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Does cortisol influence core executive functions? A meta-analysis of acute cortisol administration effects on working memory, inhibition, and set-shifting

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Summary The hormone cortisol is often believed to play a pivotal role in the effects of stress on human cognition. This meta-analysis is an attempt to determine the effects of acute cortisol administration on core executive functions. Drawing on both rodent and stress literatures, we hypothesized that acute cortisol administration would impair working memory and set-shifting but enhance inhibition. Additionally, because cortisol is thought to exert different nongenomic (rapid) and genomic (slow) effects, we further hypothesized that the effects of cortisol would differ as a function of the delay between cortisol administration and cognitive testing. Although the overall analyses were nonsignificant, after separating the rapid, nongenomic effects of cortisol from the slower, genomic effects of cortisol, the rapid effects of cortisol enhanced response inhibition, $g^{+} = 0.113$, $p = .016$, but impaired working memory, $g^{+} = -0.315$, $p = .008$, although these effects reversed over time. Contrary to our hypotheses, there was no effect of cortisol administration on set-shifting. Thus, although we did not find support for the idea that increases in cortisol influence set-shifting, we found that acute increases in cortisol exert differential effects on working memory and inhibition over time.

1. Introduction

1.1. Executive function

When studying complex cognition in humans, *executive function*—the construct that underlies our ability to flexibly control our thoughts and actions—comes to the forefront.

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Executive function is a general ability comprised of three interrelated core processes (Miyake et al., 2000; Diamond, 2013). To enhance clarity, we will use the term ''executive function'' only to reference the general factor of executive function (that is, the latent ability facilitating performance across all executive function tasks) and use the name of each core executive function when referencing that specific function. The first core executive function is *working memory*, which allows people to integrate new and old information. Second, *inhibition* enables both cognitive inhibition (the ability to inhibit irrelevant information and selectively attend to goal-relevant information) and response inhibition (the ability to inhibit a prepotent response). Third, *set-shifting* allows people to flexibly shift between modes of thought.

Core executive functions are assessed using multiple tasks (cf. Diamond, 2013). For example, a common working memory task is the *n*-back, which requires participants to indicate whether a given stimulus was the same stimulus they were shown *n* trials previously—thus requiring constant updating of working memory. A common inhibition task is the flanker task, which requires a participant to report the direction of an arrow in the center of the screen, which is flanked by irrelevant arrows either pointing in the same direction or pointing in the opposite direction as the target. The cost in reaction time when the target is flanked by arrows pointing in the opposite direction is an inverse index of inhibition. Finally, a typical set-shifting task is the trail-making test, which requires participants to draw a line connecting numbered circles (e.g., 1-2-3-4-5-6) in one part of the task and a line connecting circles that alternate between numbers and letters (e.g., 1-A-2-B-3-C) in the second part of the task. The difference in time taken to complete the different parts of the task indicates a participant's mental flexibility.

1.2. Stress, cortisol, and executive function

Previous research consistently indicates that stress tends to impair performance on tasks that make use of working memory (e.g., Schoofs et al., 2008, 2009) and set-shifting (e.g., Alexander et al., 2007; Plessow et al., 2011), although the effects of stress on inhibition are less clear (Scholz et al., 2009; Schwabe et al., 2013). One promising explanation of stress-induced influences on core executive functions is found in the stress hormone cortisol (i.e., Butts et al., 2011). Thus, a discussion of the system governing cortisol is in order.

The stress response occurs the moment the brain detects a physical or perceived threat, resulting in the initiation of ''allostasis,'' or the maintenance of bodily stability through change (McEwen, 2004). Activating one pathway of allostasis, stressors upregulate activity in the paraventricular nucleus (PVN) of the hypothalamus, which then secretes corticotropin releasing hormone (CRH); CRH then acts on the pituitary gland and promotes the release of adrenocorticotropin hormone (ACTH); ACTH in turn acts on the adrenal gland to stimulate the synthesis and release of the cortisol (Ulrich-Lai and Herman, 2009). This is known as the hypothalamic—pituitary—adrenal (HPA) axis, and it is primarily through this system that cortisol is regulated.

Acute increases in glucocorticoids—the class of hormones to which cortisol belongs—function primarily to mobilize the body's resources in order to combat or evade the stress-provoking stimulus. Receptors for glucocorticoids exist throughout the brain and, notably, they are concentrated within brain regions supporting core executive functions (Reul and de Kloet, 1985). The effects of glucocorticoids are variable, however, as glucocorticoids can exert both rapid-acting, *nongenomic effects*—effects of cortisol brought about without modulation of gene expression—and slow, *genomic effects*—effects of cortisol brought about by modulation of gene expression—(cf. Joëls et al., 2011). Thus, cortisol can act through multiple pathways to enable the body to combat or evade the stress-inducing stimulus.

Despite the interconnection of stress, cortisol, and neural activity, it is unclear whether cortisol actually influences core executive functions. Previous research has indeed found correlations between cortisol and working memory, both at baseline (Li et al., 2006; Franz et al., 2011) and in response to stress (Oei et al., 2006; Taverniers et al., 2010). However, these data are inconsistent: some studies have found an inverse relationship between cortisol and working memory (e.g., Oei et al., 2006), whereas others have found a positive relationship (e.g., Stauble et al., 2013). One potential reason for these discrepancies is that cortisol may interact with other components of the stress response to exert effects on cognition (e.g., Schwabe et al., 2012). In contrast, the mediating effects of cortisol in the effects of stress on inhibition are slightly more established, as one previous study found that blocking a receptor for cortisol blocked the effects of stress on inhibition (Schwabe et al., 2013). Nonetheless, it is unclear from the prior study if cortisol is both necessary and sufficient to improve inhibition or if it is simply necessary (and thus not a true cause). Finally, the impairing effects of stress on set-shifting are related to salivary cortisol (Plessow et al., 2011), but the correlational nature of these data preclude causal inferences.

Experimentally manipulating cortisol through exogenous administration is a useful method for determining if acute increases in cortisol actually influence core executive functions. Because endogenous cortisol is synthesized outside the brain and readily crosses the blood-brain barrier, exogenously administered cortisol should influence neural processes in the same way as endogenously synthesized cortisol. Indeed, a recent meta-analysis demonstrated that exogenously administered cortisol significantly impairs long-term memory retrieval (Het et al., 2005), illustrating the validity of this methodology for uncovering the effects of cortisol on cognitive processes.

2. Current research

2.1. Main hypotheses

A number of studies have already investigated the effects of cortisol administration on one or more core executive functions. Thus, our goal in this study is to aggregate these results using meta-analytic techniques in an attempt to determine the true effect of acute cortisol administration on each of the core executive functions. Given the heterogeneous nature of the stress and working memory or inhibition