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Early life stressors and genetic influences on the development of bipolar disorder: The roles of childhood abuse and brain-derived neurotrophic factor

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ABSTRACT

Objectives: Although there is increasing research exploring the psychosocial influences and biological underpinnings of bipolar disorder, relatively few studies have specifically examined the interplay between these factors in the development of this illness. Social–biological models within a developmental psychopathology perspective are necessary to advance our understanding of the processes involved in the onset and course of bipolar disorder. This article presents a review of the empirical literature linking childhood abuse to bipolar disorder, the research to date on the possible role of brain-derived neurotrophic factor (BDNF) in the development of this disorder, followed by a discussion of how childhood abuse may interact with BDNF.
Methods: A literature search was conducted using Psycinfo to identify relevant articles on childhood abuse, BDNF, and bipolar disorder.
Results: The extant research implicates both childhood abuse and BDNF in the etiology of bipolar disorder. Specifically, there is growing evidence associating early abuse to the development of bipolar disorder. Similarly, the BDNF Val66 allele has been linked with increased susceptibility to bipolar disorder. Based on existing research, a genetic diathesis-transactional stress model is proposed incorporating childhood abuse and the BDNF gene in the pathogenesis of bipolar disorder.
Conclusions: Although there is some support for this model, the relatively modest amount of relevant literature highlights the need for further research. An integrative theoretical framework including both social and biological processes in bipolar disorder is important for the development of effective prevention and treatment strategies for this disorder.

Introduction

Bipolar disorder is a severe and recurrent illness afflicting approximately 1.5% of the US population (Hyman, 2000) and between 0.5% and 3.5% of the world population (Kleinman et al., 2003). It often involves significant impairment in multiple areas of functioning, including suicide, divorce, alcohol abuse, and erratic work history (Angst, Stassen, Clayton, & Angst, 2002; Goodwin & Jamison, 1990; Strakowski, DelBello, Fleck, & Arndt, 2000). Indeed, bipolar disorder has been ranked the sixth leading cause of disability among people ages 15–44 worldwide (Murray & Lopez, 1996). In addition, the legal and treatment costs, and lost income associated with this disorder have been estimated to exceed $45.2 billion (Wyatt & Henter, 1995). It is therefore important to develop a clear understanding of the joint influence of psychosocial and neurobiological factors involved in the etiology of bipolar disorder, so as ultimately to enhance the development of prevention and treatment strategies for this disorder.

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Several recent reviews found that life events tend to precede both depressive and manic or hypomanic episodes in bipolar disorder (e.g., Alloy et al., 2005; Alloy, Reilly-Harrington, Fresco, & Flannery-Schroeder, 2006; Johnson, 2005; Johnson & Kizer, 2002). Moreover, according to the harsh environment hypothesis, individuals with bipolar disorder tend to experience more stressful life events that contribute to the onset of their disorder, and consequently are likely to report more negative events (Grandin, Alloy, & Abramson, 2007). In support of this position, individuals with bipolar disorder reported experiencing more stressful childhood life events prior to the onset of their condition than did demographically matched normal controls at the same age, with greater total negative events predicting earlier onset of bipolar disorder (Grandin et al., 2007).

The current article focuses on how one specific type of early life stressor, childhood abuse, may be related to the development of bipolar disorder. This article begins by presenting a brief review of the empirical literature linking childhood abuse to bipolar disorder. Next, this article discusses the extant studies on one possible neurobiological risk factor for bipolar disorder, polymorphisms in the brain-derived neurotrophic factor (BDNF) gene, and follows with a discussion of how childhood abuse may interact with BDNF. Finally, a genetic diathesis-transactional stress model is proposed incorporating childhood abuse and the BDNF gene in the pathogenesis of bipolar disorder.

Childhood abuse and bipolar disorder

Despite the clear public health cost of bipolar disorder, in comparison to research on depression and other forms of psychopathology, there have been relatively few studies to date focusing on the developmental antecedents of bipolar disorder in general, and the role of childhood abuse specifically (Alloy, Abramson, Smith, Gibb, & Neeren, 2006; Brown, McBride, Bauer, & Williford, 2005; Grandin et al., 2007; Kauer-Sant'Anna et al., 2007). Heightening the need for more research in this area is the potential for early stressful life events to have an enduring adverse effect on neurochemistry, brain structure, and affective behavior (Kaufman, Plotsky, Nemeroff, & Charney, 2000; Leverich et al., 2002; Post, Leverich, Xing, & Weiss, 2001). It is also worth noting that childhood maltreatment has been implicated in other forms of psychopathology, including depression (Gibb, Butler, & Beck, 2003; Spertus, Yehuda, Wong, Halligan, & Seremetis, 2003; Toth, Manly, & Cicchetti, 1992), anxiety (Gibb et al., 2003; Spertus et al., 2003), schizophrenia (Read, van Os, Morrison, & Ross, 2005), posttraumatic stress (Spertus et al., 2003), and substance use disorders (Kendler et al., 2000).

Although the findings to date have been somewhat inconsistent, there is nevertheless some modest but growing support for the existence of a link between childhood abuse experiences and the later development of bipolar disorder (see Alloy et al., 2005; Alloy, Abramson, Smith, et al., 2006; Alloy, Abramson, Walshaw, Keyser, & Gerstein, 2006 for more detail). Several retrospective studies have found that individuals with bipolar disorder report a higher rate of childhood abuse than do those with unipolar depression (Hyun, Friedman, & Dunner, 2000; Levitan et al., 1998) or normal controls (Neeren, Alloy, & Abramson, 2008). In the largest study to date, approximately half of bipolar disorder patients reported a history of severe childhood abuse (Leverich et al., 2002), a finding that has been replicated in another study (Goldberg & Garno, 2005). In contrast, other studies have observed higher rates of childhood abuse in unipolar patients than in bipolar disorder patients (Wexler, Lyons, Lyons, & Mazure, 1997), or no difference in rates between bipolar disorder patients and patients with no history of psychiatric illness (Coverdale & Turbott, 2000). It should be noted, however, that Coverdale and Turbott (2000) did not examine the rates of abuse specifically for bipolar disorder, but were more interested in determining the prevalence of abuse in psychiatric outpatients in general relative to controls. Consequently, this study included a rather diagnostically heterogeneous sample, consisting mostly of schizophrenic or schizoaffective patients (62.6%) and relatively few bipolar disorder patients (15.6%), and making it difficult to determine the degree to which their findings are reflective of bipolar disorder.

Related to this, a major problem with the existing literature is that many of the studies were not designed specifically to test the relationship between abuse history and bipolar disorder, or suffered from significant methodological limitations. The majority of studies utilized retrospective designs, in which adult participants recalled childhood events, introducing the possibility of memory recall bias. This concern is particularly relevant to bipolar disorder, as there is some evidence that this disorder is associated with some forms of neurocognitive impairment, including deficits in verbal memory (Robinson et al., 2006; Savitz, van der Merwe, Stein, Solms, & Ramesar, 2007; Senturk et al., 2007). Similarly, most of the studies failed to control for bipolar disorder individuals' current mood states, and by extension, possible mood-congruent memory biases or reporting biases (Brown & Harris, 1978). A further complication is that very few studies have attempted to determine whether reported childhood abuse experiences temporally preceded, and thus contributed to, the onset of bipolar disorder. Another limitation with many of the extant studies is the absence of an appropriate control group. That is, several studies compared rates of abuse in bipolar disorder and depression, or included no controls, and consequently it is impossible to ascertain whether individuals with bipolar disorder differ from healthy controls in childhood abuse history. Finally, there is considerable variability across studies in the operationalization of childhood abuse, with some studies encapsulating early abuse under broader constructs (e.g., traumatic events or life stress), while still others used measures with questionable psychometric properties (e.g., only one- or two-item measures of childhood abuse).

When the methodological soundness of the studies is taken into consideration, greater support for the link between childhood abuse and bipolar disorder is demonstrated in the methodologically stronger studies than in the studies more affected by methodological limitations (Alloy, Abramson, Smith, et al. 2006). In addition, there is stronger evidence that greater experiences of childhood abuse may be predictive of earlier onset of bipolar disorder (Garno, Goldberg, Ramirez, & Ritzler, 2005; Suppes et al., 2001). Thus, although there is some support for the role of early abuse experiences in the

development of bipolar disorder, more research addressing limitations of past studies is required before firm conclusions can be drawn regarding this relationship.

What remains even more unclear, however, are the potential processes underlying the association between early experiences of abuse and the emergence of bipolar disorder, as most past studies have tended to focus primarily on determining the existence of this relationship. Delineating some of the possible developmental mechanisms relating childhood abuse to bipolar disorder would be especially informative for designing effective prevention and treatment programs.

Brain-derived neurotrophic factor and bipolar disorder

One possibility comes from a line of research suggesting the existence of a genetic diathesis for bipolar disorder involving BDNF. The BDNF gene is located on the short arm of chromosome 11, or more specifically, the 11p13 region, which is in close proximity to D11S987, a marker linked with susceptibility to bipolar disorder (Pato et al., 2004). As the most abundant neuroprotein in the brain, BDNF is involved in a multitude of neural processes throughout development. During early development, it serves an important role in neurogenesis, neuronal maintenance, and maturation of normal neural developmental pathways. In adulthood, it continues to be essential for synaptic plasticity, dendritic growth, as well as hippocampal long-term potentiation (LTP) associated with learning and memory (Kang & Schuman, 1995; Palomino et al., 2006; Post, 2007).

Although relatively little is currently known about the neurobiological processes underlying bipolar disorder (Kauer-Sant'Anna et al., 2007), the BDNF Val66 allele recently has been hypothesized to confer susceptibility to the development of bipolar disorder, whereas the BDNF Met66 allele has been associated with neurocognitive deficits characteristic of this illness (see Post, 2007 for more detail). This polymorphism alters the amino acid structure of the protein from which BDNF is cleaved by substituting the amino acid valine (val) with methionine (met) on codon 66 of the nucleotide. Although this polymorphism does not alter the activity of the mature protein, it influences the regulated secretion of BDNF by altering the composition of its precursor protein (Egan et al., 2003). In support of a connection between BDNF functioning and bipolar disorder, plasma BDNF levels appear to be negatively correlated with the severity of manic and depressive symptoms in bipolar disorder and lower than in healthy controls (Cunha et al., 2006; Machado-Vieira et al., 2007; Monteleone, Serritella, Martiadis, & Maj, 2008). Relative to individuals with non-specific psychosis, those with bipolar disorder demonstrate a significant decrease in plasma BDNF levels shortly after first-episode onset (Palomino et al., 2006). Furthermore, several studies using large North American, British, and European samples have found an association between the Val66 BDNF allele and bipolar disorder (Lohoff et al., 2005; Neves-Pereira et al., 2002; Sklar et al., 2002; Vincze et al., 2008). This preferential transmission of the Val66 allele has also been observed in children with the early-onset subtype of bipolar disorder (Geller et al., 2004). Studies with Asian (Hong et al., 2003; Nakata et al., 2003), and Belgian (Oswald et al., 2004) samples, however, have failed to replicate this finding. This discrepancy in the findings partially may be accounted for by ethnic variations in frequency and sensitivity to BDNF polymorphisms (Hong et al., 2003). Consistent with this possibility, the frequency of the Val66 allele has been found to be higher in North American and British samples (e.g., 79% in Lohoff et al., 2005; 77% in Neves-Pereira et al., 2002; 83% in Sklar et al., 2002) than in Chinese (52%; Hong et al., 2003), or Japanese ones (58%; Nakata et al., 2003).

A number of studies have also documented, in association with BDNF irregularities, neurocognitive deficits similar to ones observed in individuals with bipolar disorder. The neuroprotective properties of BDNF are perhaps most observable in the hippocampus, where the BDNF gene is most strongly expressed (Savitz et al., 2007), making it also an ideal site for noting any deleterious effects of BDNF polymorphisms or other potential mechanisms that may lead to dysregulation of BDNF levels. With this in mind, several studies have found decreased hippocampus volume, and increased hippocampal activation during learning and memory tasks in healthy individuals with BDNF Met66 allele relative to those without it (Bueller et al., 2006; Egan et al., 2003). One of these studies also observed reduced levels of hippocampal N-acetyl aspartate (NAA), a putative intracellular marker of neuronal integrity and synaptic abundance, in individuals with the BDNF Met66 allele (Egan et al., 2003). Consistent with these findings, abnormal hippocampal activation and poorer performance on verbal episodic memory tasks also have been linked to Met66 polymorphisms (Egan et al., 2003; Hariri et al., 2003). Furthermore, one study with bipolar individuals (Rybakowski, Borkowska, Czerski, Skibinska, & Hauser, 2003) found that the Val66Met allele, when compared to the Val66Val allele, was associated with poorer performance on the Wisconsin Card Sort Test, a standard test of working memory and executive functioning.

As previously mentioned, similar deficits in verbal memory also have been implicated in bipolar disorder independent of mood state (Robinson et al., 2006; Savitz et al., 2007; Senturk et al., 2007), and are suggestive of a trait deficit in hippocampal functioning. There has been mixed evidence of reduced hippocampal volume in bipolar disorder, although it is unclear from the literature whether this change temporally precedes or is subsequent to the onset of bipolar disorder (Blumberg et al., 2003). Finally, bipolar disorder has been associated with diminished neuroplasticity and cell survival (Manji, Moore, Rajkowska, & Chen, 2000), possibly reflecting impairments in neuroprotective factors such as BDNF.

Support for a link between BDNF and bipolar disorder also comes from a few psychopharmacological studies using animal models. Specifically, lithium and valproate, two commonly used mood stabilizers for the treatment of bipolar disorder, appear to increase BDNF levels in rodent hippocampus and frontal cortex (Einat et al., 2003; Hashimoto et al., 2002; Machado-Vieira et al., 2007; Omata et al., 2008). In one of these studies, mutant mice lacking the BDNF gene exhibited distinct behaviors characteristic of manic states in humans, including hyperactivity and risk-taking behavior (Einat et al., 2003). As is the case

with all animal model studies, however, a degree of caution needs to be applied when extending the implication of these findings to humans.

It should be noted, however, that the better functioning Val66 BDNF allele, rather than the Met66 allele, has been associated with higher risk, and early onset of bipolar disorder (Rybakowski et al., 2003; see Post, 2007). Thus, exactly how the Met allele of the Val66Met polymorphism relates to bipolar disorder in general, and the neurocognitive deficits observed in this disorder specifically, is not yet clear.

Childhood abuse and brain-derived neurotrophic factor

As with bipolar disorder, several studies have linked stress with irregularities in BDNF expression and functioning. In animal models, rodents exposed to neonatal stressors experience significant decreases in hippocampal BDNF levels (Post, 2007). If these neonatal stressors are repetitive, long-term reductions in BDNF levels persisting into adulthood are observed (Post, 2007). Chronic, but not acute, stress in adult animals likewise has been linked to diminished hippocampal BDNF (Duman, 1998). Similarly, in human studies, acute and chronic stress consistently have been related to inhibition of hippocampal BDNF synthesis, and resulting reductions in BDNF levels (Machado-Vieira et al., 2007; Savitz et al., 2007). Furthermore, damage to the hippocampus appears to result in reduced BDNF mRNA expression in the prefrontal cortex (Rybakowski et al., 2003).

Neurocognitive studies on childhood abuse have produced findings similar to ones for bipolar disorder and BDNF. Verbal memory impairment has been reported in individuals with a history of childhood abuse when compared to controls matched by age, gender, education level, and IQ (Savitz et al., 2007). In addition, there is some evidence that the duration of childhood sexual abuse may be strongly related to a variety of memory deficits in women without a PTSD diagnosis (Navalta, Polcari, Webster, Boghossian, & Teicher, 2006). Matching these findings, a few neuroimaging studies have recorded decreases in volume in the left hippocampus among participants with early abuse relative to controls (Savitz et al., 2007). Similar to the situation with research on hippocampal volume in bipolar disorder, there have also been some conflicting findings in this area, and it remains unclear whether this hippocampal change precedes or is a consequence of abuse.

Only very recently have researchers begun to examine an issue more directly relevant to the current focus: the effects of early abuse experiences on BDNF. In the sole study to date assessing BDNF levels in patients with a history of childhood abuse, those with a history of trauma, particularly sexual abuse, had significantly lower serum BDNF levels relative to those with no past trauma, even after controlling for mood state (Kauer-Sant'Anna et al., 2007). As this study consisted entirely of bipolar patients, however, it cannot be determined whether individuals with childhood abuse experiences but no history of bipolar disorder differ from those with no bipolar disorder in BDNF levels. Furthermore, the cross-sectional nature of this study, in addition to the inclusion of traumatic events experienced during adulthood, make it impossible to determine temporal or causal relations between BDNF levels, early abuse experiences, and the first onset of bipolar disorder. Future research in this area will hopefully further elucidate the nature of the relationship between BDNF and childhood abuse experiences.

A genetic diathesis-transactional stress model of bipolar disorder

Although there is increasing evidence that childhood abuse is a significant risk factor for bipolar disorder, not all abused children develop this disorder. Similarly, not all individuals with the BDNF Val66 allele and neurobiologically susceptible to bipolar disorder end up with this condition. Converging evidence from the different lines of research discussed above are suggestive of a diathesis-transactional stress interaction between these two risk factors. According to this model, individuals with the Val66 allele are at increased risk for bipolar disorder when exposed to childhood abuse. The stress produced by early abuse experiences may lead to decreases in the expression of neurotrophic factors, and this effect is magnified in individuals with genetic susceptibility. Areas of the brain known to be particularly vulnerable to the neurotoxic effects of stress, such as the hippocampus, experience neuronal atrophy, and this process is exacerbated by the significantly decreased presence of neuroprotective agents such as BDNF. Hippocampal damage results in reduced BDNF mRNA expression in other areas of the brain (Rybakowski et al., 2003). The diminished levels of BDNF may, in turn, produce a stress sensitization effect in that it leaves these individuals even more responsive to future abuse and other stressors. Suggestive of this possibility, BDNF has been implicated in the regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, one of the main biological stress-response systems, with lower BDNF levels being associated with higher HPA axis activity (Schüle et al., 2006). The potential increased sensitivity to stress could mean that otherwise benign or mild stress experiences may now be perceived as significant. In this manner, the model features reciprocally transactional processes, with neurobiological vulnerability to bipolar disorder itself contributing to the experience of future stresses. Over time, especially with repeated abuse or other stress during brain development, the absence of adequate neurotrophic factors could lead to a scarring effect, leaving lasting structural disorganization (e.g., hippocampal volume reduction), and related cognitive impairments (e.g., deficits in verbal memory), such as those characteristic of bipolar disorder.

Interestingly, one recent study examined the relation between BDNF and childhood sexual abuse in a sample of individuals with bipolar disorder and their relatives (Savitz et al., 2007). Specifically, sexual abuse history was negatively correlated with memory task performance, and this effect was moderated by the presence of the Met66 allele. A similar experimental design could be adopted in evaluating the relation between the Val66 allele, BDNF levels and childhood abuse.

It should be noted, however, that this model only outlines the interaction of two of multiple possible vulnerability factors for bipolar disorder. It is likely that there are several different potential pathways involved in the pathogenesis of this disorder, and, as is evident from some of the studies discussed, not all individuals with bipolar disorder have a history of childhood abuse or the BDNF Val66 allele. Rather, the heterogeneous nature of bipolar disorder is strongly suggestive of a polygenic disorder. Indeed, the Val66 allele is likely just one of several BDNF polymorphisms specifically, and a variety of genetic risk factors in general for bipolar disorder (Post, 2007). Similarly, other social factors, such as poor parenting, and cognitive processes, such as Behavioral Approach System (BAS)-relevant cognitive styles, may also relate to risk for bipolar disorder (Alloy, Abramson, Walshaw, et al., 2006). Finally, several temperamental characteristics, such as emotional regulation difficulty, have also been proposed to contribute to risk for bipolar disorder (Hirshfeld-Becker et al., 2003).

Future directions

In summary, the existing research indicates that both childhood abuse experiences and BDNF likely play significant roles in the etiology of bipolar disorder. Based on the current research, a diathesis-transactional stress model was proposed in which childhood abuse interacts with BDNF polymorphisms to increase risk for bipolar disorder. Though there is some support for this model, the modest amount of relevant literature highlights the need for additional research.

As mentioned earlier in this article, the research on the link between early abuse and bipolar disorder is characterized by several significant methodological limitations. These limitations in part reflect that very few studies specifically examined this association. As several past studies have assessed for the presence of childhood abuse as part of more general constructs like trauma or stressful life events, greater specificity is required in measures of childhood abuse. Many studies consider only certain kinds of abuse experiences, such as childhood physical abuse or childhood sexual abuse, or assess them collectively under general childhood abuse experiences. Very few extant studies specifically include assessments of childhood emotional abuse, and this construct was not considered in any analyses. It would be important for future studies to measure these three types of abuse separately as well as total abuse experience, so as to assess for the possibility that these abuse types differ in their association with bipolar disorder, and by extension, differentially interact with BDNF or other mechanisms in the pathogenesis of bipolar disorder. The emerging finding that, when compared to physical or sexual maltreatment, emotional maltreatment may be more related to the development of depression, and particularly cognitive risk for depression (Gibb, 2002), is congruent with this possibility. In addition to assessing the unique contribution of different types of early abuse to bipolar disorder, it would be important to evaluate the possibility of specific effects of multiple forms of abuse and other stressors (Copeland, Shanahan, Costello, & Angold, 2009), especially considering that multiple forms of childhood abuse and other stressors frequently co-occur (Copeland et al., 2009; Finkelhor, Ormrod, & Turner, 2009; Gladstone et al., 2004). It would also be essential to document the timing of these abuse experiences so as to determine whether they temporally preceded the emergence of bipolar disorder.

Related to this need for finer-level analyses of specific types of childhood abuse and other forms of stress, both separately and in combination with each other, consideration should also be given in future research to specific characteristics of childhood abuse experiences that may be particularly predictive of psychopathology, including the source, severity, and duration of abuse. It may stand to reason, for example, that abuse from a close friend or relative would have a more deleterious effect, and accompanied by feelings of confusion and betrayal, than would abuse perpetrated by a stranger or acquaintance. In terms of severity of abuse, more violent forms of childhood abuse (i.e., physical abuse and violent sexual abuse) have been found to be more strongly related to number of lifetime suicide attempts than relatively less violent forms of abuse (i.e., molestation and verbal abuse; Joiner et al., 2007). Thus, special care should be taken in future studies adequately to capture the complexity of early abuse experiences.

In terms of BDNF, future prospective studies are required to track changes in serum BDNF levels among individuals with and without genetic susceptibility relative to early abuse experiences and first-episode onset of bipolar disorder so as to strengthen our understanding of the nature of its relationship with childhood abuse and bipolar disorder. Incidentally, this may also allow for a tentative test of the proposed genetic diathesis-transactional stress model, as the BDNF gene could be used as a basis for comparing reported levels of abuse or general stress. Similarly, comparisons could be made between high and low serum BDNF levels in terms of subsequent reports of stress, controlling for past abuse or stress. Another hypothesis based on this model that could be tested concurrently is that abuse experiences would predict decreases in serum BDNF levels.

A promising strategy for testing the association between abuse, BDNF, and bipolar disorder, particularly within the framework of the genetic diathesis-transactional stress model presented above, is a high-risk design. Such an approach would involve selecting individuals with no history of bipolar disorder, but at high-risk versus low-risk for developing this illness, based on hypothesized genetic (BDNF Val66 allele) or psychosocial vulnerabilities (childhood abuse experiences). High-risk and low-risk individuals may then be compared prospectively in terms of likelihood of eventually developing bipolar disorder. Given that previously abused children are at significantly higher risk than non-abused children for future victimization (Barnes, Noll, Putnam, & Trickett, 2009; Swanston et al., 2002; Widom, Czaja, & Dutton, 2008), it may also be possible prospectively to assess abuse experiences and changes in BDNF levels. Similar high-risk designs have been previously used in studying both unipolar and bipolar affective disorders (e.g., Alloy, Just, & Panzarella, 1997; Depue, Kleinman, Davis, Hutchinson, & Krauss, 1985; Iacoviello, Alloy, Abramson, Whitehouse, & Hogan, 2006).

Finally, the extant research collectively lends weight to the argument that significant early life stressors can have an enduring influence on neurochemistry and brain structure. For this reason also, it is crucial for future research to delineate the neurobiological sequelae of childhood abuse as well as the neurobiological processes underlying the development of bipolar disorder, so as to identify more specific targets for designing effective prevention and treatment strategies.

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