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# Differentiating anticipatory from reactive cortisol responses to psychosocial stress

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**Summary** Most psychosocial stress studies assess the overall cortisol response without further identifying the temporal dynamics within hormone levels. It has been shown, however, that the amplitude of anticipatory cortisol stress levels has a unique predictive value for psychological health. So far, no "best practice" in how to investigate the anticipatory cortisol stress response has emerged. The goal of the current research was to develop a protocol that would allow for a sensitive and easy-to-implement laboratory-based investigation into anticipatory cortisol stress levels. We initially tested 26 healthy men in either an anticipation- or stress-only condition of the Trier Social Stress Test (TSST) to map the distinct timelines of anticipatory and reactive cortisol release profiles (study 1). Subsequently, we administered the TSST to 50 healthy men such that the cortisol responses to anticipatory and reactive stress components could be dissociated (study 2). In both studies we sampled saliva cortisol at high frequency (at baseline, during 10 min of anticipation and during and after 10 min of acute stress) and the current mood state pre- and post-stress. We found anticipatory responder rates of 20% and 40%, with peak anticipatory cortisol levels between 14 and 20 min after onset of anticipation. Visible changes in reactive cortisol levels occurred only after the termination of the acute stressor. We conclude that the best practice to detect a maximum number of anticipatory responders in the TSST would be to extend the anticipation phase to 15 min. In doing so, the anticipatory cortisol peak could be captured at a time-point of the actual stressor that is uninfluenced by reactive cortisol levels. Overall, we could reveal several features of anticipatory responders. Most importantly, there was a positive correlation between anticipatory and reactive stress responses. There was no association between anticipatory cortisol and alpha-amylase as well as subjective—psychological stress

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responses. Future studies will have to determine whether the anticipatory responders differ with respect to various stress-sensitive parameters like sex, personality, psychological wellbeing or chronic stress.


## 1. Introduction

The hypothalamic–pituitary–adrenal (HPA) axis is a major neuroendocrine stress system. Upon stimulation, levels of the HPA axis' final output product cortisol gradually increase until a peak is reached at 20–30 min after stressor onset. Cortisol levels fall back to baseline values within the following 90 min (Kirschbaum and Hellhammer, 2000). Psychosocial stress is a reliable trigger of the HPA axis in humans. A review of the literature shows that most psychosocial stress studies assess the overall cortisol stress response without further identifying the temporal dynamics within cortisol levels, i.e., anticipatory and reactive hormone surges are rarely distinguished (Dickerson and Kemeny, 2004; Foley and Kirschbaum, 2010).

However, previous studies have shown that the amplitude of an anticipatory cortisol stress response explains unique variance in psychological health. Specifically, early anticipatory rather than reactive cortisol stress responses were associated with early life adversity (Hardie et al., 2002), PTSD (Bremner et al., 2003), phobia (Alpers et al., 2003), resilience (Mikolajczak et al., 2008), alexithymia (de Timary et al., 2008) and depressive symptoms and aggression in children exposed to early peer victimization (Rudolph et al., 2010, 2011). Different studies pursued different strategies to investigate the anticipatory cortisol stress response, without a "best practice" approach emerging so far. Starcke et al. (2008) refrained from administering an acute stressor altogether. Studies interested in both anticipatory and reactive cortisol levels examined either naturalistic (Alpers et al., 2003) or laboratory-based (Hardie et al., 2002; Bremner et al., 2003; de Timary et al., 2008; Mikolajczak et al., 2008; Rudolph et al., 2010, 2011) stressors. In the naturalistic setting, participants are aware of the occurrence and nature of the impending stressor well in advance. There is hence ample time for the anticipatory stress response to fully develop. However, uncontrollable acute stressors may co-occur within the same time period and interfere with anticipatory stress. Since the anticipatory stress-sensitive participants already enter the experimental situation with elevated cortisol levels, the determination of a proper baseline for the reactive stress constitutes an additional problem. In the laboratory setting, only the response to short-term anticipation can be captured. However, by revealing the exact nature of the acute stressor just shortly prior to its onset, the occurrence of uncontrollable influences during the anticipation phase and differences in baseline hormone levels can be controlled for. Studies have not consequently exploited these advantages of laboratory-based stress induction. Often, baseline cortisol levels were utilized as a proxy of the unspecific anticipatory stress response to the testing situation per se, which implies that the source and timing of potential anticipatory stress remained unconsidered (Hardie et al., 2002; de Timary et al., 2008; Mikolajczak et al., 2008; Rudolph et al., 2010, 2011).

The goal of the current research was to develop a protocol that would allow for a sensitive and easy-to-implement laboratory-based investigation into the anticipatory cortisol stress response. To this purpose, we administered the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) in such a way that the cortisol responses to anticipatory and reactive stress components could be dissociated. Levine and Coe (1985) have reported that it takes 7 min until detectable increases in stress-induced circulating cortisol levels occur. To validate this timeline for the current context (i.e., to obtain an indication as to when measurable changes in salivary cortisol levels following anticipatory and reactive stress could be expected), we initially tested 26 participants in either an anticipation-only ($n = 14$) or a stress-only ($n = 12$) TSST condition. Saliva cortisol was sampled at high frequency: at baseline, in 2-min intervals throughout anticipation (10 min), acute stress (10 min) and the following 12 min and in 10-min intervals thereafter. In a subsequent study, 50 participants underwent the complete TSST procedure (including 10 min of both anticipatory and acute stress), again using a high-frequency sampling procedure. Based on the timeline results of study 1, we could thus capture the anticipatory stress response and determine its interaction with the onset of reactive stress. We hypothesized to find two groups with distinct cortisol release profiles: Anticipatory responders with a physiologically relevant increase in cortisol levels early into the task (before the acute stressor could have triggered HPA axis activity) and reactive responders with a physiologically relevant increase in cortisol levels only after the acute stressor could have had a measurable effect. A physiological relevant increase in cortisol levels was defined as an elevation of at least 2.5 nmol/l over the individual baseline level, as defined previously (Van Cauter and Refetoff, 1985). Aiming to more closely characterize the anticipatory stress response, we compared additional stress markers (salivary alpha-amylase and subjective–psychological stress responses) between anticipation- and stress-only (study 1) and responder (study 2) groups.

## 2. Materials and methods

### 2.1. Participants

Male participants between 18 and 30 years of age were recruited by posting ads on the electronic billboard of the McGill University website. Women were excluded to avoid the confounding effects of hormonal status on cortisol levels (Kajantie and Phillips, 2006). Given a potential influence on cortisol and alpha-amylase activity, information about recreational drug use, medical and psychological history was assessed in a telephone interview. Regular recreational drug users (cannabis within the past two months, any other recreational drug within the past year), habitual smokers (more than five cigarettes per week) and individuals