Hypothalamic-pituitary-adrenal axis

The **hypothalamic-pituitary-adrenal (HPA) axis** is a major neuroendocrine system that controls the body's **stress response** and plays a key role in **homeostasis**, **immune function**, **mood**, **digestion**, **energy metabolism**, and more.

Raff et al. studied HPA axis dynamics in 20 experienced fifth-generation fighter pilots (18 men/2 women) by measuring salivary cortisol at various times from bedtime the night before a flight training to awakening the morning after the flight training. We also measured plasma ACTH and serum cortisol the day before the flight and immediately following the flight. These findings were correlated with prior pilot flight experience and subjective assessments of pain and stress.

Seven (35%) of the pilots demonstrated normal salivary cortisol levels at all time points despite one having a high index of pain. Lower pre-flight salivary cortisol was correlated with more flight hours in the year leading up to the flight exercise. Flight day awakening salivary cortisol was inversely correlated with pilot-reported post-flight stress. In general, there were no other major correlations suggesting a disconnect between an objective measure of stress via HPA axis dynamics and subjective indices of stress and pain.

The acute HPA axis response in some experienced fighter pilots habituates to the stressor of flying a fighter jet during a training exercise. The experience of the pilot was a determinant of their HPA axis stress response [1)].

The study includes only 20 participants (18 male, 2 female), a cohort too small to derive statistically robust conclusions, particularly given the known interindividual variability in HPA axis function. Furthermore, the near-total exclusion of women prevents any meaningful sex-based interpretation, despite clear sex differences in HPA axis regulation.

Critical factors known to influence cortisol and ACTH levels — including sleep quality, circadian phase, dietary intake, hydration, stimulant consumption, and baseline psychological traits — are neither controlled nor discussed. Without rigorous standardization, the hormonal measurements cannot be reliably attributed to the flight experience, undermining internal validity.

The authors identify limited and weak correlations (e.g., lower pre-flight cortisol associated with recent flight experience), while the majority of comparisons yield no significant relationships. Rather than acknowledging the likely role of insufficient statistical power, the authors interpret these findings as a "disconnect" between objective and subjective stress — a conclusion that is methodologically unsupported and speculative at best.

The central thesis of habituation to stress is presented without mechanistic evidence or longitudinal data. The assertion is based on a cross-sectional snapshot from a single training event and extrapolated beyond the data's resolution. True demonstration of HPA axis habituation would require repeated measures across multiple exposures with appropriate within-subject controls.

The study lacks transparency in statistical reporting. Key metrics such as effect sizes, confidence intervals, p-values, and correction methods for multiple comparisons are omitted. Additionally, there

is no mention of inter- or intra-individual variability in cortisol responses, which is a critical consideration in psychoneuroendocrinology research.

The subjective stress and pain assessments are neither defined nor referenced to validated scales (e.g., Perceived Stress Scale, Visual Analog Scale). Timing of these assessments in relation to hormone sampling is also not clarified, making any correlation analysis questionable.

While the subject matter — HPA axis regulation under high-performance stress — is worthy of investigation, the current study by Raff et al. lacks the methodological rigor and statistical robustness to support its claims. The small sample size, inadequate control of confounders, absence of validated psychometric tools, and speculative interpretation of results render its conclusions about HPA axis habituation premature and potentially misleading.

Further research in this area should prioritize larger, sex-balanced samples, rigorous experimental controls, validated psychological instruments, and repeated measures over time to adequately assess stress adaptation in elite operational environments.

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Raff H, Hainsworth KR, Cutlan R, Sherman KA, Stemper BD. Flight-associated cortisol dynamics and subjective assessments of pain and stress in fighter pilots: an exploratory study. Eur J Appl Physiol. 2025 Jun 13. doi: 10.1007/s00421-025-05837-8. Epub ahead of print. PMID: 40512180.