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Population variation in neuroendocrine activity is associated with behavioral inhibition and hemispheric brain structure in young rhesus monkeys

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Summary Population variation in hypothalamic-pituitary-adrenal (HPA) activity and reactivity was assessed in a healthy sample of 48 juvenile rhesus monkeys. Cluster analysis of the HPA profiles revealed four distinct neuroendocrine phenotypes based on six indices of HPA functioning. Behavioral reactivity was also evaluated in response to novel stimuli, and revealed marked differences between animals in the highest- and lowest-cortisol clusters. Specifically, animals in the high-cortisol cluster showed larger stress-induced cortisol responses and blunted feedback sensitivity to dexamethasone. They were also emotionally reactive, displayed more aggressive behaviors, and were less likely to approach novel objects. In contrast, monkeys in the low-cortisol cluster were more likely to approach and explore novel objects. Representative animals with high or low cortisol profiles were scanned with Magnetic Resonance Imaging to evaluate structural differences in global and regional gray matter (GM) and white matter (WM) volumes. Monkeys with higher cortisol reactivity evinced less hemispheric brain asymmetry, due to decreased GM in the right hemisphere. Stress reactivity was inversely related to global GM and positively related to total cerebrospinal fluid volume. This inverse relationship was also observed in several

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stress-sensitive regions, including prefrontal and frontal cortices. Our study demonstrates that population variation in pituitary-adrenal activity is related to behavioral disposition and cerebral structure in this nonhuman primate species.

1. Introduction

There has been long-standing interest in characterizing individual differences in the activity of the hypothalamic-pituitary-adrenal (HPA) axis and its relationship to behavioral and neural measures in both humans and animals. Despite daily variation related to biorhythms and acute changes in stress-responsive hormones such as cortisol (Hruschka et al., 2005; Shirtcliff et al., 2005), hormone secretion and behavioral reactivity are related in a stable manner (Capitanio et al., 1998; Byrne and Suomi, 2003). Some have proposed that this variation reflects distinct endophenotypes and provides a unique means to distinguish subgroups vulnerable to stress-related illness and disease (Chrousos and Gold, 1992; Heim et al., 2000; Wüst et al., 2005). For instance, surveys of healthy individuals have shown that approximately 10% of individuals do not show the typical diurnal decline in cortisol levels across the day (Smyth et al., 1997; Kirschbaum et al., 1999; Stone et al., 2001). Approximately 30% of participants do not respond with the usual increase in cortisol levels to arousing laboratory stressors (Kirschbaum et al., 1993; Dickerson and Kemeny, 2004). Individual differences in HPA activity become evident at a young age, and emerge while children are still in good health. Nevertheless, many researchers have concluded that this variation in HPA responses is an important indicator of vulnerability and can either promote health or have deleterious consequences (Plotsky et al., 1998; McEwen, 2007; Del Giudice et al., 2011). Determining whether flattened profiles or other aberrant characteristics of HPA activity are associated with behavioral profiles is thus of interest in both animals and humans.

In the current study, natural population variation in several defining features of HPA activity was determined in the rhesus monkey, a commonly studied nonhuman primate. The measures included: (a) basal levels, (b) stress responsiveness, (c) the daily rhythm with a focus on peak levels and the diurnal decline, and (d) sensitivity of the HPA axis to negative feedback, which was induced by administering dexamethasone (Dex), a synthetic glucocorticoid. Variation in HPA activity was expected to range from moderate to exaggerated stress responses, from clear to flattened diurnal rhythms, and from a high sensitivity to resistance to glucocorticoid feedback. Cluster analysis was used to create a taxonomy of HPA activity without preconceived constraints about the number of profiles or defining features. Furthering our understanding of phenotypic variation in a healthy young primate population is a crucial step toward ascertaining whether particular components of this variation reflect distinct behavioral dispositions and characteristics of neural structure.

Another advantage of examining rhesus macaques is that they have been described as outgoing or inhibited, behavioral traits that appear similar to fundamental features of human personality (Stevenson-Hinde et al., 1980; Suomi, 1997). Approach or avoidance tendencies in the presence of novel objects or in unfamiliar settings have been used as an index of temperament, similar to our approach in this study. Increased HPA activity has been associated with aspects of behavioral inhibition and the neural limbic circuitry that regulates emotional and behavioral responses to novel and challenging situations (Nachmias et al., 1996; Kalin et al., 2000). Our assessment thus included tests of the monkeys' willingness to approach novel stimulus objects. We hypothesized that monkeys with high HPA activity would be more behaviorally inhibited and/or emotionally reactive in the context of novel objects when compared to animals with lower HPA activity. Following the delineation of population variation in HPA activity and identification of behavioral response profiles, two subgroups were selected for a neuroimaging phase to determine what neuroanatomical characteristics were also associated with this continuum.

Many structural features of the brain, including regional and global brain volumes, have been associated with emotional behavior in animals and with affective and psychiatric conditions in humans (Gur et al., 1999; McEwen, 2000). The neural circuitry of fear and anxiety largely overlaps the neural pathways governing the neuroendocrine stress response (LeDoux, 2000). High HPA activity, due to repeated or severe stress during development, can also lead to altered brain structure and function (Bremner, 1999). The hippocampus, amygdala, prefrontal cortex (PFC), and anterior cingulate are stress-sensitive (Vyas et al., 2002; Cerqueira et al., 2007; McEwen, 2007) and are influenced by glucocorticoids (Herman et al., 2003). In addition, high levels of glucocorticoids, due either to endogenous secretion or pharmacological administration, can result in hippocampal damage, including granule cell loss, dendritic atrophy, and impairments in cognitive function (Uno et al., 1994; Gould et al., 1997; Lupien et al., 2009). There is also a parallel literature indicating that the relative asymmetry of the hemispheres, as well as the predominant activational pattern of the left and right frontal poles, is associated with emotional and cognitive function (Geschwind and Galaburda, 1985; Fox et al., 2005; Ganzel et al., 2013). Therefore, we hypothesized that structural differences would be apparent at the global, regional and hemispheric level in animals with high HPA activity. Exploratory analyses were conducted to determine whether there were volumetric differences in the frontal cortex and hippocampus. Our study demonstrates that young monkeys can be categorized into distinct neuroendocrine subgroups, which also reflect significant differences in emotional and exploratory behavior and cortical brain structure.

2. Methods

2.1. Subjects and housing

Forty-eight juvenile rhesus macaques (18 male, 30 female) were evaluated in this survey of neuroendocrine phenotypes.