Topical Review: The Emerging Field of Epigenetics: Informing Models of Pediatric Trauma and Physical Health

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Abstract

Objective Trauma experienced during childhood and adolescence has been linked to a number of chronic medical concerns. We highlight major findings from the pediatric trauma literature to provide a model for understanding this association. Methods Studies examining the effects of trauma were systematically reviewed and synthesized into a model proposing a central role for epigenetics in the ways that childhood experiences can affect health. Results Early hypothalamic pituitary adrenal (HPA) axis response may impact initial trauma experience, with downstream effects on posttrauma adjustment reflected in posttrauma neurobiology, psychological health, and physical health. Conclusions Prospective research with children and adolescents exposed to trauma is needed to better characterize the genetic and epigenetic influences on the course of HPA and immune processes as related to posttrauma psychological and physical health outcomes.

Key words: adjustment; genetics and genetic disorders; posttraumatic stress.

Converging evidence points to the effects of childhood abuse on poorer physical health (Dutton et al., 2006; Irish, Kobayashi, & Delahanty, 2010; Schnurr & Green, 2003; Zinzow et al., 2011) and increased medical service utilization (Golding, Stein, Siegel, Burnam, & Sorenson, 1988; Koss, Koss, & Woodruff, 1991). Some have argued that physical health should be considered alongside depression and posttraumatic stress disorder (PTSD) in the cluster of deleterious outcomes of trauma (Schnurr & Green, 2004). One potential explanation for the co-occurrence of psychological and physical health outcomes of trauma may be a common underlying neurobiology, including peri-traumatic recruitment of the body’s stress system (the hypothalamic pituitary adrenal axis [HPA axis], Figure 1) and, later, continued activation of components of the stress response. HPA axis activity is closely tied to immune function, with trauma- and PTSD-related immune and inflammatory processes associated with HPA axis dysregulation (Depino, 2010; Gill, 2009; Silverman, Heim, Nater, Marques, & Sternberg, 2010; Vidović, 2007). However, given that not all abused children develop deleterious psychological and physical concerns, what predicts (and maintains) HPA axis disruption posttrauma? How does trauma during childhood translate to chronic physical health concerns? This review addresses a gap in the field of pediatric psychology, integrating findings across a number of research paradigms including emerging evidence from the field of genetics and epigenetics to provide a theoretical perspective that may help explain the link between children’s trauma exposure and physical health problems. The present article is intended to provide an accessible and integrated framework for pediatric psychologists.
who encounter children and adolescents in the acute aftermath of trauma (i.e., injury, abuse, assault, etc), during potentially traumatic experiences (i.e., life-threatening illness, potentially traumatic medical procedures, etc), and in medical treatment settings where children may have a (known or undocumented) history of trauma.

**Developmental Traumatology Model and HPA Axis Functioning in Pediatric Trauma**

The HPA axis, shown in Figure 1, is implicated in both the acute stress response and in chronic adaptations to stress. Psychological stress induces the release of corticotropin-releasing hormone (CRH). CRH availability is partly regulated by CRH binding protein (CRHBP), which can decrease the CRH available for CRHR1 activation. CRH induces release of adrenocorticotropin (ACTH) and then the secretion of cortisol from the adrenal cortex. Cortisol binds to the glucocorticoid receptor (NR3C1) which plays important roles in the negative feedback loop of the HPA axis. Cortisol promotes expression of anti-inflammatory proteins while repressing the expression of pro-inflammatory ones (i.e., IL6, TNFa) and activates/reactivates viral antibodies (i.e., CMV, HSV-1, EBV).

**Figure 1.** HPA axis and Immune Outcomes. *Note.* In response to stress, the hypothalamus releases corticotropin-releasing hormone (CRH). CRH availability is partly regulated by CRH binding protein (CRHBP), which can decrease the CRH available for CRHR1 activation. CRH induces release of adrenocorticotropin (ACTH) and then the secretion of cortisol from the adrenal cortex. Cortisol binds to the glucocorticoid receptor (NR3C1) which plays important roles in the negative feedback loop of the HPA axis. Cortisol promotes expression of anti-inflammatory proteins while repressing the expression of pro-inflammatory ones (i.e., IL6, TNFa) and activates/reactivates viral antibodies (i.e., CMV, HSV-1, EBV).

**Box 1. Key Terms**

- **Hypothalamic pituitary adrenal (HPA) axis**—the body’s major stress response system. See Figure 1.
- **Genetics**—The science of heredity (e.g., transmission of traits from generation to generation) and genes (e.g., basic unit of inheritance, a region of Deoxyribonucleic Acid [DNA])
- **Genotype**—The specific combination of alleles (or genetic markers) at a given locus.
- **Epigenetics**—Scientific study of chemical modifications that regulate chromatin structure and/or DNA access, which may in turn alter transcription in the region. See Figure 2.
- **DNA Methylation (DNAm)**—A type of epigenetic modification involving the covalent coupling of methyl groups to cytosine (a nucleotide found in DNA). DNAm occurs primarily at sites in the genome where a cytosine is followed by a guanine nucleotide in DNA sequence—genomic regions enriched for these pairings are called “CpG” islands.
- **Cytokines**—Proteins involved in the immune response.
- **T cell**—A leukocyte (or white blood cell) critical to immune system’s ability to adaptively identify and fight infection.

biological perturbations observed in individuals who have experienced childhood trauma, De Bellis (2001) outlined a “developmental traumatology” model. (Readers are encouraged to read De Bellis’s seminal
paper, as only components relevant to the present purpose are described herein.) Relative to trauma during adulthood, the developmental traumatology model posits that childhood maltreatment is particularly harmful, as it has the potential to impact neurodevelopment through regulation of biological stress systems, which “either maintain homeostasis in the face of chronic and severe stress or permanently change in response to the stressor” (p. 541). The model asserts that biological stress system responses will be influenced both by the nature of the trauma and by individual “genetic vulnerabilities.” Natural extension of this model proposes that (a) a subgroup of trauma-exposed children respond to early trauma with a HPA response that places them at risk for developing PTSD and that (b) this peri-trauma HPA response in childhood results in chronic alterations in the HPA axis, which in turn alter subsequent peri-trauma HPA responses and increase risk for later PTSD following a second trauma (Delahanty & Nugent, 2006).

We examined peri-trauma HPA axis indicators within hours of trauma as predictors of PTSD in hospitalized pediatric accident survivors (ages 8–18 years), with findings supporting an association of high peri-traumatic cortisol with higher 6-week PTSD symptom severity (Delahanty, Nugent, Christopher, & Walsh, 2003). Similarly, a study of child survivors of motor vehicle accidents reported a positive association between high acute posttrauma cortisol (salivary cortisol at 6 pm and 9 pm) and subsequent PTSD and cortisol (Pervanidou et al., 2007). Importantly, strength and direction of the relationship between early cortisol and subsequent PTSD may be developmentally specific. During early childhood, HPA axis activation in response to stress may be attenuated, with the adult stress-responsive HPA system beginning to develop between 6 and 17 years of age (Gunnar & Quevedo, 2007). There is evidence that, in adults, low cortisol in the aftermath of trauma predicts the development of PTSD (Delahanty & Nugent, 2006). Further compounding the complexity of this research, in addition to the developmental effects, prior experiences may be important to peri-traumatic HPA response. For example, adult research with women has shown lower plasma cortisol in women with a history of prior trauma (Resnick, Yehuda, Pitman, & Foy, 1995). We observed that children with a prior trauma history showed a pattern of acute cortisol and subsequent PTSD that was more similar to the patterns observed in adults, such that youth with prior trauma tended toward higher levels of PTSD symptoms and lower urinary cortisol levels (Delahanty & Nugent, 2006). These findings lend support to theories that children who experience early trauma are at increased risk for developing PTSD following subsequent traumas, possibly partly owing to the early trauma-induced alterations in HPA stress responding.

Time elapsed since the trauma is another critical consideration. One recent study reported a positive and linear association of PTSD symptoms with cortisol in recently traumatized youth (within 1 year) but a negative association in youth whose trauma had occurred 1 year prior (Weems & Carrion, 2007). At 5 years posttrauma, children with the most PTSD symptoms had lower baseline salivary cortisol levels and greater cortisol suppression by dexamethasone (Le-Niculescu, 2009). Time since trauma has also been observed to be important to health outcomes, with evidence that recent adversity uniquely predicts poor health, somatic concerns, and health problems (Flaherty et al., 2013).

Trauma and Physical Health: Role of HPA Axis Functioning

Only a few studies have examined health outcomes associated with abuse during childhood/adolescence (Gianconia et al., 1995; Kean, Kelsay, Wamboldt, & Wamboldt, 2006; Seng, Graham-Bermann, Clark, McCarthy, & Ronis, 2005). Seng and colleagues (2005) provide perhaps the strongest data regarding the relationships between trauma, PTSD, and health outcomes in their epidemiologic case-control analysis of Medicaid eligibility and paid-claims data in girls. Victimization, often mediated by PTSD, was associated with a striking number of disease categories. Adolescents with PTSD were at increased risk for 12 disease categories ranging from an odds ratio of 2.1 for blood disorder to 5.2 for irritable bowel syndrome. Particularly among adolescents, comorbid depression was found to further increase risk for negative health outcomes beyond risk associated with PTSD alone. Among girls (0–8 years), PTSD diagnosis increased risk for 9 of 12 disease categories, with odds ratios ranging from 1.4 for digestive disorders to 3.4 for circulatory disorders. Importantly, the authors noted that PTSD was associated with risk for “objective disease states” such as circulatory problems and infections and not only subjective somatic complaints. Gianconia and colleagues (1995) conducted the only longitudinal investigation of health and PTSD diagnosis in adolescents, reporting increased likelihood that adolescents would rate their health as poor if they had PTSD (37.5%) than if they were trauma exposed without PTSD (21.3%) or if they had no PTSD/trauma history (10%). Most likely, the chronic health outcomes commonly observed in adults with child abuse histories are being established during childhood and adolescence.

Trauma and PTSD also evidence a relationship with viral suppression. Participants with PTSD evidence a higher antibody response to normally latent cytomegalovirus (Uddin et al., 2010). Similar recent research reported that Epstein Barr Virus was associated with
early abuse in an investigation of young adults (Slopen, McLaughlin, Dunn, & Koenen, 2013). Pointing to a developmental process, an adult study of ongoing trauma reported lower Herpes Simplex Virus-1 (HSV-1) in abused women (Garcia-Linares, Sanchez-Lorente, Coe, & Martinez, 2004), whereas a study of adolescents found higher HSV-1 antibodies in physically abused and postinstitutionalized adolescents relative to the nonabused controls (Shirtcliff, Coe, & Pollak, 2009).

Genetic and Epigenetic Influences Following Trauma: An Adapted Framework for the Developmental Traumatology Model

Reviewed here, we propose that the association between early trauma and later health concerns may function through the effects of extreme stress on genetic and epigenetic markers, which may exert: (1) direct influence on immune system markers and (2) indirect influence on immune system function through sustained influence on the immunomodulatory HPA axis. To best unpack these relationships, we briefly touch on relevant research in genetics and epigenetics, followed by an overview of evidence for the effects of trauma on epigenetic influence on immune function, and ending with an overview of evidence for the effects of trauma on epigenetic influence on HPA function and corresponding immune/health outcomes.

Genetic Predictors

Between-individual variation in this initial stress response, and associated outcomes of trauma, may be determined in part by genotype. A number of studies have demonstrated that HPA markers predict the development of depression and PTSD in adults with childhood trauma (see Laryea, Arnett, & Muglia, 2012 for a recent review). For example, in one of the only studies to examine genetic predictors of acute PTSD symptoms in children, we examined Corticotropin Releasing Hormone Type 1 Receptor gene (CRHR1) in pediatric injury patients (Amstadter et al., 2011). CRHR1 (rs12944712) was significantly related to higher levels of acute PTSD symptoms and to a sharper decrease in symptoms over time. Although genotype can inform who may be vulnerable to the effects of trauma, as a stable influence it is unlikely to fully explain the dynamic processes and chronic changes initiated by early life experiences.

Epigenetic Influences

In contrast, epigenetic mechanisms offer a plausible means by which externally experienced events, including childhood trauma, can become translated into mental and physical disorders (Toyokawa, Uddin, Koenen, & Galea, 2012). The term “epigenetics” refers to the regulation of genetic functions mediated through mechanisms independent of changes to DNA sequences. Epigenetic modifications refer to stable, but reversible, chemical modifications that regulate chromatin structure and/or DNA accessibility, which in turn alter the transcriptional activity of the surrounding loci. Illustrated in Figure 2, DNA methylation (DNAm) is the covalent modification of DNA in which methyl groups are coupled to cytosine. Depending on the genomic location in which it occurs, high levels of DNAm can either interfere with or enhance transcription. Epigenetics have been the focus of increasing interest in mental illness, partly owing to the paucity of genes conclusively linked to risk of mental illness as well as mounting evidence that epigenetic factors change in response to external experiences (Champagne et al., 2006; Weaver et al., 2004). As potential regulators of DNA accessibility and activity, epigenetic factors offer a mechanism by which the environment—and, in particular, one’s response to the environment—can moderate the effects of genes (Rutter, Moffit, & Caspi, 2006).

Figure 2. DNA methylation. Note. DNA double helix portrayed on the left, showing within the box a segment of methylated DNA (circles). Zooming in on this boxed region shows nucleotide base pairing as well as methylated cytosines (circles with “M”).

Trauma and Epigenetic Alterations in the Immune System

In the first study of DNAm and PTSD, we investigated trauma-exposed adults from a community-based, representative sample (Uddin et al., 2010). Differences in DNAm between PTSD participants relative to trauma-exposed controls occurred disproportionately in regions coding for immune function. Furthermore, these
altered gene expression in stress responses. The authors conclude that these findings suggest that stress-induced DNA methylation changes play a key role in the regulation of immune responses and that the strongest support for DNA methylation changes as a mediator for the relationship between expression changes and PTSD was observed in cases with child abuse. Relative to trauma-exposed participants without PTSD, those with PTSD (both those with and without a child abuse history) showed DNA methylation differences across a number of pathways including immune networks. Of note, the investigation did not assess for childhood trauma besides child abuse, limiting generalizations to other types of trauma during childhood (i.e., serious MVA, burn, etc).

Trauma and Epigenetic Alterations to the HPA Axis

Genetics and epigenetics may also provide the critical mechanisms whereby childhood peri-trauma HPA axis response results in long-term alterations in HPA and immune activity. Specifically, genetic factors may predict peri-traumatic HPA response and resulting cortisol levels. In turn, peri-traumatic increases in glucocorticoids (GC) such as cortisol during early life induce epigenetic changes in HPA axis genes (e.g., FKBPS), both in brain tissue (Klengel et al., 2013; Yang et al., 2012) and peripheral blood (Klengel et al., 2013; Lee et al., 2010, 2011). GC-induced DNA methylation changes persist long after cessation of GC exposure (Klengel et al., 2013; Lee et al., 2010, 2011), suggesting that stress-induced GC cascades have long-lasting consequences for HPA

Table I. CpG Sites Differentially Methylated in PTSD/Trauma in Both Uddin et al. (2010) and Smith et al. (2011) Investigations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Site</th>
<th>+/-</th>
<th>T, P</th>
<th>Protein description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCL1</td>
<td>cg17181262</td>
<td>–</td>
<td>T, P</td>
<td>Chemokine (C-C motif) ligand 1 is an inflammatory cytokine secreted by activated T cells.</td>
</tr>
<tr>
<td>CD2</td>
<td>cg16719404</td>
<td>–</td>
<td>P</td>
<td>Cluster of differentiation 2 (CD2) is a T-cell surface antigen.</td>
</tr>
<tr>
<td>CXCL1</td>
<td>cg02029926</td>
<td>+</td>
<td>T, P</td>
<td>Chemokine (C-X-C motif) ligand 1 is a cytokine belonging to the CXC chemokine family; plays a role in inflammation.</td>
</tr>
<tr>
<td>ENTPD1</td>
<td>cg04451770</td>
<td>+</td>
<td>P</td>
<td>Ectonucleoside triphosphate diphosphohydrolase is involved in the generation of adenosine, which plays a key role in mediation of immune suppression.</td>
</tr>
<tr>
<td>HSPB6</td>
<td>cg15125472</td>
<td>+</td>
<td>T</td>
<td>Small heat shock protein 20 is a molecular chaperone implicated in prevention of stress-induced aggregation of partially denatured proteins.</td>
</tr>
<tr>
<td>F8</td>
<td>cg06306751</td>
<td>-</td>
<td>T</td>
<td>Coagulation factor VIII, procoagulant component is a blood clotting protein.</td>
</tr>
<tr>
<td>FUT3</td>
<td>cg09001777</td>
<td>+</td>
<td>P</td>
<td>Fucosyltransferase 3 (galactoside 3(4)-L-fucosyltransferase, Lewis blood group) is involved in inflammation and bacterial adhesion; secondarily absorbed to red blood cells.</td>
</tr>
<tr>
<td>GBP1</td>
<td>cg07970007</td>
<td>–</td>
<td>P</td>
<td>Guanylate binding protein 1, interferon-inducible is involved in IFN-gamma response, either in infection or in inflammation.</td>
</tr>
<tr>
<td>IFI16</td>
<td>cg13406950</td>
<td>–</td>
<td>T</td>
<td>Interferon, gamma-inducible protein 16 is a hematopoietic IFN-gamma inducible nuclear antigen with 200 amino acid repeats cytokine.</td>
</tr>
<tr>
<td>IFI35</td>
<td>cg08090640</td>
<td>+</td>
<td>T</td>
<td>Interferon-induced protein 35 is induced by IFN-gamma; implicated in response to virus- and cytokine- and chemokine-mediated signaling pathways.</td>
</tr>
<tr>
<td>KLRG1</td>
<td>cg14913610</td>
<td>+</td>
<td>P</td>
<td>Killer cell lectin-like receptor subfamily G, member 1 is a natural killer cell receptor expressed by T cells with impaired proliferative capacity; relevant to cell senescence.</td>
</tr>
<tr>
<td>SLAMF7</td>
<td>cg07837085</td>
<td>+</td>
<td>P</td>
<td>SLAM family member 7 is a CD2-like receptor-activating cytotoxic cells (CD8+ T cells).</td>
</tr>
<tr>
<td>TLR1</td>
<td>cg03430998</td>
<td>+</td>
<td>T</td>
<td>Toll-like receptor (TLR) 1 is involved in pathogen recognition and activation of cytokines for innate immunity. Influences on IL1, IL6, and TNF-z.</td>
</tr>
</tbody>
</table>

Note. +/– indicate whether DNA methylation is increased versus decreased relative to comparisons. T/P indicates whether findings supported methylation differences associated with trauma (T), PTSD (P), or both (T,P). As all participants in the Uddin et al. (2010) investigation were trauma-exposed, all markers listed here were associated with PTSD in the Uddin et al. (2010) investigation.
Trauma and Epigenetic Influences on Immune Function Through the HPA Axis

As illustrated in Figure 1, the immune system is closely tied with the HPA axis. PTSD-associated immune dysfunction may be influenced by epigenetic profiles consistent with immune system overactivation and impaired development of normal neural–immune interactions (Uddin et al., 2010). As such, early trauma could result in DNAm-mediated alterations in immune profiles that, in turn, may be associated with increased risk for deleterious physical health outcomes such as asthma and irritable bowel syndrome. To explore functional changes associated with immune system DNAm, Smith et al. (2011) replicated Uddin and colleagues’ (2010) DNAm findings and then tested pro- and anti-inflammatory cytokines in plasma of adults. Consistent with prior adult PTSD research (Gill, Vythilingam, & Page, 2008; Smith et al., 2011; Sutherland, Alexander, & Hutchison, 2003; von Känel et al., 2007), decreased interleukin (IL)-4 levels were associated with PTSD and increased tumor necrosis factor alpha (TNF-α) levels were associated with childhood trauma. Although, one study reported that this significant effect disappeared when analyses adjusted for time since trauma (von Känel et al., 2007). Studies have also shown IL-6 baseline and reactivity differences associated with maltreatment in childhood and adolescence (Bertone-Johnson, Whitcomb, Missmer, Karlson, & Rich-Edwards, 2012; Carpenter et al., 2010). Adults with PTSD evidence increased IL-6 relative to traumatized and healthy controls (Gill et al., 2008; Maes et al., 1999). Though we focus here on only a few markers as examples, it is important to note that the immune system is tremendously complex, with considerations of the relationship between HPA and immune system function introducing another layer of complexity. Nonetheless, it is noteworthy that these immune biomarkers have also been implicated in the most commonly observed adolescent health correlates of trauma history including irritable bowel syndrome (Camilleri & Katzka, 2012; Liebregts et al., 2007), chronic fatigue (Bansal, Bradley, Bishop, Kiani-Alikhan, & Ford, 2012; Maes, Twisk, & Ringel, 2012), and asthma (Babu et al., 2011; Chai, Han, Lee, & Song, 2011; Elena Alexeevna, 2013; Lykouras, 2008; Oettgen, 2011; Ricciardolo, 2013; Zhang et al., 2011).

Developmental Context and Trauma

Supporting the developmental importance of early trauma, methylation/demethylation in youth is approximately three times greater than in adults (Labonté, 2012). Further, 8 of the top 10 age-demethylated gene ontologies are directly relevant to PTSD/trauma as well as physical health: including response to stimulus, response to external stimulus, immune response, immune system process, response to wounding, response to stress, inflammatory response, and innate immune response.

Conclusions and Recommendations for Future Directions

As described herein, emerging research supports a consistent developmental process whereby (for a subset of individuals) early traumatic experiences evoke a cascade of system-wide changes that persist into adulthood and are associated with both deleterious psychological and physical health outcomes. These effects of trauma may include symptoms of PTSD; however, as illustrated in Table 1, many of the effects described herein were related to trauma exposure without necessarily involving clinically significant symptoms of PTSD.

Limitations of the Literature

Much more research is needed to inform our understanding of the role that epigenetics may play in explaining the association between pediatric trauma and health outcomes. A number of critical questions remain. For example, do certain types of trauma (such as childhood maltreatment as compared with single occasion accidental trauma) confer differential influence on DNAm and expected expression and health outcomes? Are there “critical periods” during which children or adolescents are particularly vulnerable to the effects of trauma? How might positive environmental influences (i.e., supportive family) buffer the effects of trauma? As proposed here, the assumption is that the peri-traumatic stress response results in systemic changes that are maintained (at least partly) through DNAm profiles. However, to truly characterize this course, researchers would need to assess DNAm (as well as expression, HPA and immune functioning, and psychological symptoms) before trauma, shortly following trauma, and then repeatedly over a number of years posttrauma. A particularly exciting question for the field is whether treatment (pharmacological or behavioral) could reverse these DNAm alterations. Initial research in nonpediatric populations suggests this is a possibility (Yehuda et al., 2013; Perroud et al., 2013).

Implications for Pediatric Psychology

As described here, there is emerging evidence to suggest that traumatic experiences during early life may have a measureable impact on physical health
outcomes, even without diagnostic levels of PTSD. As such, a thorough assessment of trauma history is always important, even when there is no reason to believe that the child has experienced trauma. For psychologists working with kids following trauma, it is important to know that there is reason to believe that genetic factors might moderate response to psychosocial treatment and that psychosocial treatments might even change methylation profiles (Bakermans-Kranenburg, Van IJzendoorn, Mesman, Alink, & Juffer, 2008; Beach et al., 2009; Beevers & McGeary, 2012; Brody, Beach, Philibert, Chen, & McBride Murry, 2009; Feldstein Ewing, LaChance, Bryan, & Hutchison, 2009; Gibb, Beevers, & McGeary, 2012; Perroud et al., 2013). In other words, there is evidence that response to psychosocial treatment may be partly related to their genetic constitution. Additionally, although negative experiences like trauma can alter DNA methylation (DNAm) profiles, positive experiences such as involvement in psychosocial treatment may also alter DNAm. Future research may also permit the development of medications that can be used to alter DNAm profiles. For example, research using an animal model of maternal maltreatment showed that pharmacologic manipulation could reverse the epigenetic changes and associated behavior in rodents exposed to poor maternal care (Liberman, Mashoodh, Thompson, Dolinoy, & Champagne, 2012; Weaver et al., 2004, 2005). Additionally, given the burgeoning of research related to genetic and epigenetic pathways for understanding physical and mental health outcomes as well as commercially available genotyping, psychologists may wish to continue to develop their own understanding of existing genetic paradigms including their limitations. More research is needed, particularly prospectively and in controlled settings, with trauma-exposed youth, to more fully characterize the neurobiological course of HPA and immune outcomes as influenced by genetic and epigenetic factors.

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