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Editorial Perspective: Childhood maltreatment – the problematic *unisex assumption*

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Abstract

Childhood maltreatment (CM) is a heterogeneous group of childhood adversities that can range from different forms of abuse (physical, sexual, emotional) or neglect (physical, emotional, cognitive), to severe bullying by peers. With an annual estimated cost of $500 billion in the US alone, CM is recognized as one of the most significant risk factors for a range of psychiatric and medical conditions (White and Kaffman, 2019). Further, rates of numerous psychiatric, neurological, and medical conditions differ significantly between males and females (Gillies and McArthur, 2010), inspiring decades of research on how sex moderates consequences of CM (Gershon et al., 2008). Although vulnerability to CM has been reported to vary by sex, very few findings have been consistent across studies. Moreover, most work to date has focused on how sex alters the frequencies of different psychopathologies in maltreated individuals, with little attention to whether different developmental processes may underlie these psychopathologies in males and females (White and Kaffman, 2019). The primary goal of this editorial is to advocate for more effective research strategies to address these questions. We first examine the rationale for studying sex as an important moderator of consequences of CM, briefly summarize some of the most consistent clinical findings, and discuss the implications of sex in treatment response. We then highlight important obstacles that contribute to the large number of inconsistent findings and make five recommendations on how to move forward.

Keywords

Sex differences; childhood maltreatment; psychopathology; early life stress; animal models

The role of sex in CM outcomes and the problematic *unisex assumption*

Although male and female brains, physiology, and immune systems share considerable similarities, there are important differences that may at least partially reflect distinct and specialized divergencies in reproductive strategies between males and females (White and Kaffman, 2019). In mammals, these differences are established by a surge of testosterone in males during a critical period of development (e.g. second trimester in humans and embryonic day 18 to postnatal day 8 in rodents, see Gillies and McArthur, 2010). High

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levels of testosterone are aromatized and locally converted to estrogen, leading to several structural and functional differences between the brains of males and females. For instance, aromatization of testosterone in the anteroventral periventricular nucleus (AVPV) induces a wave of apoptosis in GABAergic neurons in males. This male-specific developmental process is responsible for the smaller AVPV nucleus and the pulsatile pattern of gonadotropin-releasing hormone (GnRH) release in males that is distinct from the cyclical pattern of GnRH release that drives ovulation in females (Gillies and McArthur, 2010).

Sexually dimorphic variations that emerge early in development are maintained and accentuated by different levels of sex hormones produced during reproductive age (i.e. estrogens and progesterone in females and testosterone in males). This variability in sex hormones is thought to account for important sex differences in multiple psychopathologies and are implicated in the different ways males and females respond to injury, stress, and medications (Gillies and McArthur, 2010). Despite these important differences, most psychiatric and medical conditions are treated using "a *unisex-model"* in which sex differences are ignored and males and females are assumed to respond similarly to most treatment modalities (Gillies and McArthur, 2010, Beery and Zucker, 2011).

Sex-differences in the vulnerabilities of males and females to consequences of CM have been extensively reported, but few findings have been consistent across different studies, reviewed in (White and Kaffman, 2019). Some of the most compelling evidence comes from imaging showing that exposure to CM causes more pronounced reduction in the size of the hippocampus and the corpus callosum in males compared to females. Sex differences in prefrontal cortex activation and connectivity were also reported in the few fMRI studies that had sufficient power to examine CM by sex interaction (White and Kaffman, 2019). In addition, a systematic review conducted by Gershon et al. (2008) found that more than half of the 19 studies conducted in adolescents reported significant sex by CM interaction that were notable for worse clinical outcomes in males exposed to CM. Interestingly, no consistent sex by CM interaction was found in the 14 studies examining this issue in adulthood (Gershon et al., 2008), a finding that was replicated in three additional large meta-analyses (White and Kaffman, 2019).

It is important to note that similar clinical presentation in males and females, may be mediated by very different mechanisms, requiring sex-specific interventions. This notion is supported by task-mediated fMRI work showing pronounced differences in prefrontal cortex activation in maltreated males and females despite no sex differences in the performance of the task (Crozier et al., 2014). Additionally, postmortem genomic work in humans, coupled with viral mediated gene manipulation in mice, indicated that reduced levels of the phosphatase Dusp6 in the medial prefrontal cortex may mediate depression in women while overexpression of the transcription factor Emx1 may drive depression in men (Labonte et al., 2017). Interestingly, these sex-specific changes led to similar increases in spontaneous firing of glutamatergic neurons in the mPFC (Labonte et al., 2017). Together, these findings suggest that different mechanisms converge in male and females to produce major depression and suggests that some interventions will have sex-specific effects when treating depression.

In summary, although many details regarding the moderating effects of sex on CM are yet to be elucidated, a growing body of work has indicated that some forms of CM affect males and females differently. Clarifying this issue will likely lead to more effective interventions that are desperately needed to address the enormous clinical and economic burden associated with CM.

Challenges and obstacles

As previously mentioned, the role of sex in moderating outcomes associated with CM in humans is mixed. More than 50 studies, including several systematic reviews and meta-analyses, have examined this issue. Some studies concluded that females are more vulnerable, others maintained that males show higher rates of psychopathology. A third group of studies proposed a more nuanced and complex relationship between sex and CM indicating that psychological outcomes depend on many factors such as the subtype of maltreatment, the timing of trauma, genetic vulnerability, comorbidities, the specific circuit involved, and the developmental stage when the outcomes are assed (White and Kaffman, 2019).

These conflicting results are not surprising given the difficulty of quantifying the severity of CM. These challenges are related to the heterogeneity of the adversities and the way in which they interact with one another (White and Kaffman, 2019). Specifically, different subtypes of CM (e.g. physical abuse vs. emotional neglect) cause different neurodevelopmental and behavioral outcomes. Moreover, pure forms of CM are rarely encountered; in most cases, CM is characterized by several interacting adversities that affect the risk for psychopathology. Sex plays an important role in this complex interaction because it impacts both the prevalence and the severity of certain forms of CM. For example, while men experience lower prevalence of sexual abuse, young males are more likely to experience severe and frequent sexual abuse perpetuated by adolescent males while females are more likely to be abused by adult males (Gauthier-Duchesne et al., 2017). Work by MacMillan et al. (2001) provides a good example of how these differences may complicate the interpretation of data with regard to the moderating effects of sex on psychopathology. For instance, adult women exposed to childhood physical abuse, and to a lesser extent sexual abuse, were more likely than males exposed to the same CM to meet criteria for either depression, substance use disorder, or antisocial behavior (MacMillan et al., 2001). Importantly, 33% of the physically abused women in this study were also sexually abused while only 11% of the men that were physically abused reported sexual abuse (MacMillan et al., 2001). These differences raise the possibility that the increased vulnerability seen in women may be due to more severe trauma and not actual sex differences.

Sex differences also create unique challenges with regard to the appropriate comparison group (White and Kaffman, 2019). For instance, the rates of internalizing disorders are almost twice as high in females, raising the question of whether a direct comparison between males and females is appropriate. Another unresolved methodological question is how to address differences in sexual maturation between males and females. Females enter puberty 18 months before males, suggesting that the comparison should be made based on Tanner

phase. This issue is further complicated by work showing that CM accelerates entry into puberty in females, with less clear data available on this issue in males.

Perhaps one of the most important obstacles for progress is the lack of a standardized assessment tool that faithfully characterizes the complexity and heterogeneity of CM. Currently, different diagnostic tools are used to assess CM making it practically impossible to compare outcomes across studies or to conduct meaningful meta-analyses. Moreover, almost all of these assessment tools use the cumulative-risk assessment model that adds up the number of adversities. One criticism of the cumulative-risk assessment model is that it does not distinguish between adversities that cause different developmental outcomes; e.g., physical abuse and emotional neglect (White and Kaffman, 2019, McLaughlin and Sheridan, 2016).

Most of the work to date has focused on the relative rates of psychopathologies in male and females exposed to CM, with little attention paid to whether these psychopathologies are mediated by similar developmental changes. We suspect that the paucity of research in this area is mediated by the tenuous assumption that comparable symptoms in males and females are most likely mediated by similar mechanisms (White and Kaffman, 2019, Gillies and McArthur, 2010, Beery and Zucker, 2011). We view this *"unisex assumption"* as an important obstacle for effectively examining this issue in clinical and preclinical settings.

The lack of animal studies examining the moderating effects of sex on consequences of early life adversity is particularly regretful given the many parallel outcomes reported in animals exposed to early life stress and the ability to standardize variables that are difficult to control in clinical settings. Moreover, recent advances in imaging of small rodents has allowed researchers to more directly compare findings from preclinical studies to clinical findings. This creates a unique opportunity to fine-tune preclinical models to better understand the mechanisms underlying outcomes in humans exposed to early adversity, reviewed in (White and Kaffman, 2019).

Recommendations for moving forward

The first recommendation is to replace the *unisex assumption* with an attempt to clarify how sex moderates the effects of CM on neurodevelopment, psychiatric consequences, and treatment outcomes. Such effort should recognize that similar presentation does not necessarily mean similar mechanism, and the interaction between CM and sex is likely to be complex and circuit specific.

Second, we advocate for the implementation of a uniformly accepted scale to assess CM across all funded studies and publications. Such a scale should be guided by the threat/deprivation conceptual model to better map the complexity and heterogeneity of the CM experiences (White and Kaffman, 2019, McLaughlin and Sheridan, 2016). This is not a call for the elimination of all other scales, but rather an effort to include one common scale that will allow for better comparisons between studies and help conduct meaningful meta-analyses.

Third, future research should capitalize on the best emerging models of the multivariate structure of CM-induced psychopathologies in order to capture the complexities associated with the potential comorbidities in either sex, such as p-factor modelling or network approaches (Caspi et al., 2014, Bringmann et al., 2013).

Fourth, additional studies using objective outcomes, i.e., imaging, neurocognitive testing, and peripheral markers would provide important details about how different types of CM alter specific circuits in males and females. Such studies should preregister sex as an explicit variable in their hypothesis and be adequately powered to resolve important discrepancies described above.

Fifth, preclinical work in rodents and non-human primates, which to date has focused mainly on outcomes in males, should drive much of this effort by examining neurodevelopmental and behavioral outcomes in both males and females (White and Kaffman, 2019). Such studies should also consider the deprivation/threat as a conceptual model and utilize human imaging modalities such as resting state MRI and high-resolution diffusion MRI. These imaging tools provide a particularly promising area of translational research and when coupled with optogenetic and molecular tools can rigorously clarify how these structural and functional changes alter complex behavior in males and females.

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