

An Introduction to the Female Macaque Model of Social Subordination Stress

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Chronic stress is a causal and sustaining factor in a number of adverse health outcomes in humans (Beckie 2012), including cardiovascular disease and stroke, psychiatric problems, addiction, abnormal adolescent development, accelerated cognitive decline, eating disorders, immune system compromise, and infertility. Importantly, these stress-induced disorders are often comorbid. In human populations, the stressors can take many forms ranging from traumatic physical or psychosocial events; caregiver stress; loss of social partners; low socioeconomic status; or everyday family or work hassles. In general, the specific parameters of the stress response to these experiences can vary depending on whether the stressor exposure is acute, recurring, or acute imposed on the background of chronic stress. Acute stressors engage cortico-limbic circuits and activate sympathetic, immune, and limbic–hypothalamic–pituitary–adrenal (LHPA) pathways which orchestrate a coordinated sequence of responses, universally used to define “stress,” that function to deal with the challenge and restore homeostasis (Schulkin et al. 1994; Herman et al. 2003; Choi et al. 2008; Jankord and Herman 2008; Ulrich-Lai and Herman 2009; McEwen and Wingfield 2010). With repeated exposure to familiar stressors, individuals adapt and do not continue to exhibit exaggerated stress hormone or behavioral responses (Bhatnagar and Dallman 1998; Bhatnagar et al. 1998, 2006; Bhatnagar and Vining 2003; Armario 2006; Jaferi and Bhatnagar 2006). However, in the face of recurring novel, uncontrollable, and unpredictable stressors, a dysregulation of central and peripheral circuits regulating the stress response occurs (Koolhaas et al. 2011; Herman 2013), often expressed as the development of tissue-specific glucocorticoid resistance (Avitsur et al. 2001), emergence of a proinflammatory condition (Silverman and Sternberg 2012), exacerbated glucocorticoid responses to novel stressors (Dallman et al. 1992), and increased central

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signaling of corticotropin-releasing factor (CRF) (Bale 2005) and arginine vasopressin (AVP) (Lightman 2008). These signals may act independently or synergistically to mediate the pathophysiology of stress-induced disorders.

1 Rodent Models of Stressor Exposure

A number of animal models have been developed to examine how chronic stressor exposure, designed to mimic the adverse events experienced by human populations, induces and sustains pathophysiological changes that resemble stress-induced disorders in people (Anisman and Matheson 2005; Tamashiro et al. 2005; Huhman 2006; Toth and Neumann 2013). Acute and/or chronic exposure to physical stressors such as restraint, foot shock, or cold are well-established approaches that have been used to determine stress neurobiology and development of stress-related disorders (Jaggi et al. 2011). However, physical and psychosocial stressors produce differences in the pattern and time course of behavioral neurobiological responses, circulating corticosterone, and plasticity-related gene expression (Kavushansky et al. 2009; Herman 2013), and much of the stress human beings experience is social in nature. The chronic variable stress paradigm (Herman et al. 1995) exposes rats to 6 weeks of different mild stressors, including physical stressors and social isolation. This paradigm produces animals that show increased corticosterone levels and a range of other phenotypes including altered fear learning, anhedonia, and dysfunction in cortico-limbic–brain stem circuits that are informative for modeling stress-induced disorders in people (Dalla et al. 2005; Flak et al. 2009, 2012; McGuire et al. 2010; Solomon et al. 2011).

Other rodent models employ a social stressor as the central component. In order to understand the possible consequences of early-life stress, rodent models impose separation of the dam from her litter at specific postnatal time points (Nishi et al. 2014; Marco et al. 2015). The stressors for the pups are more than just the social isolation and inability to nurse but also include removal of maternal behaviors known to be important for pup neurobehavioral development (Buwalda et al. 2011). A widely used model of social stressor exposure in adult rodents is the social defeat paradigm, in which an animal receives daily exposure to a more aggressive intruder for a defined number of days but is housed away from the intruder (Huhman 2006). The experience produces sustained activation of the LHPA axis and specific changes in neurochemical circuits within mesolimbic regions in both male and female rodents (Huhman 2006; Razzoli et al. 2009). Indeed, the submissive behavior persists in a subset of males for up to a month (Huhman et al. 2003), whereas response to defeat is diminished in females. Repeated exposure to social defeat produces neurobiological changes in cortico-striatal–cortico-limbic circuits that produce a number of stress-related phenotypes including depressive-like behavior (Hollis and Kabbaj 2014), susceptibility to psychostimulant self-administration (Yap and Miczek 2007), and social fear and anxiety (Toth et al. 2013).

A modification of the social defeat paradigm is the social subordination model, which has taken two forms in rodent studies. In the social subordination paradigm, a target male is exposed briefly (~ 5 min) to a more aggressive intruder for a fixed number of days. The target male is housed with the more aggressive resident continually for several weeks, but in protective housing, such behavioral encounters do not occur outside of the daily brief exposures. This paradigm, although not widely used, produces a phenotype different than that of repeated social defeat. For example, rats experiencing social subordination stress show a reduction of BDNF in the ventral tegmental area, reduced extracellular dopamine in the nucleus accumbens, and an anhedonia-like response to cocaine compared with intermittent socially defeated rats, reflecting a different neurobiological responses to the two different social experiences (Miczek et al. 2011).

The visible burrow system is an expansion of the pair-housing in the social subordination model. In this paradigm, groups of male rats are housed socially with several females for two weeks. Males quickly form a dominance hierarchy, and subordinate males exhibit a number of changes characteristic of chronic stress, including neurobiological changes in limbic circuits as well as reproductive and metabolic deficits (Blanchard et al. 1993, 1995; Hardy et al. 2002; Tamashiro et al. 2004; Choi et al. 2006). In addition, this model has several notable features. First, animals are given intermittent recovery periods from social housing during which previously subordinate males respond differently than dominant males, most typically with excess food intake and weight gain (Tamashiro et al. 2004). However, the subordinate phenotype is maintained with re-exposure to the social housing (Lucas et al. 2004; Tamashiro et al. 2007). Secondly, a subgroup of subordinate males is classified as nonresponders, showing a diminished response in corticosterone to an acute restraint during the social housing period (Watanabe et al. 1995; Lucas et al. 2004), a profile analogous to the attenuated stress hormone activity described for post-traumatic stress disorder (Yehuda 2002; Meewisse et al. 2007). Importantly, despite this reduced glucocorticoid response, these males show more altered dopaminergic tone in mesolimbic regions than other subordinate or dominant animals (Lucas et al. 2004). However, because females of the strain of rats used do not form a hierarchy when housed socially, this particular paradigm cannot be used to evaluate adverse consequences of chronic social stress in females (Tamashiro et al. 2004). Nonetheless, because most animal species exhibit some form of a social hierarchy as a part of their social organization, studies of subordinate versus dominant group members are informative.

Together, these paradigms represent well-established approaches that have significantly advanced our understanding of how chronic exposure to social stressors produces lasting changes in behavior and physiology. Indeed, rodent studies are invaluable in that the minimal resources required for their execution permit carefully controlled longitudinal studies, resulting in a vast literature explaining these animals' physiology and behavior. Additionally, investigators can utilize these rodent models to employ genetic and molecular tools to define mechanisms. Specific paradigms are more appropriate for modeling certain stressful events in people. For example, the social defeat model reflects the type of circumscribed yet

traumatic series of events experienced by people that often lead to a post-traumatic stress disorder (PTSD). These paradigms employ a repeated uncontrollable or unpredictable type of stressor known to be a critical predisposing factor for a dysregulated stress response (Koolhaas et al. 2011). However, because the stressor is discontinued after a specific duration, these paradigms only partially model the continual daily exposure to stressors experienced by people and implicated in the development of stress-induced diseases. The social subordination paradigms used in rodents best model this type of experience in people. However, these too only approximate the allostatic load that reflects the accumulation of stress over time (McEwen 1998). We simply have a poor understanding of the duration of stress accumulation for the emergence of many stress-related phenotypes.

2 Macaque Social Subordination Model

The use of nonhuman primates provides a complementary model to study the impact of continual exposure to social stressors, imposed by social subordination in group-living animals, on a number of health-related phenotypes (Meyer and Hamel 2014; Phillips et al. 2014). Although the stressor is most typically social subordination (Sapolsky 2005), the effects of social separation from group mates (Watson et al. 1998; Lyons et al. 1999), longer-term social isolation (Shively et al. 1989), and intruder paradigms (Strawn et al. 1991) have also been evaluated. Often the consequences of these stressors are analyzed in the context of social status (Michopoulos et al. 2012b). Furthermore, a number of approaches have been used to evaluate the long-term consequence of early stress on neurobehavioral development including peer-rearing and imposing foraging demands (Worlein 2014), as well as comparing neglectful to more nurturing mothers (Howell et al. 2013b). Although diverse species of both captive (Levine et al. 1997; Abbott et al. 1998; French et al. 2007) and free-ranging primates (Sapolsky et al. 1997; Crockford et al. 2008; Gesquiere et al. 2011; Runcie et al. 2013) have served as models of social stressor exposure on a number of phenotypes, captive, provisioned groups of macaques, most notably rhesus (*Macaca mulatta*) and cynomolgus monkeys (*M. fascicularis*), have been more widely used given their prominent role in biobehavioral research.

In multimale and multifemale groups of rhesus and cynomolgus macaques, the social structure is a matrilineal-based dominance hierarchy with nonnatal adult males integrating into specific ranks through alliances with natal females (Sade 1967; Bernstein 1970). However, regardless of group size, this linear dominance hierarchy functions to maintain group stability, but ironically is enforced by more dominant animals aggressing their subordinate group mates (Bernstein and Gordon 1974; Bernstein 1976). While an animal's position within the hierarchy can be enforced through contact aggression, most often subordinate status is imposed by the threat of aggression or harassment (Bernstein and Gordon 1974; Bernstein 1976; Shively et al. 1986), which often appears random, not precipitated by any



Fig. 1 A dominant female rhesus monkey harassing a more subordinate female by slightly biting her lip

infraction of the rules by the subordinate, and is thus unpredictable (see Fig. 1) (Silk 2002). Subordinates attempt to forestall or terminate these interactions by emitting submissive behaviors, which is the defining feature of social subordination in macaque groups (Altmann 1962; Sade 1967). In addition to the frequent harassment, a consequence of subordinate status is reduced control of their social–physical environment and delayed access to resources (Bernstein 1970). Even in captive, provisioned groups where food is readily available, subordinates may be limited as to when they can feed and where they can locate within the housing structure.

Subordination in female rhesus and cynomolgus monkeys produces a phenotype similar to other animal models of social stressor exposure. Although studies are mixed whether subordinate females have higher morning cortisol concentrations (Sassenrath 1970; Gust et al. 1993; Shively et al. 1997b; Shively 1998a; Stavisky et al. 2001; Czoty et al. 2009; Michopoulos et al. 2012b), a consequence of continual harassment experienced by subordinate females is LHPA dysregulation, evidenced by reduced glucocorticoid negative feedback (Shively et al. 1997b; Wilson et al. 2005; Jarrell et al. 2008; Michopoulos et al. 2012b), consistent with data from other animal models of social subordination (Avitsur et al. 2001). This impaired negative feedback is associated with a decrease of glucocorticoid receptors in the hippocampus (Brooke et al. 1994) similar to that observed in rodents (Sapolsky et al. 1985). The increased glucocorticoid resistance shown by subordinate females is also associated with a proinflammatory condition (Tung et al. 2012). Furthermore, the adrenal response to ACTH is impaired, although whether

the response is reduced (Michopoulos et al. 2012b) or exacerbated (Shively et al. 1997b) may be dependent on the diet fed the animals and the amount of visceral obesity present (Shively et al. 2009a). Furthermore, subordinate females show greater heart rate variability, particularly in response to novel situations, indicative of greater sympathetic tone (Shively 1998b).

With respect to males, the data are less clear. Free-ranging male rhesus monkeys on Cayo Santiago show a rank-related gradient of fecal cortisol concentrations with lowest levels in the more dominant males (Higham et al. 2013). Data from captive all-male groups of cynomolgus monkeys show little evidence of impaired LHPA function by subordinates (Botchin et al. 1994) but rather as a consequence of continual changes in rank (Brooke et al. 1994; Capitanio et al. 1998). This pattern of response is perhaps understandable given a male macaque's life history of frequently emigrating to new groups.

Often, animals categorized as high social status are compared to those of low social status, an approach similar to the analysis of socioeconomic status effects in people (Marmot 2006). This convention has a long history, particularly in studies with captive groups (Gordon et al. 1978; Wilson et al. 1978; Kaplan et al. 1982; Shively and Clarkson 1988). The rationale for this approach is to primarily increase statistical power in the face of limited and expensive resources by comparing animals that receive little aggression and submit infrequently to those that receive proportionately more aggression and more frequently terminate these interactions by submitting. However, the question of a dose–effect relationship of subordination is an important one as it assumes that as subordination increases, so does the impairment of stress regulatory mechanisms and functional outcomes. While clearly this may not be the case universally, several data sets using this statistical approach suggest that indeed there is a rank gradient in impaired stress hormone regulation (Michopoulos et al. 2012b; Higham et al. 2013) and a resulting phenotype (Tung et al. 2012; Wilson et al. 2013). An alternative to using ordinal rank or status categories is the calculation of Elo-rating scores, in which higher scores correspond to higher status (Albers and de Vries 2001). The Elo method updates an animal's score after each dominance interaction. Importantly, ratings distinguish individuals that may be of similar ranks but are quite distinguishable based on the number of agonistic interactions. Using such measures as linear mixed models of specific rank effects, rather than analysis of categorical group differences of dominant versus subordinate animals in traditional ANOVA models, may provide a better resolution of subordination dosing effects. A related question is whether social subordination in group-living animals represents a model of low socioeconomic status in people (Cavigelli and Chaudhry 2012). While there are many similarities, including access to resources and degree of control over one's social environment, there are several differences. People must navigate many status hierarchies in their daily lives, while macaques navigate one. Again, using categories of social status or SES assumes the experience of being low ranked is similar, for which there is no basis. Analysis of rank–dose effects, whether using ordinal rank or Elo scores in macaques or amount of psychosocial trauma in people (Levine et al. 2015), holds the promise of providing better resolution to stress-induced outcomes.

Social subordination in female macaques results in a number of phenotypes that resemble stress-induced disorders in people and other animal models (Michopoulos et al. 2012a). Several of these phenotypes will be presented in this volume, highlighting the utility and translational value of using macaque models to elucidate the adverse effects of psychosocial stress on a range of health-related conditions for men and women. The studies show that social subordination increases indices of cardiovascular disease (Williams et al. 1994; Kaplan et al. 1996); psychostimulant abuse self-administration (Morgan et al. 2002); reproductive compromise (Adams et al. 1985; Pope et al. 1986; Michopoulos et al. 2009; Kaplan et al. 2010); immune dysfunction (Gust et al. 1991; Paiardini et al. 2009; Tung et al. 2012) and a greater risk of infection (Cohen et al. 1997); disordered eating (Michopoulos et al. 2012c; Johnson et al. 2013); visceral obesity (Shively et al. 2009b); and depressive-like behavior (Shively and Willard 2011). Because macaques show a protracted period of adolescent development similar to that of children, the impact of social status on neurobehavioral development can also be examined (Howell et al. 2013a; Wilson et al. 2013). Despite the value of using this model for these targeted problems, the subordinate phenotype remains incompletely defined across a number of behavioral and physiological parameters particularly with respect to understanding how a gradient of social subordination predicts increasingly poorer health outcomes.

It should be emphasized that a subordinate phenotype does not necessarily represent a pathological condition but rather represents how a social stressor produces health outcomes that model human disease and/or disorders. Given that dominance hierarchies have evolved in virtually all gregarious animal species, including humans, it seems likely that subordinate characteristics represent adaptations that enable individuals to navigate their social environments and to cope with social challenges. For example, neuroimaging studies reveal differences in binding potential across a number of monoaminergic receptor subtypes (Shively et al. 1997a, 2006; Grant et al. 1998; Michopoulos et al. 2014) as well as developmental differences in white matter integrity (Howell et al. 2014), which may mimic particular stress-induced outcomes in humans or other species. Furthermore, there is evidence of structural effects on gray matter density (e.g., reduced in PFC, superior temporal sulcus (STS), and amygdala) measured by MRI in subordinate adult male rhesus monkeys (Sallet et al. 2011). Recent studies using resting state functional MRI reveal social status-dependent brain circuits involving some of these same regions such as the PFC and STS as well as a circuit that included the amygdala, brain stem, and portions of the striatum (Noonan et al. 2014). Together, these data suggest that the experience of being subordinate produces these differences in brain structure and function that in turn result in behavioral or physiological differences that may function to facilitate attending to cues to successfully navigate the social environment and minimize the risk of aggression from more dominant animals (Silk 2002). These speculations are consistent with the findings of increased white matter tracts in ventromedial PFC of squirrel monkeys exposed to early-life stress, an observation that was interpreted as “adaptive,” preparing the individual to cope with challenges in their environment (Katz et al. 2009). Thus, different positions in the social hierarchy likely lead to different strategies for

animals in dealing with threatening or uncertain situations. Indeed, emerging studies of human beings suggest that indicators of socioeconomic status are related to patterns of brain neurotransmission, brain morphology, and brain functionality which in turn are implicated in disease etiology (Gianaros and Manuck 2010). Such observations underscore the value of nonhuman primate studies of social neurobiology. A question that arises is how the experience of being subordinate is mitigated by social support or buffering (Abbott et al. 2003). This may be particularly important for animals embedded in their natal groups where kin relationships are strong. On the other hand, the consequences of subordination may be exacerbated in small, experimentally created group in which no preexisting alliances exist. The behaviors and their associated biological signals that lessen the impact of social status are not understood.

There are several unique features that differentiate this model from more typical laboratory animal paradigms. The dominance hierarchy is defined by matrilineal relations and is thus female-based (Bernstein 1970), providing an important opportunity to study stress-induced disorders in females which is not always possible in rodent models. Secondly, because infants assume the rank of their mothers, it is possible to study the impact continuous stressor exposure on neurobehavioral development (Zehr et al. 2005; Wilson et al. 2013; Howell et al. 2014). In addition, while studies can be done on large breeding groups of macaques in free-ranging (Hoffman et al. 2010; Parker et al. 2010; Brent et al. 2011) or captive environments (Walker et al. 1984; Wilson et al. 1986; McCowan et al. 2011; Rommек et al. 2011), small groups can be safely formed with unfamiliar females (Kaplan et al. 1984; Mook et al. 2004) or males (Kaplan et al. 1982), even balancing group composition by previous social history and specific gene polymorphisms (Jarrell et al. 2008). Furthermore, this strategy allows for groups to be rearranged to assess the acute social instability (Manuck et al. 1983; Capitanio and Cole 2015) or the lasting effects of acquiring a new rank (Shively and Clarkson 1994; Shively et al. 1997b). Finally, given the phylogenetic closeness of Old World monkeys to humans compared to nonprimate mammals, brain regions, such as the prefrontal cortex (PFC), that govern executive control over emotional behavior and stress responsivity (McEwen and Morrison 2013) show considerable structural similarity between macaques and humans (Kolb 1984; Reep 1984; Preuss 1995; Van Eden and Buijs 2000; Heidbreder and Groenewegen 2003; Petrides et al. 2012; Yeterian et al. 2012).

In summary, the application of macaque models of social subordination can complement studies of stress-induced disorders in people. The unique advantage of such models, however, is the opportunities to perform prospective studies to determine how stress-induced outcomes emerge by the imposition of social subordination through the creation of new groups or rearranging previously established ranks. Relatedly, the model also provides the opportunity to disentangle the effects of the prenatal, in utero environment and the genetic contribution of the mother from the postnatal experience through cross-fostering. Using pedigreed populations of macaques, it is feasible to determine the heritable contribution of traits linked to

(e.g., aggressiveness) or the consequence of (e.g., cortisol) social status. The goal was to use these valuable models to understand the contribution of accumulating stress on health outcomes in people.

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