

Peer Problems and Hyperactivity–Impulsivity Among Norwegian and American Children: The Role of 5-HTTLPR

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Peer problems are linked to attention deficit hyperactivity disorder (ADHD) symptoms and the serotonin system is thought to be involved in ADHD-related behavior. Hence, from a Gene \times Environment perspective, the serotonin transporter 5-HTTLPR may play a moderating role. In two large community samples, the moderating role of 5-HTTLPR was examined related to more hyperactivity–impulsivity symptoms (HI symptoms) predicted by more peer problems. In Study 1, involving 642 Norwegian children, results indicated that for *s*-allele carriers only, caregiver-reported peer problems at age 4 predicted more parent-reported HI symptoms at age 6. In Study 2, similar results emerged involving 482 American children. Discussion focuses on differential sensitivity to the adverse effects of poor peer relations.

Research on the effects of various forms of peer problems, such as peer rejection (Asher & Coie, 1990), social exclusion, and bully victimization (Arseneault, Bowes, & Shakoor, 2010; Olweus, 1978), indicates that a harsh and unfriendly peer context undermines children's ability to self-regulate, both immediately and in the longer term (Baumeister, DeWall, Ciarocco, & Twenge, 2005; Eisenberger, Lieberman, & Williams, 2003; Stenseng, Belsky, Skalicka, & Wichstrøm, 2014). In a recent three-wave study of Norwegian children, Stenseng, Belsky, Skalicka, and Wichstrøm (2016) found that peer rejection at ages 4 and 6 predicted increased attention deficit hyperactivity disorder (ADHD) symptoms of hyperactivity–impulsivity (HI) and inattentiveness across period of 2 years. Similar results from the United States (Hoza, 2007) and Taiwan (Tseng, Kawabata, Shur-Fen Gau, & Crick, 2014) indicate that ADHD symptoms are linked to peer functioning.

Despite the repeated observation that peer problems may intensify ADHD-related behavior, only limited consideration has been given to the possibility that children's genetic makeup may moderate such an adverse effect. Oades (2007) proposed that the serotonin system may underlie cognitive impulsivity in ADHD, and this idea has received empirical support (Oades, 2008; Sonuga-Barke et al., 2011). Accordingly, in their two-mode model of self-regulation, Carver, Johnson, and Joormann (2008, 2009) describe how low serotonergic activity determined by the serotonin transporter 5-HTTLPR may serve as a biopsychological basis for highly impulsive behavior. Given these associations between ADHD and serotonin, as well as the burgeoning developmental literature on Gene \times Environment (G \times E) interaction, we investigate whether *peer effects* vary as a function of children's serotonergic makeup—using two separate samples, one of Norwegian and the other of American children—while focusing on the role of the 5-HTTLPR polymorphism.

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The Serotonin Transporter Gene, 5-HTTLPR

The serotonin transporter gene (*SERT*, also known as *SLC6A4*), more specifically, the serotonin transporter-linked promoter region (*5-HTTLPR*), has been implicated repeatedly in research on $G \times E$ interaction involving children (for meta-analyses, see Karg, Burmeister, Shedden, & Sen, 2011; Van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012). This region is involved in cortical serotonergic transcription and transmission, which is associated with regulation of both mood and cognition (Canli & Lesch, 2007; Carver et al., 2008, 2009; Karg et al., 2011; Kretschmer, Sentse, Dijkstra, & Veenstra, 2014; Sugden et al., 2010).

The *5-HTTLPR* shows genetic variation consisting of a 44-base pair insertion or deletion, resulting in production of two alleles, referred to as the long (*l*, 16-repeat) and short (*s*, 14-repeat) variants. Relative to short-allele carriers, individuals who are homozygous for the long-allele (*ll*) of the *5-HTTLPR* possess increased serotonin reuptake, transporter expression, and efficiency of transcription (Heils et al., 1996; Oades, 2010). The *ll* carriers express about twice as many serotonin transporters as compared to carriers of one or two *s* alleles (Friedel & Heinz, 2010). Hence, it is assumed that the *s* allele is associated with increased extracellular serotonin levels (Kalueff, Olivier, Nonkes, & Homberg, 2010), thereby contributing to less emotional stability among its carriers (e.g., Carver et al., 2008) and that *l* homozygotes, consequently, are less affected by harsh environments than *s* carriers (Canli & Lesch, 2007; Van Ijzendoorn et al., 2012).

Gene–Environment Interaction

This genetically based differential sensitivity to environmental influences has been documented in several studies (Karg et al., 2011; Van Ijzendoorn et al., 2012) and, most notably for purposes of this report, also in relation to peer problems. For example, Sugden et al. (2010) observed that children homozygous for the *s* allele were, relative to *l*-allele carriers, at greater risk of developing emotional problems (i.e., withdrawal, anxiety, depression) at age 12 when having experienced victimization at age 5. Likewise, Iyer, Dougall, and Jensen-Campbell (2013) reported that the experience of being bullied predicted adolescent depression among *s* carriers but not *l*-allele homozygotes, with corresponding results emerging in a study of adolescent girls (Benjet, Thompson, & Gotlib, 2010).

To date, developmental scholars have mostly focused on how *5-HTTLPR* interacts with environmental factors to foster emotional as opposed to behavioral problems. In particular, it has been shown that *s* carriers are more sensitive to the adverse effects of stress in childhood than *l* homozygotes (Bogdan, Agrawal, Gaffrey, Tillman, & Luby, 2014; Caspi et al., 2003; Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2012; Petersen et al., 2012; Uher et al., 2011). Relevant in this regard is Carver et al.'s (2008, 2009) two-mode model of self-regulation, which stipulates that low serotonergic functioning may lead to both impulsive (e.g., aggression) and inhibited behavior (e.g., depression). These scholars specifically suggest that low serotonergic functioning is related not only to negative emotions, such as fear, anger, and sadness, but also to traits such as impulsivity and hostility. They base their argument partly on studies in which serotonergic functioning has been reduced experimentally, as these indicate, for example, that individuals under serotonergic deprivation display disinhibited responses in “go versus no go” tasks (Crockett, Clark, Tabibnia, Lieberman, & Robbins, 2008; Walderhaug et al., 2002, 2007). Such results lend support to the idea central to the current inquiry: that low serotonin transcription is associated with increased sensitivity to develop ADHD-related behavior in early childhood when experiencing difficult life circumstances, such as peer rejection.

Problems With Peers

Given evidence that regulative capability is a limited resource that diminishes temporarily when used (i.e., “Strength Theory”; Baumeister, Bratslavsky, Muraven, & Tice, 1998), it seems likely that *s* carriers who experience peer problems—a situation in which high demands are placed on a child's regulatory system—will tend to become increasingly dysregulated relative to *l* homozygotes under such circumstances. Furthermore, because self-regulation is involved in many everyday tasks and behaviors, it seems likely that a situation at, for example, school that strains coping capacity also will affect other life domains. In other words, negative peer experiences at school may affect children's behavior in the family.

Buttressing this claim is Dalley and Roiser's (2012) review addressing the role of serotonin and dopamine in impulsivity. These scholars concluded that serotonin is involved in impulsive behavior while contending that further research on such

mechanisms may provide insights into the etiology of ADHD. Even though the diagnosis of ADHD is beyond the scope of the present inquiry, it seems reasonable to test the possible differentiating role of 5-HTTLPR in the development of impulsivity and hyperactivity in a community sample, given that children with ADHD are quantitatively—and not qualitatively—different from their nondiagnosed peers with regard to regulatory capabilities (Barkley, 1997; Coghill & Sonuga-Barke, 2012). Because HI symptoms typically are displayed at an earlier age than inattentive symptoms (Nigg, 2001) and thus are more reliably measured among preschool children, who are the focus of this report, we focus solely on such symptoms in the empirical work presented herein.

ADHD, Regulatory Abilities, and 5-HTTLPR

As already implied, the number of studies examining links between 5-HTTLPR and internalized problems is quite large. On the other hand, to our knowledge, only five $G \times E$ studies have investigated behavioral functioning reflecting hyperactivity and impulsivity. In the first such work, Carver et al. (2011) tested—and found support for—their aforementioned model, observing that *s*-carrying adults who retrospectively reported childhood adversity (e.g., threat, abuse) scored higher on impulsivity than *l* homozygotes who reported similar experiences while growing up. Subsequently, Meer et al. (2014) found that stressful life events, also measured retrospectively, disproportionately predicted an increase in ADHD severity from age 6 to 17 but only among *s* carriers. Kochanska, Philibert, and Barry (2009) reported, based on a small sample of preschool children ($N = 89$), that insecure attachment forecast poor effortful control, again only among *s* carriers. Most recently, in a sample of MRI-scanned adolescents, Meer et al. (2015) found childhood stress to be associated with less gray matter volume in brain regions involved in executive functioning, with *s* carriers showing significantly less gray matter than *l* homozygotes. Notable as well is Retz et al.'s (2008) earlier work on a sample of young adult delinquents, which showed that ADHD symptoms among *s* carriers increased as a function of their self-reported adverse childhood environment, whereas this was not the case for *l* homozygotes. Despite this empirical evidence, as well as Carver et al.'s (2008, 2009) theoretical arguments, few studies have investigated whether—and how—*sociocontextual* conditions are differently linked to the development of

regulatory problems among *s* carriers and *l* homozygotes.

The Significance of Replication

Recent years have witnessed an outpouring of concern regarding the replicability of scientific findings (Jasny, Chin, Chong, & Vignieri, 2011). Perhaps nowhere has this issue emerged so forcefully in the human behavioral sciences as in research involving measured genes. Much of this concern originated in the disappointment that arose when initial and significant genotype–phenotype associations could not be repeated in subsequent studies (Hamer, 2002; Insel & Collins, 2003). When attention turned to $G \times E$ interaction, following the publication of pioneering work of Caspi et al. (2003), it was not long before issues of replication arose here as well. The situation no doubt became especially confusing when different meta-analyses of the supposedly same $G \times E$ interaction (involving stressful life events, 5-HTTLPR, and depression) yielded radically different conclusions (e.g., Risch et al., 2009; Uher & McGuffin, 2010). Duncan and Keller (2011) even went so far as to claim that most reported $G \times E$ findings are likely false positives.

The interplay of genes and environment is of course extremely complex, and in some cases—where several genes are hypothesized to operate together in the same direction—several genes are combined into a genetic risk score (Belsky & Beaver, 2011; Belsky & Israel, 2014). This approach was not chosen in the present study, partly because there is limited consensus around which genes and gene variants are associated with HI vulnerability or ADHD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), but primarily because our hypotheses were based on recent findings specifically linking 5-HTTLPR to the moderation of ADHD (Meer et al., 2014, 2015).

To be noted as well is that we do not undertake a comparative evaluation of diathesis–stress and differential–susceptibility frameworks of $G \times E$ interaction. Although the former framework stipulates that some children are more adversely affected by negative influences than others (Monroe & Simons, 1991), central to the latter is the view that the very same children who are most vulnerable to adversity also benefit disproportionately from its opposite, peer acceptance (Belsky & Pluess, 2009, 2013; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011). Even though new data analytic methods

have been developed to distinguish between these models (Widaman et al., 2012; Roisman et al., 2012), they are not employed in this report because this investigation focuses on the “dark side” of peer relations (peer problems) and regulatory abilities (HI) and not the “bright side” (peer acceptance, controlled behavior). Thus, the current inquiry is not well positioned to evaluate the “for-better-and-for-worse” pattern of environmental effects that define the differential susceptibility framework.

The Current Study

The current report, informed by concerns for the replicability of candidate gene-related findings, addresses the $G \times E$ question under consideration using two separate samples. More specifically, we extend peer-related $G \times E$ research focused on 5-HTTLPR by testing the proposition that the previously identified adverse effect of peer problems on symptoms of ADHD is conditioned by the child’s genetic makeup. Consistent with previous findings (Arseneault et al., 2006; Stenseng et al., 2014), the first (main effect) hypothesis is that more peer problems in preschool (i.e., at age 4) will predict *increases* in HI symptoms 2 years later when children are in school. Second, and based on the aforementioned analysis that the efficiency of the serotonergic system affects children’s reactions to adverse influences (Sugden et al., 2010; Uher et al., 2011), including impulsive behavior (Carver et al., 2008, 2009; Carver et al., 2011), we predict that the general adverse effect of peer problems will be more pronounced in the case of *s* than *ll* carriers. These hypotheses are tested in two large community samples of children, first one from Norway (Study 1: Trondheim Early Secure Study [TESS]) and second one from the United States (Study 2: The NICHD Study of Early Child Care and Youth Development [NICHD SECCYD]), with the second study seeking to replicate findings from the first study using similar, if not always, identical measurements. Analyses are conducted by means of structural equation modeling (SEM) and controlled for gender effects. Notably, dopamine genes were also available in these two samples, and because some of these genes (*DAT1*, *DRD4*, *COMT*) have been linked to ADHD in previous studies (e.g., Faraone et al., 2005), $G \times E$ effects of these genes were analyzed. However, none of these were found to have a significant replicated $G \times E$ effect (see Appendix S1).

Study 1

Methods

Participants

The TESS (e.g., Wichstrom et al., 2012) comprises participants from two birth cohorts (born 2003 or 2004) of children and their parents living in the city of Trondheim in Norway. Of the 1,250 children invited to participate, 936 (74.9%) participants were tested. Dropout rate did not vary by behavioral functioning (as measured using the Strengths and Difficulties Questionnaire; $\chi^2 = 5.70$, $df = 3$, $p = .13$) or gender ($\chi^2 = 0.23$, $df = 1$, $p = .63$). A total of 762 children (50.5% boys) participated in follow-up assessment 2 years later (T2), and 642 of these children were genotyped. Response rates among teachers were 90.6%. Teachers had known the child for an average of 13 months. Children genotyped did not diverge from those not genotyped on the study variables (gender: odds ratio [OR] = .99, confidence interval [CI] = [0.77–1.29]; peer problems: OR = 0.89, CI = [0.74–1.09]; HI symptoms at T1: OR = 1.03, CI = [0.89–1.20]; HI symptoms at T2: OR = 1.01, CI = [0.88–1.15]).

Procedure

Parents and children were invited to participate in the study when attending the regular health checkup for 4-year-olds. The health nurse at the local well-child clinic informed parents that the study was longitudinal and focused on mental health among children. Written consent was obtained according to procedures approved by the Regional Committee for Medical and Health Research Ethics. Families were invited to the university for further participation in the study, usually conducted within 2 weeks after their well-child clinic visit (in 2007 and 2008). Parental and child data were collected by means of interviews and questionnaires. Diagnostic psychiatric interviews were conducted by assistants with relevant formal education trained to perform the interview related to the child. Teacher data were collected by means of questionnaires sent to day-care centers (together with information about the study), requesting that the preschool teacher who knew the child best filled out the forms. Children were reexamined with their parents at the clinic 2 years later, at T2 (in 2009 and 2010), including the collection of saliva samples for genotyping.

Measures

Peer problems. The Teacher Report Form (C-TRF) from the Achenbach System of Empirically Based Assessment (Achenbach & Rescorla, 2000) was used to measure peer problems in preschool. An item pool of six items was made from the C-TRF comprising items corresponding with typical peer problems, such as social rejection (Asher & Coie, 1990; Ladd, 2006; Reijntjes et al., 2010), and they were subsequently explored by means of factor analysis and reliability analyses. Three items were finally chosen according to criteria of theoretical validity and statistical reliability: “Not liked by other children/pupils,” “Doesn’t get along with other children/pupils,” and “Gets teased a lot.” Teachers rated each item for each child using a three point scale ranging from 1 (*not true*) through 2 (*somewhat or sometimes true*) to 3 (*very true or often true*). Cronbach’s alpha for the construct was .75, and all factor loadings > .52. Validity of the measurement has been supported in a previous study (Stenseng et al., 2014). Invariances of the factor loadings across the groups (*s* vs. *ll* carriers) were also tested, yielding a nonsignificant result, $\Delta\chi^2(1) = 0.97, p = .32$.

HI symptoms. The Preschool Age Psychiatric Assessment (PAPA; Egger et al., 2006) was used to measure symptoms of hyperactivity and impulsivity at both measurement occasions. The PAPA is a semistructured diagnostic interview developed to assess psychiatric diagnoses in children ages 2–6 based on the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. [DSM–IV]; American Psychiatric Association). The preschool version of the interview applies a semistructured protocol with parents as informants. Questions developed to clinically assess *Hyperactivity and Impulsivity* in the ADHD section were used in the parental interview. The aggregated sum of symptoms was used in the subsequent analyses. The highest amount of possible symptoms was 9. Mean values and standard deviations of the regulatory problems score are presented in Table 1.

Genotyping. Polymerase chain reaction (PCR) of the 5-HTTLPR polymorphism was performed with the Ampli Taq® 360 DNA polymerase kit (Applied Biosystems, Massachusetts, USA). The amplification reactions were performed in a total volume of 25 μ l containing 10–100 ng genomic DNA, 1.25 units of AmpliTaq 360 DNA polymerase, 0.75 mM MgCl₂, 16% (v/v) 360 GC Enhancer, 0.5 mM dNTP, and 0.3 μ M of each primer. The forward primer was labeled with 6-FAM:

Table 1

Descriptives and Zero-Order Correlation for Variables Included in the Analyses, Total Sample, and *s* Carriers and *ll* Carriers Separated in the Norwegian Sample

	Total sample						<i>s</i> Carriers (N = 448)					<i>ll</i> Carriers (N = 194)						
	M	SD	1	2	3	4	M	SD	1	2	3	4	M	SD	1	2	3	4
1. Peer problems, age 4	3.22	0.72	1				3.25	0.77	1				3.18	0.58	1			
2. Hyperactivity–Impulsivity, age 4	0.84	1.38	0.18**	1			0.81	1.38	0.18**	1			0.89	1.56	0.10	1		
3. Hyperactivity–Impulsivity, age 6	0.81	1.50	0.21**	0.38**	1		0.88	1.56	0.23**	0.33**	1		0.74	1.41	–0.04	0.47**	1	
4. Gender ¹	1.50	0.50	0.11**	0.05	0.11**	1	1.48	0.50	0.14**	0.10*	0.17**	1	1.54	0.50	0.01	–0.04	0.02	1

Note. ¹Girl = 1, Boy = 2. * $p < .05$, ** $p < .01$.

carboxyfluorescein 5'-GGC GTT GCC GCT CTG AAT GC-3' and the reverse primer was 5'-GAG GGA CTG AGC TGG ACA ACC AC-3'. The fragments were amplified with denaturation at 95°C for 5 min and subjected to 35 cycles at 95°C for 30 s, 63°C for 30 s, 72°C for 1 min, and a final extension at 72°C for 10 min. The 5-HTTLPR marker was genotyped by size separation of the PCR product on the ABI 3,730 DNA Analyzer (Applied Biosystems) and sized utilizing the GeneScan 600 LIZ Size Standard (Applied Biosystems) and the ABI PRISM Gene Mapper[®] software, version 4.0 (Applied Biosystems). The 5-HTTLPR genotype frequencies were consistent with the Hardy-Weinberg equilibrium ($\chi^2 = 2.77$, $p = .10$). One hundred and sixteen (18.1%) children were identified as *ss* homozygotes, 332 (51.1%) children were identified as heterozygous *s/l*, and 194 (31.1%) children as *l* homozygotes. Genotypes were unrelated to peer problems in the sample ($r = -.034$, $p = .37$), HI symptoms at T1 ($r = .031$, $p = .34$) and T2 ($r = .051$, $p = .17$), as well as gender ($r = .002$, $p = .89$).

Results

Preliminary data analyses pertaining to change over time and the intercorrelation of measurements are presented first. Primary analyses follow, evaluating whether 5-HTTLPR moderates the effect of early peer problems on later (HI symptoms), after taking into account earlier symptoms (and child gender).

Preliminary Analyses

Consistent with previous studies of 5-HTTLPR polymorphism, *ss* carriers and *sl* carriers were aggregated into one group of *s* carriers (for a review, see Karg et al., 2011). In order to compare mean levels of peer problems and HI symptoms at T1 and T2 for *s* carriers and *l* homozygotes, *t* tests were performed. Results showed that the total sample exhibited less HI symptoms at age 6 than at age 4 ($M = 0.84$ vs. $M = 0.81$), but this age-related difference was not statistically significant ($t = 0.58$, $p = .56$). The mean level of HI symptoms decreased across these ages among *ll* carriers ($M = 0.89$ vs. $M = 0.74$), whereas it increased among *s* carriers ($M = 0.81$ vs. $M = 0.88$), but these differential trends also proved not to be statistically significant ($t = 0.70$, $p = .48$ among *s* carriers, and $t = -0.16$, $p = .87$ among *ll* carriers). Moreover, peer problems were not significantly different across the two genotypic groups ($t = 0.64$, $p = .53$), with the same being

true of HI symptoms at age 4 ($t = -0.63$, $p = .53$) and at age 6 ($t = 0.08$, $p = .93$).

Correlation analyses conducted on the entire sample (see Table 1) revealed that more peer problems at age 4 was associated with more HI symptoms at ages 4 and 6. Boys scored higher on both peer problems and HI symptoms at both ages of measurement. Finally, a differentiated pattern of bivariate associations emerged across the two genotypic groups (see Table 1), such that among *s* carriers, more peer problems at age 4 was associated with more symptoms at both ages 4 and 6, whereas these relations were nonsignificant among *l* homozygotes.

Primary Analyses

Structural equation modeling was performed in Mplus 7.11 (Muthén & Muthén, 2010). In the structural equation model, we tested the effect of preschool peer problems at age 4 on the development of HI symptoms at age 6, taking into account the stability of such symptoms, as well as the moderational role of the 5-HTTLPR polymorphism. All structural analyses were performed using the maximum likelihood estimator. Missing values were treated according to the full information maximum likelihood procedure. Judgments of model fits were made according to recommendations of Hu and Bentler (1999; see also Marsh, Hau, & Wen, 2004). Regarded as reasonable indicators of good fit of a model are values of the comparative fit index (CFI) and the Tucker-Lewis index (TLI) close to 0.95, and values of the root mean squared error of approximation (RMSEA) and the standardized root mean squared residual (SRMR) less than 0.06 and 0.08, respectively.

Multigroup analyses were run to compare *s* carriers with *l* homozygotes in the Gene \times Peer Problems analyses. In this procedure, all paths in the model are initially freely estimated for both allelic groups, but selected paths are subsequently fixed to be identical in the comparative analyses. In the present study, the path from preschool peer problems to regulatory problems at age 6 was first freely estimated in the two groups but subsequently constrained to be equal. The Satorra-Bentler chi-square test (Satorra & Bentler, 2001) and the delta CFI (Cheung & Rensvold, 2002) were used to evaluate differences in the constrained versus the freely estimated model. A significant chi-square difference or CFI discrepancy (preferably close to or above .01) between the two models would indicate a moderational effect by 5-HTTLPR on the path from peer

problems at age 4 to change in HI symptoms from ages 4 to 6. Note that this analysis strategy tests the model on each group independently, so that every path for each group may vary in the analyses.

The measure of HI symptoms comprised an aggregated score rather than operationalized as a latent variable due to the high number of items (Little, Cunningham, Shahar, & Widaman, 2002). The structural model was then specified. First, in order to control for the baseline level of HI symptoms in the sample, HI symptoms at age 6 were autoregressed on HI symptoms at age 4. Second, peer problems were included as a predictor of HI symptoms at age 6. Third, preschool peer problems were allowed to correlate with symptoms at age 4 to control for shared variance of the two constructs. Fourth, gender was included as an exogenous predictor in the model. The full model was then tested on the total sample of genotyped children, showing excellent model fit: $\chi^2(7, N = 642) = 8.16, p = .32, TLI = 0.99, CFI = 0.99, RMSEA = 0.016, SRMR = 0.017$. The full model is illustrated in Figure 1.

In the total sample, more peer problems at age 4 predicted elevated levels of HI symptoms at age 6, controlling for symptoms at age 4, and thus increases in HI symptoms over time ($\beta = .17, p = .005$). Also, more HI symptoms at age 4 predicted more symptoms at age 6 ($\beta = .29, p < .001$). Being a boy predicted more T1 symptoms ($\beta = .07, p = .040$) and peer problems ($\beta = .11, p = .002$). Peer problems and symptoms at age 4 were not significantly correlated ($r = .09, p = .069$).

Multigroup analyses of *s* carriers ($N = 448$) and of *l* homozygotes ($N = 194$) fitted the data very well, $\chi^2(18, N = 642) = 16.76, p = .54, TLI = 1.00, CFI = 1.00, RMSEA = 0.000, SRMR = 0.033$.

Inspection of the paths in the multigroup model proved consistent with predictions: More preschool peer problems predicted increases in HI symptoms over time in the case of *s* carriers ($\beta = .21, p = .002$, see Figure 1) but not among *l* carriers ($\beta = -.02, p = .76$, see Table 2). This moderation effect by the 5-HTTLPR polymorphism was highly significant, $\Delta\chi^2(1) = 7.67, p = .005, \Delta CFI = 0.018$ (see Figure 2). Subsequent analyses comparing the effect of peer

Table 2
Standardized Regression Effects and Correlations and *p* Values From Structural Equation Modeling Analyses in the Norwegian Sample

Path/correlation	Total sample		<i>s</i> Carriers ($N = 448$)		<i>l</i> Carriers ($N = 194$)	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
“A” (Peer problems → HI symptoms age 6)	.17	.005	.21	.002	-.02	.754
“B” (HI symptoms age 4 → HI symptoms age 6)	.29	< .001	.26	< .001	.36	< .001
“C” (Gender → HI symptoms age 4)	.07	.040	.05	.222	.11	.067
“D” (Gender → Peer problems)	.11	.002	.14	.001	.06	.415
“E” (Peer problems ↔ HI symptoms)	.09	.069	.10	.121	.12	.086

Note. Capital letters corresponds to paths in Figure 1 (total sample and *s* carriers and *l* carriers separated. Moderation indicated in bold). HI = hyperactivity–impulsivity.

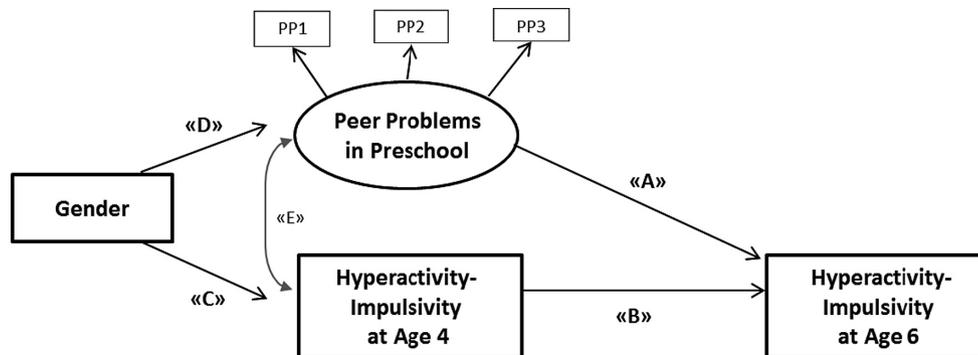


Figure 1. Structural equation model tested on the total samples, *s* carriers, and *l* carriers. Paths and covariates are indicated by capital letters corresponding to estimates in Tables 2 and 4.

Note. Range of factor loadings of the latent construct of “Peer problems” are presented in the text, as well as model fit indices. Hyperactivity–impulsivity at 54 months and in Grade 1 were measured as latent constructs in the American sample (see Results, Study 2).

problems between *ss* carriers and *sl* carriers yielded no significant group difference, $\Delta\chi^2(1) = 0.32$, $p = .57$, supporting the original aggregation of the two groups.

Brief Discussion

Study 1 showed—using data from a two-wave longitudinal study of Norwegian children—that more peer problems in preschool, as reported by teachers at age 4, predicted more HI symptoms at age 6, as measured through a parental reported diagnostic interview (PAPA; Egger et al., 2006). Most notably, however, multigroup analyses revealed that this adverse effect of early peer

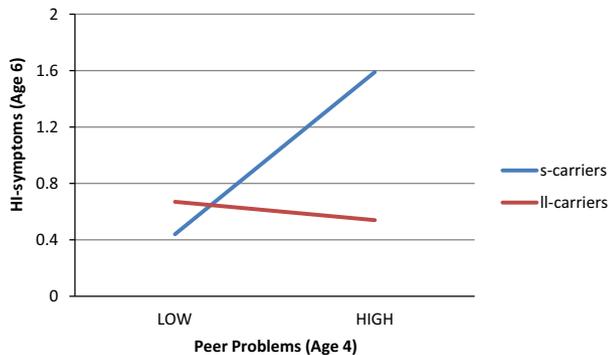


Figure 2. Interaction plot of the $G \times E$ effect in the Norwegian sample: *s* carriers who experienced a high degree of peer problems at age 4 were reported to have more HI symptoms at age 6 compared to *l* homozygotes (controlled for gender and HI symptoms at age 4; low = 3, high = 6).

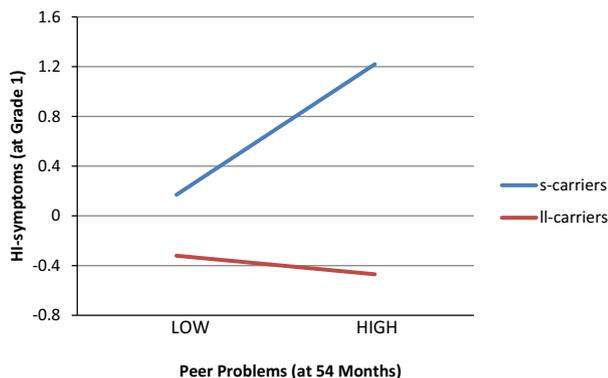


Figure 3. Interaction plot of the $G \times E$ effect in the American sample: *s* carriers who experienced a high degree of peer problems at 54 months were reported to have more HI symptoms at Grade 1 compared to *l* homozygotes.

Note. Computed on sum scores, controlled for gender and HI symptoms at 54 months; low = 0, high = 5.

problems in the development of HI symptoms was restricted to *s* carriers of the *5-HTTLPR* polymorphism. In other words, cortical serotonergic functioning determined by the 5-HT gene moderated the effect of peer problems on HI symptoms in our sample of prepubertal children.

Study 2

Participants

The NICHD SECCYD recruited 1,364 families through hospital visits shortly after the birth of a child in 1991 at 10 U.S. locations (for detailed description of recruitment procedures and sample characteristics, see NICHD Early Child Care Research Network, 2005). During selected 24-hr intervals, all women giving birth ($N = 8,986$) were screened for eligibility. From that group, 1,364 families completed a home interview when the infant was 1-month-old and became the study participants. In terms of demographic characteristics, 26% of the mothers had no more than a high-school education at the time of enrollment, 21% had incomes no greater than 200% of the poverty level at sixth grade, and 22% were minority (i.e., not non-Hispanic European American). All aspects of the larger study met with ethical approval by all institutions involved in the data collections.

The analysis sample for Study 2 was drawn from the 8 (of 10) data collection sites that secured ethical approval for DNA collection and included only the Caucasian children on whom DNA was obtained (following parental approval) and for whom the *5-HTTLPR* genotype was successfully assayed ($N = 567$). Furthermore, children whose parents reported 0 hr of nonparental care per week were excluded, given the absence of information on peer experiences in child care, resulting in a final analysis sample of 482 children (boys = 236). Although measurements of peer problems and HI symptoms were made in Study 1 at ages 4 and 6, related measurements in Study 2 were obtained at 54 months ($M = 4.82$ years, $SD = 0.18$) and in first grade ($M = 6.84$ years, $SD = 0.32$).

Measures

Peer Problems

Study 1 constructed a preschool-peer problem measure from the TRF (Achenbach & Rescorla, 2000); for Study 2, this measurement was based on

the 54-month caregiver report, relying on the exact same three items from the Caregiver–Teacher Report Form (C-TRF), that is, “not liked by other children,” “doesn’t get along with others,” “gets teased by other children”. Caregivers rated each item for each child on a 3-point Likert scale ranging from 0 (*not true*) through 1 (*somewhat or sometimes true*) to 2 (*very true or often true*). Cronbach’s alpha for this composite was .69. Invariance of the measurement across the groups (*s* vs. *ll* carriers) yielded a nonsignificant result, $\Delta\chi^2(1) = 0.28, p = .60$.

HI Problems

Study 1 relied on a semistructured parental interview (i.e., PAPA) based on the *DSM–IV* (American Psychiatric Association), but this measurement was not available in the NICHD SECCYD. Thus, we constructed a three-item HI problem score based on the *DSM*-oriented Attention Deficit/Hyperactivity Problem Scale (Achenbach, Dumenci, & Rescorla, 2003) using the mother-reported Child Behavior Checklist at 54 months and in Grade 1. Items that most similar to the *DSM–IV* scoring of symptoms were, “can’t concentrate attention for long time,” “can’t sit still, restless or hyperactive,” and “impulsivity or act without thinking.” Each item was rated on a 3-point scale ranging from 0 (*not true*) through 1 (*somewhat or sometimes true*) to 2 (*very true or often true*). A fourth item—“talks too much”—was also considered, but exploratory and confirmatory factor analyses showed that this fitted poorly with the other items (factor loadings .51 and .52). Cronbach’s alpha was .67 and .71, respectively, for the 54-month and Grade 1 HI problems composite. In contrast to the statistical analyses in Study 1, the modest number of items made it possible to treat this measurement as a latent construct.

5-HTTLPR

DNA extraction and genotyping was conducted at the Genome Core Facility in the Huck Institute for Life Sciences at Penn State University. The assay was performed in 1X Taq Gold Buffer, 1.8 mM final concentration of $MgCl_2$, 10% DMSO, 0.2 mM dNTPs, 0.1 mM deazo GTP, 0.6 μ M primers, 40 ng of DNA, and 1 U of Taq Gold (Applied Biosystems, Foster City, CA) in a volume of 15 μ l. The primer sequences were forward, 5'-VIC-GGCGTTGCCGC TCTGAATGC-3' and reverse, 5'-GAGGGACTGAG CTGGACAACCAC-3'. One microliter was removed and placed in a 96-well plate and 10 μ l of formamide containing LIZ-500 standard (Applied

Biosystems, Foster City, CA). The plate was run using a Fragment Analysis protocol in the 3730XL DNA Analyzer (Applied Biosystems, Foster City, CA). Fragments were analyzed using Genemapper software (Applied Biosystems, Foster City, CA) with PCR products of 484 or 528 bp. The 5-HTTLPR genotype frequencies were consistent with the Hardy–Weinberg equilibrium ($\chi^2 = 0.20, p = .66$). Hundred and four participants (21.6%) were identified as *ss* homozygotes, 245 (50.8%) children were identified as heterozygous *s/l*, and 133 (27.6%) children as *l* homozygotes. In the light of Study 1, we aggregated *ss* and *sl* individuals into an *s*-carrier group of 349 children.

Results

Preliminary Analyses

The total sample scored significantly lower for the HI problems at Grade 1 than at 54 months (1.28 vs. 1.49; $t = 3.45, p = .001$). The mean level of HI problems significantly decreased from 54 months to Grade 1 in both *s* carriers (1.42 vs. 1.24; $t = 2.40, p = .02$) and *l* homozygotes (1.70 vs. 1.40; $t = 2.74, p = .007$). Fifty-four-month HI scores were marginally different across the two genotypic groups ($t = 1.85, p = .07$), with the difference proving insignificant at the later age ($t = 1.19, p = .23$). Correlation analyses revealed that more peer problems at 54 months was associated with greater HI problems at both 54 months and Grade 1. Boys scored higher on peer and HI problems at both measurement occasions (see Table 3).

Primary Analyses

This study tested the exact same effects as Study 1, that is, the impact of 54-month peer problems on the development of HI problems after accounting for gender, the stability of the peer problems, and the moderating effect of the 5-HTTLPR genotype. Structural equation models were performed with the maximum likelihood estimator using Mplus 7.3 (Muthén & Muthén, 2012). Missing values were treated by the default full information maximum likelihood method. All criteria of model fit were consistent with Study 1.

After fitting models to the entire group, we once again conducted multigroup analyses to examine the 5-HTTLPR \times Peer Problems interaction. Indeed, the same SEM specified in Study 1 was tested in the NICHD sample, except that (a) we treated HI problems at both 54 months and Grade 1 as latent

Table 3
Descriptive and Zero-Order Correlation for Variables Included in the Analyses, Total Sample, and *s* Carriers and *l* Carriers Separated in the American Sample

	Total Sample				<i>s</i> Carriers (N = 348)				<i>l</i> Carriers (N = 133)									
	M	SD	1	2	3	4	M	SD	1	2	3	4	M	SD	1	2	3	4
1. Peer problems at 54 months	0.15	0.34	1				0.02	0.33	1				0.04	0.38	1			
2. Hyperactivity-Impulsivity, 54 months	0.16	0.35	0.34**	1			0.08	0.34	0.35**	1			0.15	0.38	0.33**	1		
3. Hyperactivity-Impulsivity, Grade 1	0.13	0.43	0.29**	0.64**	1		0.07	0.43	0.35**	0.61**	1		0.12	0.43	0.14	0.69**	1	
4. Gender ¹	1.49	0.50	0.15**	0.15**	0.10**	1	1.48	0.50	0.20**	0.16*	0.12**	1	1.50	0.50	0.04	0.13	0.09	1

Note. Peer problem at 54 months, hyperactivity-impulsivity at 54 months, and hyperactivity-impulsivity at Grade 1 are all latent variables. ¹Girl = 1, Boy = 2. * $p < .05$, ** $p < .01$.

Table 4
Standardized Regression Effects and Correlations and *p* Values From Structural Equation Modeling Analyses in the American Sample

Path/correlation	Total sample		<i>s</i> Carriers (N = 348)		<i>l</i> Carriers (N = 133)	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
"A" (Peer problems → HI symptoms age 6)	.08	.23	.15	.05	-.10	.42
"B" (HI symptoms age 4 → HI symptoms age 6)	.61	< .001	.56	< .001	.72	< .001
"C" (Gender → HI symptoms age 4)	.15	.005	.16	.01	.13	.18
"D" (Gender → Peer problems)	.15	.008	.20	.003	.04	.72
"E" (Peer problems ↔ HI symptoms)	.33	< .001	.33	.00	.33	.01

Note. Capital letters corresponds to paths in Figure 1 (total sample and *s* carriers and *l* carriers separated. Moderation indicated in bold). HI = hyperactivity-impulsivity.

variables; and, in order to achieve acceptable model fit (see Kline, 2010), (b) we allowed the (residuals for the) same HI items to correlate at 54 months and Grade 1 (e.g., "can't concentrate attention for long time" measured at 54 months and Grade 1 were allowed to be correlated). The full model achieved excellent model fit: $\chi^2(28, N = 481) = 39.12, p = .08, CFI = 0.989, TLI = 0.982, RMSEA = 0.029, SRMR = 0.035$.

In the Study 2, sample results proved similar to those found in Study 1 in that more HI problems at 54 months predicted problems at Grade 1 ($\beta = .61, p < .001$). Being a boy forecasted more peer problems ($\beta = .15, p = .008$) and more HI problems at 54 months ($\beta = .15, p = .005$). In contrast to Study 1, however, 54-month peer problems did not significantly predict increased HI problems in Grade 1, though the association was in the same, positive direction ($\beta = .08, p = .23$). Results also indicated that peer problems and HI symptoms were positively related at 54 months ($\beta = .33, p < .001$).

Multiple group analyses again revealed that the model dividing the entire sample into two allelic subgroups of *s* carriers ($N = 348$), and *l* homozygotes ($N = 133$) fit the data well: $\chi^2(68, N = 481) = 72.47, p = .33, CFI = 0.995, TLI = 0.994, RMSEA = 0.017, SRMR = 0.043$. Estimates of individual paths proved

consistent with predictions: more 54-month peer problems forecast greater increase in HI symptoms only in the case of *s* carriers ($\beta = .15, p = .05$), not *l* homozygotes ($\beta = -.10, p = .42$). The group difference in this effect of peer problems on HI symptoms proved marginally significant, $\Delta\chi^2(1) = 3.29, p = .069, \Delta CFI = 0.020$. Subsequent analyses comparing effects of peer problem on increased HI scores across *ss* and *sl* carriers failed to reach significance, $\Delta\chi^2(1) = 0.07, p = .79$, again supporting the decision to combine *ss* and *sl* carriers in the moderation analyses.

Brief Discussion

Drawing on data from the NICHD SECCYD, Study 2 generally replicated results of Study 1, using somewhat different measurements, collected at somewhat different ages, despite the fact that one study focused on Norwegian and the other on American children. Even though Study 2 did not indicate that more peer problems at 54 months significantly predicted increased HI problems in Grade 1 for the total sample, multiple group analyses indicated genetic moderation of this anticipated effect in a manner consistent with Study 1: The effect of early peer problem forecast increased HI problems at Grade 1 but only in the case of *s* carriers of the 5-HTTLPR polymorphism.

General Discussion

In two studies, benefiting from two large prospective community samples of preschool children from Norway and the United States, the SERT interacted with preschool peer problems, to predict change in HI symptoms. More specifically, carriers of the 5-HTTLPR short allele were more likely than *l* homozygotes to exhibit an increase in such symptoms after experiencing preschool peer problems.

It needs to be explicitly acknowledged, however, that although the multigroup SEM analysis revealed statistically significant genetic moderation in the Norwegian sample, the significance of the same $G \times E$ interaction in the smaller American sample achieved a marginal level of significance. Nevertheless, the fact that the predictive relations between earlier preschool problems and later HI symptoms proved significant only for *s* carriers and not for *l* homozygotes in both studies suggests that the reliability of the $G \times E$ effect under consideration may be dependent on the magnitude of the sample. It is also possible that the moderational effect is more

detectable in a representative community sample, like in Study 1, compared to the convenience samples from eight different sites in Study 2.

The results just summarized lend support for Carver et al.'s (2008, 2009) two-mode model of self-regulation. But notably, although the theory also describe that serotonin is involved in overly inhibited behaviors (e.g., depression), our findings are limited to the part of the theory that stipulates that serotonin is involved in impulsive behavior. As mentioned earlier, previous studies involving the 5-HTTLPR polymorphism have predominantly focused on internalizing problems (Canli & Lesch, 2007; Karg et al., 2011). The present findings, then, drawing on two large samples of preschool children, followed longitudinally, extend this work in finding that 5-HTTLPR moderates the effect of one aspect of contextual adversity, namely, early peer problems on externalizing-related problems, that is, HI. Moreover, our findings are consistent with the studies of Meer et al. (2014) and Retz et al. (2008). They found that 5-HTTLPR moderates the effects of childhood stress on adolescent and adult ADHD symptoms. Our results partly confirm these findings and indicate that research on individual differences in hyperactivity and impulsivity could benefit from including predisposed serotonergic functioning as one possible putative factor. This may possibly lead to a better understanding of the development of pathological cases of regulatory problems (e.g., ADHD) and at the same time illuminate the underlying mechanisms of emotional disorders.

The processes by which the serotonergic system operates are complex and not fully understood (e.g., Meaney, 2010). Much more is involved than the baseline level of serotonin, including sensitivity and density of several kinds of serotonin receptors, efficiency of reuptake of serotonin from the synaptic cleft, and recent history of the cell's firing, as each of these elements can influence the overall "functioning" of the serotonergic system (Carver et al., 2009). Despite current limitations with regard to the charting of these functions, it is a rather established fact that the *s* allele represents a less efficient variant of the serotonergic system compared to the *ll* variant (Friedel & Heinz, 2010; Heils et al., 1996; Oades, 2010). Nonetheless, the task of bridging the gap between molecular processes and psychological outcomes among developing children is just in its early phase. The 5-HT gene is perhaps the most investigated of the candidate genes (Franke et al., 2006), and the body of evidence supporting its role in emotional and cognitive

development is compelling (Canli & Lesch, 2007; Karg et al., 2011; Van Ijzendoorn et al., 2012). Nevertheless, many genes are surely involved in the development of regulatory abilities throughout childhood, as genes themselves may interact with each other in the process, and their basic expressions might be altered by environmental factors (Feng, Jacobsen, & Reik, 2010; Geary & Bjorklund, 2000; Ouellet-Morin et al., 2013). Indeed, it may even be the case that *5-HTTLPR* plays a moderational role in our statistical findings because of its association with other genes rather than as a result of its own direct or indirect influence on the phenomena under investigation herein (see Oades, 2008).

The present work has some limitations. Foremost, we constructed an ad hoc scale in order to measure peer problems and thus must acknowledge that a preexisting and dedicated scale designed to tap into such problems in preschool would have been preferable. To be noted, however, is that a previous study by Stenseng et al. (2014) using the Norwegian sample showed that the measurement overlaps substantially with a scale designed to measure victimization, which certainly is a severe peer problem. Nevertheless, future research should investigate the extent to which the present results derive from specific types of peer problems, such as social neglect and/or physical abuse, or from poor social relations in general.

Another possible limitation pertains to the measurement of HI symptoms. Because the measurement of symptoms in Study 1 was borrowed from a diagnostic interview created to measure symptoms of ADHD, findings should not unreservedly be generalized to the whole spectrum of regulatory abilities. Still, the majority of children in the sample were reported to have one or more symptoms of either hyperactivity or impulsivity, indicating that the measure displayed sensitivity to not only severe problems at the clinical end of the spectrum but also in the normal range (Rueda, Posner, & Rothbart, 2005).

Irrespective of these concerns, the fact that results based on the interview measure in Study 1 were more or less confirmed in Study 2, which relied on a very different measure of HI symptoms clearly indicates that the results of Study 1 (or 2) are not measure specific. Finally, and in light of gene-environment correlation (e.g., Jaffee & Price, 2007), it is plausible to suggest that children with genes for ADHD are more likely to seek out children with similar traits, which may in turn affect the behavior of the child. It is also possible that

genes for ADHD make some children more likely to experience rejection from peers. On the other hand, a recent study by Stenseng et al., (2016) is partly relevant in this context; it showed that peer rejection was more likely to lead to ADHD symptoms than vice versa through ages 4, 6, and 8 upon testing reciprocal effects. This suggests that genes for ADHD do not make children more prone to being rejected but rather suggest that genes associated with ADHD make the child susceptible to developing more symptoms from poor peer relations.

To conclude, results from two studies indicate that children's genetic makeup is involved in whether and how peer problems affect, at least within the confines of observational research, the development of HI symptoms in early childhood. In addition to other research on the *5-HTTLPR* polymorphism—which primarily indicates that *s* carriers are more vulnerable to the adverse effect of stress on emotional problems compared to *ll* carriers—we found that *s* carriers also are more vulnerable to the detrimental effect of peer problems on ADHD-related behavior. As such, the present study provides additional evidence that serotonin modifies children's reactions to environmental cues, which in our study involved a central part of children's everyday life, their peer relations.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix S1. Dopamine gene analyses