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Does cortisol moderate the environmental association between peer victimization and depression symptoms? A genetically informed twin study

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ABSTRACT

Many youths who are victimized by peers suffer from depression symptoms. However, not all bullying victims show depression symptoms and individuals' biological sensitivity may play an important moderating role in this regard. In line with this notion, peer victimization has been associated with increased depressive symptoms in youth with higher basal cortisol secretion. It is unclear, however, whether this moderating effect of cortisol really concerns the *environmental* effect of peer victimization on depression. Indeed, genetic factors can also influence individuals' environmental experiences, including peer victimization, and part of these genetic factors may be those associated with depression. Using a genetically informed design based on 159 monozygotic and 120 dizygotic twin pairs (52% girls) assessed at age 14 years, this study examined whether cortisol secretion moderates the environmental or the genetic association between peer victimization and depression symptoms. Salivary cortisol at awakening was obtained with buccal swabs during four school week days. Peer victimization and depression were assessed via self-reports. Cholesky modeling revealed that peer victimization was associated with depression symptoms via both genetic and environmental pathways. Moreover, the *environmental* association between peer victimization and depression symptoms steadily increased with increasing levels of morning cortisol. The *genetic* association between peer victimization and depression symptoms also varied, albeit less, as a function of individuals' cortisol secretion. These findings support the hypothesis that peer victimization increases internalizing psychopathology mainly in youth with heightened biological reactivity to environmental conditions.

1. Introduction

Peer victimization, defined as the use of power and aggression to cause distress or control another person, is an important problem in many schools with severe risks for the victims (Craig et al., 2009; Oriol et al., 2017). Among the immediate sequelae are internalizing problems, notably depression symptoms (Reijntjes et al., 2010). Still, not all victims experience depression symptoms. Indeed, a meta-analysis showed an average longitudinal effect size of only 0.18 (range from 0.00 to 0.44) from peer victimization to internalizing symptoms (Reijntjes et al., 2010). This modest average effect and large variability might hide moderating factors, however, that enhance or buffer the negative effect of peer victimization. One important moderating factor may be individuals' biological sensitivity to context. According to the Biological Sensitivity to Context (BSC) hypothesis (Ellis et al., 2011), some individuals are more sensitive to environmental influences–good or bad–than others. This biological sensitivity is believed to be partly rooted in genetically influenced physiological reactivity.

1.1. The moderating role of cortisol

Hormonal pathways, notably cortisol secretion, play a critical role in physiological reactivity to environmental experiences (Fries et al., 2005). Cortisol levels are typically higher at awakening and gradually

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decrease thereafter (Stone et al., 2001). There are, however, considerable inter-individual differences in diurnal cortisol secretion as well as in cortisol reactivity to acute stress, with potentially important mental health implications (Fries et al., 2005; Miller et al., 2007). Whereas lower cortisol levels are often linked with externalizing behaviors in adolescents (Alink et al., 2008), higher levels are typically associated with internalizing symptoms, including depression (Halligan et al., 2007). Moreover, elevated morning cortisol and cortisol reactivity to social stress predict increases in adolescents' depression symptoms over time (Goodyer et al., 2000; Susman et al., 1997). Individual differences in cortisol secretion may thus explain why only some victims show depression symptoms.

Several studies suggest that cortisol secretion moderates the association between stress exposure and mental health (Hagan et al., 2014; Kuhlman et al., 2017; Rudolph et al., 2011, 2010). Although these studies included a variety of stressors, cortisol measures and outcomes, findings generally indicate a stronger link between social stressors and internalizing problems in individuals with higher cortisol secretion. Cortisol as a moderator of the link between peer victimization and depression symptoms was tested in only one study (Rudolph et al., 2011). Results showed that peer victimization was associated with increased depressive symptoms in youths with high basal cortisol secretion as measured prior to a social stress task. It has been argued that pre-test cortisol levels may indicate an individual's baseline sensitivity to potential stress, both at the psychological and neurophysiological levels (Balodis et al., 2010). This finding thus seemingly supports the notion that a high biological sensitivity can exacerbate environmental influences on depressive symptoms. It is unclear, however, whether this moderating effect of cortisol really concerns the *environmental* association peer victimization and depression, as implicitly assumed by the BSC hypothesis. This question is important, as many social experiences partly arise as a consequence of individuals' genetically influenced characteristics (Jaffee and Price, 2007). Evidence from genetically informed research such as twin studies suggests that heritable factors explain over half of inter-individual differences in peer victimization (e.g., Brendgen et al., 2011). Moreover, genetic factors that influence peer rejection and victimization also influence depression symptoms (Bowes et al., 2013; Brendgen et al., 2009). Importantly, this *genetic* association between peer-related stress and depression symptoms reflects a gene-environment correlation (rGE), which is considered to indicate the effect of individuals' genetically driven characteristics (e.g., depressive behavior) on their environmental experiences (e.g., peer victimization), not the other way around (Lau and Eley, 2008). This rGE is in line with non-genetically informed studies showing that depression symptoms predict increased peer victimization (Reijntjes et al., 2010). A finding that differential cortisol secretion moderates the *genetic* association between peer victimization and depression symptoms would thus indicate moderation of the likelihood that individuals who are genetically vulnerable for depression become victims of bullying. However, such a finding would not support the BSC hypothesis, which postulates that physiological reactivity should moderate environmental effects on individuals. Only a moderating effect of cortisol on the *environmental* association between peer victimization and depression symptoms would be consistent with this hypothesis. Examining this issue may inform conceptual models and interventions to prevent depressive symptomatology in bullying victims.

2. Study objectives

We used a genetically informative design based on Monozygotic (MZ) and Dizygotic (DZ) twin pairs, whose peer victimization, salivary cortisol, and depression symptoms were assessed at age 14 years. This developmental period is of interest, as depression symptoms often increase during early adolescence (Dekker et al., 2007). Hypotheses were tested using cortisol measured in a naturalistic setting (i.e., at home). We focused on morning salivary cortisol, because (a) it may be considered to represent a "pre-challenge" measure of the HPA axis activity during the day, (b) it is partly influenced by genetic factors (Ouellet-Morin et al., 2016) contributing to stability and (c) elevated morning cortisol has been linked to elevated depression symptoms (Halligan et al., 2007), and it thus may yield results similar to those found by Rudolph et al. (2011). We expected that the association between cortisol and depression symptoms would at least partly be explained by common genetic influences. Moreover, common genetic factors should at least partly explain the correlation between peer victimization and depression symptoms, indicating rGE. However, the association between peer victimization and depression symptoms should also be partly environmentally-driven and this environmentally-driven association should be moderated by cortisol secretion levels. These hypotheses were tested controlling for several potential confounders linked to peer victimization, depression symptoms or cortisol, i.e., family adversity, harsh parenting, birth weight, pubertal status, Body Mass Index (BMI), and individuals' aggressive behavior and biological sex (e.g., Cole et al., 2014; Jessop and Turner-Cobb, 2008; Kiess et al., 1995; Rudolph et al., 2010; Wüst et al., 2005). Morning cortisol was also corrected for potential effects of awakening and sampling times, sleep duration and quality, medications, menstruation for girls, and current and persistent health conditions.

3. Material and methods

3.1. Sample

Study participants were part of a population-based sample of 448 MZ and same-sex DZ twin pairs from the greater Montreal area who were recruited at birth between November 1995 and July 1998. Twins were first seen at 5 months of age and then prospectively assessed for a variety of child and family characteristics. Ninety-five percent of parents lived together, 44% of the twins were the firstborn children, 66% of mothers and 60% of fathers were between 25 and 34 years old, 17% of mothers and 14% of fathers had not finished high school, 28% of mothers and 27% of fathers held a university degree, 83% of the parents were employed, 10% of the families received social welfare or unemployment insurance, and 30% of families had an annual income of < $30,000. Most families were of European descent (87%), 3% were of African descent, 3% were of Asian descent, and 1% were Native North Americans. Zygosity was assessed with 8–10 highly polymorphous genetic markers. Twins were diagnosed as Monozygotic when concordant for every genetic marker. When genetic material was insufficient, zygosity was determined based on physical resemblance at ages 18 months and 9 years (Spitz et al., 1996). The comparison of both methods in a subsample of 237 same-sex pairs revealed a 94% correspondence rate. The present study includes data collected in grade 8 (*mean* age = 14.07 years, *SD* = 0.30), when 279 twin pairs participated. Analyses for the present paper were performed on the 203 twin pairs (MZ males = 54, MZ females = 66, DZ males = 42, DZ females = 41) with valid data on cortisol, of whom 78% had collected saliva at awakening on each of the four collection days, 17% on three days, 4% on two days and 2% on one day. Participants with and those without valid cortisol data did not differ on any measure except with respect to aggression (see description of control variables below), with the former being less aggressive than the latter. The final study sample did not differ from those who dropped out or who were excluded due to invalid cortisol data regarding maternal or paternal education levels, paternal age at the twins' birth or child temperament at age 5 months. However, families retained in the study had higher annual revenues and mothers were older at the twins' birth. They were also less likely to be single-parent households and more likely to be Caucasian.

3.2. Procedure

Letters explaining the objectives of the study were sent to the

families, followed by a home visit. After obtaining informed consent from parents and participants, research assistants explained the collection protocol, which included sampling saliva at awakening on four collection days (Tuesdays and Thursdays on two consecutive weeks) and the one-time completion of an interview-based questionnaire by the twins. Research assistants ensured that participants (and their parents) were familiar with the material. Families were visited a second time to gather the saliva tubes and conduct the interviews. Instruments and study procedures were approved by the Ste-Justine Hospital Ethics Committee.

3.3. Main measures collected at age 14 years

Peer victimization was assessed using twins' self-reports on nine items derived from the Social Experiences Questionnaire (Crick and Grotpeter, 1996) (e.g., "During this school year, how many times has another kid called you names or said mean things to you?, ….stopped you from being in his or her group although you wanted to be?, ….pushed, hit or kicked you?, ….threatened you or said mean things about you via e-mail, chat room, or cell phone?"). Responses were given on a three-point scale ranging from 0 (never), 1 (once or twice) to 2 (often). Item scores were averaged to yield a global victimization score (*Mean* = 0.25, *SD* = 0.28, Min = 0.00, Max = 1.22, Alpha = 0.76).

Depression symptoms were assessed via the brief version of the Children's Depression Inventory (Kovacs, 1992). Twins rated the frequency of 7 items primarily concerned with depressive affect (e.g., "I feel like crying") during the previous 2 weeks on a scale from 0 (rarely) to 2 (often). Item scores were averaged (*Mean* = 0.27, *SD* = 0.26, Min = 0.00, Max = 1.77, Alpha = 0.80).

Saliva collection at awakening and cortisol analysis. Participants were provided with saliva tubes (Sarstedt©), diaries to report collection times and instructions for collection. Saliva samples were first placed in the participants' refrigerator during data collection days and then stored in freezers at −20 °C once returned to the laboratory until cortisol determination using a high sensitivity enzyme immune assay kit (Salimetrics® State College, PA, Catalogue No. 1-3102). Frozen samples were brought to room temperature to be centrifuged at 15000 × *g* (3000 rpm) for 15 min and all analyzed in one batch. The range of detection for this assay is between 0.012-3ug/dL (0.33–82.76 nmol/L). We identified 1% cortisol samples with a value greater than 3 *SDs* above the mean of their respective sampling time and replaced them by the last value within 3 *SDs*. Participants were considered "compliant" if the awakening collection was completed within the first 15 min following awakening and not distinct between the twins (≤8 min). A total of 8.61% of the samples were discarded due to noncompliance. Cortisol values were converted into nmol/L (to convert ug/dL to nmol/L, multiply by 27.588) and naturally log transformed before analyses.

Creating aggregated indicators of cortisol across several days is recommended when examining individual characteristics or experiences in relation to cortisol levels (Adam and Kumari, 2009). To this end, the four cortisol estimates (one for each collection day) were included in a confirmatory factor analysis (CFA) to derive a more stable indicator free from situational-specific variation. In these analyses, we also examined whether estimates were affected by a wide range of *potential confounding variables* (sex, time of awakening, sampling time, sleep duration and quality, medications, menstruation for girls, current health conditions such as cold, fever, allergies, as well as persistent health conditions such as diabetes). Significant confounding variables were statistically controlled in the CFA. These analyses were conducted in Mplus Version 6.11 using Full Information Maximum Likelihood estimation and the COMPLEX option adjusting standard error estimates to correct for the non-independence of observations. The CFA confirmed that the respective estimates derived at each collection day could be grouped into a global cortisol factor (χ^2 (1) = 0.94, p = 0.76; RMSEA = 0.00; CFI = 1.00). Factor scores were saved for further analyses as described below (*Mean* = 7.40 nmol, *SD* = 1.71 nmol, Min = 3.40, Max = 15.55).

3.4. Additional control variables

Pubertal Development at age 14 years was assessed with the Pubertal Development Scale (Petersen et al., 1987). Participants rated their physical development on a 4-point scale (0"no development" to 3"development is complete") on several characteristics, including: growth spurt in height, pubic hair, and skin change for boys and girls; facial hair growth and voice change in boys; breast development and menarche in girls. Item scores were averaged to create an overall pubertal development scale (Mean = 1.51, SD = 50, Min = 0.00, Max = 2.60, Alpha = 0.71).

Birthweight in kg was derived from birth records (*Mean* = 2.44, *SD* = 0.55, Min = 0.82, Max = 3.94).

Body Mass Index (BMI) at age 14 years was calculated as the participant's self-reported weight in kilograms divided by self-reported height in meters squared (BMI = kg/m^2) (*Mean* = 20.47, *SD* = 3.82, Min = 13.08, Max = 38.89).

Family adversity. A composite family stress index was created based on mother reports on: (1) family status (twins living with both biological parents or not), (2) age of the mother at the birth of the twins, (3) mother's level of education and (4) family revenue. A score of 0 was attributed to family status if the child was living with both natural parents and a score of 1 was attributed to all other cases. A score of 0 was attributed to teenaged mothers and a score of 1 was attributed to all other cases. A score of 1 was attributed to mother's level of education if the mother did not have her high school diploma and a score of 0 was attributed to all other cases. A score of 1 was attributed to family revenue if the family annual revenue was below 20 000$ more than 50% of the time since the birth of the twins and a score of 0 was attributed to all other cases. A total family stressors index was then computed by summing the individual stressors (*M* = 1.21, *SD* = 0.58, Min = 0.00, Max = 3.00).

Harsh parenting at age 14 years was assessed via mother ratings on five items adapted from the Parenting Practices Scale (Strayhorn and Weidman, 1988) (e.g., "I often hurt this child", "I sometimes hit this child when I am angry", "I often criticize this child"). Responses were given using a four-point Likert-type scale ranging from 0 (Definitely false) to 3 (Definitely true). The respective item scores were averaged to create an overall parental hostility score (Mean = 0.50, SD = 0.45, Min = 0.00, Max = 2.20, Alpha = 0.77).

Participant's own aggressive behavior at age 14 years was assessed via self-ratings on six items from the MASPAQ (LeBlanc, 1996; LeBlanc and Fréchette, 1989). Participants indicated, for instance, whether they had in the previous year "threatened to hit someone in order to force them to do something they didn't want to do?", "taken part in fights between groups of young people (gangs)", "gotten into a fistfight with someone else". Responses were given on a four-point Likert-type scale ranging from 0 (Never) to 3 (Very often). Due to their highly skewed distribution, item responses were dichotomized into 0 (Never) and 1 (At least once) and then summed to create an overall aggression score (Mean = 0.37, SD = 0.80, Min = 0.00, Max = 4.00, Alpha = 0.85).

4. Results

4.1. Correlational analyses

For all three main study variables (peer victimization, cortisol, and depression symptoms), within-twin pair correlations were higher among MZ twin pairs (who are genetically identical) than among DZ twin pairs (who on average share only half of their genes): MZ r = 0.28 and DZ r = 0.15 for peer victimization, MZ r = 0.43 and DZ r = 0.19 for cortisol secretion, MZ r = 0.46 and DZ r = 0.24 for depression symptoms. This pattern suggests that all three variables are partly influenced by genetic factors (see detailed analyses below). Phenotypic

correlations showed that peer victimization was uncorrelated with cortisol secretion ($r = 0.03$, $p = 0.55$), but positively correlated with depression symptoms ($r = 0.32$, $p = 0.001$). Cortisol secretion was also positively correlated with depression symptoms ($r = 0.13$, $p = 0.01$). In addition, cortisol secretion and depression symptoms were correlated with each of the main control variables as well as with sex (*r*s ranging from −0.14 to 0.22). Cortisol secretion and depression symptoms were therefore regressed on these confounding variables and residual values of cortisol secretion and depression symptoms were used in all subsequent analyses.

4.2. Main analyses: univariate models

In a first series of analyses, univariate variance decomposition models (Neale, 2009) were fitted to the data to estimate the relative contribution of genetic and environmental factors to victimization, cortisol secretion, and depression symptoms, respectively. By comparing within-pair correlations for MZ twins and DZ twins, sources of variability of a measured variable (phenotype) can be estimated in terms of latent additive genetic effects (A), latent shared environmental effects (C) that affect siblings in the same way, and latent nonshared environmental effects (E) that affect siblings differently (Neale, 2009). Within-twin pair correlations of the latent additive genetic factors (A) are fixed to 1.0 for MZ twins and to 0.5 for DZ twins. Within-twin pair correlations of the latent shared environmental factors (C) are fixed to 1.0 for both MZ and DZ twins. Within-twin pair correlations of the latent nonshared environmental factors (E) are fixed to 0.0 for both MZ and DZ twins. The squared path coefficients between these latent factors and the observed measures, i.e., parameters a^2, c^2, and e^2, represent partitions of variance of each phenotype, with measurement error included in e^2. All analyses were performed with the Mplus software package. There were 0.66% missing data points in the study sample stemming from variables other than cortisol. Missing data were handled using Full Information Maximum Likelihood estimation (FIML). Model fit was assessed based on the Root Mean Squared Error Approximation (RMSEA) as well as the Log-Likelihood (LL) and χ^2 statistics (see Table 1). Low and nonsignificant LL and χ^2 values and values of RMSEA below 0.08 indicate good model fit and parsimony. Inspection of the parameter estimates revealed that all three variables were influenced by additive genetic factors, explaining 28% of the variance of peer victimization, 42% of the variance of cortisol secretion, and 46% of the variance of depression symptoms. The remaining portions of variance of the three variables were explained by nonshared environmental factors, whereas shared environmental factors played no significant role.

4.3. Main analyses: multivariate model without interaction terms

Following the findings from the univariate analyses, a multivariate Cholesky model was specified where the covariance structure of peer victimization, cortisol secretion, and depression symptoms was partitioned into (1) "common" latent factors A_P and E_P that simultaneously influence peer victimization and depression symptoms, (2) "common" latent factors A_C and E_C that simultaneously influence cortisol secretion and depression symptoms, and (3) "unique" latent factors A_D and E_D that are specific to depression symptoms (see Fig. 1). Because the preliminary analyses had revealed that peer victimization was uncorrelated with morning cortisol secretion, no common factors influencing these two variables were specified. Coefficients a_P, and e_P represent the factor loadings of peer victimization on the latent factors A_P and E_P. Coefficients a_{PD} and e_{PD} represent the factor loadings of depression symptoms on the latent factors A_P and E_P. Coefficients a_C and e_C represent the factor loadings of cortisol secretion on the latent factors A_C and E_C. Coefficients a_{CD} and e_{CD} represent the factor loadings of depression symptoms on the latent factors A_C and E_C. Finally, coefficients a_D and e_D represent the factor loadings of depression symptoms on the latent factors A_D and E_D. Thus, to give an example, the total variance of depression symptoms (V_D) can be expressed as $V_D = a_{PD}^2 + a_{CD}^2 + a_D^2 + e_{PD}^2 + e_{CD}^2 + e_D^2$. The relative contribution of the "common" latent genetic factor A_P to the overall genetic variance of depression symptoms $(a_{PD}^2)/(a_{PD}^2 + a_{CD}^2 + a_D^2)$ indicates the overlap or correlation between genetic influences on peer victimization and depression symptoms (rGE). The relative contribution of the "common" latent environmental factor E_P to the overall environmental variance of depression symptoms $(e_{PD}^2)/(e_{PD}^2 + e_{CD}^2 + e_D^2)$ can be interpreted as the environmental influence linking peer victimization to depression symptoms, net of rGE.

The results from the first multivariate model (without interaction terms) are shown in the upper part of Table 2. The fit indices indicated that this first model showed acceptable fit to the data. Inspection of the parameter estimates revealed that 16% $(= 0.26^2/(0.21^2 + 0.26^2 + 0.57^2))$, of the genetic factors influencing depression symptoms overlapped with those influencing cortisol secretion. Moreover, these common underlying genetic factors entirely explained the association between cortisol secretion and depression symptoms, as the common environmental influences linking these two variables were estimated to be close to zero and not significant ($e_{CD} = 0.06$, $p = 0.304$). Another 9% $(= 0.21^2/(.21^2 + 0.26^2 + 0.57^2))$, of the genetic factors influencing depression symptoms were those that also influenced peer victimization, indicating rGE. In addition, however, there was also an environmental association between peer victimization and depression symptoms ($e_{PD} = 0.22$, $p = 0.000$), which accounted for 10% $(= 0.22^2/(0.22^2 + -0.06^2 + 0.67^2))$ of environmental influences on depression symptoms.

4.4. Main analyses: multivariate model with interaction terms

Next, the Cholesky model was expanded to include two interaction terms: (1) an interaction term predicting depression symptoms between the common genetic factor A_P and Cortisol Secretion, represented by the term $\beta_{A\_PD(C)}$, and (2) an interaction term predicting depression symptoms between the common environmental factor E_P and Cortisol Secretion, represented by the term $\beta_{E\_PD(C)}$. These interaction terms tested whether the additive genetic and-or the environmental effects linking peer victimization with depression symptoms varied depending on the level of morning cortisol secretion. Since χ^2 and RMSEA are not available for a multivariate model that includes interaction terms, that model was compared to a model where these interactions terms where

Table 1
Univariate Model Results.

	A	C	E	%A^2	%C^2	%E^2	RMSEA	LL	χ^2	*p*
Peer Victimization	0.52 (0.11;.92)	0.07 (−2.29; 2.43)	0.82 (0.73; 0.91)	28.1	0.6	71.3	0.00	−754.8	0.50	0.78
Morning Cortisol	0.62 (0.50; 0.74)	0.00 (−1.58; 1.58)	0.73 (0.65; 0.82)	41.8	0.0	58.2	0.03	−581.2	0.10	0.95
Depression Symptoms	0.66 (0.37; 0.94)	0.06 (−2.72; 2.83)	0.71 (0.63;.78)	46.3	0.4	53.3	0.00	−728.4	0.09	0.96

Note. Confidence Intervals are in parentheses. All models have 4 parameters (including means) and 2 degrees of freedom.

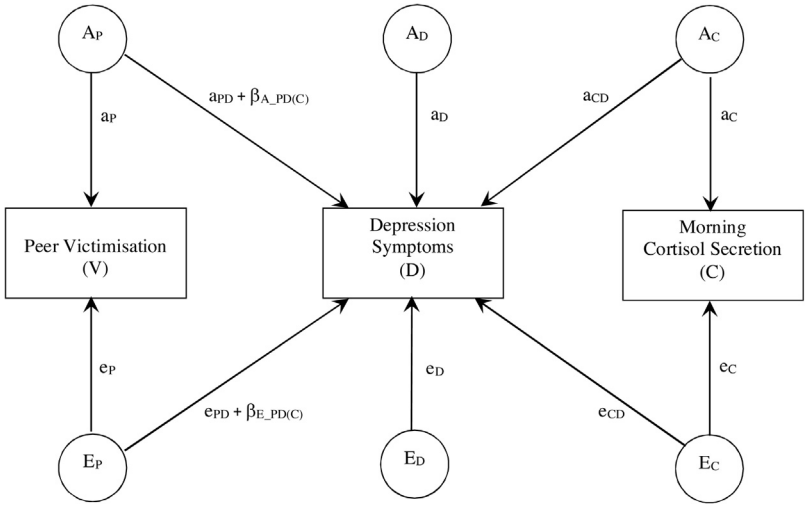

Fig. 1. Multivariate model (for one member of a twin pair) of peer victimization, cortisol secretion, and depression symptoms including interaction terms.

Table 2
Cholesky Model Results.

Model	Parameter	Estimate	LL	Number of parameters	AIC	BIC	RMSEA	χ^2 (df)	*p*
Without interaction			−2031.5	13	4089.0	4136.3	0.00	4.95 (17)	0.99
	a_P	0.52 (0.39; 0.66)							
	a_{PD}	0.21 (0.03; 0.39)							
	a_C	0.63 (0.51; 0.75)							
	a_{CD}	0.26 (0.09; 0.43)							
	a_D	0.57 (0.45; 0.69)							
	e_P	0.82 (0.74; 0.90)							
	e_{PD}	0.22 (0.12; 0.32)							
	e_C	0.73 (0.65; 0.81)							
	e_{CD}	−0.06 (−0.18; 0.06)							
	e_D	0.67 (0.60; 0.74)							
With interaction			−1572.4	15	3174.9	3224.6			
	a_P	−0.40 (−0.65; −0.15)							
	a_{PD}	0.09 (−0.20; 0.37)							
	$\beta_{A\_PD(C)}$	0.22 (0.04; 0.39)							
	a_C	0.64 (0.51; 0.76)							
	a_{CD}	0.21 (0.05; 0.36)							
	a_D	−0.47 (−0.67; −0.27)							
	e_P	0.83 (0.68; 0.97)							
	e_{PD}	0.32 (0.20; 0.43)							
	$\beta_{E\_PD(C)}$	0.13 (0.04; 0.39)							
	e_C	−0.74 (−0.82; −0.65)							
	e_{CD}	0.04 (−0.06; 0.15)							
	e_D	0.61 (0.50; 0.73)							

Note. Confidence intervals are in parentheses. No fit statistics are available in Mplus for models that include interaction terms.

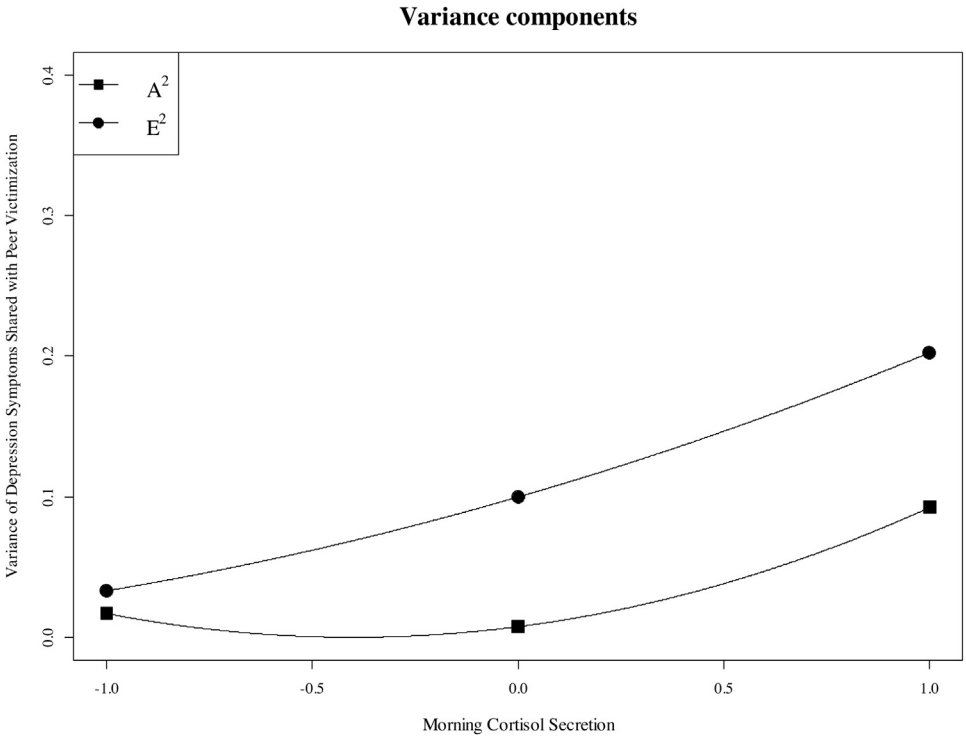

Fig. 2. Plot of the genetic and environmental variance of depression symptoms shared with peer victimization (in% of total variance of depression symptoms) as a function of morning cortisol secretion. Values for cortisol are indicated as −1 SD, the mean (0) and +1 SD.

constrained to zero using the 2LL difference test, which is equivalent to a nested χ^2 −difference test (Purcell, 2002).

The results from the second multivariate model (with interaction terms) are presented in the lower part of Table 2. The likelihood ratio test revealed that inclusion of the interaction terms in the significantly improved model fit, $2\Delta LL\ (2) = 6.68$, $p = 0.03$. Both interaction terms were statistically significant. This finding indicates that both the genetic and the environmental association between peer victimization and depression symptoms vary significantly depending on individuals' level of morning cortisol secretion. For illustrative purposes, we plotted the magnitude of the variance of depression symptoms – and of its components – that was explained by peer victimization as a function of the level of cortisol secretion (Fig. 2). As can be seen, for youth with low levels (−1 SD) of morning cortisol, both the genetic association and the environmental association between peer victimization and depression symptoms were close to zero. In other words, peer victimization was unrelated to depression symptoms in youth with very low levels of morning cortisol. However, the *environmental* association between peer victimization and depression symptoms steadily increased with increasing levels of morning cortisol. Indeed, environmental effects related to peer victimization explained around two thirds of the variance shared with depression symptoms for youth with high levels (+1 SD) of morning cortisol. The *genetic* association between peer victimization and depression symptoms also increased with increasing levels of morning cortisol, albeit to a lesser extent. Specifically, whereas there was no genetic association (i.e., no rGE) linking depression symptoms with peer victimization in individuals with low (−1SD) or moderate (mean) levels of cortisol secretion, a notable rGE emerged in individuals with high (+1SD) levels of cortisol secretion.

5. Discussion

Using a genetically informative design based on twins, the main goal of this study was to examine whether the *environmental* association between peer victimization and depression symptoms would be moderated by levels of cortisol secretion. Specifically, we aimed to test whether the environmental association between peer victimization and depression symptoms would be stronger in youth with higher levels of morning cortisol than in youth with lower levels of cortisol secretion, even when controlling for common underlying genetic influences.

Replicating findings from previous research (Happonen et al., 2002; Scourfield et al., 2003), adolescents' depression symptoms were significantly influenced by genetic factors, with the remaining variance mostly explained by environmental influences unique to each individual. Our results further showed that 16% of the genetic effects on depression symptoms were associated with individuals' susceptibility for increased cortisol secretion. Indeed, the correlation between cortisol secretion and depression symptoms was entirely explained by these common underlying genetic factors. These results concord with the notion that depression has at least in part a neurophysiological origin, notably HPA axis functioning (Wichers et al., 2008).

5.1. Genetic and environmental associations between depression symptoms and peer victimization

In addition to being linked with cortisol secretion, depression symptoms were associated with peer victimization. A significant portion of the link between peer victimization and depression symptoms was due to common underlying genetic influences, indicating rGE. The finding that genetic factors underlying depression symptoms are also linked to peer victimization concords with previous findings that youths with a genetic vulnerability for depression are more at risk than others to experience negative life events, including peer victimization (Bowes et al., 2013; Brendgen et al., 2009; Lau and Eley, 2008). However, there was also an environmental association between peer victimization and depression symptoms, which may reflect environmental influences from peer victimization to depression symptoms. This interpretation would be consistent with previous findings showing that peer victimization is a serious risk factor for the development of internalizing problems (Reijntjes et al., 2010).

5.2. The role of cortisol in the genetic and environmental associations between depression symptoms and peer victimization

Analyses revealed that both the *genetic* and the *environmental* association between peer victimization and depression symptoms varied

significantly depending on individuals' levels of cortisol secretion. Specifically, whereas there was no genetic association (i.e., no rGE) linking depression symptoms with peer victimization in individuals with low or moderate levels of cortisol secretion, a notable rGE emerged in individuals with high levels of cortisol secretion. It is possible that individuals who have both a high genetic vulnerability for depression symptoms and high levels of cortisol secretion express their negative thoughts and feelings in a way that puts them at especially high risk of victimization by peers. Indeed, because cortisol helps mobilize energy stores and facilitate behavioral responses to stress (Gunnar and Quevedo, 2007), individuals with higher than normal morning cortisol levels may be more prone than others to overreact to even mild teasing. In support of this notion, elevated cortisol secretion has been linked with withdrawal and with persistent (trait) rather than temporary (state) anxious and fearful behavior in youth (Greaves-Lord et al., 2007; Pérez-Edgar et al., 2008). Elevated cortisol has also been shown in children who react with exaggerated emotional and angry outbursts to perceived provocations or threats (Lopez-Duran et al., 2009). Peers may perceive such behavior as provocative or even amusing, which may lead to further ridiculing and harassment (Gazelle and Shell, 2017, in press). These explanations are speculative, however, and further research is needed to understand why youth with a stronger disposition for depression symptoms and elevated cortisol secretion may be more often victimized by their peers.

More central to the objective of the present study, the environmental association between peer victimization and depression symptoms also increased with increasing cortisol levels. Specifically, whereas environmental effects related to peer victimization did not predict depression symptoms in youth with very low levels of morning cortisol, environmental effects related to peer victimization explained around two thirds of the variance shared with depression symptoms for youth with high levels of morning cortisol. The finding that cortisol moderates the *environmental* association between peer victimization and depression symptoms may be interpreted as concordant with the Biological Sensitivity to Context (BSC) hypothesis (Ellis et al., 2011). When exposed to environmental stressors, biologically sensitive individuals may be especially vulnerable to negative consequences. This finding corroborates those from previous non-genetically informed studies showing that cortisol secretion moderates the association between stress exposure and mental health problems in youth (Hagan et al., 2014; Kuhlman et al., 2017; Rudolph et al., 2011, 2010). In particular, our results resemble those by Rudolph and colleagues showing that peer victimization is associated with increased depressive symptoms only in youths with high basal cortisol secretion. Interestingly, whereas Rudolph and colleagues examined basal cortisol in anticipation of a social stress task, the same moderating effect is observed for morning cortisol in a natural setting. It has been suggested that baseline cortisol levels prior to stress may indicate individual's baseline sensitivity to potential stress, both at the psychological and neurophysiological levels (Balodis et al., 2010). It is possible that morning cortisol levels at awakening represent a similar "pre-challenge" measure of the HPA axis activity during the day, which might further explain the similar pattern of results found in the present study and in the study conducted by Rudolph et al. (2011).

It is also worth noting that peer victimization was not directly related to morning cortisol secretion. Although some studies reported a link between extreme environmental adversity and morning cortisol, associations with adversity in normative samples are often non-significant (for a meta-analysis, see Bernard et al., 2017). It is also possible that only chronic peer victimization occurring from a young age–rather than the relatively recent victimization over the past year assessed in the present study–alters diurnal cortisol secretion. Indeed, a meta-analysis to identify the factors associated with cortisol increases in natural settings found that stressor chronicity was fundamental in predicting cortisol changes (Michaud et al., 2008). Finally, it has been suggested that the stress response system exhibits decreased plasticity and increased individual stability over time (Ellis et al., 2011; Hagan et al., 2014). This stability is also evident in the heritable components of cortisol secretion found in the present study as well as in longitudinal investigations of the circadian rhythm (Shirtcliff et al., 2012). The present results thus highlight the importance of the stress response system as a key component of BSC and add to the accumulating evidence that differential cortisol secretion may partly underlie individuals' vulnerability or resilience to the effect of stressful experiences on health outcomes.

5.3. Strengths and limitations

Disentangling genetic and environmental pathways through a genetically informed design, our study helps clarify the links between peer victimization, depression symptoms, and cortisol secretion. By collecting salivary cortisol over four days instead of a single day, we obtained more reliable measurements (Kraemer et al., 2006). Our study also has limitations. For instance, while collecting saliva at home allowed measuring cortisol levels in a natural environment, the sampling procedure was not directly controlled. Mean sampling times suggested that most participants adhered well to the protocol and control of the sampling time also helped minimize potential bias. Nevertheless, future studies should utilize track caps to electronically monitor sampling times (Kudielka et al., 2003). The relatively low levels of peer victimization in our sample precluded the distinguishing between frequent and infrequent peer victimization. Moreover, response options for the peer victimization items did not allow assessing the specific duration of victimization, which may have reduced variance and associations with other study variables, notably with cortisol secretion. The distinct time frames for the victimization measure (past year) and the depression measure (past two weeks) may also have reduced observed associations in our study. By the same token, the use of self-reports to assess peer victimization may have inflated the association with self-reported depression symptoms. However, evidence suggests that subjective rather than objective stress impacts physiological stress response and health outcomes (Adler et al., 2000). It is also important to remember that findings rest on cross-sectional data. Overall, the observed genetic association (rGE) between peer victimization and depression indicates a person-on-environment effect, whereas the observed environmental association is consistent with an environment-on-person effect. Nevertheless, future studies should include two time points within the same school year to more clearly discern directionality of effects. Generalization could also be limited since data were based on twins. However, twins and singletons show similar levels of peer victimization (Boivin et al., 2013), mood and cortisol reactivity to daily stressors (Jacobs et al., 2007). Moreover, although twins often have lower birth weight, they do not differ from singletons regarding BMI or pubertal status (Kaprio et al., 1995). Also, because study participants were mostly Caucasian and came from relatively well-off families, it is unclear whether results generalize to adolescents from other ethnic or socioeconomic backgrounds. Finally, results from this study cannot be generalized to clinical populations, who show different patterns of cortisol secretion (Goodyer et al., 1996).

5.4. Conclusions

Despite these limitations, our study provides further insights about the role of the HPA axis in individuals' vulnerability versus resilience to adverse environmental experiences. A high genetic vulnerability for depression symptoms, coupled with heightened physiological reactivity as indicated by morning cortisol secretion, is related to an increased risk of peer victimization. By the same token, individuals with heightened levels of morning cortisol are more at risk than others to suffer from depression symptoms when exposed to peer victimization. Interventions that target the moderating effect of HPA axis functioning by optimizing physiological stress regulation (e.g., Lupien et al., 2013;

Matousek et al., 2010) may thus be a promising avenue to help break the vicious cycle linking peer victimization and depression symptoms for physiologically vulnerably individuals.

Conflicts of interest

None.

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