ1: Who can be identified as youth at-risk who should be referred to selective instructions within MTSS?

RQ2: Whether and/or what contextual factors have significant impacts on deciding youth at-risk?

METHODS

Sample

Data for the current study was collected from the "Korean Children and Youth Panel Survey (KCYPS) 2018" which is longitudinal data conducted by National Youth Policy Institute in South Korea. Starting in 2018, KCYPS 2018 is designed to keep track of the educational background and characteristics of students in elementary and middle schools. We used the first and second year data of KCYPS 2018 with information of 2,590 middles school first graders in 2018. In regard to the demographic composition of the sample, the percentage of male participants were 54.2, while that of female participants were 45.8. 45.1% of the students attended schools in urban regions, 40.7% were in suburban districts, and 14.2% were in rural regions.

Variables

Indicators: Risk Factors

To assess levels of risks that participants counter and identify the risk profiles of Korean adolescents, we selected six variables among the first-year data of KCYPS 2018 as indicators; academic motivation, academic behavior, attention deficit, aggression, social withdrawal, and depression. For the academic motivation scale, the higher score indicates that the participant has a lower level of academic motivation and it includes four items such as "I do not know why I should study hard." and "I do not enjoy studying." The higher score of academic behavior scale shows that the responder is less likely to be engaged in academic-related behaviors, such as classroom activity or plan for their own learning, with four items. Both academic motivation and behavior scales were validated in Bak et al. (34) by sampling 593 elementary and secondary school students in Korea. The higher score of attention deficit scale means the participant has more difficulties concentrating on one task for an extended period of time. A total of seven items of this scale include "I do not want to finish my homework that needs concentration for a long time." and "I feel discomfort when I have to sit quietly while studying." For the aggression scale, students with higher score indicates they are more likely to be in high-temper. The six items for the aggression level include "I often disturb what someone else is doing." and "I often fight with other friends for minor reasons." Both attention deficit and aggression scales were validated through Cho and Lim (35) collecting data from 457 4 to 6^{th} graders in Korea. The social withdrawal scale was developed and standardized by Kim and Kim (36) based on the data from 518 individuals from 5 to 8^{th} grades. The higher score of the social withdrawal scale means the participants are more reluctant to show themselves or present their feelings in front of other people. For example, statements such as "I often feel shy." and "I do not want to express myself in front of many people." are included in the scale with a total of five items. Lastly, the higher level of depression indicates that students are more lethargic and feel more depressed. Ten items of depression include "I do not have interests in every circumstance." and "I want to die," which were designed and validated by Kim et al. (37). Every scale selected in order to measure abovementioned risk factors was designed to be 4-Likert scales (1 = strongly disagree, 4 = strongly agree), and the reliability of each scale was also satisfactory (**Table 1**).

TABLE 1 | The reliability of scales used to measure study variables.

	Variables	Number of items	Cronbach's a
Risk factors	Low academic motivation	4	0.905
	Low academic behavior	4	0.785
	Attention deficit	7	0.820
	Aggression	6	0.839
	Social withdrawal	5	0.874
	Depression	10	0.922
Home environment	Parent warmth	4	0.913
	Parent acceptance	4	0.789
	Parent consistency	4	0.804
School environment	Peer relationship	13	0.852
	Teacher relationship	14	0.912

Covariates: Contextual Factors

Contextual factors that presumably influence diverse difficulties faced by adolescents were incorporated in our study as covariates in order to determine whether they predict risk profiles each individual would show. These predictors were home and school environmental variables from the first-year data. For home environmental variables, three scales related to parenting attitudes were included; parental warmth, acceptance, and consistency. In the parent warmth scale, the higher score of warmth indicates that parents are more likely to keep close relationships with their children by expressing their love and kindness. Four items were included in this scale with "My parents always express love for me" for an example. The parental acceptance scale consists of four items with student's self-report of conceptualizations that their parents feel satisfactory with their children. Since the questions are in negative statements, such as "My parents make me think I am unnecessary." and "My parents are never satisfied with what I am doing," we inversely coded the response of each student to make the higher score indicate a higher level of acceptance. The parental consistency scale shows the degree of directions of parents to their children being consistent in diverse contexts. As four items of this scale also are in negative statements (e.g., "My parents often change rules for me."), the answer of these items were inversely coded. All of these scales were developed in Kim and Lee (38) and predictive validity was also confirmed based on the data of 507 middle school students in Korea.

School environmental variables consist of two independent scales; peer relationship and teacher relationship. A peer relationship scale shows how a student makes relationships with classmates, with eight items for positive relationships (e.g., "I can tell my secrets to my friends.") and five items for negative relationships (e.g., "My friends do not care for my difficulties."). To make the higher score of this scale indicate more agreeable

peer relationships, we inversely coded the answers of items negatively stated. This scale was validated in Bae et al. (39) by sampling 393 middle and high school students in Korea. Lastly, a teacher relationship scale consists of 14 items that shows whether teachers are credible, available, acceptable, and sensitive to the needs of each student (e.g., "My teacher respects my opinion," "My teacher waits for me until I answer the question."). The higher the score of this scale, the more the students are likely to have good relationships with their teachers. Kim and Kim (40) validated this scale based on the data of 2,056 individuals from elementary and middle school in Korea. All home and school environmental variables were constructed to be 4-Likert scales (1 = strongly disagree, 4 = strongly agree), and the reliability of each scale was also satisfactory (see **Table 1**).

Statistical Analysis

For the statistical analysis, we adopted Latent Profile Analysis (LPA) as a primary research method. LPA enables researchers to capture substantial groups of people whose responses to certain indicators are similar and to identify unobserved homogeneity or heterogeneity in a population (41). LPA is often called a method with a person-centered approach due to its focus on relationships between people, instead of relationships between variables (42).

In advance of performing LPA, processed in the statistical program SPSS 22.0, descriptive statistics and correlation analyses were conducted (see **Tables 2**, **3**). These analyses were to confirm the general tendencies of raw data and whether the normality assumption for LPA is fulfilled. The normality assumption is fulfilled if the absolute value of skewness is lower than 2 and that of kurtosis is under 7 (21). According to **Table 2**, the descriptive statistics of all variables inserted in LPA successfully fulfilled the normality assumption. Furthermore, **Table 3** shows that all coefficients of the correlation analysis were statistically meaningful ($p < 0.001$ for each correlation, $p < 0.05$ for family-wise error rate), and that all risk factors had negative relationships with contextual factors.

For conducting LPA, we followed a three-step approach originated from Asparouhov and Muthen (43), using the statistical program Mplus ver. 8. The first step is to determine how many latent profiles fit the data best, only including the indicators to prevent the covariates variables from affecting the classification of the latent profiles. To decide the number of profiles, AIC (Akaike's Information Criterion), BIC (Bayesian Information Criterion), saBIC (sample-size adjusted Bayesian Information Criterion) were utilized, and the lower values of those indicators indicate the better fit. In addition, we used LMR (Lo-Mendell-Rubin) and BLRT (Bootstrapped Likelihood Ratio Test) statistics, which compare model fits by testing significance level of difference between the current profile classification (N = k) and one less profile (N = k-1). If p-values of LMR and BLRT are below 0.05, the current model fit (N = k) has improved from the former model (N=k-1). Lastly, we also used entropy which is a value that represents the clarity of each profile membership, ranging from 0 to 1. Entropy that is below 0.60 indicates about 20% of the participants were mistakenly classified in profiles, whereas that over 0.8 shows the profiles of over 90% of participants were successfully determined (44). Entropy about 0.7 is generally accepted in LPA studies. For the second step, the most likely class is created, where every individual with the highest membership probability is assigned to a profile. In the third step, the contextual factors are incorporated to the model so as to conduct a multinomial logistic regression analysis within the Mplus program.

RESULTS

Risk Profiles of Adolescents

To solve the first research question, the latent profile model fit indicators were compared stepwise as **Table 4** shows. The values of AIC, BIC, saBIC, and entropy decreased as the number of latent profiles was progressively added. However, the significance levels of LMR and BLRT were above 0.05 in a 5-profile model, which shows that the 4-profile model has the best fitness among all models. In addition, the entropy for the 4-profile model was 0.75, showing the acceptable level of clarity across the four latent profiles. As the 4-profile model also showed that every individual with the highest membership probability is assigned to a profile (see **Table 5**), we determined the number of latent profiles as four.

Figure 1 visualizes four risk profiles in a line graph. The horizontal axis represents the categories of diverse risks faced by adolescents, while the vertical axis indicates the mean values of standardized scores for each indicator. Each profile had approximately 16.8% (434 individuals; Group 1), 12.8% (331 individuals; Group 2), 41.9% (1,084 individuals; Group 3), and 28.6% (741 individuals; Group 4) of the total sample. Group 1 was named a "high risk" group since students in this profile showed the highest mean values across all indicators, whereas we called Group 4 a "low risk" group as they had the lowest mean values. Group 2 and 3 were named "moderate risk" groups because their mean values were located between high and low risk groups, but their patterns were slightly different from each other. In group 2, the mean values of aggression, social withdrawal, and depression that show social-emotional-behavioral (SEB) risks are higher than those of academic motivation and behavior which indicate academic risks. In group 3, however, the mean values of academic (ACA) risks are higher than those of social-emotional-behavioral (SEB) risks. Thus, we can regard group 2 as a "moderate-SEB (M-SEB) risk" group and group 3 as a "moderate-ACA (M-ACA) risk" group. Among four groups, students in the high risk group are able to be identified as youth at-risk since those students showed the highest levels of risks across all indicators, and the percentage of students included in this group was 16.8%, which was identical with the typical proportion of students (15–25%) who should be referred to selective interventions within MTSS (4, 45).

Contextual Factors of Risk Profiles

A multinomial logistic regression was conducted in order to figure out whether and/or exactly what contextual factors have significant impacts on deciding youths at-risk who were included in the high risk group (see **Table 6**). When setting a low risk group as the reference, all home and school environmental variables had statistically significant impacts on falling into a high risk group. To be specific, the possibility to be included

TABLE 2 | The descriptive statistics of study variables.

	Variables	Mean	Standard deviation	Skewness	Kurtosis
Risk factors	Low academic motivation	1.96	0.74	0.53	−0.11
	Low academic behavior	1.95	0.64	0.30	−0.29
	Attention deficit	2.17	0.56	−0.06	−0.02
	Aggression	1.91	0.59	0.11	−0.54
	Social withdrawal	2.15	0.75	0.15	−0.61
	Depression	1.80	0.64	0.62	0.03
Home environment	Parental warmness	3.37	0.58	−0.54	−0.10
	Parental acceptance	3.23	0.62	−0.79	0.79
	Parental consistency	3.00	0.64	−0.26	−0.07
School environment	Peer relationship	3.13	0.43	−0.09	0.29
	Teacher relationship	2.81	0.50	−0.15	1.03

TABLE 3 | A correlation analysis of study variables.

	1	2	3	4	5	6	7	8	9	10
1	1									
2	0.643	1								
3	0.464	0.504	1							
4	0.399	0.399	0.605	1						
5	0.277	0.299	0.304	0.396	1					
6	0.409	0.378	0.391	0.596	0.552	1				
7	−0.316	−0.302	−0.252	−0.324	−0.195	−0.368	1			
8	−0.299	−0.257	−0.278	−0.347	−0.152	−0.348	0.458	1		
9	−0.343	−0.295	−0.337	−0.412	−0.256	−0.380	0.417	0.482	1	
10	−0.307	−0.345	−0.277	−0.381	−0.338	−0.381	0.343	0.306	0.299	1
11	−0.338	−0.342	−0.307	−0.297	−0.236	−0.312	0.374	0.210	0.237	0.390

1, low academic motivation; 2, low academic behavior; 3, attention deficit; 4, aggression; 5, social withdrawal; 6, depression; 7, parent warmness; 8, parent acceptance; 9, parent consistency; 10, peer relationship; 11, teacher relationship.

TABLE 4 | A latent profile analysis to identify risk profiles of Korean adolescents.

	AIC	BIC	saBIC	Entropy	LMR (*p*)	BLRT (*p*)	Percentage for each profile				
							1	2	3	4	5
1-profile	30736.35	30806.67	30768.54	-	-	-	100.0				
2-profile	26998.05	27109.38	27049.01	0.81	0.000	0.000	58.8	41.2			
3-profile	26132.63	26284.97	26202.36	0.76	0.001	0.000	50.4	27.4	22.2		
4-profile	25704.73	25898.09	25793.24	0.75	0.003	0.000	41.9	28.6	16.8	12.8	
5-profile	25445.56	25679.93	25552.84	0.75	0.274	0.000	38.3	27.6	18.9	9.0	6.2

in a high risk group can be 43.1% lower when one level of parental warmth is increased, 55.4% lower when one level of parental acceptance is increased, 85.8% lower when one level of parental consistency is improved, 94.1% lower when one level of peer relationship is enhanced, and 85.9% lower when one level of teacher relationship is improved. If we set M-ACA risk group as a reference, the possibility to become a high risk group can be 47.2% lower when one level of parental warmth is improved, 43.0% lower when one level of parental acceptance is enhanced, 50.2% lower when one level of parental consistency is increased, 88.2% lower when one level of peer relationship is improved, and 64.3% lower when one level of teacher relationship is enhanced. Lastly, when setting a M-SEB risk group as a reference, the possibility to become a high risk group can be 23.8% lower when one level of parental acceptance is improved, 54.0% lower when one level of parental consistency is enhanced, 64.3% lower when one level of peer relationship is increased, and 67.4% lower when one level of teacher relationship is improved, while parental warmth and consistency did not have significant impacts.

DISCUSSION

In the current study, we performed a latent profile analysis on risk profiles of Korean adolescents with the relation of contextual factors. Before describing some meaningful implications for future research and practice, we emphasize that the analysis was only derived from the 1st year data of KCYPS 2018, and the results should be taken into consideration with caution.

Risk Profiles of Korean Adolescents

We could identify four risk profiles of Korean adolescents: the high-risk group, the M-ACA risk group, the M-SEB risk group, and the low-risk group. These profiles were determined based on the major risk factors faced by Korean adolescents, encompassing social, emotional, behavioral, and academic domains. This analytic result supports the previous study, having classified the latent classes of students at-risk rated by their teachers; the overall high-risk group, social and behavioral risk group, and the academic risk group (33). The percentage of students included in the high-risk group was 16.8%, which corroborates the typical proportion of students (15–25%) who should be referred to the selective interventions in the MTSS as well (4, 45). Therefore, it can be concluded that through LPA, we were able to identify students in the high-risk group as youths at-risk who should be referred to more intensive instructions within MTSS. Youth at-risk identified from the current study showed the highest levels of risks among four risk profiles across social, emotional, behavioral, and academic domains. Through this result, MTSS, a comprehensive framework aimed to address the interplay of social, emotional, behavioral, and academic functioning in the classroom (24, 25), can be suggested as the most suitable educational service for youth at-risk.

TABLE 5 | Average latent profile probabilities for most likely latent profile membership (row) by latent profiles (column).

	Profile 1	Profile 2	Profile 3	Profile 4
Profile 1	0.919	0.000	0.040	0.041
Profile 2	0.000	0.863	0.019	0.118
Profile 3	0.070	0.015	0.788	0.127
Profile 4	0.026	0.060	0.065	0.848

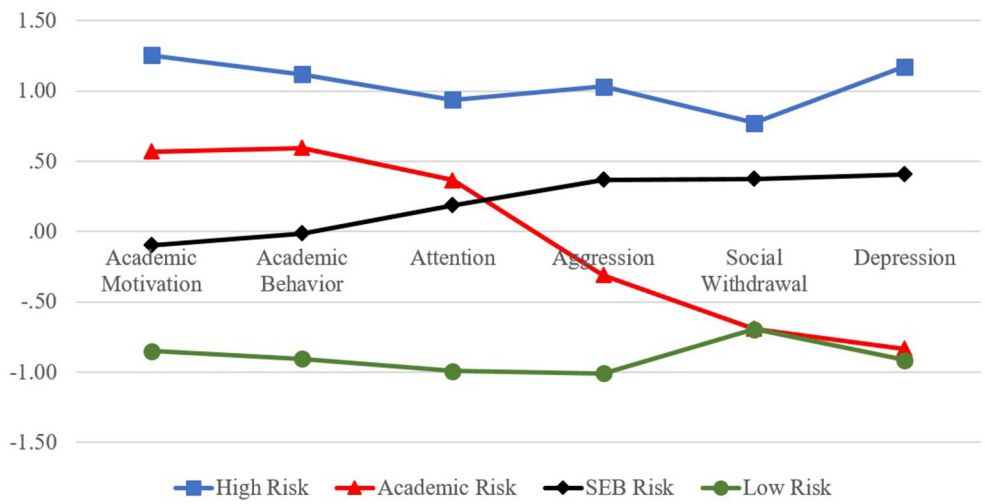

FIGURE 1 | Risk profiles of Korean adolescents.

TABLE 6 | Tests of multinomial logistic regressions using the three-step procedure.

	High risk VS. Low risk		High risk VS. M-ACA risk		High risk VS. M-SEB risk	
	Odds ratio	*P*-value	Odds ratio	*P*-value	Odds ratio	*p*-value
Home environment						
Parent warmth	0.569	0.003	0.528	0.010	0.762	0.072
Parent acceptance	0.446	0.000	0.570	0.018	0.762	0.036
Parent consistency	0.142	0.000	0.498	0.001	0.460	0.000
School environment						
Peer relationship	0.059	0.000	0.118	0.000	0.357	0.000
Teacher relationship	0.141	0.000	0.357	0.000	0.326	0.000

The groups written next to 'VS.' are used as reference groups in each regression.

It was also found that the M-SEB group showed higher risks in aggression, social withdrawal, and depression than in academic behavior and academic motivation, while the M-ACA group indicated the opposite result. Through this result, risk factors incorporated in the latent profile analysis can be easily classified into two clusters–one for the SEB risks and the other for the academic risks, and we can conclude that some students need more SEB support than academic one whereas, others need more academic support than SEB one. Therefore, it can be suggested that instructions in MTSS should be planned in two tracks, with one with services for academic functioning and the other for SEB adaptation. According to Briesch et al. (46), conceptual models for MTSS are often configured as a "double triangle," encompassing tiered interventions to enhance both academic and behavioral competencies. During the actual implementation, however, the nature of guidelines for MTSS mainly was based on academic domains of services, which led educators to assume that procedures for addressing academic challenges are identically applicable to SEB domains as well (47). We should note that there are some critical differences between the actual implementation of MTSS in academic and SEB domains in terms of types of interventions, tools and frequency for assessments, and criteria for assessing response to interventions (46, 48). Therefore, it is highly required to build systematic assessment and intervention systems centering on the unique characteristics of SEB challenges which can be distinguished from academic ones.

Luckily, recent studies attempted to develop standardized assessments and intervention programs customized to address student's SEB challenges within MTSS. For instance, Harrell-Williams et al. (49) developed a Behavioral and Emotional Screening System (BESS) to screen students who have problems in behavior and emotions and refer them to tier 2 interventions. Kilgus et al. (9) also devised a universal screening assessment tool named Social, Academic, and Emotional Behavior Risk Screener (SAEBRS), whose result shows student's social and emotional behavior level extracted from academic behavior. Additionally, there have been developed some tier 2 interventions targeting students with SEB challenges, such as Check-In/Check-Out (50) for improving social and behavioral competencies and the Resilience Education Program (51) for enhancing emotional competencies and addressing internalizing problems.

Unlike other risk factors, however, the level of attention deficit in the M-SEB group had no significant difference from that in the M-ACA group. This result demonstrates that the attention problems of students are highly likely to have comorbidity both with SEB and academic challenges, being the typical characteristics of defining youth at-risk. Therefore, adolescents suffering from being immersed in school lessons need to be referred to detailed assessments as soon as possible in order for the early identification of youth at risk.

Contextual Factors Affecting Risk Profiles

Home and school environmental factors, which were included as covariates in the LPA, significantly influenced the risk profiles of Korean adolescents. Specifically, the present study suggested that compared to both low and M-ACA risk groups, the students in the high-risk group were impacted by all contextual factors included in the research model. It was also found that compared to the M-SEB risk group, parental acceptance, parental consistency, peer and teacher relationships were also significantly affected the probability of deciding youth at-risk. These results support numerous former studies investigating the effect of home and environmental variables such as relationships with parents, peers, and teachers on school adjustment as well as the overall well-being of students (21, 22, 52, 53). According to Kim et al. (54), the inconsistent parenting attitude mediated the effect of school adjustment on student's life satisfaction, which consequently led students to low satisfaction in their lives overall. Furthermore, it was also demonstrated that school environmental factors such as relationships with peers and teachers had significant influences on students' mental health as well as overall self-concept that are crucial to school and adulthood adjustment (21, 23). Based on the results of former and current studies, we can thus conclude that home and school environmental variables, including relationships with parents, peers, and teachers, are highly recommended to be considered when planning the educational support for youth at-risk.

Although it is imperative to consider the necessity of adaptive instructions with a responsive decision-making process for each student within MTSS (27, 55), the adaptation has been implemented in a limited way. Majeika et al. (55) described two ways of adaptation: a horizontal adaptation which is based on student characteristics and contextual factors, and a vertical adaptation grounded on data indicating a student's response to intervention. As MTSS is initially designed to develop tiered intervention programs based on student's response to intervention, it has been common to consider a vertical adaptation process. However, teachers have often ignored the effect of contextual factors on student's performances and interventions within MTSS (27). In addition to the result of the current study that contextual factors have significant effects on deciding youth at-risk, we now have to take a more active stance toward horizontal adaptations when implementing MTSS in school settings.

One of the most effective ways to initiate horizontal adaptations is to manage social dynamics surrounding each student and classroom (29). Social dynamics indicate the social roles and relationships with significant others, and unhealthy social dynamics may inhibit students' performance despite being able to perform it (56). Hence, teachers must be accurately aware of social dynamics in classrooms and manage them to help operate instructional practices (57). The social dynamics management is thus aimed to provide students with opportunities to develop relationships with peers who support and complement one another's strengths and the development of new skills, beliefs, and values by teachers being attuned to the peer culture and social hierarchy and monitoring the dynamics of power in classrooms (32). In order to accomplish these goals, Farmer et al. (29) suggested a few strategies to manage classroom social dynamics as follows successfully: using information about the peer system to help guide classroom arrangement and behavior management strategies; monitoring whether students feel safe and socially comfortable in the classroom; changing contexts to prevent negative roles, interactive patterns, and social

relationships. Additionally, as interactions with parents became significant factors predicting youth at-risk, it is also necessary to intervene in social dynamics at home as well as in the classrooms. Kim (58) articulated that counseling and intervention strategies for parents of students at-risk should be different across students' major problems (e.g., low academic motivation and competencies, depressive symptoms, social withdrawal, and other hidden handicaps) and parenting types (e.g., controlling vs. permissive, autocratic vs. pushover). Although there have been several guidelines for managing social dynamics in classrooms and at home, we still need to develop how these strategies can be flexibly incorporated in general and targeted educational services within MTSS (32). This is what educators should strive for.

Limitations and Suggestions for Future Research

There were some limitations related to the data sources we used in this research. Due to the limited arrangement of variables included in the data, the number of risk factors was only six, which may be marginal to encompass all types of difficulties faced by adolescents. For example, it is more plausible to incorporate each student's actual academic performance to assess academic challenges accurately. However, academic motivation and behavior scales were alternatively used to identify students' academic risks because KCYPS 2018 did not provide information on students' actual academic performance. Similarly, although temperament risk factors such as effortful control may also significantly impact deciding youth at-risk (19, 20), they were not able to be included in the present study. The contextual factors included in this study were also limited. Other than teacher, peer, and parent relationships, the social-economic status of each family may have significantly influenced the development of risk factors. The following study thus needs to design more extensive models to identify youth at-risk by adding other risk and contextual variables.

Upon this, we only used the first-year data of KCYPS since participants were not obligated to report their levels of risks during the survey of the following year. In other words, there were a significant number of missing data in the second-year data, which led us to decide to use only the first-year data from middle school 1st graders. The risk profiles of middle school 1st graders may not reflect the general tendency of adolescents of all ages (12–18). Therefore, future research should incorporate older youths in the analysis to confirm the findings from the current research.

Lastly, the current study's findings can be more robust if corroborated by biological evidence such as changes in area and degree of brain activation observed by EEG or fMRI. Due to a lack of prior research discovering the effect of social relationships with peers, teachers, or parents on the biological markers of youth at-risk, the present study had limitations in predicting possible outcomes of horizontal adaptations. Hence, future studies need to demonstrate objective biomarkers that can be influenced by social dynamics of youth at-risk and predict expecting outcomes of horizontal adaptation in the long term.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The dataset is from the national survey by the National Youth Policy Institute in the Republic of Korea in 2018, and the authors do not have the right to release the dataset. Requests to access these datasets should be directed to JH, lifewizard@snu.ac.kr.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DK writing of the first and final draft of the manuscript, interpretation of analysis, concept and design of the research, and final approval for publication. JL writing of the first and final draft of the manuscript, acquisition of data, interpretation of analysis, concept and design of the research, and final approval for publication. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.796928/full#supplementary-material

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Corrigendum: Risk Profiles of Korean Adolescents in Relations With Contextual Factors: Implications for Multi-Tiered Systems of Support

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In the original article, there was an error in the supplementary material. Although the authors declared that they do not have the right to release the dataset in the Data Availability Statement, the raw dataset was mistakenly incorporated in the supplementary material. New supplementary material has been published which does not contain the data that the authors do not have the right to release.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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Pharmacological Enhancement of Extinction Retention in Non-stressed Adolescent Rats but Not Those Exposed to Chronic Corticosterone

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Individuals exposed to chronic adverse experiences in childhood and adolescence are at increased risk of developing neuropsychiatric illnesses such as mood and anxiety disorders. Symptoms of anxiety disorders can often be reduced through exposure therapy, which is based on the process of extinction. Although chronic stress in adolescence is known to exacerbate the impaired extinction of learned fear during this period of development, it remains unclear whether exposure to stressors in adolescence qualitatively affects the mechanisms underlying fear extinction. Brain-derived neurotrophic factor (BDNF) and its principle receptor, tropomyosin receptor kinase B (TrkB), are involved in neuroplasticity underlying fear extinction. The small-molecule TrkB agonist 7,8-dihydroxyflavone (7,8-DHF) improves fear extinction and reduces fear relapse (reinstatement) in adult mice when administered prior to extinction training but its effects in younger ages are unknown. In this study we tested whether 7,8-DHF enhances extinction retention and leads to less renewal in both stressed and non-stressed adolescent rats. Pre-extinction injection of 7,8-DHF led to lower levels of CS-elicited freezing in both the extinction and conditioning contexts in non-stressed adolescent male rats, but not in those given 7 days of corticosterone. These findings indicate that chronic stress interferes with the effectiveness of pharmacological agonism of TrkB in enhancing fear extinction in adolescence. A greater understanding of the mechanisms underlying extinction in adolescence and the effect of chronic corticosterone exposure on those mechanisms may inform a deeper understanding of the etiology and treatment of pediatric stress-related disorders.

Keywords: adolescent, extinction, rat, tropomyosin receptor kinase B, 7,8-dihydroxyflavone, chronic stress

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INTRODUCTION

Adolescence is often termed a period of "storm and stress" (Buchanan and Hughes, 2011). Further, stress-sensitive areas of the brain, such as the prefrontal cortex, hippocampus, and amygdala, undergo substantial modification during adolescence (Teicher et al., 2016), as do several hormonal systems, including the system primarily involved in responding to acute and chronic stressors [i.e., the hypothalamic-pituitary-adrenal (HPA) axis; Romeo, 2013]. These brain regions and hormonal

systems play an integral part in emotion regulation, a facet of cognition that is undergoing substantial development during adolescence (Hartley and Phelps, 2009). Hence, it is perhaps unsurprising that this period of development is one in which many psychiatric disorders, including anxiety disorders, first emerge (Beesdo et al., 2009). Furthermore, for adolescents exposed to adversity before the age of 18, the vulnerability of developing a stress-related disorder, either during adolescence or later in life, is increased (Edwards et al., 2003; Cabrera et al., 2007; Cloitre et al., 2019). It has been suggested that the link between adverse experiences in childhood and adolescence and the later development of psychiatric disorders like anxiety may be mediated by disruptions in an individual's capacity to regulate their emotions when faced with later stressors (Burns et al., 2010; Barlow et al., 2017; Cloitre et al., 2019). Moreover, the neural and physiological systems affected by chronic stress are also those involved in emotion regulation (McEwen et al., 2015). Given that adolescence is a period of development in which the neural systems important for emotion regulation are undergoing maturation, exposure to chronic stress may have particularly profound effects on the mental health of adolescents (Tottenham and Galván, 2016). Unfortunately, many adolescents are exposed to such adversity, with Kessler et al. (2010) reporting that 40% of people are exposed to chronic stress before adulthood. While there has been increased interest in the learning and memory processes involved in emotion regulation in adolescence in the last decade (Baker and Richardson, 2017; Cisler and Herringa, 2021), the impact of chronic stress on these processes is not well understood. In other words, although adolescents are thought to be particularly vulnerable to the effects of traumatic experiences, there is little research into the impact of such experiences on processes related to emotion regulation.

One important process of emotion regulation is extinction of learned fear (Sotres-Bayon et al., 2006). A particularly robust difference in learning and memory processes reported in adolescence is diminished extinction of Pavlovian fear conditioning. Pavlovian fear conditioning refers to a behavioral paradigm where an initially neutral cue is paired with an aversive stimulus (Unconditioned Stimulus; US). This results in the cue, now referred to as a conditioned stimulus (CS), eliciting conditioned fear responses (CRs). Extinction training refers to a procedure where the CS is repeatedly presented without the US, which leads to a reduction in the CRs (Anagnostaras et al., 2015). The retention of extinction can be assessed later by presenting the CS again and involves the retrieval of a safety memory that competes for expression with the original fear memory (Bouton, 2004; Lonsdorf et al., 2019). Diminished retention of cued fear extinction is reported in adolescent rats relative to older and younger animals despite a similar reduction in fear responses during extinction training while adolescent mice exhibit deficits in extinction learning and retention of both cued and context fear (for review see Bisby et al., 2021). Diminished learning or retention of cued fear extinction has also been reported in humans (e.g., Pattwell et al., 2012; Ganella et al., 2017). As the maintenance of extinction is a challenge for exposure-based treatments for clinical anxiety and fear-related disorders in youth and adults (Rauch et al., 2012; Vervliet et al., 2013; Kodal et al., 2018), understanding the processes which strengthen extinction retention in adolescence in animal and human laboratory studies may ultimately provide insight into clinical interventions to reduce excessive fear in this age group.

Preclinical research has identified several methods which enhance extinction retention in adolescent rats, broadly falling into behavioral and pharmacological interventions. One example of a behavioral approach is doubling the amount of extinction training given to adolescents, which leads to equivalent extinction retention as observed in adult animals (e.g., McCallum et al., 2010). In terms of a pharmacological adjunct, the partial NMDA receptor agonist D-Cycloserine (DCS) improves subsequent extinction retention in adolescent rats when administered immediately following extinction training (McCallum et al., 2010), similar to its effects in adults (Walker et al., 2002; Ledgerwood et al., 2003).

An important consideration in the use of behavioral or pharmacological interventions to enhance extinction is that exposure to chronic stress can affect their efficacy in adolescent rats (Stylianakis et al., 2019). Specifically, exposure to chronic stress during adolescence impairs extinction retention even after extended extinction training. For example, in one study chronic stress during early adolescence (27–33 days old) was modeled by having rats drink corticosterone-infused water for 7 days (Den et al., 2014). This type of stressor has been shown to mimic the neural and physiological effects of other types of stress, such as repeated restraint stress and chronic social stress (Luine et al., 1993; McKittrick et al., 2000; Cook and Wellman, 2004; Radley et al., 2006; Jeong et al., 2013; Hoffman et al., 2014; Kaplowitz et al., 2016). Adolescent rats exposed to corticosterone displayed significantly higher CS-elicited freezing at the extinction retention test, as compared to rats exposed to vehicle or water, which did not differ from each other, following extended extinction training (Den et al., 2014). In another set of experiments, Stylianakis et al. (2019) replicated those effects and further reported that pharmacological enhancement of extinction retention by DCS in adolescent rats was abolished when animals had been exposed to chronic corticosterone in their drinking water. These findings suggest that two methods that have been shown to ameliorate the extinction retention deficit in non-stressed adolescent rats, extended extinction training and DCS, do not facilitate extinction retention in adolescents exposed to chronic stress. Moreover, this work provides evidence for the idea that chronic stressor exposure during adolescence has particularly deleterious effects on extinction processes (i.e., similar effects of the chronic stress were not observed in younger or older rats).

Based on these findings, alternative methods to enhance extinction retention in stress-exposed adolescents need to be explored. In addition, awareness that chronic stress can impair extinction processes could be useful in clinical settings where excessive fears are targeted with extinction (i.e., exposure; Graham and Milad, 2011). Therefore, here we examined the potential of an alternative pharmacological adjunct, 7,8-dihydroxyflavone (7,8-DHF), to improve fear extinction retention in adolescent rats exposed to chronic corticosterone. This adjunct was chosen based on a report that the administration

of 7,8-DHF prior to extinction enhanced cued fear extinction in male mice (Tohyama et al., 2020), as well as a study which found that administration of 7,8-DHF prior to extinction reduced fear responses during extinction training in both non-stressed adult mice as well as those exposed to immobilization stress prior to fear conditioning (Andero et al., 2011). The non-stressed mice given 7,8-DHF also exhibited less relapse (i.e., reinstatement) of extinguished fear, compared to those given an injection of the vehicle. This adjunct is proposed to be a tropomyosin receptor kinase B (TrkB) agonist (Jang et al., 2010; Liu et al., 2014), and there is evidence 7,8-DHF upregulates phosphorylation of TrkB in the amygdala, a key region for extinction learning, when delivered systemically in mice (Andero et al., 2011). In the present study, we examined the efficacy of 7,8-DHF in facilitating fear extinction learning and retention (and reducing relapse) in non-stressed adolescent rats as well as those exposed to chronic corticosterone.

MATERIALS AND METHODS

Subjects

Subjects were 116 experimentally naïve male Sprague-Dawley rats, bred and housed in the School of Psychology at UNSW Sydney. Rats were maintained in a humidity- and temperature-controlled room on a 12-h light/dark cycle (lights on at 0700). Animals were weaned at postnatal day (P)21-P22 and housed with two or three other rats in plastic boxes (60 cm long × 30 cm wide × 12 cm high) with wire tops (total height 27.5 cm). A maximum of one animal per litter was allocated into each experimental group. Water and food were available *ad libitum*. Animals from a given stress condition were housed together, but were randomly allocated to drug condition (i.e., 7,8-DHF or vehicle). All animals were treated in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (8th Edition, 2013). The Animal Care and Ethics Committee at UNSW Sydney approved all procedures.

Apparatus

All behavioral procedures occurred in two sets of chambers (24 cm long × 30 cm wide × 21 cm high; Med Associates). One set of chambers was used as Context A and the other as Context B. Each chamber was fitted with a speaker to deliver a white-noise CS. Chambers were enclosed in sound-attenuating cabinets. Each cabinet was fitted with a camera on the rear wall through which behavior was digitally recorded *via* computer-based recording software (Blue Iris). Each cabinet also contained a ventilation fan that provided a low level of background noise (∼58 dB). CS and US presentations were controlled by Med-PC V software. The chambers were cleaned with tap water after each experimental session.

Context A

The two identical chambers referred to as Context A were constructed of stainless-steel walls with a Perspex door and ceiling. The floor consisted of stainless-steel rods spaced 16 mm apart. Underneath the rods was a stainless-steel tray containing corncob bedding. A clear Perspex sheet divided the chamber into two triangular spaces and the rat was placed into the side that housed the speaker. The only sources of lighting in Context A were red LEDs on the ceiling of the cabinet.

Context B

The Context B chambers were constructed of similar materials to Context A but they differed in terms of size, visual features, lighting, and flooring. Specifically, sheets of paper with 2.5 cm vertical black-and-white stripes covered the outside of the Perspex ceiling and door in these chambers. A clear Perspex sheet covered the grid floor and there was no Perspex divider in the Context B chambers. A white light was placed on top of the chambers to provide additional lighting (∼4 lux, Deglitch light meter QM1587) to the red light.

Procedure

Pellet Implantation

In experiments for Analysis 2, animals in the chronic stress condition were subcutaneously implanted with a 30 mg 7-day release corticosterone pellet (4.3 mg per day average corticosterone release; pellet was 7 mm in diameter) composed of a proprietary matrix of cholesterol, cellulose, lactose, phosphates, and stearates designed to facilitate continuous diffusion of corticosterone over 7 days (Innovative Research of America, Sarasota, FL, United States). The pellet implantation occurred 5 days before the start of the handling procedures (i.e., implantation on P28 ± 1 day) to ensure animals received 7 days of corticosterone exposure before fear conditioning. Animals housed together were implanted with pellets on the same day. Placebo pellets, purchased from the same supplier, were the same size and consisted of the same matrix without the corticosterone. Dose and duration of hormone administration were chosen based on the average daily dose consumed by rats across 7 days of corticosterone administration in drinking water in our previous studies on extinction in stressed adolescent rats (i.e., Den et al., 2014; Stylianakis et al., 2019). Before implantation of pellets, animals received a pre-emptive subcutaneous (s.c.) injection of the non-steroidal anti-inflammatory analgesic Carprofen (5 mg/kg; 1 ml/kg). Following this, rats were anaesthetized by being placed in a chamber connected to a gas nozzle delivering 1–5% isoflurane in oxygen (33 ml/min). Once the rat was anaesthetized, it was removed from the induction chamber and placed in a nosepiece that supplied the isoflurane in oxygen throughout the surgery, which did not last more than 10 min (and usually much less than that). The body temperature of the animal was maintained during and post-surgery with the use of a heat pad. Following the onset of stable anesthesia (as verified by paw pinch), an injection of 0.1 ml of the local anesthetic bupivacaine (0.5%) was given at the site of incision. Using a scalpel blade, a ∼2 cm incision was made in the skin above the scapula. The skin was pulled open using surgical skin hooks, and a corticosterone or placebo pellet was implanted 0.5 cm under the incision between the skin and muscle tissue. After the pellet had been inserted, the skin was sewn together with surgical sutures and surgical staples and Vetbond Tissue Adhesive was applied to the incision area. Post-surgical infection was minimized by injecting rats with a

prophylactic dose of procaine penicillin (150 mg/ml, 0.6 ml/kg s.c.). The wellbeing of the rats was monitored daily for 7 days, which included taking their weight.

7,8-DHF Administration

Rats were given an intraperitoneal (i.p.) injection of 5 mg/kg 7,8-DHF (7,8-dihydroxyflavone hydrate; Sigma-Aldrich D5446-10MG) dissolved in 17% dimethyl sulfoxide (DMSO; Sigma) and phosphate-buffered saline (PBS; pH 7.2; Andero et al., 2011) or vehicle (17% DMSO in PBS). After being dissolved in DMSO and PBS, the 7,8-DHF solution was kept refrigerated for up to 48 h. 7,8-DHF was administered 1 h prior to extinction. The injection was administered as a volume of 1 ml/kg.

Behavioral Procedures

The behavioral procedures started when animals were between P32 and 34, and consisted of handling and pre-exposure, fear conditioning, extinction training, an extinction-retention test, and a renewal test. Each procedure was separated by ∼24 h and occurred around the same time of day (between 15:00 and 17:00 to ensure that all animals were at a similar point in their diurnal corticosterone cycle; Maywood et al., 2007).

Handling and Pre-exposure

Rats were handled for 4 min each day for two consecutive days. On each of these days, all rats were pre-exposed to Context A for 8 min to familiarize them with this context.

Fear Conditioning

Fear conditioning occurred in Context A. Following a 2-min adaptation period, rats were given three pairings of a white noise CS (7 dB above background noise levels, 10 s duration) and a scrambled foot-shock US (0.45 mA, 1 s duration). The US was presented in the last second of the CS so that the stimuli co-terminated. The three CS-US pairings were separated by inter-trial intervals (ITIs) of 135 and 85 s (mean ITI was 110 s). These conditioning parameters were based on those used by Stylianakis et al. (2019).

Extinction Training

Extinction training took place in Context B to minimize the possibility that freezing at extinction could be attributed to learned fear of the context, as opposed to fear of the CS. After a 2-min adaptation period, rats received 30 non-reinforced presentations of the white noise CS (10 s each, 10 s ITI).

Extinction Retention Test

Extinction retention was tested in Context B. Following a 2-min adaptation period, rats received a 2-min CS presentation. The longer CS duration at test than at conditioning and extinction is a standard procedure in many of our studies on fear extinction retention in developing and adult rats (e.g., McCallum et al., 2010). However, as noted in a recent systematic review, adolescent rats exhibit comparable impairment in extinction whether the CS is presented continuously for 2 min or *via* multiple 10 s presentations (see Bisby et al., 2021).

Renewal Test

Renewal was tested in Context A (i.e., ABA renewal was assessed). Following a 2-min adaptation period, rats received a 2-min CS presentation.

Scoring

Freezing was operationalized as the absence of movement other than that necessary for respiration (Fanselow, 1980). Rats were scored as freezing or not freezing every 3 s during the adaptation (pre-CS) period as well as the CS presentations at conditioning, extinction, the extinction retention test, and the renewal test. The percentage of time spent freezing was calculated for each animal, with percentage of time freezing calculated for each of the three conditioning trials, five blocks at extinction (with each block consisting of six extinction trials), and the extinction retention and renewal tests. A random sample (∼30%) of the CS-elicited freezing at the extinction retention and renewal tests was cross-scored by an individual who was blind to the experimental condition of subjects. Inter-rater reliability was very high (r = 0.94–0.96 across the experiments reported here).

Adrenal Glands and Bodyweights

A subset of animals implanted with a corticosterone (n = 25, 13 injected with 7,8-DHF; included in Analysis 2) or placebo pellet (n = 17, 7 injected with 7,8-DHF; included in Analysis 1) were weighed on the day of extinction training and following the last behavioral test before euthanasia using carbon dioxide. The animals' abdomens were cut laterally to expose the kidneys and the adrenal glands were excised from above the kidney with visible fat removed. The adrenal glands were weighed as a pair [on a Mettler Toledo, MTL 025-MET balance; Readability (d) = 0.1 mg].

Analysis

The aim of this study was to determine the efficacy of 7,8-DHF in ameliorating the extinction retention deficit in non-stressed adolescent rats and, if so, then test the efficacy of this adjunct in chronically stressed adolescent rats. Two overarching analyses were conducted, each involving pooled data from three experiments with vehicle and 7,8-DHF groups (see **Supplementary Material** for numbers of animals per experiment included in the analyses). Analysis 1 was conducted on data from experiments with non-stressed adolescent rats. In all three of those experiments, adolescent rats were handled for 2 days before undergoing conditioning 24 h later. The following day, the rats were injected with either 7,8-DHF or vehicle 1 h before extinction training, and 24 h after this they underwent an extinction retention test before undergoing a renewal test the following day. A subset of rats [n = 8 injected with 7,8-DHF (out of a total of n = 29 animals in the final data set), n = 11 injected with vehicle (out of a total of n = 33 in the final data set)] included in Analysis 1 were implanted with a placebo pellet at P28 (±1 day), 5 days before the first day of handling. Analysis 2 compared data collected from rats implanted with a corticosterone pellet at P28 (±1 day), which all underwent the same behavioral procedure 5 days later as in Analysis 1. The aim of Analysis 1 was to examine the efficacy of 7,8-DHF on extinction retention in non-stressed

adolescent rats, while the aim of Analysis 2 was to examine the efficacy of 7,8-DHF on rats exposed to chronic corticosterone.

All statistical analyses were conducted using SPSS Version 26. A significance value of $p = 0.05$ was applied to all analyses. In all analyses, the experiment number (coded as a nominal variable) was included as a factor to detect whether any group main effects or interactions varied by the experimental replication. Pre-CS freezing data at each session was analyzed using ANOVA with group (vehicle or 7,8-DHF) and experiment as between-subjects factors. CS-elicited freezing during conditioning and extinction were analyzed using separate mixed-model ANOVAs with group and experiment as between-subjects factors and trial or block of six CSs as a repeated measure factor for conditioning and extinction analyses, respectively. When the assumption of sphericity was violated for repeated measure ANOVAs, the Greenhouse-Geisser procedure was followed to adjust degrees of freedom and p values. CS-elicited freezing at the extinction retention and renewal tests were analyzed using separate ANOVAs with group and experiment as between-subjects factors. Given that renewal can be viewed as the degree of relapse outside the extinction context, a subsequent mixed-model ANOVA compared freezing across groups across tests, with test as a repeated measures factor. Interactions were explored with simple main effects. Bodyweight and adrenal gland weight as a percentage of bodyweight were analyzed with 2 × 2 ANOVAs with factors of drug (vehicle or 7,8-DHF) and pellet (placebo or corticosterone). Measures of effect sizes are also given (partial η^2 for the above analyses where small effect size = 0.001, medium effect size = 0.059, and large effect size = 0.138; Richardson, 2011).

Exclusion criteria were applied such that any rat that did not show evidence of learning the CS-US association at conditioning (<6% freezing on block 1 of extinction training) or had failed to learn during extinction (> 94% freezing across the final four blocks of extinction training) was excluded from the analysis. This resulted in the exclusion of nine rats from the 7,8-DHF group in Analysis 1, four rats from the 7,8-DHF group in Analysis 2, and one rat from the vehicle group in Analysis 2. In addition, the extinction data of three rats in the 7,8-DHF group and the renewal results of three rats in the control group of Analysis 1 were not included in the analysis due to experimenter error (e.g., recording failure). Furthermore, three of the rats that had their adrenal glands excised did not have their weight recorded at 2 days post-pellet washout due to errors in weight recording.

RESULTS

Analysis 1

We initially compared the behavioral data of those implanted with a placebo pellet to those not implanted with a pellet in rats injected with 7,8-DHF or vehicle. These analyses confirmed that placebo pellet implantation did not affect behavior during any pre-CS period, conditioning, extinction, extinction retention or renewal [7,8-DHF group: largest $F_{(3.12,74.79)} = 2.38$, $p = 0.074$, $\eta_p^2 = 0.090$, extinction block by pellet interaction; vehicle group: largest $F_{(1,31)} = 2.38$, $p = 0.13$, $\eta_p^2 = 0.071$, pellet effect for conditioning pre-CS]. Therefore, the subsequent analyses disregarded whether animals had pellets or not.

Pre-CS

Table 1 provides levels of pre-CS freezing across sessions for data included in Analysis 1. Pre-CS freezing did not differ between groups at conditioning [$F_{(1,56)} = 1.37$, $p = 0.25$, $\eta_p^2 = 0.024$], extinction training [$F_{(1,53)} = 0.27$, $p = 0.61$, $\eta_p^2 = 0.005$], the extinction retention test [$F_{(1,56)} = 3.39$, $p = 0.071$, $\eta_p^2 = 0.057$], or the renewal test [$F_{(1,53)} = 0.71$, $p = 0.79$, $\eta_p^2 = 0.001$]. An effect of experiment or interaction of experiment with group was not detected at conditioning, the extinction retention test, or the renewal test [largest $F_{(2,53)} = 3.00$, $p = 0.058$, $\eta_p^2 = 0.102$, experiment main effect at renewal]. Pre-CS freezing in the 7,8-DHF and vehicle groups varied at extinction training across experiments [experiment effect: $F_{(2,53)} = 1.24$, $p = 0.30$, $\eta_p^2 = 0.045$; interaction: $F_{(2,53)} = 3.57$, $p = 0.035$, $\eta_p^2 = 0.119$] such that the pre-CS freezing was slightly higher in the vehicle controls ($M = 10.28$) relative to the 7,8-DHF group ($M = 1.25$) in one out of three experiments [$F_{(1,53)} = 5.40$, $p = 0.024$, $\eta_p^2 = 0.092$; other Fs ≤ 1.97, $p \leq 0.166$, $\eta_p^2 \leq 0.036$]. Overall, these results suggest that pre-CS freezing was relatively low across most sessions and was largely unaffected by group.

Conditioning and Extinction

Figures 1A,B show that the 7,8-DHF and vehicle group exhibited a comparable increase in CS-elicited freezing during conditioning and a comparable decrease in CS-elicited freezing across extinction training. This description was confirmed with a mixed-model ANOVA revealing a trial main effect at conditioning [$F_{(2,112)} = 122.70$, $p < 0.001$, $\eta_p^2 = 0.687$] but no group or experiment effects or interactions [largest $F_{(2,56)} = 1.31$, $p = 0.28$, $\eta_p^2 = 0.045$, experiment effect].

A mixed-model ANOVA of the extinction training data detected a block main effect [$F_{(2.76,146.28)} = 48.34$, $p < 0.001$, $\eta_p^2 = 0.477$], but no main effects of group [$F_{(1,53)} = 2.48$, $p = 0.12$, $\eta_p^2 = 0.045$] or experiment [$F_{(2,53)} = 0.24$, $p = 0.79$, $\eta_p^2 = 0.009$], nor an interaction of block by group [$F_{(2.76,146.28)} = 0.52$, $p = 0.65$, $\eta_p^2 = 0.010$]. The effects of block and group did not vary by experiment [block by experiment interaction: $F_{(5.52,146.28)} = 1.02$, $p = 0.41$, $\eta_p^2 = 0.037$; group by experiment interaction: $F_{(2,53)} = 0.21$, $p = 0.82$, $\eta_p^2 = 0.008$]. Whilst a block by group by experiment interaction was detected [$F_{(5.52,146.28)} = 3.54$, $p = 0.003$, $\eta_p^2 = 0.118$], follow-up ANOVAs with simple main effects examining group differences across block separately across experiments did not reveal any meaningful differences in the

TABLE 1 | Mean (SEM) pre-CS freezing across sessions for data included in Analysis 1.

	Vehicle $n = 33$	7,8-DHF $n = 29$
Conditioning	0.83 (0.39)	0.34 (0.20)
Extinction	3.86 (1.88)	3.08 (1.05)
Extinction retention test	7.96 (2.53)	2.41 (0.73)
Renewal test	5.33 (2.00)	6.64 (2.28)

Due to missing cases, n = 26 at extinction training in the 7,8-DHF group and n = 30 in the vehicle group at the renewal test.

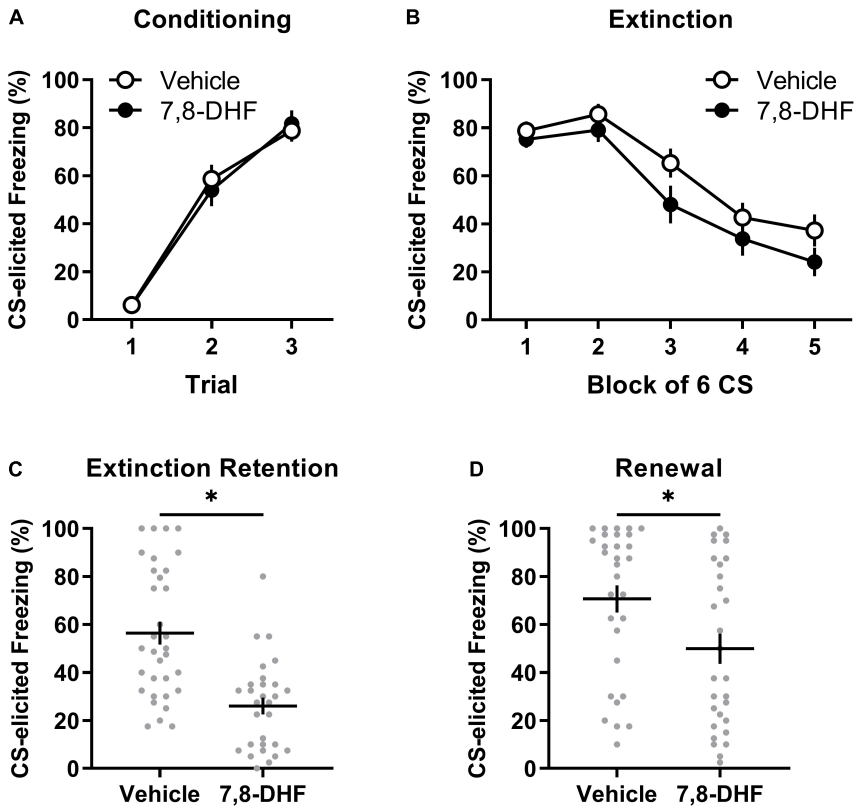

FIGURE 1 | Adolescent non-stressed rats exhibit lower levels of freezing when tested in either the extinction or conditioning contexts when 7,8-DHF is combined with extinction training. Data included in Analysis 1 are represented by mean (±SEM) levels of CS-elicited freezing at Conditioning **(A)** and Extinction **(B)**. CS-elicited freezing data at the Extinction Retention **(C)** and Renewal tests **(D)** are shown as individual dot plots with mean (±SEM). Asterisk represents significant ($p < 0.01$) group difference. Group sizes were $n = 33$ for vehicle and $n = 29$ for 7,8-DHF with the exception of $n = 26$ for 7,8-DHF at extinction training and $n = 30$ for vehicle at the renewal test.

rate of extinction between 7,8-DHF or vehicle groups; the 7,8-DHF group ($M = 20.56$) had significantly lower freezing than the vehicle group ($M = 51.24$) only at block 4 in one experiment ($p = 0.033$). Overall, these results indicate that 7,8-DHF did not affect average levels of CS-freezing or the rate of extinction.

Extinction Retention Test

Figure 1C illustrates that rats injected with 7,8-DHF before extinction training had lower levels of CS-elicited freezing at the extinction retention test compared to those injected with vehicle, as confirmed by a group main effect [$F_{(1,56)} = 25.91$, $p < 0.001$, $\eta_p^2 = 0.316$]. The group effect was consistent across experiments [largest $F_{(2,56)} = 0.60$, $p = 0.55$, $\eta_p^2 = 0.021$, group by experiment interaction]. This suggests that 7,8-DHF improved extinction retention in non-stressed adolescent rats.

Renewal

There was a significant difference in level of CS-elicited freezing between groups, with those injected with 7,8-DHF exhibiting lower levels than those injected with vehicle, suggesting less renewal in the 7,8-DHF-treated group [$F_{(1,53)} = 7.40$, $p = 0.009$, $\eta_p^2 = 0.122$, see **Figure 1D**]. The group difference was consistent across experiments [experiment effect: $F_{(2,53)} = 2.42$, $p = 0.10$, $\eta_p^2 = 0.084$; group by experiment interaction: $F_{(2,53)} = 1.42$, $p = 0.25$, $\eta_p^2 = 0.051$].

Given that renewal can be quantified as the degree of relapse when performance is tested outside of the extinction training context, a subsequent analysis examined whether each group had significant changes in freezing from the retention test (Context B) to the renewal test (Context A). A mixed-model ANOVA on CS-elicited freezing was conducted with drug (7,8-DHF or vehicle) as a between-group factor and test (extinction retention test or renewal) as a within-subjects factor. This analysis revealed a main effect of test [$F_{(1,57)} = 21.37$, $p < 0.001$, $\eta_p^2 = 0.273$], indicative of renewal, and a main effect of drug [$F_{(1,57)} = 17.86$, $p < 0.001$, $\eta_p^2 = 0.239$], but no significant test by drug interaction [$F_{(1,57)} = 2.18$, $p = 0.15$, $\eta_p^2 = 0.037$]. These results confirm that, on average, 7,8-DHF reduced post-extinction freezing but suggest that both 7,8-DHF and vehicle groups had a comparable degree of renewal of fear outside of the extinction context.

Overall, the results of this analysis demonstrate that 7,8-DHF administered before extinction training does not affect within-session extinction but reduces fear responses at subsequent extinction retention and renewal tests in non-stressed adolescent rats. These results suggest 7,8-DHF enhances the consolidation of the extinction memory.

Analysis 2

This analysis involved adolescent rats chronically exposed to corticosterone (*via* an implanted, slow-release pellet). Twenty-four rats were injected with 7,8-DHF and sixteen with vehicle.

Pre-CS

As shown in **Table 2**, pre-CS freezing did not differ between groups at conditioning [$F_{(1,35)} = 0.00$, $p = 1.00$, $\eta_p^2 = 0.000$], extinction training [$F_{(1,35)} = 0.79$, $p = 0.38$, $\eta_p^2 = 0.022$], extinction retention test [$F_{(1,35)} = 2.25$, $p = 0.14$, $\eta_p^2 = 0.060$], or renewal [$F_{(1,35)} = 0.61$, $p = 0.44$, $\eta_p^2 = 0.017$]. Furthermore, there were no effects of experiment or group by experiment interactions during pre-CS freezing at conditioning, extinction training, extinction retention test, or renewal [largest $F_{(1,35)} = 2.89$, $p = 0.10$, $\eta_p^2 = 0.076$, group by experiment interaction at extinction training].

Conditioning and Extinction

Figures 2A,B show that the 7,8-DHF and vehicle groups exhibited a comparable increase in CS-elicited freezing during conditioning and a comparable decrease in CS-elicited freezing across extinction training. This description of the results was confirmed with a mixed-model ANOVA revealing a trial main effect at conditioning [$F_{(2,70)} = 58.16$, $p < 0.001$, $\eta_p^2 = 0.624$] with no group or experiment effects or interactions being detected [largest $F_{(2,35)} = 2.46$, $p = 0.10$, $\eta_p^2 = 0.123$, experiment effect].

A mixed-model ANOVA of the extinction data detected a block main effect [$F_{(3.03,105.94)} = 17.29$, $p < 0.001$, $\eta_p^2 = 0.331$] and an experiment effect [$F_{(2,35)} = 3.47$, $p = 0.042$, $\eta_p^2 = 0.166$]. However, Tukey's *post hoc* tests on the experiment main effect did not detect any significant differences in average freezing across experiments (smallest $p = 0.051$). No effect of group or interactions were detected [largest $F_{(1,35)} = 2.81$, $p = 0.10$, $\eta_p^2 = 0.074$, group by experiment interaction].

Extinction Retention Test

As shown in **Figure 2C**, rats injected with 7,8-DHF did not exhibit significantly different levels of CS-elicited freezing compared to those injected with vehicle [$F_{(1,35)} = 0.001$, $p = 0.97$, $\eta_p^2 = 0.000$]. This suggests that 7,8-DHF did not improve extinction retention in chronically stressed adolescent rats. While there was no effect of experiment [$F_{(2,35)} = 1.53$, $p = 0.23$, $\eta_p^2 = 0.080$], there was a significant group by experiment interaction [$F_{(1,35)} = 4.20$, $p = 0.048$, $\eta_p^2 = 0.107$]. This interaction was further explored by simple main effects, which found no significant effect of group within each experiment [largest $p = 0.064$, 95% CI = (−1.28, 42.95)], suggesting that group differences within experiments were not significant.

TABLE 2 | Mean (SEM) pre-CS freezing across sessions for data included in Analysis 2.

	Vehicle *n* = 16	7,8-DHF *n* = 24
Conditioning	1.41 (0.82)	1.04 (0.94)
Extinction	7.21 (4.62)	7.42 (2.98)
Extinction retention test	12.50 (5.76)	3.13 (1.15)
Renewal test	12.03 (5.87)	3.44 (1.80)

Renewal

The groups did not differ in level of CS-elicited freezing on the renewal test [$F_{(1,35)} = 1.30$, $p = 0.26$, $\eta_p^2 = 0.036$, see **Figure 2D**]. The group difference was consistent across experiments [experiment effect: $F_{(2,35)} = 1.15$, $p = 0.33$, $\eta_p^2 = 0.062$; group by experiment interaction: $F_{(1,35)} = 0.13$, $p = 0.72$, $\eta_p^2 = 0.004$].

As in Analysis 1, a subsequent mixed-model ANOVA examined whether each group had significant changes in CS-elicited freezing from the retention test (Context B) to the renewal test (Context A). This ANOVA had drug (7,8-DHF or vehicle) as a between-group factor and test (extinction retention test or renewal) as a within-subjects factor. This analysis revealed a main effect of test [$F_{(1,38)} = 8.21$, $p = 0.007$, $\eta_p^2 = 0.178$], indicative of renewal, but no main effect of drug [$F_{(1,38)} = 3.01$, $p = 0.09$, $\eta_p^2 = 0.073$] or drug by test interaction [$F_{(1,38)} = 0.55$, $p = 0.47$, $\eta_p^2 = 0.014$]. These results suggest that both 7,8-DHF and vehicle groups had a comparable degree of renewal of fear outside of the extinction context.

Adrenal Glands and Bodyweight

Adrenal weights differed between groups, with the animals implanted with corticosterone pellets ($n = 25$) having smaller adrenals as a percentage of bodyweight compared to those implanted with the placebo pellets [$n = 17$; $F_{(1,38)} = 49.23$, $p < 0.001$, $\eta_p^2 = 0.564$, as shown in **Figure 3A**]. Relative to those implanted with placebo pellets, animals with corticosterone pellets had lower bodyweight 2 days after corticosterone treatment cessation [$F_{(1,35)} = 4.12$, $p = 0.050$, $\eta_p^2 = 0.105$, see **Figure 3B**]; however, bodyweight did not differ between groups four days after treatment cessation [$F_{(1,38)} = 1.84$, $p = 0.18$, $\eta_p^2 = 0.046$, see **Figure 3C**]. There were no significant differences between adrenal gland weight and bodyweight at either 2 or 4 days washout in animals injected with 7,8-DHF or vehicle in either the corticosterone-exposed group or the group exposed to placebo [largest drug effect or interaction: $F_{(1,38)} = 1.03$, $p = 0.32$, $\eta_p^2 = 0.026$, drug effect for adrenal glands as a percentage of bodyweight].

DISCUSSION

The overarching aim of the experiments reported in this paper was to firstly determine the efficacy of the TrkB agonist 7,8-DHF in ameliorating the extinction retention deficit in non-stressed adolescent rats. Upon finding that 7,8-DHF did indeed improve extinction retention in non-stressed adolescents, we sought to examine whether 7,8-DHF was efficacious in ameliorating the extinction retention deficit in chronically stressed adolescent rats. Compared to vehicle, 7,8-DHF administration (i.p.) 1 h before extinction training facilitated extinction retention (as indicated by lower levels of CS-elicited freezing) in both the extinction and the conditioning contexts in non-stressed adolescent rats (Analysis 1). However,

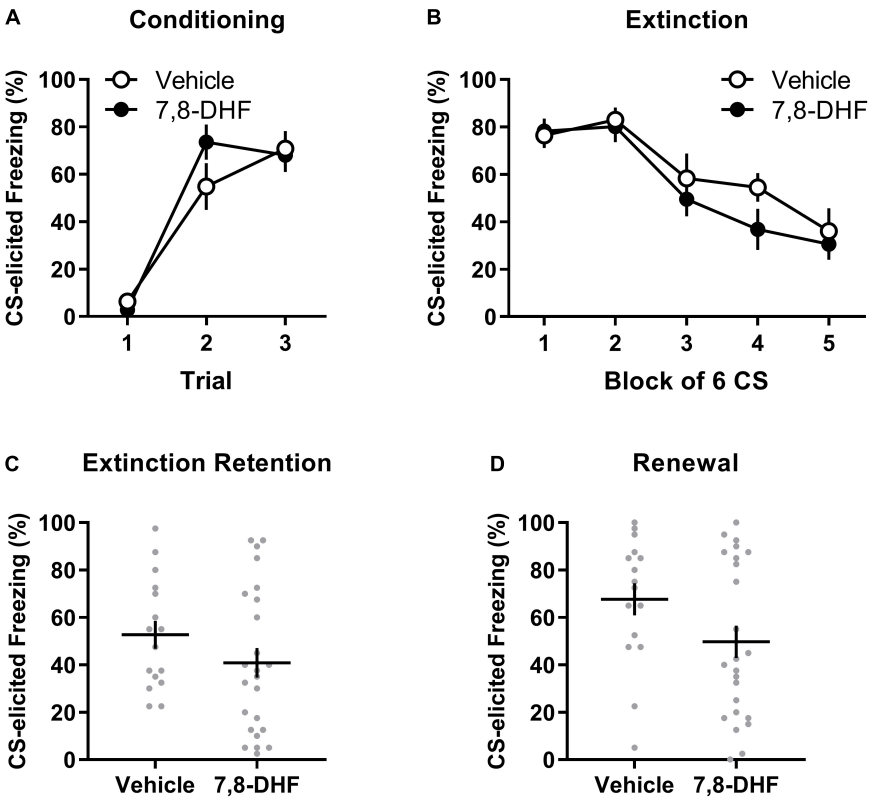

FIGURE 2 | 7,8-DHF combined with extinction training does not affect CS-elicited freezing during extinction training or tests of extinction retention and renewal in adolescent rats exposed to corticosterone. Data included in Analysis 2 are represented by mean (±SEM) levels of CS-elicited freezing at Conditioning **(A)** and Extinction **(B)**. CS-elicited freezing data at the Extinction Retention **(C)** and Renewal **(D)** tests are shown as individual dot plots with mean (±SEM). Group sizes were $n = 16$ for vehicle and $n = 24$ for 7,8-DHF.

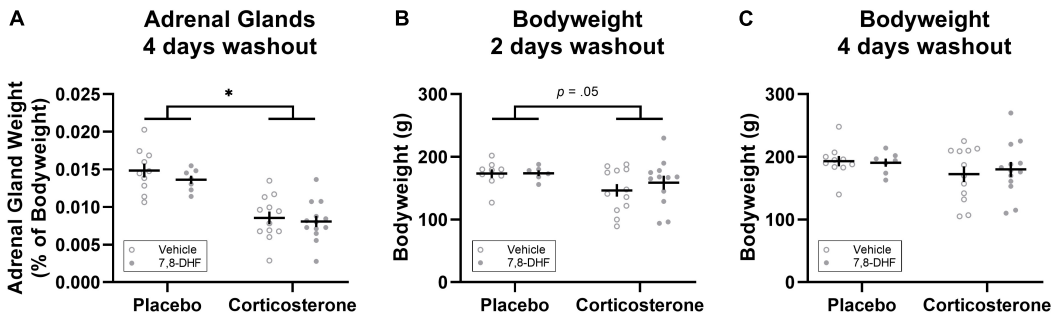

FIGURE 3 | Corticosterone pellet exposure reduced adrenal gland weight as a percentage of bodyweight **(A)** and bodyweight 2 days after treatment cessation **(B)** but did not affect bodyweight 4 days after treatment cessation **(C)** relative to placebo treatment. Data is shown as individual dot plots with mean (±SEM). Asterisk represents significant ($p < 0.001$) group difference. Group sizes were $n = 17$ for the placebo (vehicle $n = 10$, 7,8-DHF $n = 7$) and $n = 25$ for the corticosterone (vehicle $n = 12$, 7,8-DHF $n = 13$) group at 4 days washout, and $n = 15$ for the placebo (vehicle $n = 9$, 7,8-DHF $n = 6$) and $n = 24$ for the corticosterone (vehicle $n = 12$, 7,8-DHF $n = 12$) group at 2 days washout.

7,8-DHF administration had no impact in chronically stressed adolescent rats (i.e., those implanted with a 7-day-release corticosterone pellet; Analysis 2). These results contrast with those of Andero et al. (2011) and Tohyama et al. (2020) that 7,8-DHF enhanced within-session extinction in non-stressed adult mice and those exposed to immobilization stress. The possibility of a species difference is supported by the consistency of our results with reports that genetic antagonism of TrkB-mediated signaling in the amygdala of rats impairs the retention of fear extinction whilst leaving the acquisition of extinction intact (Chhatwal et al., 2006). A comparison of the results of the present study across the stressed (i.e., corticosterone-exposed) and non-stressed conditions indicates that a history of elevated stress hormone exposure interferes

with the efficacy of 7,8-DHF in enhancing the maintenance of fear extinction.

Past research has shown that, compared to juvenile and adult animals, non-stressed adolescents have diminished extinction retention (McCallum et al., 2010; Pattwell et al., 2012; Bisby et al., 2021). However, this extinction retention deficit can be ameliorated by an injection of a partial NMDA receptor agonist (i.e., DCS) or giving extended extinction training (McCallum et al., 2010). In contrast, neither of these treatments facilitate extinction retention in adolescent rats exposed to 7 days of corticosterone in their drinking water (Den et al., 2014; Stylianakis et al., 2019). In the present study, 7,8-DHF was also found to facilitate extinction retention in non-stressed adolescents but not in rats exposed to chronic elevated levels of corticosterone (*via* slow release implanted pellets). Therefore, it is clear that chronic corticosterone exposure diminishes the effectiveness of at least one behavioral and two pharmacological approaches to enhancing extinction retention in adolescence.

One potential explanation for why chronic corticosterone reduces the maintenance of fear extinction in adolescent rats is that such exposure downregulates subunits of the NMDA receptors within critical brain regions that are necessary for extinction consolidation. The activation of NMDA receptors and their downstream signaling cascades (e.g., mitogen activated protein kinases) are crucial for the protein synthesis underlying the formation of long-term memories, such as extinction memories, at least in adult animals (Burgos-Robles et al., 2007; Orsini and Maren, 2012). NMDA receptors are also important for extinction retention in non-stressed adolescents, but only after extended extinction training or an injection of DCS (see Baker and Richardson, 2017). One pathway through which BDNF's binding to TrkB receptors is hypothesized to facilitate extinction is by modulating glutamate release, resulting in increased glutamate binding to NMDA receptors, which in turn increases synaptic plasticity (Andero et al., 2011; Andero and Ressler, 2012). However, there is evidence to suggest that corticosterone exposure decreases the expression of NMDA receptor subunits in the prefrontal cortex. For example, Gourley et al. (2009) found that levels of the NMDA receptor subunit NR2B were decreased in the ventral medial prefrontal cortex (vmPFC) of adult rats that exhibited impaired extinction as a result of chronic corticosterone exposure, with the vmPFC being a region of the brain that is particularly important for extinction retention (Quirk et al., 2006). Moreover, NR2B levels in the vmPFC were correlated with extinction retention, with lower levels of NR2B being associated with poorer extinction retention. Should corticosterone exposure during adolescence also lead to a decrease in the NMDA receptor subunit NR2B, then this could be the mechanism by which the efficacy of extended extinction, DCS, and 7,8-DHF in improving extinction retention in adolescent rats is reduced (Den et al., 2014; Stylianakis et al., 2019; the present study). In order to test this hypothesis, future research could compare the phosphorylation of NMDA receptors following extended extinction, 7,8-DHF, and DCS exposure in non-stressed and chronically stressed adolescents.

As 7,8-DHF did not improve extinction retention in adolescent rats exposed to chronic stress, it is important to consider alternate means by which extinction retention can be improved in this population. In line with this, another area for future research is the examination of the efficacy of 7,8-DHF following extended extinction training in animals exposed to chronic stress. While non-stressed adolescents demonstrate good extinction retention following extended extinction training, those that have been exposed to chronic stress continue to exhibit poor extinction retention even following extended extinction training (Stylianakis et al., 2019). This suggests that adolescents exposed to chronic stress may have a weaker extinction memory relative to non-stressed adolescent rats, making it more difficult for 7,8-DHF (or DCS, as in Stylianakis et al., 2019) to enhance extinction retention. Hence, an injection of 7,8-DHF coupled with further extinction may result in a stronger extinction memory, leading to improved extinction retention.

The experiments described were not without their limitations. One limitation pertains to the use of 7,8-DHF. Whilst this adjunct was initially proposed to be a tropomyosin receptor kinase B (TrkB) agonist (Jang et al., 2010; Liu et al., 2014), and there is evidence that 7,8-DHF (at 5 mg/kg, the same dose as used in the current study) upregulates phosphorylation of TrkB in the amygdala 1 and 2 h after systemic delivery in adult mice (Andero et al., 2011), the pharmacology of 7,8-DHF is more complex than initially assumed. Several alternative targets than TrkB receptors may mediate its neurobehavioral actions *in vivo*, including activation of adenosine receptors (Pankiewicz et al., 2021). In addition, as we administered the drug systemically it is not possible to deduce whether 7,8-DHF acted centrally to facilitate extinction retention in non-stressed adolescent rats. Consequently, future experiments are needed examining the pharmacokinetics of this drug in the adolescent brain and the phosphorylation of TrkB receptors, or activation of possible alternative targets, in extinction-relevant brain regions. For example, it would be of interest to determine whether 7,8-DHF upregulates TrkB phosphorylation or neural activity in the ventral hippocampal, vmPFC, and amygdala, three regions that have been shown to be important for extinction retention, at least in adults (Chhatwal et al., 2006; Peters et al., 2010) and that are hypothesized to be under-recruited in the adolescent during the consolidation of fear extinction (Zimmermann et al., 2019). Furthermore, although a 5 mg/kg dose of 7,8-DHF was found to be effective in facilitating extinction retention in non-stressed adolescent rats in the present study, no other doses were tested. Future studies should test lower doses to establish a threshold dose (i.e., the dose at which effects are first seen) as well as higher doses (which provides information about limits and safety of higher doses), especially in chronic corticosterone-exposed adolescent rats, given that a 5 mg/kg dose of 7,8-DHF did not facilitate extinction retention in those animals.

Another limitation of the experiments reported here is that no measures of stress hormone levels in the blood of the adolescent rats were taken in order to confirm that the corticosterone pellet implantation did indeed increase circulating corticosterone levels. However, measures of adrenal glands that were taken 4 days following the cessation of corticosterone exposure show that chronic corticosterone exposure resulted in significantly reduced adrenal weights, replicating past studies with chronic

exogenous corticosterone administration in the drinking water of adolescent male rats (e.g., Kaplowitz et al., 2016; Stylianakis et al., 2019). In addition, animals with corticosterone pellets had lower bodyweights 2 days after treatment cessation (i.e., on the day of extinction training) which recovered to similar levels as placebo treated animals 4 days after treatment cessation. Thus, the changes in adrenal gland weight and bodyweight confirm that administration of corticosterone *via* these slow-release pellets had a physiological effect on the adolescents in these experiments.

A third limitation of these studies derives from the way animals were exposed to chronic stress (*via* the implantation of corticosterone pellets). While exposure to chronic elevated levels of corticosterone does indeed lead to behavioral and neural changes that also occur following other chronic stress induction procedures (Luine et al., 1993; McKittrick et al., 2000; Cook and Wellman, 2004; Radley et al., 2006), an animal's stress response consists of the release of a number of other stress hormones, each of which have specific impacts upon the brain (Charmandari et al., 2005). Therefore, it would be of interest to determine if the diminishment of 7,8-DHF's effects on extinction following corticosterone exposure are replicated using different methods of inducing chronic stress (e.g., chronic restraint, which would result in the activation of the HPA axis in its entirety).

Future work may also seek to extend the present work in male adolescent rats by testing whether 7,8-DHF enhances fear extinction consolidation in adolescent females and whether chronic stress interferes with such an effect. Not only are fluctuations in estradiol levels across the rodent estrous cycle associated with varying effectiveness of extinction in adolescent female rats (Perry et al., 2020) but 7,8-DHF was reported to hinder extinction learning in adult female mice (Tohyama et al., 2020), or exert no influence on extinction learning, retention, or renewal (Baker-Andresen et al., 2013). Those effects in females are in stark contrast to the enhancement of fear extinction in male adult mice (Andero et al., 2011; Tohyama et al., 2020) and adolescent male rats (non-stressed) reported in the current study. Whilst age-dependent effects are possible, the possibility of sex-specific effects of 7,8-DHF on fear extinction requires addressing.

Concluding Statement

The experiments described here demonstrate that whilst 7,8-DHF facilitates extinction retention in male non-stressed adolescents it does not facilitate extinction retention in adolescents exposed to chronic stress, at least when the same extinction conditions are used. These results add to the broader literature which has demonstrated that two other approaches that facilitate extinction retention in non-stressed rats, DCS and extended extinction, do not facilitate extinction retention in those exposed to chronic stress. These results provide further insight into the etiology and treatment of pediatric stress-related disorders, and call for further research into the mechanisms underlying the extinction retention deficit in chronically stressed adolescents, and for methods by which this deficit can be ameliorated.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Animal Care and Ethics Committee at UNSW Sydney.

AUTHOR CONTRIBUTIONS

AS collected all the data and wrote the first draft of the manuscript. AS and KB did all the statistical analyses. KB and RR edited the manuscript and provided funding for the study. All authors contributed to the conceptualization and design of the study, worked on subsequent drafts of the manuscript, and agreed on the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.822709/full#supplementary-material

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Acute (*R,S*)-Ketamine Administration Induces Sex-Specific Behavioral Effects in Adolescent but Not Aged Mice

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(*R*,*S*)-ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that was originally developed as an anesthetic. Most recently, (*R*,*S*)-ketamine has been used as a rapid-acting antidepressant, and we have reported that (*R*,*S*)-ketamine can also be a prophylactic against stress in adult mice. However, most pre-clinical studies have been performed in adult mice. It is still unknown how an acute (*R*,*S*)-ketamine injection influences behavior across the lifespan (e.g., to adolescent or aged populations). Here, we administered saline or (*R*,*S*)-ketamine at varying doses to adolescent (5-week-old) and aged (24-month-old) 129S6/SvEv mice of both sexes. One hour later, behavioral despair, avoidance, locomotion, perseverative behavior, or contextual fear discrimination (CFD) was assessed. A separate cohort of mice was sacrificed 1 h following saline or (*R*,*S*)-ketamine administration. Brains were processed to quantify the marker of inflammation Cyclooxygenase 2 (Cox-2) expression to determine whether the acute effects of (*R*,*S*)-ketamine were partially mediated by changes in brain inflammation. Our findings show that (*R,S*)-ketamine reduced behavioral despair and perseverative behavior in adolescent female, but not male, mice and facilitated CFD in both sexes at specific doses. (*R,S*)-ketamine reduced Cox-2 expression specifically in ventral CA3 (vCA3) of male mice. Notably, (*R*,*S*)-ketamine was not effective in aged mice. These results underscore the need for sex- and age-specific approaches to test (*R,S*)-ketamine efficacy across the lifespan.

Keywords: adolescence, aging, behavioral despair, contextual fear discrimination, ketamine

INTRODUCTION

(*R,S*)-ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, was originally developed as an anesthetic and safer alternative to phencyclidine (PCP). It is still used for short-term procedural sedation in the emergency department setting in a wide age range (Rosenbaum et al., 2021). Most recently, (*R,S*)-ketamine, has emerged as a rapid-acting and long-lasting antidepressant

and as a prophylactic against stress in both humans (Berman et al., 2000; Zarate et al., 2006; Murrough et al., 2013; Ma et al., 2019) and mice (Kavalali and Monteggia, 2015; Altemus et al., 2014; Amat et al., 2016; Brachman et al., 2016; Zanos et al., 2016; McGowan et al., 2017; Dolzani et al., 2018). In contrast to traditional antidepressants which take weeks to reach efficacy and require daily administration to be effective, (*R,S*)-ketamine acts within 2 h of administration (Murrough et al., 2013) in patients with major depressive disorder (MDD). Morever (*R,S*)-ketamine effects can last up to 2 weeks following injection (Zarate et al., 2006; Murrough et al., 2013).

Despite the prevalence of (*R,S*)-ketamine among children as an anesthetic (Dolansky et al., 2008; Dwyer et al., 2017), few studies have examined whether (*R,S*)-ketamine is effective in treating adolescent mood disorders (Papolos et al., 2013; Dwyer et al., 2017; Cullen et al., 2018; Zarrinnegar et al., 2019). Similarly, (*R,S*)-ketamine is used as an anesthetic in older adults (Wickström et al., 1982; Maneglia and Cousin, 1988), often combined with other drugs (Willman and Andolfatto, 2007; Andolfatto et al., 2012). However, there are few data about (*R,S*)-ketamine efficacy as an antidepressant in elderly patients (i.e., > 60 years old) (Szymkowicz et al., 2014; Heard et al., 2017; Medeiros da Frota Ribeiro and Riva-Posse, 2017; Bahr et al., 2019; Bryant et al., 2019; Pennybaker et al., 2021), and there are no preclinical studies on (*R,S*)-ketamine's antidepressant effects in aged mice. Two studies in elderly patients showed that (*R,S*)-ketamine successfully reduced depressive symptomatology (Srivastava et al., 2015; Medeiros da Frota Ribeiro and Riva-Posse, 2017), while two other studies showed that (*R,S*)-ketamine was effective immediately after the injection, but not over time, suggesting that (*R,S*)-ketamine has low efficacy in elderly patients (George et al., 2017; Bryant et al., 2019). However, in these studies, (*R,S*)-ketamine was often given on top of other antidepressants, in patients with co-morbid disorders that weren't statistically controlled for, and without taking into consideration sex differences. Importantly, the aforementioned studies have shown that (*R,S*)-ketamine is effective within 1 h of administration in both adolescent and aged subjects (Papolos et al., 2013; Srivastava et al., 2015) and does not induce any psychotomimetic effects 1 h post-administration (Papolos et al., 2013; Srivastava et al., 2015). Therefore, 1 h could be the optimal time point for testing (*R,S*)-ketamine efficacy in adolescent or aged subjects.

Recently, inflammatory mediators, such as cytokines, enzymes, and metabolites levels, have been used as biomarkers for depressive behavior (Wright et al., 2005; Haroon et al., 2012; Strawbridge et al., 2017). In particular, Cox-2, an enzyme that mediates inflammation by synthesizing prostaglandins, is increased in depressed patients (Galecki et al., 2012). Interestingly, (*R,S*)-ketamine has been shown to have anti-inflammatory properties in depressed patients with peripheral inflammation (De Kock et al., 2013; Zanos et al., 2018; Verdonk et al., 2019). While the potential of (*R,S*)-ketamine to produce anti-inflammatory actions has been shown (Yli-Hankala et al., 1992; Meyer and Lázaro Da Silva, 2004; Shaked et al., 2004; Gurfinkel et al., 2006; De Kock et al., 2013). None of the previous studies directly evaluate (*R,S*)-ketamine's impact on Cox-2 expression in the brain. If (*R,S*)-ketamine changes Cox-2 expression in adolescent or aged mice is as of yet unknown.

Here, in order to better understand the acute effect of (*R,S*)-ketamine administration in adolescent and aged populations, male and female adolescent or aged mice were injected with saline or (*R,S*)-ketamine at one of varying doses. One hour later, behavioral despair, avoidance, locomotion, perseverative behavior, and CFD were assessed. (*R,S*)-ketamine attenuated behavioral despair and perseverative behaviors in adolescent female, but not male, mice and facilitated CFD in both sexes. Overall, there were no effects of (*R,S*)-ketamine in aged mice. Moreover, Cox-2 expression was increased in the hippocampus (HPC) of aged mice as compared to adolescent mice. (*R,S*)-ketamine administration specifically reduced the expression of Cox-2 in ventral CA3 (vCA3) in adolescent male mice. In summary, this study showed that (*R,S*)-ketamine impacts behavior in a sex-, dose-, and age-dependent manner perhaps by differentially altering Cox-2 expression. This study will contribute to informing clinical studies on (*R,S*)-ketamine efficacy across the lifespan.

MATERIALS AND METHODS

Mice

For adolescent studies, male and female 129S6/SvEvTac mice were purchased from Taconic (Hudson, NY, United States) at 4 weeks of age. For aged studies, 129S6/SvEvTac mice were purchased from Taconic and bred in-house. The pups were then aged to 24 months of age. Mice were housed 5 per cage in a 12-h (06:00–18:00) light-dark colony room at 22°C. Food and water were provided *ad libitum*. Behavioral tests were performed during the light phase. All experiments were approved by the Institutional Animal Care and Use Committee (IACUC) at NYSPI.

Drugs

A single injection of saline (0.9% NaCl) or (*R,S*)-ketamine (Fort Dodge Animal Health, Fort Dodge, IA, United States) (10, 30, or 100 mg/kg) was administered at 5 weeks or 24 months of age once during the course of each experiment. All drugs were prepared in physiological saline and administered intraperitoneally (i.p.) in volumes of 0.1 cc per 10 mg body weight.

Behavioral Assays

Forced Swim Test

The FST was used to assay behavioral despair as previously described (Brachman et al., 2016; Mastrodonato et al., 2020). In this test, an animal placed in a container filled with water, will first make efforts to escape but eventually will exhibit immobility, which is thought to reflect a failure of persistence in escape-directed behavior (i.e., behavioral despair). The term behavioral despair aligns with the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC). The RDocC suggest that researchers should consider multiple levels of disease complexity (e.g., genetics, behavior, or circuitry) when studying

aspects of psychiatric disorders, such as depression, with the goal of identifying mechanisms which may translate to human conditions. While no single test can capture the full complexity of a human disorder, the FST in particular lacks mechanistic specificity. However, this test has been useful to study the stress-induced behavioral phenotype and dose response curves of drugs [e.g., (*R,S*)-ketamine] over time. In this study, mice were placed into clear plastic buckets 20 cm in diameter and 23 cm deep filled 2/3 of the way with 22°C water. Mice were videotaped from the side for 6 min on 2 consecutive days. Immobility time was assessed by time spent floating. Average immobility time for day 2 of the FST was calculated for min 3–6 (4 min in total).

Locomotor Activity Test

The LA was administered as previously described (Brachman et al., 2016; Mastrodonato et al., 2018). Briefly, motor activity was quantified in two Plexiglas open field (OF) boxes 50 cm × 50 cm (MED Associates, Georgia, VT, United States). Mice were individually placed in the center of the OF box and allowed to explore the field for 10 min. Total distance traveled was quantified by using ANY-maze behavior tracking software (ANY-maze, RRID:SCR_014289, Stoelting, Wood Dale, IL, United States).

Elevated Plus Maze

Elevated plus maze was performed as previously described (Brachman et al., 2016; Mastrodonato et al., 2018). Briefly, the testing was conducted in a plus-cross-shaped apparatus consisting of 4 arms, 2 open and 2 enclosed by walls, linked by a central platform at a height of 50 cm from the floor. Mice were individually placed in the center of the maze facing an open arm and could explore the maze for 5 min. The time spent in the open arms was used as an index of anxiety. Videos were scored using ANY-maze tracking software (ANY-maze, RRID:SCR_014289, Stoelting, Wood Dale, IL, United States).

Marble Burying

The MB assay was performed in a clean cage (10.5 in ×5.5 in) containing soft pliable Beta Chip bedding (Northeastern Products Corp, Warrensburg, NY, United States). The cage contained 16 marbles set up in four rows of four marbles across. Mice were given 30 min to explore and bury. At the end of the assay, the number of marbles buried was calculated.

Contextual Fear Discrimination

In the CFD assay (Sahay et al., 2011; Mastrodonato et al., 2018), mice were exposed to a 1-shock CFC training. Mice received a single 2 s foot shock of 0.75 mA after being placed in the context for 180 s and were removed 15 s following the shock (i.e., 197 s). Mice were then exposed to two contexts daily. One context was the CFC context where the mice were shocked daily (context A), and the other context was a similar, novel context without a shock (context B). For context A, mice received 1-shock CFC daily as described above. For context B, mice were placed in the CFC chamber for 180 s with no shock. Each day, time spent freezing in each context was calculated as a percentage. The contextual information is listed in **Supplementary Table 1**.

Brain Processing

Mice were deeply anesthetized, and brains were processed as previously described in Denny et al. (2014), Cazzulino et al. (2016), and Pavlova et al. (2018). Brains were then frozen in optimal cutting temperature (OCT) medium and sliced into 100 μm sections using a cryostat.

Cox-2 Immunohistochemistry

An iDISCO-based immunohistochemistry protocol was performed (Pavlova et al., 2018). Briefly, sections were washed in 1X phosphate buffered saline (PBS) in three increments of 10 min each, then dehydrated in 50% MeOH for 2.5 h. Sections were then washed in 0.2% PBS with TritonX-100 (PBST) in three increments of 10 min each and placed in blocking solution [10% normal donkey serum (NDS)/0.1% PBST] for 2 h. After blocking, sections were washed in three increments of 10 min each in 0.1% PBST. Sections were then incubated in a solution of primary antibody mouse monoclonal IgG anti-Cox-2 (1:200, Santa Cruz Biotechnology Cat# sc-376861, RRID:AB_2722522, Santa Cruz, CA, United States) in 10% NDS/0.1% PBST for 3 days at 4°C. On day 4, sections were washed in three increments of 10 min each in 1X PBS and incubated in secondary antibody solution consisting of Alexa 647 conjugated Goat Anti-Mouse IgG (1:250, Molecular Probes Cat# A-21235, RRID:AB_2535804, Waltham, MA, United States) in 10% NDS/1X PBS overnight. The next day, sections were washed in three increments of 10 min each in 1X PBS. Sections were mounted on slides and allowed to dry for approximately 20 min before adding mounting medium Fluoromount G (Electron Microscopy Sciences, Hatfield, PA, United States) and a coverslip.

Confocal Microscopy

All samples were imaged on a confocal scanning microscope (Leica TCS SP8, Leica Microsystems Inc., Wetzlar, Germany) with two simultaneous PMT detectors, as previously described (Pavlova et al., 2018). Fluorescence from Alexa Fluor 647 was excited at 634 nm and detected at 650–700 nm. Sections were imaged with a dry Leica 20 × objective (NA 0.70, working distance 0.5 mm), with a pixel size of 1.08 × 1.08 μm^2, a z step of 3 μm, and z-stack of 24 μm. Fields of view were stitched together to form tiled images by using an automated stage and the tiling function and algorithm of the LAS X software (Leica Application Suite X, RRID:SCR_013673, Wetzlar, Germany).

Cell Quantification

An investigator blind to treatment manually circled the granule cell layer (GCL) of the DG or the pyramidal layer (PL) of CA3 throughout the entire rostro-caudal axis of the hippocampus (HPC) using Fiji (Fiji, RRID:SCR_002285, Dresden, Germany) (Mastrodonato et al., 2018). The mean intensity of Cox-2 expression was measured bilaterally using Fiji (Mastrodonato et al., 2018) and normalized to the area of the GCL or PL.

Statistical Analysis

All data were analyzed using Prism 8.0 (GraphPad Prism, RRID:SCR_002798, La Jolla, CA, United States). Alpha was set

to 0.05 for all analyses. Overall, the effect of Age, Time, and Drug was analyzed using an analysis of variance (ANOVA), using repeated measures where appropriate. *Post hoc* Dunnett and Sidak tests were used where appropriate. *A priori* comparisons were undertaken when there was no significant Drug x Age interactions when a main effect of Drug was statistically significant to evaluate the impact of the Drug within the adolescent or aged cohorts. Male and female mice were tested separately to avoid any possible confounding effects due to hormonal variation, therefore they were analyzed separately.

The effect of Drug on Cox-2 expression (mean intensity) was analyzed using *t*-tests. All statistical tests and *p* values are listed in **Supplementary Table 2**. A summary of behavioral findings is listed in **Supplementary Table 3**.

RESULTS

Acute (*R,S*)-Ketamine Reduces Behavioral Despair and Perseverative Behavior in Female, but Not Male, Adolescent Mice

To determine if an acute injection of (*R,S*)-ketamine could impact behavior in adolescent or aged mice, male and female mice were injected with saline or (*R,S*)-ketamine at varying doses (**Figure 1A**). Doses were chosen based on previous studies in adolescent (Parise et al., 2021) and adult mice (Brachman et al., 2016; McGowan et al., 2017; Mastrodonato et al., 2018; Chen et al., 2020). Since aged mice were bred in-house, and therefore, only a limited number of mice were available for each experiment, only the previously identified doses for adult mice (30 mg/kg for males and 10 mg/kg for females) were chosen for aged experiments. One hour later, mice were assayed in the FST. During day 1 of the FST, adolescent male and female mice exhibited similar immobility time compared to aged male mice [Age: $F_{(1,48)} = 0.888$, $p = 0.350$; Age: $F_{(1,39)} = 0.040$, $p = 0.842$, respectively] (**Figures 1B,C**). (*R,S*)-ketamine did not impact immobility time in any group [Drug: $F_{(1,48)} = 0.180$, $p = 0.673$; Drug: $F_{(1,39)} = 0.026$, $p = 0.872$]. During day 2 of the FST, all groups of adolescent and aged male mice had comparable immobility time [Drug: $F_{(1,48)} = 0.685$, $p = 0.412$; Age: $F_{(1,48)} = 0.061$, $p = 0.806$] (**Figure 1D**). However, (*R,S*)-ketamine-injected female mice (10 mg/kg) exhibited decreased immobility time compared to saline-injected female mice ($p = 0.026$) (**Figure 1E**). (*R,S*)-ketamine did not alter immobility time in aged female mice ($p = 0.528$).

In the LA, adolescent mice traveled significantly more than aged mice [Drug: $F_{(1,48)} = 0.001$, $p = 0.969$; Drug: $F_{(1,39)} = 0.039$, $p = 0.844$, respectively] (**Figures 1F,G**). (*R,S*)-ketamine did not impact the distance traveled in any groups. In the EPM, adolescent and aged male mice spent a comparable time in the open arms [Drug: $F_{(1,48)} = 0.005$, $p = 0.942$; Age: $F_{(1,48)} = 0.944$, $p = 0.336$] (**Figure 1H**). Adolescent female mice spent significantly more time in the open arms than aged female mice [Age: $F_{(1,39)} = 15.710$; $p = 0.0003$] (**Figure 1I**). (*R,S*)-ketamine did not impact behavior in the EPM in any groups. In the MB task, adolescent and aged male mice buried a comparable number of marbles [Drug: $F_{(1,48)} = 1.449$, $p = 0.234$; Age: $F_{(1,48)} = 0.125$, $p = 0.724$] (**Figure 1J**). (*R,S*)-ketamine did not impact MB behavior in the male groups [Drug: $F_{(1,48)} = 1.449$, $p = 0.234$]. In female mice, there was a significant effect of Age on the percent of marbles buried [Drug: $F_{(1,39)} = 23.820$, $p < 0.0001$] (**Figure 1K**). Adolescent (*R,S*)-ketamine-injected mice (all doses) buried significantly fewer marbles than saline-injected mice. Both groups of aged female mice buried a comparable number of marbles. These data indicate that an acute injection of (*R,S*)-ketamine does not impact behavior in adolescent or aged male mice, but decreases behavioral despair and perseverative behavior in adolescent female mice.

To investigate whether the lack of (*R,S*)-ketamine effect in some of the behavioral assays was due to time delay from drug injection, we next tested three separate cohorts of adolescent mice in the LA (**Figure 2A**), EPM (**Figure 2D**), and MB (**Figure 2G**) 1 h following saline or (*R,S*)-ketamine administration. Since only a limited number of aged mice were available, and (*R,S*)-ketamine was not effective in any behavioral tasks in the previous experiment (**Figure 1**), aged mice were not tested here. In the LA, all groups of male and female mice traveled comparably [Drug = $F_{(3,16)} = 1.938$, $p = 0.164$; Drug = $F_{(3,13)} = 0.570$, $p = 0.644$, respectively] (**Figures 2B,C**). In the EPM, all groups of adolescent male mice spent a comparable time in the open arms [Drug = $F_{(3,16)} = 2.491$, $p = 0.097$] (**Figure 2E**). However, in female mice, adolescent (*R,S*)-ketamine-injected mice (10 mg/kg) spent more time in the open arms than saline-injected mice [Drug = $F_{(3,16)} = 4.231$, $p = 0.022$] (**Figure 2F**). In contrast to what we observed when MB was administered 5 days following saline or (*R,S*)-ketamine administration, here, in the MB assay, adolescent male and female mice administered saline or (*R,S*)-ketamine buried a similar number of marbles [Drug = $F_{(3,16)} = 0.306$, $p = 0.820$; Drug = $F_{(3,16)} = 1.141$, $p = 0.885$, respectively] (**Figures 2H,I**). These data suggest that (*R,S*)-ketamine efficacy is time- and sex-dependent.

Acute (*R,S*)-Ketamine Administration Facilitates Contextual Fear Discrimination in Adolescent but Not Aged Mice

A recent study showed that a single dose of (*R,S*)-ketamine administered 22 h after CFC alleviated fear memory generalization in adult C57BL/6 mice (Asim et al., 2020). However, it remains to be determined if an acute (*R,S*)-ketamine administration could reduce fear generalization in adolescent or aged mice. Here, adolescent and aged mice were injected with saline or (*R,S*)-ketamine and administered a CFD paradigm 1 h later (**Figure 3A**). In saline mice, there was not a significant effect of Context [$F_{(1,12)} = 2.220$, $p = 0.162$], but there was a significant effect of Time [$F_{(8,96)} = 6.161$, $p = 0.0001$], and an interaction of Time x Context [$F_{(8,96)} = 3.540$, $p = 0.001$]. Unlike adult male mice (Mastrodonato et al., 2018), saline-treated adolescent male mice could only discriminate between the two contexts on day 9 ($p = 0.010$) (**Figures 3B,J,K**). (*R,S*)-ketamine-injected male mice (10 or 100 mg/kg) started discriminating on days 10

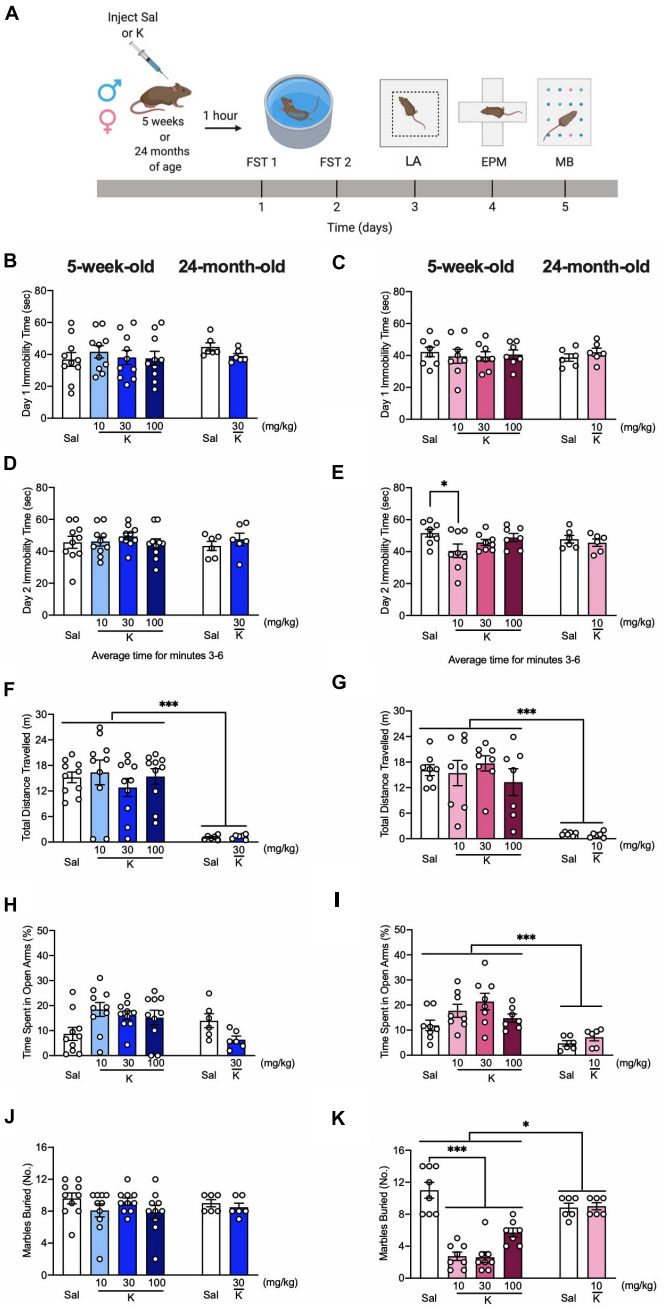

FIGURE 1 | Acute (*R,S*)-ketamine administration decreases behavioral despair and perseverative behavior in adolescent female, but not male mice. **(A)** Experimental design. **(B)** Five-week-old male mice administered saline or (*R,S*)-ketamine exhibited similar immobility time to 24-month-old male mice on day 1 of FST. (*R,S*)-ketamine did not impact immobility time in any groups of male mice. **(C)** Five-week-old and 24-month-old female mice administered saline or (*R,S*)-ketamine exhibited similar immobility time on day 1 of FST. (*R,S*)-ketamine did not impact immobility time in any groups. **(D)** All groups of 5-week-old and both groups of 24-month-old male mice had comparable immobility time on day 2 of the FST. **(E)** Five-week-old female mice administered (*R,S*)-ketamine (10 mg/kg) exhibited reduced immobility time when compared with female mice administered saline. Both groups of 24-month-old female mice had comparable immobility time on day 2 of the FST. **(F,G)** (*R,S*)-ketamine did not affect the distance traveled in the LA in 5-week-old and 24-month old male and female mice. However, 24-four-month-old male and female mice traveled significantly less than 5-week-old mice. **(H)** Five-week- and 24-month-old male mice spent a comparable time in the open arms. **(I)** Five-week-old female mice spent a more time in the open arms than 24-month-old female mice. (*R,S*)-ketamine did not impact behavior in any groups. **(J)** During the MB task, all groups of male mice buried a comparable number of marbles. **(K)** All groups of 5-week-old female mice administered (*R,S*)-ketamine buried significantly fewer marbles when compared with female mice administered saline. Five-week-old female mice buried significantly fewer marbles than 24-month-old female mice. Both groups of 24-month-old female mice buried a comparable number of marbles. (n = 6–10 mice per group). Error bars represent ± SEM. $^{*}p < 0.05$. $^{***}p < 0.0001$. Sal, saline; K, (*R,S*)-ketamine; FST, forced swim test; LA, locomotor activity test; EPM, elevated plus maze; MB, marble burying; sec, second; mg, milligram; kg, kilogram; m, meter; No, number.

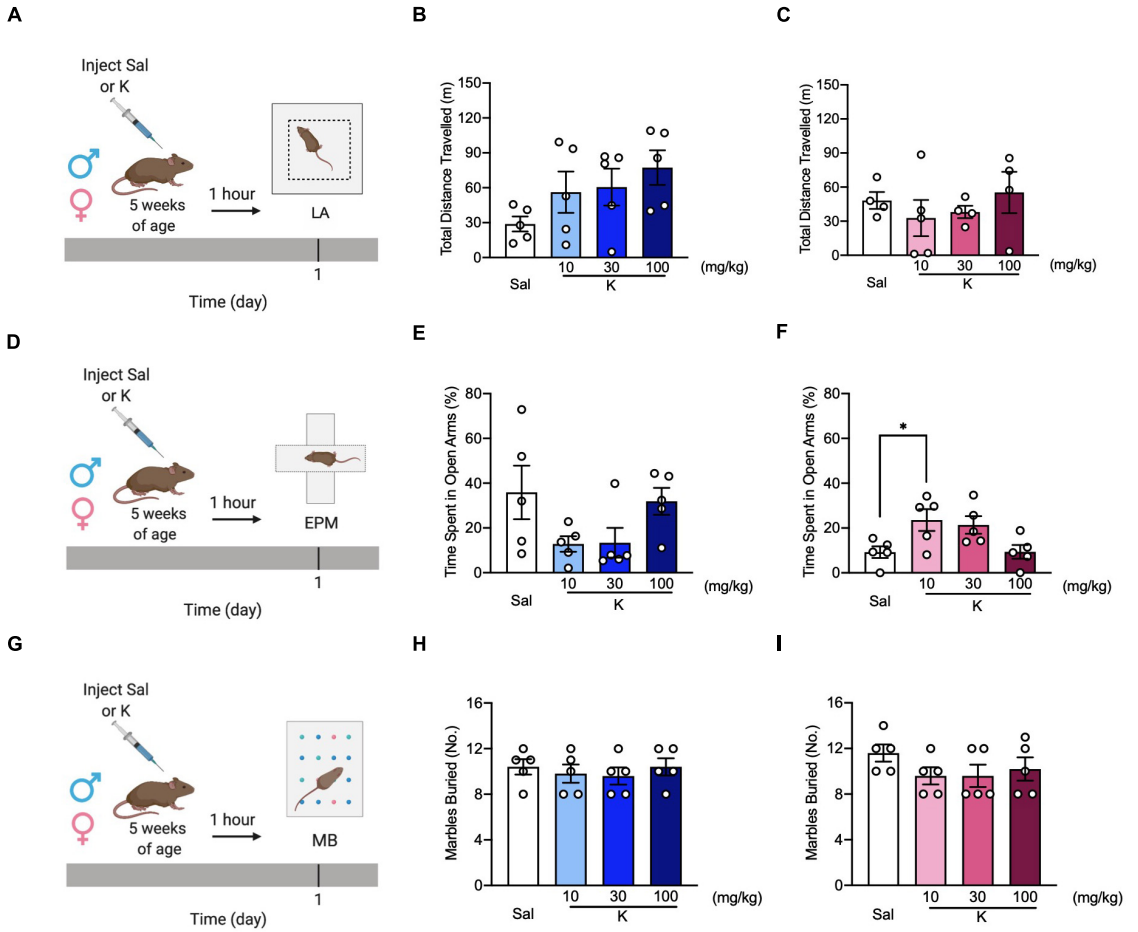

FIGURE 2 | (*R,S*)-ketamine decreases avoidance behavior without affecting locomotor activity and perseverative behavior in adolescent mice. **(A)** Experimental design. **(B,C)** Male and female 5-week-old mice showed comparable distance traveled in the LA. **(D)** Experimental design. **(E)** All groups of 5-week-old male mice spent a similar time in the open arms of the EPM. **(F)** Five-week-old female mice administered (*R,S*)-ketamine (10 mg/kg) spent significantly more time in the open arms of the EPM compared to saline mice. **(G)** Experimental design. **(H,I)** Male and female of 5-week-old mice buried a comparable number of marbles. (*n* = 4–5 mice per group). Error bars represent ± SEM. * $p < 0.05$. Sal, saline; K, (*R,S*)-ketamine; LA, locomotor activity test; EPM, elevated plus maze; MB, marble burying; mg, milligram; kg, kilogram; m, meter.

or 8, respectively [Context: $F_{(1,8)} = 8.062$ $p = 0.021$; Context: $F_{(1,8)} = 28.760$, $p = 0.0007$, respectively]. (**Figures 3C,E,J,K**). However, adolescent male mice administered (*R,S*)-ketamine (30 mg/kg) initially had increased fear generalization on days 2 ($p = 0.0008$) and 3 ($p = 0.032$), but discriminated starting on day 5 [Context: $F_{(1,12)} = 14.480$, $p = 0.002$] (**Figures 3D,J,K**). By day 10, (*R,S*)-ketamine-injected male (30 or 100 mg/kg, but not 10 mg/kg) mice showed improved discrimination ratios when compared to saline-injected male mice [Drug: $F_{(3,20)} = 3.802$, $p = 0.026$] (**Figures 3J**).

Interestingly, in contrast to males, there was a significant effect of Context [$F_{(1,12)} = 8.708$, $p = 0.012$], Time [$F_{(8,96)} = 7.465$, $p < 0.0001$], and an interaction of Context x Time [$F_{(8,96)} = 5.046$, $p < 0.0001$] in saline-injected female mice. Saline-injected adolescent female mice discriminated starting on day 6 ($p = 0.005$) (**Figures 3F,L,M**). Adolescent (*R,S*)-ketamine-injected female mice (10 mg/kg) initially showed increased fear generalization on day 2 ($p = 0.014$). However, (*R,S*)-ketamine-injected female mice (10 or 30 mg/kg) could discriminate starting on day 5 [Context: $F_{(1,14)} = 20.680$, $p = 0.0005$; Context: $F_{(1,8)} = 30.720$, $p = 0.0005$, respectively] (**Figures 3G,H,L,M**), (*R,S*)-ketamine-injected female mice (100 mg/kg) could discriminate starting on day 9 [Context: $F_{(1,8)} = 42.130$, $p = 0.0002$] (**Figures 3I,L,M**). By day 10, all groups of female mice showed similar discrimination ratios [Drug: $F_{(3,21)} = 0.293$, $p = 0.830$] (**Figure 3L**).

Notably, saline- or (*R,S*)-ketamine-injected aged mice could not discriminate between the two contexts over the 10 days of CFD testing [Context: $F_{(1,8)} = 0.451$, $p = 0.520$; Context: $F_{(1,8)} = 1.985$, $p = 0.196$, respectively] and exhibited comparable discrimination ratios on day 10 (Drug: $p = 0.986$; Drug: $p = 0.899$, respectively) (**Figures 3N–U**). These data are in accord with prior studies showing impaired CFD in aged mice (Wu et al., 2015), and indicate that dose-specific, acute (*R,S*)-ketamine

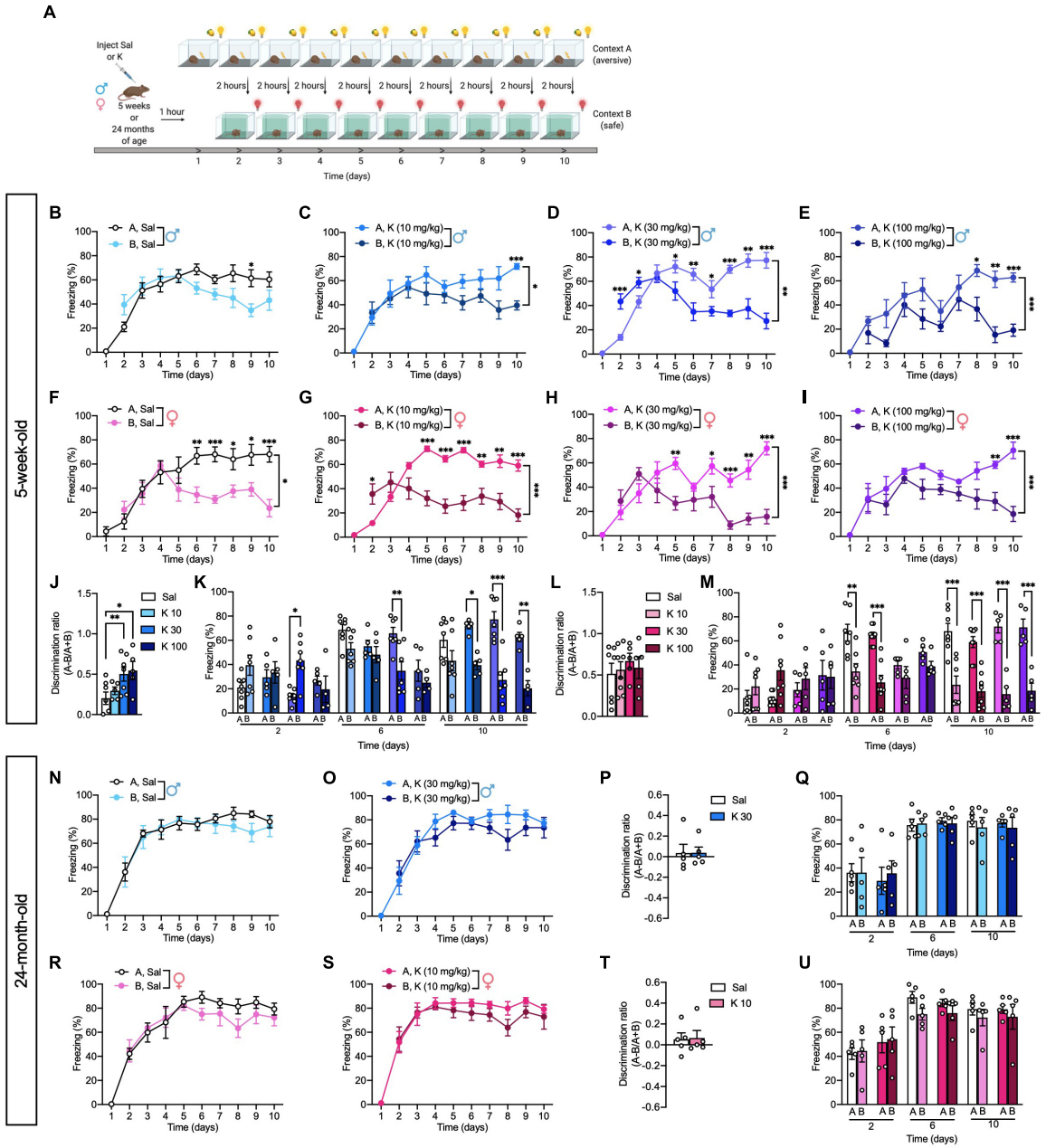

FIGURE 3 | Acute (*R,S*)-ketamine facilitates contextual fear discrimination in adolescent but not aged male mice. **(A)** Experimental design. **(B)** Saline-injected male mice could not discriminate between the two contexts. **(C)** (*R,S*)-ketamine-injected male mice (10 mg/kg) could discriminate between the two contexts only on day 10. **(D)** (*R,S*)-ketamine-injected male mice (30 mg/kg) initially had increased fear generalization on day 2, but could discriminate starting on day 5. **(E)** (*R,S*)-ketamine-injected male mice (100 mg/kg) could discriminate between the two contexts starting from day 8. **(F)** Saline-injected female mice could discriminate between the two contexts starting on day 6. **(G,H)** (*R,S*)-ketamine-injected female mice (10 and 30 mg/kg) could discriminate between the two contexts starting on day 5. **(I)** (*R,S*)-ketamine-injected female mice (100 mg/kg) could discriminate starting on day 9. **(J)** (*R,S*)-ketamine-injected male mice (30 or 100 mg/kg) exhibited improved discrimination ratios on day 10. **(K)** (*R,S*)-ketamine-injected male mice (30 mg/kg) showed increased fear generalization on days 2 and 3, however, they could discriminate between the two contexts on day 6. On day 10, (*R,S*)-ketamine-injected male mice (all doses) could discriminate between the two contexts. **(L)** All groups of female mice exhibited comparable discrimination ratios on day 10. **(M)** Saline- or (*R,S*)-ketamine-injected female mice could not discriminate between the two contexts on day 2. On day 6 Saline- or (*R,S*)-ketamine-injected female mice (10 mg/kg) could discriminate. On day 10, all groups of mice could discriminate. **(N,O)** Twenty-four-month-old male saline- or (*R,S*)-ketamine-injected mice could not discriminate between the two contexts over the 10 days. **(P)** Both groups of male mice exhibited comparable discrimination ratios on day 10. **(Q)** On Days 2, 6, and 10, all groups exhibited comparable freezing. **(R,S)** Twenty-four-month-old saline- or (*R,S*)-ketamine-injected female mice could not discriminate between the two contexts over the 10 days. **(T)** Both groups of female mice exhibited comparable discrimination ratios on day 10. **(U)** On Days 2, 6, and 10, all groups exhibited comparable freezing. (n = 5–10 mice per group). Error bars represent ± SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$. Sal, saline; K, (*R,S*)-ketamine; mg, milligram; kg, kilogram.

administration is effective at facilitating CFD in adolescent, but not aged mice.

(*R*,*S*)-Ketamine Decreases Cox-2 Expression in vCA3 of Adolescent but Not Aged Mice

To assess whether the sex- and age-specific effects of (*R*,*S*)-ketamine on behavior could be associated with changes in inflammation, we quantified the expression of Cox-2, as proxy of inflammation (Galecki et al., 2012). Since we had previously found that (*R*,*S*)-ketamine administration changes neural activity in the DG and CA3 regions of the HPC (Mastrodonato et al., 2018), we measured Cox-2 expression across the HPC, specifically in the dorsal and ventral DG and CA3 subregions (**Figures 4A,B**). In the dorsal HPC, 24-month-old male mice had increased expression of Cox-2 in the DG and CA3 when compared with 5-week-old male mice [Age: $F_{(1,13)} = 23.870$, $p = 0.0003$; Age: $F_{(1,13)} = 38.000$, $p < 0.0001$, respectively] (**Figures 4C,D**). (*R*,*S*)-ketamine did not impact Cox-2 expression in either group [Drug: $F_{(1,13)} = 1.790$, $p = 0.203$; Drug: $F_{(1,13)} = 0.086$, $p = 0.773$, respectively]. Similarly, in the dorsal HPC, 24-month-old female mice had increased expression of Cox-2 in the DG and CA3 when compared with 5-week-old female mice [Age: $F_{(1,12)} = 6.221$, $p = 0.028$; Age: $F_{(1,12)} = 8.507$, $p = 0.013$, respectively] (**Figures 4E,F**). (*R*,*S*)-ketamine did not impact Cox-2 expression in either region [Drug: $F_{(1,12)} = 0.487$, $p = 0.499$; Drug: $F_{(1,12)} = 0.281$, $p = 0.605$, respectively].

In the ventral HPC, 24-month-old male mice had increased expression of Cox-2 in the DG and CA3 when compared with 5-week-old male mice [Age: $F_{(1,13)} = 9.443$, $p = 0.009$; Age: $F_{(1,12)} = 15.520$, $p = 0.002$, respectively] (**Figures 4G,H**). (*R*,*S*)-ketamine did not impact Cox-2 expression in either group in the ventral DG (vDG) [Drug: $F_{(1,13)} = 1.821$, $p = 0.200$]. However, 5-week-old male mice administered (*R*,*S*)-ketamine had decreased expression of Cox-2 in ventral CA3 (vCA3) when compared with saline-treated mice [Drug: $F_{(1,12)} = 4.711$, $p = 0.049$] (**Figure 4H**). (*R*,*S*)-ketamine did not impact Cox-2 expression in vCA3 in 24-month-old mice [Drug: $F_{(1,12)} = 0.236$, $p = 0.636$]. Five-week-old female mice had a similar level of Cox-2 expression in the vDG when compared to 24-month-old female mice [Age: $F_{(1,12)} = 2.973$, $p = 0.110$] (**Figure 4I**). Twenty-four-month-old female mice had increased expression of Cox-2 in vCA3 when compared with 5-week-old female mice [Age: $F_{(1,12)} = 8.096$, $p = 0.015$] (**Figure 4J**). (*R*,*S*)-ketamine did not impact Cox-2 expression in any of these groups [Drug: $F_{(1,12)} = 0.819$, $p = 0.383$]. These data suggest that (*R*,*S*)-ketamine effects might be partially due to the reduced expression of Cox-2 in vCA3 in 5-week-old male mice. Moreover, these findings are consistent with our previous data showing that vCA3 mediates (*R*,*S*)-ketamine efficacy against stress (Mastrodonato et al., 2018).

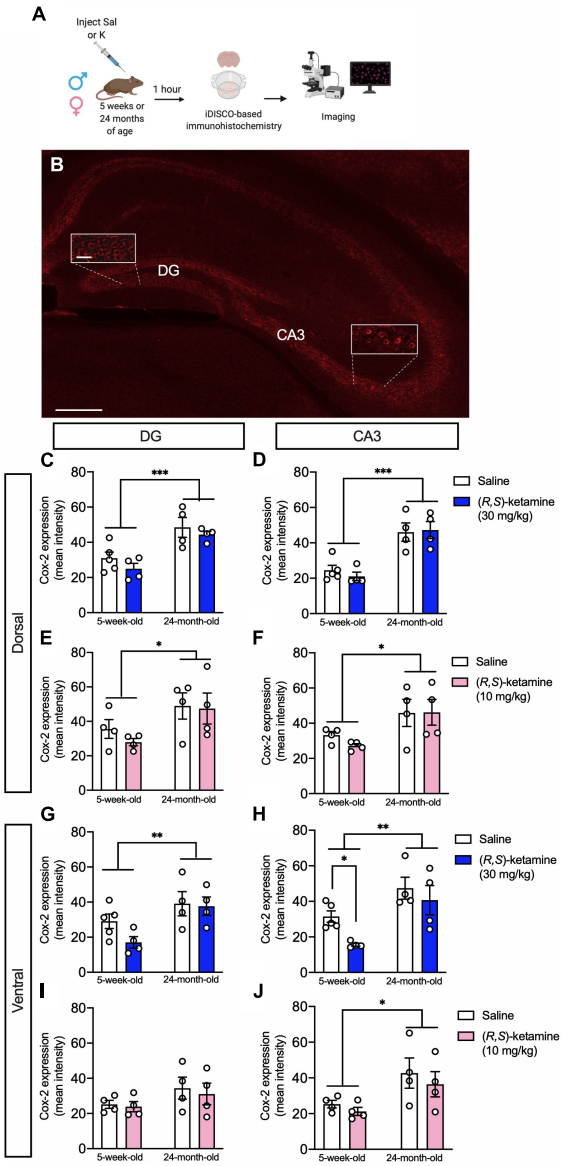

FIGURE 4 | (*R*,*S*)-ketamine selectively decreases Cox-2 expression in ventral CA3 of adolescent male mice. **(A)** Experimental design. **(B)** Cox-2 expression in the hippocampus. Scale bar: 250 and 25 μm (inset). **(C,D)** Twenty-four-month-old male mice had increased Cox-2 expression in the dorsal DG and dorsal CA3 when compared with 5-week-old mice. (*R*,*S*)-ketamine did not impact Cox-2 expression. **(E,F)** Twenty-four-month-old female mice had increased Cox-2 expression in the dorsal DG and dorsal CA3 when compared with 5-week-old mice. (*R*,*S*)-ketamine did not impact Cox-2 expression in either region. **(G,H)** Twenty-four-month-old male mice had increased Cox-2 expression in the ventral DG and ventral CA3 when compared with 5-week-old mice. (*R*,*S*)-ketamine did not impact Cox-2 expression in the ventral DG. However, in 5-week-old male mice, (*R*,*S*)-ketamine decreased Cox-2 expression in ventral CA3. **(I)** All groups of female mice showed similar level of Cox-2 expression in the ventral DG. (*R*,*S*)-ketamine did not impact Cox-2 expression. **(J)** Twenty-four-month-old female mice had increased Cox-2 expression in vCA3 when compared to 5-week-old mice. (*R*,*S*)-ketamine did not impact Cox-2 expression. Error bars represent ± SEM. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Sal, saline; K, (*R*,*S*)-ketamine; DG, dentate gyrus; CA3, Cornu Ammonis region 3; iDISCO, immunolabeling-enabled three-dimensional imaging of solvent-cleared organs.

DISCUSSION

Here, we report for the first time that a single injection of (*R*,*S*)-ketamine, administered acutely, impacts behavior in adolescent, but not aged mice depending on sex and dose. Specifically, we

found that (*R,S*)-ketamine administration reduced behavioral despair and perseverative behavior in female, but not male, mice and facilitated CFD in both sexes at specific doses.

In contrast to two different studies in male C57BL/6J and BALB/cJ mice, here, we found that (*R,S*)-ketamine administration (10 mg/kg) decreases behavioral despair (Zanos et al., 2016; Pham et al., 2018) in female mice. Although our data did not indicate antidepressant efficacy in male mice, our results may be specific to the drug doses, mouse strains, or behavioral paradigms we utilized. Moreover, it is possible that (*R,S*)-ketamine effects are more rapid in females than in males, similarly to what has been shown by a previous study (Franceschelli et al., 2015). Additional studies in humans have shown that (*R,S*)-ketamine has a rapid antidepressant effect in adolescents (Dwyer et al., 2017; Cullen et al., 2018; Zarrinnegar et al., 2019), but sex was not considered as biological variable. Previous works have also shown that testing mice of different genetic backgrounds in the same behavioral assays can lead to opposing conclusions, suggesting that a variety of mouse strains should be tested to determine (*R,S*)-ketamine efficacy (Sittig et al., 2016).

A recent study found that acute (*R,S*)-ketamine administration reduces locomotor activity and enhances avoidance behavior in adolescent male C57BL/6 mice (Shin et al., 2019). However, in this study, the authors administered (*R,S*)-ketamine at a different dose (15 mg/kg) than the one we used here, used mice of a different strain, and administered maternal separation early in life. Moreover, the effect of (*R,S*)-ketamine on behavioral despair, avoidance or compulsive behaviors were not investigated, and whether there was a sex- or age-specific effect was also not examined. In general the use of a different time of administration, sex, dose and/or mouse strain (McDougall et al., 2017; Shin et al., 2019) might explain why we could not find a significant (*R,S*)-ketamine effect in the LA experiment, and highlight the importance of these parameters in optimizing (*R,S*)-ketamine efficacy.

(*R,S*)-ketamine administration did not affect avoidance behavior 4 days following injection, consistent with previous studies showing the lack of an anxiolytic effect with (*R,S*)-ketamine (Autry et al., 2011; Brachman et al., 2016). However, (*R,S*)-ketamine decreased avoidance behavior in adolescent female mice 1 h following administration, suggesting that (*R,S*)-ketamine selectively affects avoidance behavior in a time-dependent manner. Future studies will assess additional time points for (*R,S*)-ketamine efficacy determining the most effective time windows of administration. Interestingly, we found that (*R,S*)-ketamine decreases compulsive behavior in adolescent female, but not male mice, suggesting the opportunity to treat compulsive-related disorders, such as obsessive compulsive disorder OCD (Rodriguez et al., 2013, 2015; Davis et al., 2021), specifically in a female population. Interestingly, while we found that (*R,S*)-ketamine decreases perseverative behavior only in adolescent females, it did not affect perseverative behavior when administered 1 h before MB testing, indicating that the time of administration is critical to observe an improvement in perseverative behavior.

Since impaired CFD is a symptom often observed in anxiety disorders, we assessed if the (*R,S*)-ketamine was effective against CFD in adolescent and aged mice (Altemus et al., 2014). Similar to adult mice (Mastrodonato et al., 2018), (*R,S*)-ketamine (30 mg/kg)-administered adolescent male mice and (*R,S*)-ketamine (10 mg/kg)-administered adolescent female mice discriminated faster than their saline-injected controls. Intriguingly, we also found that adolescent saline-injected male mice were impaired in CFD and showed fear generalization at 5 weeks of age (i.e., P35). These results are consistent with a previous study showing that there is an adolescent window of vulnerability (i.e., a "sensitive period") in which adolescent male mice have impaired fear responses (Pattwell et al., 2016). Notably, adolescent saline-injected female mice did not show impaired CFD at P35, indicating that the neural circuits mediating fear behavior might be different between male and females at this age. These data are of critical importance because they indicate that (*R,S*)-ketamine could potentially be used to treat pathological fear generalization in anxiety disorders, which are prevalent during adolescence (Kessler et al., 2005). Moreover, these data suggest that the dose of (*R,S*)-ketamine will strongly determine its efficacy.

Interestingly, aged mice of both sexes could not discriminate (Wu et al., 2015), which is in accord with a previous study showing that aged mice are impaired in CFD when compared with young mice (Wu et al., 2015). (*R,S*)-ketamine did not facilitate CFD in aged mice. These results are also in line with recent studies showing that Spravato® (esketamine) is less effective in older adults (i.e., > 60 years old) (Bahr et al., 2019) and that (*R,S*)-ketamine infusions are not effective in geriatric patients suffering from treatment-resistant depression (TRD) (Szymkowicz et al., 2014). These findings, therefore, indicate the necessity of testing different (*R,S*)-ketamine doses and protocols of administration in the geriatric population. Future work will be also needed to investigate a variety of doses and/or combined drug administration in aged mice.

Here, we evaluated whether inflammatory changes in the HPC could parallel the behavioral findings by examining Cox-2 expression 1 h following an injection of saline or (*R,S*)-ketamine. Interestingly, in addition to its antidepressant properties, (*R,S*)-ketamine has been shown to be an anti-inflammatory drug (Zanos et al., 2018; Verdonk et al., 2019) that regulates Cox-2 expression in several body tissues including the brain (Galecki et al., 2012; De Kock et al., 2013). We found that Cox-2 is significantly increased in the HPC of aged mice, which is in accord with mice and human data showing that several inflammatory markers increase with aging (Singh and Newman, 2011). Moreover, we found that (*R,S*)-ketamine selectively decreased Cox-2 expression in vCA3 of adolescent male mice. Ongoing experiments are clarifying whether Cox-2 levels are changed following different windows of administration of (*R,S*)-ketamine.

In summary, the present study highlights the necessity of age-, dose- and sex-specific pharmacological interventions to improve behavior. Future studies will investigate sex-specific brain circuits mechanisms that result in these behavioral effects with the ultimate aim to translate scientific data into practical applications that are effective for each sex.

LIMITATIONS OF THE STUDY

There are some limitations in this study that could be addressed in future research. First, only the 1-h post-injection time point was analyzed rather than the 2 and 24 h-time points that are commonly used in preclinical and clinical studies (Zarate et al., 2006; Murrough et al., 2013; Zanos et al., 2016). However, there is considerable evidence that 1 h is an optimal time point. Numerous studies showed that (*R,S*)-ketamine is effective within 1 h of administration in adolescent, and aged subjects (Papolos et al., 2013; Srivastava et al., 2015; Zanos et al., 2016). In adolescent subjects, intranasal (*R,S*)-ketamine (30–120 mg) produces a significant therapeutic response within 1 h of administration that is sustained up to 72–96 h (Papolos et al., 2013). In aged subjects, (*R,S*)-ketamine (0.5 mg/kg) significantly reduces depressive symptoms (i.e., decreases the Hamilton depression rating scale (HAMD) scores of 65%) within 1 h of administration (Srivastava et al., 2015; George et al., 2017). The antidepressant response is sustained but not increased in the next 24 h post infusion (Srivastava et al., 2015). Finally, a recent study in adult mice has also shown that (*R,S*)-ketamine is effective at 1 h post-injection in adult mice (Zanos et al., 2016). Additionally, although short time points may be associated with side-effects, we did not see observe any side effects with respect to locomotion 1 h following injection. While locomotion assessment might not account for all the psychotomimetic effects, other studies have shown that they occur in less than 1-h post-administration (Papolos et al., 2013; Srivastava et al., 2015; Zanos et al., 2016).

Second, only a single injection of (*R,S*)-ketamine was tested in the elderly. Other studies have showed that repeated treatments resulted in higher likelihood of remission or longer time to relapse up to 6 months following infusions (George et al., 2017; Bryant et al., 2019), however, patients failed to sustain a response if the infusions were too far apart, therefore suggesting that repeated infusions may confer greater protection against depression, but they might need to be administered at greater frequency to be effective. Therefore, testing the effects of repeated injections might add to the findings of this analysis. This will be included in a new line of work.

Third, in this work we sought to investigate (*R,S*)-ketamine effects in adolescent and aged mice, and we did not include adult animals. However, we have previously published work showing the effects of varying doses of (*R,S*)-ketamine in adult male and female mice. In adult mice, we found that a single prophylactic injection of (*R,S*)-ketamine (30 mg/kg), but not 10 or 90 mg/kg, decreased behavioral despair and attenuated learned fear (Brachman et al., 2016; McGowan et al., 2017; Mastrodonato et al., 2018). In female mice, (*R,S*)-ketamine and its metabolite (2*R*,6*R*)-hydroxynorketamine [(2*R*,6*R*)-HNK] decreased behavioral despair, but did not attenuate learned fear (Chen et al., 2020). In female mice, (*R,S*)-ketamine was effective at a lower dose (10 mg/kg) than in male mice. Moreover, we showed that ovarian-derived hormones mediate the prophylactic actions of (*R,S*)-ketamine effects in female mice. These data further suggest that (*R,S*)-ketamine effects are age- and sex-specific and therefore emphasize the need for age- and sex-specific approaches to the prevention and treatment of psychiatric disorders.

Lastly, we did not found any amnesic effects following a single (*R,S*)-ketamine (30 mg/kg) administration in 129S6/SvEv mice (Brachman et al., 2016; Mastrodonato et al., 2018). Additionally, a recent paper found that a single injection of (*R,S*)-ketamine (30 mg/kg) administered 22 h after fear conditioning to C57BL/6 male mice, significantly facilitates CFD up to 2 weeks following injection (Asim et al., 2020). However, other rodent studies have shown that chronic injections of (*R,S*)-ketamine (30 mg/kg) induced learning and memory deficits (Neill et al., 2010; Tan et al., 2011). Therefore, it is not conclusive whether these findings will generalize to other mouse strains. We will investigate this in future work.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Animal Care and Use Committee (IACUC) at NYSPI.

AUTHOR CONTRIBUTIONS

AM and CD and JJM contributed to the conception and design of the work. AM, NK, and IP contributed to the acquisition of data. AM and CD contributed to the analysis and interpretation of data for the work, drafting the work and revising it critically for important intellectual content. AM, CD, NK, IP, JCM, and JJM approved the version of the manuscript to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.852010/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Feeling Unsafe at School Among Adolescents in 13 Asian and European Countries: Occurrence and Associated Factors

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Background: Research on perceived school safety has been largely limited to studies conducted in Western countries and there has been a lack of large-scale cross-national studies on the topic.

Methods: The present study examined the occurrence of adolescents who felt unsafe at school and the associated factors of perceived school safety in 13 Asian and European countries. The data were based on 21,688 adolescents aged 13-15 (11,028 girls, 10,660 boys) who completed self-administered surveys between 2011 and 2017. Logistic regression analyses were used to estimate odds ratios and 95% confidence intervals.

Findings: The number of adolescents who felt unsafe at school varied widely across countries, with a mean occurrence of 31.4% for the total sample: 31.3% for girls, and 31.1% for boys. The findings revealed strong independent associations between feeling unsafe and individual and school-related factors, such as being bullied, emotional and behavioral problems and feeling that teachers did not care. The study also found large variations in perceived school safety between schools in many countries.

Conclusion: The findings emphasize the need to create safe educational environments for all students, based on positive relationships with teachers and peers. School-based

interventions to prevent bullying and promote mental health should be a natural part of school safety promotion.

Keywords: school safety, school climate, mental health, adolescent, associated factors, feeling unsafe, cross-national comparisons, occurrence

INTRODUCTION

A safe school environment is essential for the educational success and development of children and young people. The United Nations' Educational, Scientific and Cultural Organization defines school safety as the process of establishing and maintaining a school that provides a physically, cognitively, and emotionally safe space where students and staff can carry out learning activities (1).

Perceived school safety has mainly been studied in western countries. A recent systematic review of 43 studies showed the mean occurrence of unsafe school environments was ∼19% and ranged from 6.1 to 69.1% (2). Feeling safe at school has been reported to be associated with various predictors, including bullying and youth violence (3, 4), lower academic achievements (5) and better relationships with teachers (6). Feeling unsafe may have a negative impact on mental health, which may persist throughout life. It has been associated with mental health issues among adolescents, such as depressive symptoms, suicidal behavior and self-harm (7, 8).

Although school safety is often included in studies as one of the aspects of a school environment, a recent systematic review reported a lack of consensus on what constituted a school climate (9). School climate has been reported to be associated with socioemotional and behavioral outcomes (10). However, it is not clear whether perceived school safety in itself accounts for these associations or if they can be explained by other aspects of a school climate, such as the institutional environment.

According to the systematic review, most of the studies on perceived school safety were published between 2016 and 2020, indicating an increasing research interest in this topic (2). However, very few cross-national studies have been conducted and all of these only compared perceived school safety between two countries (11–13). In addition, there is no well-established definition of school safety (14). The impact of feeling unsafe at school on mental health outcomes, and the association with surrounding environments, such as school characteristics, has been understudied (15, 16). This study contributes to this growing area of research by exploring perceived school safety in 13 countries using the same study method in all of the countries.

This study explored perceived school safety in 13 Asian and European countries. The first aim was to report the cross-national comparisons of the occurrence of adolescents feeling unsafe at school in 13 Asian and European countries. The second aim was to assess the associations between perceived school safety and individual factors (e.g., sex and emotional and behavioral difficulties) and school-related factors (e.g., school type and location). We also wanted to see whether there were any variations in the probability of feeling unsafe in different schools in each country. This was the first large-scale cross-national study to examine the occurrence of school safety and its associations with individual and school characteristics.

METHODS

The Eurasian Child Mental Health Study group is a large, international study body that conducts cross-national research on the wellbeing and mental health of children and adolescents (17). This study was part of the Eurasian Child Mental Health Study and comprised 13 countries: China, Finland, Greece, India, Indonesia, Iran, Israel, Japan, Lithuania, Norway, Russia, Singapore, and Vietnam.

Sample

We surveyed 28,427 adolescents in the 13 countries between 2011 and 2017. The median response rate was 88.9% and varied from 51.7% in Indonesia to 97.1% in Iran. Because there were variations in the age ranges in the total samples across countries, we focused on adolescents aged 13-15 years to make the data more comparable. After the age restriction, a total of 21,688 adolescents (50.8% girls) from 200 schools were included. Their mean age was 13.9 years and the mean number of schools in the 13 countries was 16. The mean number of participants was 1,679 and ranged from 946 in Vietnam to 2,988 in Finland. The survey year and the characteristics of each country's study sample are presented in **Table 1**.

Questionnaire and Procedure

The current study was conducted using a self-administered survey, which was based on a questionnaire previously used among adolescents in Finland (18, 19). The questionnaires were translated into the local language and back-translated for accuracy (20). All students at school at the time of the survey were invited to participate and completed the questionnaires during school hours. The questionnaires were collected by the teachers in 11 countries and returned to the researchers and were completed electronically in Norway and Singapore.

Ethics

The researchers obtained ethical approval from the Institutional Review Boards in their countries and obtained permission from the schools. Participation was voluntary and anonymity was guaranteed. Consent was obtained from the parents or school authorities, according to each country's policies. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Measures

School safety was assessed by a single item: "I feel safe at school." The possible answers were never, sometimes, often and always.

TABLE 1 | Demographic characteristics of the 13 countries.

Country	Survey year	Total *N*	Sex (girl) *N* (%)	Age Mean (SD) [range]	School location (urban) *N* (%)	School type (public) *N* (%)	Number of schools
China	2016	2,119	1040 (49.1)	13.8 (0.8) [13-15]	819 (36.8)	1,779 (79.9)	10
Finland	2014	2,982	1493 (50.1)	14.1 (0.8) [13-15]	2,686 (89.9)	2,988 (100)	13
Greece	2016	1,040	556 (53.5)*	13.6 (0.6) [13-15]	750 (72.1)	1,040 (100)	14
India	2016	1,672	864 (51.7)	13.6 (0.7) [13-15]	1,420 (84.9)	209 (12.5)	11
Indonesia	2016	1,023	542 (53.0)	13.5 (0.6) [13-15]	1,024 (100)	656 (64.1)	5
Iran	2016	1,178	557 (47.3)	14.3 (0.8) [13-15]	1,178 (100)	1,036 (87.9)	16
Israel	2014	1,277	698 (54.7)*	14.0 (0.8) [13-15]	1,101 (100)	1,246 (97.4)	10
Japan	2011	1,828	943 (51.6)	13.9 (0.3) [13-14]	833 (45.5)	1,831 (100)	17
Lithuania	2016	2,507	1256 (50.1)	14.1 (0.8) [13-15]	1,353 (53.8)	2,515 (100)	17
Norway	2017	1,900	946 (49.8)	13.9 (0.8) [13-15]	1,611 (84.8)	1,742 (99.4)	45
Russia	2015	1,051	546 (52.0)	14.1 (0.8) [13-15]	1,051 (100)	1,051 (100)	20
Singapore	2014	2,165	1103 (50.9)	14.0 (0.8) [13-15]	2,165 (100)	2,165 (100)	24
Vietnam	2016	946	484 (51.2)	13.9 (0.8) [13-15]	946 (100)	946 (100)	3

The chi-square test for equal proportions was used to analyze sex distribution. Asterisk (*) indicates statistical significance, $p < 0.05$.

Because the never category was very small in some countries, such as 2.2% in Finland, we combined the responses into binary outcomes. We did this by pooling never and sometimes and then often and always. This enabled us to compare the different countries. The *a priori* reference category for the 13 countries was Finland, as it had the lowest occurrence of adolescents who felt unsafe at school. The adolescents' ages were subdivided into 13, 14, and 15 years of age and the reference category was 13 years old. Gender was dichotomized into girls and boys.

To assess bullying victimization, a definition of bullying was provided: "A student is getting bullied, if another student or a group of students repeatedly treats him/her negatively or in an insulting manner. It is difficult for the bullied student to defend himself/herself. Bullying can be intermittent or continuous. Bullying can be verbal (e.g., calling names, threatening), physical (e.g., hitting, pushing) or psychological (e.g., spreading rumors, avoiding, excluding). Continuous nasty or insulting teasing is also bullying." Cyberbullying was defined as: "Repeated mocking on the Internet, bullying *via* emails or text messages or spreading insulting material about another person on the Internet." The students were asked, "How often have you been bullied in school in the past 6 months?," "How often have you been bullied away from school in the past 6 months?" for traditional bullying and the options were never, less than once a week, more than once a week, and most days. Cyberbullying was measured by asking "During the past 6 months, how often have you been cyberbullied?" and the options were never, less than once a week, more than once a week, and almost every day. For all bullying questions, we combined the responses into binary outcomes: no for never and yes for the other responses. After that, we combined these variables and compared adolescents who were not bullied, who were only traditionally bullied, who were only cyberbullied, and who were both traditionally and cyberbullied.

Emotional and behavioral difficulties were assessed with a self-report version of the Strengths and Difficulties Questionnaire (SDQ). Five subscales measured emotional symptoms, conduct problems, hyperactivity, peer problems and prosocial behavior and each had five items (21). Because our study sample represented the general population, we followed Goodman's advice and used the broader internalizing subscales, covering emotional symptoms and peer problems, and the externalizing subscales, covering conduct problems and hyperactivity symptoms. The adolescents were asked if they had overall difficulties with their emotions, concentration, behavior or getting along with other people. This question is part of the SDQ impact supplement and was thought to provide useful further insight into psychiatric cases and the need for health services. The possible answers were no, yes minor difficulties, yes definite difficulties or yes severe difficulties. These were coded as no, mild, moderate and severe difficulties and combined into three categories: no versus mild vs. moderate and severe.

Their views on teachers were measured by a single item: "Teachers care about me." The possible answers were never, sometimes, often and always. We combined never and sometime and often and always.

School characteristics were assessed by the type and location of the school. Researchers from each country selected a mixture of rural and urban and public and privately funded study schools. The reference categories were public schools for type and urban schools for location.

Statistical Analysis

The responses from all countries were pooled to create various descriptive statistics. First, an unadjusted univariate logistic regression was conducted to identify any association between school safety and explanatory variables. Significant interactions ($p < 0.1$) were found between sex and other explanatory variables: country, bullying victimization, SDQ externalizing symptoms, perceived difficulties and whether teachers cared. Sex-specific analysis and reporting are encouraged in health research

to understand the implications of the differences for preventive intervention and treatment following the raising awareness of sex difference in health and women's underrepresentation or exclusion in research data (22, 23). Therefore, further analyses were conducted separately for sex. Second, the regression analyses were adjusted for age and country. Third, the regression analyses were adjusted for all the other explanatory variables. The multivariate analyses were performed using two models, because information about perceived difficulties were missing from Japan and Israel. We used multivariable regression analysis to adjust for all the explanatory variables, except perceived difficulties (model one). Then we included perceived difficulties, but excluded Israel and Japan (model two). Finally, a logistic regression model was used to estimate the probabilities of feeling unsafe in different schools in each country. This was done separately for girls and boys including school as an explanatory variable and adjustment was made for age. We included 200 schools and the mean number of schools in the 13 countries was 16. If a school had <10 girls or boys who felt unsafe at school, it was excluded from the analyses for this sex. Two-sided p-values of <0.05 were considered statistically significant, with the exception of the interaction analysis ($p < 0.1$). The statistical analyses used SAS 9.4 for Windows (SAS Institute Inc. Cary, NC, USA).

RESULTS

Table 2 summarizes the responses and explanatory variables from the 13 countries. The occurrence of adolescents who felt unsafe at school, based on the different categories of explanatory variables and the results of the regression analysis, are shown separately for girls (**Table 3**) and boys (**Table 4**). This shows that 31.4% of the total sample felt unsafe and the occurrence was 31.3% for the girls and 31.1% for the boys. The interaction between safety and sex was significant for several explanatory variables, namely country, bullying victimization, SDQ externalizing subscale, whether teachers cared and perceived difficulties.

Tables 3, **4** provide separate odds ratios (ORs) by sex for the explanatory variables. When we adjusted the data for age and country, the same variables from the unadjusted univariate logistic regression remained significant, except school location for boys. In multivariate model one, a significant association was noted between feeling unsafe and just being traditionally bullied (girls OR 1.83, 95% CI 1.59-2.10 and boys OR 1.67, 95% CI 1.47-1.90) and combined traditional and cyberbullying (girls OR 2.70, 95% CI 2.20-3.31 and boys OR 2.04, 95% CI 1.66-2.52). Cyberbullying was significantly associated with feeling unsafe for girls but not for boys (OR 1.53, 95% CI 1.23-1.9). When it came to emotional and behavioral difficulties, there were significant associations between feeling unsafe and both internalizing behavior (girls OR 1.10, 95% CI 1.08-1.12 and boys 1.10, 95% CI 1.08-1.12) and externalizing behavior (girls OR 1.06, 95% CI 1.04-1.08 and boys OR 1.03, 95% CI 1.02-1.05). The same was true if they felt their teachers were less caring (girls OR 5.35, 95% CI 4.81-5.95 and boys OR 5.42, 95% CI 4.86-6.04). Most countries reported higher odds for feeling unsafe than the reference country, Finland, except Israeli girls. The greatest odds were in Japan (girls OR 20.15, 95% CI 15.58-26.07 and boys OR 21.86, 95% CI 16.60-28.77).

The same variables from model one remained significant in model two. A significant association was also found between feeling unsafe and moderate and severe perceived difficulties (girls OR 1.18, 95% CI 1.04-1.34 and boys OR 1.00, 95% CI 0.88-1.13). However, only girls had mild perceived difficulties (OR 1.55, 95% 1.29-1.86). There were no significant associations between age and feeling unsafe in both multivariate models.

School type and location were not significantly associated with girls feeling unsafe after adjustment. Public schools remained associated with boys feeling unsafe throughout the analyses (OR 1.30, 95% 1.05-1.61), but no significant association was found with school location after the data were adjusted.

Because a strong association was found between feeling unsafe and combined traditional and cyberbullying, a *post-hoc* analysis

TABLE 2 | Summary of responses and explanatory variables in the 13 participating countries.

Variables	*N*	Mean	%	SD
School safety				
Always/often	14,749	..	68.6	..
Never/sometimes	6,739	..	31.4	..
Sex				
Girls	11,028	..	50.8	..
Boys	10,660	..	49.2	..
Age				
13	6,953	..	31.9	..
14	9,147	..	41.9	..
15	5,722	..	26.2	..
Bullying victimization				
Not victimized	15,256	..	71.9	..
Traditional only	3,722	..	17.5	..
Cyber only	1,005	..	4.7	..
Combined	1,238	..	5.8	..
Emotional and behavioral difficulties				
Externalizing	..	6.22	..	3.09
Internalizing	..	5.51	..	3.40
Perceived difficulties				
No	8825	..	44.7	..
Mild	8140	..	41.2	..
Moderate/severe	2787	..	14.1	..
Teacher care				
Always/often	11950	..	55.9	..
Never/sometimes	9442	..	44.1	..
School type				
Public	19204	..	88.6	..
Private	2464	..	11.4	..
School location				
Urban	16937	..	78.3	..
Rural	4700	..	21.7	..

SD, standard deviation.

TABLE 3 | Univariate and multivariate analyses of the explanatory variables associated with feeling unsafe at school among girls.

Variables	Category	Never/sometimes safe		Univariate analysis	Multivariate analysis	
					Model 1[a]	Model 2[b]
		N (%)	Mean (SD)	OR (95%CI)		
Sex	Girl	3,415 (31.3)	..	..	..	..
Country	Finland	171 (11.5)	..	Reference	Reference	Reference
	Norway	131 (13.9)	..	1.24 (0.97-1.58)	1.96 (1.48-2.61)*	1.88 (1.41–2.51)*
	Israel	101 (14.6)	..	1.31 (1.00-1.70)*	1.31 (0.94-1.82)	..
	Greece	101 (18.2)	..	1.70 (1.30-2.23)*	3.02 (2.22–4.11)*	3.01 (2.21–4.12)*
	India	153 (17.8)	..	1.66 (1.31–2.10)*	3.33 (2.32–4.80)*	3.67 (2.53–5.31)*
	Iran	139 (25.6)	..	2.64 (2.06–3.39)*	2.35 (1.76–3.13)*	2.46 (1.84–3.29)*
	Indonesia	164 (30.3)	..	3.33 (2.61–4.24)*	3.74 (2.79–5.00)*	3.74 (2.79–5.02)*
	Lithuania	387 (31.4)	..	3.50 (2.87–4.28)*	3.45 (2.73–4.37)*	3.65 (2.87–4.65)*
	Singapore	390 (35.4)	..	4.21 (3.43–5.15)*	5.50 (4.36–6.94)*	5.65 (4.46–7.15)*
	China	499 (48.8)	..	7.30 (5.97–8.93)*	11.03 (8.58–14.17)*	11.59 (8.95–15.01)*
	Russia	294 (54.7)	..	9.24 (7.32–11.66)*	9.05 (6.93–11.82)*	9.09 (6.94–11.92)*
	Vietnam	239 (49.6)	..	7.54 (5.94–9.58)*	7.91 (6.03–10.39)*	8.28 (6.27–10.94)*
	Japan	646 (69.8)	..	17.76 (14.36–21.96)*	20.15 (15.58–26.07)*	..
Age	13	1,024 (28.5)	..	Reference	Reference	Reference
	14	1,647 (35.7)	..	1.39 (1.27–1.53)*	0.92 (0.81–1.04)	0.94 (0.83–1.07)
	15	744 (27.3)	..	0.94 (0.84–1.05)	0.88 (0.76–1.01)	0.91 (0.79–1.05)
Bullying victimization	Not victimized	2,085 (26.5)	..	Reference	Reference	Reference
	Traditional only	725 (43.3)	..	2.11 (1.90–2.36)*	1.83 (1.59–2.10)*	1.83 (1.58–2.12)*
	Cyber only	191 (35.7)	..	1.54 (1.28–1.85)*	1.53 (1.23–1.91)*	1.50 (1.19–1.89)*
	Combined	340 (52.3)	..	3.04 (2.58–3.57)*	2.70 (2.20–3.31)*	2.55 (2.06–3.15)*
Emotional and behavioral difficulties	Externalizing	..	7.07 (3.03)	1.60 (1.54–1.67)*	1.06 (1.04–1.08)*	1.06 (1.03–1.08)*
	Internalizing	..	7.35 (3.61)	1.72 (1.65–1.80)*	1.10 (1.08–1.12)*	1.09 (1.07–1.11)*
Perceived difficulties	No	703 (18.1)	..	Reference	Reference	Reference
	Mild	1,378 (32.0)	..	2.31 (2.08–2.57)*	..	1.18 (1.04–1.34)*
	Moderate/Severe	665 (38.9)	..	3.56 (3.11–4.08)*	..	1.55 (1.29–1.86)*
Teacher care	Always/Often	893 (14.4)	..	Reference	Reference	Reference
	Never/Sometimes	2,499 (53.5)	..	6.82 (6.22–7.47)*	5.35 (4.81–5.95)*	5.14 (4.58–5.77)*
School type	Private	302 (26.1)	..	Reference	Reference	Reference
	Public	3,103 (32.1)	..	1.33 (1.16–1.53)*	0.88 (0.68–1.13)	0.90 (0.70–1.16)
School location	Urban	2,430 (28.5)	..	Reference	Reference	Reference
	Rural	959 (42.2)	..	1.84 (1.67–2.02)*	1.07 (0.92–1.23)	1.05 (0.89–1.23)

Differences in the numbers of participants between tables are due to missing information. Asterisk (*) indicates statistical significance ($p < 0.05$). SD, standard deviation; OR, odds ratio; CI, confidence interval. [a]Adjusted for all explanatory variables, except perceived difficulties. [b]Adjusted for all explanatory variables, excluding Japan and Israel.

examined whether this combined victimization more strongly related to feeling unsafe than traditional bullying only and cyberbullying only. This revealed that combined victimization was more strongly associated with feeling unsafe than traditional bullying only (girls OR 0.59, 95% CI 0.49-0.72 and boys OR 0.74, 95% CI 0.60-0.90) or cyberbullying only (girls OR 0.46, 95% CI 0.36-0.60 and boys OR 0.53, 95% CI 0.40-0.69). The same additional analysis was conducted on perceived difficulties and this revealed that moderate or severe perceived difficulties were more strongly associated with feeling unsafe than mild perceived difficulties (girls OR 1.54 95% CI 1.36-1.75 and boys OR 1.42, 95% CI 1.22-1.66).

Figure 1 shows the predicted probabilities of feeling unsafe at different schools, by country and sex. For girls, the range in predicted probabilities of feeling unsafe between schools was smallest in Vietnam (0.43-0.55, mean 0.5, range 0.13) and largest in Japan (0.41-1.00, mean 0.72, range 0.59). For boys, it was smallest in Vietnam (0.48-0.58, mean 0.53, range 0.10) and largest in Russia (0.23-0.77, mean 0.48, range 0.54).

DISCUSSION

This study had three key findings. First, a striking proportion of approximately 30% of the adolescents did not feel safe at school and there were large variations across the 13 Asian and European countries, from 11.5% in Finland to 69.8% in Japan for girls and from 7.7% in Norway to 68.2% in Japan for boys. Second, a strong independent association was found between feeling unsafe

TABLE 4 | Univariate and multivariate analyses of the explanatory variables associated with feeling unsafe at school among boys.

Variables	Category	Never/sometimes safe		Univariate analysis	Multivariate analysis	
					Model 1[a]	Model 2[b]
		N (%)	Mean (SD)	OR (95%CI)		
Sex	Boy	3,252 (31.1)	..	..	..	..
Country	Finland	131 (8.9)	..	Reference	Reference	Reference
	Norway	73 (7.7)	..	0.85 (0.63–1.15)	1.42 (1.02–1.99)*	1.41 (1.01–1.98)*
	Israel	81 (14.2)	..	1.68 (1.25–2.26)*	1.52 (1.06–2.17)*	..
	Greece	116 (24.2)	..	3.25 (2.47–4.28)*	4.59 (3.36–6.28)*	4.75 (3.46–6.51)*
	India	209 (26.3)	..	3.63 (2.86–4.62)*	6.95 (4.98–9.70)*	7.24 (5.17–10.14)*
	Iran	211 (34.3)	..	5.33 (4.17–6.81)*	4.22 (3.21–5.56)*	4.19 (3.18–5.53)*
	Indonesia	145 (30.2)	..	4.40 (3.38–5.74)*	5.78 (4.23–7.90)*	5.56 (4.05–7.64)*
	Lithuania	425 (35.4)	..	5.58 (4.50–6.92)*	4.35 (3.40–5.57)*	4.58 (3.56–5.87)*
	Singapore	363 (34.3)	..	5.32 (4.27–6.63)*	6.78 (5.28–8.69)*	6.73 (5.23–8.65)*
	China	457 (44.1)	..	8.04 (6.47–9.99)*	10.43 (8.01–13.57)*	11.36 (8.67–14.89)*
	Russia	220 (45.9)	..	8.67 (6.73–11.18)*	7.43 (5.57–9.91)*	7.43 (5.55–9.94)*
	Vietnam	243 (52.6)	..	11.33 (8.77–14.63)*	9.98 (7.46–13.35)*	9.92 (7.38–13.33)*
	Japan	578 (68.2)	..	21.93 (17.42–27.61)*	21.86 (16.60–28.77)*	..
Age	13	890 (27.7)	..	Reference	Reference	Reference
	14	1,561 (36.1)	..	1.47 (1.33–1.62)*	1.02 (0.90–1.16)	1.02 (0.89–1.16)
	15	801 (27.6)	..	0.99 (0.89–1.11)	0.97 (0.84–1.11)	0.99 (0.85–1.14)
Bullying victimization	Not victimized	1,939 (27.1)	..	Reference	Reference	Reference
	Traditional only	805 (40.3)	..	1.82 (1.64–2.02)*	1.67 (1.47–1.90)*	1.65 (1.44–1.89)*
	Cyber only	152 (33.2)	..	1.34 (1.10–1.64)*	1.08 (0.86–1.37)	1.03 (0.81–1.31)
	Combined	265 (46.7)	..	2.37 (1.99–2.81)*	2.04 (1.66–2.52)*	1.98 (1.59–2.48)*
Emotional and behavioral difficulties	Externalizing	..	7.19 (3.09)	1.49 (1.43–1.56)*	1.03 (1.02–1.05)*	1.03 (1.01–1.05)*
	Internalizing	..	6.05 (3.50)	1.67 (1.60–1.74)*	1.10 (1.08–1.12)*	1.11 (1.09–1.13)*
Perceived difficulties	No	1,086 (22.8)	..	Reference	Reference	Reference
	Mild	1,175 (31.9)	..	1.73 (1.57–1.91)*	..	1.00 (0.88–1.13)
	Moderate/Severe	388 (37.4)	..	2.46 (2.11–2.87)*	..	1.25 (1.03–1.52)*
Teacher care	Always/Often	853 (15.0)	..	Reference	Reference	Reference
	Never/Sometimes	2,377 (50.7)	..	5.83 (5.32–6.40)*	5.42 (4.86–6.04)*	5.53 (4.91–6.21)*
School type	Private	368 (28.5)	..	Reference	Reference	Reference
	Public	2,878 (31.7)	..	1.16 (1.02–1.32)*	1.28 (1.03–1.58)*	1.30 (1.05–1.61)*
School location	Urban	2,336 (28.6)	..	Reference	Reference	Reference
	Rural	896 (41.0)	..	1.74 (1.58–1.92)*	1.06 (0.92–1.22)	0.94 (0.80–1.10)

Differences in the numbers of participants between tables are due to missing information. Asterisk (*) indicates statistical significance ($p < 0.05$). SD, standard deviation; OR, odds ratio; CI, confidence interval. [a]Adjusted for all explanatory variables, except perceived difficulties. [b]Adjusted for all explanatory variables, excluding Japan and Israel.

and individual and school-related factors, such as being bullied and emotional and behavioral difficulties. Third, there were large variations in the probability of perceived school safety between schools in many countries.

The fact that nearly one-third of adolescents did not feel safe at school suggests that violence and insecurity in society could be highly associated with these fears. Finland and Norway are Nordic welfare states and the occurrence of adolescents who felt unsafe was very low. In contrast, Japanese adolescents were most likely to feel unsafe, despite living in a highly developed country with significantly low crime rates and a comparatively modest social safety net (24, 25). The reasons for these variations were unclear, but they may reflect cultural and social differences.

Adolescents were more likely to feel unsafe at school if they lived in countries with greater power distance and collectivistic cultures. Power distance is the degree to which countries accept the hierarchy of power and collectivism refers to a value that emphasize on conformity to group harmony rather than individual interests (26). A previous study of 31 countries found that adolescents who lived in such countries felt less connected with school communities than students who lived in countries that focused on individuals and had more equal power (27). Teacher-centered and strictly disciplined education within cultures high in power distance may inhibit positive teacher-student relationships, in contrast to cultures where teachers and students are perceived as more equal (28). Moreover, the highly

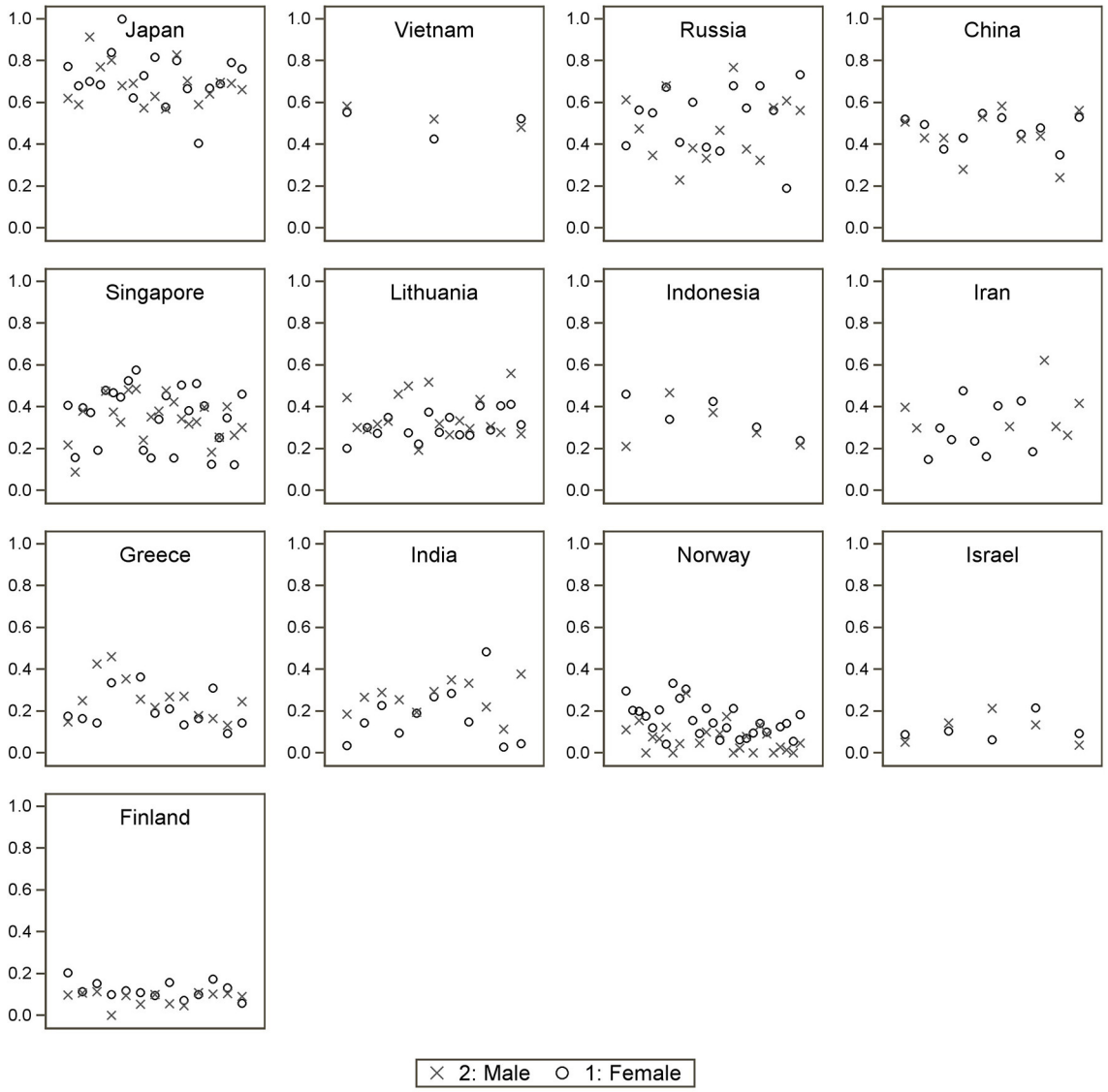

FIGURE 1 | Predicted probabilities of feeling unsafe at school by school and country, adjusted for age. The X axis shows schools in random order.

competitive and stressful environment in Asian schools may reduce feelings of safety (29), as excessive academic distress has been linked with emotional and behavioral difficulties (30). In addition, corporal punishment is still legal in one-third of the countries in the world and students could feel less safe if they received or witnessed physical punishment at school (31).

Individual Factors Associated With Feeling Unsafe

This was the first large scale cross-national study to assess whether being victimized by traditional bullying, cyberbullying or the combination of these was associated with feeling unsafe at school. We found that both traditional victimization and combined victimization were strongly associated with feeling unsafe for both sexes. However, cyberbullying victimization was only associated with feeling unsafe in girls, who are generally more likely to be cyberbullied than boys (32).

We found that both internalizing and externalizing symptoms were significantly associated with feeling unsafe. In addition, moderate and severe perceived difficulties were independently associated with feeling unsafe in both sexes. Longitudinal studies have shown that both witnessing violence and victimization at school predicted later internalizing and externalizing problems (33, 34). Individuals with mental health difficulties may start feeling unsafe because they perceive a lack of social support or stigma (35). However, the mechanisms between mental health symptoms and feeling unsafe need clarification. For example, bullying victimization has been associated with both emotional

and behavioral difficulties and feeling unsafe at school but the causes and directions of these are unknown (4, 36).

We did not find any significant differences between the age groups, in contrast to previous studies that found differences in perceived school safety between younger and older students (11, 37). This may be explained by the limited age range of 13-15 years in our study, compared to wider age ranges in other studies.

School Factors Associated With Feeling Unsafe

The fact that both sexes felt unsafe if they perceived that teachers did not care was a striking finding. In contrast, good teacher-student relationships, with secure attachments, have been associated with increased psychosocial wellbeing and reduced mental health issues (38). In our study, boys were more likely to feel unsafe at public, than private schools, but no difference was found in girls. Physical conflicts and gang-related activity tend to be lower in private schools (39). Furthermore, bullying and physical aggression are more common among boys (40), which may explain why girls were not affected.

Variations in the Probability of Feeling Unsafe in Different Schools by Country

We found variations in the probability of feeling unsafe in different schools in the 13 countries. In some countries, like Finland, the variations were quite small and this could reflect the homogenous quality of education across the country (41). Private schools often require high tuition fees, compared to Government-funded schools, which may contribute to the variation between schools, especially in countries that included private schools. Our findings emphasize the importance of providing safe educational environments for all students, regardless of their background or the schools they attend.

STRENGTHS AND LIMITATIONS

The strength of our study included the use of same measures from large number of countries. The same definition of bullying and cyberbullying were provided in all countries. However, there were some limitations. First, the surveys were conducted in certain regions of those countries. Therefore, the generalisability of the results is subject to certain limitations. For instance, the occurrence rate refers to occurrence in that geographical area which participated in the study and may not represent the whole country. This lack of sample representativeness is a common methodological issue in cross-national research (42). However, we aimed to include all the schools in specific geographical area in the countries to increase the representativeness. Second, we tried to select public and private schools in both urban and rural locations. However, the sample largely consisted of private schools in countries like India and Indonesia and some countries, like Finland, did not include any private schools. This discrepancy was partially due to the different educational systems. For example, in Finland, there are only few private schools whereas, in some countries, these are the mainstream. Additionally, the number of schools we included on the studies varies across countries. This may have affected the representativeness of the study. Third, we did not have data on classroom teachers such as their qualification and length of experience in the education which are also known to be associated with school climate and bullying (43, 44). Fourth, it is possible that some meanings were slightly changed when the questionnaires were translated, such as the definitions of safety. Cultural factors may also have influenced some of the variation in the occurrencebecause the interpretation of concepts such as feeling of safety or bullying can differ across cultures and languages. In addition, the restriction of the survey to adolescents currently attending school and present on the day of the survey may have also led to some underreporting of occurrence of students who feel unsafe at school as bullying and perceived lack of safety at school are associated with higher risk of absenteeism (45). Lastly, the cross-sectional study design was purely observational, and no causal inference can be drawn from the findings.

CONCLUSION

Nearly one-third of the adolescents we studied felt unsafe at school, which was really striking and creates a challenge for societies. Safe educational environments are based on building care and trust with teachers and promoting positive interactions with others, rather than being socially isolated. They can also create a backdrop for positive developments in adolescence and prevent bullying. This makes school safety a critical issue for both educational systems and public health. Adolescents who experienced mental health difficulties or were bullied were more likely to feel unsafe at school. This emphasizes the need for school-based, anti-bullying interventions and mental health promotion. These should include initiatives such as psychoeducation, and social–emotional learning programs to prevent behavioral problems and enhance the prosocial competence of all children. Our findings highlight inequality in securing a safe educational environment for students within, and among, countries. There is clearly a need for strategies to promote educational environments where all students can feel safe and be protected.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Boards in each countries by the researchers and obtained permission from the schools (e.g., The Ethics Committee at the University of Turku in Finland). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

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AUTHOR CONTRIBUTIONS

AS, AK, SO, HKY, HKA, GK, SL, LLI, MH, SP, LS, JS, HS, TW, and ZZ contributed to the general study conception and design. Study design and data collection in each country was performed by the authors in the participating countries. Data management and harmonization was performed by LS. Data analysis was planned by AS, YM, ET, LLE, and performed by LS. The first draft of the manuscript was written by YM, ET, LLE, LS, and AS. All authors including those in the EACMHS Study Group commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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ORIGINAL RESEARCH
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Comparing Childhood Characteristics of Adopted and Non-adopted Individuals Deceased by Suicide

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Objective: Across the globe more than 35,000 children a year are adopted by non-relatives, and some studies suggest that adopted individuals may be more vulnerable to developing mental disorders. To map the differences in suicide risk factors in adopted and non-adopted individuals, this study will compare the development of mental disorders as well as life events occurring before the age of 18 for both adopted and non-adopted individuals deceased by suicide.

Methods: This study included 13 adopted and 26 non-adopted individuals deceased by suicide as well as 26 non-adopted living control individuals. Cases were taken from a data bank created over the last decade by researchers of [our institution] comprising a mixture of 700 suicide cases and living control individuals aged from 14 to 84. Adopted and non-adopted individuals deceased by suicide; adopted individuals deceased by suicide and non-adopted living control individuals were each compared on Axis I and II disorders, early life events, and burdens of adversity.

Results: Results show significant differences, with a higher rate of Attention Deficit Hyperactivity Disorder, mental health comorbidity and Cluster C personality disorders among adopted individuals. Furthermore, adopted individuals have higher adversity scores prior to the age of 15.

Conclusion: This study underlines the fact that adoptive families need to be supported throughout adoption. Health care professionals need specialized training on this matter, and the psychological challenges adopted individuals face need to be treated at the earliest juncture.

Keywords: adoption, developmental course, risk factors, suicide, youth—young adults

INTRODUCTION

Across the globe, more than 35,000 children a year are adopted by non-relatives. Fortunately, the majority of adopted individuals are in good physical and mental health (1, 2). The knowledge that they were given up for adoption, or the experience of adverse early life events may be counteracted by a nurturing family environment (3). Some authors refer to the capacity to overcome early adversity, transforming experiences into resilience, especially when adoptive parents are sensitive to issues relating to the origins of their adopted child (4, 5).

However, when compared to the general population, a significantly large proportion of adopted individuals will develop mental disorders during childhood or later in life, which suggests that adopted individuals may be more prone to developing mental disorders (6–8). Recent data suggests that biological inheritance may be involved in the development of mental disorders among adopted individuals (9, 10); family antecedent of mental disorders accounts for 33–43% of suicide risk in adopted individuals (11, 12) as well as a proportion of mood disorders and substance abuse (9, 10). In addition, early life exposure to institutional deprivation may have a negative effect during the development process, and may increase the presence of mental disorders (13–16). For example, some studies reveal that adopted individuals may have a higher risk of externalizing disorders such as Attention Deficit Hyperactivity Disorder (ADHD) (2, 17), substance abuse (18), as well as a higher risk of suicide attempts (19).

Suicide is the second leading cause of death among people aged 15–24 and suicide prevention is a public health priority (WHO). Since adoption was during several decades an increasing trend worldwide, and adopted individuals may be more vulnerable to suicide, it is important to consider the specific risk variables these individuals may have to bear, and if prevention strategies need to be adapted for this specific population (20).

To map the differences in suicide risk factors in adopted and non-adopted individuals, this study will compare the development of mental disorders as well as life events occurring before the age of 18 for both adopted and non-adopted individuals deceased by suicide.

PATIENTS AND METHODS

Participants and Recruitment

Thanks to an ongoing partnership between (our institution) and the Quebec Coroner's Office, for the past two decades several research groups [Dumais et al. (21); Kim et al. (22); Séguin et al. (23–25)] have been able to document the life trajectories of individuals deceased by suicide by interviewing their bereaved family members (23, 24, 26). The protocol is as follows: the family receives an introductory letter from the coroner's office, then a research assistant follows up with a telephone call. A trained mental health clinician then contacts the family members in order to present the study. If the family members agree to participate in our study an appointment is made, and the interview process begins 3–4 months after the suicide. Two interviews, each approximately 3 h long, are conducted for each suicide case. Approximately 75% of the close relatives referred by the coroner's office agreed to participate in the study.

Control participants were interviewed over the course of several studies. Most control individuals were participants from the general population identified through a snowball sampling method and an informant who had known the control participants were interviewed (23). This procedure has been previously described by Dumais et al. (21) and Kim et al. (22). All participants signed a consent form and the research held REB approval.

Over the last decade, researchers have created a data bank comprising a mixture of 700 suicide cases and control participants, aged 14–84 (23, 24, 26). In this data bank, we identified 13 cases of adopted individuals deceased by suicide which were compared with 26 non-adopted individuals deceased by suicide, and with 26 non-adopted living control individuals.

Measurements

Data on common sociodemographic characteristics, life events and mental health characteristics were collected.

Interview to Determine Post-mortem Diagnosis

The post-mortem diagnosis was assessed using a psychological autopsy method (27). During the interview semi-structured questionnaires were administered using the DSM-IV Structured Clinical Interview for both Axis I and Axis II disorders (SCID I and II) (28), with an informant who had known the deceased well (26). Hospital files were also examined to corroborate this information and determine whether a diagnosis of mental disorder was present.

A case vignette was then drafted and discussed by a panel of experts, to determine the post-mortem diagnosis by consensus. This panel was composed of researchers from our team, clinical practitioners, psychiatrists, and psychologists.

A series of studies over the past decade have established the concordance of DSM diagnoses generated by informant reports in conjunction with chart diagnoses and the psychological autopsy method, which have been proven to have good reliability (27, 29, 30). The same interview methodology was applied to a control group (with a proxy-based interview or direct interview if proxy was unavailable).

Interview to Retrace Life Trajectory

The Life Trajectory Calendar interview method was borrowed from Life History Calendar research (30). The questionnaire uses a Life History Calendar to reconstruct the major events in an individual's life as an aid to accurately recall significant life experiences. The calendar explores several clearly described variables from all life spheres; furthermore the frequency, severity and duration of each variable is indicated on the calendar. Narrative methodology requires clinical case histories (case vignettes), and Life History Calendars were drafted after the interviews; the Life History Calendar makes it possible to pinpoint the occurrence of specific events (both positive and negative). The frequency, severity and duration of each

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder.

event is recorded, and classified in a specific life sphere such as: events associated with early adversity (abuse, neglect, presence of violence, etc.,); events associated with academic life (interruptions, successes, failures, education path etc.); events associated with professional life (unemployment, stress at work, promotions, etc.,); events associated with social life (presence or absence of social support, friends, colleagues, etc.,); events involving the onset of interpersonal difficulties (difficulties associated with mental health, suicide attempts, illness, etc.,). The Life History Calendar approach, as underlined in a previous paper, assists in identifying proximal and distal life events, which helps to understand the life trajectories of individuals deceased by suicide (24). This interesting approach also allows the burden of adversity over the life trajectory to be quantified (24). For this study we targeted the variables occurring before the age of 19 years old.

Burden of Adversity

A variable of 5-year periods for measuring the burden of adversity was developed in order to combine events occurring during a specific period of age into a 'summary variable. The value of this global variable identified as the "burden of adversity" was determined by a panel of experts (25). From clinical case histories, the panel analyzed the life trajectories of each individual and gave an overall adversity rating for each five-year period. The overall burden of adversity assessments ranged from severe (rating 1 or 2), to moderate (3 or 4), to low (5 or 6). In all cases, the experts rated each five-year period independently before reaching a consensus through discussion. When studying the clinical case histories, the intra-pair agreement rating in our panel of experts for each five-year period ranged from 76 to 97%; the lowest agreement was found in the 0–4-year age group studied (24).

Analysis

In the aforementioned data bank, there were 13 adopted individuals among the 305 suicide cases. Each adopted individual deceased by suicide was matched (1:2) with a non-adopted individual deceased by suicide by age, gender, and region of study (New Brunswick, Ontario, or Québec) at the moment of death. Each adopted individual was also matched with a non-adopted living control individual (1:2) by the same variables (also matched by age, gender and region of study, at the time of interview for the control individuals).

Analyses were made by comparing Axis I and II disorders, early life events, and the burdens of adversity between adopted and non-adopted individuals deceased by suicide, and between adopted individuals deceased by suicide and non-adopted living control individuals. Axis I disorders were distinguished by 2 periods: the 12 months prior to death (individuals deceased by suicide) or the 12 months prior to the interview (living individuals) and the period preceding the12 months prior to the suicide or interview. We also compared the age of suicide of deceased adopted and non-adopted individuals. Comparisons were made using the Chi Square and Student's *t*-test, with $p < 0.05$ for significance. Analyses were carried out with SAS 9.4 software.

RESULTS

This study included 65 individual cases: 13 adopted individuals deceased by suicide, 26 non-adopted individuals deceased by suicide, and 26 non-adopted living control individuals. Each group was 54% male.

The mean (*SD*) age at the time of adoption was 10 months (18), while the mean age of suicide for both adopted and non-adopted individuals ($n = 39$) was 33.8 (19.6), from 13 to 83.

Adopted vs. Non-adopted Individuals Deceased by Suicide

Comparisons of Axis I or II disorders between adopted and non-adopted individuals deceased by suicide show no difference for Axis I diagnoses in the 12 month period prior to death (**Table 1**). For the period preceding the 12 months prior to death, Attention Deficit Hyperactivity Disorder ($p < 0.0001$) and having two or

TABLE 1 | Comparison of an Axis I and II disorders in the 12 months prior to suicide, and the period preceding the 12 months prior to suicide between adopted and non-adopted individuals ($n = 39$).

Characteristics	Adopted individuals deceased by suicide ($n = 13$)	Non-adopted individuals deceased by suicide ($n = 26$)	Chi2 value	*p*-value
12 months prior to suicide				
Mood disorder	9	15	0.17	0.68
Substance abuse and dependence disorder	6	8	0.89	0.34
Psychosis/schizophrenia	0	2	1.07	0.29
Adjustment disorder	1	4	0.46	0.49
Eating disorder	1	1	0.25	0.62
Two or more disorders	6	10	0.21	0.64
Total with only one DX	4	11	0.49	0.49
Period preceding the 12 months prior to suicide				
Substance abuse and dependence disorder	7	7	2.72	0.10
Mood disorder	5	6	1	0.32
Attention Deficit Hyperactivity Disorder	3	0	6.5	0.01*
Anxiety disorder	2	1	1.62	0.23
Gambling	1	3	0.13	0.72
Eating disorder	1	1	0.25	0.63
Psychosis/schizophrenia	0	1	0.5	0.48
Total with only one DX	5	10	0	1
Two or more disorders	7	3	8.15	0.004*
Axis II disorder				
Cluster A	1	0	2.09	0.15
Cluster B	6	6	2.16	0.14
Cluster C	5	3	3.84	0.04*

** significant value with Chi2 test.*

TABLE 2 | Childhood life-events comparison between adopted and non-adopted individuals deceased by suicide ($n = 39$).

Characteristics	Adopted individuals deceased by suicide ($n = 13$)	Non-adopted individuals deceased by suicide ($n = 26$)	p*
Age 0–4			
Discipline/neglect/tensions in the parent-child relationship	9	11	0.11
Sexual/physical abuse	5	6	0.31
Age 5–9			
Discipline/neglect/tensions in the parent-child relationship	8	12	0.36
Sexual/physical abuse	3	4	0.55
Academic difficulties	1	3	0.71
Age 10–14			
Discipline/neglect/tensions in the parent-child relationship	7	13	0.82
Mental health problems	8	8	0.08
Sexual/physical abuse	5	6	0.31
Academic difficulties	2	4	1
Substance abuse	1	3	0.71
Age 15–19			
Discipline/neglect/tensions in the parent-child relationship	9	17	0.81
Mental health problems	7	12	0.39
Sexual/physical abuse	4	8	1
Academic difficulties	3	2	0.13

p-value with Chi2 test.

TABLE 3 | Comparison of the burden of adversity score depending on age between adopted and non-adopted individuals deceased by suicide ($n = 39$).

Adversity score *the lower the score number, the higher the burden*	Adopted individuals deceased by suicide ($n = 13$) Mean (SD)	Non-adopted individuals deceased by suicide ($n = 26$) mean (SD)	p
Age 0–4	3.9 (1.8)	5.2 (1.1)	0.01*
Age 5–9	3.4 (1.1)	4.5 (2.3)	0.009*
Age 10–14	3.1 (2.4)	4.1 (1.3)	0.02*
Age 14–19	3.3 (0.9)	4.0 (1.5)	0.14

significant value with Student test.

more Axis I diagnoses ($p = 0.004$) are over-represented among adopted individuals. The same can be said for for Axis II Cluster C personality disorders ($p = 0.04$).

As for life events occuring prior to the age of 19 (**Table 2**), there was no difference between groups.

However, adopted individuals deceased by suicide have moderate adversity scores compared with the low adversity scores measured in non-adopted individuals deceased by suicide (see **Table 3**, **Figure 1**). The difference in adversity scoring is significant: from age 0 to 4 (3.9 vs. 5.3, $p = 0.003$), from 5 to 9 years old (3.4 vs. 5.0, $p < 0.0001$) and from age 10–14 (3.1 vs. 4.7, $p < 0.003$). The difference is however non-significant in the 15–19 age bracket ($p = 0.14$).

Lastly, there is no significant difference in the presence and number of past suicide attempts in adopted and non-adopted individuals deceased by suicide ($0.07 < p < 0.49$).

Adopted Individuals Deceased by Suicide vs. Control Individuals

Comparisons of Axis I or II disorders between adopted individuals deceased by suicide vs. control individuals show significant differences in mood disorders ($p < 0.0001$), substance abuse ($p = 0.04$) and the presence of two or more Axis I diagnoses ($p = 0.0002$). These characteristics are over-represented among adopted individuals deceased by suicide. There is no difference for Axis I diagnoses in the period preceding the 12-months prior to their death or interview ($0.06 < p < 1$). There are significant differences for Axis II: adopted individuals deceased by suicide have higher incidences of Cluster B and C personality disorders compared with control individuals ($p = 0.005$ for both).

When looking at life events prior to the age of 19, adopted individuals deceased by suicide have higher rates of the variable "discipline/neglect/tensions in parent-child-relationship" ($p = 0.04$) and more mental health problems from the age of 10 years old ($p = 0.02$) compared with non-adopted living control individuals.

Finally, adversity scores are all significantly higher for individuals deceased by suicide with $p < 0.003$ for each period (see **Figure 1**).

DISCUSSION

The aim of this study was to compare adopted with non-adopted individuals deceased by suicide to find a potential specificity in adopted individuals deceased by suicide. Results show significant differences: a higher incidence of ADHD, mental health comorbidity and Cluster C personality disorders among adopted individuals. Moreover, adopted individuals have higher adversity scores prior to the age of 15.

Adopted individuals cumulate two or more Axis I diagnosis in the period preceding the 12 months prior to death, including ADHD. According to the literature, ADHD diagnosis is significantly higher in adopted individuals (17), which may be explained by several factors. One of these factors may be immaturity of the mother: giving up one's baby for adoption may be associated with teenage pregnancy and Halmøy and colleagues (31) concluded from a large population-based study, that adults with ADHD were more likely to be firstborns and to have a younger maternal age at delivery. Another factor may be mental disorders and/or substance abuse, as well as alcohol or drug absorption *in utero* (32, 33). These factors may in fact be consequences of a history of ADHD in the parents

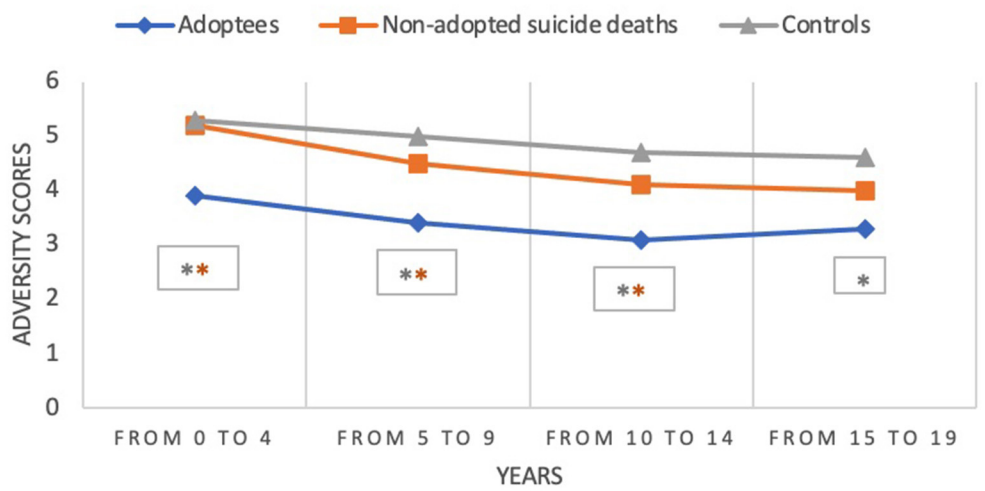

FIGURE 1 | Burden of adversity scores comparing adopted and non-adopted individuals deceased by suicide, and non-adopted living control individuals ($n = 65$). *$p < 0.05$. The orange line compares adopted and non-adopted individuals deceased by suicide, and the silver line compares adopted and control individuals. The lower the score number, the higher the burden of adversity.

which increases the risk of ADHD in the adopted child (34–36). Equally, if we focus on parental substance abuse, infants may suffer withdrawal symptoms, which is associated with a higher risk of anxiety, a trait shared in the personality disorders found in the adopted individuals examined in this study. Indeed, personality disorders included in Cluster C of Axis II are Avoidant, Dependent, and Obsessive-Compulsive Personality Disorders. The weight of heredity may have both direct and indirect impact in the development of mental disorders among adopted individuals and may partly explain the cumulation of Axis I diagnoses.

Aside from the heredity factor, the early trauma of abandonment in adopted individuals may disturb the quality of attachment and their relationship with adoptive parents. Attachment disorders may also be explained by excessive expectations from the parents that lead to feelings of disappointment. Among the individuals in this study, Cluster B personality disorders were diagnosed in 6 of the 13 adopted individuals. We may hypothesize that, perhaps unsurprisingly, due to early separation from their biological parents some of the individuals studied may have been traumatized at an early stage in life, and may have therefore developed an attachment disorder (1), a characteristic often associated with Cluster B personality disorders such as borderline personality disorder.

If we focus on suicide risk factors, anxiety and borderline personality disorders are both well-known suicide risk factors, as is the impulsivity found in ADHD diagnosis (23, 37). So adopted individuals cumulate Axis I and Axis II mental health disorders for several reasons, and these diagnoses are all associated with a higher risk of suicide.

Furthermore, in all individuals deceased by suicide, mental health problems appear early: between 10 and 14 years old. The mean age of suicide is approximately 33, which underlines that suicide prevention strategies must be embedded from childhood. Of course, family relationships play a buffering role to protect family members against some risk factors, including the risk of suicide and we do not study here the quality of adoptive parents and their child (38).

Even if adopted and non-adopted individuals deceased by suicide have the same types of adverse early life events, adopted individuals have an increased early life adversity burden, even if they were adopted in their first year of the life. May we therefore hypothesize that some adopted individuals were less resilient, and so less able to overcome their early-life trauma (5)?

If we summarize the "profile" of adopted individuals deceased by suicide: they have a greater combination of psychiatric comorbidities and they have higher adversity scores in comparison with non-adopted individuals deceased by suicide compared with the control group. In addition, they have a higher rate of mood disorder and substance abuse during the 12 months prior to suicide compared with individuals from the general population deceased by suicide. They also have higher rate of Cluster B and C personality disorders, as usually described in their life trajectory (23).

That is why it is crucial to be attentive to adopted individuals, a population that may present higher hereditary risk factors for mental disorders, as underlined in the literature (9, 10). The recommendation for special attention may be also linked to this question: do adopted individuals have more psychiatric diagnoses because their parents are more attentive to their psychological development, as described by some authors (8)? Would this explain why adopted individuals often have more diagnoses? In this study, diagnoses have been made in the same way for adopted and non-adopted individuals through interviews of their informants, so the results should have not be influenced by the fact of been or not been adopted. But in situations in which

the individual has been adopted, professionals run the risk of trivializing symptoms in saying "it"s just due to their being adopted', as perhaps may occur when dealing with their anxiety issues. We know adopted individuals need care, at least as much if not more than than their non-adopted peers: professionals must therefore be trained specifically to take into account an adopted individual's background when providing care.

This study has some limitations due to the retrospective methods employed, specifically regarding memory biases. However, a series of studies over the past decade have established agreement between DSM diagnoses based on informant report and those based on medical charts (39) and have shown the psychological autopsy method to be reliable (29, 40, 41). As is common in this kind of study, the control individuals are not representative of the general population, as they were generally recruited from friends or neighbors who share environmental and associative mating determinants of mental disorders, which may explain the high rate of mental disorder among control individuals (42). At last, we have no information about adoption between national and international. However, the fact that this is an original study is a strength, as this kind of research has not been done on suicide subjects before, plus we matched individuals on gender, age and region of study to limit biases.

CONCLUSION

Adopted individuals who die by suicide have higher adversity scores in early life, even if they were adopted in their first year of life. Besides the potential trauma of abandonment, they may have hereditary risk factors for mental disorders. Youth caregivers have to be carefull to these risks of suicide in general and in adopted children in particular.

The adoptive family need to be supported throughout adoption, health care professionals need specific training, and psychological difficulties need to be cared for at the earliest possible juncture.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Boards of the Douglas Mental Health Institute (Montreal) and of the Université du Québec en Outaouais. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FL and MS conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. C-EG, FL, and AL designed the data collection instruments, collected data, carried out the initial analysis, and reviewed and revised the manuscript. FB and ML critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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The relationship between father absence and hostility among Chinese depressed youths: A serial mediation model and the role of self-esteem and frustration tolerance

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Background: While the association between father absence and youth hostility has been well-documented among depressed youths, there is a lack of research on the potential mechanism underlying such an association. This study aimed to test a serial mediation model of self-esteem and frustration tolerance on the link between father absence and youth hostility.
Methods: A total of 137 Chinese youths with major depressive disorder were recruited from Wuhan Mental Health Center. They completed a survey including the Father Absence Questionnaire to measure father absence, the Chinese Hostility Inventory (CHI) to measure hostility, the Psychological Endurance Questionnaire to measure frustration tolerance, and the Self-esteem Scale (SES) to measure self-esteem. A series of multiple linear regression models were employed to assess the associations among father absence, self-esteem, frustration tolerance, and hostility.
Results: Although father absence was modestly associated with hostility ($r = 0.30$, $p < 0.001$), subsequent serial mediation analysis showed that father absence was not directly related to hostility ($\beta = 0.06$, $p = 0.29$) when self-esteem and frustration tolerance were included in the model. High levels of father absence had an adverse effect on levels of self-esteem, which decreased levels of frustration tolerance, and thus higher levels of hostility among depressed youths. The indirect effects of father absence on hostility through self-esteem, frustration tolerance, as well as through self-esteem and frustration tolerance serially accounted for 28%, 24%, and 24% of the total effect, respectively.
Conclusion: Our study tested a serial mediation model of self-esteem and frustration tolerance as mediators between father absence and hostility among depressed youths. The findings strengthened our understanding of the potential mechanism underlying the association between self-esteem and frustration tolerance, which may provide useful guidance for future intervention programs.

KEYWORDS

major depressive disorder, father absence, self-esteem, frustration tolerance, hostility

Abbreviations
CHI, short form chinese hostility inventory; SES, self-esteem scale; CI, confidence intervals.

Introduction

Globally, major depressive disorder affects over 300 million people and is estimated to be the second leading cause of disability-adjusted life years (1, 2). Major depressive disorder (MDD) has an early onset that usually begins in childhood or young adulthood and is associated with a high risk of suicide (1, 3). The youth are at high risk for developing major depressive disorder, with an estimated prevalence ranging from 8% to 20% before 18 (4–6). According to the World Health Organization, major depressive disorder is the second most common cause of death among people aged 15–29 (1). Major depressive disorder in young people not only negatively affects the individuals themselves, but also causes a significant social and economic burden to the individual's family and to society (7, 8).

The close link between major depressive disorder and hostility has been widely reported in many studies, with hostility playing an essential role in both the onset and the sustainment of major depressive disorder (9–12). Hostility refers to negative beliefs and affection towards others and is characterized by negative attitudes such as suspicion, cynicism, and mistrust (13). Hostility is associated with both externalizing behaviors such as bullying and aggression, and internalizing affect disorders such as anxiety and depression (14). Previous research has consistently shown an elevated risk for hostility in depressed youths, with these individuals showing a much higher prevalence and level of hostility than non-depressed youths, as reported by both the individuals themselves and their parents (15). In fact, the most recent version of the Diagnostic and statistical manual of mental disorders (5th ed.) has listed the sustained presence of hostility as part of the diagnostic criteria for major depressive disorder in children and adolescents (16).

Understanding the causes and mechanism of hostility among depressed youths carries significant clinical implications in guiding future prevention and intervention strategies to promote better recovery. Among various risk factors reported in the literature, lack of parental care has been listed as an important contributor to hostility in the youths (17–19). Karen Horney (20) mentioned in her book "The Neurotic Personality of Our Time" that children will feel insecure if they do not receive or lack genuine care from their parents in childhood, thus triggering hostility. Father absence, the most common type of parental care lacking in the male-dominant world, plays an important role in youth hostility. Father absence is a broad term that encompasses a wide range of circumstances, which can be generally classified into physical absence (such as non-existence in one's life, death, divorce, absence for work commitments, incarceration, or institutionalization), and functional absence (such as absence due to disinterest or neglect despite physical presence) (21). An overwhelming majority of studies have documented the important and positive role a father's presence played in promoting youths' physical, psychological, and social development and adjustment (21, 22). Such positive impacts are even independent of the mother's presence and other social and familial factors (23). While the causal association between father absence and hostility has been well-documented, there is a lack of research on the potential mechanism underlying such an association in young people.

Two potential pathways between father absence and hostility in young people are issues around self-esteem and frustration tolerance. Self-esteem is defined as the "individual"s subjective evaluation of her or his worth as a person" (24). Abundant evidence has shown father absence has a significant impact on self-esteem (25–28). One study reported that youths brought up in single families, especially those where the father was absent, showed significantly lower levels of self-esteem than adolescents brought up in two-parent families (25). Lower self-esteem has been documented to be associated with a range of adverse health outcomes among young people, including depression, hostility, and violence. Longitudinal studies have demonstrated low self-esteem as an important contributing risk factor predicting later hostility and violent behaviors (29, 30).

Frustration tolerance is defined as "an effective response to blocked-goal attainment" (31) and is characterized by "a negative emotional response triggered after the omission and/or devaluation of an expected reward" (32). Low frustration tolerance is an irrational belief that aversive situations cannot be adapted to or tolerated (33). Studies showed that individuals with an absent father have low frustration tolerance, and those with low frustration tolerance are at high risk of experiencing hostility (34, 35). In Martin and Dahlen's study on the relationship of irrational beliefs and anger, they found low frustration tolerance triggered anger expression, with a moderate effect size (34). In addition, low self-esteem has been shown to affect low frustration tolerance and one study showed that self-esteem levels influenced coping styles through frustration tolerance (36).

Previous evidence suggested that self-esteem and frustration tolerance may mediate the relationship between father absence and hostility. So far, however, no study has examined these potential mediators empirically. The present study used a clinical sample diagnosed with major depressive disorder to assess the relationship between father absence and hostility. We assessed self-esteem and frustration tolerance as mediators of this relationship and hypothesized that the relationship of father absence and hostility would be associated with self-esteem and frustration tolerance.

Materials and methods

Participants

The study was a cross-sectional survey conducted from September 2020 to February 2021 in Affiliated Wuhan Mental Health Center, Tongji Medical College of Huazhong University of Science and Technology. The center is Hubei's largest public mental health care provider and has 950 psychiatric beds and provides around 300,000 outpatient consultations annually. The depression ward is a department of this hospital, which mainly treats patients with major depressive disorder and bipolar disorder, with 60 authorized beds. A total of 137 eligible patients with major depressive disorder were enrolled from the depression department.

The inclusion criteria were as follows: (1) diagnosis of Major Depressive Disorder according to International Classification of Diseases, 10th revision, based on a review of medical records and a clinical interview; (2) aged 12–25 years old (the age boundary

standard refers to previous research (37) and the characteristics of the development of youths' self-concepts (38)); (3) able to communicate and understand the survey instructions; (4) willing to provide written informed consent.

The exclusion criteria were as follows: (1) coexisting developmental delay, or other severe organic disorders; (2) drug or alcohol abuse; (3) comorbid schizophrenia; (4) difficulty in communication due to severe physical or mental diseases.

We distributed the questionnaires to patients who met the above criteria and written informed consent forms were signed by all participants and their guardians (when necessary). Potential participants were made aware that participation was entirely voluntary and that they could refuse to take part without any penalty. Participants were reassured anonymity and confidentiality. The study protocol was approved by the Ethics Committee of Wuhan Mental Health Center.

Measures

Father absence

Father absence was measured by the Father Absence Questionnaire developed by Zhu (39). The questionnaire is a widely used domestic scale for father absence assessment in China and includes two items: physical absence and functional absence. The total score ranges from 2 to 7, with higher scores implying a higher level of father absence.

Hostility

Hostility was measured by the Chinese Hostility Inventory (CHI) compiled by Lin (40), which was adapted from Spielberger's State-Trait anger expression inventory and anger expression scale (41, 42). The CHI is a 20-item scale under four domains: hostile cognition, hostile emotion, expression of hostility, and suppression of hostility. Each item is scored on a 5-point Likert scale from 1 (strongly agree) to 5 (strongly disagree). The total score ranges from 20 to 100 points, with a higher score indicating a higher hostility degree. The Cronbach's alpha of the CHI was 0.89 in the present study, indicating well-qualified internal consistency.

Frustration tolerance

Frustration tolerance was assessed by the Psychological Frustration Tolerance Questionnaire compiled by Xie, Wu, and Qin (43). The questionnaire includes 30 "yes-no" questions to assess youths' tolerance to various frustrating situations. Each item with a "yes" answer is counted as 1 point, and "no" is counted as 0 point. 12 negatively expressed items are reversely scored. The total score ranges from 0 to 30, with higher scores indicating higher levels of frustration tolerance. The Cronbach's alpha of the Questionnaire was 0.86 in the present study, which demonstrated well-qualified internal reliability in our sample.

Self-esteem

Self-esteem was assessed by the Rosenberg Self-Esteem Scale (SES) (1965). The SES is a unidimensional questionnaire consisting of 10 items, in which items 3, 5, 8, 9, and 10 are reversely scored. Each item is scored on a 4-point Likert-type scale from 1 (strongly disagree) to 4 (strongly agree). The total score ranges from 10 to 40, with higher scores reflecting higher levels of self-esteem. The Cronbach's alpha of the SES was 0.85 in the present study.

Procedure

The survey was conducted in Wuhan Mental Health Center. A total of 137 individuals with major depressive disorder completed an anonymous survey, which took approximately 40 min to complete. Three researchers reviewed the questionnaire for the study. After getting approval from the director and ward nurse, researchers visited each ward to approach each eligible patient and explained the purpose and process of the study to the patients and their families. After providing written informed consent, each eligible patient was invited to complete a questionnaire with the researchers' assistance when necessary.

Statistical analysis

SPSS 21.0 was used for data cleaning, coding, and preliminary analysis. All continuous variables were standardized. We used Spearman correlations to evaluate the associations among variables. Mediation analyses were carried out using SPSS PROCESS v.3.2 macro (44). A serial mediation model was proposed with self-esteem and frustration tolerance as first and second-order mediators in the association between father absence and hostility. In this study, we controlled for gender and age and bootstrapped 5,000 samples from the data. A 95% bootstrap confidence interval (CI) that did not include zero was considered significant.

Results

Participant characteristics

Participants consisted of 137 youths, including 56 (40.88%) males and 81 (59.12%) females. The mean age was 18.41 years (SD:3.69 years). Of the total sample, 77 (56.20%) came from rural (vs. city) and 52 (38%) were the "only-child." The mean level of frustration tolerance is 13.10 (SD: 6.50); self-esteem, 24.02 (SD: 6.29); hostility, 63.54(SD: 14.23).

Common method deviation test

Harman's single factor test showed 18 factors with characteristic roots greater than 1. The first factor explained 20.61% of the variance, which was less than the critical value of 40% (45), indicating there was no obvious common method deviation in this study.

Correlational analysis

Table 1 showed intercorrelations among variables and all correlations were significant ($p < 0.001$). Father absence was negatively correlated with self-esteem and frustration tolerance. Hostility was negatively correlated with self-esteem and frustration tolerance. Both hypothesized mediators, self-esteem, and frustration tolerance, were positively correlated with each other. Since the correlation coefficients between certain variables seem to be quite high ($r \geq 0.70$), we did the further statistical analysis and precluded multicollinearity between variables (VIF < 10, tolerance values were all greater than 0.4).

Serial mediation analysis model

The correlation analysis results above showed that self-esteem and frustration tolerance met the statistical requirements for mediation testing (46). A serial mediation analysis was carried out using Model 6 in the PROCESS macro for SPSS (44), with father absence as the independent variable, hostility as the dependent variable, self-esteem and frustration tolerance as two mediators, while controlling for gender and age.

As shown in Table 2 and Figure 1, the total effect of father absence on hostility was significant ($\beta = 0.25$, $p < 0.01$). In addition, the direct effect of father absence on hostility was non-significant when mediators (self-esteem and frustration tolerance) were added ($p > 0.05$), indicating a significant full mediation effect. The total indirect effect of father absence on hostility was also significant. Both mediators, self-esteem and frustration tolerance, showed a significant effect on hostility, as represented by corresponding mediator paths. Furthermore, a significant indirect effect was found for father absence through self-esteem and frustration. The indirect effects of father absence on hostility through self-esteem, frustration tolerance, as well as through self-esteem and frustration tolerance serially accounted for 28%, 24%, and 24% of the total effect, respectively. These results showed that father absence did not directly influence hostility, but through low self-esteem and frustration.

TABLE 1 Descriptive statistics and correlation of variables.

	1	2	3	4
1. Father absence				
2. Self-esteem	−0.25***			
3. Frustration tolerance	−0.34***	0.74***		
4. Hostility	0.30***	−0.64***	−0.69***	
M ± SD	3.68 ± 1.13	24.10 ± 6.34	13.12 ± 6.48	63.41 ± 14.26

***$p < 0.001$.

Discussion

Previous research has shown that high levels of depressive symptoms were strongly associated with high levels of hostility (47). Hostility has been reported to be related to escape-avoidance coping styles and substance use (48). For young people, higher levels of hostility are usually more likely to have interpersonal conflict and rejection. And depressed youths are at higher risk for future hostility than their non-depressed counterparts (15). Therefore, it is necessary to pay attention to the hostility in depressed youths.

The main purpose of this study was to examine the possible roles of self-esteem and frustration tolerance as mediators of the relationship between father absence and hostility in depressed youths. Our results suggested that a lower level of self-esteem, resulting from father absence, was associated with lower levels of frustration tolerance and higher levels of hostility. This indirect path was statistically significant, rendering the direct path from father absence to hostility statistically insignificant. This indicated that the relationship between father absence and hostility was fully, serially mediated by self-esteem and frustration tolerance. To the best of our knowledge, this is the first empirical study in China investigating the relationship between father absence, self-esteem, frustration tolerance, and hostility in youths with major depressive disorder. This study, for the first time, also pointed out the role of self-esteem and frustration tolerance in explaining the link between father absence and hostility.

The positive relationship between father absence and hostility is consistent with previous studies. A growing body of research has shown the negative impacts of father absence on young people, and how the impacts on hostility and delinquency (49–51). Compared to youths with father, the youths with absent father report more hostility. The youths with father absence often suffer

TABLE 2 Bootstrap analysis of the mediation effect test.

Mediation Path	Point Estimate	Bootstrap S.E.	BOOSTRAP 5,000 TIMES 95% CI		Effect percentage
			Lower	Upper	
Total indirect effect (ab)	0.19	0.05	0.09	0.29	76%
Ind 1(a1b1)	0.07	0.03	0.02	0.13	28%
Ind 2 (a2b2)	0.06	0.03	0.01	0.11	24%
Ind 3 (a1a3b2)	0.06	0.03	0.02	0.12	24%

Ind 1: Father absence → Self-esteem → Hostility level; Ind 2: Father absence → frustration tolerance → Hostility level; Ind 3: Father absence → Self-esteem → frustration tolerance → Hostility level.

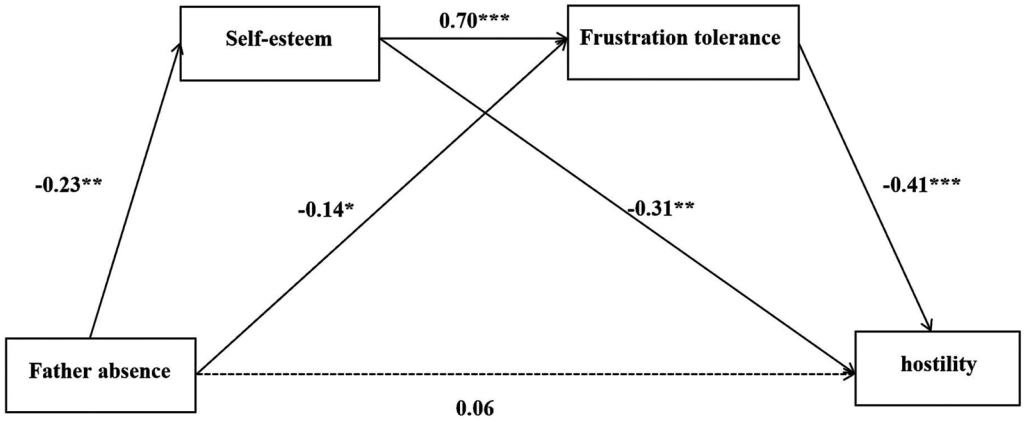

FIGURE 1
Mediation model between father absence and hostility level.

chronically from more negative events and pressures (52), and they thus tend to experience more negative affect, which in turn facilitates hostility. In addition, studies have indicated father absence has a negative effect on an individual's social-emotional development, well-being, cognitive ability and mental health and the psychological harm experienced during childhood persists throughout the life course (52).

Central to our research findings was the examination of how self-esteem and frustration tolerance were postulated as jointly mediating variables in the relationship between father absence and hostility in a model. In this regard, we tested three mediation models including two simple mediations and one serial mediation. Our findings demonstrated that the serial multiple mediation effect of self-esteem and frustration tolerance in sequence and the separate mediation effect of them were both statistically significant.

The study indicated that self-esteem was an important mediator in explaining the relationship between father absence and hostility in depressed youths. In a family with a father absence, children receive less encouragement or praise from their fathers, thus resulting in lower levels of self-evaluation. Lower self-evaluation makes it easier to internalize negative evaluations from the outside world, causing lower levels of self-esteem. This process is compatible with Sociometer Theory, illustrating how valued and socially accepted youths are in the eyes of others (53). Young people easily adopt the views that caregivers have about them. Thus, disapproving, unresponsive, and uninterested parents negatively impact self-esteem levels in their children. And low self-esteem will negatively impact an individual's social links, causing the individual to be inconsistent with social norms, thus increasing hostile behaviors (54). Rogers believes that if there is a lack of positive self-attention, individuals are more prone to hostility (55). Boden et al. followed a birth cohort till the age of 25 and found that lower self-esteem at age 15 predicted greater risks of violent offending and higher levels of hostility at ages 18, 21, and 25 (30). In short, a higher level of father absence was associated with a lower level of self-esteem, which was further associated with a higher level of hostility.

Having a high frustration tolerance allows an individual to tolerate setbacks and adopt a positive mental attitude when experiencing adversity, trauma or major negative events (56). Consistent with the existing literature, we found father absence had an indirect effect on hostility through the mediation of frustration tolerance. This finding was compatible with the frustration-hostility theory illustrating that when a person's motivation or behavior is frustrated, it will produce offensive and aggressive reactions (57). Many personality characteristics and willpower qualities are related to how the father brings up the child (21, 22). For instance, depressed youths whose fathers are absent have low levels of frustration tolerance and mental resilience due to a lack of psychological support from their fathers (58). And low frustration tolerance is strongly correlated with high levels of hostility (59). Compared with ordinary teenagers, depressed youths tend to experience more negative events and pressures and a strong sense of frustration, resulting in stronger hostility. High frustration tolerance may be said to act as a positive psychological resource that can buffer against the negative consequences of father absence and reduce the level of hostility.

In addition, a unique finding of the study was that self-esteem and frustration tolerance act as mediators, influencing the father absence-hostility relationship. The results illustrated that self-esteem and frustration tolerance may induce hostility in depressed young people whose fathers are absent. This implied that depressed youths whose fathers are absent have lower self-esteem and tend to adopt negative methods such as self-blame, withdrawal, and fantasies to cope with setbacks. Easily defeated by setbacks, thus, they become hostile. While those with high self-esteem can better regulate their mood and behavior, and thus have good psychological adaptability (60). They can deal with frustration in a more active way and have a higher level of endurance. A high level of self-esteem may improve an individual's frustration tolerance by using some positive coping styles (60).

These findings have important implications for understanding the relationship between father absence and hostility. From the perspective of the serial mediation effect of self-esteem and frustration tolerance on the relationship between father absence and hostility, improving a depressed youth's self-esteem and frustration tolerance will be beneficial for reducing hostility.

Therefore, some measures should be taken to enhance self-esteem and frustration tolerance in depressed youths. Regarding self-esteem, for youths who lack parental support, therapeutic interventions (e.g., family therapy) focusing on the interpersonal relationship between the individuals and their parents may be helpful (61). In terms of frustration tolerance, psychological education programs could be carried out to enhance positive self-efficacy and psychological problem-solving competencies. In addition, a study showed that painting group psychological counseling to improve self-esteem was an effective method to enhance frustration tolerance (62). Overall, our findings provide a new perspective for reducing the hostility degree of depressed youths. In the future, researchers and practitioners should further investigate the approaches of lowing the depressed youth's hostility by enhancing self-esteem and frustration tolerance.

Limitations

Several limitations should be acknowledged when interpreting the findings in the study. First, the cross-sectional design of the study may preclude any causal relationships among the variables to be drawn. However, our serial mediation model is built upon robust evidence from past longitudinal studies, and we believe our model still provides useful information and suggests causal relationships, which warrant future longitudinal studies for further validation. Second, we tested the model in a clinical sample of depressed youths in Wuhan Mental Health Center, which may not be representative of depressed youths in other areas, and moreover, non-depressed youths. In addition, the participants were all inpatients with major depressive disorder, ignoring those in outpatient department, which could result in potential selection bias. Further research is needed to determine whether the model is applicable to outpatients with major depressive disorder. In conclusion, future studies may consider testing this model in depressed youths in outpatient department and other areas, as well as young people in the general community. Third, we did not assess other potential unobserved confounders, such as the severity of depressive symptoms and the use of antidepressant drugs, which should be assessed and controlled for in future studies to test the model more robustly. Forth, Major Depressive Disorder (MDD) is a heterogeneous disease and treating this group as a single group may mask differences between sub-groups of MDD patients. Despite these limitations, our study serves as a first attempt to test a serial mediation model of father absence and hostility mediated by self-esteem and frustration tolerance among depressed youths and provides useful information and guidance for future studies.

Conclusions

Our study tested a serial mediation model of self-esteem and frustration tolerance as mediators between father absence and hostility among depressed youths. Our results suggested that high levels of father absence had an adverse effect on levels of self-esteem, which decreased levels of frustration tolerance, and thus higher levels of hostility among depressed youths. These findings provided implications for future intervention programs to focus on improving self-esteem and frustration tolerance among depressed youths with father absence to reduce their hostility levels.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of the Wuhan mental health center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

X-GL, W-TL and L-ZL: conceptualized and designed the study. L-ZL and YL: supervised the data collection. X-GL and L-ZL: undertook the recruitment of subjects and managed the data. W-TL,YL and L-ZL: accounted for the quality control. LY and FX provided statistical advice on the study design and data analysis. X-GL and Sullivan JS : drafted the manuscript. W-TL: obtained funding and supervised the study. FX and Sullivan JS: provided linguistic assistance during the revision of this manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The reviewer [BZ] declared a shared affiliation with the author [WL] to the handling editor at the time of review.

Publisher's note

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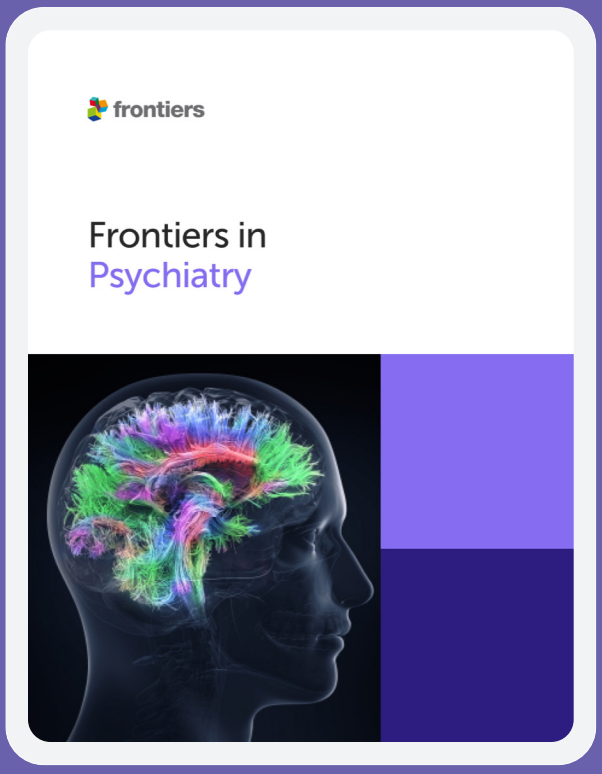

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