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Original Article
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Association Between Childhood Trauma and Anhedonia-Related Symptoms: The Mediation Role of Trait Anhedonia and Circulating Proteins

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ABSTRACT

Background: Though accumulating evidence suggests an association between childhood trauma and anhedonia, further analysis is needed to consider specific traumatic dimensions, both traits and state anhedonia, and the role of circulating proteins. Therefore, this study investigated the association between different types of childhood traumas and their influence on anhedonia-related symptoms, and to evaluate the influence of anhedonia traits and plasma proteins as mediators.

Methods: This study included 170 patients with schizophrenia, bipolar disorder, major depressive disorder, and healthy controls aged 19–65 years. Multiple reaction monitoring was performed to quantify plasma proteins, and 464 proteins were analyzed. The association between childhood trauma dimensions, anhedonic traits, and related symptoms was analyzed with linear regression. A series of mediation analyses was performed to determine whether anhedonic traits and plasma proteins mediated the association between childhood trauma and anhedonia-related symptoms.

Results: Childhood emotional neglect was significantly associated with anhedonic traits and anhedonia-related symptoms. Mediation analysis revealed that the indirect effect of anhedonic traits for childhood emotional neglect on anhedonia-related symptoms (effect = 0.037; bias-corrected CI, 0.009 to 0.070) was statistically significant. The indirect effect

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Disclosure

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Data Availability Statement

The data that support the findings of this study are available from the corresponding authors (Youngsoo Kim, Yong Min Ahn), upon reasonable request.

of plasma TNR5 for anhedonic traits on anhedonia-related symptoms was statistically significant (effect = −0.011; bias-corrected CI, −0.026 to −0.002). Serial mediation analysis revealed that the indirect effect of childhood emotional neglect on anhedonia-related symptoms via anhedonic traits and TNR5 was statistically significant (effect = 0.007; bias-corrected CI, 0.001 to 0.017).

Conclusion: Anhedonic traits and plasma TNR5 protein levels serially mediated the association between childhood emotional neglect and anhedonia-related symptoms. The study highlights the importance of considering both psychopathological traits and biological correlates when investigating the association between childhood trauma and psychopathological symptoms.

Keywords: Childhood Emotional Neglect; Anhedonia; Proteomics; Serial Mediation; TNR5

INTRODUCTION

Childhood trauma is commonly experienced across the globe, as more than one-third of the population is known to experience some kind of adversity.[1] Accumulating evidence suggests that these traumas are risk factors for the onset of major psychiatric disorders in adulthood including schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD).[2-4] Recent studies have focused on linking specific dimensions of childhood traumatic advertises with current or lifetime psychopathologies.[5,6]

Anhedonia refers to a loss of or decreased ability to experience pleasure in previously enjoyable activities.[7] It is one of the core features of depression and an important component of SCZ.[8,9] Anhedonia can be defined as a current state as well as a personality trait, and there is evidence that trait anhedonia affects state anhedonia.[10] However, trait-state disjunction of anhedonia has been reviewed in SCZ patients.[11] Therefore, it is important to differentiate these traits and states.[5,10,11]

Studies have investigated the association between childhood trauma and anhedonia symptoms, but there have been discrepancies regarding the significant trauma dimension, and the analyses have been mostly based on a single psychiatric condition.[5,12-15] A recent study investigated the mediating role of dysfunctional attitudes,[15] and an animal study linked early life adversity with anhedonia through mast cell activation.[16] However, it is still unclear how adversities in developmental periods affect current symptoms and which factors mediate this association. Childhood trauma is associated with reward deficiency, and anhedonia traits.[5,13,17] Therefore, it is relevant to see if anhedonia traits mediate the association between childhood trauma and current anhedonic symptoms.

The proposed mechanisms linking childhood trauma with current psychiatric manifestations include the overactivity of the hypothalamic-pituitary-adrenal axis and chronic alteration of inflammatory and immune-related pathways, which are reflected in plasma proteins.[18,19] Our previous transdiagnostic studies showed that negative symptoms were associated with latent classes constructed by pathological proteins, and childhood trauma was associated with plasma protein networks that are involved in the regulation of complement and coagulation pathways.[20,21] Therefore, integrating plasma proteomes, which reflect systematic biological functions, might also help us understand the link between childhood adversities and adult psychiatric symptoms.

Author Contributions

Conceptualization: Rhee SJ, Shin D[1], Shin D[2], Song Y, Joo EJ, Jung HY, Roh S, Lee SH, Kim H, Bang M, Kim Y[2], Ahn YM. Formal analysis: Rhee SJ, Shin D[1]. Funding acquisition: Rhee SJ, Kim Y[2], Ahn YM. Methodology: Shin D[1], Lee J, Kim Y[1], Kim Y[2]. Resources: Rhee SJ, Shin D[2], Song Y, Joo EJ, Jung HY, Roh S, Lee SH, Kim H, Bang M, Lee KY, Ahn YM. Supervision: Kim Y[2], Ahn YM. Writing - original draft: Rhee SJ, Shin D[1]. Writing - review & editing: Shin D[2], Song Y, Joo EJ, Jung HY, Roh S, Lee SH, Kim H, Bang M, Lee KY, Lee J, Kim Y[1], Kim Y[2], Ahn YM.

Shin D[1], Dongyoon Shin; Shin D[2], Daun Shin.
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In this context, this study aimed to investigate the association between different types of specific childhood traumas and their influence on anhedonia-related symptoms in a transdiagnostic sample of SCZ, BD, MDD, and healthy controls (HC). Furthermore, the influence of anhedonia traits and plasma proteins was analyzed to investigate their roles as mediation factors.

METHODS

Clinical samples

This study was based on our previous study that differentiated major psychiatric disorders from plasma proteins.[22] The Temporal Experience of Pleasure Scale (TEPS) was introduced in the study in the third year, and a total of 191 participants, aged 19–65 years, from six hospitals completed this scale. Considering plasma protein quantification, 16 participants were from a different preparation batch and were excluded. Finally, we excluded five participants whose Young Mania Rating Scale (YMRS) total score was > 12 to rule out those with (hypo) manic symptoms.[23] The final study population comprised 170 participants (33 SCZ, 46 BD, 54 MDD, and 37 HC). Patients were diagnosed as per the Diagnostic and Statistical Manual of Mental Disorders, fifth edition. HC were recruited via advertisement, whom had no psychiatric diagnosis and no known psychiatric family history within second-degree relatives. Participants were excluded based on the following criteria: use of anti-inflammatory analgesics for the previous two weeks; history of neuromodulation/neurosurgery; central nervous system diseases; cancer; tuberculosis; current lactation/pregnancy; history of substance abuse other than alcohol, caffeine, and nicotine; intensive psychotherapy for the previous two months; predicted intellectual disability; and difficulty in interpreting Korean.[22]

Plasma samples from each participant were collected in a 6-mL ethylenediaminetetraacetic acid tube (ref 367863, Becton; Dickinson and Company, Trenton, NJ, USA), and centrifuged at 1,100–1,300 g for 10–15 minutes at room temperature or 4°C. The supernatant was collected and stored in Eppendorf tubes at –70°C or lower until use.

Demographics and clinical features

Demographic features considered in the analysis included age, sex, body mass index (BMI), alcohol use, exercise, smoking, blood collection time, and fasting time.[22] Age and BMI were analyzed as continuous variables. Sex (female, male), alcohol use (no, yes), exercise (no, yes), smoking (no, yes), blood collection time (AM, PM), and fasting time (< 8 hours, ≥ 8 hours) were analyzed as dichotomous variables. Alcohol use was based on frequency: at least one drink once per week. Exercise was classified according to the World Health Organization recommendation of moderate-intensity physical activity for at least 30 minutes once per week.[24]

Childhood trauma was measured using the Childhood Trauma Questionnaire-Short Form (CTQ-SF), a self-report scale containing 28 items.[25] This scale retrospectively evaluates traumatic experiences, including physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. Based on the 5-point Likert scale, the sub-scores of each dimension, and the total score of these 5 dimensions were used in the analysis. Depressive symptoms were measured using the Montgomery-Asberg Depression Rating Scale (MADRS), which consists of 10 items.[26] To consider both the necessity to control non-anhedonic depressive symptoms and avoid multicollinearity, the MADRS was divided into two dimensions. Anhedonia-related symptoms were based on a recent factor analysis of

the MADRS, which was constructed using items of apparent sadness, reported sadness, lassitude, and inability to feel.[27] The remaining scores were added to serve as a proxy for non-anhedonic depressive symptoms. As there are studies that have defined an anhedonic factor that additionally includes the loss of concentration item,[28-32] a sensitivity analysis was performed. Anhedonic traits were measured using the TEPS.[33] The 18-item scale measures anticipatory and consummatory anhedonia, with lower scores representing anhedonia, and the total score was used. Finally, (hypo)manic symptoms were measured using the 11-item YMRS.[34]

Plasma proteomic quantification

Specific methods have been described in our previous study.[22] In brief, highly abundant proteins were depleted on a MARS-6 (Agilent Technologies, Santa Clara, CA, USA) column, followed by concentration and digestion with trypsin, and then de-saltation. After centrifugation, the supernatant was spiked with stable isotope-labelled internal standard (SIS) peptides. Liquid chromatography-multiple reaction monitoring-mass spectrometry (LC-MRM-MS) was performed with a 1260 Infinity HPLC system equipped with a Jetstream electrospray source coupled to an Agilent 6490 triple quadrupole MS (Agilent Technologies). Raw data from the LC-MRM-MS analysis were processed using Skyline (version 19.1.0; MacCoss Lab, Seattle, WA, USA). Peptide quantification was calculated with the peak area ratio (PAR), defined as the ratio of the endogenous to SIS peptide peak area. The PAR values of the 588 target peptides were normalized to the area of the heavy β-galactosidase peptide for analysis. After excluding peptides with PAR values ≤ 0.01 or ≥ 100 for at least 5% of the final study population, and substituting the levels of proteins with mean values when multiple peptides were quantified, a total of 464 proteins were subjected to statistical analysis.

Statistical analyses

Descriptive statistics were used to analyze the participants' characteristics. The association between each childhood trauma dimension and anhedonic traits/related symptoms was analyzed using linear regression, controlling for age, sex, BMI, diagnosis, non-anhedonic depressive symptoms, alcohol consumption, exercise, and smoking. For the specific childhood trauma dimension that was associated with both anhedonic traits and anhedonia-related symptoms, mediation analysis was performed to determine whether anhedonic traits mediated the association between the specific childhood trauma dimension and anhedonia-related symptoms.

Next, to see if plasma proteins mediated the associations between these clinical traits/symptoms, the association between these clinical traits/symptoms were analyzed with linear regression, controlling for age, sex, BMI, diagnosis, non-anhedonic depressive symptoms, alcohol consumption, exercise, smoking, blood collection time, and fasting time. Protein candidates for mediation were selected if they were associated with the specific childhood trauma dimension and anhedonia-related symptoms, or if they were associated with anhedonic traits and anhedonia-related symptoms,[35] and if they were not associated with hospital type in an analysis of variance (ANOVA) analysis. For candidate plasma proteins, ANOVA analysis was performed to see if they were pathognomonic, and mediation analysis was performed to determine whether individual plasma proteins mediated the association between these clinical traits/symptoms. Finally, for proteins that were significant mediators, an integrated mediation model was used to model the association between clinical traits/symptoms and plasma proteins.

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Statistical analyses for demographical or clinical and targeted proteomic data were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA) and R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org). Mediation analysis was performed using the PROCESS MACRO software.[36] Model 4 was used for the mediation analysis with one mediator, and model 6 was used for serial mediation. The bias-corrected 95% confidence interval (CI) was calculated using 5,000 bootstrapping resamples. Statistical tests were two-tailed, and statistical significance was set a *P* value of < 0.05.

Ethics statement

This study was performed in accordance with the latest version of the Declaration of Helsinki. The study design was reviewed by the Institutional Review Boards (IRBs) of Seoul National University Hospital (IRB No. 1806-106-951) and all the other participating hospitals. Informed consent was obtained from all of the participants.

RESULTS

Demographic and clinical characteristics

The demographic and clinical characteristics of the study population are summarized in **Table 1**. The average age was 36.92 ± 13.56, and 34.7% were male. The mean value of anhedonia-related symptoms from the MADRS was 6.90 ± 5.78, and the mean value of the TEPS was 68.54 ± 16.13. The emotional neglect dimension was the highest among the CTQ-SF, with a mean value of 13.04 ± 6.22.

Table 1. Demographic and clinical characteristics of the study population (N = 170)

Characteristics	Values
Age, yr	36.92 ± 13.56
Sex (male)	59 (34.7)
BMI, kg/m^2	23.98 ± 3.99
Alcohol drinking (at least once a week)	59 (34.7)
Exercise (moderate)	67 (39.4)
Current smoker	69 (40.6)
Blood collection time: AM	64 (37.6)
Fasting time: at least 8 hr	63 (37.1)
Psychiatric disorders	
Schizophrenia	33 (19.4)
Bipolar disorder	46 (27.1)
Major depressive disorder	54 (31.8)
Healthy controls	37 (21.8)
YMRS score	2.28 ± 3.23
MADRS score	
Anhedonia-related symptoms	6.90 ± 5.78
Non-anhedonic depressive symptoms	8.91 ± 6.28
TEPS score	68.54 ± 16.13
CTQ score	
Physical abuse	8.53 ± 4.74
Emotional abuse	9.82 ± 5.23
Sexual abuse	6.25 ± 2.80
Physical neglect	8.92 ± 3.45
Emotional neglect	13.04 ± 6.22

Values are presented as mean ± standard deviation or number (%).
BMI = body mass index, YMRS = Young Mania Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, TEPS = Temporal Experience of Pleasure Scale, CTQ = Childhood Trauma Questionnaire.

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Table 2. Association between childhood trauma type and anhedonic traits, and anhedonia-related symptoms

Childhood trauma	Anhedonic traits		Anhedonia-related symptoms	
	β	*P* value[a]	β	*P* value[a]
Physical abuse	−0.014	0.835	−0.030	0.513
Emotional abuse	−0.099	0.154	0.033	0.481
Sexual abuse	0.046	0.471	0.006	0.883
Physical neglect	−0.075	0.239	0.083	0.058
Emotional neglect	−0.243	**< 0.001**	0.135	**0.004**

Adjusted for age, sex, body mass index, diagnosis, non-anhedonic depressive symptoms, alcohol, exercise, and smoking.
β = standardized coefficients.
[a]Bold-face *P* values are significant at $P < 0.05$.

The association between childhood trauma, anhedonic traits, and anhedonia-related symptoms

After controlling for covariates, only emotional neglect was associated with anhedonic traits (β = −0.243, $P < 0.001$) and anhedonia-related symptoms (β = 0.135, $P = 0.004$) (**Table 2**). Mediation analysis revealed that the total effect (effect = 0.126; 95% CI, 0.041 to 0.210; $P = 0.004$), direct effect of childhood emotional neglect on anhedonia-related symptoms (effect = 0.089; 95% CI, 0.004 to 0.175; $P = 0.041$), and indirect effect of anhedonic traits for emotional neglect on anhedonia-related symptoms (effect = 0.037; bias-corrected CI, 0.009 to 0.070) were statistically significant. Thus, anhedonic traits partially mediated the association between childhood emotional neglect and anhedonia-related symptoms (**Fig. 1**).

The association between plasma proteins and childhood emotional neglect and anhedonic traits, and anhedonia-related symptoms

Next, the association between plasma proteins and childhood emotional neglect, anhedonic traits, and anhedonia-related symptoms were analyzed using linear regression. PVR and TETN proteins were both significant between childhood emotional neglect and anhedonia-related symptoms, and CBLN2, CD5L, RL18, and TNR5 were significant between anhedonic traits and anhedonia-related symptoms. In an additional ANOVA, none of these six proteins

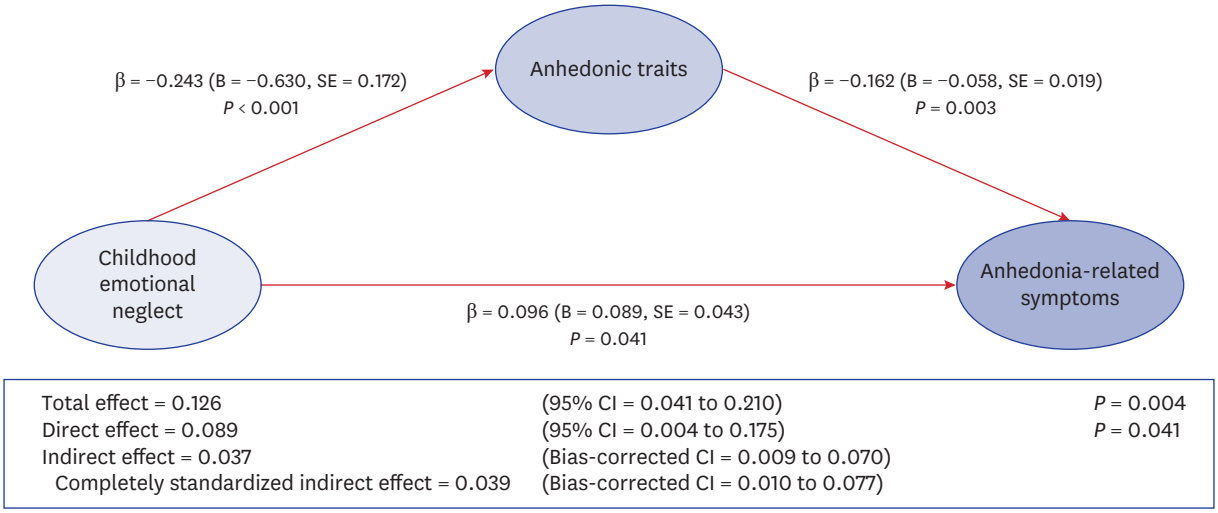

Fig. 1. Mediation analysis for childhood emotional neglect on anhedonia-related symptoms via anhedonic traits. The analysis was controlled for age, sex, body mass index, diagnosis, non-anhedonic depressive symptoms, alcohol consumption, exercise, and smoking. For the indirect effect, the bias-corrected 95% CI was calculated with 5,000 bootstrapping resamples. The lines in red are statistically significant paths.
β = standardized coefficients, B = unstandardized coefficients, SE = unstandardized coefficients standard error, CI = confidence interval.

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Table 3. Indirect effect of each plasma protein

Variables	Effect	BootSE	BootLLCI	BootULCI
Childhood emotional neglect → Plasma protein → Anhedonia-related symptoms				
PVR	0.015	0.096	−0.001	0.036
TETN	0.011	0.011	−0.003	0.039
Anhedonic traits → Plasma protein → Anhedonia-related symptoms				
CBLN2	−0.005	0.005	−0.017	0.001
CD5L	−0.006	0.005	−0.016	0.003
RL18	−0.005	0.004	−0.014	0.001
TNR5	**−0.011**	**0.006**	−0.026	−0.002

Adjusted for age, sex, body mass index, diagnosis, non-anhedonic depressive symptoms, alcohol, exercise, smoking, blood collection time, and fasting time.
Bold-faced values are significant based on bootstrapping.
SE = standard error, LLCI = low limit confidence interval, ULCI = upper limit confidence interval.

were significantly associated with hospital type. Therefore, these six proteins were significant for testing their mediation roles in the subsequent analysis. None of the levels of these proteins differed between diagnosis (**Supplementary Table 1**).

Association between childhood emotional neglect and anhedonia-related symptoms: mediation of plasma proteins

Mediation analysis was performed to determine whether plasma PVR and TETN proteins mediated the association between childhood emotional neglect and anhedonia-related symptoms and whether plasma CBLN2, CD5L, RL18, and TNR5 proteins mediated the association between anhedonic traits and anhedonia-related symptoms. Only the indirect effect of TNR5 for anhedonic traits on anhedonia-related symptoms was significant (effect = −0.011; bias-corrected CI, −0.026 to −0.002) (**Table 3**). The total effect (effect = −0.071; 95% CI, −0.108 to −0.034; $P < 0.001$) and direct effect of anhedonic traits on anhedonia-related symptoms (effect = −0.060; 95% CI, −0.097 to −0.022; $P = 0.002$) were significant; thus, plasma TNR5 partially mediated the association between anhedonic traits and anhedonia-related symptoms (**Fig. 2**).

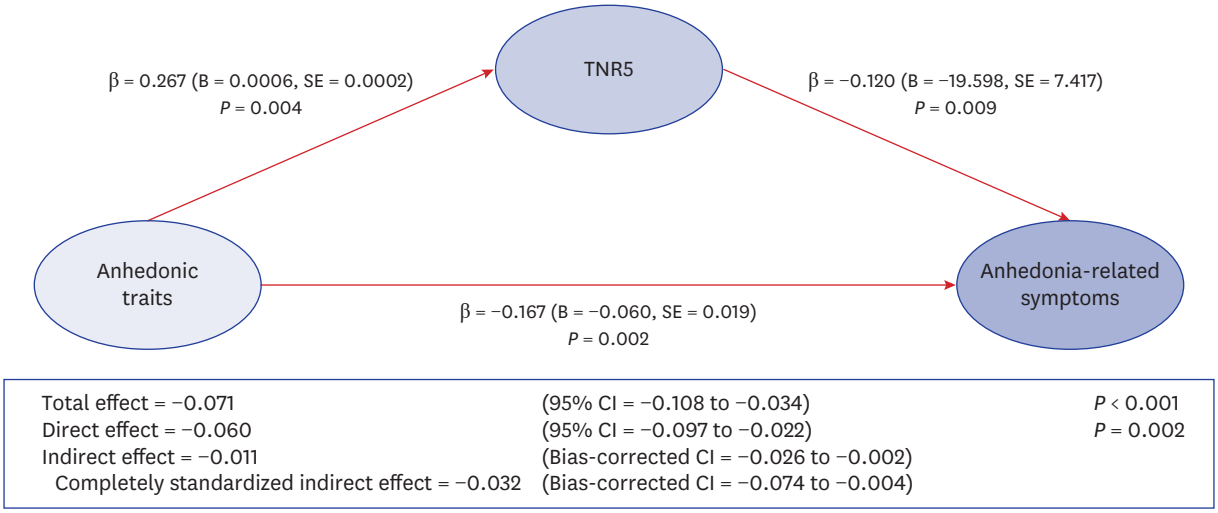

Fig. 2. Mediation analysis for anhedonic traits on anhedonia-related symptoms via plasma TNR5. The analysis was controlled for age, sex, body mass index, diagnosis, non-anhedonic depressive symptoms, alcohol consumption, exercise, smoking, blood collection time, and fasting time. For the indirect effect, the bias-corrected 95% CI was calculated with 5,000 bootstrapping resamples. The lines in red are statistically significant paths.
β = standardized coefficients, B = unstandardized coefficients, SE = unstandardized coefficients standard error, CI = confidence interval.

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Table 4. Indirect effect of the serial mediation model

Variables	Effect	BootSE	BootLLCI	BootULCI
Total	**0.045**	**0.020**	0.009	0.086
Childhood emotional neglect → Anhedonic traits → Anhedonia-related symptoms	**0.032**	**0.016**	0.004	0.065
Childhood emotional neglect → Plasma TNR5 → Anhedonia-related symptoms	0.006	0.011	−0.011	0.033
Childhood emotional neglect → Anhedonic traits → Plasma TNR5 → Anhedonia-related symptoms	**0.007**	**0.004**	0.001	0.017

Adjusted for age, sex, body mass index, diagnosis, non-anhedonic depressive symptoms, alcohol, exercise, smoking, blood collection time, and fasting time.
Bold-faces are significant based on bootstrapping.
SE = standard error, LLCI = low limit confidence interval, ULCI = upper limit confidence interval.

Serial mediation of anhedonic traits and plasma TNR5 on childhood emotional neglect and anhedonia-related symptoms

Serial mediation analysis was performed based on the previous mediation analysis. The total effect (effect = 0.124; 95% CI, 0.039 to 0.208; $P = 0.004$) of childhood emotional neglect on anhedonia-related symptoms was statistically significant, but not the direct effect (effect = 0.079; 95% CI, −0.006 to 0.163; $P = 0.068$). The total indirect effect of anhedonic traits and plasma TNR5 for childhood emotional neglect on anhedonia-related symptoms (effect = 0.045; bias-corrected CI, 0.009 to 0.086) was statistically significant. Specifically, the indirect effect of anhedonic traits for childhood emotional neglect on anhedonia-related symptoms (effect = 0.032; bias-corrected CI, 0.004 to 0.065) and the serial indirect effect of anhedonic traits and plasma TNR5 for childhood emotional neglect on anhedonia-related symptoms (effect = 0.007; bias-corrected CI, 0.001 to 0.017) were statistically significant (**Table 4**, **Fig. 3**).

Sensitivity analysis

Including the loss of concentration as an anhedonia-related symptom revealed similar findings. There were two differences when considering the statistical significance. Anhedonic traits fully and not partially mediated the association between childhood emotional neglect and anhedonia-related symptoms; in the serial mediation, only the serial effect of

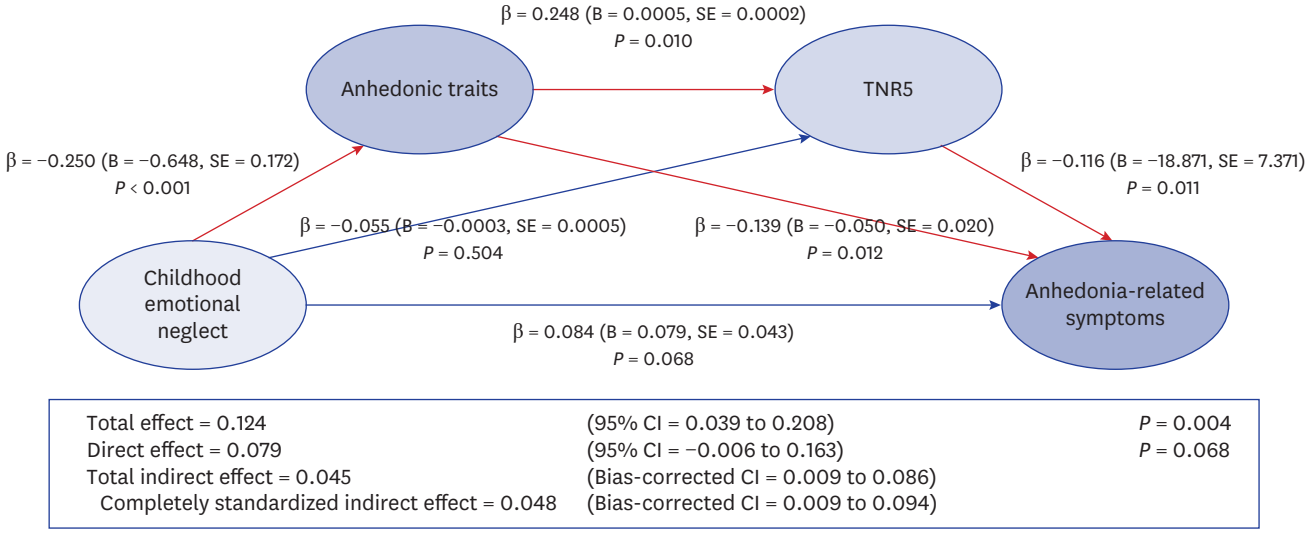

Fig. 3. Serial mediation for childhood emotional neglect on anhedonia-related symptoms via anhedonic traits and plasma TNR5. The analysis was controlled for age, sex, body mass index, diagnosis, non-anhedonic depressive symptoms, alcohol consumption, exercise, smoking, blood collection time, and fasting time. For the indirect effect, the bias-corrected 95% CI was calculated with 5,000 bootstrapping resamples. The lines in red are statistically significant paths and lines in blue are non-significant paths.
β = standardized coefficients, B = unstandardized coefficients, SE = unstandardized coefficients standard error, CI = confidence interval.

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anhedonic traits and plasma TNR5 for childhood emotional neglect on anhedonia-related symptoms was statistically significant among the indirect effects (**Supplementary Figs. 1-3**, **Supplementary Table 2**).

DISCUSSION

In the present study, the impact of different dimensions of childhood adversities had different relationships with anhedonia-related symptoms. Childhood emotional neglect was the only dimension that was statistically significant in a transdiagnostic sample of psychosis-affective disorders and HC. The serial mediation model revealed that the association between childhood emotional neglect and anhedonia-related symptoms was mediated by anhedonic traits and plasma TNR5.

The present study replicated previous studies showing that childhood emotional neglect is an adversity associated with anhedonia-related symptoms.[5,6,12-15,17] However, a study of adolescents with MDD and HC by Sonmez et al.[14] revealed that the associations of these adversities with anhedonia were not statistically significant after controlling for depressive symptoms. Our study not only differed in participant's age but also controlled non-anhedonic depressive symptoms, which could explain the discrepancy.

The present study's findings are also in line with a study that included participants from an early detection center specializing in clinical high-risk psychosis, in which childhood emotional neglect was associated with social anhedonia traits.[17] Thus, the present study extends previous findings considering the association between childhood emotional neglect and anhedonia, not only to a continuous phenomenon in those with psychosis-affective disorders and HC, but also to a continuous phenomenon of both traits and symptoms related to anhedonia. Cohen et al.[12] revealed that childhood emotional neglect not only predicted levels of anhedonia but also its increase over time. Therefore, the increased risk over time might explain the anhedonia-related depressive property for those who experienced childhood emotional neglect in our transdiagnostic sample and the mediation role of anhedonic traits.

Accumulating evidence suggests that those who experience childhood neglect have defects in the reward circuit.[37] Childhood emotional neglect is known to be associated with blunted development of reward-related ventral striatum activity in adolescence,[38] which could explain its effects on both anhedonic traits and related symptoms. However, the mechanism between childhood emotional neglect and anhedonia requires further investigation, as there may be other psychopathologies that function as mediators. For instance, Wang et al.[15] revealed that dysfunctional attitudes mediated childhood emotional neglect and anhedonic symptoms in patients with MDD.

Interestingly, plasma TNR5 mediated the association between anhedonic traits and related symptoms. Although there is increasing evidence of chronic inflammation with childhood adversities, our results showed that anhedonic traits, a consequence of childhood emotional neglect, are associated with immune functions, which affect anhedonia-related symptoms. There is evidence that early neglect is associated with low adult hair cortisol concentration, which was reported to be a vulnerability risk factor for trauma-related symptoms among those with trauma.[39] In addition, early childhood neglect is associated with orexin levels,[40]

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which is also known for its role in the modulation of the reward system.[41] These analyses were based on a single biological marker and did not simultaneously analyze multiple biological correlates. Our study showed that no significant plasma protein markers directly mediated the association between childhood emotional neglect and anhedonia-related symptoms. However, as the levels of cortisol or orexin were not measured in our study, direct comparisons were limited.

TNR5 (gene name: CD40) is known to bind to the CD40 ligand, and the activation of CD40 is important in the initiation and sustainment of inflammatory response.[42] Its relations in central nervous system diseases are under investigation as abnormal expression of CD40 is harmful to the survival of neural tissue.[42] Our study is in line with a recent study which revealed that current levels of anhedonia, but not the history of recurrent MDD, was related to endotoxin-evoked immune-responses, including higher stimulated levels of tumor necrosis factor (TNF)-α and sCDL40.[43] It is also in line with an animal study which revealed that the CD40 agonist antibody decreased consumption of and motivation for saccharin (gustatory award).[44] The behavioral effects were preceded by increased circulating TNF-α,[44] which has been repeatedly reported to be related to anhedonia.[45-47] Moreover, increased inflammation was associated with decreased connectivity in corticostriatal award circurity.[48] Studies have shown that higher levels of the CD40-CD40 ligand are pathognomonic, as they induce inflammation cascades.[44] Therefore, further investigations regarding anhedonic traits, anhedonia chronicity and its association with the CD40-CD40 ligand cascade are warranted.

Some limitations of this study should be considered. First, it was cross-sectional in nature. Even though the chronological order of the measures were considered, causal interpretations are limited. The assessment of childhood trauma and anhedonia traits carries a risk of recall bias, and longitudinal studies are warranted in the future. Second, the evaluation of anhedonia-related symptoms was based on a MADRS factor score with only a few questions, which has limited evaluations considering the sophisticated dimensions of anhedonia. However, the factor is known to have high correlations with measures for specific anhedonia symptoms.[28] Third, there could have been other factors that were not considered in the present analysis, including genetic and environmental factors. Fourth, the proteins were quantified in the plasma, which limits their functional interpretation. Finally, a larger sample size is required to validate the findings of this study, and to analyze each disorder separately.

In conclusion, anhedonic traits and plasma TNR5 serially mediated the association between childhood emotional neglect and anhedonia-related symptoms. Our study highlights the importance of considering both psychopathological traits and biological correlates when investigating the association between childhood trauma and psychopathological symptoms.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Significant plasma proteins with childhood emotional neglect/anhedonic traits and anhedonia-related symptoms, and the association with hospital type, and diagnosis

Supplementary Table 2

Indirect effect of the serial mediation model, when including loss of concentration as an anhedonia-related symptoms

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Supplementary Fig. 1

Mediation analysis for childhood emotional neglect on anhedonia-related symptoms via anhedonic traits, when including loss of concentration as an anhedonia-related symptom.

Supplementary Fig. 2

Mediation analysis for anhedonic traits on anhedonia-related symptoms via plasma TNR5, when including loss of concentration as an anhedonia-related symptom.

Supplementary Fig. 3

Serial mediation analysis for childhood emotional neglect on anhedonia-related symptoms via anhedonic traits and plasma TNR5, when including loss of concentration as an anhedonia-related symptom.

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