

Nonhuman Primate Models of Neuropsychiatric Disorders: Influences of Early Rearing, Genetics, and Epigenetics

Amanda M. Dettmer and Stephen J. Suomi

Abstract

This report reviews the scientific literature from the past several decades that focuses on nonhuman primates (NHPs) as models of neuropsychiatric disorders, including anxiety, and alcoholism. In particular, we highlight the approaches, advantages, and disadvantages of the rearing, genetic, and epigenetic methodologies behind these studies as a means of evaluating the application of these methods in assessing disorders in NHPs as models of human disease. Finally, we describe the contributions the NHP studies have made to neuropsychiatric research and areas for future research.

Key Words: early life adversity; epigenetics; genetics; neuropsychiatric disorders; nonhuman primate; rhesus macaque

Introduction

Nonhuman primates (NHPs), particularly *Macaca* species, have been utilized as models for neuropsychiatric disorders since the mid-20th century. Macaques, in particular rhesus monkeys (*Macaca mulatta*), serve as valuable models for human disorders owing to their genetic, physiologic, neuroanatomic, and behavioral similarity to humans (Gibbs et al. 2007). In addition, after humans, rhesus monkeys are the most widely distributed primates on earth (Southwick et al. 1996). From Harlow's first investigations in the 1960s into behavioral pathologies resulting from maternal deprivation (Arling and Harlow 1967; Harlow 1960; Harlow and Harlow 1961) to studies in the 1990s and 2000s of neurohormones underlying these and other disorders (Barr et al. 2003; Barr, Newman, Shannon et al. 2004; Higley et al. 1992; Higley, Haseert et al. 1991; Winslow

et al. 2003) to very recent studies examining genetic and epigenetic influences on the incidence of neuropsychiatric-like disorders (Higham et al. 2011; Provencal et al. 2012), macaque studies have contributed significantly to our understanding of similar disorders in humans. Despite the clear advantages of utilizing the macaque model for human neuropsychiatric disorders, limitations exist and persist in the methodologies and interpretations of such studies. This report highlights the strengths and limitations of the early rearing, genetic, and epigenetic methodologies of macaque neuropsychiatric studies and ends by describing the findings of the past 10 to 15 years that have advanced our knowledge of the underlying mechanisms of neuropsychiatric disorders in humans. In particular, we focus on such NHP studies examining anxiety, impulsive aggression/antisocial behavior, and alcoholism.

NHP Models of Neuropsychiatric Disorders: Assessment of Methodology

Characterizing Neuropsychiatric Disorders in NHPs: Influences of Early Life History

The majority of studies utilizing NHPs as models of neuropsychiatric disorders have relied on young monkeys exposed to early life adversity in the form of experimental rearing conditions, though in recent years more studies have emerged with normally reared monkeys. The rationale for these studies is the strength of attachment that both human and NHP infants form with their mothers or caregivers, a bond that becomes dysfunctional in response to early insult. This section briefly describes the behavioral methodologies of these studies by providing their historical development and applicability to humans.

Anxiety and Behavioral Inhibition

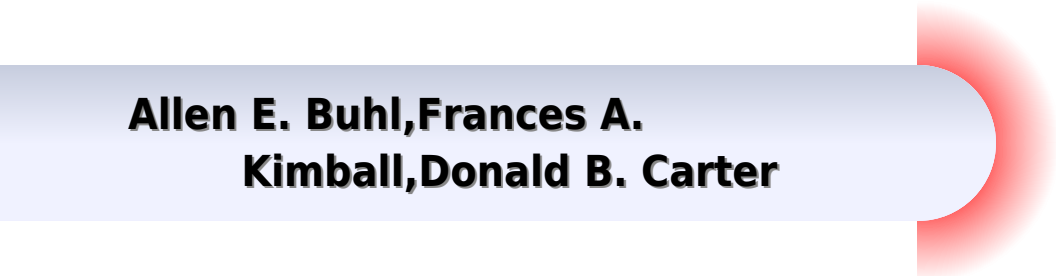
Studies examining anxious behavior and depressive symptoms in rhesus monkeys have historically relied on behavioral assessments that examine monkeys' reactions to social separations and reunions, social status manipulations, and novel objects or intruders and monkeys' behaviors in an undisturbed social setting. Though several studies have established that adult monkeys, such as cynomolgus macaques (*Macaca*

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