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Behavioral and dominance rank effects on the hypothalamic-pituitary-adrenal axis and immune system in adult female rhesus macaques

By

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B.A., Reed College, 2009

Biology

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An abstract submitted to the Faculty of the

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Abstract

Behavioral and dominance rank effects on the hypothalamic-pituitary-adrenal axis and immune system in adult female rhesus macaques

By Jordan N. Kohn

In many mammals, including humans, social groups are organized into dominance hierarchies in which an individual's position in the hierarchy determines stress exposure and has important implications for health and mortality risk. Alterations in the hypothalamic-pituitary-adrenal (HPA) axis and the immune system are frequently observed in chronically stressed individuals and have been implicated in the pathophysiology of a number of psychiatric and somatic illnesses, including depression and cardiovascular disease. Importantly, an individual's behavior can modify the effects of chronic stress on physiology, thus serving as a protective or vulnerability factor in the development of stress-associated illness. However, establishing causal links between the social environment and physiological outcomes is challenging in studies with human populations. In this dissertation, we suggest that dominance rank and social behavior interact to affect HPA axis regulation in adult female rhesus macaques, and that rank alters the immune system's response to stress challenge. Through a series of longitudinal experiments, we demonstrate that glucocorticoid sensitivity and negative feedback are diminished by low dominance rank, and that animals with certain behavioral phenotypes may be more sensitive to these effects. Furthermore, we show that low rank is associated with decreased immune cell sensitivity to glucocorticoids and downregulation of genes involved in immune cell adhesion. This dissertation provides evidence that social dominance rank has causal but plastic effects on neuroendocrine and immune system parameters and provides insight into the biological mechanisms by which chronic stress is associated with psychiatric and somatic diseases.

The effects of behavior and dominance rank on the stress system and immune function in adult female rhesus macaques

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Chapter 1: Introduction

In 1984, the largest ever prospective study of social health gradients reported that employment status was directly related to physical health: individuals at the lowest employment tier (manual laborers) were at three times the risk of death relative to those at the top (administrators) (Marmot et al., 1984). Since the Whitehall study, the links between adverse social experience and disease have become increasingly clear. Epidemiological studies indicate that prolonged exposure to social adversity, such as low socioeconomic status (SES) (Loucks et al., 2009), can predispose individuals to certain illnesses throughout the lifespan, including depression (Slavich and Irwin, 2014), atherosclerosis (Glozier et al., 2013), diabetes (Heraclides et al., 2012), metabolic syndrome (Tamashiro et al., 2011), and autoimmune disease (Kemeny and Schedlowski, 2007). In particular, two biological processes involved in the stress response, 1) glucocorticoid signaling by the hypothalamic-pituitary-adrenal (HPA) axis, and 2) inflammatory signaling by the immune system, are modified by prolonged social adversity and may serve as risk factors for disease or mechanisms of pathogenesis (McEwen, 2012; Miller et al., 2007). Cross-sectional and experimental studies in humans have laid the foundation to investigate these biological mechanisms, though many questions remain unanswered due to the inherent limitations of conducting human research and the complexity of human social experience, which is difficult to recapitulate in most animal models. To that end, nonhuman primate models serve an important role in understanding the linkages between social factors and health (Phillips et al., 2014). The goal of this dissertation is to examine the hypothesis that social status (i.e., dominance rank) alters social behavior, HPA axis regulation, and immune cell sensitivity to glucocorticoids in female rhesus macaques. The studies herein provide evidence that social adversity, or low dominance rank in our rhesus macaque model, causally induces a socially isolated, passive behavioral phenotype, impaired glucocorticoid negative feedback by the HPA axis, decreased immune cell sensitivity to glucocorticoids, and downregulation of genes involved in immune cell adhesion.

This introduction provides a comprehensive review of the literature supporting the hypothesis that prolonged exposure to adverse social conditions (i.e., chronic psychosocial stress) is associated

with altered neuroendocrine and immune function in humans and nonhuman primates. We begin by introducing the concepts of stress, the stress response, and chronic psychosocial stress, including their roles in the increasing prevalence of certain diseases among Western societies. We follow with a brief overview of neuroendocrine and immune responses to acute stressors, their interactions, and behavioral moderators of those responses. We then discuss the physiological adaptations that occur within both the neuroendocrine and immune systems in chronically stressed humans, as well as findings from translational nonhuman primate models of chronic psychosocial stress, specifically those involving dominance rank and social instability. Finally, we highlight persistent gaps in our understanding of how chronic stress alters the HPA axis and immune system, and offer a rationale for the experimental work in this dissertation.

For the purposes of this introduction, the following definitions will be used. Stress is a state of perceived or actual threat to an organism's homeostasis, and stressors are stimuli that disrupt that homeostatic state. Stressors can be either physical or psychological in nature, typically occur as discrete events, but can also be prolonged and consistent challenges to homeostasis. Regardless of their source, stressors evoke stress responses, which involve the activation of a number of dynamic, integrative processes in order to restore homeostatic setpoints (Chrousos and Gold, 1992; Chrousos et al., 1988) and to prepare the organism for subsequent challenge. Peripheral effector molecules released during the stress response, particularly glucocorticoids secreted from the adrenal cortex and catecholamines released by sympathetic nervous system activation, feedback upon and regulate ongoing processes within the central nervous system, thus creating bidirectional links between the body and brain. Although the stress response is essential for survival, homeostatic setpoints can be perturbed if stressors of excessive frequency, duration, and intensity are experienced, often with profound consequences for organismal health and survival.

1.1. Chronic psychosocial stress is frequently associated with psychiatric and somatic illness

Psychosocial stressors are social stimuli that evoke a physiological stress response. In humans and other social mammals, psychosocial stressors typically involve threats to an individual's social image or standing, sometimes referred to as the "social self" (Dickerson et al., 2004). Among most social mammals, physical (e.g., food, shelter, water) and social resources (e.g., peers, affiliation) tend to be distributed according to social standing, with higher status individuals receiving a larger or higher quality allocation (de Waal, 1986). Thus, survival and reproductive success of the individual depend upon inclusion within a social group inclusion and positive status within it. It follows that situations perceived as potential challenges to social status tend to elicit powerful physiological stress responses in social mammals (Gruenewald et al., 2004). In humans, psychosocial stressors range in intensity and duration, from brief social evaluative threat during public speaking (Kirschbaum et al., 1993) to decades of isolation from one's social network (Cacioppo et al., 2014). Interestingly, there is considerable overlap between the neural substrates involved in processing experiences of physical pain and those of social disconnection (Eisenberger, 2012). Furthermore, positive social information activates key reward areas in humans and nonhuman primates (Chang et al., 2013), such as the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and nucleus accumbens, illustrating the evolutionary significance of maintaining our social inclusion.

An individual's interpretation of social situations as threatening or non-threatening depends upon perception, which is shaped by one's social history, early-life experiences, genetic background, and pre-natal stressor exposure, among many other factors. Psychosocial stressors can therefore be viewed as a product of cognitive appraisals and emotional responses (Lazarus, 1966), the outcome of which determines the intensity and magnitude of the physiological stress response. For example, individuals with more positive emotional affect exhibit more rapid cardiovascular

recovery following a standardized laboratory stressor, and smaller increases in fibrinogen, an acute-phase biomarker of immune activation (Dockray and Steptoe, 2010). Conversely, individuals with neurotic tendencies are more threat-sensitive and exhibit more cardiovascular reactivity, a marker of sympathetic nervous system activation, in response to social challenge (Schneider, 2004). In fact, a meta-analysis of 729 studies of experimental cognitive challenges and public speaking stressors, found that positive psychological traits were associated with decreased HPA axis reactivity, while hostility and aggressive traits were associated with increased cardiovascular reactivity (Chida and Hamer, 2008), suggesting that physiological responses to social stressors are moderated by individual differences in cognitive and emotional processing (McEwen and Stellar, 1993).

As highly social mammals, humans frequently experience social challenges of sufficient intensity, duration, and novelty to initiate a stress response. Acute activation of the stress response enhances survival in the face of challenge via behavioral adaptations, including increased vigilance, analgesia, and cognition, and physiological changes, such as vasodilation, improved cardiovascular tone, and suppression of vegetative functions. However, repeated activation of the stress response and the release of stress effector molecules, particularly glucocorticoids and proinflammatory cytokines, can shift physiological systems outside of their optimal operating ranges (Romero et al., 2009), compromising their capacity to maintain normal baseline activity and adequately respond to future challenges. One conceptual framework, known as allostatic load, conceptualizes chronic psychosocial stress as a cumulative "wear and tear" on the body over a lifetime of repeated adaptations to life's demands (Seeman et al., 2010; McEwen and Stellar, 1993). Allostatic load considers the additive and interactive nature of these adaptations and the rate of load accumulation. In other words, the initiation and progression of biological changes (i.e., "load") are determined by individual factors such as one's history of stressor exposure, cognitive and emotional disposition, or social status (McEwen and Wingfield, 2003). Within this

framework, sufficient load leads to allostatic overload and pathology as biological systems establish new homeostatic setpoints with pathological consequences (Juster et al., 2010). For instance, glucocorticoids released during the stress response stimulate food-seeking behavior, which is adaptive if energetic demands are high (e.g., during exercise), but facilitates insulin resistance and visceral adipose deposition if energy intake continually exceeds demand, as in stress eating (La Fleur et al., 2004). The working hypothesis is then that chronically stressed humans accumulate allostatic load more quickly (Sabbah et al., 2008), and that similar allostatic processes occur in nonhuman primates (Howell and Sanchez, 2011). It is worth noting, however, that in some environmental contexts the physiologic states that result from chronic stress may serve adaptive functions (Boyce and Ellis, 2005; Del et al., 2011). Similarly, behavioral states associated with depression (which frequently follows from chronic stress), such as social withdrawal and hypervigilance, may support host defense in situations in which infection risk is high (Raison and Miller, 2012).

Regardless of the heuristic used to model how deleterious health effects result from chronic psychosocial stress exposure in social mammals, there is indisputable experimental and epidemiological evidence that unrelenting, uncontrollable psychosocial challenges are detrimental to health and survival in most contexts. Sources of chronic psychosocial stress most frequently studied include high levels of job stress (Chandola et al., 2010), fatigue and burnout, persistent social isolation (Eisenberger and Cole, 2012), caregiving (Jeckel et al., 2010), and low SES (Chen and Miller, 2013). Numerous clinical and laboratory studies have demonstrated increased rates of clinical depression (Kendler et al., 1999), greater likelihood of infection following antigen exposure (Cohen et al., 2012), reactivation of latent viruses and impaired wound healing (Godbout and Glaser, 2006), and attenuated responses to vaccination (Burns et al., 2003) in people experiencing chronic psychosocial stress. Chronic stress is also a significant predictor of all-cause mortality risk (Keller et al., 2012; Krueger and Chang, 2008). Despite developments in

westernized societies that have facilitated dramatic increases in longevity over the past century, such as improved nutrition, sanitation, vaccination, health care access, and contraception, the burden of chronic mental and physical illnesses continues to grow. As of 2005, thirty million Americans were living with mental illness, forty-seven percent had been diagnosed with at least 1 chronic disease, such as diabetes, cancer, or hypertension, and epidemiological trends indicated that the incidence of virtually every chronic illness will increase by 2023 (Bodenheimer et al., 2009). Furthermore, nearly one-quarter of Americans report extreme levels of stress, and 40% report year-to-year increases in stress compared to the previous year (Anderson et al., 2011). One explanation for this phenomenon is urbanization, specifically that the urban environment is inherently more stressful for humans than rural settings. Longitudinal studies suggest that urbanization has causal effects on mental illness (van Os et al., 2010), and meta-analyses show that city-dwellers suffer increased rates of anxiety and mood disorders (Peen et al., 2010). These effects are potentially mediated by social evaluative threat exposures, which occur far more frequently in urban environments and may explain positive associations between urbanicity and amygdala activation in response to social stressors (Lederbogen et al., 2011). Although many of these findings are correlational, they demonstrate the vital role of the social environment as a mediator of stress and chronic disease burden, and highlight the need for a deeper mechanistic understanding of the physiological and psychological links between stress and disease.

1.2. Neuroendocrine regulation of the stress response

In order to elucidate the links between chronic psychosocial stress and the development of mental and somatic illness, it is crucial to understand the neuroendocrine regulators of the stress response, specifically the HPA axis and the sympathetic branch of the autonomic nervous system. As its name implies, the hypothalamic-pituitary-adrenal axis consists of three tissues that play a vital role in regulating an organism's metabolic, reproductive, and immunological homeostasis.

Under basal conditions, secretion of steroid hormones by the adrenal cortex follows a diurnal pattern (Ota et al., 2012) and coordinates the function of multiple organs (Dickmeis, 2009). However, activation by an acute stressor initiates a series of top-down events as follows: 1) activation of cortico-limbic regions within the CNS, 2) integration of those signals by the hypothalamus and release of corticotrophin-releasing hormone (CRH) into the anterior pituitary, 3) secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary into the bloodstream, and 4) promotion of adrenocortical activity, which culminates in glucocorticoid synthesis and release into peripheral circulation. The second major pathway involved in the stress response is the sympathetic arm of the autonomic nervous system (i.e., SNS), which consists of a disynaptic neural circuit that sends projections to nearly every major organ of the body, including the heart, spleen, lymph nodes, and thymus. Although the SNS is not central to the experiments conducted as part of this dissertation, its strong effects on immune function and implication in stress-related illness necessitate its discussion. The SNS originates with brainstem neurons in the locus coeruleus (LC) that send cholinergic (ACh) preganglionic projections to sympathetic ganglia located in paravertebral chains beside the spinal cord. Postganglionic fibers project from there into target tissues and secrete norepinephrine (NE) upon activation (Hansen, 2014). Some presynaptic fibers also terminate in the adrenal medulla, wherein chromaffin cells release a mixture of epinephrine (80%) and NE (20%) into circulation upon stimulation (Vollmer, 1996). The SNS operates in dynamic balance with the parasympathetic nervous system (PNS), which innervates many of the same organs via a disynaptic circuit, but exerts opposing effects on target tissues. In addition to facilitating physiological processes that occur in the absence of stressors (e.g., digestion, heart rate reduction), the PNS is engaged following the acute stress response in order to constrain ongoing SNS activity (Ulrich-Lai and Herman, 2009).

Initiation of the stress response by social stimuli begins with activation of cortico-limbic circuits involved in memory, social appraisal, and emotionality, specifically the hippocampus, prefrontal

cortex (PFC), and amygdala (Smith and Vale, 2006). Neuronal projections from these limbic regions converge upon the paraventricular nucleus (PVN) of the hypothalamus and signal to parvocellular neurons to synthesize and secrete corticotropin-releasing hormone (CRH), a 41 amino acid peptide. Projections from the PVN reciprocally innervate LC neurons in the brainstem, forming a positive feedback loop between the HPA axis and SNS that facilitates co-activation of both systems in response to stressors (Chrousos and Gold, 1992; Kiss and Aguilera, 1992). As a primary integration center of the hypothalamus, the PVN receives afferent signals from an array of neurotransmitters and neuromodulators, including excitatory signals via serotonin (5-HT) (Calogero et al., 1990; Fuller, 1996, 1992), acetylcholine (Buckingham and Hodges, 1979), and neuropeptide Y (NPY) (Krysiak et al., 1999), and inhibitory signaling from γ-aminobutyric acid (GABA) (Bartanusz et al., 2004), endogenous opioids (Overton and Fisher, 1989), and glucocorticoids (GCs) (Keller-Wood, 1988; Keller-Wood and Dallman, 1984). Interestingly, changes in receptor expression by PVN neurons have been observed for many, if not all, of the aforementioned neurotransmitters in rodent models of stress (Herman et al., 2008). Structural and functional differences in the hippocampus, amygdala, and PFC are associated with HPA axis (Pruessner et al., 2010) and SNS activity (Ulrich-Lai and Herman, 2009), highlighting the importance of the CNS to the stress response.

Secretion of CRH out of the PVN occurs via hypophyseal portal vessels, which transport CRH to the anterior pituitary where it binds the G-protein coupled, corticotropin releasing hormone R1 receptor (CRHR1) expressed in pituitary corticotropes. Activation of CRHR1 by ligand stimulates adenyl cyclase and downstream activation of cyclic adenosine monophosphate (cAMP) pathways that facilitate adrenocorticotropic hormone (ACTH) release into the bloodstream. ACTH targets melanocortin 2 receptors (MC2R) located in parenchymal cells of the adrenal cortex, inducing cAMP-dependent events that upregulate cholesterol uptake (the substrate for steroid hormone synthesis) and promote steroidogenesis (Chung et al., 1997; Hu et al., 2001; Liu

and Simpson, 1997), culminating in glucocorticoid biosynthesis. Glucocorticoids (cortisol in humans and nonhuman primates, corticosterone in rodents) are synthesized *de novo* and secreted into circulation as end products of HPA axis activation. Glucocorticoids act primarily upon cytosolic glucocorticoid receptors (GR) that are widely distributed in the brain and throughout peripheral tissues. Because of its relatively low binding affinity for ligand, GR is mainly occupied when glucocorticoid concentrations are high (e.g., during the stress response). Glucocorticoids freely cross the plasma membrane and bind cytosolic GR (Bamberger et al., 1995), resulting in conformational changes and dissociation from a co-chaperone complex that maintains GR in an inactive state (Wochnik et al., 2005). Following nuclear translocation of the activated receptor complex, interactions between GR and the genome occur via zinc finger motifs on the alpha subunit of GR and glucocorticoid responsive elements (GRE) (i.e., nucleotide sequences) within genomic DNA (La Baer and Yamamoto, 1994). In this way, glucocorticoids act as canonical transcription factors, potentiating the transcription of genes in proximity to GREs. Activated GR can also indirectly bind DNA via intermediate, DNA-bound transcription factors to repress transcriptional activity of target genes (Kassel and Herrlich, 2007). Glucocorticoids can also affect cellular function through shorter-acting, non-genomic mechanisms, such as binding to membrane-bound GR to activate intracellular second messenger pathways (Boldizsar et al., 2013), though studies of stress-associated changes in the HPA axis predominately focus on GR-mediated processes.

Central to the dynamics and kinetics of the HPA axis response to stressors is its rapid, multi-level negative feedback, which is mediated by glucocorticoids, ACTH (Sawchenko and Arias, 1995), and other CNS neurotransmitters (Di et al., 2003). GR is highly expressed within the anterior pituitary, PVN, hippocampus, and PFC, and GR-dependent signaling in these regions facilitate negative feedback upon the axis (Laryea et al., 2015), thereby inhibiting ACTH and further GC release following stressor cessation. The time course of negative control varies from fast-paced

suppression occurring within minutes, possibly via non-genomic actions of GR (Russell et al., 2010), to longer-lasting suppression of the axis for several hours by genomic actions (Charron and Drouin, 1986; Myers et al., 1992). Importantly, social mammals are able suppress ongoing HPA axis activity by affiliative social contact with peers (i.e., social buffering), which occurs via oxytocin, dopamine, and endogenous opioid signaling to limbic and hypothalamic regions that regulate CRH and ACTH release (Ditzen and Heinrichs, 2014; Kikusui et al., 2006).

1.3. Effects of chronic stress on glucocorticoid signaling

As homeostatic regulators, glucocorticoids (and catecholamines) are primarily catabolic, delivering energetic substrates to tissues via gluconeogenesis, glycogenolysis, and lipolysis, suppressing non-vital physiological processes (e.g. reproduction, growth, digestion), and regulating immune function (Charmandari et al., 2005; Chrousos and Gold, 1992; Dufour et al., 2009). Thus, sustained exposure to stress hormones can have profoundly deleterious effects on the organism. In fact, hypercortisolemia is implicated in a number of chronic diseases, including metabolic syndrome (Chrousos, 2000), depression (Pariante, 2003), obesity (Incollingo Rodriguez et al., 2015), and cardiovascular disease (Reynolds et al., 2010), though others are associated with reduced basal or stimulated cortisol production (e.g., post-traumatic stress disorder, fibromyalgia, chronic fatigue syndrome; Fries et al., 2005; Heim et al., 2000). Despite these differences, reductions in glucocorticoid signaling, in other words a weakening of glucocorticoid-mediated signal transduction (i.e., glucocorticoid resistance), are consistently observed in stress-related diseases (Raison and Miller, 2003).

In experimental studies of chronically stressed individuals, glucocorticoid resistance manifests as changes in HPA axis responsiveness (i.e., glucocorticoid secretion) to acute stressors, insensitivity to cortisol suppression by synthetic glucocorticoid (i.e., impaired negative feedback), or blunted

anti-inflammatory responses to glucocorticoid treatment of pathogen-stimulated immune cells. Changes in brain regions located upstream of HPA axis activation partially mediate changes in HPA responsiveness, such as decreased hippocampal volume (Lyons et al., 2007) or CRHR1 modifications (Flandreau et al., 2012; Keen-Rhinehart et al., 2009); however, lower GR density or function impairment is central to weakened negative feedback and blunted anti-inflammatory signaling (Silverman and Sternberg, 2012). For example, mRNA transcripts of the inactive β isoform of GR, which heterodimerizes with the active α subunit to decrease nuclear translocation of activated GR, are elevated in individuals with glucocorticoid-resistant diseases (Lewis-Tuffin and Cidlowski, 2006). Furthermore, allelic variants that increase FKBP5 expression, a component of the inhibitory GR co-chaperone complex, lead to decreased negative feedback and are over-represented in individuals with clinical depression (Binder, 2009). Downregulation of GR expression has been observed within the hippocampus (Knable et al., 2004; McGowan et al., 2009; Patel et al., 2008), amygdala (Perlman et al., 2004), pituitary (De Kloet et al., 1998), and immune cells (de Kloet et al., 2007; Matsubara et al., 2006; Nikkheslat et al., 2015) of chronically stressed individuals, and insensitivity to a synthetic glucocorticoid (e.g., dexamethasone) is one of the most commonly observed HPA axis changes (Raison and Miller, 2003). Regardless of the precise molecular mechanism involved in its development, glucocorticoid insensitivity in multiple tissues is commonly observed in stress-associated psychiatric and somatic illnesses, with serious implications for immunoregulation.

1.4. Immunological responses to acute and chronic stress

Glucocorticoids affect the immune system in two complementary ways: the suppression of inflammatory responses and the promotion of anti-inflammatory processes, both of which are critical for regulating the immune response to acute stressors. The immune system consists of two divisions: 1) the innate immune system, encompassing monocytes, neutrophils, and natural killer

(NK) lymphocytes, provides a "first-line," non-specific defense via phagocytic and inflammatory activity; and 2) the adaptive immune system, consisting mainly of T lymphocytes and B cells, which provide pathogen-specific defense via cell-mediated and antibody-mediated responses. Immune processes from both the innate and acquired systems are activated by psychogenic challenge, many of which are triggered by catecholamines and glucocorticoids. For instance, postganglionic sympathetic nerves directly innervate the primary (e.g. bone marrow, thymus) and secondary organs (e.g. spleen, lymph nodes) of the immune system and release NE in response to stressors (Sanders and Kohm, 2002). Within primary organs, NE regulates the production, fate, and differentiation of white blood cells (i.e. leukocytes) (Madden et al., 1994) by promoting hematopoiesis through activation of β_2-adrenergic (β_2-AR) and α_1-adrenergic (α_1-AR) receptors (Maestroni and Conti, 1994) in bone marrow and influencing T cell proliferation, maturation, and receptor (TCR) diversity in the thymus (Williams et al., 1981). In addition to affecting immune processes within primary and secondary organs, acute psychosocial stressors evoke significant changes in inflammatory signals (Yamakawa et al., 2009) and circulating immune cell numbers and proportions (Dhabhar et al., 1995) that are mediated by neuroendocrine activation.

Acute stressors trigger a cascade of inflammatory signals in leukocytes, despite the absence of pathogen stimulation. Laboratory stressors involving social threat, evaluation, or rejection (e.g. Trier Social Stress Test: Kirschbaum et al., 1993), reliably evoke increases in circulating markers of inflammation, including but not limited to proinflammatory signaling molecules (e.g., interleukins [IL-1β, IL-2, IL-8], tumor necrosis factor-alpha [TNF-α], C-reactive protein, interferon [IFN-γ], anti-inflammatory signals (e.g., IL-4, IL-10), and IL-6, which has both pro- and anti-inflammatory properties (Segerstrom and Miller, 2004; Steptoe et al., 2007). Many of the acute increases in inflammatory signaling are attributable to catecholamine upregulation DNA nuclear factor kappa-B (NF-kB) DNA binding activity (Bierhaus et al., 2003), a transcription factor that functions as a lynchpin in the inflammatory response by driving expression of

inflammatory factors (i.e., cytokines) (Raison et al., 2006). While acute cytokine release is adaptive in that it primes the immune system to respond to injury or pathogen exposure (Dhabhar, 2009), sustained elevation of these immunologic stress mediators (i.e., chronic inflammation) is pathological and consistently associated with stress-related diseases, such as depression and cardiovascular disease (reviewed in Slavich and Irwin, 2014).

Elevated levels of inflammation in stress-related illnesses can be partially attributed to glucocorticoid resistance in immune cells. Normally, glucocorticoids tightly regulate inflammatory responses, particularly via the selection of T-helper cell 1 (Th1) versus Th2 responses (Braun et al., 1997). Glucocorticoids inhibit the production of Th1 responses by downregulating IL-2, IL-12, and TNFα, and promoting Th2 cytokine production, such as IL-10, IL-4, and transforming growth factor (TGF)-β (Elenkov and Chrousos, 2002). This shift in Th1/Th2 balance protects against ongoing cytotoxic effects of Th1 effectors during acute stress. This inhibitory process occurs via GR-mediated repression of NF-κB activity (Unlap and Jope, 1995) and other transcription factors that mediate the inflammatory response (Newton, 2013). Conversely, transcription of anti-inflammatory cytokines, such as IL-10, is enhanced by GR (Hodge et al., 1999). Thus, glucocorticoid resistance, combined with SNS hyperactivity (Andrews et al., 2013; Irwin and Cole, 2011), which can also increase NF-kB signaling (Kolmus et al., 2015), may tilt the balance between pro-inflammatory and anti-inflammatory cytokines via increased NF-κB signaling and decreased GR signaling (Rohleder, 2012). Recent evidence from genome-wide transcriptional studies of leukocytes in humans (Cole et al., 2015; Miller et al., 2008; Powell et al., 2013) and nonhuman primates (Tung et al., 2012) supports this hypothesis.

In addition to inflammatory signaling, acute catecholamine release increases circulating numbers of leukocytes and changes proportions of leukocyte subsets (Benschop et al., 1996). This process is partly mediated via β_2-ARs and GRs, by decreasing cell-cell interactions at the vascular

endothelium due to changes in adhesion molecule expression (Elenkov et al., 2000; Dhabhar et al., 2012, 1995) and increased chemotaxis (Redwine et al., 2003). Leukocytes mobilized into the bloodstream carry out immunosurveillance functions and "home in" on target tissues, an important feature of host defense (Jonsdottir, 2000). Changes in leukocyte mobilization and adhesion molecule expression have been reported in depression (Redwine et al., 2010), caregiving stress (Redwine et al., 2004), fibromyalgia (Macedo et al., 2007), hypertension (Dimitrov et al., 2013), and in animal models of chronic stress (Dhabhar and Mcewen, 1997; Zieziulewicz et al., 2013). Increased leukocyte adhesion is also involved in the pathophysiology of atherosclerosis (Schnoor et al., 2015) and inflammatory conditions (Palmer et al., 2006). While chronically stressed mice exhibit similar leukocyte adhesion and trafficking responses (Marcondes and Zhukov, 2011), phylogenetic and social differences between mice and humans challenge the translational relevance of such models.

1.5. Chronic social stress models in nonhuman primates

Translational animal models of stress must exhibit adequate similarity to humans with respect to pathogenesis, risk factors, protective factors, and the biological systems affected. Because social influences are key determinants of human health, a valid model should recapitulate the role of social factors on health. For instance, affiliative relationships in humans confer important health benefits, whereas the absence of social support has detrimental effects on health, and a recent meta-analysis estimated that socially-integrated individuals across all ages had a 50% decreased likelihood of mortality compared to those with poor or insufficient social relationships (Holt-Lunstad et al., 2010). Similarly, the absence of stable, affiliative relationships is a powerful stressor for nonhuman primates, often with long-lasting biological consequences. For example, high levels of social integration and greater social bond strength improve reproductive success (Silk et al., 2003) and increase lifespan in baboons (Archie et al., 2014; Silk et al., 2010) and Barbary

macaques (McFarland and Majolo, 2013). Conversely, social adversity in the form of low dominance rank can impair reproductive function (Wilson et al., 2013) and increase cardiovascular disease risk in nonhuman primates (Kaplan and Manuck, 1999; reviewed in Sapolsky, 2004). While some of these relationships between social factors and health outcomes are shared by other mammals (Cameron et al., 2009; Yee et al., 2008), the overlaps between nonhuman primates and humans are substantial (Sapolsky, 2005). Like humans, most nonhuman primates are remarkably social and have evolved homologous cognitive and neural mechanisms to navigate their social worlds (Rushworth et al., 2013), such as activation of reward areas in the brain during social decision-making and activation of the stress response to social isolation (reviewed in Chang et al., 2013). In addition, psychosocial stressors function as primary drivers of physiological stress, unlike other animal models (e.g., rodents) that more frequently experience physical dangers in the wild. For these reasons, and their phylogenetic relatedness to humans, nonhuman primates occupy a unique position as ideal models to study the effects of social factors on health and disease.

Nonhuman primate models of acute and chronic stress either utilize spontaneous activities occurring in the wild, or experimentally manipulate social conditions in captive populations. Most of the studies to date have investigated the effects of social instability, low social dominance rank, and weak social bonds on neuroendocrine and immune parameters (Meyer and Hamel, 2014). In the following sections, we focus on the use of low social dominance rank and social instability as experimental paradigms of psychosocial stress. In both, the extent to which an individual's subjective social experience is stressful depends upon the species, social group, sex, and individual differences. For instance, rank within a dominance hierarchy may be associated with 1) low or high levels of aggression, 2) varying degrees of social support, 3) frequent or infrequent rank challenges, or 4) differential resource allocation. In addition, experimental models of stress sometimes do not have distinct boundaries, but blur into one another: rank within the social

hierarchy may interact with hierarchy stability to influence the degree of stress exposure. These factors may predict physiological endpoints (Abbott et al., 2003; Sapolsky, 2005). In other words, conceptualizing a linear dominance hierarchy as a simple pecking order in which more subordination correlates with more stress is an oversimplification. While these nuances may pose challenges for experimental design and implementation, the complexity of nonhuman primate social environments affords an opportunity to examine correlates of social experience that are often difficult to empirically assess in humans, and have therefore become the basis for developing sophisticated models of psychosocial stress in nonhuman primates.

1.5.1. Dominance rank

Group-living animals tend to establish and maintain social hierarchies as a means of creating social predictability and maximizing survival. Despite the benefits to group and species survival, hierarchies come with costs to particular individuals at the bottom, middle, or top of the social ladder. Dominance in nonhuman primates is a learned, dynamic relationship that exists between individuals living in a social group and is typically maintained by intimidation, threat, harassment, and occasional contact aggression (Bernstein et al., 1974). More subordinate (i.e., lower-ranking) animals tend to receive higher rates of aggression, both in captive and wild populations, and manifest more anxiety- and depressive-like behaviors than dominants, which can been attributed to unpredictability and lack of control over their social environment. Lower-ranking individuals generally have decreased lifespan (Blomquist and Turnquist, 2011) and reproductive output (Dubuc et al., 2013; Pusey et al., 1997) compared to higher-ranking conspecifics (when hierarchies are stable), and are at greater risk for illnesses similar to those seen in low SES (the human corollary of low rank), such as atherosclerosis (Kaplan et al., 2009, 1982), type II diabetes (Bauer et al., 2010), and depression (Shively et al., 1997). Some negative health outcomes for subordinates result from proximate causes, such as limited access to preferential foods (Koenig et

al., 2004) or breeding opportunities (Dubuc et al., 2013); however, others occur downstream of allostatic processes in response to repeatedly engaging in and losing dominance interactions (i.e. the 'stress of subordination') (Sapolsky, 2005). However, when social groups are unstable or maintaining dominance necessitates very frequent aggression, high-ranking animals tend to exhibit stress-associated neuroendocrine and immune changes (i.e. the 'stress of dominance'). Short-term activation of the stress response following agonistic encounters is likely adaptive for dominants and subordinates (e.g. increasing vigilance, mobilizing energy for escape), whereas chronic activation increases allostatic load. It is important to consider, however, an ecological perspective that integrates allostatic processes within alternative life history strategies (Demas and Carlton, 2015). For instance, decreased reproductive output in lower-ranking individuals may reflect an adaptive energetic trade-off that redirects metabolic resources into physiological processes with more proximal fitness benefits.

1.5.2. Social instability

Periods of social group instability, which occur during group formation, newcomer introduction, or rank-reversals are often associated with increased rates of submission and aggression in monkeys (Bernstein et al., 1974; Mendoza, 1978; Shively et al., 1986) and baboons (Sapolsky, 1983). During these periods, the dominance hierarchy of the emergent group is being established and stress may derive from social unpredictability and increased competition for opportunities to ascend in rank. Experimental studies have systematically imposed unstable social environments in various ways to recapitulate the stress of instability, such as housing relocation (Gust et al., 1992), which often involves social separation from groupmates. Other strategies involve exposing animals over multiple weeks to temporary social groups that are iteratively reformed with unknown members, creating a context in which stable dominance hierarchies cannot form, agonistic/asocial behaviors increase, and affiliative behaviors decrease (Capitanio et al., 1998;

Cohen et al., 1997). Social instability in humans (e.g., neighborhood violence) is more prevalent in low SES communities (Crouch et al., 2000) and is independently associated with increased risk of cardiovascular disease (Sundquist et al., 2006) and poorer health (Boynton-Jarrett et al., 2008). In addition, daily routines tend to be more unstable (i.e., unpredictability) in low SES populations (Evans and English, 2002), which may mediate increases in cortisol output observed in adolescents (Chen et al., 2010) and poorer health in children from low SES families (Kamp Dush et al., 2013).

1.5.3. Dominance rank affects neuroendocrine and immune parameters

Studies of nonhuman primate dominance hierarchies paint a mixed picture of the effect of rank on stress physiology due to the complexities of the social environment, sex, and differences in life history. For instance, lower dominance rank is most often associated with elevated cortisol in females, whereas higher rank is often associated with elevated cortisol in males; though the stability of an individual's rank may mediate these relationships (Cavigelli and Chaudhry, 2012). A recent review of nonhuman primate hierarchies across species suggests that the "stress of subordination", whereby low rank correlates with higher mean cortisol levels, results from chronically elevated baseline cortisol production, whereas the "stress of dominance" results from relatively frequent or intense cortisol spikes due to agonistic encounters (Cavigelli and Caruso, 2015). The authors conclude that patterns of glucocorticoid production across the hierarchy reveal different profiles that inform rank differences in health outcomes. Evaluating rank effects on SNS activity is difficult because catecholamines are rapidly degraded in serum and their metabolites are poorly preserved in feces. However, lower-ranking animals have demonstrated alterations in SNS-associated cardiac parameters, such as decreased circadian heart rate variation (female cynomolgus monkeys: Shively and Day, 2015) and delayed blood pressure recovery from

adrenergic challenge (male baboons: Sapolsky and Share, 1994), although it is unclear whether these actually reflect increased sympathetic and/or decreased parasympathetic tone.

Assessments of immune function in free-ranging nonhuman primates typically focus on parasite load. Generally, dominant males to be more parasitized (baboons: Hausfater and Watson, 1976; chimpanzees: Muehlenbein and Watts, 2010), possibly explained by energetic trade-offs made investing more in reproduction (e.g. testosterone production) (Muehlenbein and Bribiescas, 2005), copulation (Alberts et al., 1996), and agonism, and less in immune defenses (Habig et al., 2015). However, other studies suggest that dominant males heal more quickly from cutaneous injury (Archie et al., 2012), suggesting that certain immune responses are favored in dominant animals (e.g., Th1 vs. Th2 responses) (Archie, 2013; Lee, 2006). Captive studies of *in vivo* viral challenge have found that subordinate males are more susceptible to adenovirus infection (Cohen et al., 1997), despite having stronger antibody responses to other viruses (Cunnick et al., 1991). Lymphocyte enumeration studies have found decreased T cell numbers and proportions among subordinate females (Paiardini et al., 2009; Tung et al., 2012; but see Gordon et al., 1992), which may mediate reductions in viral immunity.

Group-living female rhesus monkeys (*Macaca mulatta*) and cynomolgus macaques (*Macaca fasicularis*) exhibit "stress of subordination." Multiple studies report that lower-ranking females are less sensitive to cortisol suppression by exogenous glucocorticoids (Arce et al., 2010; Kohn et al., 2016; Michopoulos et al., 2012b; Shively et al., 1997), less sensitive to ACTH stimulation (Shively, 1998), have fewer numbers and proportions of circulating T lymphocytes (Paiardini et al., 2009; Tung et al., 2012), and upregulate inflammatory gene transcription (Tung et al., 2012), in addition to worsened metabolic (Michopoulos et al., 2012a) and monoaminergic profiles (Shively and Day, 2015). Gene transcriptional profiles of leukocytes exposed to pathogens *ex vivo* also suggest that subordinates have suppressed viral (acquired) immunity, coupled with a

hyperinflammatory response (Snyder-Mackler et al., 2016b). Studies of socially defeated mice and low SES or chronically stressed adults have yielded similar findings (Miller et al., 2014, 2008; Powell et al., 2013).

In summary, dominance rank in nonhuman primates strongly affects neuroendocrine and immune system parameters, with fitness and survival consequences. In particular, there are striking similarities between low-ranking female macaques and low SES humans, who experience more frequent psychosocial stressors (Brady and Matthews, 2002) and exhibit poorer health (Chen and Miller, 2013). Importantly, biological processes observed in stress-related pathology in humans, specifically inflammation (Paul et al., 2008) and GC resistance (Miller et al., 2009), are also found in subordinate female rhesus monkeys. In addition to stressor exposure, weaker social bonds are a mortality risk factors in humans (Fujiwara and Kawachi, 2008) and nonhuman primates (Silk et al., 2010). Thus, social dominance rank in nonhuman primates, particularly subordinate female rhesus macaques, provides a valid translational model of chronic stress.

1.5.4. Social instability affects neuroendocrine and immune parameters

During periods of instability, dominant males generally increase glucocorticoid production (Bergman et al., 2005; Setchell et al., 2010), whereas subordinate females tend to secrete more glucocorticoids (Emery Thompson et al., 2010; Foerster and Monfort, 2010; Sousa et al., 2005), though there are exceptions (Gesquiere et al., 2011). Similar to social subordination stress, the amount of aggression received during instability partially mediates glucocorticoid increases in males (Alberts et al., 1992; Sapolsky, 1992). Relocation stress in captive primates leads to hypercortisolism (baboons: O'Connor et al., 2011; but see, pigtailed macaques: Crockett et al., 2000) and insensitivity to CRH stimulation regardless of sex (long-tailed macaques: Crockett et al., 1993). Interestingly, relocation with a preferred social partner buffers hypercortisolemia in marmosets (Taylor et al., 2015), squirrel and titi monkeys (Hennessy et al., 1995; Norcross and

Newman, 1999), though not in tufted-ear marmosets *(Callithrix kuhli)* (Smith et al., 1998). Group formation stress induces hypercortisolemia in male squirrel monkeys (Mendoza, 1978) and female rhesus macaques (Goo and Sassenrath, 1980), and hierarchy stabilization returns cortisol levels to baseline (Johnson et al., 1996), suggesting that social instability induces significant, but reversible changes in the HPA axis.

Many of the early studies of social instability focused on adaptive immune function. Relocation and social separation of juvenile rhesus macaques from their natal groups into peer housing or individual housing decreased T lymphocyte numbers ($CD4^+$ and $CD8^+$) (Gust et al., 1992), even after plasma cortisol levels recovered to baseline (Gordon et al., 1992). Decreased T lymphocyte counts may result from GC-induced T cell apoptosis (Cohen, 1992; Lépine et al., 2005) or stress-induced trafficking of T cells out of circulation (Dhabhar et al., 1995). Prolonged social instability in monkeys also decreases T cell proliferation in response to mitogen stimulation (Cohen et al., 1992), an effect buffered by social affiliation, and reduces IgG antibody production following immunization against tetanus (Cunnick et al., 1991) and herpes viruses (Line et al., 1996). Social instability also decreased survival and increased viral load in SIV-infected monkeys (Capitanio and Lerche, 1998). Interestingly, rates of social affiliation predicted viral load irrespective of social condition, suggesting that prosocial behaviors can buffer adaptive immunity. Subsequent studies of SIV-infected monkeys have implicated increased lymph node innervation by SNS fibers in higher viral loads (Sloan et al., 2008), coupled with decreased helper T cell numbers (Sloan et al., 2007) and higher catecholamine levels (Capitanio and Cole, 2015). Interestingly, the relationship between social instability and SIV progression was mediated by decreased expression of type-I interferon (IFN) response genes and NK cell lytic activity, both of which suppress viral replication, and is consistent with transcriptional profiles in subordinate female (Snyder-Mackler et al., 2016b) and socially isolated male rhesus monkeys (Cole et al., 2015). Interestingly, social instability in male monkeys also decreases leukocyte sensitivity to endogenous GC regulation (Cole et al.,

2009), a phenomenon found in socially-stressed humans (Cole, 2008). Glucocorticoid-induced redistribution is important in Th1-type cell-mediated immunity against wounding and certain carcinomas (Dhabhar, 2009), and for defense against common cold viruses (Cohen et al., 2012). Taken together, these data demonstrate that instability of the social environment, which is associated with decreased affiliation and increased aggression, alters neuroendocrine and immune parameters, which can have functional implications for viral resistance and immunosurveillance.

1.6. Study rationale and objectives

The following chapters describe two comprehensive investigations designed to further explore the effects of dominance rank on neuroendocrine and immune system parameters in group-housed adult female rhesus macaques. As discussed, female rhesus monkeys tend to exhibit a "stress of subordination" neuroendocrine phenotype, primarily characterized by impaired glucocorticoid negative feedback. Notably, some lower-ranking animals do not succumb to this phenomenon. In these animals, resilience to subordination stress may be due to individual differences in certain behavioral tendencies (e.g., personality) that influence physiological responses to chronic stress. For instance, low ranking, but highly prosocial animals may engage in more affiliative behaviors than expected given their rank, thereby buffering the HPA axis and conferring resilience to subordination stress. However, few studies have been able to investigate this possibility because most social behaviors are rank-dependent, so differentiating between the effects of personality versus rank on behavior and physiology has been challenging. In order to overcome this challenge, in our first set of experiments we constructed 9 social groups of adult females, assessed behavior and measures of glucocorticoid regulation, and then rearranged each female's group membership mid-study, enabling us to examine each female in two different social environments (i.e., ranks) across time. We hypothesized that the effects of low rank on glucocorticoid regulation would be moderated by prosocial behavioral tendencies and that the effects of higher rank would

be moderated by anxious tendencies. Lastly, our experimental design permitted us to examine whether improvements in rank would improve glucocorticoid sensitivity, establishing causality to rank effects on the HPA axis.

In addition to the effects of low dominance rank on glucocorticoid regulation by the HPA axis, our second set of experiments investigated whether low rank would desensitize immune cells to redistribution by an acute stressor. As discussed, low rank and other forms of chronic psychosocial stress desensitize immune cells to anti-inflammatory signaling by glucocorticoids, which is mostly GR-mediated. Immune cell redistribution in response to acute stress is an essential feature of immunity, but can be pathological (e.g., atherosclerosis, asthma) if cells are repeatedly trafficked into target tissues due to chronic stress. Leukocyte mobilization and trafficking is mediated in part by glucocorticoid-induced changes in cellular adhesion molecule (CAM) expression on the cell surface, and evidence suggests that chronic stress can desensitize leukocytes to redistribution by glucocorticoids. However, no studies have investigated whether chronic stress modifies CAM gene expression, or whether CAM gene expression is associated with *in vivo* leukocyte sensitivity to redistribution by GCs. Furthermore, it is not known whether chronic stress affects redistribution of some immune cell subtypes more than others. To address these questions, we utilized the same social group design as in the first experiment to test whether low dominance rank would be associated with leukocyte insensitivity to the redistributional effects of an acute psychosocial stressor, and whether resistance to cortisol suppression by dexamethasone would predict leukocyte insensitivity to redistribution. Furthermore, we tested whether low rank would causally increase CAM mRNA expression and whether higher mRNA levels predicted increased leukocyte distribution.

The closing chapter provides a summary of all findings from the experiments carried out in this dissertation and revisits the strengths and limitations of each. We then explore the implications of

these results within the context of the extant literature on chronic stress and conclude with suggestions for future studies aimed at addressing the questions raised by the results of these experiments and others that remain in the fields of psychoneuroendocrinology and psychoneuroimmunology.

Chapter 2: Dominance rank causally affects personality and glucocorticoid regulation in female rhesus macaques

2.1. Abstract

Low social status is frequently associated with heightened exposure to social stressors and altered glucocorticoid regulation by the hypothalamic-pituitary-adrenal (HPA) axis. Additionally, personality differences can affect how individuals behave in response to social conditions, and thus may aggravate or protect against the effects of low status on HPA function. Disentangling the relative importance of personality from the effects of the social environment on the HPA axis has been challenging, since social status can predict aspects of behavior, and both can remain stable across the lifespan. To do so here, we studied an animal model of social status and social behavior, the rhesus macaque (*Macaca mulatta*). We performed two sequential experimental manipulations of dominance rank (i.e., social status) in 45 adult females, allowing us to characterize personality and glucocorticoid regulation (based on sensitivity to administration of the exogenous glucocorticoid, dexamethasone) in each individual while she occupied two different dominance ranks. We identified two behavioral characteristics, termed 'social approachability' and 'boldness,' which were highly social status-dependent. Social approachability and a third dimension, anxiousness, were also associated with cortisol dynamics in low status females, suggesting that behavioral tendencies may sensitize individuals to the effects of low status on HPA axis function. Finally, we found that improvements in dominance rank increased dexamethasone-induced acute cortisol suppression and glucocorticoid negative feedback. Our findings indicate that social status causally affects both behavioral tendencies and glucocorticoid regulation, and that some behavioral tendencies also independently affect cortisol levels, beyond the effects of rank. Together, they highlight the importance of considering personality and social status together when investigating their effects on HPA axis function.

2.2. Introduction

In many mammals, including humans, social groups are organized into dominance hierarchies in which an individual's position in the hierarchy has important consequences for reproductive success, access to resources, and, in some cases, health and mortality risk. These effects are thought to arise in part through unequal distribution of exposure to socio-environmental stressors (Sapolsky, 2005). Stressful experiences in mammals activate the hypothalamic-pituitary-adrenal (HPA) axis, triggering a neuroendocrine cascade that produces glucocorticoids (GC) (e.g. cortisol) and is adaptive in the short-term, but pathological when chronically activated (Cavigelli and Chaudhry, 2012; Miller et al., 2007). Notably, while low status is often associated with chronic stress, some low status individuals do not exhibit elevated cortisol levels (Dowd et al., 2009). This observation has motivated an increased research focus on factors that may interact with social experience to affect physiology (Capitanio, 2011; Hodes et al., 2014), including individual differences in behavior or temperament (e.g. "personality"). However, because many social behaviors are status-dependent, disentangling the effects of personality on GC regulation from those of status presents a major challenge to understanding vulnerability to stress exposure.

Group-living nonhuman primates provide a valuable opportunity to address this gap. Like humans, many nonhuman primate species must navigate complex social relationships, including strictly enforced dominance hierarchies, to survive and reproduce. Within these groups, dominance rank has been associated with altered neuroendocrine function (reviewed in Sapolsky, 2005) and survival (Blomquist et al., 2011), although the magnitude and directionality of rank effects vary depending on the social dynamics of the species, population, and sex (Abbott et al., 2003; Gesquiere et al., 2011; Michopoulos et al., 2012b), as well as the statistical power and design of the study (Cavigelli and Caruso, 2015). Further, within species, the effects of occupying a particular rank can vary across individuals. For example, in species in which low rank predicts hypercortisolemia, engagement in affiliative behaviors (e.g. grooming, contact, huddling) has been hypothesized to moderate ("socially buffer") this effect (reviewed in Hostinar et al., 2014). If rates

of affiliative behavior reflect stable behavioral tendencies, they may therefore help explain why some animals are more resilient to social status-induced stress than others.

In support of this idea, factor analytic studies of nonhuman primate behavior suggest that high rates of affiliative behavior can reflect stable behavioral tendencies (e.g., "sociability") (reviewed in Freeman and Gosling, 2010). However, affiliative behaviors are often collinear with dominance rank (e.g., higher-ranking individuals engage in more affiliation and have stronger bonds than low-ranking individuals: Seyfarth et al., 2013; Snyder-Mackler et al., 2016; but see Archie et al., 2014; Silk et al., 2010). Thus, attributing affiliation rates to an individual's personality (or other intrinsic factors, such as age and social history), as opposed to dominance rank, remains challenging. Other dimensions of personality encounter the same problem. For instance, although self-grooming rates can be temporally stable (Maestripieri, 2000) and have been argued to capture anxious temperament (Fairbanks and Jorgensen, 2011), they can also be rank-dependent, with low-ranking individuals tending to self-groom more frequently than high-ranking individuals (Pavani et al., 1991). The ability of personality traits to moderate the response to rank-induced social stressors thus depends on the degree to which they themselves are affected by rank (McGuire et al., 1994), as opposed to stable across social situations (Uher et al., 2013).

A number of studies in nonhuman primates have reported associations between personality and cortisol levels, though few have investigated them jointly in the context of dominance rank. Generally, prosocial behaviors that load onto a "sociability" dimension are associated with lower cortisol (Seyfarth et al., 2012), whereas more aggressive and anxious temperaments tend to be associated with higher cortisol (Capitanio et al., 2004; Erickson et al., 2005). These effects could be explained if personality traits exert direct effects on neuroendocrine function (overlapping brain regions govern both emotional behavior and the physiological stress response: Short et al., 2014), or if they indirectly influence cortisol levels by shaping how individuals cope with acute

stressors (Taylor et al., 2015), particularly aggression received from more dominant social partners (Capitanio, 2011). However, while a handful of studies have considered both personality and dominance rank effects on cortisol levels in primates (Anestis et al., 2006; Seyfarth et al., 2012), differentiating between the two remains a challenge. For example, Seyfarth et al. found that wild adult female baboons with stronger bonds had lower fecal GC levels, but these females also tended to be higher-ranking than females with weak social bonds (Seyfarth et al., 2012).

In this study, we attempt to overcome this challenge by assessing the relative contributions of dominance rank and personality to GC regulation in group-housed adult female rhesus macaques. We consider three indices of GC regulation by the HPA axis: diurnal cortisol, GC negative feedback, and sensitivity to acute GC challenge. Captive primate models provide a translational opportunity to explore the link between personality, dominance rank, and physiology because social group membership can be systematically rearranged and monitored in ways that are impossible in research with humans or wild nonhuman primates. To take advantage of this possibility, we first constructed 9 new social groups of adult females (5 per group), and then employed a mid-study social group rearrangement in which the same females were reorganized into new social groups in which almost all of them occupied new positions (Snyder-Mackler et al., 2016a). This approach enabled us to examine each female in two different social environments across time. We hypothesized that: (1) behavioral tendencies would be causally affected by dominance rank, but exhibit partial stability across social contexts, indicative of "personality" (Funder and Colvin, 1991); (2) the effects of low dominance rank on cortisol levels (Michopoulos et al., 2012b) would be moderated by prosocial behavioral tendencies, such that highly affiliative, low ranking females would exhibit fewer signs of GC dysregulation than less affiliative, low ranking females; (3) the effects of high rank would be moderated by anxious tendencies, such that high anxiety, high ranking females would exhibit more signs of GC dysregulation than low anxiety, high ranking females; and (4) improvements in social status would improve HPA

sensitivity and responsiveness to GCs, as suggested by prior studies on the plasticity of responses to social conditions (Shively et al., 1997; Snyder-Mackler et al., 2016a; Tung et al., 2012).

2.3. Methods

2.3.1. Study subjects

Study subjects were 45 adult female rhesus macaques housed in nine, mixed-age social groups of five females each at the Yerkes National Primate Research Center (YNPRC; see Table S2.1 for detailed demographic information). Group formation initially began in January 2013 using a previously established protocol (described in Snyder-Mackler et al., 2016). Briefly, sexually mature (age range = 3-20 years, median age at the start of the study = 6.8 yr), reproductively intact females at the YNPRC Field Station were serially introduced to indoor run housing (10 m x 10 m) over 2 – 15 weeks until all groups included five unrelated adult females (Table S2.1). Females were randomized into groups and order of introduction, with the following exceptions: we avoided co-housing females who had previously had social contact with one another (of 180 total co-housed dyads throughout the study, 97% had no prior social contact), and we avoided co-housing females who were close kin (e.g., full sibling, half sibling, parent-offspring, grandparent-grandoffspring). In this paradigm, females introduced earlier tend to subsequently occupy higher dominance ranks. Animals had unrestricted access to typical low-fat, high-fiber nonhuman primate diet throughout the study, and the Emory University Institutional Animal Care and Use Committee approved all procedures in accordance with the Animal Welfare Act and the NIH "Guide for the Care and Use of Laboratory Animals."

The present study was divided into two phases: Phase 1 (February 2013 – March 2014) and Phase 2 (April 2014 – March 2015). Starting dates for each group and phase were defined by the date of

completion of group formation (after addition of the fifth and final female into each group; note that start of group formation was staggered for logistical reasons: see Table S2.1). Phase 1 groups were formed as described above, whereas Phase 2 groups consisted of the same 45 individuals systematically reorganized into new groups (Table S2.1). Specifically, groups in Phase 2 were comprised of females who all shared the same or similar dominance ranks in Phase 1 (maximum difference of 1 ordinal rank value), a strategy that altered the ordinal dominance ranks of the majority (36 of the 45) of subjects across the two phases. In both phases, order of introduction strongly predicted Elo rating (Phase 1: r = -0.54, $P < 0.001$; Phase 2: r = -0.68, $P < 0.001$), a measure of dominance rank in which higher scores correspond to higher status (Albers and de Vries, 2001; Elo, 1978; Neumann et al., 2011a), such that females entering into the group earlier occupied higher ranks by the time of group stabilization. As intended by our study design, an individual's rank in Phase 1 was uncorrelated with her rank in Phase 2 (r = .063, P = 0.68). Female age was correlated with dominance rank in Phase 1 (r = 0.56, $P < 0.001$), but not in Phase 2 (r = .27, P = 0.07); however, we included age as a covariate in all of our analyses for both phases.

2.3.2. Behavioral characterization

Behavioral data were collected weekly during 30 min focal observations. During these observations, a trained observer recorded the behavioral activities of all five individuals residing in the "focal" group according to an established ethogram (Snyder-Mackler et al., 2016; because of the small group sizes, observers could effectively watch all animals in a group at one time). We collected a total of 398 hours of focal observations on the 18 groups (mean per group = 22.1 h, range = 14.5 – 27.5 h; totals = 223.5 h in Phase 1, and 175 h in Phase 2). To control for differences in hours observed across groups, we calculated all behavioral frequencies and durations per hour observed. Inter-observer reliability among three trained observers exceeded

0.9. In total, we analyzed 10 behavioral measurements. Two captured dominance interactions: the frequency of aggressive behaviors, defined by threats, slaps, grabs, bites, and chases, and the frequency of submissive behaviors, which included grimaces, withdrawals, and screams. Two captured anxiety-like, "displacement" behaviors (Aureli and Whiten, 2009): time spent self-grooming and the frequency of self-scratching bouts. Finally, six captured affiliation-related behaviors: time spent in passive, physical contact with groupmates that did not involve grooming or aggression; time spent grooming one or more groupmates; time being groomed by one or more groupmates; the frequency of approaches in which the focal female initiated a proximity behavior toward another female (defined as sitting less than 1 m away for > 3s); the frequency of approaches received by the focal female from groupmates; and time spent alone, a negative measure of affiliation during which the focal female was more than 1 m away from any groupmate (i.e., not in proximity to others).

Data from Phase 1 and Phase 2 were analyzed separately such that each female had a measure of each behavior during Phase 1 and a separate measure during Phase 2. Only behavioral data collected following the completion of group formation was used (i.e. after the fifth and final female had been introduced into a group). Data were recorded on a notebook computer using a data acquisition program ("WinObs") that records behavior in an actor-behavior-recipient format (Graves and Wallen, 2006).

2.3.3. Dominance rank assignment

We assigned dominance ranks using the Elo rating method, in which higher ratings correspond to higher rank/social status (Elo, 1978; Neumann et al., 2011a). The Elo method updates an individual's rating after each dominance interaction based on the pre-interaction probability that she would win or lose the encounter. We opted to use Elo ratings, as opposed to ordinal ranks,

because they distinguish adjacently ranked individuals that are matched in relative dominance (e.g. Elo ratings of 1,500 versus 1,490) from those that are more clearly differentiated (e.g. Elo ratings of 1,500 versus 1,000). We determined Elo ratings from all dyadic dominance interactions that took place after each group was fully formed. Each individual's initial Elo rating was set at 1000, and the baseline number of points gained or lost during a dominance interaction (k) was set to 100. This number was then weighted for each interaction by the expected probability of that individual winning or losing, based on a logistic function that was updated following each dominance interaction (Albers and de Vries, 2001). Dominance hierarchies were rapidly established after group formation and highly stable within each study phase. Specifically, Elo ratings at the end of each study phase were significantly correlated with Elo ratings at 10 weeks post-group formation, for both phases (r_{88} = 0.89, $P < 0.001$). Final Elo ratings within each study phase were converted to z-scores for statistical analyses, unless otherwise specified, and all Elo computations were performed using the *EloRating* package (v 0.43) in R (R Development Core Team, 2014).

2.3.4. Behavioral Analysis

To represent correlated behaviors using a minimum number of independent dimensions, we carried out principal components analysis (PCA) using the *prcomp* function in R. We performed PCA on a 90 x 10 matrix of behavioral data, with a row for each female-study phase combination (45 females x 2 phases) and a column for each of the 10 behaviors we studied. We used a bootstrapping procedure with 10,000 iterations to generate 95% confidence intervals (CI) of the eigenvalues of each principal component (PC). From the resulting PCA, we retained only PCs where the lower bound of the 95% CI was ≥1 (Table 2.1), and applied an orthogonal varimax rotation to generate standardized factor loadings and component scores using the principal function in the R package *psych* (Revelle, 2015). We used linear mixed effects models (LMM) to

examine whether the three resulting standardized component scores for each subject were associated with dominance rank or chronological age (fixed effects), with social group modeled as a random effect. To generate rank, age, and social group-independent measures of the three dominant behavioral tendencies, we extracted residual component scores from each LMM. These values were used to ask whether personality attributes that could not be explained by rank or age (i.e. were orthogonal to rank and age) explain GC regulatory differences (see section 2.3.7). Finally, to test for causal effects of changes in dominance rank on behavioral tendencies, we modeled the change between Phase 2 and Phase 1 component scores as a function of change in Elo rating (ΔElo), age, and phase 1 component score. This approach took advantage of the longitudinal nature of our study design, complementing our cross-sectional analyses on females in Phase 1.

2.3.5. Sampling and assay procedures

All animals were habituated to removal from their groups for conscious venipuncture using established procedures (Michopoulos et al., 2012b). The order in which females from a group entered the venipuncture caging was unrelated to rank, and all individuals from the same group were sampled on the same day. Blood samples were obtained using Vacutainer serum separator tubes within 10 min from entering the animal area to minimize arousal, and females were back in their group within 10 min after completing the sampling procedure. Serum separator tubes were immediately placed on ice and centrifuged at 2000 x *g* for 15 min using an Allegra 6R refrigerated centrifuge (Beckman Coulter, Inc.). Sera were stored at -20 °C until assayed in duplicate. All groups were sampled 9-12 months from the beginning of group formation and cortisol assessments for a given animal were completed within a mean window of 61 days (range: 14-102 d). Blood samples were collected at the end of the typical breeding season in both study phases (January-March).

For cortisol and dexamethasone quantitation, we used LC/MS instead of antibody-based assays, such as ELISA, as the latter are known to cross-react with off-target ligands and metabolites, whereas the former precisely quantifies the ligand of interest and is considered the gold standard for quantification of steroid hormone analysis (Soldin and Soldin, 2009). For cortisol quantification, serum samples (100 µl) were placed into a 96-well block with 10 µl of internal standard (d4-cortisol) and were extracted using an ISOLUTE SLE+ 200 plate (Biotage, Sweden), then reconstituted in 100 µl of LC solvent (0.1% formic acid in H_2O:0.1% formic acid in methanol, 65:35, V:V). 10 µl extraction solution was analyzed by LC-ESI-tandem mass spectrometry using a Discovery 5 cm × 2.1 mm C18 column (Supelco, PA) eluted at flow rate of 0.5 ml/min. Cortisol and d4-Cortisol were identified at m/z pairs of 363.1/121.1 and 367.3/125.2 by AB Sciex TripleQuad 6500. For dexamethasone quantification, serum samples (250 µl) were placed into a 96-well block with internal standard (flumethasone) and were extracted using an Oasis HLB 96-well plate (Waters, MA), then reconstituted in 100 µl of LC solvent (2 mM Ammonium Acetate, 0.1% formic acid in H_2O:2 mM Ammonium Acetate, 0.1% formic acid in methanol, 55:45, V:V). 20 µl extract was analyzed by LC-ESI-tandem mass spectrometry using a Waters BEH C18, 50 X 2.1 mm. Dexamethasone and flumethasone were identified at m/z pairs of 393.0/354.9 and 411.1/253.0 by AB Sciex TripleQuad 6500. Cortisol and dexamethasone concentrations for each sample were calculated using linear regression analysis of a standard curve. The quantification ranges for the cortisol and dexamethasone assays were 0.1 -100 µg/dl and 1.0 -100 ng/ml, respectively. For each run, calibration standards were prepared at concentrations of 0, 0.1, 0.5, 1, 5, 10, 20, 50, 75, 100 µg/dl for cortisol, and 0, 0.1, 1.0, 5.0, 10, 20, 50, 75, 100 ng/ml for dexamethasone, and three fortified quality control samples were also analyzed in duplicate in each run. The intra- and inter-assay percentage coefficients of variation (%CV) for cortisol and dexamethasone were 1.21% and 5.78%, and 3.82% and 10.1%, respectively. All assays were performed by the Yerkes NPRC Biomarkers Core Laboratory.

For the diurnal cortisol and dexamethasone suppression tests, cortisol measurements were largely in agreement between the two study phases (Table 2.1). For the dexamethasone challenge test (DCT), absolute values of cortisol systematically differed between phase 1 and phase 2. Although samples from each phase were run at different times (i.e., batched within phase), the source of this difference is unknown, as the samples from both phases were collected at the same time of year (Jan – March), by the same technicians, and assayed by the same laboratory technician using the same LC/MS procedure, and quality control parameters for the assays did not differ. Importantly, however, all statistical tests were conducted on the change in values from baseline measured in the same phase.

2.3.6. Diurnal cortisol and responsiveness to dexamethasone

Diurnal cortisol levels were assayed for all females from serum samples collected 1 h after sunrise (0800 h), at 1100 h, and 1 h before sunset (1700 h) on the same day. This assessment was repeated once in each study phase, resulting in six total, unstimulated cortisol measurements per subject. We also evaluated subjects after two independent 0.125 mg/kg intramuscular (IM) doses of dexamethasone (Dex). The first Dex assessment measured GC negative feedback using a Dex suppression test (DST), conducted over a 24 h timescale to measure escape from Dex suppression. Specifically, Dex injection for the DST occurred immediately after the final diurnal cortisol sample was collected at 1700 hours. This allowed us to use the 1100 h diurnal cortisol sample from the same day as the baseline measurement for the DST, with another 1100 h sample collected at 1100 h the following day (24 h later) to quantify cortisol levels following injection. The second Dex injection, for a dexamethasone challenge test (DCT), was used to measure short-term sensitivity to suppression of endogenous cortisol (mimicking the response to an acute stressor) and conducted over a shorter timescale. Baseline serum samples collected at 0800 h were immediately

followed by Dex injection. Serum was then collected at 1.5 h and 4.5 h post-injection to measure circulating levels of cortisol (see Figure S2.1 for a visual schematic of all cortisol assessment procedures; see Table S2.2 for raw cortisol values). To control for individual differences in Dex metabolism, which may depend on age or other variables (Pasquali et al., 2002), we measured serum Dex concentration in the same samples (Table S2.2) and used this value as a covariate in the DST and DCT analyses (Table S2.3).

2.3.7. Statistical analysis of cortisol measures

Diurnal cortisol. To analyze the diurnal cortisol data as a function of dominance rank and/or behavioral tendencies (controlled for rank and age), we performed two analyses. First, we modeled raw serum cortisol levels (3 values for each female) using linear mixed models (LMM) in the *lme4* package, including time (in hours) and age as fixed effects and a random effect of study subject (Bates et al., 2014). Second, we modeled diurnal cortisol slope (1700 h - 0800 h cortisol) / 9 h, which we summarized as a single value per female per phase, using linear models (LM). To control for possible correlations between slope and intercept, we included 0800 h cortisol levels as a covariate for the slope analysis (Table S2.3).

Dexamethasone suppression test. For all DST analyses of rank and behavioral tendencies (controlled for rank and age), we used LMs to analyze the difference between pre-Dex and post-Dex serum cortisol levels as the outcome variable, controlling for pre-Dex serum cortisol concentration and age as a covariate (Egbewale et al., 2014) (Table S2.3).

Dexamethasone challenge test. For the DCT, we used LMs to analyze the effects of rank and behavioral tendencies (controlled for rank and age) on both an "immediate" response to Dex, captured by the difference between pre-Dex and 1.5 h post-Dex serum cortisol levels, and the

short-term, but more delayed response, captured by the difference between pre-Dex and 4.5 h post-Dex cortisol levels. As for diurnal cortisol, we controlled for chronological age and slope-intercept correlations (by including pre-Dex cortisol levels as a covariate in each model) (Table S2.3).

Effects of changes in rank on glucocorticoid regulation. In the three sets of analyses above, we performed a cross-sectional analysis on data from Phase 1 only. However, we also collected parallel data in Phase 2 to test whether improvements (or declines) in rank across phases causally affected glucocorticoid regulation in a longitudinal analysis within individuals. To do so, we implemented linear models of between-phase changes in (a) diurnal cortisol slope; (b) cortisol suppression by Dex (DST); and (c) change in sensitivity to acute Dex at 1.5 h and 4.5 h (DCT), in all cases as a function of change in Elo rating (ΔElo) across phases. We included age, Phase 1 Elo rating (which affects the possible values of ΔElo), and cortisol levels from parallel tests of GC regulation in Phase 1 as model covariates (Table S2.4). To evaluate the possibility that more complex, non-linear models better describe the relationships between rank and cortisol, we also implemented generalized additive models (GAMs) using the *mgcv* package in R (Wood, 2011). GAM results did not qualitatively differ from the linear model results so are shown in Table S4 instead of the main text.

We conducted all statistical analyses using R (v3.1.0). Model residuals were visually inspected for homoscedasticity, and normality was assessed using the Wilks-Shapiro test (all p-values > 0.05). Standardized residuals with an absolute value > 3 were excluded from the final models. Variance inflation factors (VIF) were < 3 for all predictors of interest. Model degrees of freedom (df), t-statistics, and p-values for fixed effects in LMMs were calculated using the *lmerTest* package (Kuznetsova et al., 2015). Goodness-of-fit chi-squared statistics and P-values were determined using the *lrtest* function in the *lmtest* package (Zeileis and Hothorn, 2002) (Table S2.5).

2.4. Results

2.4.1. Behavioral characterization

Principal components analysis (PCA) on the ten behaviors recorded from all females indicated that the first three principal components (PC) cumulatively explained 58% of the total variance in the correlation matrix ($N = 90$, $df = 18$, $\chi^2 = 109.2$, $P < 0.001$). All of the behavioral variables loaded onto at least one of the three PCs with an absolute value > 0.49 (Table 2.2). According to the specific behaviors that loaded onto each PC, individuals who scored high on component 1 (PC1) spent less time alone and were more likely to be groomed, approached by, and spend time in physical contact with groupmates. Individuals who scored high on component 2 (PC2) were more aggressive and less submissive, as well as more likely to approach and groom groupmates. Individuals scoring high on component 3 (PC3) had the highest rates of self-scratching and spent more time self-grooming. Based on the component factor loadings and prior studies of rhesus macaque personality (Freeman and Gosling, 2010; Weiss et al., 2011), we conceptualized PC1 as an individual's social approachability, PC2 as confidence and impulsivity, and PC3 as the expression of anxiety. We used the term "social approachability" for PC1 because it specifically captures approaches and grooming directed to the focal animal, as opposed to the directionally agnostic terms 'sociability,' 'social integration,' or 'composite sociality' used in the broader behavioral literature on nonhuman primates (Capitanio, 1999; Archie et al., 2014; Silk, 2007); note that approaches and grooming initiated by the focal animal are captured more strongly by PC2. For ease of discussion, we refer to PC1 as "social approachability," PC2 as "boldness," and PC3 as "anxiousness."

2.4.1.1. Predictors of behavioral tendencies

We tested the hypothesis that a female's age and dominance rank would be associated with her social approachability (PC1), boldness (PC2), and anxiousness (PC3) scores. Across the two study phases, we found that older females were less socially approachable (PC1: β_{age} = -0.078, t_{87} = -2.89, P = 0.005), less bold (PC2: β_{age} = -0.069, t_{84} = -3.58, P < 0.001), and less anxious (PC3: β_{age} = -0.079, t_{85} = -3.02, P = 0.003) than younger females, and that higher-ranking females were more socially approachable (PC1: β_{Elo} = 0.36, t_{87} = 3.15, P = 0.002) and bolder (PC2: β_{Elo} = 0.85, t_{77} = 11.0, P < 0.001), but not less anxious (PC3: β_{Elo} = -0.03, t_{75} = -0.250, P = 0.80), than lower-ranking females. Because rates of aggression differed across social groups, we also tested whether group-level aggression predicted higher rates of anxiety among resident females, but did not find any association (PC3: $\beta_{group\_aggression/hr}$ = -0.20, t_{88} = -1.32, P = 0.19). The results of this analysis suggest that rank and age affect behavioral tendency, and that apart from levels of anxiety, "personality" attributes are primarily dependent on rank.

2.4.1.2. Causal effects of social context on behavioral tendencies

Based on our analyses of rank and behavioral tendencies in phase 1, we took advantage of the social group rearrangement at the study midpoint to test whether social approachability, boldness, and anxiousness would change in tandem with changes in dominance rank. Controlling for age and PC scores in phase 1, we found that experimentally manipulated changes in a female's Elo rating between phase 1 and phase 2 (ΔElo) were positively associated with changes in her social approachability ($PC1_{phase2}$: $\beta_{\Delta Elo}$ = 0.35, t_{41} = 2.28, P = 0.028) and boldness ($PC2_{phase2}$: $\beta_{\Delta Elo}$ = 0.96, t_{41} = 8.03, P < 0.001) in phase 2. In other words, improvements in rank increased component scores on PC1 and PC2 (Fig. 2.1), suggesting that social approachability and boldness were causally affected by an individual's social status. Improved rank was not associated with changes in anxiousness ($PC3_{phase2}$: $\beta_{\Delta Elo}$ = -0.06, t_{41} = -0.46, P = 0.65), supporting the idea that some, but not all, of an individual's behavioral tendencies are status-dependent.

2.4.1.3. Stability of behavioral tendencies across social contexts

No study to our knowledge has tested for cross-situational behavioral consistency in rhesus macaques after moving the same animals to a new social group where they occupied different dominance ranks. We therefore tested whether behavioral tendencies would be stable across the two study phases when controlling for rank and age effects (i.e., by using component scores that were orthogonal to rank and age). We found that boldness in phase 1 predicted phase 2 boldness (β_{PC2_phase1} = 0.45, t_{40} = 2.92, P = 0.006), and that anxiousness scores were weakly correlated across phases (β_{PC3_phase1} = 0.36, t_{40} = 1.82, P = 0.077). Social approachability was not correlated within-subjects (β_{PC1_phase1} = 0.08, t_{40} = 0.52, P = 0.61). Interestingly, after controlling for rank and age, social approachability and boldness were inversely related (r = -0.36, P < 0.001) throughout the study, whereas anxiousness was not associated with social approachability (r = -0.10, P = 0.36) or boldness (r = 0.04, P = 0.67).

2.4.2. Effects of rank and behavioral tendency on glucocorticoid regulation.

2.4.2.1. Diurnal cortisol

As expected, cortisol significantly decreased from morning to late afternoon (β_{time} = -0.46, t_{85} = -8.14, P < 0.001), consistent with the well-established diurnal cortisol rhythm. We did not find a main effect of rank or age on serum cortisol ($\beta_{time:Elo}$ = 0.04, t_{85} = 0.68, P = 0.50; β_{age} = 0.16, t_{85} = 1.23, P = 0.23); however, higher-ranking females who scored high on anxiousness (PC3) had elevated cortisol levels (i.e., increased output) throughout the day ($\beta_{Elo:PC3}$ = 1.33, t_{36} = 2.07, P = 0.046) (Fig. 2.2A). In addition, females who scored higher on social approachability than expected for their rank and age had a blunted diurnal rhythm, as shown by a smaller dynamic range across

the 3 timepoints ($\beta_{time:PC1}$ = 0.16, t_{85} = 0.68, P = 0.010) (Fig. 2.2B) and a somewhat shallower slope from 0800 to 1700 h (β_{PC1} = -0.12, t_{35} = -1.77, P = 0.085). Boldness was not associated with cortisol output or diurnal cortisol rhythm (Table S2.3).

2.4.2.2. Glucocorticoid negative feedback (DST)

As expected, Dex administration significantly reduced circulating cortisol levels (t_{89} = -11.5, P < 0.001). Both higher pre-Dex serum cortisol levels and serum Dex levels at the 24 h time point, the latter of which may reflect differences in Dex metabolism across subjects, predicted larger decreases in cortisol between pre- and post-Dex (24 h) samples ($\beta_{Cortisol\_preDex}$ = 0.60, t_{34} = 3.87, P < 0.001 and β_{Dex} = 1.62, t_{34} = 3.42, P = 0.002). However, we found no significant associations between negative feedback and age, dominance rank, or any of our three measures of behavioral tendency before (data not shown) or after controlling for differences in serum Dex concentration (Table S2.3).

2.4.2.3. Sensitivity to acute glucocorticoid challenge (DCT)

Serum cortisol levels were lower at 1.5 h (t_{43} = -3.04, P = 0.004) and 4.5 h after Dex administration (t_{43} = -8.26, P < 0.001). After controlling for baseline cortisol levels and serum Dex concentration at both post-Dex timepoints, which, as expected, predicted lower cortisol levels (1.5 h: β_{Dex} = -0.14, t_{34} = -3.69, P < 0.001; 4.5 h: β_{Dex} = -0.16, t_{34} = -2.21, P = 0.034), we found that Elo rating was positively associated with changes in cortisol at 4.5 h post-Dex (β_{Elo} = 0.70, t_{34} = 2.14, P = 0.039), though not at 1.5 h post-Dex (β_{Elo} = 0.26, t_{34} = 1.01, P = 0.32), providing some evidence for heightened Dex sensitivity among higher-ranking females. Age was not associated with changes in cortisol in this test (Table S2.3). Rank effects on Dex sensitivity at both timepoints differed somewhat depending on a female's social approachability score (1.5 h: $\beta_{Elo:PC1}$ = 0.43, t_{34}

= 2.24, P = 0.031; 4.5 h: $\beta_{Elo:PC1}$ = 0.43, t_{34} = 2.03, P = 0.051), such that only in more socially approachable females was higher rank associated with increased Dex sensitivity (Fig. 2.3A). We also found that more anxious females were more sensitive to Dex at 1.5 h (β_{PC3} = 0.66, t_{34} = 2.54, P = 0.016) (Fig. 2.3B), though this association was not significant at 4.5 h (β_{PC3} = 0.51, t_{34} = 1.68, P = 0.10). Decreases in cortisol in the DCT were not associated with glucocorticoid negative feedback in the DST (1.5 h: r = 0.01, P = 0.94; 4.5 h: r = -0.10, P = 0.53).

2.4.3. Causal effects of dominance rank on glucocorticoid regulation

The cross-sectional analyses above vary in their support of rank effects on measures of GC regulation, which is in part expected because different testing protocols capture different phases of HPA axis function (Herman et al., 2016). However, they are also less powerful than longitudinal analyses within females, when occupying different ranks. Thus, we reassessed our cortisol measures in each female at the end of the second phase of the study and modeled the effect of ΔElo on changes in cortisol across phases. We found that improvements in rank led to increased glucocorticoid negative feedback (DST: $\beta_{\Delta Elo}$ = 3.11, t_{40} = 2.22, P = 0.032) and increased sensitivity to acute Dex suppression at both timepoints (DCT: 1.5 h: $\beta_{\Delta Elo}$ = 1.36, t_{39} = 2.20, P = 0.034; 4.5 h: $\beta_{\Delta Elo}$ = 2.56, t_{39} = 2.87, P = 0.007) (Fig. 2.4). Diurnal cortisol slope was not affected by rank change ($\beta_{\Delta Elo}$ = 0.05, t_{41} = 0.21, P = 0.83), suggesting that improved rank causally improved stress-related regulation of cortisol by the HPA axis, but not basal cortisol output under unstimulated conditions.

2.5. Discussion

2.5.1. Behavioral characterization

To our knowledge, this study is the first to characterize behavioral tendencies ('personality') in rhesus macaques living in two completely different social environments (i.e., groups with non-overlapping composition, where study subjects occupied different social ranks in each group). Our results show that dominance rank is a major driver of several dimensions of personality, especially boldness and social approachability, although some intra-individual stability of boldness and anxiousness is detectable across groups and ranks. After controlling for rank, we also found that age predicted behavioral tendency, which may reflect overall age-associated declines in activity level (Moscrip et al., 2000) or more specific behavioral fluctuations that have been reported to occur with age in pigtail macaques (*Macaca nemestrina*) (Sussman et al., 2014). Together, these findings suggest that some behavioral tendencies in female rhesus macaques are more stable and trait-like (e.g. anxiousness), others are fluid and rank-dependent (e.g. social approachability), and others may be both trait-like and plastic (e.g. boldness) (Brent et al., 2014).

By definition, personality connotes behavioral stability across time and context. However, few studies of primate behavior have closely considered the interdependence between behavior and social context when attributing "personality" or temperament to an individual (Freeman and Gosling, 2010). Our results therefore pose a unique challenge for defining primate personality, since determinations of personality have tended to rely upon observational data gathered from individuals living in relatively stable social contexts (although see McGuire et al., 1994). Even if standardized testing is used to assess behavioral responses to fixed stimuli (e.g. approach-avoidance, human intruder) and observations are conducted without peers to limit social constraints, an individual's behavioral repertoire likely remains under the influence of their present social conditions, especially dominance rank. In particular, because rhesus macaques are thought to be highly despotic relative to other macaque species (James Adams et al., 2015), behavioral tendencies in rhesus macaques may be more influenced by dominance rank than in other species. Additionally, behavioral tendencies in wild nonhuman primates may also act as

significant determinants of rank change (Konečná et al., 2012). Our study was not designed to address this aspect of interdependency between rank and behavioral tendencies, since it was structured to specifically identify the causal effects of experimentally manipulated rank. However, this question will be important to address in future work, for instance by structuring social group formation based on standardized behavioral testing outcomes, or by exploring behavioral factors that predict deviation from matrilineally inherited dominance rank in wild populations (Lea et al., 2014).

2.5.2. Effects of rank and behavioral tendencies on glucocorticoid regulation

We performed three assessments of glucocorticoid regulation: one focused on diurnal cortisol levels, one on short-term sensitivity to Dex suppression (DCT), and one on sensitivity to Dex suppression over 24 h (DST). Scores on these three measures were uncorrelated with each other, supporting the notion that regulation of cortisol by the HPA axis involves distinct physiological processes (e.g. reactivity, recovery) that cannot be indexed by a single measurement or test (Herman et al., 2016). However, the results from the DCT and DST tests—the two that simulate the HPA response to cortisol release rather than cortisol output throughout the day—converge to support a contribution of dominance rank on glucocorticoid sensitivity. We observed this pattern in both the effects of rank changes across study phases (DST and DCT, Fig. 2.4) and in the effects of rank on Dex suppression in Phase 1 data alone (DCT). In agreement with previous studies (Michopoulos et al., 2012b; Shively et al., 1997), low ranking, presumably chronically stressed females, were consistently less sensitive to Dex suppression in all three analyses. In contrast, the lack of clear evidence for rank effects on diurnal cortisol dovetails with recent arguments that rank-baseline GC correlations, even when present, require multiple repeated measurements per individual to detect (Cavigelli and Chaudhry, 2012). Furthermore, it is possible that more complex, non-linear relationships between rank and glucocorticoid regulation exist (Cavigelli and

Caruso, 2015; Gesquiere et al., 2011), which necessitates further exploration with larger sample sizes.

Behavioral tendencies orthogonal to rank and age additionally contributed to glucocorticoid regulation in our sample. Females who scored higher on our anxiousness dimension (PC3) exhibited some evidence for increased sensitivity to Dex in the DCT (Fig. 2.3B), while females who scored higher on the social approachability dimension (PC1) showed blunted diurnal cortisol rhythms throughout the day (Fig. 2.2B). Further, we identified some evidence that behavioral tendencies moderate rank effects on glucocorticoid regulation. Specifically, we found that lower-ranking females who had higher scores on social approachability (PC1) than expected for their rank were less sensitive to acute Dex challenge, and lower-ranking females who had higher scores on anxiousness (PC3) than expected for rank secreted less cortisol throughout the day. These findings were unexpected and contrary to our initial predictions, as they seem to contradict reports that social affiliation is stress buffering (Ditzen and Heinrichs, 2014; Sanchez et al., 2015; Young et al., 2014), and that anxiousness is associated with increased cortisol output (Shackman et al., 2013).

We believe this apparent contradiction may be resolved by returning to our original definition of behavioral tendencies. Specifically, each of our behavioral components was defined by a composite suite of behaviors that may reflect different psychosocial states depending on a female's social status. PC1 was largely defined by the frequency and duration of "affiliative" interactions (e.g. groom, approach) that were initiated by a female's groupmates (Table 2.2), but not by affiliation per se. Indeed, approaches by higher-ranking individuals can be precursors to received threats or aggression as well as affiliative behavior, whereas approaches by lower-ranking groupmates are more likely to be non-threatening (i.e., the type of interaction that strengthens social bonds: Snyder-Mackler et al., 2016). Similarly, we characterized PC3 as "anxiousness"

because self-directed behaviors tend to increase during situations of uncertainty, social tension, or danger in nonhuman primates (reviewed in Aureli and Whiten, 2009). However, our observational methods did not permit us to examine whether these behaviors followed received aggression, so it is not clear whether self-scratching and self-grooming truly capture 'anxiousness' in this model. Thus, while our decision to attach simple terms to the behavioral PCs we calculated follows the precedent set by the literature (Freeman and Gosling, 2010), our findings suggest a need for caution in studies of animal 'personality'—especially in using terms like 'sociability' with normative or value-laden connotations. Additionally, future studies on animal behavior should avoid assuming a monotonic relationship between personality and physiology without first considering social context, including the contribution of social hierarchies.

2.6. Limitations

The current study has several limitations. First, because we studied only females, we cannot assess whether our findings generalize to male nonhuman primates, in which rank-GC correlations have been extensively described (Abbott et al., 2003; Cavigelli and Caruso, 2015; Gesquiere et al., 2011; Sapolsky, 1989). Second, our study design did not allow us to take into account variation in individual life histories (e.g. maternal experience, parity, birth weight) as a predictor of either behavior or cortisol: because our sample consisted of females across a large range of ages, differences in life history could be large. Similarly, we were not able to assess the effects of other individual characteristics, such as genotype (although our within-subjects analysis provides some measure of control for this source of variance). Third, because females were housed in varying social and demographic conditions prior to entering the study, we were not able to investigate the potential effects of historical dominance rank. This limitation is offset to a degree by evidence that the effects of rank are largely plastic after rank changes (Snyder-Mackler et al., 2016a; Tung et al., 2012), at least in this paradigm. Finally, our behavioral observations were conducted solely within

social groups of captive rhesus macaques. Future studies would benefit from combining social group observations with standardized behavioral testing paradigms, such as the human intruder test (Kalin and Shelton, 2003), or by testing whether our findings generalize to natural populations.

Table 2.1. Mean ± SEM levels of diurnal serum cortisol (ug/dl) for LHPA axis assessments.

Time of day	0800	1100	1700
A			
Diurnal Rhythm			
Phase 1	14.64 ± 0.48	12.05 ± 0.45	9.91 ± 0.60
Phase 2	14.89 ± 0.99	15.67 ± 0.83	10.92 ± 0.89
B			
Dexamethasone Suppression Test			
Phase 1	-	5.33 ± 0.44	-
Phase 2	-	6.21 ± 0.96	-
Time of day	0800	0930	1230
C[1]			
Dexamethasone Challenge Test			
Phase 1	5.71 ± 0.36	5.00 ± 0.33	2.39 ± 0.20
Phase 2	20.94 ± 0.90	16.86 ± 0.58	6.92 ± 0.30

[1]DCT cortisol measurements were systematically lower in Phase 1 than Phase 2. See Section 2.3.5 for additional details.

Table 2.2. Standardized, varimax-rotated factor loadings of social behaviors in principal components analysis (PCA)

Category	Behavior	PC1 (Social Desirability)	PC2 (Boldness)	PC3 (Anxiousness)
Dominance	Aggression (F)	-0.01	**0.72**	-0.17
	Submissive Gestures (F)	-0.16	**-0.70**	0.26
Anxiety	Self-Scratching Bouts (F)	0.13	0.03	**0.79**
	Self-Grooming (D)	-0.13	-0.05	0.49
Affiliation	Alone (D)	**-0.81**	-0.47	0.05
	Approaches Given (F)	0.40	**0.51**	0.21
	Approaches Received (F)	**0.78**	-0.18	0.05
	Contact (D)	**0.71**	0.09	-0.25
	Grooming Received (D)	**0.58**	0.40	0.14
	Grooming Given (D)	0.05	**0.75**	0.33
	Eigenvalue	3.19 (2.71, 3.82)	1.40 (1.34, 1.87)	1.20 (1.10, 1.48)
	Cumulative % Variance	32	46	58

Bold typeface indicates the strongest factor loadings ($|r| > 0.50$)

Eigenvalues with confidence intervals are shown, calculated from a bootstrapped distribution ($k = 10{,}000$)

D: duration (min/h); F: frequency (events/h).

Figure 2.1. Relationships between changes in Elo rating and changes in behavioral tendency. Changes in Elo rating from phase 1 to phase 2 were positively associated with changes in behavioral component scores from phase 1 to phase 2 for (A) social approachability (PC1: P = 0.028) and (B) boldness (PC2: $P = 6.0 \times 10^{-10}$), but not (C) anxiousness (PC3: P = 0.65), adjusted for age and phase 1 component score. More positive values along the x-axis reflect larger increases in rank, whereas more negative values reflect larger decreases in rank between phase 1 and phase 2.

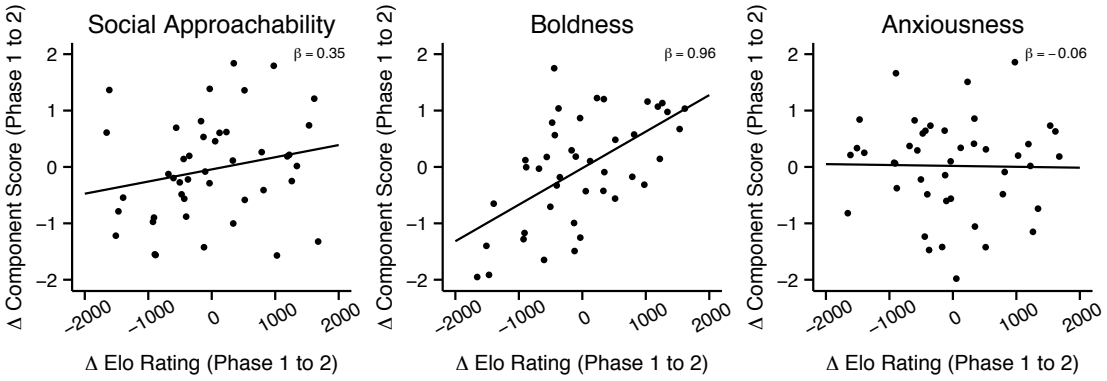


Figure 2.2. Relationships between Elo rating, behavioral tendency, and diurnal serum cortisol in Phase 1. (A) Among females with higher anxiousness (residual PC3 score; right panel) higher rank predicted increased cortisol output ($\beta_{Elo*\ PC3} = 0.16$, $t_{88} = 2.63$, $P = 0.010$). (B) Females who scored higher in social approachability (residual PC1 score; middle and right panels) had smaller diurnal decreases in cortisol than females with low residual PC1 scores ($\beta_{PC1*time} = 0.16$, $t_{88} = 2.63$, $P = 0.010$; left panel). Component scores are split into tertiles for visualization only; statistical models reported in the main text were fit using continuously distributed component scores (Table S2.3), but Pearson correlation (A) and β_{time} (B) for each tertile are shown in each panel to provide a summary of the stratified data.

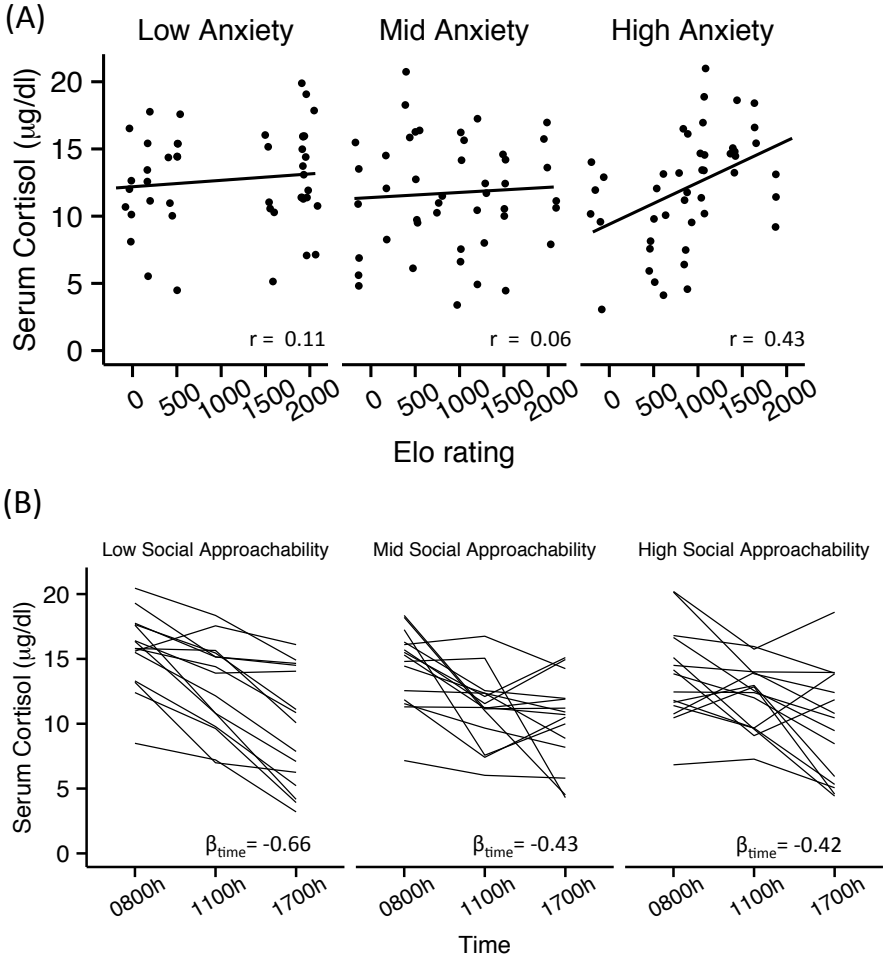


Figure 2.3. Relationships between Elo rating, behavioral tendency, and the cortisol response to acute dexamethasone challenge (DCT) in Phase 1. Dexamethasone (0.125 mg/kg) was administered at 0800 h immediately following baseline serum collection. Adjusting for other model predictors (Table S2.3), more positive y-axis values (i.e., larger change from baseline) indicate greater suppression of cortisol by Dex. (A) At 1.5h post-Dex administration, social approachability (residual PC1 scores) had rank-dependent effects on cortisol suppression ($\beta_{Elo*PC1}$ = 0.43, t_{34} = 2.24, P = 0.031): rank predicted sensitivity to Dex only among females who scored high on PC1. (B) At 1.5h post-Dex, anxiousness (residual PC3) was associated with increased cortisol suppression by Dex (1.5 h: β_{PC3} = 0.67, t_{34} = 2.54, P = 0.016). Component scores are split into tertiles for visualization only; statistical models reported in the main text were fit using continuously distributed component scores (Table S2.3), but Pearson correlations (A) for each tertile are shown to provide a summary of the stratified data.

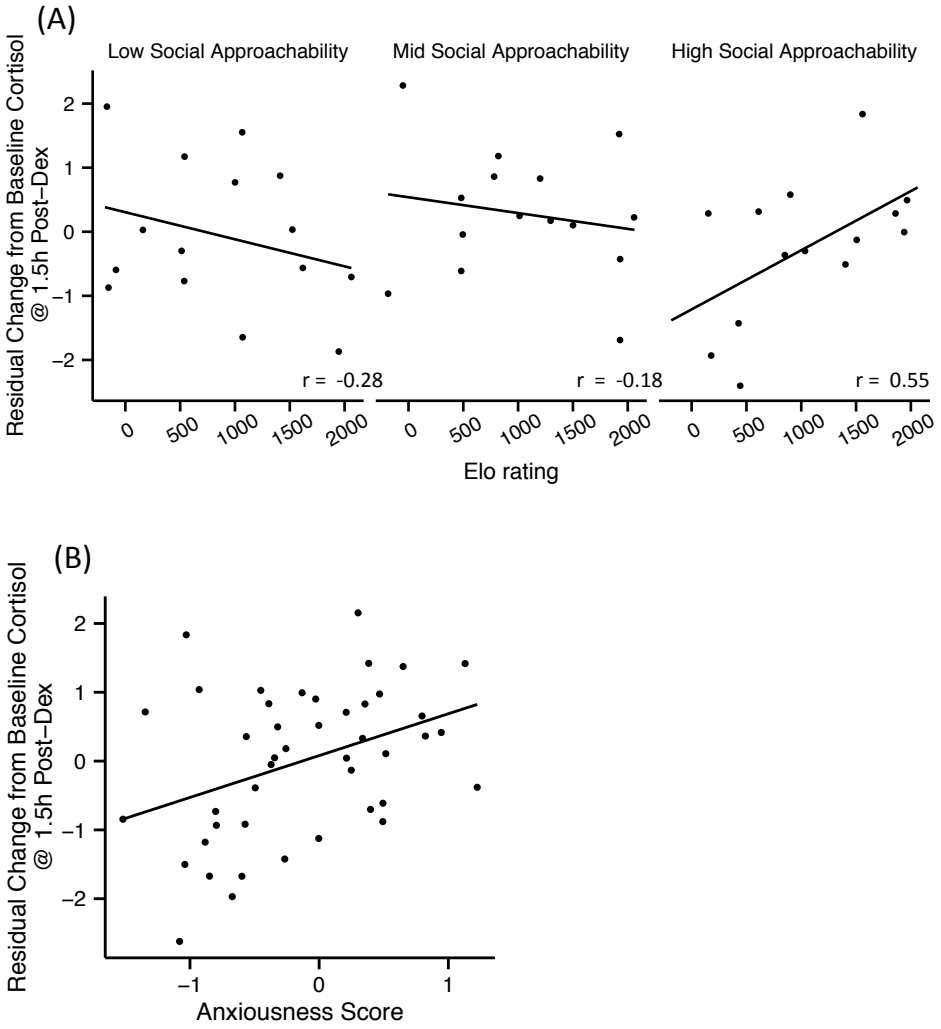


Figure 2.4. Changes in dominance rank causally affected glucocorticoid regulation. Improved Elo rating (i.e. rank) in phase 2 was associated with increased glucocorticoid negative feedback, as measured by (A) dexamethasone suppression of cortisol, and (B) increased sensitivity to acute dexamethasone challenge at both 1.5 h and 4.5 h post-Dex administration. Change in glucocorticoid negative feedback values from phase 1 to phase 2 (A) and change in sensitivity to acute Dex challenge (B) shown on the y-axis, adjusted for phase 1 values and phase 1 Elo rating. Significance (p-values) tests based LM results shown in Table S2.4.

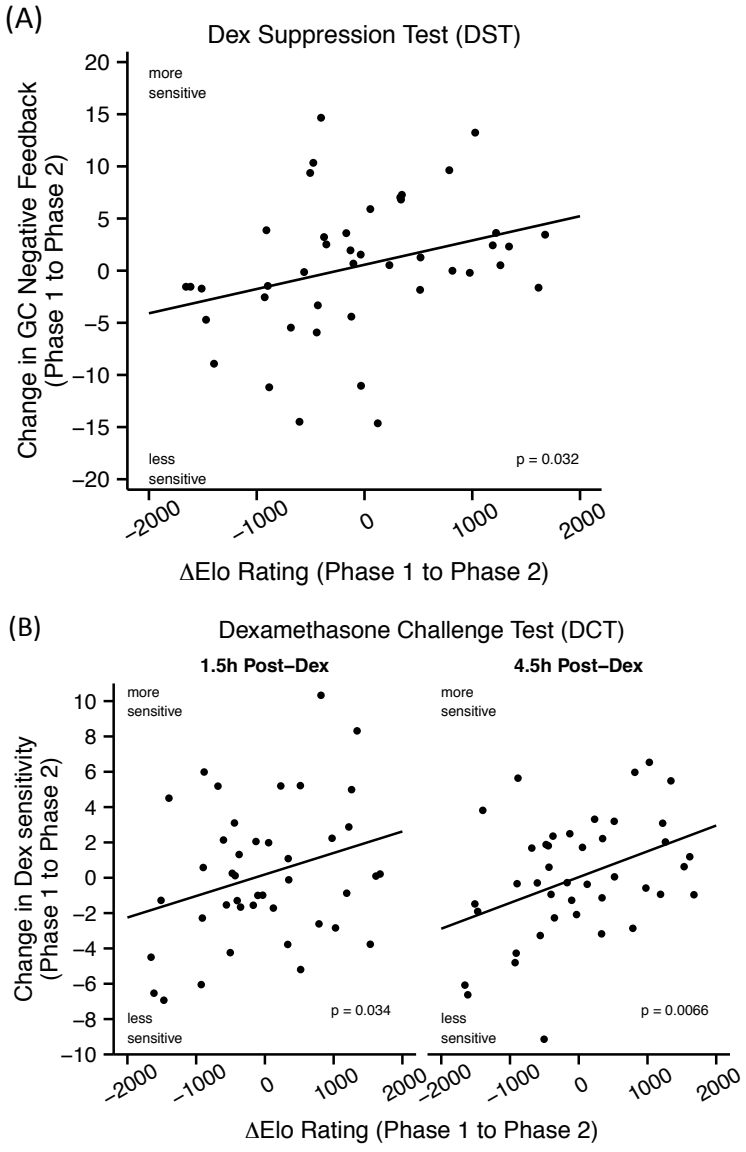


Table S2.1. Study subject characteristics and changes in glucocorticoid assessment outcomes between study phases. Standardized, varimax-rotated principal component (PC) scores were derived from principal components analysis (PCA) on ten social behaviors, adjusting for age, Elo rating, and social group. Cortisol changes were calculated as the difference between each female's respective measurement in phase 1 and phase 2 (phase 2 measurement − phase 1 measurement), where larger (more positive) values reflect increased diurnal slope or stronger suppression of cortisol by dexamethasone treatment.

	Phase 1									Phase 2								Cortisol change between Phases 1 and 2			
Female	Group	Age at intro (yr)	Order of intro	Date of Intro	Elo	Rank	PC1 Score	PC2 Score	PC3 Score	Group	Order of intro	Date of Intro	Elo	Rank	PC1 Score	PC2 Score	PC3 Score	Diurnal cortisol slope	DST	DCT (1.5h)	DCT (4.5h)
R01	A	8.5	1	1/14/13	1947	1	-0.45	0.71	-1.29	L	1	5/8/14	1504	2	0.217	2.121	-1.071	0.73	1.76	-8.95	-17.24
R02	A	15	2	1/14/13	1412	2	-1.07	0.05	-0.54	P	1	6/2/14	1751	2	-1.300	1.510	1.155	-0.47	10.59	-0.25	-9.5
R03	A	6.8	3	1/22/13	178	4	0.65	-1.13	-1.34	N	2	3/18/14	1793	1	1.329	0.897	0.806	0.13	-4.23	-6.47	-20.41
R04	A	4.5	4	1/29/13	443	5	1.53	-1.40	-1.40	K	4	4/7/14	-160	5	0.012	-1.895	1.020	1.52	-12.39	-9.05	-17.65
R05	A	5.8	5	3/20/13	820	3	0.39	-0.12	-0.04	R	2	4/10/14	651	3	1.019	0.400	-0.800	0.17	7.17	-1.92	-11.64
R06	B	8.8	1	1/28/13	1930	1	-0.01	0.83	-1.10	P	5	6/10/14	1033	4	-1.518	0.528	1.884	-0.25	9.80	-3.68	-9.38
R07	B	12.7	2	1/28/13	1296	2	-0.09	0.03	-0.97	L	3	5/12/14	613	4	-0.331	0.231	0.571	0.93	-1.30	-4.74	-13.29
R08	B	8.6	3	1/29/13	900	3	0.96	-0.32	-0.02	R	5	4/24/14	497	4	-0.893	-0.226	0.091	0.05	18.50	0.00	-5.63
R09	B	5.7	4	2/5/13	-154	5	-1.37	-1.37	-0.37	O	5	3/27/14	1036	3	0.490	0.853	0.914	1.90	2.37	-2.80	-8.07
R10	B	5.6	5	2/13/13	428	4	0.60	-0.01	-0.12	J	2	3/24/14	1769	1	0.212	1.111	-0.147	1.12	4.05	-8.11	-14.85
R11	C	8.8	1	2/4/13	1201	4	0.10	0.48	-0.46	R	3	4/14/14	1432	2	0.657	1.533	1.941	0.55	4.98	-5.01	-12.62
R12	C	6.7	2	2/4/13	537	2	-1.03	0.26	-1.00	J	3	3/25/14	1053	3	1.586	-0.338	-1.132	0.51	-2.54	-7.05	-16.68
R13	C	13.7	3	2/13/13	1860	1	0.33	0.49	-0.23	P	2	6/2/14	1485	1	-0.513	1.436	-1.050	-0.41	9.47	-4.13	-12.85
R14	C	5.5	4	2/26/13	152	5	0.34	-0.09	0.36	N	1	3/18/14	1828	2	-1.101	2.404	0.937	0.51	1.90	-1.71	-7.92
R15	C	4.8	5	3/26/13	850	3	1.02	-0.31	0.70	Q	5	6/16/14	-60	5	-0.665	-1.130	0.940	0.61	6.91	-1.58	-7.74
R16	D	8.9	1	2/11/13	1965	1	1.42	0.44	-1.25	Q	3	5/19/14	1081	3	-1.613	0.301	-0.207	0.40	-5.24	-8.40	-15.76
R17	D	4.7	2	2/11/13	1524	2	-0.38	3.01	-2.17	M	4	4/28/14	13	4	-1.092	-0.445	0.227	0.57	3.86	-2.73	-7.47
R18	D	7.9	3	2/13/13	513	4	-1.51	-0.57	-0.38	J	1	3/24/14	1774	2	-0.070	1.157	-0.679	0.59	0.65	-5.69	-14.68
R19	D	5.7	4	2/20/13	-168	5	-2.25	-1.63	-0.56	N	5	3/31/14	1053	3	0.574	-0.144	0.466	-1.87	1.20	-5.82	-13.96
R20	D	17	5	2/26/13	1066	3	-1.20	-0.23	-1.07	R	1	4/10/14	1882	1	-0.812	0.839	0.008	0.12	-0.67	-8.46	-19.78
R21	E	4.9	1	2/11/13	1501	2	0.47	0.49	0.33	L	2	5/8/14	941	3	0.948	0.429	1.044	0.25	6.44	-1.16	-7.65

R22	E	4.7	2	2/11/13	-51	5	-0.14	-1.47	-0.84	O	4	3/24/14	-83	5	1.685	-1.515	-0.189	0.28	-11.22	-0.01	-8.86
R23	E	5.7	3	2/14/13	781	3	-0.25	-0.43	0.05	J	5	4/7/14	-145	5	-0.729	-1.257	0.723	0.45	-1.28	1.73	-5.20
R24	E	8.7	4	2/20/13	611	4	1.58	-0.46	0.63	K	5	4/14/14	481	4	0.732	-0.993	1.497	-1.61	1.77	-5.21	-13.63
R25	E	15.2	5	3/11/13	2058	1	-0.32	0.59	-0.72	Q	2	5/15/14	1625	2	-0.904	1.011	0.881	0.76	6.13	-4.00	-12.38
R26	F	15.2	1	2/25/13	1922	1	-0.25	0.05	-1.89	Q	4	5/28/14	526	4	-0.888	-0.345	0.109	0.63	-2.20	-7.36	-14.59
R27	F	5.7	2	2/25/13	1403	2	1.05	1.04	0.30	M	5	4/16/14	1049	5	0.372	0.227	1.465	-1.55	7.00	-1.39	-8.34
R28	F	11.9	3	2/26/13	1034	3	1.29	-1.21	0.27	K	1	4/1/14	2011	1	1.565	-0.391	2.475	0.24	0.80	-3.29	-13.76
R29	F	8.8	4	3/7/13	481	4	-0.55	-0.94	-0.98	O	2	3/18/14	604	4	0.675	0.047	0.600	-2.85	-16.28	-3.95	-10.38
R30	F	6.8	5	3/11/13	160	5	-1.87	-1.03	-1.12	N	3	3/19/14	492	4	0.382	-0.537	0.660	-0.07	5.33	0.67	-6.77
R31	G	16.9	1	3/4/13	1939	1	1.19	-0.42	-1.82	P	3	6/3/14	325	5	0.838	-1.839	0.066	0.37	5.06	3.11	-0.26
R32	G	7.7	2	3/4/13	540	4	-1.01	0.54	-0.80	K	2	4/1/14	1567	2	-1.480	1.491	0.519	-0.97	12.26	0.27	-23.77
R33	G	4.7	3	3/13/13	1001	3	-0.17	0.60	-0.42	M	3	4/23/14	497	3	0.034	-0.431	0.292	-2.81	12.74	0.88	-1.52
R34	G	7.8	4	3/20/13	1506	2	0.84	1.10	-0.67	L	4	5/15/14	36	5	-0.736	-1.456	1.219	-0.01	0.44	-2.71	-3.16
R35	G	4.1	5	4/1/13	-86	5	-1.94	-1.32	1.28	O	3	3/19/14	1447	2	1.187	0.437	1.812	-0.24	NA	-4.95	-7.13
R36	H	5.8	1	3/11/13	1559	2	1.57	-0.44	-1.56	L	5	5/20/14	1906	1	1.718	-0.001	-1.002	0.84	12.76	-5.62	-12.03
R37	H	9.9	2	3/11/13	495	4	-0.36	-0.35	0.94	J	4	3/31/14	549	4	0.700	-0.383	-1.043	0.44	6.54	-5.47	-13.44
R38	H	12	3	3/13/13	2062	1	-1.80	0.10	-0.95	P	4	6/8/14	406	3	0.559	-1.687	-0.601	-0.63	7.15	1.56	-3.18
R39	H	9.9	4	3/19/13	1070	3	-1.28	-0.02	0.30	M	1	4/15/14	1857	1	0.306	0.026	0.176	-1.93	11.85	-1.82	-8.87
R40	H	6	5	6/23/13	-186	5	-0.76	-1.17	0.58	O	1	3/18/14	1996	1	2.343	1.041	-0.007	0.45	-1.56	-0.89	-5.24
R41	I	19.8	1	4/1/13	1931	1	-0.14	-0.31	-1.77	Q	1	5/15/14	1828	1	-0.711	0.471	-0.781	0.43	9.56	-3.07	-8.63
R42	I	2.8	2	4/1/13	1013	3	0.61	0.19	0.05	R	4	4/21/14	538	5	-0.105	0.924	1.292	-2.37	14.11	-2.74	-10
R43	I	2.9	3	4/2/13	481	5	0.38	-0.95	1.54	K	3	4/2/14	1001	3	-0.197	0.324	1.492	0.21	3.25	-3.08	-6.95
R44	I	3.7	4	4/10/13	1619	2	0.08	1.42	1.12	M	2	4/15/14	1584	2	0.067	1.340	1.132	-1.32	5.65	NA	NA
R45	I	3.6	5	4/17/13	-44	4	0.31	-1.11	-0.62	N	4	3/24/14	-166	5	-1.075	-1.680	0.321	-0.24	-6.64	NA	NA

Table S2.2. Serum cortisol (μg/dl) and dexamethasone (ng/dl) levels at each sampling time point for all GC assessments in Phases 1 and 2.

	Phase 1										**Phase 2**									
	Diurnal Cortisol			**DST**		**DCT**					**Diurnal Cortisol**			**DST**		**DCT**				
				Cortisol	Dex	Cortisol		Dex	Cortisol	Dex				Cortisol	Dex		Cortisol	Dex	Cortisol	Dex
Female	800	1100	1700	1100		800	930		1230		800	1100	1700	1100		800	930		1230	
R01	15.5	12.15	7.86	5.23	3.68	1.65	4.51	34.15	3.37	18.6	20.21	11.94	6.00	3.26	2.72	23.35	17.26	49.65	7.83	26.65
R02	19.3	15.15	14.65	5.28	4.52	7.33	4.13	31	1.89	18.7	22.71	23.19	22.30	2.73	3.28	22.81	19.36	66.4	7.87	39.95
R03	11.65	12.95	5.93	2.99	2.68	1.73	4.77	34.9	6.61	15.95	15.24	9.98	8.32	4.25	1.72	22.43	19	49.35	6.9	22.55
R04	11.8	9.67	13.85	8.15	1.36	1.41	5.24	27.25	5.11	13.2	20.59	10.96	8.93	21.83	4.26	20.31	15.09	39.15	6.36	16.5
R05	16.3	12.55	11.95	9.86	2.49	3.92	1.62	27.9	3.03	13.1	17.60	16.30	11.70	6.44	2.06	19.72	15.5	54.15	7.19	29.35
R06	18.35	11.15	11.2	13.5	1.65	8.52	8.95	34.6	3.64	16.35	19.94	25.22	15.04	17.77	1.02	19.93	16.68	43.65	5.67	22.85
R07	12.55	12.35	8.87	4.97	2.50	8.18	7.16	40.2	2.39	18.4	26.25	16.20	14.20	10.12	1.23	25.29	19.53	59.6	6.21	24.7
R08	16.65	12.55	9.46	9.49	3.30	11.1	7.63	33.9	3.65	18.25	22.40	25.10	14.75	3.54	2.88	24.31	20.84	62.55	11.23	39.9
R09	13.2	6.99	6.25	7.76	1.36	7.62	6.99	31.1	2.23	12.6	26.25	16.75	2.23	15.15	0.61	17.2	13.77	51.8	3.74	23.3
R10	20.2	15.75	18.6	13.5	0.65	10.45	8.6	32.75	2.8	14.3	20.35	12.80	8.64	6.5	1.66	32.33	22.37	61.5	9.83	28.25
R11	18.2	11	4.51	5.58	1.86	8.55	5.7	30.8	2.05	14.1	25.45	15.46	6.85	5.06	2.35	28.07	20.21	48.05	8.95	23.3
R12	17.75	15.15	14.5	5.33	1.05	4.48	4.29	31.25	1.77	12.95	19.19	16.53	11.33	9.25	1.43	26.5	19.26	55.5	7.11	27
R13	13.85	12	8.45	2.58	4.02	5.06	3.88	36.65	1.84	21.9	15.13	20.17	13.42	1.28	3.45	22.92	17.61	61.45	6.85	42
R14	14.15	9.08	11.85	2.11	1.24	6.41	2.99	25.65	1	12.1	14.64	11.28	7.77	2.41	1.1	19.27	14.14	52.5	5.94	25.8
R15	6.83	7.27	5.06	2.83	2.17	3.84	3.75	31.65	1.78	17.1	12.35	12.94	5.08	1.59	2.34	16.39	14.72	54.3	6.59	28.05
R16	16.8	15.95	13.9	4.39	1.96	5.91	4.69	36.9	2.01	15.5	9.44	7.60	2.97	1.28	1.87	29.16	19.54	53.05	9.5	27.9
R17	15.8	14.4	10.85	7.65	3.04	7.42	7.99	35.35	2.35	19.65	20.01	13.82	9.91	3.21	5.53	19.91	17.75	53.9	7.37	29.95
R18	13.3	9.78	5.22	2.37	3.08	6.2	5.75	36.2	1.72	17.45	17.79	10.42	4.40	2.36	3.66	29.52	23.38	54.8	10.36	12.65
R19	16.35	10.8	4.17	5.79	1.14	4.55	2.95	31.65	1.01	14.55	12.99	14.06	17.62	7.85	1.85	22.65	15.23	45.6	5.15	19.2
R20	20.45	18.35	14.9	1.76	5.85	5.7	3.86	41.65	1.17	20.45	16.90	16.95	10.24	1.03	4.86	31.92	21.62	60.9	7.61	35.2
R21	15.3	11.2	11.9	7.26	1.98	4.12	2.68	26.95	1.2	17.15	16.58	15.82	10.91	5.44	2.02	14.52	11.92	42.05	3.95	19.6
R22	17.25	7.57	9.99	6.7	1.49	5.34	2.65	29.25	0.82	12.45	11.75	10.90	1.93	21.25	1.25	18	15.3	44.05	4.62	26.8
R23	11.3	11.25	10.7	3.24	2.00	3.55	2.4	30.25	0.71	13.2	13.35	8.61	8.66	1.88	1.46	14.43	15.01	49.85	6.39	25.2
R24	10.45	12.85	4.57	3.39	1.94	4.02	2.93	29.9	1.01	12.8	4.20	13.95	12.85	2.72	1.38	21.13	14.83	49.9	4.49	26.35
R25	11.85	7.41	10.5	3.52	3.29	2.82	3.11	38.45	0.95	16.4	10.51	11.78	2.33	1.76	2.33	21.42	17.71	54.8	7.17	33.9
R26	15.7	11.55	14.95	2.52	3.83	3.91	2.8	34.15	0.99	19.25	12.68	8.18	6.26	1.35	3.26	25.24	16.77	60.15	7.73	32.45
R27	14.5	14	13.95	6.04	0.65	4.4	3.4	27.55	1.14	12.55	3.98	23.00	17.40	8.04	0.44	16.05	13.66	41.9	4.45	2.8

R28	10.75	13.95	10.79	1.99	3.74	4.07	4.05	35.95	1.59	19.25	18.49	17.00	16.39	4.24	5.08	25.49	22.18	64.75	9.25	35.4
R29	14.8	15.05	4.3	3.57	2.73	3.95	4.36	30.1	1.85	14.95	3.47	21.50	18.65	26.3	3.29	17.94	14.4	53.4	5.46	30
R30	17.65	15.45	11.1	8.01	2.29	5.43	4.14	26.9	1.08	9.96	15.33	16.27	9.37	3.5	2.57	21.88	21.26	52.95	10.76	25.7
R31	20.15	13.85	12.4	4.3	5.07	11.2	10.85	55.6	4.42	30	16.57	15.66	5.47	1.05	3.25	13.25	16.01	63.45	6.21	38.75
R32	15.8	15.65	10.07	5.09	2.79	2.78	0.89	34.7	5.81	13.6	19.35	24.60	22.35	1.78	1.71	29.53	27.91	59.5	8.79	31.35
R33	8.49	7.21	3.2	1.66	2.29	5.02	4.31	39	1.67	18.25	3.55	20.15	23.55	1.86	1.27	8.2	8.37	42.35	3.33	22.85
R34	15.1	9.58	4.42	1.97	4.67	6.97	8.07	50.85	3.23	23.1	14.70	9.09	4.07	1.04	0.48	15.89	14.28	43.95	8.99	27.75
R35	12.4	9.63	3.92	4.08	1.21	6.2	6.45	35.05	2.71	14.1	8.52	3.72	2.20	21.7	1	13.88	9.18	43.9	3.26	19.15
R36	11.4	9.66	5.32	2.22	4.18	4.17	3.68	40.15	2.49	21.45	27.70	21.85	14.05	1.65	3.29	20.57	14.46	59.5	6.86	31.2
R37	11.55	9.66	8.18	3.76	2.15	3.54	2.85	32.85	1.07	15.45	18.33	16.66	10.99	4.22	1.75	21.61	15.45	56.8	5.7	30.75
R38	17.6	10.8	7.09	4.94	3.25	8.17	7.21	36.1	3.79	19.95	12.88	16.23	8.06	3.22	1.7	15.47	16.07	56.75	7.91	31.2
R39	16.4	13.9	14.05	4.54	4.45	6.07	7.13	41	3.56	22.45	5.35	24.60	20.40	3.39	3.86	19.55	18.79	69.95	8.17	41.95
R40	14.45	12.35	10.9	3.85	1.46	6.41	5.34	28.85	2.36	12.61	14.30	15.75	6.70	8.81	2.36	14.37	12.41	69.05	5.08	37.05
R41	15.5	12.1	15.1	8.41	2.68	6.32	6.82	40.65	2.54	20.35	17.13	14.32	12.85	1.07	2.49	20.71	18.14	66.95	8.3	38.35
R42	16.1	16.75	14.25	12.05	1.43	8.49	6.63	33.5	2.62	12.7	2.37	29.05	21.85	10.24	1.49	22	17.4	43.65	6.13	21.45
R43	7.16	6.02	5.8	3.71	1.47	4.77	3.47	29.15	2.72	13.35	9.11	9.44	5.84	3.88	0.73	15.17	10.79	42.9	6.17	21.9
R44	15.6	17.55	16.1	5.84	3.38	9.58	8.26	43	3.28	24.2	3.15	19.10	15.55	1.74	4.37	NA	NA	NA	NA	NA
R45	12.45	12.4	10.45	6.25	1.21	NA	NA	NA	NA	NA	11.09	10.07	11.22	10.56	0.01	NA	NA	NA	NA	NA

Table S2.3. Linear regression (LM) and linear mixed-effects model (LMM) results testing the effects of behavioral tendencies, Elo rating (i.e. rank), and their interactions, on assessments of LHPA axis regulation in adult female rhesus macaques. R^2 represents proportion of total variance explained by the fixed effects in each model. Elo ratings were converted to a standardized normal distribution. A female's behavioral tendency scores were residuals of an LMM that regressed out her Elo rating, age, and group membership. Boldface indicates $P \leq 0.05$.

LHPA Axis Assessment	Outcome Measure	Independent variable	β	SE	*t*	*P*	R^2
Diurnal Cortisol	Serum Cortisol (μg/dl)	**Time**	**-0.46**	**0.06**	**-8.14**	**2.9×10^{-12}**	39.00%
		Age	0.16	0.13	1.23	0.226	
		Elo Rating	0.43	0.63	0.68	0.5	
		Social Approachability	-0.7	0.51	-1.37	0.176	
		Boldness	1.71	0.87	1.98	0.053	
		Anxiousness	-0.42	0.67	-0.62	0.536	
		Time x Elo Rating	0.04	0.05	0.68	0.5	
		Time x Social Approachability	**0.16**	**0.06**	**2.63**	**0.01**	
		Time x Boldness	0.07	0.1	0.72	0.472	
		Time x Anxiousness	0.1	0.08	1.33	0.187	
		Elo Rating x Social Approachability	0.3	0.42	0.7	0.487	
		Elo Rating x Boldness	-1.59	0.89	-1.79	0.081	
		Elo Rating x Anxiousness	**1.33**	**0.64**	**2.07**	**0.046**	
	Serum Cortisol Slope (μg/dl/h: 0800 to 1700 h)	Cortisol @ 0800 h	0.04	0.02	1.64	0.11	10.30%
		Age	0	0.02	-0.08	0.937	
		Elo	-0.05	0.08	-0.64	0.525	
		Social Approachability	-0.12	0.07	-1.77	0.085	
		Boldness	-0.12	0.12	-1.01	0.319	
		Anxiousness	-0.11	0.09	-1.22	0.23	
		Elo Rating x Social Approachability	0.04	0.06	0.63	0.532	
		Elo Rating x Boldness	0.08	0.13	0.63	0.532	
		Elo Rating x Anxiousness	-0.11	0.09	-1.13	0.264	
Dexamethasone Suppression Test	Δ Serum Cortisol (μg/dl: Pre- to Post-Dex)	**Pre-Dex Cortisol**	**0.6**	**0.15**	**3.87**	**0.0005**	49.60%
		Dexamethasone (ng/ml)	**1.62**	**0.47**	**3.42**	**0.002**	
		Age	-0.05	0.16	-0.3	0.77	
		Elo Rating	-0.79	0.62	-1.29	0.206	
		Social Approachability	0.21	0.45	0.46	0.646	
		Boldness	0.67	0.85	0.79	0.433	
		Anxiousness	0.7	0.61	1.16	0.253	

		Elo Rating x Social Approachability	0.28	0.43	0.66	0.515	
		Elo Rating x Boldness	-1.15	0.92	-1.25	0.219	
		Elo Rating x Anxiousness	0.14	0.68	0.21	0.835	
Dexamethasone Challenge Test	Δ Serum Cortisol (μg/dl: Pre- to 1.5 h Post-Dex)	**Pre-Dex Cortisol**	**0.35**	**0.08**	**4.44**	**9.1×10^{-5}**	47.90%
		Dexamethasone (ng/ml)	**-0.14**	**0.04**	**-3.69**	**0.0008**	
		Age	0.06	0.06	1.03	0.311	
		Elo Rating	0.26	0.26	1.01	0.317	
		Social Approachability	0.06	0.19	0.31	0.756	
		Boldness	0.63	0.34	1.38	0.072	
		Anxiousness	**0.66**	**0.26**	**2.54**	**0.016**	
		Elo Rating x Social Approachability	**0.43**	**0.19**	**2.24**	**0.031**	
		Elo Rating x Boldness	**-1.00**	**0.37**	**-2.71**	**0.011**	
		Elo Rating x Anxiousness	0.46	0.28	0.72	0.111	
	Δ Serum Cortisol (μg/dl: Pre- to 4.5 h Post-Dex)	**Pre-Dex Cortisol**	**0.99**	**0.09**	**10.8**	**1.5×10^{-12}**	76.20%
		Dexamethasone (ng/ml)	**-0.16**	**0.07**	**-2.21**	**0.034**	
		Elo Rating	**0.7**	**0.33**	**2.14**	**0.039**	
		Age	0.07	0.07	1	0.326	
		Social Approachability	-0.12	0.22	-0.56	0.582	
		Boldness	0.01	0.4	0.02	0.98	
		Anxiousness	0.51	0.3	1.68	0.103	
		Elo Rating x Social Approachability	0.43	0.21	2.03	0.051	
		Elo Rating x Boldness	0.25	0.43	0.58	0.569	
		Elo Rating x Anxiousness	0.14	0.33	0.43	0.671	

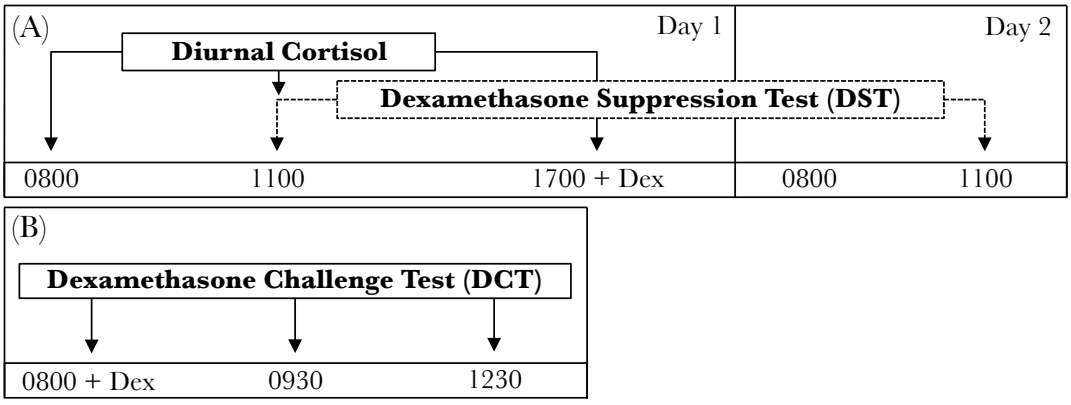
Table S2.4. Linear regression and generalized additive model (GAM) results testing the effect of rank change on changes in LHPA axis regulation. Delta (Δ) Elo rating is the difference between phase 2 and phase 1 values, converted to a standardized normal distribution. Cortisol outcome measurements in phase 1 and Elo rating in phase 1 were both included as covariates in each LM and GAM.

			Linear Model (LM)				Generalized Additive Model (GAM)		
LHPA Axis Assessment	Outcome Measure	Independent variable	β	Std. Error	*t*	*P*	edf	*F*	*P*
Diurnal Cortisol	Δ Cortisol Slope (Phase 2 – Phase 1)	Cortisol Slope (Phase 1)	0.52	0.42	1.26	0.217	5.78	1.57	0.178
		Elo Rating (Phase 1)	0.03	0.22	0.15	0.882	1.43	0.26	0.737
		Δ Elo Rating (Phase 2 – Phase 1)	0.05	0.23	0.21	0.832	2.08	1.41	0.253
Dexamethasone Suppression Test	Δ Cortisol (Phase 2) – Δ Cortisol (Phase 1)	**Δ Cortisol (Phase 1)**	**-0.59**	**0.28**	**-2.15**	**0.038**	**2.11**	**4.88**	**0.008**
		Elo Rating (Phase 1)	**4.98**	**1.38**	**3.61**	**0.0008**	**4.11**	**6.3**	**0.0002**
		Δ Elo Rating (Phase 2 – Phase 1)	**3.11**	**1.4**	**2.22**	**0.032**	**1**	**10.4**	**0.003**
Dexamethasone Challenge Test	Δ Cortisol @ 1.5 h (Phase 2) – Δ Cortisol @ 1.5 h (Phase 1)	**Δ Cortisol @ 1.5 h (Phase 1)**	**-0.79**	**0.28**	**-2.81**	**0.008**	**2.48**	**3.6**	**0.022**
		Elo Rating (Phase 1)	0.83	0.63	1.33	0.191	1	2.58	0.117
		Δ Elo Rating (Phase 2 – Phase 1)	**1.36**	**0.62**	**2.2**	**0.034**	**1.32**	**4.38**	**0.028**
	Δ Cortisol @ 4.5 h (Phase 2) – Δ Cortisol @ 4.5 h (Phase 1)	**Δ Cortisol @ 4.5 h (Phase 1)**	**-0.97**	**0.24**	**-4.04**	**0.0002**	**1.92**	**9.04**	**0.0004**
		Elo Rating (Phase 1)	1.63	0.91	1.79	0.081	1	3.81	0.059
		Δ Elo Rating (Phase 2 – Phase 1)	**2.56**	**0.89**	**2.87**	**0.007**	**3.68**	**3.92**	**0.008**

Table S2.5. Likelihood ratio testing results comparing regression models with and without each significant predictor of interest ($P < 0.05$) shown in Tables S2.3 and S2.4. *P*-values based on twice the difference in log-likelihoods for the two nested models (i.e. with and without the specified predictor) compared to a Chi-squared distribution.

LHPA Axis Assessment	Outcome Measure	Independent variable	χ^2	ΔAIC	*P*
Diurnal Cortisol	Serum Cortisol (μg/dl)	Time x Social Approachability	2.9	0.9	0.089
		Elo Rating x Anxiousness	5.1	3.11	**0.024**
Dexamethasone Challenge Test	Δ Serum Cortisol (μg/dl: Pre- to 1.5 h Post-Dex)	Anxiousness	7.63	5.63	**0.006**
		Elo Rating x Social Approachability	6.34	4.07	**0.025**
		Elo Rating x Boldness	8.58	6.58	**0.003**
	Δ Serum Cortisol (μg/dl: Pre- to 4.5 h Post-Dex)	Elo Rating	5.59	3.59	**0.018**
		Elo Rating x Social Approachability	6.95	3.02	**0.043**
Dexamethasone Suppression Test	Δ Cortisol (Phase 2) – Δ Cortisol (Phase 1)	Elo Rating	12.4	10.4	**0.0004**
		Δ Elo Rating (Phase 2 – Phase 1)	5.11	3.11	**0.024**
Dexamethasone Challenge Test	Δ Cortisol @ 1.5 h (Phase 2) – Δ Cortisol @ 1.5 h (Phase 1)	Δ Elo Rating (Phase 2 – Phase 1)	5.04	3.04	**0.024**
	Δ Cortisol @ 4.5 h (Phase 2) – Δ Cortisol @ 4.5 h (Phase 1)	Δ Elo Rating (Phase 2 – Phase 1)	8.23	6.23	**0.004**

Figure S2.1. Sampling outline for LHPA axis measurements. Diurnal cortisol assessment and the dexamethasone suppression test (DST) were conducted on two consecutive days in both study phases, shown in (A). Arrowheads show sample collection times of day and dexamethasone injections, where indicated. Samples for diurnal cortisol were collected at 0800, 1100, and 1700 h. Samples for the DST were collected at 1100 h on two consecutive days, with the first 1100 h sample shared with the diurnal cortisol assessment. The dexamethasone challenge test (DCT) was administered on average 61 d following each female's diurnal cortisol and DST assessments, and samples were collected at approximately 0800, 0930, and 1230 h over a single day, indicated in (B).



Chapter 3: Low dominance rank desensitizes peripheral blood leukocytes to redistribution by glucocorticoids and down-regulates adhesion molecule expression in female rhesus macaques.

3.1. Abstract

Glucocorticoids released by the hypothalamic-pituitary-adrenal (HPA) axis in response to acute stressors direct circulating white blood cells (e.g., leukocytes) into target tissues, thereby enhancing the immune system response to injury or pathogen exposure. However, unrelenting stressors desensitize leukocytes to glucocorticoid signals, which may suppress leukocyte mobilization by cortisol and increase leukocyte infiltration into tissues implicated in inflammatory diseases. In order to test whether chronic psychosocial stress causally affects leukocyte trafficking, as well as the role of glucocorticoid sensitivity and cellular adhesion molecule (CAM) expression in trafficking dynamics, we studied an animal model of social subordination stress in adult female rhesus macaques (*Macaca mulatta*). We performed two sequential experimental manipulations of dominance rank in 45 adult females, allowing us to characterize leukocyte responses to acute psychosocial and pharmacological challenges in each individual while she occupied two different dominance ranks. We found that low social rank was associated with decreased mobilization of classical monocytes and decreased recovery of T lymphocytes post-challenge. Low dominance rank was causally associated with decreased CAM mRNA expression across the five major leukocyte subtypes we studied, although expression levels only influenced trafficking dynamics in B cells. Finally, we found that resistance to cortisol suppression by dexamethasone predicted smaller proportional changes in monocytes and cytotoxic T cells following dexamethasone challenge, suggesting that glucocorticoid resistance manifests simultaneously in the HPA axis and in certain immune cell types. Our findings indicate that certain immune cell subtypes (e.g., monocytes, T lymphocytes) succumb to glucocorticoid insensitivity to redistribution more readily than others (B cells, NK cells), which may play a role in the pathophysiology of chronic stress-associated inflammatory conditions, autoimmune diseases, and mood disorders.

3.2. Introduction

Regulation of leukocyte distribution throughout the body is an important intersection between the hypothalamic-pituitary-adrenal (HPA) axis and immune system. Stressful experiences in mammals stimulate the release of glucocorticoids, which facilitate rapid mobilization of white blood cells (leukocytes) into the bloodstream, followed by leukocyte trafficking out of blood and into target tissues. Stressor-induced leukocyte redistribution is considered an adaptive, essential component of the immune response (Dhabhar, 2009) and has been experimentally demonstrated to enhance immunity following wounding (reviewed in Dhabhar, 2013) and antigen exposure (Edwards et al., 2006). By contrast, repeated activation of the body's stress response systems, which occurs in chronic social stress, leads to allostatic changes in the body's stress response systems that are linked to immunosuppression and autoimmunity (Kemeny and Schedlowski, 2007). Despite the involvement of leukocyte trafficking in the pathophysiology of many inflammatory conditions (cardiovascular disease: Galkina and Ley, 2007; Swirski and Nahrendorf, 2013; asthma: Lommatzsch et al., 2006; rheumatoid arthritis: Palmer et al., 2006), and likely role in mood and anxiety disorders (Hodes et al., 2015; Miller, 2010; Wohleb et al., 2015), surprisingly little is known about how chronic stress affects leukocyte redistribution during an acute stress response.

Physiological responses to acute stressors are typically biphasic, beginning with activation of complex adaptive pathways, and ending as the affected systems return to their baseline state. Glucocorticoid (GC) secretion from the adrenal cortex generally follows this biphasic pattern and functions as a primary negative regulator of the stressor-evoked immune response via glucocorticoid receptor (GR)-mediated inhibition of proinflammatory signaling (Smoak and Cidlowski, 2004). However, under chronic stress conditions, the HPA axis response to acute stressors may be hyper-reactive, hypo-reactive, or delayed in returning to baseline (reviewed in Chida and Hamer, 2008), and HPA axis dysregulation is frequently associated with a

hyperinflammatory state (Rohleder et al., 2010). In particular, leukocyte insensitivity to GCs may result from various post-translational modifications to GR (Pace et al., 2007; Silverman and Sternberg, 2012) or reduced GR expression (Pariante, 2004; although see Miller et al., 2008), and functional impairments in GR signaling have been demonstrated via increased cytokine responses to *ex vivo* antigen stimulation (Engler et al., 2005; Miller et al., 2005). Recent studies in chronically stressed humans (Cole, 2008) and rhesus monkeys (Cole et al., 2009) suggest that decreased leukocyte redistribution by cortisol may also be a functional biomarker of GC insensitivity. However, these studies focused on total numbers, proportions, and ratios of the most abundant circulating leukocytes (i.e., neutrophils, monocytes, and lymphocytes), which are heterogeneous with respect to GR expression (Gotovac et al., 2003; Strickland et al., 2001), sensitivity to redistribution by GCs (Dhabhar et al., 2012, 1995), and mobilization in response to an acute psychological stressor (Bosch et al., 2005, 2003). Thus it remains unclear whether certain leukocyte subtypes are more or less susceptible to the effects of chronic social stress on redistribution by GCs, which is important to understanding the mechanisms by which GC insensitivity is linked to inflammatory disease and mood disorders.

There is emerging evidence that increased proinflammatory and decreased GR-mediated signaling in chronic stress may be more pronounced in particular lymphoid or myeloid cell subsets (Cole, 2010). For instance, Cole et al. found that differential gene expression signatures in peripheral blood leukocytes from socially isolated humans originated from monocytes, dendritic cells, and B cells, but not from helper T ($CD4^+$), cytotoxic T ($CD8^+$), or natural killer cells (Cole et al., 2011; though helper T cells were implicated in rhesus macaques exposed to early life stress (Cole et al., 2012). More recently, classical monocytes ($CD14^+CD16^-$), but not non-classical monocytes ($CD14^+CD16^+$), were identified as the cellular source of blunted GR-mediated signaling in monocytes from chronically stressed humans and rhesus monkeys (Cole et al., 2015; Miller et al., 2014). Interestingly, leukocytes from the same animals exhibited redistributional

insensitivity to endogenous cortisol levels (Cole et al., 2015), though lymphoid and myeloid subsets were not assessed. Furthermore, these studies attributed gene expression signatures to each cell subtype by applying a bioinformatic tool to expression data derived from all blood leukocytes, rather than isolating and independently profiling each subset, so the extent to which transcriptional profiles are shared across subsets is difficult to interpret.

Leukocyte redistribution by glucocorticoids occurs via many of the same mechanisms that mediate immune cell trafficking in normal surveillance pathways or to sites of inflammation. For instance, leukocyte attachment to vascular endothelium (a critical step in leukocyte trafficking) is dependent upon conformational changes in cellular adhesion molecules (CAMs) (Laudanna and Alon, 2005), and CAM expression on the leukocyte surface is increased by acute psychological stressors (Greeson et al., 2009; Redwine et al., 2003) and decreased by synthetic glucocorticoids (Dhabhar et al., 2012; Goulding et al., 1999). Leukocyte CAMs are transmembrane proteins from the integrin and selectin families (e.g., LFA-1, Mac1, VLA-4, L-selectin) (Schnoor et al., 2015), some of which contain GR-binding sites within promoter regions or are transcriptionally activated by nuclear factor kappa B (NF-kB), which is regulated by GR (Pitzalis et al., 2002). Importantly, leukocyte subtypes express CAM proteins on the cell surface at different levels (Dimitrov et al., 2010a), which may mediate differences in subset mobilization and trafficking in response to GCs and acute psychological stressors (Besedovsky et al., 2014; Bosch et al., 2005; Cavalcanti et al., 2007; Dhabhar et al., 2012; Freier et al., 2010). In response to acute stressors, leukocytes, particularly monocytes and T lymphocytes, can cross the blood-brain-barrier (BBB) via interactions with endothelial CAMs and influence the local neuroinflammatory milieu, thus impacting mood and behavior (Miller and Raison, 2016). More specifically, monocyte infiltration into the CNS following repeated social defeat increases anxiety-like behavior in mice (Wohleb et al., 2014, 2013), whereas T lymphocyte (particularly $CD4^+$) ingress into the brain may serve neuroprotective and anti-inflammatory functions that inoculate against the development of stress-

induced depressive behavior (Miller, 2010). It is possible that altered responsiveness of these cells to glucocorticoids or differential CAM expression in chronic stress may mediate their recruitment into the CNS and subsequent effects on neuroinflammation and behavior. Despite the involvement of GC signaling in regulating CAMs, to our knowledge no studies have investigated whether chronic stress modifies CAM gene expression, or whether CAM gene expression is associated with *in vivo* leukocyte sensitivity to redistribution by GCs.

In this study, we attempt to elucidate the effects of the social environment, glucocorticoid sensitivity, and CAMs on leukocyte redistribution. To accomplish this, we assessed the relative contributions of chronic stress (as measured by dominance rank in macaques), cortisol dynamics, and basal CAM mRNA expression in FACS-isolated subtypes on the *in vivo* redistributional response of neutrophils, monocytes, T cells, B cells, and natural killer cells to acute psychosocial and pharmacological challenges in group-housed adult female rhesus macaques. We performed two assessments of leukocyte redistribution: (1) absolute changes circulating cell numbers following brief social separation stress, and (2) relative changes in blood composition following pharmacological challenge with the synthetic glucocorticoid, dexamethasone (Dex). Captive primate models provide a translational opportunity to investigate the links between dominance rank and stress physiology because social group membership can be systematically reorganized in ways that are simply not feasible with humans or wild nonhuman primates. To take advantage of this, we constructed new social groups of adult females and employed a mid-study social group rearrangement, allowing us to longitudinally assess the same females living in two distinct social groups at different social ranks. We hypothesized that: (1) low dominance rank would be associated with leukocyte insensitivity to the redistributional effects of cortisol and Dex; (2) resistance to cortisol suppression by Dex would predict leukocyte insensitivity to redistribution; (3) low dominance rank would be associated with increased leukocyte expression of CAMs; (4) higher CAM expression levels would be predict increased leukocyte redistribution; and (5) increased

monocyte and decreased T lymphocyte redistribution by Dex would predict behavioral tendencies associated with depression and anxiety disorders.

3.3. Methods

3.3.1. Study subjects and dominance rank assignment

Study subjects were 45 adult female rhesus macaques (*Macaca mulatta*) housed in nine, mixed-age social groups of five females each at the Yerkes National Primate Research Center (YNPRC). Group formation began in January 2013 with serial introduction of sexually mature, reproductively intact females into indoor run housing over a 2-15 week period until all groups included five unrelated adult females (see Snyder-Mackler et al., 2016 for complete description of group formation procedure). In this paradigm, females introduced earlier occupied higher Elo ratings, a continuous measure of dominance rank in which higher scores correspond to higher status (order of group entry and Elo rating: Phase 1: $r = -0.54$, $p < 0.001$, $n = 45$ females; Phase 2: $r = -0.68$, $p < 0.001$, $n = 45$ females). The Elo method updates an individual's rating following each dominance interaction based on the pre-interaction probability that she would win or lose the agonistic encounter (Albers and de Vries, 2001; Elo, 1978; Neumann et al., 2011b) and distinguishes adjacently ranked individuals that are closely matched in relative dominance from those that are more clearly differentiated. We calculated Elo ratings from all dyadic dominance interactions that occurred after each group was fully formed, which were derived from 398 h of weekly focal observations on the 18 groups (mean per group = 22.1 h, range = 14.5 – 27.5 h; totals = 223.5 h in Phase 1, and 175 h in Phase 2). Each subject's initial Elo rating was set at 1000, and the baseline number of points granted or deducted following an interaction (k) was set to 100. The number of points was then weighted for each subsequent interaction by the expected probability of that individual winning or losing, based on a logistic function that was updated

following each dominance interaction. Dominance hierarchies were rapidly established following group formation and rearrangements, and Elo ratings at the end of each study phase were highly correlated with ratings at 10 weeks post-group formation (r_{88} = 0.89, $P < 0.001$). Female age was correlated with dominance rank in Phase 1 (r_{88} = 0.56, $P < 0.001$), but not in Phase 2 (r_{88} = 0.27, $P = 0.07$); however, to control for the known effects of age on leukocyte proportions and function (Stervbo et al., 2015a, 2015b) we included age as a covariate in all of our analyses. Final Elo ratings within each study phase were converted to z-scores for statistical analysis and Elo computations were performed using the *EloRating* package (v 0.43) in *R*.

The present study was divided into two phases: Phase 1 (February 2013 – March 2014) and Phase 2 (April 2014 – March 2015), and the same 45 subjects were studied in each phase. Phase 2 groups were comprised of females who all shared the same or similar dominance ranks in Phase 1 (maximum difference of 1 ordinal rank value), which altered ranks in 80% (36 of 45) of subjects across the two phases such that Elo ratings in Phase 2 were uncorrelated with ratings in Phase 1 (r_{88} = 0.063, P = 0.68). This allowed us to test for and infer causal effects of rank on our physiological measures of interest. In both phases, behavioral observations started after the last (fifth) female was introduced into the group, and biological sample collection started 10-16 weeks thereafter to ensure that rank hierarchies were stably established. Females were randomized into groups, and we avoided co-housing females who had previously had social contact with one another (97% of 180 total co-housed dyads had no prior social contact). Close kin were not housed in the same groups. Animals had unrestricted access to typical low-fat, high fiber nonhuman primate diet throughout the study, and the Emory University Institutional Animal Care and Use Committee approved all procedures in accordance with the Animal Welfare Act and the NIH "Guide for the Care and Use of Laboratory Animals."

3.3.2. Social separation stressor and dexamethasone challenge

In order to test whether dominance rank and cortisol regulation were associated with leukocyte redistribution in response to an acute psychosocial stressor, in Phase 1 of the study we temporarily removed each female from her social group for 30 min and collected multiple blood samples to quantify serum cortisol levels and leukocyte counts. Brief periods of social separation (SS) reliably increase serum cortisol in group-housed rhesus macaques (Arce et al., 2010). In this assessment, baseline blood samples were obtained at 0800 h within 10 min of entering the animal group housing area to minimize arousal. The subject was then removed from her social group and transported in a transfer box (18 x 15 x 26 in.) to a test cage measuring 0.7 m x 0.6 m x 0.8 m in an unfamiliar location. At the end of a 30 min separation period, a post-SS blood sample (0845 h) was collected and the subject was immediately returned to home caging. A third blood sample was obtained at 1 h post-SS (0945 h), followed by a fourth and final sample at 4 h post-SS (1245 h) to assess recovery from the stressor (Table S3.2). Groupmates were all tested in the same week, and testing of all 45 subjects was carried out from late October 2013 to early December 2013. All animals were trained for conscious venipuncture using established procedures (Michopoulos et al., 2012b).

We also evaluated subjects after receiving a 0.125-mg/kg intramuscular (IM) dose of dexamethasone (Dex) once in both study phases (i.e., such that each female occupied two different dominance ranks) in order to test for causal effects of cortisol regulation and dominance rank on leukocyte redistributional sensitivity to glucocorticoids (GC). Specifically, this assessment captured short-term sensitivity to suppression of endogenous cortisol by the HPA axis. Baseline blood samples were collected at 0800 h, immediately prior to Dex injection, and a second post-Dex blood sample was collected 1.5 h later to measure changes in blood composition of circulating leukocytes, serum cortisol, and dexamethasone levels (Table S3.2).

3.3.3. Cortisol assay and flow cytometry

To measure leukocyte composition, cortisol, and dexamethasone levels in peripheral blood at each time point, we drew 6mL total of blood without anesthesia from each female into a 2-ml EDTA-treated tube and a 4-ml Vacutainer serum separator tube. Both tubes were immediately placed on ice and the 4-ml tube was centrifuged at 2,000 x *g* for 15 min using an Allegra 6R refrigerated centrifuge (Beckman Coulter, Inc.). Sera were stored at -20 °C until assayed for cortisol and dexamethasone in duplicate using LC/MS (for complete description of cortisol and dexamethasone quantification methods, see Section 2.3.5). From the 2mL tube, approximately 500 µl of blood was transferred into a polystyrene flow cytometry tube in a sterile hood, washed once with Dulbecco's phosphate-buffered saline (D-PBS) + 0.5% bovine serum albumin (BSA) and stained in the dark for 30 min at 20 °C with antibodies to identify 9 different leukocyte subtypes: helper T cells ($CD3^+/CD16^-/CD4^+/CD8^-$), cytotoxic T cells ($CD3^+/CD16^-/CD4^+/CD8^-$), double-positive T cells ($CD3^+/CD16^-/CD4^+/CD8^+$), natural killer (NK) cells ($CD3^-/CD16^+$), natural killer T (NKT) cells ($CD3^+/CD16^+$), $CD8^-$ B cells ($CD3^-/CD16^-/CD8^-/CD20^+$), $CD8^+$ B cells ($CD3^-/CD16^-/CD8^-/CD20^+$), classical monocytes ($CD14^+/CD16^-$), and non-classical monocytes ($CD14^+/CD16^+$) (see Supplementary Table S3.8 for complete listing of conjugated antibodies). Red blood cells were lysed for 10 min using BD-FACS Lysis Solution (BD Biosciences, San Jose, CA) and stained cells were washed twice in D-PBS + 0.5% BSA, then fixed in 1% paraformaldehyde for acquisition on an LSR-II flow cytometer (Beckton-Dickinson, Franklin Lakes, NJ). Single-stained compensation controls were run in parallel to experimental samples using anti-mouse Ig-κ polystyrene BD CompBeads according to manufacturer protocols (BD Biosciences, San Jose, CA). The remaining fraction of blood (1.5 ml) was used for complete blood counts (CBC), recorded using a Sysmex KX21N automated cell counter. We used FlowJo software (v.9.5.4 Tree Star, Inc., Ashland, OR) to quantify relative cell counts (i.e., proportions), as indicated in Fig S3.1. Total numbers of lymphocyte and monocyte subsets were obtained by

multiplying percentage values obtained from the flow cytometer by the corresponding sample's total lymphocyte and monocyte counts obtained from the CBC.

3.3.4. Gene expression in FACS-isolated leukocyte subtypes

FACS and library construction. To measure gene expression levels in purified cell populations, we drew 12-20 ml of blood from each female, purified the PBMC fraction using density gradient centrifugation, and performed fluorescent-activated cell sorting (FACS) on a BD FACSAria machine housed at the Duke Human Vaccine Institute Flow Cytometry Core. Cell types were sorted as follows: helper T cells ($CD3^+/CD4^+/CD8^-$), cytotoxic T cells ($CD3^+/CD4^-/CD8^+$), classical monocytes ($CD3^-/CD20^-/HLA\text{-}DR^+/CD14^+$), natural killer cells ($CD3^-/CD20^-/HLA\text{-}DR^-/CD16^+$), and B cells ($CD3^-/CD20^+/HLA\text{-}DR^+$) (see Figure S3.1 for visual representation of sorting strategy; see Table S3.8 for antibodies). RNA-sequencing (RNA-seq) libraries for each sample were constructed using the NEBNext Ultra RNA Library Prep Kit (New England Biolabs, Ipswich, MA) from 200 ng of total RNA using the NEBNext Poly(A) mRNA Magnetic Isolation Module. The mRNA was reverse transcribed into cDNA, ligated to Illumina adapters, size-selected to a median of ~350 bp, and amplified via PCR for 13 cycles. Each sample was tagged with a unique molecular barcode and 10-12 pooled samples were run on an Illumina HiSeq 2500 with single-end 100 base-pair sequencing.

Read alignment and count normalization. After sequencing, adapter sequences were trimmed from read ends using *Trim Galore!* (v0.2.7), which were then mapped to the rhesus macaque genome (*MacaM,* v7.6.8) (Zimin et al., 2014) using the STAR 2-pass method (Dobin and Gingeras, 2015). Reads that uniquely mapped to each annotated *MacaM* gene were collated using *HTSeq-count* (v0.6.1) with the "intersection-nonempty" option (Anders et al., 2014). Lowly expressed genes in each cell type (median RPKM ≤ 2) were then filtered out, and read count matrices normalized using the

voom function from the *limma* package in R (Ritchie et al., 2015). Normalized expression values were then modeled as a function of the sample female's social group membership (9 social groups in each phase, 18 distinct groups in total) in order to control for biological variation related to differences in group dynamics and technical batch effects associated with sample collection and processing. Thus, residuals of the model relating normalized expression to social group identity were used as the primary outcome measure in subsequent analyses.

Genotyping and rank effects on gene expression. We used genotype data to control for genetic relatedness among individuals in our analyses (although pairwise genetic relatedness in our sample population was low, several close kin were included in the data set, though never housed in the same social group). To accomplish this, we combined RNA-seq reads for all five purified cell types for each female and called variants using HaplotypeCaller from the Genome Analysis Toolkit (GATK v3.3.0), adhering to "best practices" for variant calling in RNA-seq (Genome Analysis Tool Kit Development Team, Broad Institute). After genotyping, sites that passed the following filters were retained: quality score ≥ 100; QD < 2.0; MQ < 35.0; FS > 60.0; HaplotypeScore > 13.0; MQRankSum < -12.5; and ReadPosRankSum < -8.0. Kinship was estimated with the program lcMLkin (Lipatov et al., 2015) using single nucleotide variants that were genotyped in all 45 females and thinned to be at least 10 kb apart (N = 54,165).

To identify genes that were significantly affected by dominance rank, we used a linear mixed-effects model (LMM) that controls for relatedness within the sample (Kang et al., 2008; Yu et al., 2006; Zhou and Stephens, 2012) and analyzed each of the five data sets (i.e., cell types) separately using the R package *EMMREML* (Akdemir and Godfrey, 2015). For each gene in the cell type-specific data set, the effect of dominance rank on gene expression levels across phases was estimated using the following model:

$$y = \mu + r\beta + a\gamma + Zu + \varepsilon,$$

$$u \sim MVN(0, \sigma_u^2 K),$$
$$\varepsilon \sim MVN(0, \sigma_e^2 I)$$

where y is the n by 1 vector of residual gene expression levels for the n samples collected in Phase 1 and Phase 2; μ is the intercept, r is an n by 1 vector of Elo ratings and β is its effect size; and a is an n by 1 vector of female age in years at the time of sample collection and γ is its effect size. The m by 1 vector u is a random effects term to control for kinship and other sources of genetic structure. Here, m is the number of unique females in the analysis (m = 45), the m-by-m matrix K contains estimates of pairwise relatedness derived from a 45 x 54,165 genotype data set, σ_u^2 is the genetic variance component (0 for a non-heritable trait, but most gene expression levels are heritable: Tung et al., 2015; Wright et al., 2014), and Z is an incidence matrix of 1's and 0's that maps measurements in Phase 1 and Phase 2 to individuals in the random effects term (thus controlling for repeated measurements for the same individual across phases). Residual errors are represented by ε, an n by 1 vector, where σ_e^2 represents the environmental variance component (unstructured by genetic relatedness), I is the identity matrix, and MVN denotes the multivariate normal distribution. For each data set and gene, we tested the null hypothesis that $\beta = 0$ versus the alternative hypothesis, $\beta \neq 0$. Empirical null distributions for rank effects in these models were produced by permuting female dominance rank and re-running the analyses 1000 times using randomized rank values (for complete description of statistical methods used, see Snyder-Mackler et al., 2016).

3.3.5. Statistical analysis

Cortisol and leukocyte redistributional responses to brief social separation. In order to evaluate the temporal dynamics of the acute cortisol response to social separation (SS), we used three measures: 1) "reactivity," which we defined as the percent change in serum cortisol between baseline and post-stressor peak levels; 2) "recovery," which we defined as the percentage of the baseline value that

cortisol levels returned to after the peak ((post-stressor peak – post-peak trough) / (cortisol peak – baseline)); and 3) area under the curve (AUC), which captures cumulative cortisol output across all time points (Pruessner et al., 2003). We used linear models (LM) to test for effects of age and dominance rank (Elo) on each cortisol measurement. In order to test for effects of SS on changes in circulating leukocyte subsets (in units of cells/μL blood), paired t-tests were used to compare subset counts between 1) pre- and immediately post-SS timepoints (i.e., reactivity), and 2) immediately post-SS and 4h post-SS timepoints (i.e., recovery). In order to test whether dominance rank moderated effects of cortisol reactivity or recovery on redistribution of each leukocyte subset, we implemented linear mixed models (LMM) in the *lme4* package (Bates et al., 2014) to model subset reactivity or recovery as the outcome variable, and controlled for baseline count differences and chronological age (in years) by including both as fixed effect covariates in each model. Day of testing was included as a random effect, which also accounted for variation in immunophenotyping as all blood samples collected on the same day were stained, fixed, and quantified by flow cytometry in the same batch.

Causal effects of rank on dexamethasone-induced changes in blood composition. For the analysis above, we performed a cross-sectional analysis on data from Phase 1 only. However, we also collected data in both Phase 1 and Phase 2 on serum cortisol and blood leukocyte compositional changes following dexamethasone administration, which allowed us to test for effects of rank and glucocorticoid sensitivity in a longitudinal analysis within subjects. Unlike our Phase 1 cross-sectional analysis, our longitudinal analysis did not include parallel complete blood counts (CBCs) for absolute neutrophil, monocyte, and lymphocyte quantification. Instead, we re-ran the flow cytometry panels from the social separation stressor and captured changes in the proportional representation of monocyte and lymphocyte subsets in response to Dex (see Section 3.3.3). First, we tested for effects of Dex on serum cortisol levels and circulating subset proportions by paired t-test (Table S3.3) separately in each phase. We then combined the Phase 1 and Phase 2 Dex

assessments to test whether dominance rank moderated the effect of Dex on subset proportions by using LMMs with random effects of subject (to control for repeated measurements) and testing day, and age and baseline proportion as fixed-effect covariates (Table S3.7). Finally, we tested whether sensitivity to acute cortisol suppression by Dex, which we defined as the percent change in cortisol between pre- and post-Dex serum samples (i.e., %Δcortisol), predicted Dex-induced changes in subset representation by adding %Δcortisol as a fixed effect and evaluating changes in model fit. Goodness-of-fit chi-squared statistics, Akaike's AIC for model comparisons, and associated *P*-values were determined using the *anova* function in the *lmerTest* package.

Effects of leukocyte redistribution on behavioral tendencies. We tested whether increased monocyte sensitivity and decreased $CD4^+$ T lymphocyte sensitivity to redistribution by Dex predicted behavioral tendencies reflective of depressive- and anxiety-like behavior. To accomplish this, we used LMMs to model each behavioral component score (e.g., Social Approachability, Boldness, and Anxiousness; see Section 2.4.1) across both Phase 1 and Phase 2 with fixed effects of %Δclassical monocytes and %Δ$CD4^+$ T cells, serum Dex concentration at 1.5 h post-administration as a fixed-effect covariate, and random effects of subject and testing day.

Effects of rank on adhesion gene expression. To test for causal effects of dominance rank on leukocyte adhesion gene expression, we focused our analyses on an a priori-defined set of 146 genes that code for cellular adhesion molecules (CAMs) in rhesus macaques (KEGG: mcc04514; Kanehisa and Goto, 2000; Kanehisa et al., 2016). Because CAMs are not only expressed in leukocytes (e.g., endothelium, neurons, platelets cells), only 45% (65 of 146) of genes were detectably expressed in the five leukocyte subtypes analyzed. We applied two tests for significant rank-adhesion gene expression associations in each cell type: 1) a hypergeometric test, (*phyper* function in R), which evaluates the null hypothesis that significant rank-associated genes, which we defined as $P < 0.05$, are not over-represented within the CAM gene set compared to a random sampling of all

expressed genes within the same cell type, and 2) a Kolmogorov-Smirnov test, which evaluates the null hypothesis that the distribution of test statistics (e.g., *P* values) describing rank-expression associations for CAM genes was drawn from the same distribution of rank-expression associations for all expressed genes.

Because we analyzed each cell type in isolation using these methods, we also tested whether rank-expression associations were shared across cell types to a greater extent in the CAM set versus the genome-wide set. For each gene that was expressed in at least 2 cell types (86%; 56 of 65 genes), we computed the proportion of cells for which the directionality of its rank-expression association was shared. For instance, if gene A was expressed in 4 of the 5 cell types, and the effect of dominance rank (β) was negative in 3 of the 4 cells, then the concordance would be 3/4, or 75%. We compared the mean concordance among CAM genes to an empirical null distribution, which was based on the randomly sampling 56 genes from the genome-wide set, calculating the mean concordance, and re-running the analysis 10,000 times. This allowed us to test the null hypothesis that concordance among CAM genes was not significantly greater than expected given the genome-wide background.

Finally, we tested whether low dominance rank was associated with up- or down-regulation of CAMs. To do so, we calculated the mean effect of dominance rank (β) for the aforementioned 56 CAM genes and compared it to an empirical distribution of mean rank effects by randomly selecting 56 genes from the genome-wide set, calculating the mean effect of rank, and re-running the analysis 10,000 times. We then tested the null hypothesis that the directionality of rank-expression associations for CAM genes was not different than rank-expression associations across the genome.

Effects of CAM gene expression on leukocyte redistribution. To test whether CAM gene expression was predictive of changes in blood composition in response to Dex treatment, we first represented expression levels in the 26 CAM genes expressed in all 5 isolated cell subtypes using a minimum number of independent dimensions by performing principal components analysis (PCA). To do so, we implemented the *principal* function in the *psych* package in R (Revelle, 2015) on five (one per cell subtype) 90 x 26 matrices of subject-wise expression data, with a row for each female-study phase combination (45 females x 2 phases) and a column for each CAM gene. We retained the first 2 principal components (PCs), which cumulatively explained between 33.1 - 42.8% of the total variance in the correlation matrix for each cell type (Table S3.5), in order restrict degrees of freedom in subsequent LMMs and applied an orthogonal varimax rotation to generate standardized factor loadings and subject-wise component scores. In order to examine whether CAM gene expression in each cell type predicted Dex-induced changes in that cell type's representation in blood, we added PC1 and PC2 as fixed effects to the LMMs implemented above and tested for improvements in model fit using likelihood ratio tests as described above against the simpler models containing only dominance rank, serum Dex, and cortisol response parameters (Table S3.7).

We conducted all statistical analyses using R (v3.1.0). Model residuals for LMs and LMMs were visually inspected for homoscedasticity, and normality was assessed using the Shapiro-Wilk test (all *P*-values > 0.05). Standardized residuals with an absolute variance > 4 were excluded from final models. Model degrees of freedom (*df*), t-statistics, and *P*-values for fixed effects in LMMs were calculated using the *lmerTest* package (Kuznetsova et al., 2015). The *P*-values we report within the main text, figures, and tables were not adjusted for multiple comparisons; however, because we tested the same hypothesis multiple times across immune cell subtypes throughout our results, we performed Bonferroni corrections in order to control the family-wise error rate and we report when $P_{adj} < 0.05$.

3.4. Results

3.4.1. Rank associations with basal leukocyte counts

We tested whether low dominance rank was associated with an elevated neutrophil to lymphocyte ratio (NLR), a biomarker of systemic inflammation (Guthrie et al., 2013), or other differences in leukocyte subsets previously attributed to chronic stress, such as reduced numbers of cytotoxic T and NK cells (Segerstrom and Miller, 2004). Adjusting for age and batch effects, we found that lower-ranking females tended to have elevated neutrophil counts (β_{Elo} = -1057, t_{42} = -1.91, P = 0.063) and fewer total lymphocytes (β_{Elo} = 448, t_{29} = 1.76, P = 0.089), and that low dominance rank predicted higher NLR (β_{Elo} = -0.46, t_{36} = -2.53, P = 0.016). Older females had fewer total monocytes (β_{age} = -29.5, t_{36} = -2.05, P = 0.047), though dominance rank did not predict monocyte numbers (β_{Elo} = -24.9, t_{36} = -0.43, P = 0.67). Total leukocyte counts also did not differ by rank (β_{Elo} = -664, t_{36} = -0.96, P = 0.35), although older females had lower leukocyte counts (β_{age} = -518, t_{36} = -3.13, P = 0.003). Among monocyte and lymphocyte subsets, we found that lower-ranking females tended to have fewer cytotoxic T ($CD3^+CD16^-CD4^-CD8^+$) cells (β_{Elo} = 211, t_{36} = 2.00, P = 0.053), consistent with previous findings in socially subordinate rhesus macaques (Paiardini et al., 2009; Tung et al., 2012); however, dominance rank was not associated with basal cell counts in the other 8 subsets analyzed (Table S3.2).

3.4.2. Leukocyte and cortisol responses to social separation

As expected, circulating neutrophil counts increased significantly (i.e., neutrophilia) from baseline following brief social separation (SS) stress (1 h post-SS: t_{37} = 7.02, P < 0.001), while total monocyte and lymphocyte counts significantly decreased (post-SS monocytes: t_{37} = -4.90, P <

0.001; post-SS lymphocytes: t_{37} = -7.92, $P < 0.001$). Within the monocyte pool, numbers of both classical ($CD14^+CD16^-$) and non-classical ($CD14^+CD16^+$) monocytes decreased significantly post-SS, as did all lymphocyte subsets (except for $CD8^-$ B cells: t_{37} = 0.48, P = 0.64; Table S1), representing cell trafficking out of the bloodstream and into target tissues. By 4h post-SS, total lymphocyte and monocyte counts, and all subsets (except for NK and NKT cells), had significantly recovered relative to post-stressor levels, while neutrophil counts remained elevated (Table S3.1). Serum cortisol also significantly increased from baseline (13.7 ± 4.34 μg/dl) to post-SS (21.9 ± 3.83 μg/dl; t_{43} = 15.3, $P < 0.001$) and decreased significantly from the post-SS peak to the 1h (18.9 ± 4.29 μg/dl; t_{43} = -5.82, $P < 0.001$) and 4h post-SS timepoints (10.1 ± 3.63 μg/dl; t_{43} = -17.5, $P < 0.001$). Notably, females with larger increases in cortisol from baseline to the post-SS peak (i.e., higher cortisol reactivity) had smaller decreases from post-SS peak to 4h post-stressor time point (i.e., delayed cortisol recovery) (r = -0.52, t_{42} = -3.99, $P < 0.001$). However, neither cortisol reactivity nor cortisol recovery was associated with total cortisol output as measured by area under the curve (reactivity: r = 0.01, t_{42} = 0.01, P = 0.99; recovery: r = 0.13, t_{42} = 0.84, P = 0.41).

3.4.3. Rank effects on cortisol and leukocyte responses to separation

We found that dominance rank did not predict the cortisol response to SS in terms of reactivity (β_{Elo} = 0.05, t_{40} = 0.08, P = 0.94), recovery (β_{Elo} = 0.04, t_{40} = 0.06, P = 0.96), or $AUC_{cortisol}$ (β_{Elo} = 1.09, t_{40} = 0.56, P = 0.58). Although there were no significant associations between rank and cortisol, we tested whether leukocytes in lower-ranking females would be less responsive to changes in serum cortisol than higher-ranking females. We found that the association between monocyte trafficking (i.e., the change in cell counts from baseline to immediately post-SS) and cortisol reactivity was significantly stronger in higher-ranking versus lower-ranking females ($\beta_{Elo*Cort\_React}$ = 19.0, t_{32} = 2.14, P = 0.040) (Fig. 3.1A); however, rank did not affect relationships

between cortisol reactivity and trafficking of lymphocyte subsets (Table S3.3). We then tested whether associations between leukocyte recovery (i.e., the change in cell counts from post-SS to 4h post-SS) and cortisol recovery would be affected by dominance rank and found that T cell recovery was more strongly correlated with cortisol recovery in higher-ranking than lower-ranking females (cytotoxic T cells: $\beta_{Elo*Cort\_Recov} = 233$, $t_{32} = 2.68$, $P = 0.013$; helper T cells: $\beta_{Elo*Cort\_Recov} = 168$, $t_{32} = 2.01$, $P = 0.055$) (Fig. 3.1B), suggesting that T lymphocytes in lower-ranking females were less responsive to cortisol redistribution signals. No significant associations between cell recovery and dominance rank or cortisol recovery were observed in other subsets (Table S3.3).

3.4.4. Causal effects of rank and GC sensitivity on leukocyte response to Dex

Assessing the same measure twice in each female when occupying different dominance ranks allowed us to infer direct causal effects of rank on redistribution and afforded us more statistical power than the cross-sectional analyses above. In both study phases, there were significant post-Dex decreases in helper T cell (mean ± SEM: -10.8 ± 1.4%), cytotoxic T cell (-11.7 ± 2.3%), double-positive T cell (-20.6 ± 1.8%), and $CD8^+$ B cell proportions (-3.65 ± 7.7%) from baseline, and significant increases in classical monocyte (47.6 ± 5.7%), $CD8^-$ B cell (93.7 ± 61.8%), and NK cell (49.0 ± 13.6%) representation, while proportions of non-classical monocytes and NKT cells were not affected by Dex in both phases (Table S3.6).

Higher serum dexamethasone levels predicted larger changes in monocytes ($\beta_{Dex} = 0.19$, $t_{46} = 5.33$, $P < 0.001$), cytotoxic T cells ($\beta_{Dex} = -0.14$, $t_{73} = -4.59$, $P < 0.001$), double-positive T cells ($\beta_{Dex} = -0.05$, $t_{39} = -4.77$, $P < 0.001$), and B cells ($\beta_{Dex} = -0.06$, $t_{41} = -2.15$, $P = 0.038$) across both study phases, adjusting for age and baseline cell proportions. We thus tested the hypothesis that Dex-induced changes in cell proportions would be abrogated in lower-ranking females, and found

evidence that the association between double-positive T cell proportions and serum Dex levels was weaker in lower-ranking females ($\beta_{Dex*Elo}$ = -0.02, t_{55} = -2.23, P = 0.030; Fig. 3.3A). Although we did not detect rank effects in other cell subtypes (Table S3.7), we tested whether decreased sensitivity to cortisol suppression by Dex was associated with decreased leukocyte sensitivity to redistribution by Dex by re-running the above LMMs with percent change in cortisol (pre- to post-Dex) as a fixed effect. As expected, Dex administration led to acute decreases in serum cortisol (Table S3.6), and lower-ranking females tended to be less sensitive to cortisol suppression (β_{Elo} = -0.33, t_{72} = -1.69, P = 0.096). However, we found that, regardless of rank, insensitivity to cortisol suppression predicted smaller Dex-induced changes in classical monocyte ($\beta_{\Delta CORT}$ = -0.06, t_{55} = -2.39, P = 0.020) and cytotoxic T cell ($\beta_{\Delta CORT}$ = 0.05, t_{50} = 2.36, P = 0.022) proportions, but not in the other five cell types analyzed (Table S3.7; Fig. 3.3B). Lastly, we found that baseline proportions of classical monocytes were higher in lower-ranking females (β_{Elo} = -0.78, t_{48} = -2.29, P = 0.027), but there were no significant baseline differences in other cell types.

3.4.5. Rank effects on CAM gene expression

Previous studies in humans and rhesus macaques have reported associations between chronic social stress and increased activity of pro-inflammatory transcription factors (e.g., nuclear factor kappa-B), which are known to induce the expression of genes involved in leukocyte adhesion (Kaur et al., 2001) (Bunting et al., 2007). We therefore tested the hypothesis that low dominance rank would be associated with increased basal expression (i.e., upregulation) of leukocyte adhesion genes (N = 65) by transcriptionally profiling five leukocyte subtypes (monocytes, helper T, cytotoxic T, NK, and B cells). In purified monocytes ($CD14^+HLA\text{-}DR^+$) and B cells ($CD3^-CD20^+HLA\text{-}DR^+$), and to a lesser extent NK cells ($CD3^-CD20^-HLA\text{-}DR^-CD16^+$), we detected enrichment of significant associations between dominance rank and expression among adhesion genes relative to all expressed genes (Fisher's Exact Test: P_{mono} = 0.013, P_{B_cells} = 0.008, P_{NK_cells} =

0.054; K-S Test: $D^{+}_{mono} = 0.30$, $P_{mono} = 4.8x10^{-4}$; $D^{+}_{B\_cells} = 0.19$, $P_{B\_cells} = 0.028$; $D^{+}_{NK\_cells} = 0.19$, $P_{NK\_cells} = 0.082$). There was some evidence for enrichment of rank-adhesion gene expression associations in helper T cells (Fisher's Exact Test: $P = 0.14$; K-S Test: $D^{+} = 0.23$, $P = 0.005$), but not cytotoxic T cells (Fisher's Exact Test: $P = 0.53$; K-S Test: $D^{+}=0.06$; $P = 0.74$). We also tested for heterogeneity of rank-adhesion gene expression associations across the five cell types, and found that for adhesion genes expressed in at least 2 cell types (N = 56; Table S3.4), rank-expression associations were mostly concordant across cell types (75.2%), but no moreso than in all expressed genes (N = 9085; 77.2% concordance). However, in contrast to our hypothesis, low dominance rank was associated with downregulation of adhesion gene expression (38 of 56 genes: 67.9%) on average across all five subtypes, but not with downregulation across the entire genome (4507 of 9085 genes: 49.6%; $P = 0.0018$) (Fig. 3.2).

3.4.6. Effects of CAM gene expression on changes in blood composition

We tested the hypothesis that CAM gene expression would predict Dex-induced changes in leukocyte composition. We re-ran the LMMs above and included each female's respective PC1 and PC2 scores as fixed effects, and found that in B cells, higher PC1 scores were associated with smaller proportional changes following Dex ($\beta_{PC1} = 0.75$, $t_{67} = 2.97$, $P = 0.0041$), whereas higher PC2 scores were associated with larger changes ($\beta_{PC2} = -0.79$, $t_{66} = -2.84$, $P = 0.0060$; Table S3.7) (Fig. 3.4). Of note, these relationships remained significant after applying a highly stringent Bonferroni correction for multiple comparisons (n = 5) across cell types ($P_{PC1} = 0.021$, $P_{PC2} = 0.030$). There was additional evidence that scores on PC1 and PC2 in NK cells together predicted NK cell redistribution ($\chi^2 = 8.48$, df = 3, $P = 0.037$), but scores on each component individually did not ($\beta_{PC1} = 0.72$, $t_{67} = 1.56$, $P = 0.13$; $\beta_{PC2} = -0.83$, $t_{67} = -1.53$, $P = 0.14$). Scores on PC1 and PC2 did not predict redistribution by Dex in the other three cell types analyzed (monocytes, helper T, cytotoxic T cells; Table S3.7).

3.4.7. Associations between leukocyte redistribution by Dex and behavioral tendency

We tested the hypothesis that increased redistributional sensitivity of classical monocytes and decreased sensitivity of $CD4^+$ T cells to Dex would predict behavioral tendencies associated with a depressive- or anxiety-like phenotype (e.g., decreased Social Approachability, decreased Boldness, and increased Anxiousness; see Section 2.4.1 for behavioral analysis), controlling for the effects of dominance rank, age, and social group. Although redistributional sensitivity of classical monocytes did not predict any of the three behavioral tendencies examined (Table S3.9), we found that decreased sensitivity of $CD4^+$ T cells to Dex predicted lower scores on Boldness ($\beta_{\Delta CD4^+}$ = -0.15, t_{79} = -3.14, P = 0.0024), which notably remained significant after Bonferroni correction for tests of all three behavioral tendencies (P_{adj} = 0.007).

3.5. Discussion

3.5.1. Dominance rank effects on basal leukocyte numbers

In the present study, we found that lower-ranking females had an increased baseline ratio of circulating neutrophils to lymphocytes (NLR), a biomarker of inflammation (Guthrie et al., 2013). Importantly, there were no rank differences in total leukocyte counts, confirming that increased NLR was not attributable to a higher prevalence of infection in lower-ranking females. Our finding is consistent with an increased NLR found in juvenile male rhesus monkeys after 1-3 weeks of novel housing stress (Amaral et al., 2013) and with our previous report that lower dominance rank in group-housed adult females was associated with a proinflammatory basal transcriptional profile in peripheral blood mononuclear cells (PBMCs) (Tung et al., 2012). Lower-ranking females receive more aggression, tend to receive less grooming, and are more socially isolated than their higher-ranked groupmates (Kohn et al., 2016; Snyder-Mackler et al., 2016a).

Thus, the inflammatory phenotype observed in social subordinates, measured here by NLR, may result from chronic activation of the stress response as well as a relative absence of social buffering by affiliative contact (Ditzen and Heinrichs, 2014). Importantly, social dominance in rhesus macaques is generally imposed through intimidation, rather than direct physical aggression, so immunologic differences in lower-ranking females are likely attributable to psychosocial factors, rather than wounding or injury. Furthermore, we found that lower-ranking females had fewer cytotoxic T cells, consistent with previous findings in captive adult females reported by our group (Paiardini et al., 2009; Tung et al., 2012) and in chronically stressed human populations (Herbert and Cohen, 1993; Zorrilla et al., 2001), which is possibly indicative of increased disease susceptibility given the central role of $CD8^+$ T cells as effectors of the immune response to pathogens.

3.5.2. Dominance rank effects on cortisol responses and leukocyte redistribution

Cortisol responses to brief social separation stress (SS) in Phase 1 did not differ by dominance rank, which is consistent with prior studies of acute stress responses in female rhesus macaques (Arce et al., 2010; Collura et al., 2009) and in chronically-stressed human populations (reviewed in Chida and Hamer, 2008). On the other hand, sensitivity to synthetic glucocorticoid treatment on HPA dynamics (e.g., Dex, ACTH-Dex, CRH-Dex) may be a more reliable indicator of cortisol dysregulation in primates (Jarrell et al., 2008; Michopoulos et al., 2012b; Shively et al., 1997), which is supported by our longitudinal findings that suggest a causal link between low rank and Dex resistance. We also found that low dominance rank decreased monocyte trafficking by GCs, but not in other leukocyte subsets. Interestingly, our finding in monocytes was restricted to the classical ($CD14^+CD16^-$), rather than the non-classical ($CD14^+CD16^+$) subpopulation, and aligns with a recent report of impaired GR signaling in classical monocytes from socially isolated male rhesus monkeys (Cole et al., 2015). Furthermore, our results imply that low rank causally

and selectively expanded classical monocyte representation in blood, a possible consequence of increased myelopoiesis by chronic sympathetic nervous system (SNS) activation (Engler et al., 2004; Powell et al., 2013). Given their phagocytic and inflammatory functions, increased classical monocyte representation may be adaptive in social environments where physical wounding and bacterial exposures are prevalent, but may facilitate disease pathogenesis (e.g., atherosclerosis) in contemporary environments where social threats are primarily psychogenic (Idzkowska et al., 2015).

We also found that post-stressor recovery of T lymphocytes from lower-ranking females was delayed relative to cortisol recovery from post-stressor peak levels, and that the correlation between double-positive T cell proportions and serum Dex levels were significantly attenuated in lower-ranking animals. As cortisol levels decline following a stressful event, T lymphocyte numbers in the bloodstream return (increase) to baseline (Dhabhar et al., 1995) as they migrate out of the tissues into which they were trafficked (e.g., skin). T lymphocyte adhesion to target tissues is CAM-dependent, and although we did not find evidence for increased basal CAM mRNA expression in T cells, it is possible that acute stress-induced post-translational activation of CAMs (e.g., glycosylation, phosphorylation) was more pronounced in lower-ranking females (Bauer et al., 2001). Indeed, there is evidence in mice that repeated stressors alter T lymphocyte infiltration into skin (Dhabhar, 2013), which may be beneficial for protection against some cutaneous diseases, but pathological in others (Buske-Kirschbaum et al., 2007).

3.5.3. Dominance rank effects on CAM gene expression

Expression of CAMs on the leukocyte surface is critical for adherence to endothelial cell receptors (e.g. E-selectin, ICAM-1, VCAM-1) on the surface of target tissues, although few studies have investigated leukocyte CAM expression in the context of chronic stress. Contrary to our initial

hypothesis, we found evidence for downregulation of CAM gene expression across monocyte, helper T, cytotoxic T, B cell, and natural killer cells in lower-ranking females, with the strongest signals occurring in monocytes and B cells, and to a lesser extent within NK cells. Because proinflammatory mediators (e.g., chemokines) upregulate CAM expression on the cell surface, we expected lower-ranking females, previously shown to have increased inflammatory gene expression (Snyder-Mackler et al., 2016b), to express higher levels of CAM mRNAs. Furthermore, CAM upregulation has been implicated in stress-associated inflammatory disorders, including fibromyalgia (Macedo et al., 2007), atherosclerosis (Galkina and Ley, 2007), and rheumatoid arthritis (Palmer et al., 2006). However, it is possible that downregulation of CAM genes in subordinate females reflects a compensatory response to repeated CAM induction by acute stressors and their hormonal effectors.

It is worth noting that the immunostaining procedure used to isolate monocytes for gene expression profiling did not include the CD16 antibody. Thus, downregulation of CAM expression may reflect the aforementioned increases in classical versus non-classical monocyte representation observed in lower-ranking females, the latter of which may be more responsive to CAM induction by inflammatory stimuli (Thaler et al., 2016). Although it is unclear why basal CAM gene transcription in some lymphoid cells (B cells, NK cells) would be more sensitive to the social environment than in others (helper T, cytotoxic T), it is important to note that the rank-expression relationships we did observe were generally plastic. In other words, rank and CAM gene expression were associated in these cells across both phases of the study, despite rank rearrangements at the midpoint, suggesting that changes in dominance rank are quickly reflected in basal CAM transcription within long-lived cells of lymphoid origin.

3.5.4. Effects of glucocorticoid sensitivity and CAM gene expression on leukocyte redistribution

We found that resistance to cortisol suppression predicted decreased monocyte and cytotoxic T cell redistribution by Dex, suggesting that glucocorticoid resistance may manifest simultaneously in both the HPA axis and select compartments of the immune system (Cohen et al., 2012). This observation is generally consistent with reports by Cole and colleagues that the relationship between endogenous cortisol concentrations and specific leukocyte subpopulations can be interpreted as an index of HPA axis dysregulation or GC sensitivity (Capitanio et al., 2011; Cole, 2008; Cole et al., 2009). Such a tool may be useful in assessing GC sensitivity in psychiatric populations, such as depression or PTSD (Rohleder et al., 2010), for whom GC sensitivity may predict treatment outcomes (Ising et al., 2007). It is important to mention that our statistical models included serum dexamethasone concentration as a fixed effect because inter-individual differences in Dex metabolism can complicate the interpretation of cortisol suppression test results (Menke et al., 2016).

In addition, we found that basal expression of CAM mRNAs in isolated B cells was a significant predictor of Dex-induced changes in circulating B cell proportions. This finding implies that basal adhesion molecule expression has functional implications during the acute stress response, and suggests that steady-state CAM mRNA levels correspond to CAM protein expression on the cell surface, at least in B cells. Closer examination of the genes that load onto each principal component reveals that 4 of the 6 integrin-family genes (ITGAL, ITGAM, ITGB2, ITGB7; loadings = 0.67 – 0.90) and 5 of the 7 class II major histocompatibility complex (MHC) genes analyzed (MAMU-DMA, MAMU-DPA, MAMU-DQA1, MAMU-DRA, MAMU-DRB1; loadings = 0.43 – 0.66) loaded strongly and positively onto PC1. Higher PC1 scores were associated with larger increases in Dex-induced B cell representation, which may have been mediated by increased mobilization by Dex, decreased adhesion to endothelial targets, or both. Since ligated MHC class II molecules negatively regulate B cell adhesion (Ahsmann et al., 1997), and integrin-family molecules positively regulate adhesion (Schnoor et al., 2015), it is challenging

to understand how higher expression levels of both synergized to increase circulating B cell representation by Dex. Most notably, L-selectin (CD62L) strongly loaded onto PC2, for which higher scores were associated with smaller increases in B cell representation post-Dex. However, GC-induced trafficking has been shown to occur similarly within $CD62L^+$ and $CD62L^-$ B cell subsets (Dhabhar et al., 2012), so it is likely that the correlation between PC2 scores and redistribution was driven by other CAM genes that loaded strongly onto that component (e.g., ICAM2, ITGA4). It is important to mention that our findings related to CAM mRNA expression in B cells are correlational. Thus, we cannot determine whether altered CAM mRNA expression is causally related to redistributional changes, or simply reflects a transcriptional profile that co-occurs with other cellular modifications to affect redistribution by GCs.

3.5.5. Associations between leukocyte redistribution and behavioral tendency

Our longitudinal analysis suggests that decreased sensitivity of $CD4^+$ T lymphocytes to redistribution by Dex was associated with a more submissive, socially withdrawn behavioral phenotype (i.e., lower scores on the Boldness component; see Table 2.2 for PCA factor loadings). Although our experimental model did not allow us to identify the tissues into which $CD4^+$ T lymphocytes trafficked, psychological stressors reliably recruit T lymphocytes to the mouse brain via glucocorticoid-dependent CAM increases (Lewitus et al., 2008) and enhancement of choroid plexus permeability (Shechter et al., 2013). Interestingly, an anti-inflammatory subset of $CD4^+$ T lymphocytes, known as regulatory T cells (Treg: $CD4^+CD25^+Foxp3^+$), have been implicated as protective factors against the development of stress-induced depression or anxiety-like behavior (Clark et al., 2016; Kim et al., 2012), whereas a pro-inflammatory Th17 $CD4^+$ T cell subset may increase stress vulnerability (Beurel et al., 2013), although the mechanisms by which this occurs are poorly understood (Miller, 2010). While our immunophenotyping panel did not differentiate between functionally distinct $CD4^+$ subsets, it is possible that larger percent decreases in

circulating CD4+ T cells following Dex administration reflect increased Treg trafficking into the brain, thus conferring a "stress-resilient" behavioral phenotype to these animals. Future studies are needed to investigate whether differences in redistributional sensitivity within CD4+ T lymphocyte subsets (e.g., Tregs, Th17, Teff) may serve as immunological biomarkers of behavioral resilience to later stress exposure, as previously demonstrated in mice with IL-6 hyper-secretion (Hodes et al., 2014).

3.5.6. Limitations and future directions

The present study has several limitations. First, because the study was conducted in captive, female rhesus macaques, we cannot assess whether our findings will generalize to male nonhuman primates. However, as referenced above, similar findings have been reported in captive male rhesus macaque populations exposed to prolonged social instability (Cole et al., 2009). Second, we focused our analyses on the role of glucocorticoid signaling in leukocyte redistribution; however, adrenergic signaling via the SNS also mediates chronic stress-associated changes in leukocyte gene transcription, redistribution during acute stress, and CAM activation (Cole et al., 2015; Dhabhar et al., 2012; Dimitrov et al., 2010b; Kolmus et al., 2015). It is therefore possible that rank-associated differences in adrenergic signaling could explain additional variance in leukocyte redistribution in response to an acute stressor, and SNS reactivity in this model could be captured using biotelemetry (Shively and Day, 2015). Third, we studied CAM expression in isolated leukocytes at the mRNA level, and thus cannot evaluate whether our findings translate into CAM protein levels on the cell surface, the activational state of those proteins, or CAM expression on endothelial cells. Future studies utilizing parallel flow cytometry could assess whether CAM mRNA levels correlate with their surface expression. Similarly, leukocytes with decreased CAM mRNA levels or decreased sensitivity to *in vivo* redistribution by stress hormone may retain their capacity to migrate along chemotactic gradients or adhere to activated endothelial cells, so *ex vivo*

assays on isolated leukocyte subpopulations are important tools for exploring this possibility (Redwine et al., 2003). Fourth, it is important to note that only a handful of our findings passed the statistical significance threshold of $P = 0.05$ after correcting for multiple hypothesis tests using the Bonferroni method, specifically 1) associations between CAM expression levels in B cells and Dex-induced changes in B cell proportions, and 2) associations between Boldness scores and changes in $CD4^+$ T lymphocyte proportions in response to Dex, both of which were part of the longitudinal analysis. It is likely that despite repeated measurements within-subjects, small sample sizes resulted in insufficient statistical power to detect meaningful effects of dominance rank and glucocorticoid sensitivity on immune cell redistribution utilizing the analytical approach undertaken in this study. However, these results do provide preliminary evidence that classical monocytes and T lymphocytes may be most sensitive to stress-associated changes in sensitivity to glucocorticoid signals, highlighting the need for future experimentation assessing these specific leukocyte subtypes. Finally, our findings have important implications for the pathophysiology of psychiatric diseases, such as depression and anxiety. As discussed, circulating leukocytes can be recruited into the brain via the same chemotactic signals and adhesion processes observed in the periphery where they potentiate neuroinflammatory signaling, and thereby facilitate cognitive, mood, and behavioral disturbances (Wohleb et al., 2015). Thus, identifying the molecular mediators of differences in leukocyte adhesion and hormonal sensitivity found in chronic stress, in addition to characterizing the specific leukocyte subsets involved, is key to understanding the biological underpinnings of mental illness and other stress-associated diseases.

Figure 3.1. Relationships between dominance rank, cortisol and leukocyte responses to brief social separation stress (SS). (A) Larger increases in cortisol between baseline and post-SS samples (i.e., cortisol reactivity) were associated with larger decreases in numbers (i.e., trafficking) of circulating classical monocytes, except in lower-ranking females ($\beta_{Elo*Cort\_Reactivity}$ = 19.0, t_{32} = 2.14, P = 0.040). (B) The relationship between decreases in cortisol between post-SS peak and 4h post-SS samples (i.e., cortisol recovery) and increased circulating T cell numbers was affected by dominance rank. Elo ratings were split into tertiles for visualization only; statistical models reported in the main text were fit using continuously distributed Elo ratings (Table S3.3), but Pearson correlations (B) for each tertile are shown to provide a summary of the stratified data. Closed points: helper T cells ($CD3^+CD4^+CD8^+$); open points: cytotoxic T cells ($CD3^+CD4^-CD8^+$).

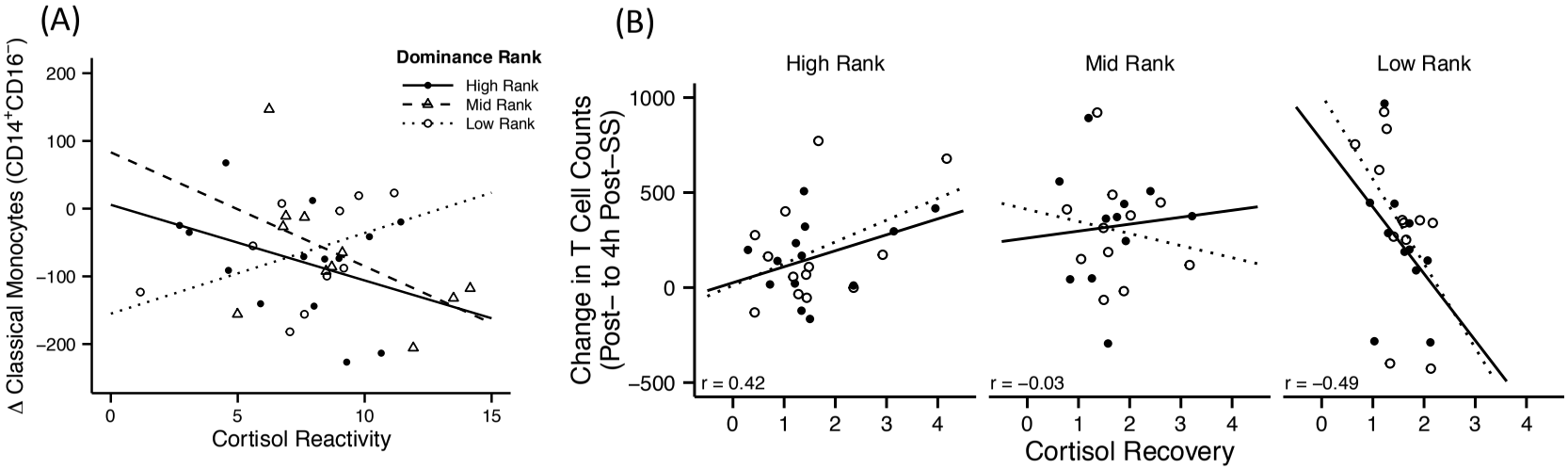


Figure 3.2. Effect sizes (i.e., beta) for relationships between Elo rating (i.e., dominance rank) and basal expression levels for genes expressed in at least 2 of the 5 FACS-isolated leukocyte subtypes (helper T cells, cytotoxic T cells, monocytes, natural killer cells, and B cells) analyzed across both study phases. Within the full genome-wide gene set (N = 9085), dominance rank had a positive effect on expression levels in 4507 genes (49.6%; top left panel), whereas among genes involved in cellular adhesion (N = 56), rank was positively associated with expression levels in 38 genes (67.9%; right panel). Y-axis markings (top left panel) and gene names (top right panel) in red represent genes with positive rank-expression associations averaged across cell types; markings and names in blue reflect genes with negative rank-expression associations. Effect size distributions for both the background and CAM gene sets shown in bottom panel. Dotted lines show mean beta values for background set ($\beta = 0.0012 \pm 0.04$) and CAM genes ($\beta = 0.018 \pm 0.05$).

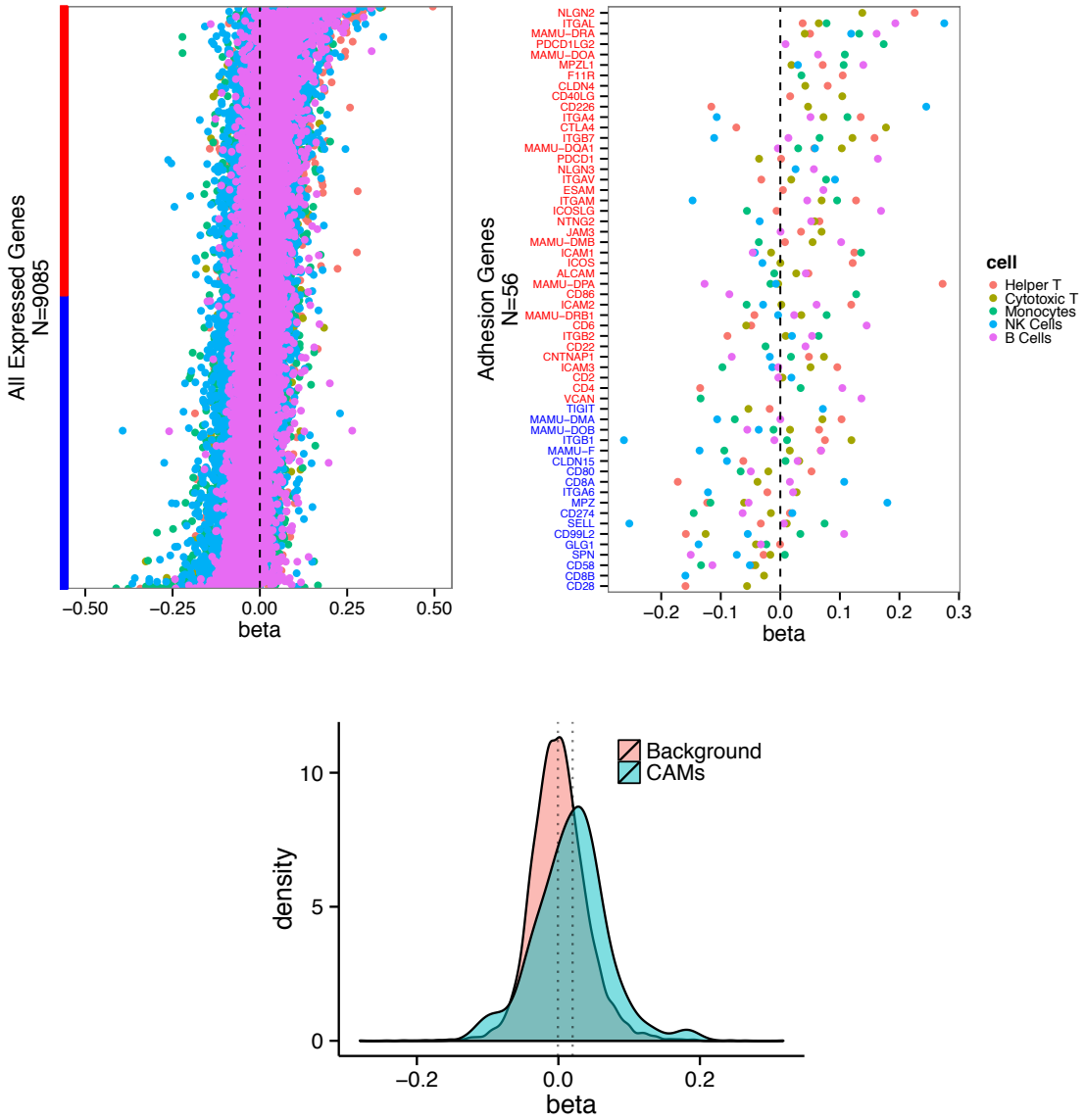


Figure 3.3. Associations between dominance rank, cortisol suppression, and relative changes in circulating leukocyte proportions in response to *in vivo* dexamethasone treatment. (A) The inverse relationship between serum Dex levels and changes in circulating double-positive T cells ($CD3^+CD4^+CD8^+$) was strongest in higher-ranking females across both study phases. Dominance rank was split into tertiles for visualization only; statistical models reported in the main text were fit using continuously distributed component scores (Table S7), but Pearson correlations for each tertile are shown to provide a summary of the stratified data. (B) Decreased sensitivity to endogenous cortisol suppression by Dex (more positive x-axis values) was associated with smaller Dex-induced increases in classical monocyte (left panel) and decreases in cytotoxic T cell ($CD3^+CD4^-CD8^+$) proportions in both phases. Residual changes in composition are shown, adjusted for age and baseline composition.

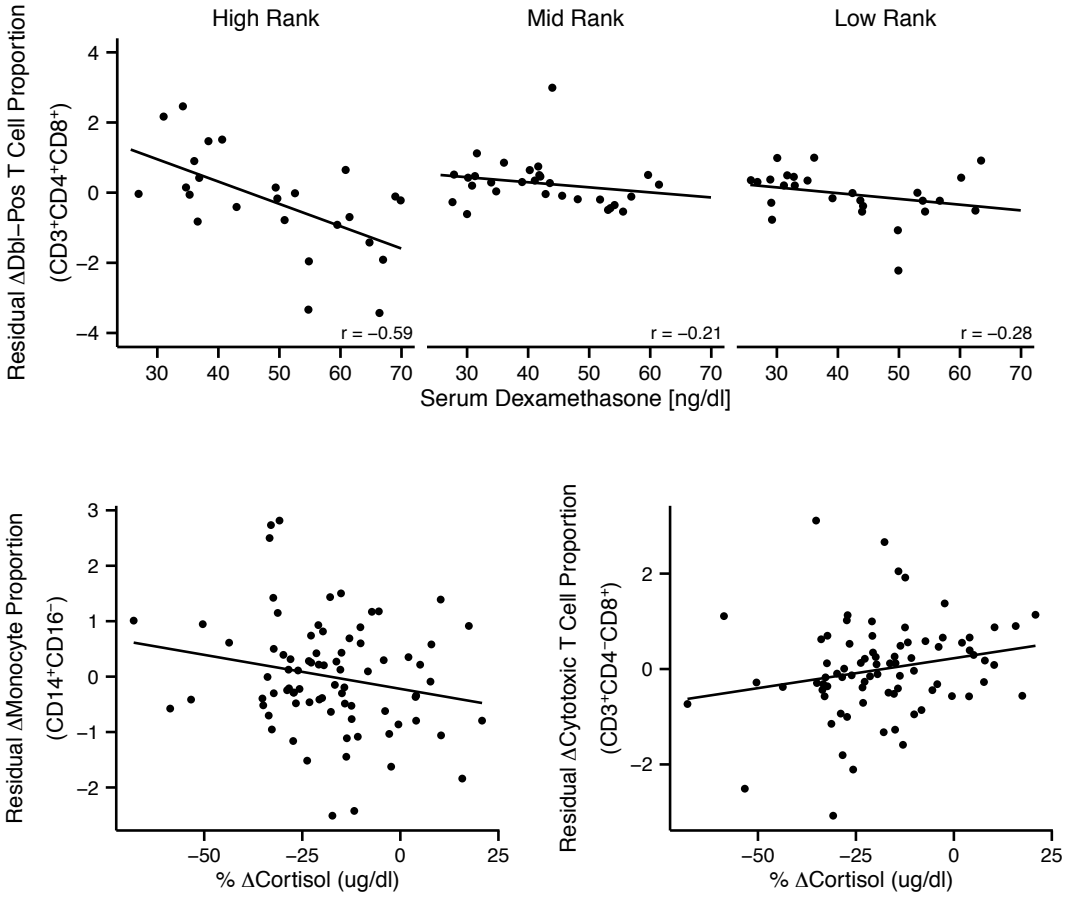


Figure 3.4. Associations between CAM gene expression in isolated B cells and relative changes in circulating B cell proportions in response to *in vivo* dexamethasone treatment. Females with higher scores on PC1 (i.e., expression of CAM genes that loaded onto PC1 within B cells) exhibited larger increases in B cell representation following Dex (left panel; $\beta_{PC1} = 0.75$, $t_{67} = 2.97$, $P = 0.0041$), whereas higher PC2 scores predicted smaller proportional changes in B cells (right panel; $\beta_{PC2} = -0.79$, $t_{66} = -2.84$, $P = 0.0060$).

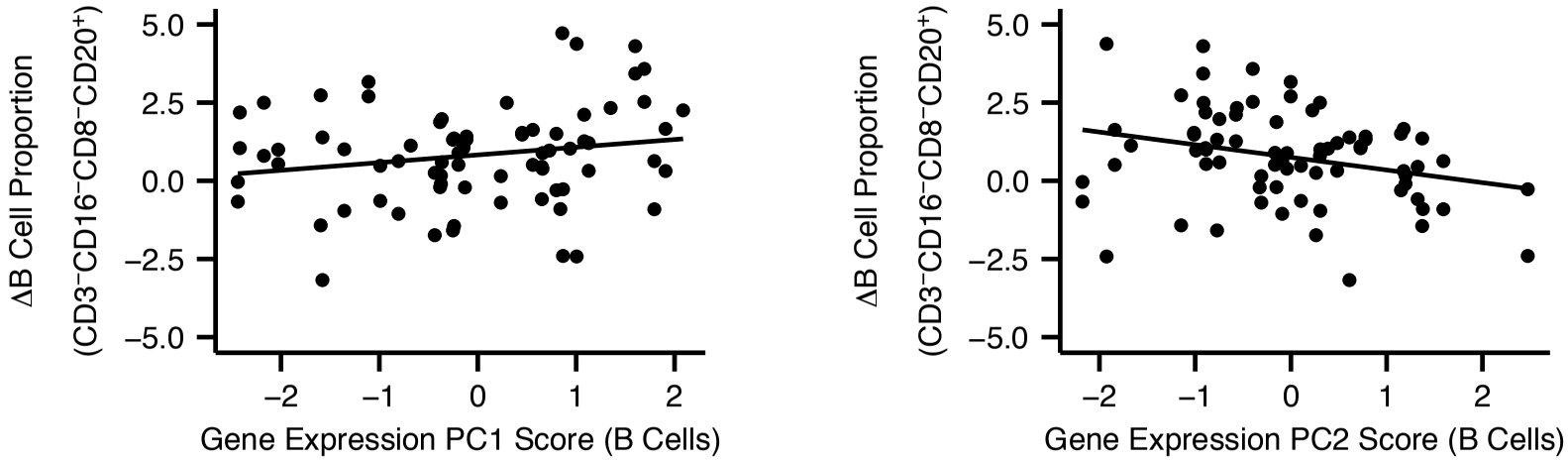


Figure 3.5. Associations between Boldness score (based on PCA) and percent change in circulating T helper cell proportion in response to *in vivo* dexamethasone treatment. Larger post-Dex decreases in helper T cell ($CD3^+CD4^+CD8^-$) proportions predicted higher component scores on Boldness behaviors than expected given an animal's dominance rank and age across both study phases (see Sections 2.4.1.1, 2.4.1.2; Table S2.2) ($\beta_{\Delta CD4^+} = -0.15$, $t_{79} = -3.14$, $P = 0.0024$).

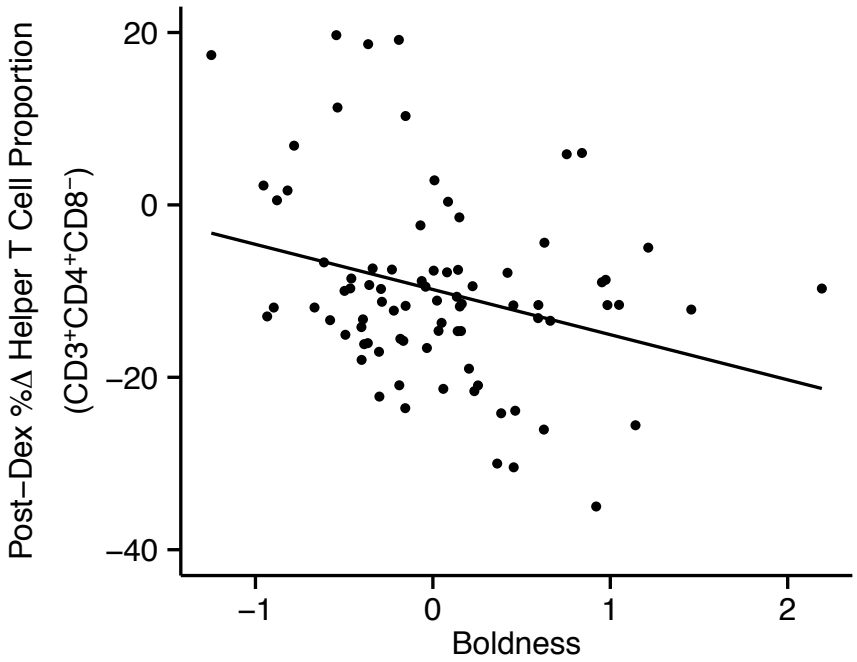


Figure S3.1. Examples of the (A) fluorescent-activated cell sorting (FACS) of PBMCs and (B) whole blood immunophenotyping strategies for one representative sample, visualized using FlowJo software (Treestar Inc., Ashland, OR). For whole blood samples (B), an electronic gate was placed around the lymphocyte and monocyte populations in the forward scatter (FSC)-area and side scatter (SSC)-area mode and cellular debris were excluded based on size and granularity. Singlet cells were selected based on FSC-H x FSC-A. Scatter against PerCP-Cy5.5 and PE fluorescence was used to identify and gate $CD3^{+}CD16^{-}$ cells (T cells) and $CD3^{-}CD16^{+}$ (natural killer cells; NK). The expression of CD4 and CD8 was determined on the $CD3^{+}CD16^{-}$ gate to identify helper T cells, cytotoxic T cells, and double-positive T cells. Expression of CD20 and CD8 was determined on the $CD3^{-}CD16^{-}$ gate to identify $CD8^{-}$ and $CD8^{+}$ B cell populations. Finally, expression of CD14 and CD16 was determined on the monocyte gate to differentiate classical from non-classical monocytes.

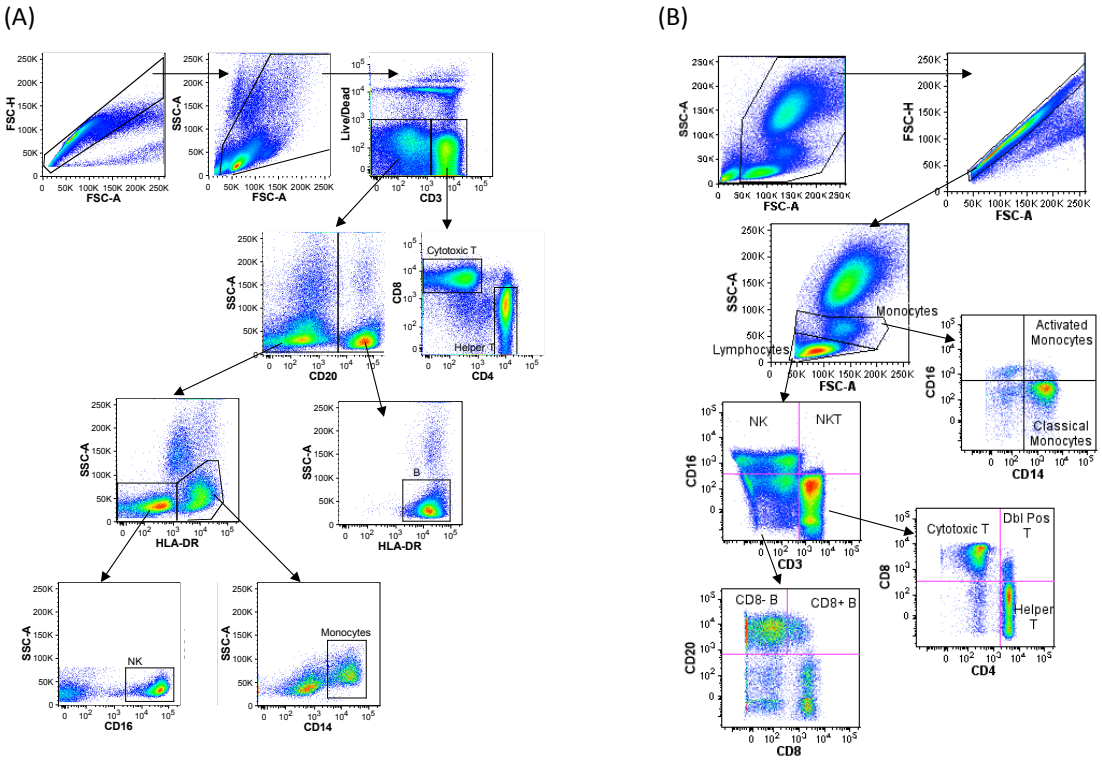


Figure S3.2. Sampling outline for acute stress challenges. For the acute social separation (SS) stressor in Phase 1 (top panel), baseline blood samples were collected at 0800 h for cortisol and immunophenotyping. Subjects were then exposed to 30 min isolation (see Section 3.3.2) and a post-SS sample was immediately collected. Additional post-SS samples were collected at 1h and 4h post stressor cessation. For the dexamethasone challenge in Phase 1 and Phase 2 (bottom panel), baseline blood samples were collected at 0800 h, immediately followed by IM Dex injection (0.125 mg/kg), and a second blood sample was collected at 1.5 h following Dex administration.

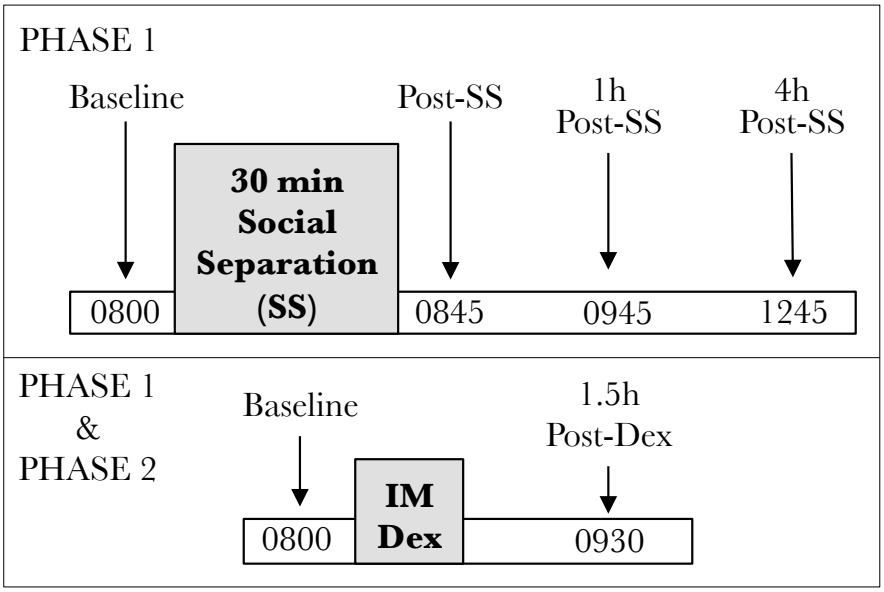


Table S3.1. Total number of peripheral blood leukocytes and subsets in response to a 30 min social separation stressor (mean +/- SEM).

					Reactivity (Pre- to Post-SS)			Recovery (Post- to 4h Post-SS)		
Cell type	Pre-SS (cells/μL)	Post-SS (cells/μL)	1h post-SS (cells/μL)	4h post-SS (cells/μL)	*t*	*df*	*P*	*t*	*df*	*P*
Complete Blood Count										
Total Neutrophils	5391 ± 3257	5785 ± 4008	10447 ± 5561	9658 ± 3641	7.02	37	< 0.001	-1.30	35	0.20
Total Monocytes	855 ± 310	744 ± 354	1171 ± 502	1108 ± 383	-4.90	37	< 0.001	7.50	35	< 0.001
Total Lymphocytes	3914 ± 1470	3215 ± 1392	3313 ± 1274	4227 ± 1553	-7.92	37	< 0.001	5.52	35	< 0.001
Flow Cytometry										
Classical Monocytes ($CD14^+CD16^-$)	512 ± 214	445 ± 237	825 ± 359	725 ± 287	-3.28	37	0.002	7.10	35	< 0.001
Activated Monocytes ($CD14^+CD16^+$)	78 ± 50	63 ± 43	67 ± 50	81 ± 59	-4.86	36	< 0.001	4.44	34	< 0.001
Helper T Cells ($CD3^+CD16^-CD4^+CD8^-$)	1110 ± 487	913 ± 439	1008 ± 444	1196 ± 499	-7.99	37	< 0.001	5.05	35	< 0.001
Cytotoxic T Cells ($CD3^+CD16^-CD4^-CD8^+$)	1013 ± 590	768 ± 503	769 ± 455	1046 ± 555	-6.75	37	< 0.001	4.67	35	< 0.001
Double-Positive T Cells ($CD3^+CD16^-CD4^+CD8^+$)	214 ± 357	149 ± 229	113 ± 208	209 ± 328	-2.90	37	0.006	2.74	35	0.010
$CD8^-$ B Cells ($CD3^-CD16^-CD20^+CD8^-$)	536 ± 318	554 ± 364	538 ± 316	712 ± 406	0.48	37	0.64	6.22	35	< 0.001
$CD8^+$ B Cells ($CD3^-CD16^-CD20^+CD8^+$)	101 ± 81	87 ± 66	86 ± 60	189 ± 136	-4.27	37	< 0.001	7.66	35	< 0.001
NK Cells ($CD3^-CD16^+$)	643 ± 375	490 ± 314	519 ± 335	563 ± 335	-4.93	36	< 0.001	1.19	34	0.24
NKT Cells ($CD3^+CD16^+$)	22 ± 55	17 ± 39	16 ± 37	20 ± 52	-2.15	36	0.038	1.25	34	0.22

Paired *t*-tests were used to test for significant differences between timepoints. SS: social separation

Table S3.2. Linear mixed-effects model (LMM) results for assocations between dominance rank and basal leukocyte counts.

Leukocyte Assessment	Outcome Measure	Independent variable	β	SE	*t*	*P*
Resting state (Pre-SS)	Total Neutrophils (CBC)	Age	-240	138	-1.74	0.089
		Elo Rating	-1056	552	-1.91	0.063
	Total Monocytes (CBC)	**Age**	**-29.5**	**14.4**	**-2.05**	**0.047**
		Elo Rating	-24.9	57.5	-0.43	0.67
	Total Lymphocytes (CBC)	Age	-248	63.5	-3.92	< 0.001
		Elo Rating	448	254	1.76	0.089
	Total Neutrophils (CBC) : Total Lymphocytes (CBC)	Age	0.02	0.04	0.44	0.66
		Elo Rating	**-0.46**	**0.18**	**-2.53**	**0.016**
	Classical Monocytes ($CD14^+CD16^-$)	**Age**	**-22.0**	**9.67**	**-2.28**	**0.029**
		Elo Rating	-19.6	38.7	-0.51	0.62
	Activated Monocytes ($CD14^+CD16^+$)	Age	-1.73	2.59	-0.67	0.51
		Elo Rating	9.68	10.4	0.93	0.36
	Helper T Cells ($CD3^+CD16^-CD4^+CD8^-$)	**Age**	**-77.0**	**21.6**	**-3.57**	**0.001**
		Elo Rating	135.0	86.4	1.57	0.13
	Cytotoxic T Cells ($CD3^+CD16^-CD4^-CD8^+$)	**Age**	**-93.3**	**26.4**	**-3.53**	**0.001**
		Elo Rating	211	106	2.00	0.053
	Double-Positive T Cells ($CD3^+CD16^-CD4^+CD8^+$)	Age	30.3	15.6	1.94	0.062
		Elo Rating	-53.7	64.2	-0.84	0.41
	$CD8^-$ B Cells ($CD3^-CD16^-CD20^+CD8^-$)	**Age**	**-43.7**	**14.7**	**-2.98**	**0.005**
		Elo Rating	64.5	58.6	1.10	0.28
	$CD8^+$ B Cells ($CD3^-CD16^-CD20^+CD8^+$)	Age	-6.56	4.05	-1.62	0.11
		Elo Rating	10.2	16.2	0.63	0.53
	NK Cells ($CD3^-CD16^+$)	**Age**	**-43.6**	**18.0**	**-2.42**	**0.021**
		Elo Rating	83.3	72.5	1.15	0.26
	NKT Cells ($CD3^+CD16^+$)	Age	-4.09	2.67	-1.54	0.13
		Elo Rating	6.56	10.8	0.61	0.55

LMMs include random effect of testing day

Table S3.3. Linear mixed-effects model (LMM) results for assocations between dominance rank, cortisol, and acute separation stressor-induced redistribution of circulating leukocyte numbers.

Leukocyte Assessment	Outcome Measure	Independent variable	β	SE	*t*	*P*
Trafficking (Pre- to Post-SS)	ΔTotal Neutrophils (CBC)	Pre-SS Neutrophils (CBC)	0.26	0.19	1.37	0.18
		Age	108	171	0.63	0.53
		Elo Rating	-619	1578	-0.39	0.70
		Cortisol Reactivity	-197	184	-1.07	0.30
		Elo x Cortisol Reactivity	185	203	0.91	0.37
	ΔTotal Monocytes (CBC)	Pre-SS Monocytes (CBC)	-0.02	0.01	-0.23	0.82
		Age	-17.8	8.80	-2.03	0.051
		Elo Rating	-114	78.8	-1.45	0.16
		Cortisol Reactivity	-1.47	9.35	-0.16	0.88
		Elo x Cortisol Reactivity	**21.1**	**9.77**	**2.16**	**0.038**
	ΔTotal Lymphocytes (CBC)	**Pre-SS Lymphocytes (CBC)**	**0.23**	**0.08**	**2.95**	**0.006**
		Age	4.25	35.6	0.12	0.91
		Elo Rating	-10.7	268	-0.04	0.97
		Cortisol Reactivity	-23.5	34.0	-0.69	0.49
		Elo x Cortisol Reactivity	-2.22	34.1	-0.07	0.95
	ΔClassical Monocytes ($CD14^+CD16^-$)	Pre-SS Classical Monocytes	0.09	0.13	0.69	0.50
		Age	-11.2	7.68	-1.46	0.16
		Elo Rating	-106	71.8	-1.47	0.15
		Cortisol Reactivity	-4.03	7.83	-0.52	0.61
		Elo x Cortisol Reactivity	**19.0**	**8.89**	**2.14**	**0.04**
	ΔActivated Monocytes ($CD14^+CD16^+$)	**Pre-SS Activated Monocytes**	**0.20**	**0.06**	**3.16**	**0.004**
		Age	-1.07	0.99	-1.08	0.29
		Elo Rating	-5.29	9.00	-0.59	0.56
		Cortisol Reactivity	-1.29	1.10	-1.18	0.25
		Elo x Cortisol Reactivity	1.22	1.12	1.09	0.28
	ΔHelper T Cells ($CD3^+CD16^-CD4^+CD8^-$)	**Pre-SS Helper T Cells**	**0.18**	**0.04**	**4.03**	**< 0.001**
		Age	-12.40	6.96	-1.78	0.086
		Elo Rating	2.50	52.9	0.05	0.96
		Cortisol Reactivity	-0.67	6.66	-0.10	0.92
		Elo x Cortisol Reactivity	7.01	6.64	1.06	0.30
	ΔCytotoxic T Cells ($CD3^+CD16^-CD4^-CD8^+$)	**Pre-SS Cytotoxic T Cells**	**0.13**	**0.05**	**2.73**	**0.011**
		Age	-6.34	8.44	-0.75	0.46

		Elo Rating	-36.0	67.2	-0.54	0.60
		Cortisol Reactivity	-6.10	8.26	-0.74	0.47
		Elo x Cortisol Reactivity	7.04	8.63	0.82	0.42
	ΔDouble-Positive T Cells ($CD3^+CD16^-CD4^+CD8^+$)	**Pre-SS Double-Positive T Cells**	**0.45**	**0.01**	**35.4**	**< 0.001**
		Age	-0.44	1.31	-0.34	0.74
		Elo Rating	5.12	10.7	0.48	0.64
		Cortisol Reactivity	-2.06	1.26	-1.64	0.11
		Elo x Cortisol Reactivity	-1.20	1.33	-0.90	0.38
	ΔCD8$^+$ B Cells ($CD3^-CD16^-CD20^+CD8^+$)	**Pre-SS CD8$^+$ B Cells**	**0.25**	**0.04**	**6.55**	**< 0.001**
		Age	1.13	0.97	1.17	0.25
		Elo Rating	1.13	8.61	0.13	0.90
		Cortisol Reactivity	-0.43	1.01	-0.43	0.67
		Elo x Cortisol Reactivity	-0.14	1.09	-0.13	0.90
	ΔNK Cells ($CD3^-CD16^+$)	**Pre-SS NK Cells**	**0.22**	**0.06**	**3.92**	**< 0.001**
		Age	-2.72	6.31	-0.43	0.67
		Elo Rating	44.0	55.3	0.80	0.43
		Cortisol Reactivity	-3.82	6.68	-0.57	0.57
		Elo x Cortisol Reactivity	-8.96	7.08	-1.27	0.22
	ΔNKT Cells ($CD3^+CD16^+$)	**Pre-SS NKT Cells**	**0.30**	**0.01**	**24.8**	**< 0.001**
		Age	-0.20	0.21	-0.96	0.34
		Elo Rating	2.40	1.93	1.25	0.22
		Cortisol Reactivity	**-0.62**	**0.22**	**-2.76**	**0.01**
		Elo x Cortisol Reactivity	-0.23	0.24	-0.96	0.34
Recovery (Post- to 4h Post-SS)	ΔTotal Monocytes (CBC)	Post-SS Monocytes (CBC)	-0.28	0.14	-2.00	0.054
		Age	6.35	15.0	0.42	0.67
		Elo Rating	-71.9	137	-0.52	0.60
		Cortisol Recovery	-65.0	68.8	-0.94	0.35
		Elo x Cortisol Recovery	19.1	85.0	0.22	0.82
	ΔTotal Lymphocytes (CBC)	Post-SS Lymphocytes (CBC)	-0.28	0.14	-2.04	0.052
		Age	-79.3	57.6	-1.38	0.18
		Elo Rating	-801	465	-1.72	0.097
		Cortisol Recovery	-260	232	-1.12	0.27
		Elo x Cortisol Recovery	445	280	1.59	0.12
	ΔClassical Monocytes ($CD14^+CD16^-$)	**Post-SS Classical Monocytes**	**-0.34**	**0.16**	**-2.08**	**0.046**
		Age	11.6	11.6	1	0.33
		Elo Rating	-94.0	107	-0.88	0.39
		Cortisol Recovery	-52.6	53.7	-0.98	0.34

	Elo x Cortisol Recovery	19.6	66.4	0.3	0.77
ΔActivated Monocytes ($CD14^+CD16^+$)	Post-SS Activated Monocytes	0.17	0.11	1.57	0.13
	Age	0.21	1.50	0.14	0.89
	Elo Rating	6.18	14.3	0.43	0.67
	Cortisol Recovery	-2.34	7.25	-0.32	0.75
	Elo x Cortisol Recovery	-3.94	8.62	-0.46	0.65
ΔHelper T Cells ($CD3^+CD16^-CD4^+CD8^-$)	**Post-SS Helper T Cells**	**-0.29**	**0.12**	**-2.4**	**0.025**
	Age	**-40.4**	**16.70**	**-2.41**	**0.023**
	Elo Rating	-253	135	-1.89	0.074
	Cortisol Recovery	-64.0	70.7	-0.91	0.37
	Elo x Cortisol Recovery	168	83.3	2.01	0.055
ΔCytotoxic T Cells ($CD3^+CD16^-CD4^-CD8^+$)	Post-SS Cytotoxic T Cells	-0.18	0.13	-1.44	0.16
	Age	-14.90	17.80	-0.84	0.41
	Elo Rating	**-396.00**	**140.00**	**-2.82**	**0.009**
	Cortisol Recovery	-104.00	73.90	-1.4	0.17
	Elo x Cortisol Recovery	**233.00**	**87.10**	**2.68**	**0.013**
ΔDouble-Positive T Cells ($CD3^+CD16^-CD4^+CD8^+$)	**Post-SS Double-Positive T Cells**	**0.20**	**0.05**	**4.1**	**< 0.001**
	Age	4.08	2.88	1.42	0.17
	Elo Rating	-47.3	23.7	-2.00	0.057
	Cortisol Recovery	-2.59	12.0	-0.22	0.83
	Elo x Cortisol Recovery	17.80	14.6	1.22	0.23
Δ$CD8^-$ B Cells ($CD3^-CD16^-CD20^+CD8^-$)	Post-SS $CD8^-$ B Cells	0.01	0.07	0.20	0.84
	Age	-5.99	7.72	-0.78	0.44
	Elo Rating	-109	66.2	-1.65	0.11
	Cortisol Recovery	-19.8	31.4	-0.63	0.53
	Elo x Cortisol Recovery	54.0	39.5	1.37	0.18
Δ$CD8^+$ B Cells ($CD3^-CD16^-CD20^+CD8^+$)	**Post-SS $CD8^+$ B Cells**	**0.90**	**0.16**	**5.75**	**< 0.001**
	Age	0.83	3.29	0.25	0.80
	Elo Rating	-34.0	29.7	-1.15	0.26
	Cortisol Recovery	-4.35	14.5	-0.30	0.77
	Elo x Cortisol Recovery	13.4	17.9	0.75	0.46

Table S3.4. Associations between Elo rating (dominance rank) and basal gene expression in FACS-purified leukocyte subtypes combined across study Phases 1 & 2. Gene set derived from KEGG Pathway database (CAMs: mcc04514). Significance tests based on linear mixed-effects models within each cell type, controlling for age, social group membership, and genetic relatedness between subjects. Q-value (FDR) calculations performed using the smoother method described in Storey and Tibshirani (2003). All listed genes were expressed in at least 2 cell types. Bold typeface indicates FDR < 10%. NA: expression level not pass minimum theshold filter.

	Helper T Cells ($CD3^+CD4^+CD8^-$)			Cytotoxic T Cells ($CD3^+CD4^-CD8^+$)			Monocytes ($CD3^-CD20^-CD14^+$HLA-DR^+)			Natural Killer Cells ($CD3^-CD20^-$HLA-DR^-CD16^+)			B Cells ($CD3^-CD20^+$HLA-DR^+)		
gene	*P*	β	q	*P*	β	q	*P*	β	q	*P*	β	q	*P*	β	q
ALCAM	0.320	0.047	0.367	0.437	0.027	0.534	0.818	-0.010	0.315	NA	NA	NA	0.404	0.043	0.576
CD2	0.946	-0.002	0.761	0.917	0.004	0.673	NA	NA	NA	0.789	0.019	0.167	0.953	-0.003	0.946
CD226	0.075	-0.116	0.170	0.210	0.047	0.534	NA	NA	NA	0.002	0.245	**0.003**	NA	NA	NA
CD274	0.648	0.016	0.599	0.619	-0.016	0.612	0.172	-0.145	0.118	0.627	0.020	0.155	0.010	-0.063	**0.060**
CD28	0.004	-0.159	**0.034**	0.338	-0.056	0.534	NA	NA	NA	NA	NA	NA	NA	NA	NA
CD4	0.064	-0.135	0.161	NA	NA	NA	0.328	0.034	0.185	NA	NA	NA	0.006	0.104	**0.039**
CD40LG	0.670	0.016	0.605	0.019	0.104	0.156	NA	NA	NA	NA	NA	NA	NA	NA	NA
CD58	0.179	-0.047	0.262	0.313	-0.042	0.534	0.009	-0.133	**0.031**	0.196	-0.051	**0.081**	0.002	-0.114	**0.024**
CD6	0.148	-0.049	0.224	0.411	-0.057	0.534	NA	NA	NA	NA	NA	NA	0.000	0.145	**0.006**
CD80	0.111	0.052	0.183	0.673	-0.020	0.612	0.225	-0.067	0.137	NA	NA	NA	0.556	-0.050	0.686
CD8A	0.080	-0.172	0.170	0.661	-0.038	0.612	NA	NA	NA	0.022	0.107	**0.013**	0.503	0.016	0.638
CD99L2	0.317	-0.159	0.367	0.481	-0.125	0.536	0.683	0.034	0.304	0.493	-0.055	0.137	0.028	0.107	0.116
CLDN15	0.111	-0.062	0.183	0.610	0.032	0.612	0.805	0.009	0.315	0.086	-0.090	**0.040**	0.236	0.029	0.399
CLDN4	0.105	0.080	0.183	0.474	0.042	0.536	NA	NA	NA	NA	NA	NA	NA	NA	NA
CNTNAP1	0.264	0.048	0.334	0.163	0.073	0.526	0.762	0.018	0.310	0.707	-0.018	0.160	0.135	-0.082	0.333
CTLA4	0.410	-0.074	0.432	0.012	0.177	0.125	NA	NA	NA	NA	NA	NA	NA	NA	NA
ESAM	0.954	0.004	0.761	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.210	0.072	0.399
F11R	0.053	0.105	0.161	NA	NA	NA	0.657	0.035	0.304	NA	NA	NA	NA	NA	NA
GLG1	0.991	0.000	0.767	0.361	-0.041	0.534	0.692	-0.023	0.304	0.008	-0.137	**0.009**	0.450	-0.033	0.594
ICAM1	0.002	0.124	**0.034**	0.769	-0.015	0.617	0.026	0.136	**0.058**	0.263	-0.043	**0.098**	0.352	-0.046	0.518
ICAM2	0.097	0.119	0.183	0.965	0.002	0.693	0.150	-0.057	0.108	0.534	-0.029	0.137	0.138	0.061	0.333
ICAM3	0.003	0.096	**0.034**	0.362	0.051	0.534	0.147	-0.097	0.108	0.711	-0.013	0.160	0.939	-0.003	0.946
ICOS	0.011	0.122	**0.062**	0.999	0.000	0.701	NA	NA	NA	0.437	-0.030	0.137	NA	NA	NA
ICOSLG	0.920	-0.006	0.761	NA	NA	NA	0.136	-0.056	0.108	NA	NA	NA	0.017	0.169	**0.087**

ITGA4	0.078	0.135	0.170	0.262	0.072	0.534	0.060	0.113	0.106	0.019	-0.107	**0.013**	0.108	0.051	0.290
ITGA6	0.592	-0.022	0.573	0.504	0.027	0.543	NA	NA	NA	0.071	-0.122	**0.038**	0.862	0.021	0.917
ITGAL	0.245	0.037	0.320	0.096	0.065	0.400	0.263	0.078	0.154	0.000	0.275	**0.000**	0.003	0.193	**0.024**
ITGAM	0.060	0.127	0.161	0.217	0.069	0.534	0.010	0.095	**0.031**	0.444	-0.147	0.137	0.175	0.045	0.389
ITGAV	0.372	-0.032	0.415	0.671	0.018	0.612	0.415	0.077	0.219	0.000	0.092	**0.001**	NA	NA	NA
ITGB1	0.316	0.075	0.367	0.099	0.119	0.400	0.728	0.011	0.310	0.022	-0.263	**0.013**	0.716	-0.010	0.817
ITGB2	0.033	-0.089	0.141	0.885	0.009	0.673	0.143	0.064	0.108	0.504	0.020	0.137	0.227	0.053	0.399
ITGB7	0.041	0.158	0.156	0.073	0.121	0.393	0.127	0.066	0.108	0.249	-0.111	**0.097**	0.683	0.014	0.799
JAM3	0.604	0.035	0.573	0.332	0.069	0.534	NA	NA	NA	NA	NA	NA	0.989	0.000	0.950
MAMU-DMA	0.059	0.103	0.161	0.213	0.071	0.534	0.111	-0.076	0.108	0.388	-0.106	0.137	0.999	0.000	0.950
MAMU-DMB	0.874	0.008	0.753	0.378	0.054	0.534	0.484	-0.036	0.241	NA	NA	NA	0.001	0.102	**0.012**
MAMU-DOB	0.033	0.065	0.141	0.702	0.016	0.612	0.863	-0.011	0.315	0.507	-0.036	0.137	0.229	-0.056	0.399
MAMU-DPA	0.010	0.273	**0.062**	0.913	-0.004	0.673	0.865	-0.017	0.315	0.781	-0.007	0.167	0.004	-0.127	0.033
MAMU-DQA1	0.409	0.057	0.432	0.006	0.103	0.103	0.534	0.030	0.256	0.023	0.058	**0.013**	0.920	-0.004	0.946
MAMU-DRA	0.205	0.050	0.288	0.125	0.041	0.450	0.114	0.132	0.108	0.022	0.119	**0.013**	0.067	0.162	0.235
MAMU-DRB1	0.116	-0.044	0.183	0.381	0.035	0.534	0.487	0.078	0.241	0.942	-0.004	0.194	0.448	0.023	0.594
MAMU-F	0.218	0.068	0.295	0.744	0.016	0.616	0.213	-0.094	0.135	0.002	-0.136	**0.003**	0.258	0.068	0.420
MPZ	0.063	-0.123	0.161	0.409	-0.061	0.534	0.129	-0.117	0.108	0.022	0.180	**0.013**	0.456	-0.053	0.594
MPZL1	0.089	0.071	0.178	0.743	0.019	0.616	0.183	0.106	0.121	0.536	0.030	0.137	0.099	0.139	0.290
NLGN2	0.000	0.226	**0.003**	0.003	0.138	0.101	NA	NA	NA	NA	NA	NA	NA	NA	NA
NTNG2	0.010	0.066	**0.062**	0.035	0.058	0.224	NA	NA	NA	0.531	-0.035	0.137	0.334	0.052	0.508
PDCD1	0.963	0.001	0.761	0.447	-0.036	0.534	NA	NA	NA	NA	NA	NA	0.000	0.164	**0.006**
SELL	0.423	-0.033	0.433	0.783	0.011	0.617	0.113	0.074	0.108	0.002	-0.254	**0.003**	0.864	0.006	0.917
SPN	0.518	-0.028	0.517	0.688	-0.017	0.612	0.875	0.008	0.315	0.108	-0.073	**0.047**	0.019	-0.150	0.088
TIGIT	0.742	-0.018	0.655	0.252	-0.054	0.534	NA	NA	NA	0.077	0.071	**0.038**	NA	NA	NA
CD8B	NA	NA	NA	0.435	-0.027	0.534	NA	NA	NA	0.000	-0.159	**0.001**	NA	NA	NA
CD22	NA	NA	NA	NA	NA	NA	0.372	-0.025	0.203	NA	NA	NA	0.214	0.042	0.399
CD86	NA	NA	NA	NA	NA	NA	0.080	0.127	0.108	NA	NA	NA	0.098	-0.086	0.290
MAMU-DOA	NA	NA	NA	NA	NA	NA	0.006	0.108	**0.031**	NA	NA	NA	0.179	0.063	0.389
PDCD1LG2	NA	NA	NA	NA	NA	NA	0.001	0.174	**0.018**	NA	NA	NA	0.856	0.009	0.917
VCAN	NA	NA	NA	NA	NA	NA	0.024	-0.134	**0.058**	NA	NA	NA	0.034	0.136	0.131
NLGN3	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.659	0.026	0.157	0.285	0.056	0.448

Table S3.5. Standardized, varimax-rotated factor loadings of subject-wise adhesion gene expression values in principal components analysis (PCA). Genes listed were detectably expressed in all 5 cell types.

	Helper T Cells (CD3+CD4+CD8-)		Cytotoxic T Cells (CD3+CD4-CD8+)		Monocytes (CD3-CD20-CD14+HLA-DR+)		Natural Killer Cells (CD3-CD20-HLA-DR-CD16+)		B Cells (CD3-CD20+HLA-DR+)	
gene	PC1	PC2	PC1	PC2	PC1	PC2	PC1	PC2	PC1	PC2
CD274	0.205	**-0.573**	0.361	0.090	-0.423	-0.306	-0.303	0.193	-0.006	**-0.561**
CD58	**0.643**	-0.050	0.228	0.233	-0.434	-0.199	0.004	0.220	0.435	-0.332
CD99L2	**0.801**	0.034	**0.653**	0.457	**0.815**	0.094	**0.694**	0.270	**0.567**	0.117
CLDN15	-0.224	-0.184	-0.174	0.204	0.017	0.267	0.181	**-0.629**	-0.039	0.249
CNTNAP1	-0.330	0.318	-0.441	**0.511**	-0.295	-0.398	**-0.590**	-0.219	-0.179	0.305
GLG1	-0.304	**0.583**	-0.307	0.494	**0.579**	-0.121	-0.129	0.329	0.173	0.324
ICAM1	0.159	**-0.612**	0.104	-0.207	-0.465	-0.083	0.029	0.064	-0.207	-0.276
ICAM2	0.065	**0.526**	-0.082	0.078	**0.745**	-0.258	0.470	-0.326	0.152	**0.792**
ICAM3	**0.601**	0.255	**0.706**	0.010	0.222	**0.669**	**0.765**	0.069	0.228	0.270
ITGA4	0.265	-0.046	0.280	**0.712**	**0.660**	-0.255	-0.029	**0.572**	0.135	**0.678**
ITGAL	**0.785**	-0.270	0.424	**0.787**	**0.827**	-0.412	**0.595**	0.119	**0.682**	0.091
ITGAM	**0.533**	**-0.567**	0.305	0.466	0.184	**0.634**	0.485	**-0.534**	**0.696**	-0.249
ITGB1	0.293	0.409	0.304	0.168	0.198	**-0.603**	-0.102	**0.741**	-0.355	0.152
ITGB2	**0.835**	-0.225	**0.584**	**0.589**	**0.873**	0.056	**0.922**	-0.188	**0.897**	0.081
ITGB7	-0.041	**0.632**	0.007	0.129	-0.010	0.370	**0.556**	-0.337	**0.674**	0.152
MAMU-DMA	**0.573**	0.100	**0.549**	-0.106	0.020	**0.648**	0.055	0.299	0.425	0.398
MAMU-DOB	0.258	0.279	0.038	0.372	0.199	0.022	0.316	-0.070	0.049	**0.792**
MAMU-DPA	**0.821**	-0.404	**0.849**	0.095	0.484	0.357	**0.576**	0.348	**0.537**	0.332
MAMU-DQA1	**0.661**	-0.207	**0.607**	0.092	0.057	-0.054	-0.018	**0.589**	**0.617**	0.230
MAMU-DRA	**0.799**	-0.054	**0.740**	-0.215	-0.110	0.357	0.203	**0.505**	**0.557**	0.218
MAMU-DRB1	**0.837**	-0.145	**0.782**	-0.015	0.429	**0.508**	0.298	**0.642**	**0.661**	0.060
MAMU-F	0.034	-0.262	0.114	0.141	0.430	0.204	0.482	-0.451	0.137	0.035
MPZ	**0.543**	0.394	0.457	-0.026	-0.156	0.469	0.324	-0.058	0.101	0.123
MPZL1	0.439	0.194	-0.073	**0.582**	-0.089	0.032	-0.216	-0.286	-0.006	**0.752**
SELL	0.085	**0.856**	-0.050	-0.027	-0.003	0.637	0.315	0.143	0.100	**0.686**
SPN	**0.631**	-0.222	0.200	**0.705**	**0.649**	**-0.666**	**0.542**	0.199	**0.664**	-0.012
Eigenvalue	7.6	3.5	5.6	3.1	5.4	4.1	4.9	3.7	5.8	3.5
Cumulative % Variance	27.8	42.8	19.4	33.6	20.5	36.3	18.8	33.1	19.7	35.5

Bold typeface indicates the strongest factor loadings ($|r| > 0.50$)

Table S3.6. Mean (±SD) proportions of monocyte and lymphocyte subpopulations in circulation and serum cortisol levels before and 1.5h after dexamethasone administration (intramuscular; 0.125 mg/kg). Monocyte and lymphocyte gates were applied based on size and granularity, and subtype proportions were calculated by dividing the number of each respective cell subtype by all monocytes and lymphocytes acquired. At least 100,000 events were acquired within monocyte and lymphocyte gates for all samples at both timepoints.

	Phase 1				**Phase 2**			
	Cell Proportion (%)				Cell Proportion (%)			
Cell type	Pre-Dex	Post-Dex	t_{40}	P	Pre-Dex	Post-Dex	t_{41}	P
Classical Monocytes ($CD14^+CD16^-$)	9.6 ± 3.9	11.1 ± 4.9	2.51	0.016	8.50 ± 3.2	13.91 ± 4.8	9.47	< 0.001
Activated Monocytes ($CD14^+CD16^+$)	1.02 ± 1.0	1.07 ± 1.1	0.49	0.63	1.10 ± 0.8	1.37 ± 0.8	3.42	0.001
Helper T Cells ($CD3^+CD16^-CD4^+CD8^-$)	28.2 ± 7.6	25.1 ± 6.4	-6.41	< 0.001	27.1 ± 7.4	24.0 ± 7.1	-5.58	< 0.001
Cytotoxic T Cells ($CD3^+CD16^-CD4^-CD8^+$)	25.3 ± 8.2	23.6 ± 8.8	-4.56	< 0.001	27.6 ± 9.4	23.5 ± 11.9	-3.07	0.004
Double-Positive T Cells ($CD3^+CD16^-CD4^+CD8^+$)	5.86 ± 8.7	5.11 ± 7.9	-3.66	< 0.001	7.97 ± 11.6	6.15 ± 10.6	-5.40	< 0.001
$CD8^-$ B Cells ($CD3^-CD16^-CD20^+CD8^-$)	12.0 ± 6.8	14.0 ± 6.5	3.10	0.004	11.4 ± 5.3	12.1 ± 6.0	2.61	0.012
$CD8^+$ B Cells ($CD3^-CD16^-CD20^+CD8^+$)	2.03 ± 1.4	1.62 ± 1.0	-3.42	0.001	1.87 ± 1.1	1.52 ± 0.9	-4.62	< 0.001
NK Cells ($CD3^-CD16^+$)	14.0 ± 8.1	17.3 ± 8.7	4.02	< 0.001	13.9 ± 8.5	16.9 ± 9.5	5.61	< 0.001
NKT Cells ($CD3^+CD16^+$)	1.89 ± 3.7	0.88 ± 0.7	-1.72	0.09	0.49 ± 0.6	0.51 ± 0.6	0.38	0.71
Cortisol (ug/dl)	5.71 ± 2.4	5.00 ± 2.2	-3.04	0.004	20.9 ± 5.4	16.9 ± 3.8	-9.15	< 0.001
Dexamethasone (ng/dl)	0	34.4 ± 6.1			0	53.7 ± 8.3		

Paired *t*-tests were used to test for significant differences between timepoints.

Table S3.7. Linear mixed-effects model (LMM) results for assocations between dominance rank and dexamethasone-induced changes in peripheral blood composition at 1.5h post-Dex in both study phases. Outcome measures were defined as the change in the proportion of each cell type (i.e., arithmetic difference between representation in pre- and post-Dex samples) where more negative values reflect greater changes in proportion. Study subject identity and flow cytometry batch number were included as random effects in all LMMs. Parameter estimates for best-fitting model (in boldface) shown. AIC-based Chi-squared tests between best-fitting/most parsimonious and higher-order models.

Outcome Measure	Model	Independent variable	β	SE	*t*	*P*	Model AIC (*P*)
Δ %Classical Monocytes ($CD14^+CD16^-$)		Baseline % Classical Monocytes	-0.10	0.12	-0.79	0.43	
		Age	-0.23	0.12	-1.86	0.07	
	1	**[Dexamethasone]**	**0.19**	**0.04**	**5.33**	**< 0.001**	446.1
		Elo Rating	-0.66	1.58	-0.42	0.68	
		Elo x [Dex]	0.01	0.03	0.10	0.92	
	2	**Δ %Cortisol**	**-0.06**	**0.02**	**-2.39**	**0.02**	**442.7 (0.020)**
	3	PC1_Expression	0.06	0.35	0.18	0.86	445.9 (0.66)
		PC2_Expression	0.29	0.37	0.77	0.45	
Δ %Helper T Cells ($CD3^+CD16^-CD4^+CD8^-$)		**Baseline % Helper T Cells**	**-0.17**	**0.04**	**-3.88**	**< 0.001**	
		Age	0.12	0.09	1.31	0.20	
	1	[Dexamethasone]	-0.01	0.02	-0.23	0.82	**375.9**
		Elo Rating	0.12	1.02	0.12	0.90	
		Elo x [Dex]	0.01	0.02	0.15	0.88	
	2	Δ %Cortisol	0.01	0.02	0.68	0.50	377.4 (0.49)
	3	PC1_Expression	-0.11	0.34	-0.33	0.74	379.3 (0.74)
		PC2_Expression	-0.26	0.36	0.72	0.48	
Δ %Cytotoxic T Cells ($CD3^+CD16^-CD4^-CD8^+$)		Baseline % Cytotoxic T Cells	-0.07	0.04	-1.68	0.10	
		Age	0.15	0.10	1.54	0.13	
	1	**[Dexamethasone]**	**-0.15**	**0.03**	**-4.84**	**< 0.001**	406.3
		Elo Rating	-1.42	1.30	-1.09	0.28	
		Elo x [Dex]	0.02	0.03	0.78	0.44	
	2	**Δ %Cortisol**	**0.05**	**0.02**	**2.36**	**0.02**	**402.9 (0.020)**
	3	PC1_Expression	0.10	0.34	0.29	0.78	405.9 (0.62)
		PC2_Expression	-0.26	0.28	-0.93	0.36	

Δ %Double-Positive T Cells ($CD3^+CD16^-CD4^+CD8^+$)		Baseline % Double-Positive T Cells	**-0.08**	**0.02**	**-3.83**	**< 0.001**	
	1	Age	-0.08	0.06	-1.42	0.16	**277.4**
		[Dexamethasone]	**-0.04**	**0.01**	**-4.23**	**< 0.001**	
		Elo Rating	**1.15**	**0.52**	**2.21**	**0.03**	
		Elo x [Dex]	**-0.02**	**0.01**	**-2.23**	**0.03**	
	2	Δ %Cortisol	-0.01	0.01	-0.10	0.92	279.4 (0.96)
Δ %CD8- B Cells ($CD3^-CD16^-CD20^+CD8^-$)		Baseline % CD8- B Cells	-0.07	0.06	-1.18	0.24	
		Age	-0.02	0.11	-0.21	0.84	
	1	[Dexamethasone]	-0.04	0.03	-1.52	0.14	406.2
		Elo Rating	1.23	1.30	0.95	0.35	
		Elo x [Dex]	-0.02	0.03	-0.81	0.42	
	2	Δ %Cortisol	-0.01	0.02	-0.26	0.79	408.1 (0.80)
	3	**PC1_Expression**	**0.75**	**0.25**	**2.97**	**0.004**	**378.2 ($1.4x10^{-7}$)**
		PC2_Expression	**-0.79**	**0.28**	**-2.84**	**0.006**	
Δ %$CD8^+$ B Cells ($CD3^-CD16^-CD20^+CD8^+$)		Baseline % $CD8^+$ B Cells	**-0.37**	**0.05**	**-7.53**	**< 0.001**	
		Age	-0.01	0.02	-0.58	0.56	
	1	[Dexamethasone]	-0.01	0.01	-0.33	0.74	**112.2**
		Elo Rating	0.04	0.19	0.23	0.82	
		Elo x [Dex]	-0.01	0.01	-0.11	0.91	
	2	Δ %Cortisol	-0.01	0.01	-0.93	0.36	113.3 (0.34)
Δ %NK Cells ($CD3^-CD16^+$)		Baseline % NK Cells	0.02	0.06	0.38	0.71	
		Age	-0.12	0.14	-0.88	0.39	
	1	[Dexamethasone]	0.02	0.04	0.62	0.54	458.2
		Elo Rating	0.62	1.78	0.35	0.73	
		Elo x [Dex]	-0.01	0.04	-0.28	0.78	
	2	Δ %Cortisol	0.04	0.03	1.48	0.14	457.8 (0.12)
	3	PC1_Expression	0.72	0.46	1.56	0.13	**455.7 (0.037)**
		PC2_Expression	-0.83	0.54	-1.53	0.14	

Table S3.8. Antibodies and fluorescent labels used in cell sorting and phenotyping panels.

Marker	Clone	Fluorescent label	Company	Product number
Cell Sorting				
CD3	SP34-2	APC-Cy7	BD Biosciences	557757
CD4	L200	FITC	BD Biosciences	550628
CD8	B9.11	APC	Beckman Coulter	IM2469U
CD14	M5E2	Pacific Blue	BD Biosciences	558121
CD16	3G8	PE	BD Biosciences	555407
CD20	L27	PE-Cy7	BD Biosciences	335793
HLA-DR	G46-6	V500	BD Biosciences	561224
7-AAD Live/Dead stain	*NA*	*NA*	BD Biosciences	559925
Immunophenotyping				
CD3	SP34-2	PerCp-Cy5.5	BD Biosciences	552852
CD4	L200	FITC	BD Biosciences	550628
CD8	B9.11	APC	Beckman Coulter	IM2469U
CD14	M5E2	Pacific Blue	BD Biosciences	558121
CD16	3G8	PE	BD Biosciences	555407
CD20	L27	PE-Cy7	BD Biosciences	335793

Table S3.9. Linear mixed-effects model (LMM) results for associations between behavioral tendencies and dexamethasone-induced percent changes in classical monocyte and helper T cell proportions at 1.5h post-Dex compared to pre-Dex baseline in both study phases.

Behavioral domain	Independent variable	β	SE	t	P
Social Approachability (PC1)	Δ %Classical Monocytes ($CD14^+CD16^-$)	0.00	0.00	-0.27	0.79
	Δ %Helper T Cells ($CD3^+CD16^-CD4^+CD8^-$)	0.01	0.01	0.67	0.50
	[Dexamethasone]	0.01	0.01	1.18	0.24
Boldness (PC2)	Δ %Classical Monocytes ($CD14^+CD16^-$)	0.00	0.00	1.19	0.24
	Δ %Helper T Cells ($CD3^+CD16^-CD4^+CD8^-$)	**-0.02**	**0.00**	**-3.14**	**0.002**
	[Dexamethasone]	0.01	0.00	1.32	0.19
Anxiousness (PC3)	Δ %Classical Monocytes ($CD14^+CD16^-$)	0.00	0.00	0.02	0.98
	Δ %Helper T Cells ($CD3^+CD16^-CD4^+CD8^-$)	0.00	0.00	-0.19	0.91
	[Dexamethasone]	0.00	0.00	0.87	0.39

Chapter 4: Summary and conclusions

4.1. Summary of results

Chapter two. In chapter two, we tested the hypotheses that 1) behavioral tendencies would be causally affected by social dominance rank, but exhibit partial stability across contexts; 2) the effects of dominance rank on cortisol regulation would be moderated by prosocial and anxious behavioral tendencies; and 3) improvements in social status would increase HPA axis sensitivity and responsiveness to glucocorticoids. The results of our experiment suggest that dominance rank is a major driver of two personality dimensions, boldness and social approachability, and that boldness and anxiousness also exhibited intra-individual stability across groups and ranks. Consistent with previous reports of a "stress of subordination" HPA axis phenotype in female rhesus macaques (Michopoulos et al., 2012b), our data support a causal role of low rank in resistance to dexamethasone suppression of endogenous cortisol. Although we found evidence that behavioral tendencies moderate rank effects on glucocorticoid regulation, the data seemed to contradict our hypotheses. Specifically, lower-ranking females who were more socially approachable than expected for their rank were less sensitive to dexamethasone, and lower-ranking females who had higher scores on anxiousness secreted less cortisol throughout the day. Overall, these findings support the general hypotheses that behavioral stability across time and context (i.e., personality) is detectable in rhesus macaques and that personality domains do in fact moderate the effects of low dominance rank on glucocorticoid regulation. However, our findings also highlight the need for future studies in nonhuman primate personality to exercise caution when attributing simple, connotation-laden terminology to complex social behaviors.

Chapter three. In chapter three, we tested the hypotheses that 1) low dominance rank would be associated with leukocyte insensitivity to the redistributional effects of acute psychosocial stress and cortisol; 2) resistance to cortisol suppression by dexamethasone would predict leukocyte insensitivity to redistribution; 3) low dominance rank would be associated with increased

leukocyte expression of cellular adhesion molecules (CAMs); and 4) higher CAM expression levels would predict increased leukocyte redistribution by dexamethasone. We found that lower-ranking females had an increased ratio of circulating neutrophils to lymphocytes, a biomarker of systemic inflammation, as well as fewer cytotoxic T cells, consistent with previous findings in socially subordinate rhesus monkeys (Paiardini et al., 2009; Tung et al., 2012). Low dominance rank was associated with decreased classical monocyte trafficking and delayed T lymphocyte recovery in response to brief social separation stress, as well as increased baseline proportions of classical monocytes in circulation. Lower-ranking females were more resistant to dexamethasone suppression of cortisol, which predicted smaller changes in monocyte and cytotoxic T cell proportions in response to dexamethasone treatment. Contrary to our initial hypothesis, we found that low dominance rank was associated with downregulation of CAM genes across all five leukocyte subtypes analyzed. Finally, CAM gene expression levels in B cells were associated with trafficking differences in response to dexamethasone, but in the other cell types. Overall, the results of these experiments suggest that low dominance rank decreases monocyte and T lymphocyte sensitivity to glucocorticoid-mediated redistribution and down-regulates CAM mRNA expression in leukocytes. These findings highlight the need to further investigate how glucocorticoid resistance affects leukocyte adhesion in the pathophysiology of chronic stress-associated illnesses.

4.2. Integration of findings and concluding remarks

Using the female rhesus macaque model of chronic social subordination stress, the data gathered in these studies suggest that the social environment has powerful, causal, though plastic, effects on behavior, glucocorticoid regulation, and immune cell function. The initial hypothesis that personality would moderate the effects of low rank on cortisol dysregulation is generally supported by these data; however, interpreting the behavioral phenotypes captured by group social

observations remains difficult. Our data do clarify, however, that rank is a primary driver of social behavior in female rhesus macaques, particularly agonistic and bold behaviors required to maintain dominance, and affiliative behaviors needed to cultivate social bonds.

Our data also provide compelling evidence that subordination stress is characterized by impaired HPA axis negative feedback in this model, though not necessarily hypercortisolemia. We did not find that lower-ranking females secreted more cortisol throughout the diurnal rhythm or in response to brief social separation stress. Rather, our longitudinal analyses that revealed decreased sensitivity to acute dexamethasone challenge (from 0 – 4.5 h) and resistance to the dexamethasone suppression test (conducted over 15 h) in lower-ranking females strongly implicate GR modifications at the pituitary as the principal mediator of altered HPA axis function in this model. However, it is important to consider the chronicity of stress in our model when interpreting these longitudinal data. In both phases of the study, assessments were carried out less than one year from group hierarchy stabilization. It is possible that GR modification at the pituitary is an early HPA axis adaptation to the demands of low dominance rank, and that other changes in glucocorticoid dynamics would emerge as psychosocial stressors persist (Cavigelli and Caruso, 2015), such as altered cortisol responsivity due to adaptations in CRH signaling (Risbrough and Stein, 2006). Our findings also highlight the importance of longitudinally assessing acute responses to challenge, rather than single measurements of basal output, when evaluating the effects of social experience on stress physiology.

The results of our leukocyte analyses suggest that lower-ranking females exhibit a proinflammatory baseline phenotype in which monocytes and T lymphocytes are less sensitive to redistribution by glucocorticoids and adhesion molecule mRNA expression is downregulated. These findings support an emerging literature into the cellular and molecular mediators of chronic stress-associated diseases, in particular how perceived social isolation and loneliness may

induce neuroendocrine adaptations (Cacioppo et al., 2014) that shift the immune system toward a proinflammatory bias (Slavich and Irwin, 2014). Throughout evolutionary time, primates have co-existed alongside pathogens, having developed immunological and behavioral responses to maximize survival in a pathogen-rich environment. Because direct social contact is a primary vector of microbial exchange, behavioral tendencies have been shaped by immunological demands. For instance, "sickness behavior," characterized by lethargy and social withdrawal, is induced by infection or experimental exposure to proinflammatory cytokines (Miller and Raison, 2016). Therefore, the behavioral changes that occur as a consequence of low dominance rank in our experimental model, specifically less time spent affiliating or interacting with groupmates, may result in part from increased levels of systemic inflammation, which is supported by our longitudinal finding of increased neutrophil:lymphocyte ratios (NLR) in lower-ranking individuals. In addition, it is also possible that changes in leukocyte adhesion act as a mechanism of behavioral modulation in a proinflammatory context. For example, there is emerging evidence from animal models of depression that activated monocytes from the periphery can infiltrate brain parenchyma and the neurovasculature, thus altering behavior by neuroinflammatory signaling (Wohleb et al., 2015). Although our study did not detect rank-associated differences in CAM gene expression within monocytes specifically, it is possible that adhesion molecules were activated through post-translational modification, which our experiments were not designed to detect.

In addition, our findings broadly support the therapeutic relevance of psychosocial interventions aimed at ameliorating inflammation and stress-associated diseases. In our model, behavioral tendencies modified the effects of low rank on the HPA axis, and recent work in the same animals suggests that rank effects on transcriptional regulation in NK and helper T cells are partially mediated by affiliative behaviors (Snyder-Mackler et al., 2016b). Interestingly, affiliative behaviors (i.e., allogrooming) accounted for a greater proportion of the rank-associated variance in gene

expression, suggesting that the absence (or presence) of prosocial interactions may be more important than objective measures of social adversity (received harassment in our model) in determining the effects of social status on gene expression in immune cells. These findings are consistent with other reports of proinflammatory gene transcriptional biases in chronically lonely, socially isolated humans (Cole et al., 2015, 2007), and align with evolutionary models of immune-brain-behavior interactions (Miller and Raison, 2016). Psychosocial interventions, particularly meditation-based practices such as mindfulness-based stress reduction (MBSR), can improve negative affective responses to acute psychosocial stressors (Creswell et al., 2014; Holzel et al., 2011; Pace et al., 2009) and decrease perceived loneliness (Creswell et al., 2012). Emerging evidence suggests that such practices abrogate inflammatory signaling at the transcriptional level (Antoni et al., 2012; Black et al., 2013; Creswell et al., 2012; Kaliman et al., 2014).

Importantly, our longitudinal data suggest that regulatory processes within the HPA axis and immune system are highly plastic in adulthood. Although some biological signatures of early-life stress exposure likely persist into adulthood (Danese and McEwen, 2012), it is possible that alleviation of social adversity or changes in psychological or emotional processes that mediate social behavior may abrogate the effects of chronic stress. Nevertheless, the extent to which biological adaptations (and their effects on health outcomes) persist after stress alleviation necessitates further exploration. At the very least, our findings demonstrate that stress biomarkers characterized as risk factors for disease morbidity and mortality can be abrogated by stress alleviation, whether that occurs through improvements in objective social status (e.g., dominance rank), or subjective behavioral features associated with status (e.g., grooming behavior).

The experimental model used for these studies consists of small, female-only social groups. While this model may intensify aspects of the social gradient in rhesus macaques associated with physiological changes – especially rates of aggression and affiliative contact – it lacks other key

features of the social environment that influence stress physiology, health, and survival, such as the presence of multigenerational kin networks, intrasexual competition, and a generally more complex social structure. Expanding this model into a larger, more naturalistic social context may compromise control over some experimental factors, but might benefit from increased ecological validity and translational utility as a model of chronic psychosocial stress.

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