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The Neurobiology of Peer Victimization: Longitudinal Links to Health, Genetic Risk, and Epigenetic Mechanisms

Tracy Vaillancourt, Carleigh Sanderson, Paul Arnold,
Patricia McDougall

Recent research on peer victimization has documented the negative correlates and consequences of bullying, especially for those who are victimized. For example, relative to nonvictimized youth, those who are bullied by peers report lower self-esteem and self-worth and report that they are lonelier and socially withdrawn as well as more anxious and depressed. Bullied youth also report more headaches, stomachaches, and other somatic complaints, which may reflect stress-related illness (see reviews by Beeson & Vaillancourt, 2016; McDougall & Vaillancourt, 2015).

Prospective studies on peer victimization suggest that the aforementioned inventory of ills is the result of being abused and not a precipitator of poor treatment by peers. This finding is consistent with a robust literature that demonstrates a causal relation between exposure to stressful life events and the onset of health problems such as depression (Kendler, Karkowski, & Prescott, 1999). Longitudinal research also suggests that being bullied does not lead to the same pathological or nonpathological outcome in every individual, a concept termed *multifinality* (Cicchetti & Rogosch, 1996; see McDougall & Vaillancourt, 2015). The shared or common experience of being victimized does not mean individuals end at a single or common outcome; rather, there is marked variability (Cicchetti & Rogosch, 1996). Accordingly, understanding the impact of peer victimization in childhood requires

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an examination of other conditions and attributes that exist within a broader “system” for each child. Of recent interest in the study of peer victimization is the role of an individual’s genetic susceptibility. It has been proposed that this genetic susceptibility can make certain individuals more sensitive to negative environmental influences. However, if the environment is supportive and enriched and lacks significant adversity, it may also be associated with better outcomes (Belsky & Pluess, 2009; Boyce & Ellis, 2005). This phenomenon is known as *differential susceptibility*.

MODERATORS

Cross-sectional and longitudinal studies clearly indicate that for many bullied youth, their negative experience with peers causes them harm. This makes sense intuitively, given that the need to belong is a fundamental human motivator (Baumeister & Leary, 1995). However, what is not clear from research on bullying and health is why some youth become ill as a consequence of poor treatment by peers while others do not. To date, most research has focused on environmental characteristics (such as family and school) when trying to explain heterogeneity in outcomes. For example, studies have shown that parental involvement and positive family functioning moderate the relation between being bullied and poor health outcomes—youth with better home environments fare better when bullied than youth with poorer home environments (for example, Flouri & Buchanan, 2002). Classroom context also matters. Huitsing, Veenstra, Sainio, and Salmivalli (2012) showed that victimization can become a focal element of the classroom dynamic when only a handful of students are targeted and perceived as “social misfits.” In these instances, the impact of victimization on mental health grows more intense. The moderating role of gender also matters. In one study, peer victimization at age eight was associated with suicide attempts before age 25 for girls and women but not for boys and men (controlling for conduct and depressive symptoms; Klomek et al., 2009).

Far fewer studies have examined the moderating role of biology when examining the link between peer victimization and health, despite compelling evidence from other literatures demonstrating such an effect. These studies suggest that (a) genotypic markers of vulnerability do seem to moderate the relation between psychosocial stressors and poor health (that is, candidate gene by environment [cGxE] interactions), and (b) early adversity is linked to poorer health outcomes as a function of how genes are expressed (that is, epigenetic alterations).

cGxE Interactions and Differential Susceptibility

In 2003, Caspi and colleagues published a seminal study in which they examined the moderating role of a functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) in the relation between exposure to child maltreatment and depression outcomes at age 26. Results indicated that maltreated individuals were far more likely to be depressed in adulthood if they also had two copies of the short allele (SS) in the 5-HTTLPR. Results also indicated that the long allele (L) was protective against depression for individuals who had been abused in childhood. Although Caspi et al.’s (2003) study was not the first to examine cGxE interactions, it did receive unprecedented attention, owing in part to the strong moderating effect reported and the impact of the journal in which it appeared.

Since its publication, Caspi and colleagues' (2003) article has been cited over 7,000 times and hundreds of similar studies have been published. Most of these studies have focused on candidate genes that have neurobiological evidence supporting their examination. In the case of 5-HTTLPR, serotonin has been implicated in the development of depression, and the short allele in particular has been shown to have lower transcriptional efficiency of the promoter than the long allele (Caspi et al., 2003; Lesch et al., 1996). Other popular candidate genes include catechol-O-methyltransferase (*COMT*), dopamine transporter gene (*DAT1*), dopamine receptor D4 (*DRD4*), and monoamine oxidase A (*MAOA*), which have been linked to mental health problems in relation to being exposed to an environmental stressor. We believe that these candidate genes should also be examined in relation to the often-ignored environmental stressor of being bullied. However, before discussing the merits of their inclusion, it is important to highlight the ongoing controversy surrounding cGxE studies.

Criticisms of cGxE Research

Duncan and colleagues have been especially critical of cGxE studies in psychiatric genetics (Duncan, 2013; Duncan & Keller, 2011; Duncan, Pollastri, & Smoller, 2014; see also Dick et al., 2015). One of their main criticisms relates to the fact that cGxE studies are often not replicated. According to Duncan (2013), 96 percent of the early cGxE studies reported positive interactions and yet only 27 percent of replications were positive, suggesting a notable publication bias. Duncan and colleagues have also suggested that the rate of false discoveries is very high in cGxE studies, an assumption made in part on the basis of two negative meta-analytic findings of 14 studies (Munafò, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). A recent meta-analysis of 54 studies demonstrating strong evidence that 5-HTTLPR moderates the relation between stress and depression (Karg, Burmeister, Shedden, & Sen, 2011) was, however, dismissed by these researchers for using lax inclusion criteria.

Detractors of Duncan and colleagues (Duncan, 2013; Duncan & Keller, 2011; Duncan et al., 2014) suggested they failed to consider important reasons for lack of replication, which include the fact that many of the nonreplication studies used notably weaker methodologies, such as the inclusion of brief self-report measures of stress, retrospective accounts of exposure to life stressors, a poorly defined stressor, and the contemporaneous testing of stress and depression (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). Moreover, critics maintain that differential susceptibility, which also accounts for the role of positive environmental influences when examining the sequelae of illness, is more likely than the diathesis-stress interpretation offered by Duncan and colleagues (Pluess & Belsky, 2012).

It is essential to highlight that even the most ardent critics of cGxE research have stated that "unequivocally, more empirical research is needed to definitively determine the promise of cGxE research" and that replication attempts "should be a high priority" (Duncan et al., 2014, p. 251). However, critics have also cautioned that cGxE research needs to be conducted with particular attention paid to statistical issues such as low power, the correction of multiple testing, the use of cross-product terms, properly controlled confounders, and the estimation of genotype and environment correlations (see Dick et al., 2015). Moreover, consistent with Moffitt and Caspi's (2014) suggestion, the use of longitudinal studies is also needed so that the temporal sequence between cause and effect can be disentangled. A longitudinal approach also allows researchers to examine environmental risk factors as time limited or enduring, an approach that tends to be missing in cGxE research.

It is unquestionable that the development of mental health problems is far from straightforward. For example, although the prevailing hypothesis is that individuals with the risk allele of 5-HTTLPR are more likely to develop depression if they experience a major life stressor, as Moffitt and Caspi (2014) asserted, the minimal criterion to validly test this hypothesis is “a set of measures that can unambiguously establish that the stress came before the depression” (p. e1). Studies that use retrospective accounts of depression or other psychiatric disorders cannot meet this standard, nor can cross-sectional studies. Moreover, as Dick et al. (2015) pointed out, the choice of environment in cGxE research is as important as the choice of gene because “if the wrong form of environment is assessed or if the right form of the environment is assessed poorly” (p. 44), valid cGxE interactions will not be detected. Studies need to also be comprehensive in nature, because according to the differential susceptibility hypothesis, individuals who may be most adversely affected by poor environments (that is, being bullied) may also be the ones who procure the most benefit from supportive environments (Belsky & Pluess, 2009; Boyce & Ellis, 2005).

5-HTTLPR, MAOA, COMT, DAT, and DRD4

Several studies have shown that variants within the 5-HTTLPR moderate the relation between exposure to negative environmental influences such as maltreatment in childhood and future health outcomes such as depression (Caspi et al., 2003) and anxiety (Stein, Schork, & Gelernter, 2008). This moderating effect has also been shown to be present for the stressor of peer victimization. Sugden et al. (2010) found that children who carried the SS genotype and were bullied were at greater risk for developing emotional problems than bullied children with the SL or LL genotype. This effect was present even when controlling for pre-victimization emotional problems and other risk factors. Three other published studies have also shown that 5-HTTLPR moderates the relation between health problems and peer victimization (Banny, Cicchetti, Rogosch, Oshri, & Crick, 2013; Benjet, Thompson, & Gotlib, 2010; Iyer, Dougall, & Jensen-Campbell, 2013). Given that these studies were all cross-sectional and included fewer than 157 children, replication is still required. The only well-powered study was Sugden and colleagues’ (2010), yet this study is not representative because British twins were recruited from high-risk environments (that is, poor families, young mothers), which conflates the stress of being bullied with other environmental risks (see Lereya, Copeland, Costello, & Wolke, 2015).

The MAOA gene encodes the enzyme that metabolizes neurotransmitters like norepinephrine, serotonin, and dopamine and thus genetic variants that alter enzyme metabolism may render these neurotransmitters inactive or cause dysregulation in neurotransmission. There are several studies examining the moderating role of the low- versus high-activity alleles of a variant in the promoter region of MAOA on the development of mental health outcomes in relation to environmental stressors like child maltreatment. These studies have typically shown that children with low MAOA activity who have been exposed to a negative environmental influence are more likely to have externalizing problems, such as conduct disorder (Caspi et al., 2002; Foley et al., 2004) and attention deficit/hyperactivity disorder (ADHD; Kim-Cohen et al., 2006), than children with high MAOA activity. We know of only one published study linking MAOA to peer victimization. Whelan, Kretschmer, and Barker (2014) found that harsh parenting was associated with increased peer victimization (and perpetration) via oppositional behavior but that the effect was not moderated by MAOA genotype. More research is needed, especially when considering that peer victimization is often associated with the development of conduct problems, including aggression.

For example, in a recent article, bullied children became bullies, but, it is important to note, not all bullied children went on to bully their peers (Haltigan & Vaillancourt, 2014). Understanding this type of heterogeneity is essential for prevention and intervention work.

COMT affects dopamine and other catecholamines and has been used to index differential susceptibility (Belsky & Beaver, 2011; Voelker, Sheese, Rothbart, & Posner, 2009). Specifically, the *COMT* gene encodes the *COMT* enzyme, which degrades catecholamines such as dopamine, epinephrine, and norepinephrine. A single nucleotide polymorphism that results in a valine (Val) to methionine (Met) amino acid substitution to the protein (*COMT* Val¹⁵⁸Met) is the most commonly studied variant in this gene (Sulik et al., 2015). The Met allele results in lower *COMT* efficiency than the Val allele (Lachman et al., 1996; Lotta et al., 1995). Of relevance to the study of peer victimization is research demonstrating a relation between *COMT* Val¹⁵⁸Met and internalizing problems (McGrath et al., 2004; Olsson et al., 2005), including a recent meta-analysis demonstrating a link with anxiety traits (Lee & Prescott, 2014). Studies have also shown that Val¹⁵⁸Met may index plasticity. For example, Sulik et al. (2015) showed that although parenting was positively associated with inhibitory control for Met–Met boys and for Val–Val or Val–Met girls, it was negatively associated with internalizing symptoms for Met–Met boys. In another study, Laucht et al. (2012) reported that teenagers homozygous for the Met allele engaged in higher drinking activity at age 19 years if their parents were less involved; however, for teenagers with this same polymorphism, having involved parents was associated with reduced drinking activity. No such relation was found in individuals carrying the Val allele. *COMT*'s association with internalizing symptoms and increased problematic behavior makes it a worthy gene to consider when examining the neurobiological underpinnings of peer victimization.

The dopamine transporter gene (*DAT1*, *SLC6A3*) has been implicated in disorders such as ADHD (Cornish et al., 2005) and conduct problems (Lahey et al., 2011). A variable number tandem repeat (VNTR) polymorphism in the 3' untranslated region of *DAT1* has been well studied. The allele frequencies of this *DAT1* polymorphism vary within the population and are related to different mental health outcomes. For example, the presence of two *DAT1* VNTR 10-repeat alleles has been shown to be associated with symptoms of ADHD (Cornish et al., 2005). The moderating role of *DAT1* in the relation between negative environmental influences and mental health outcomes has also been examined. Lahey et al. (2011) reported an inverse relation between levels of positive and negative parenting at four to six years and later conduct disorder symptoms, a result that was found mostly among children with two copies of the nine-repeat allele of the VNTR (Sonuga-Barke et al., 2009). Given the established relation between peer victimization and conduct problems (Haltigan & Vaillancourt, 2014), it seems worthwhile to examine the role of *DAT1* variation in the emergence of these problems.

The dopamine receptor D4 regulates dopamine receptor activity in the brain. The *DRD4* gene contains a 48 base-pair VNTR polymorphism in Exon III, which can take the form of a long (7-repeat) or short (4-repeat) allele. The short allele is the more frequent variant (64 percent versus 20 percent for long allele; Oak, Oldenhof, & Van Tol, 2000). The *DRD4* 7-repeat allele, which has been shown to cause lower intracellular response to dopamine, is associated with disorders such as depression (López León et al., 2005), ADHD (Gizer, Ficks, & Waldman, 2009), and substance abuse (Ray et al., 2009). Externalizing behavior has also been consistently linked to the *DRD4* 7-repeat allele (Boutwell & Beaver, 2008), and *DRD4* has been shown to play a moderating role in the relation between negative environmental influences and mental health outcomes. For example, a sixfold increase in externalizing behavior problems in children exposed to insensitive parenting and carrying the *DRD4*

7-repeat allele was reported (Bakermans-Kranenburg & van IJzendoorn, 2006). Of relevance to the study of peer victimization is a study by Kretschmer, Dijkstra, Ormel, Verhulst, and Veenstra (2013), who examined the moderating role of *DRD4* in the relation between peer victimization and later delinquency in a large Dutch cohort study of youth assessed four times across the ages of 11 to 19. Results indicated that contrary to expectations, carriers of the 4-repeat homozygous variant were more susceptible to the effects of peer victimization on delinquency later in adolescence, even though the 7-repeat allele was expected to be the “risk” allele on the basis of prior studies.

Finally, a study by VanZomeren-Dohm, Pitula, Koss, Thomas, and Gunnar (2015) examined the moderating role of *FKBP5* rs1360780 in the relation between peer victimization and symptoms of depression in post-institutionalized children from 25 countries. *FKBP* is a gene that governs stress response, and the rs1360780 single nucleotide polymorphism is thought to be a functional variant of this gene (Zanner & Binder, 2014, as cited in VanZomeren-Dohm et al., 2015). Results indicated that girls who had the minor allele (TT or CT) were more depressed at higher levels of peer victimization but less depressed at lower levels of peer victimization, consistent with differential susceptibility. For boys, the CC genotype was associated with more symptoms of depression than for girls with the same CC genotype when bullied.

Taken together, studies examining cGxE interactions suggest that poorer mental health outcomes are associated with certain biological risk markers in the context of being bullied. However, in the context of a better environment, these same risk alleles may be associated with better outcomes, consistent with recent work on differential susceptibility.

EPIGENETIC MECHANISMS

DNA methylation is an epigenetic mechanism that “maintains gene activity or changes gene expression by activating or silencing the gene, resulting in the development of phenotypes that are time-dependent and are not determined by the DNA sequence at that locus” (Vaillancourt, Hymel, & McDougall, 2013, pp. 243–244). Epigenetic alterations are believed to function as a biological mechanism in which environmental signals are translated into “organismal molecular events” (Bick et al., 2012, p. 1418). The study of epigenetics in psychiatry and psychology is fairly new, heralded by a seminal study by Meaney and colleagues on maternal care in rats (Weaver et al., 2004; see review by Meaney, 2010). Using an experimental design, newborn pups were randomized to high-quality or low-quality maternal care. Individual differences in stress reactivity of adult rats were found to be influenced by the quality of their early environment, which was associated with epigenetic changes that conferred a risk or protective effect on the rats’ stress reactivity. Changes in DNA methylation resulted as a function of early adversity or nurturance, and this change had an effect on later stress reactivity. Following this landmark study, several studies have shown that exposure to adversity influences DNA methylation, which in turn influences a person’s health trajectory. For example, epigenetic alterations have been implicated in the emergence of neuropsychiatric disorders (Tsankova, Renthal, Kumar, & Nestler, 2007) and other health outcomes such as cancer (Austing et al., 2014) and diabetes (Diabetes Genetics Initiative of Broad Institute, 2007).

Of particular relevance to the study of peer victimization are studies demonstrating a pathway from early adversity (Heim & Binder 2012; Labonté et al., 2012; Shonkoff et al., 2012; Szyf & Bick, 2013), including peer victimization (Ouellet-Morin et al., 2011), to changes

in DNA methylation. For example, Essex et al. (2013) showed that exposure to maternal stress in infancy was associated with differential methylation in adolescence. Tyrka, Price, Marsit, Walters, and Carpenter (2012) found that inadequate early nurturing by caregivers, including maltreatment, was associated with increased methylation to the promoter of the type II glucocorticoid receptor gene. This change was linked to attenuated cortisol responses. This finding is intriguing insofar as several studies have also shown that bullied youth tend to have a blunted cortisol response (Kliewer, 2006; Knack, Jensen-Campbell, & Baum, 2011; Ouellet-Morin et al., 2011; Vaillancourt et al., 2008). We know of only one study that has examined epigenetic changes in relation to peer victimization. Ouellet-Morin et al. (2013) showed that increased DNA methylation of the serotonin transporter gene between ages five and 10 was found for bullied twins but not for nonbullied twins. This finding is also significant because children with higher serotonin DNA methylation had a blunted cortisol response to stress, which has been shown to causally change as a result of being bullied. Ouellet-Morin et al.'s (2013) study needs to be replicated with singletons because assisted reproductive technology, which increases the chances of having a multiple birth, has been linked to epigenetic errors (Niemitz & Feinberg, 2004).

It is clear that more research is needed to examine whether the experience of being bullied “gets under the skin” and is associated with epigenetic alterations, which in turn places youth at risk for poorer health outcomes. Although little is known about how bullying may result in epigenetic alterations that may be linked to the pathogenesis of common diseases, it nevertheless represents an important and logical area of inquiry, considering that the literature on other forms of childhood adversity points convincingly in this direction. A recent technical report published by the American Academy of Pediatrics (Shonkoff et al., 2012) states that “many adult diseases should be viewed as developmental disorders that begin early in life and that persistent health disparities associated with poverty, discrimination, or maltreatment could be reduced by the alleviation of toxic stress in childhood” (p. e232). We suspect that the intrinsic mechanism will be similar for bullied youth—we expect that genome-wide DNA methylation alterations will be induced by being bullied by peers and that these alterations will be associated with detrimental health outcomes.

Our interest in differential susceptibility makes us also question whether “recovery” from being bullied might reverse the influences of this life stress on molecular biological changes associated with detrimental outcomes. That is, can a better social environment positively influence epigenetic mechanisms and improve health? Prevalence estimates of peer victimization show a notable decline as students move into the college or university environment (Chapell et al., 2006). Schäfer et al. (2004) have speculated that the university context might serve as a “corrective experience” for young people with a history of peer victimization. The postsecondary milieu tends to be less hierarchical and more openly structured so that individuals have new opportunities for positive relationships. There is emerging evidence in the areas of physical exercise (Sanchis-Gomar et al., 2012) on epigenetic modulation suggesting that positive genetic adaptations through epigenetic mechanisms are possible.

KEY GAPS IN EVIDENCE

Our review identifies the following key gaps in evidence, which severely disadvantages us when it comes to making policy recommendations or making recommendations about bullying prevention and intervention (that is, the “alleviation of toxic stress in childhood”).

Specifically, we know little about (a) why some bullied youth develop significant mental and physical health problems as a consequence of poor peer treatment, while other youth seem to fare better (that is, the moderating role of biology in the bullying–health link is relatively unknown but worthy of more attention); (b) how the experience of being bullied may be related to epigenetic changes and how these changes are related to health outcomes; (c) how the timing, duration, and severity of peer victimization are associated with health outcomes, genetic risk, and epigenetic changes; and (d) the effects of context transitions on trajectories of peer victimization and health (and we know nothing about possible positive epigenetic changes related to transitions).

CONCLUSION

Understanding the neurobiology of peer victimization is pertinent because so many youth are negatively affected by bullying. Peer victimization causes harm to young people by significantly impairing opportunities to develop relationship capacity and by interfering with pathways to adaptive outcomes. Accordingly, we urge researchers to explore a full range of functioning that includes biological risk.

Concerns about bullying have clearly become part of public consciousness and underscore the notion that, as a society, we are no longer willing to stand by and tolerate the poor treatment of others. With this awareness, however, comes the need for accurate facts regarding the long-term impact of peer abuse. As such, it is essential to delve into the complex dynamics that perpetuate bullying in order to delineate paths to better well-being. Indeed, in the absence of a strong scientific knowledge base, we are left with nonsystematic (and occasionally damaging) approaches to intervention and prevention (for example, Merrell, Gueldner, Ross, & Isava, 2008; Ttofi & Farrington, 2011; Vreeman & Carroll, 2007).

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