When mothering goes awry: Challenges and opportunities for utilizing evidence across rodent, nonhuman primate and human studies to better define the biological consequences of negative early caregiving☆

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A B S T R A C T

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Across mammalian species, mothers shape socio-emotional development and serve as essential external regulators of infant physiology, brain development, behavior patterns, and emotional regulation. Caregiving quality, consistency and predictability shape the infant's underlying neurobiological processes. Although the requirements for "optimal" caregiving differ across species, the negative long-term consequences of the absence of needed caregiving (e.g. neglect) or the presence of harmful/aversive caregiving (e.g. physical abuse), are translatable across species. Recognizing the significant potential of cross species comparisons in terms of defining underlying mechanisms, effective translation requires consideration of the evolutionary, ecological, and fundamental biological and developmental differences between and among species. This review provides both an overview of several success stories of cross-species translations in relation to negative caregiving and a template for future studies seeking to most effectively define the underlying biological processes and advance research dedicated to mitigating the lasting negative health consequences of child maltreatment.

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Introduction

Across mammalian species, mothers shape socio-emotional development, serving as essential external regulators of infant physiology, neurodevelopment, behavior, and emotion regulation. This theory, initially proposed by Myron Hofer, has since been substantiated by a multitude of studies across a range of different mammalian species (e.g. (Hofer, 1984; Howell and Sanchez, 2011; Kuhn et al., 1991; Raineki et al., 2014; Rincon-Cortes and Sullivan, 2014). Extending from this foundational theory, variations in caregiving quality and consistency, particularly extreme deviations from the unique species typical pattern of caregiving early in life, further shape an infant's underlying neurobiological processes, leading to life-long alterations. Despite the wide variability of what comprises "optimal" or typical caregiving, even within closely related species such as the Great Apes, negative caregiving, defined in this review as the absence of needed caregiving (e.g. neglect, beyond separation consistent with species typical experiences) or the presence of harmful/aversive caregiving (e.g. physical abuse beyond

species typical exposures), is consistently linked to lasting negative neurobiological effects.

Animal models, both rodent and nonhuman primate (NHP), have been critical in delineating the persistent effects and biological mechanisms underlying early negative caregiving induced developmental psychopathology in humans. Further advances in maltreatment research now require an enhanced trans-disciplinary perspective that acknowledges both the similarities in maternal regulation of infant developmental processes across species as well as the species-specific methodological, ethological, and developmental limitations. By keeping these in mind, studies can better integrate innovative research designs that more accurately reflect negative and positive caregiving experiences in a species-specific manner. Utilization of this approach is expected to result in greater clarification of the underlying molecular pathways and neurobiological mechanisms.

In this review, we first outline potential challenges facing cross-species comparisons. Next, we showcase examples of "success" stories of translational research related to several distinct biological systems: (1) stress neuroendocrine systems, focusing predominantly on the Hypothalamic-Pituitary-Adrenal Axis (HPA), (2) neurodevelopment, focusing on the prefrontal-limbic system, and (3) epigenetic modifications, focusing on methylation. These systems were selected given the preponderance of existing data across species, established links to

negative caregiving and associated developmental psychopathology, and burgeoning data suggesting interactive pathways between them. Examples are provided in an effort to be representative, but not exhaustive. In the near future greater integration of cross-species data related to other systems, particularly the immune and autonomic nervous systems, will likely provide novel additional insight into the lasting impact of early negative caregiving beyond the systems presented here. Given the significant variation in the characterization of early life adversity across species, we further limit this review to data obtained from studies focused on physical abuse or neglect paradigms. Despite this restrictive approach, it is notable that these paradigms range from total maternal separation found in rodent models, peer reared nonhuman primate models, and human early institutional rearing, to models of both naturally occurring and environmentally induced physical abuse in rodent and nonhuman primates. Although the downstream impacts of negative caregiving may differ as a result of abuse compared to neglect, there remains substantial value to synthesizing data from various models.

We conclude by outlining critical considerations for future cross-species studies and presenting immediately addressable design challenges while highlighting the value of existing studies. Abusive caregiving, or absence of adequate caregiving (neglect), are substantial adverse infant experiences with enduring effects across biological systems and species. Translational studies across species, while methodologically complex, are needed to both identify novel targets for intervention and provide a neuro-biologically informed platform upon which to drive public health and policy change focused on mitigating the lasting impact of child maltreatment.

Conceptual and definitional challenges for cross-species comparisons

Exposure of children to neglect, physical, and emotional abuse remains a persistent and cross-cultural experience. In the United States rates of documented child maltreatment range between 8 and 11%, although determination of baseline prevalence rates remains difficult (Fallon et al., 2010). The first years of life represents a time-period of increased risk of exposure to maltreatment. This is particularly concerning given this period also represents a time when a vast array of neurodevelopment is occurring. Overall boys and girls are exposed equally to maltreatment, with the exception of sexual abuse where girls are at greater risk. Child maltreatment cuts across racial, ethnic and socioeconomic lines. Even within NHP, maltreatment is evident across all social hierarchy strata (from higher ranking animals — socially dominant, to the lowest social ranks — subordinate animals). In addition, maltreatment appears to span generations, with increased familial risk and family clustering that is replicated in rodent and NHP cross-fostering studies (Francis et al., 1999; Roth et al., 2009; Sanchez et al., 2010b). While hinting at underlying molecular and epigenetic pathways, these findings also suggest that failure to effectively intervene in the current generation may have consequences for subsequent generations. Beyond elevated risk for psychological disorders, increased risk of other biological and negative health outcomes are reported in children exposed to maltreatment, implying that multiple biological pathways are impacted (Hemmingsson et al., 2014; Nikulina and Widom, 2014; Rich-Edwards et al., 2012; Teicher et al., 2003; Widom et al., 2012). To date the molecular and neurobiological pathways leading to these negative effects, and the efficacy of interventions at alleviating biological risk, not just psychological symptom reduction, remains limited. Bridging this mechanistic gap requires effective integration of data from naturalist human studies with controlled preclinical data from animal models.

Overall definitional challenges

As a first step toward more informative cross-species comparisons, challenges, some modifiable and others that will remain important caveats, need to be recognized. One primary consideration centers on the clarification of the type of negative caregiving experienced (e.g. abuse

compared to neglect; emotional compared to physical; exposure to multiple types of abuse) and utilization of animal model systems that most effectively mirror the "human" experience. The root of this conceptual challenge arises from within the human literature. The terms childhood adversity, child maltreatment, early life stress, and toxic stress are used interchangeably, referring to a broad range of experiences that include chronic stress, traumatic experiences, extreme poverty, neglect, and physical and emotional maltreatment. Much of the current literature conceptualizes maltreatment from a chronic stress or allostatic load perspective (Cohen et al., 2013), often combining maltreatment exposures and failing to address other relevant confounders such as poverty, sex, race, and nutrition. This conceptualization of adversity, while an unfortunately accurate reflection of the human experience, limits the ability to translate findings across species as the majority of animal models focus on specific types of maltreatment, controlling the broader context in which maltreatment occurs such as nutrition, warmth, and housing. Although human studies have limited ability to control other contextual factors, analytic approaches, such as stratification of victims of physical abuse based on nutritional status, are feasible, albeit requiring larger sample sizes. An alternative approach would be to specifically create variation in these factors within animal models. For example creating a maternal separation paradigm that integrated specified variation in bedding and food. These integrative study designs are more consistent with human maltreatment and both approaches are likely to result in more translational and ecologically valid models.

Defining the type of negative caregiving

In human research maltreatment exposure is often classified as categorical. For example, studies have defined maltreatment as physical, sexual, or emotional abuse, and/or physical/emotional neglect. In addition to these categories, a substantial body of literature has focused on the neurobiological impact of extreme psychosocial neglect as a result of early institutional care, which may be distinctly different from neglect in other settings (Sheridan et al., 2010). Natural variation, as well as inducible extremes of caregiving that potentially map onto these categories, exist in both rodent and NHP species. For example, natural variations in maternal behaviors such as pup licking and grooming in rodents suggest that dams in the extreme low end of the normal distribution exhibit caregiving reflective of physical neglect in humans. In addition to studies of natural variation in caregiving, a multitude of experimental manipulations of caregiving exist in different rodent species which range from maternal restraint, variable handling and separation paradigms, to other approaches of stressing mothers to produce aberrant caregiving (i.e. reduced bedding). At the extreme end of the experimental continuum, Fleming and colleagues utilized an artificial rearing paradigm, which involves complete removal of the pup from mother and littermates from postnatal day (PND) 3 until weaning (Gonzalez et al., 2001). This particular experimental approach may be most reflective of extreme neglect and care found in institutional settings (Brett et al., 2015). As an example of more "active" negative caregiving paradigms, Sullivan and colleagues developed a rodent model of aversive caregiving within an attachment-learning paradigm (see Perry & Sullivan, 2014; Rincon-Cortes and Sullivan, 2014 for reviews). This model involves limiting bedding/nesting to the dam (PND 1-7, 3–8, or 8–12) which results in rough handling of pups, trampling and decreased bouts of nursing, mimicking the inconsistent and unpredictable characteristics of abusive human mothers (Raineki et al., 2012, 2010).

Although rodent models have significant utility for maltreatment research, NHP models may better address some questions given the closer evolutionary relation with humans and the greater similarity in terms of expected caregiving experiences (e.g. single offspring) and developmental timing. Infant maltreatment has been documented in both wild and captive populations of NHP species (Brent and Koban, 2002; Johnson et al., 1996; Maestripieri, 1998; Maestripieri and Carroll, 1998). In macaques, often during the first three months postpartum,