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Anticipatory stress associated with functional magnetic resonance imaging: Implications for psychosocial stress research

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Abstract

Stress tasks performed during functional magnetic resonance imaging (fMRI) elicit a relatively small cortisol response compared to stress tasks completed in a traditional behavioral laboratory, which may be due to apprehension of fMRI that elicits an anticipatory stress response. The present study investigated whether anticipatory stress is greater prior to research completed in an MRI environment than in a traditional behavioral laboratory. Anticipatory stress (indexed by cortisol) was greater prior to testing in the MRI environment than traditional behavioral laboratory. Furthermore, anticipation of fMRI elicited a cortisol response commensurate with the response to the stress task in the behavioral laboratory. However, in the MRI environment, post-stress cortisol was significantly lower than baseline cortisol. Taken together, these findings suggest the stress elicited by anticipation of fMRI may lead to acute elevations in cortisol prior to scanning, which may in turn disrupt the cortisol response to stress tasks performed during scanning.

Keywords

fMRI; Anticipatory Stress; Cortisol; Psychosocial Stress; Skin Conductance

I. Introduction

Excessive exposure to psychological stress disrupts emotion function and can lead to stress-related disorders (Chrousos & Gold, 1992). Thus, there is growing interest in neuroimaging techniques (e.g., functional magnetic resonance imaging; fMRI) to improve our understanding of the neural substrates of the psychosocial stress response (Allendorfer et al., 2014; Bali & Jaggi, 2015; Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009; Pruessner et al., 2008). The most popular index of psychosocial stress in humans is the hormone cortisol, which is controlled by the hypothalamic-pituitary-adrenal (HPA) axis. Prior work has repeatedly demonstrated that psychosocial stress exposure in traditional behavioral laboratory settings elicits a significant cortisol response (Bali & Jaggi, 2015; Dickerson & Kemeny, 2004; Kirschbaum, Pirke, & Hellhammer, 1993). However, similar effects have not always been demonstrated during fMRI (Allendorfer et al., 2014; Dedovic, D'Aguiar, & Pruessner, 2009; Pruessner et al., 2010). In fact, previous research has reported significantly greater cortisol levels before rather than after stress tasks completed during fMRI (Allendorfer et al., 2014; Chung et al., 2016; Hermans et al., 2011; Root et al., 2009). Thus, anticipation of fMRI may elicit an anticipatory cortisol response before participants are exposed to the stress task itself. The observed decrease in cortisol following stress tasks completed in the MRI environment may result from an acute elevation in cortisol prior to scanning that is driven by anticipatory stress that is uniquely associated with fMRI methodology. However, no prior research has investigated anticipatory stress associated with fMRI by directly comparing cortisol levels prior to fMRI to levels measured prior to participating in a traditional behavioral study. Investigating the anticipatory distress associated with fMRI would help determine its impact on the results of experimental stress tasks performed in the MRI scanner.

Prior research suggests that many individuals experience stress during MRI scanning, especially those with no prior exposure to MRI (Tessner, Walker, Hochman, & Hamann, 2006). However, preparing to safely and effectively participate in an fMRI study may also be distressing for many research participants. Volunteers for an fMRI study must complete a thorough safety screening and consent process prior to scanning due to the risk associated with the high magnetic fields used in fMRI research. The primary aim of safety screening is to ensure that participants have no ferromagnetic medical devices implanted inside their body or other safety issues that could cause harm when placed within a high magnetic field. Additional screening questions and safety concerns include, but are not limited to, tattoos containing metallic ink, pregnancy, claustrophobia, sensitivity to loud noises, and eye injuries involving metallic objects (e.g., metal slivers embedded in the eye). Additionally, participants must complete and sign a safety form to explicitly attest they have no conditions that would make undergoing MRI unsafe. Further, before entering the scanner room, participants are often inspected with a hand-held metal detector to ensure there is no metal on their body. They are also given instructions on certain safety-seeking behaviors to use during scanning (e.g., using a "squeeze ball" to set off an alarm and stop scanning), which may further increase anticipatory fear (Sloan & Telch, 2002).

While safety precautions are necessary to protect the well-being of participants, the novelty of the neuroimaging environment coupled with extensive safety precautions may direct

participants' attention to the potential dangers of scanning, portraying fMRI as a threatening and potentially harmful procedure (Mason, 1968; Ursin & Eriksen, 2004). Additionally, participants are instructed before scanning to refrain from making even minor movements while in the scanner to prevent motion artifacts. The effort to remain still is compounded by the fact that participants are warned that they will be isolated and confined inside an uncomfortable machine that makes repetitive, loud, and startling noises (Burow, Day, & Campeau, 2005; DeVries, Glasper, & Detillion, 2003; Mason, 1968; Rudy, Kuwagama, & Pugh, 1999). As a result, participants may anticipate and fear negative outcomes that could occur during scanning, such as physical harm, **claustrophobia**, or the inability to remain still (Brosschot, Gerin, & Thayer, 2006; Mason, 1968; McGlynn, Smitherman, Hammel, & Lazarte, 2007). In fact, participants commonly report feelings of apprehension prior to scanning, such as fear of an unknown procedure, harm by the machine, suffocation, and restriction (McGlynn et al., 2007; Thorpe, Salkovskis, & Dittner, 2008). In addition, the strict guidelines of MRI may lead participants to fear negative evaluation by the investigators (McGlynn et al., 2007). Further, the lack of control over the procedure and fear of social evaluation in the MRI environment may create an experience similar to an effective psychosocial stress task (Dickerson & Kemeny, 2004). Thus, simply being prepared to participate in an fMRI study may distress volunteers and elevate cortisol levels prior to scanning (Mason, 1968; McGlynn et al., 2007; Thorpe et al., 2008).

Many of the aforementioned feelings that participants experience prior to fMRI (e.g., uncontrollability, social evaluative threat, and fear of harm by the machine) are characteristic of physical and psychosocial threats. Previous research has demonstrated that exposure to physical or psychosocial threats activate the HPA axis, resulting in cortisol release (Chrousos & Gold, 1992; Dickerson & Kemeny, 2004; Gaab, Rohleder, Nater, & Ehlert, 2005; Kirschbaum et al., 1993; Rohleder, Beulen, Chen, Wolf, & Kirschbaum, 2007; Sapolsky, Romero, & Munck, 2000). Furthermore, anticipation of physical or psychosocial threats can also elevate cortisol (Chrousos & Gold, 1992; Gaab et al., 2005; Mason, 1968; Turan, 2015). Subsequently, the acute increase in circulating cortisol levels, following a stressor, transiently inhibits HPA axis activation and suppresses further secretion of cortisol (Keller-Wood, Shinsako, & Dallman, 1983; Sapolsky, Meaney, & McEwen, 1985; Sapolsky et al., 2000). Thus, if participants feel threatened by the preparation for an fMRI scan, the cortisol response to a subsequent stressor (e.g., a stress task) may be relatively weak, or even diminished, by cortisol's negative feedback loop.

The primary purpose of the present study was to determine whether anticipatory stress associated with MRI is greater than anticipatory stress in a traditional behavioral laboratory. Participants completed an experimental session in a traditional behavioral laboratory and in an MRI facility on two separate visits. Given the additional preparation, precautions, and environmental characteristics required for fMRI, we hypothesized that participants would experience greater anticipatory stress (indexed by cortisol) prior to testing in the fMRI environment than in a traditional behavioral laboratory.

Methods

Participants

Data from 57 right-handed volunteers (36 males, 21 females, mean age = 19.68, SEM = 0.15, age range = 17-22 years) recruited as part of a larger research project were included in this study. **All 57** participants **included in the analysis** completed the project in the afternoon (traditional behavioral laboratory: 3:25 PM; SD = ± 69 minutes and MRI environment: 2:48 PM; SD = ± 55 minutes) to reduce the effects of diurnal rhythms on cortisol measurements. **P**articipants provided written informed consent and all study procedures were approved by the University of Alabama at Birmingham Institutional Review Board.

Procedures

The study was completed on two non-sequential days. On the first day of testing, volunteers completed the Trier Social Stress Test (TSST) in a standard behavioral laboratory (TSST; Kirschbaum et al., 1993). The opportunity to volunteer for the subsequent MRI session that included the Montreal Imaging Stress Task (MIST) was not mentioned during recruitment or completion of the first assessment that included the TSST. Instead, volunteers were recruited independently for the MRI session, and returned at a later date to complete the MIST in an MRI setting (Dedovic et al., 2005). The average period of time between testing sessions was 6.4 months (i.e. mean = 190.89 days; SEM = 20.68 days; range = 25-937 days). The stress response was assessed by measuring cortisol and heart rate during both sessions. However, skin conductance response (SCR) was collected during the MIST only. SCR was collected during the MIST, in part, due to the nature of the larger neuroimaging project, which included another cognitive-emotional task that was completed after the MIST.

TSST

Upon arrival to the behavioral laboratory, participants were briefly introduced to the TSST during the informed consent process. Experimenters told participants they would complete a speech and math task which would be videotaped. In addition, experimenters explained heart rate and blood pressure would be measured during the task and multiple saliva samples would be collected to measure chemicals related to their body's reaction to stress. After acclimating to the lab environment and being interviewed for approximately 60 minutes, participants were asked to rest for five minutes (baseline) and then were introduced to the Trier Social Stress Test (Kirschbaum et al., 1993). The TSST consisted of a five-minute speech preparation period, a five-minute mock job interview, and a five-minute mental arithmetic task involving serial subtraction (Kirschbaum et al., 1993). During the mock job interview, participants were instructed to pretend that they were a job applicant delivering a speech in front of an evaluation panel in hopes of being hired. While giving the speech, participants sat approximately two meters away from a desk with two judges who wore white lab coats. The judges maintained neutral facial expressions and did not provide any positive verbal or nonverbal feedback. Participants were told the judges were trained to detect verbal and non-verbal stress signals and that their performance was also being video recorded. If participants ended their speech early, they were told to continue until the full five minutes had elapsed. Following the mock job interview, participants completed the

arithmetic (i.e., serial subtraction) portion of the test. Participants were instructed to subtract backwards from 996 in increments of 13 as quickly and accurately as possible. After every mistake, one of the judges instructed participants to stop and start again at 996.

MIST

Participants returned on a second day to complete the MIST during a neuroimaging session (Dedovic et al., 2005). As part of the informed consent process, participants were told the purpose of the MRI session was to learn more about emotion, learning, and memory. Experimenters explained the MRI session involved completing a neuroimaging scan that would measure the participant's brain activity during a math and rating task. In addition, participants were informed the tasks and MRI scan may be unpleasant and anxiety provoking. Participants were told saliva samples would also be collected and analyzed to determine the relationship between brain function and body chemistry. Investigators did not allude to any connection between the participant's prior completion of the TSST (behavioral laboratory) and the current study (MRI environment). Upon arrival to the MRI facility, participants filled out questionnaires and completed a task training session for approximately 60 minutes. After training, participants were inserted into the scanner and completed a modified version of the MIST, which has been detailed elsewhere (Goodman et al., 2016; Wheelock et al., 2016). Briefly, participants completed a mental arithmetic task that consisted of a Control condition followed by a Stress condition presented during two 8-minute fMRI scans. Each scan consisted of 54 math problems. Participants' responses to the math problems were used to provide corresponding real time visual feedback on task performance (e.g. 'Right', 'Wrong', or 'Time out').

Prior to the Control condition of the MIST, investigators gave positive and reassuring feedback in an attempt to lower participant stress levels. During the Control MIST, participants were given five seconds to answer each math problem and pre-recorded positive auditory feedback to reduce performance anxiety. Prior to the Stress MIST, the investigators attempted to elevate participant stress levels by setting high performance expectations. Participants were told that previous volunteers had performed well and if they did not answer more than 80% of questions correctly, their data would be unusable. Further, during the Stress MIST the participants were given pre-recorded negative auditory feedback about their performance, and failure on the math task was ensured by modulating the time in which the participant could respond in a stair-step manner such that participants answered approximately 50% of the problems correctly.

Determination of Salivary Cortisol

On each visit, whole saliva was collected by passive drool at baseline (i.e., just before the preparation period for TSST and before scanning for the MIST), and a second sample was collected 30 minutes after the onset of TSST and MIST (post-stress). Following collection, samples were frozen then shipped overnight on dry-ice to the Institute for Interdisciplinary Salivary Bioscience Research for assay. After thawing, samples were centrifuged at 3,000 rpm for 15 minutes to remove mucins. Samples were assayed for cortisol using commercially available competitive immunoassay without modification to the manufacturers recommended protocol (Salimetrics, State College, PA). The assay used 25 μl of saliva for

singlet determinations and had a range of sensitivity from 0.007 to 3 μg/dl. All samples were assayed in duplicate and the average of the duplicate assays of each sample was used in the statistical analysis. On average, intra- and inter-assay coefficients of variation were less than 10% and 15%. Four participants with cortisol values greater than 3 standard deviations from the mean were removed from the analysis to reduce the effect of extreme values.

Heart Rate

TSST—Heart rate during the TSST was measured with a Medwave Vasotrac monitor. A wrist cuff containing an internal sensor was placed on the wrist of the participants' non-dominant hand above the radial artery to measure radial pulse amplitude. Heart rate was estimated based on the number of radial pulses every 30 seconds. Baseline heart rate was computed as the average heart rate during the last 2 minutes of the 5-minute baseline period. Heart rate was averaged across the 10-minutes of speech and math tasks to obtain an overall measurement of reactivity to the TSST. Change scores were calculated by subtracting baseline heart rate from heart rate during the TSST.

MIST—Heart rate during the MIST was measured using an MR compatible photoplethysmograph placed on the index finger of the non-dominant hand. Heart rate was collected separately for Control and Stress MIST conditions and recorded at 50Hz using a Siemens Physiological Monitoring Unit. QRSTool was used to identify peaks in the pulse waveform (Allen, Chambers, & Towers, 2007). CMetX was used to calculate the average heart rate for Control and Stress MIST scans (Allen et al., 2007). Thirteen participants were excluded from the analysis because of excessive noise in heart rate data, eleven experienced equipment failure, and two participants had missing data.

Skin Conductance Response: MIST

SCR data were collected only during the MIST using an MRI compatible physiological monitoring system (Biopac Systems; Goleta, CA). SCR was sampled at 10 kHz with a pair of disposable radio-translucent electrodes (1 mm diameter, Biopac Systems; Goleta, CA) located on the thenar and hypothenar eminence of the non-dominant hand. Stimulus onsets were recorded along with SCR data using TTL pulses from Presentation software via the stimulus computer's parallel port. SCR data were low pass filtered at 1Hz and downsampled to 250 Hz using Acqknowledge 4.1.0 software. The downsampled SCR was exported to SCRalyze toolbox for further analysis (version b2.1.8) (Bach, Flandin, Friston, & Dolan, 2009). The data were then bandpass filtered with a first order Butterworth filter (highpass cutoff of 0.0159 Hz, lowpass filter of 1.0 Hz) and further downsampled to a 10 Hz sampling rate. The skin conductance time-series was then normalized (z-transformed and mean centered). Each stimulus event type (e.g. math problems, visual feedback, auditory feedback) was included as a regressor predicting SCR using the general linear model with an assumed SCR function without a time or dispersion derivative (Bach et al., 2009; Bach, Friston, & Dolan, 2013). Resultant beta coefficients for each event type were entered into a group level paired samples t-test to assess SCR to math presentation during Control and Stress MIST. Eight participants classified as non-responders and seven participants missing SCR data were excluded from the analysis.

Results

Primary Analysis

The primary aim of this study was to determine if participants experience greater anticipatory stress (indexed by cortisol) prior to testing in the MRI environment than a standard behavioral laboratory. To assess anticipatory stress to the MRI versus standard behavioral laboratory, a paired samples t-test compared baseline cortisol samples collected prior to each of the stress tasks (i.e. MIST; MRI and TSST; behavioral lab). Baseline cortisol was significantly greater in the MRI environment than the behavioral laboratory (Figure 1; t (56) = 2.872, $p < 0.01$, $\boldsymbol{d = 0.38}$). These findings suggest anticipatory stress is greater before testing in an MRI setting than in a standard behavioral laboratory environment.

Secondary Analyses

To assess the cortisol response to the stress task performed in a standard behavioral laboratory, post-TSST cortisol was compared to baseline cortisol using a paired samples t-test. Post-TSST cortisol was significantly greater than baseline cortisol (Figure 2; t (56) = 3.350, $p < 0.01$, $\boldsymbol{d = 0.44}$). Similarly, to assess the cortisol response to the stress task performed in the MRI environment post-MIST cortisol was compared to baseline cortisol using a paired samples t-test. Post-MIST cortisol was significantly lower than the baseline sample (Figure 2; t (56) = − 3.086, $p < 0.01$, $\boldsymbol{d = -0.41}$). To exclude the possibility of overall higher cortisol (baseline and post-stress) in the MRI environment, cortisol sampled after the stress task in the standard behavioral laboratory was compared to cortisol sampled after the stress task in the MRI environment. Post-stress cortisol was significantly lower in the MRI environment than the standard behavioral laboratory (Figure 2; t (56) = −3.060, $p < 0.01$, $\boldsymbol{d = -0.41}$).

To determine whether the anticipatory stress response prior to MRI was equivalent to the stress induced by a traditional stress task (i.e., the TSST), baseline cortisol sampled prior to the MRI session was compared to cortisol sampled after the TSST (i.e., in the behavioral laboratory) using a paired samples t-test. There was no significant difference between baseline cortisol sampled prior to the MRI session and cortisol sampled after the TSST in the standard behavioral laboratory (Figure 2; t (56) = 0.769, $p = 0.445$, $\boldsymbol{d = 0.10}$). Taken together, these findings suggest anticipatory stress to an MRI session is equivalent to the stress induced by exposure to a psychosocial stress task in a traditional behavioral laboratory.

Previous research suggests that prior exposure to the MRI environment reduces stress reactivity to MRI during subsequent imaging sessions (Tessner et al., 2006).Therefore, baseline cortisol of participants with at least one prior MRI (n = 12) was compared to participants with no history of MRI (n = 45) to determine if prior MRI exposure impacted anticipatory stress. There was no significant difference in baseline cortisol levels between participants with prior MRI exposure and those with no history of MRI (t (55) = 0.239; $p = 0.812$, $d = 0.03$). Other research has suggested that reactivity to an initial stress task predicts anticipatory stress responses (i.e., elevated baseline cortisol) to repetition of the stress task on later dates (Turan, 2015; Turan et al., 2015). Therefore, a correlation analysis comparing

reactivity to the TSST (post-TSST minus pre-TSST) and baseline cortisol in the MRI environment was calculated to assess the possibility that elevated baseline cortisol in the MRI environment was the result of anticipatory sensitization induced by previous exposure to the TSST. There was no significant correlation between TSST reactivity and baseline cortisol in the MRI environment ($r(56) = 0.011$, $p = 0.932$). Further, there was not a significant correlation between post-stress cortisol in the behavioral laboratory (i.e. following the TSST) and baseline cortisol in the MRI environment ($r(56) = 0.22$; $p = 0.096$). These results suggest that anticipatory sensitization was not a significant contributor to the baseline cortisol elevations observed in the MRI environment.

Heart Rate—A paired samples t-test was used to assess stress-related changes in heart rate during the TSST (i.e., Post-stress vs Pre-stress) and MIST (i.e., Stress vs Control conditions). Due to differences in heart rate data collection and analysis methods between the TSST and MIST (see methods), heart rate was not compared between the two tasks. A significant increase in heart rate was observed during the TSST in the standard behavioral laboratory (Figure 3A; $t(42) = 7.284$, $p < 0.01$, $d = 1.11$) as well as the MIST in the MRI setting (Figure 3B; $t(30) = 4.267$, $p < 0.01$, $d = 0.77$). These findings suggest that both TSST and MIST induce stress in participants.

Skin Conductance Response—SCR data were collected during the MIST in the MRI setting, but not in the behavioral laboratory, as an additional index of the emotional response to stress. A paired samples t-test demonstrated that SCR was greater during the Stress than Control condition of the MIST (Figure 3C; $t(41) = 5.279$, $p < 0.01$, $d = 0.81$). These findings demonstrate that a larger emotional response was evoked by the Stress condition compared to the Control condition of the MIST.

Discussion

Experimental psychosocial stress tasks consistently elicit a robust cortisol response in standard laboratory settings (Dickerson & Kemeny, 2004). However, stress tasks performed in the MRI environment have not always replicated these findings (Allendorfer et al., 2014; Chung et al., 2016; Hermans et al., 2011). One explanation for this disparity is that methodological characteristics of fMRI may distress participants, and elicit high levels of anticipatory stress as they are prepared for scanning, prior to their exposure to the experimental stress task. In fact, our results concur with prior research that suggests cortisol levels may actually be higher before entering the scanner than after psychosocial stress tasks performed in the scanner (Allendorfer et al., 2014; Chung et al., 2016; Hermans et al., 2011; Root et al., 2009). High levels of anticipatory stress prior to scanning may lead to an acute cortisol response, which may in turn suppress further release of cortisol through a negative feedback loop. Thus, the cortisol response to the experimental stress task itself, performed inside the MRI scanner, may be significantly diminished and lead to the often observed decrease in cortisol that has been shown in this study and reported in prior fMRI stress studies. However, to our knowledge, no prior research has directly compared differences in anticipatory stress associated with an fMRI setting versus a traditional behavioral laboratory. Therefore, the aim of the present study was to determine if anticipatory stress for tasks completed in the MRI environment elicited greater anticipatory cortisol than a traditional

behavioral laboratory. Our results suggest that participants experience greater anticipatory stress (indexed by cortisol) prior to testing in an MRI setting than a traditional behavioral laboratory. Furthermore, our results suggest the anticipation of fMRI may be as stressful as an experimental stress task performed in a traditional behavioral laboratory. This elevation of cortisol may disrupt the prototypical cortisol response elicited by experimental stress tasks and impact the results of stress tasks performed in the MRI scanner.

Prior research suggests that stress tasks performed in an MRI scanner elicit a moderate and much more heterogeneous cortisol response compared to a traditional behavioral laboratory (Dedovic, D'Aguiar, et al., 2009; Pruessner et al., 2008). Prior work has speculated that adapting a traditional psychosocial stress task for fMRI requires modifying the task in ways that inherently change and potentially weaken it (Dedovic, D'Aguiar, et al., 2009; Dedovic, Rexroth, et al., 2009). For instance, MRI physically separates participants from experimenters and requires participants to lie in the supine position, which may reduce social evaluative threat (Dedovic, Rexroth, et al., 2009; Pruessner et al., 2008). While these observations may be true, other methodological characteristics that precede exposure to an fMRI stress task may also elicit stress and impact the cortisol response (Mason, 1968; McGlynn et al., 2007; Muehlhan, Lueken, Wittchen, & Kirschbaum, 2011; Peters, Cleare, Papadopoulos, & Fu, 2011; Tessner et al., 2006; Thorpe et al., 2008; Ursin & Eriksen, 2004). For example, exposure to a novel environment, social evaluative threat, and loss of control may be experienced by fMRI study volunteers even before the stress test begins (McGlynn et al., 2007; Muehlhan et al., 2011; Peters et al., 2011; Thorpe et al., 2008; Ursin & Eriksen, 2004). Participants are also informed of the potential for physical harm, loud and startling noises, isolation, and confinement associated with fMRI prior to entering the scanner, which may also elicit stress (Burow et al., 2005; DeVries et al., 2003; Mason, 1968; Rudy et al., 1999; Sapolsky et al., 2000; Tessner et al., 2006). Thus, participants may perceive fMRI as a threatening experience, which may generate a stress response and lead to the elevated baseline cortisol levels.

While the findings of the present study suggest preparation for MRI is distressing, prior research suggests stress may continue into the scanning procedure and is greatest immediately after entering the scanner (Katz, Wilson, & Frazer, 1994; McIsaac, Thordarson, Shafran, Rachman, & Poole, 1998; Muehlhan et al., 2011; Tessner et al., 2006; Thorpe et al., 2008; Tornqvist, Mansson, Larsson, & Hallstrom, 2006). Approximately 65% of participants report some degree of anxiety while in the scanner, 35% experience moderate to severe anxiety, 13% experience a panic attack, and 4% terminate the scan prematurely (Katz et al., 1994; McIsaac et al., 1998; Thorpe et al., 2008; Tornqvist et al., 2006). Prior work suggests it takes approximately 20-40 minutes after exposure to an acute stressor for cortisol to peak (Dickerson & Kemeny, 2004; Kirschbaum et al., 1993; Sapolsky et al., 1985; Sapolsky et al., 2000). Following an acute elevation in cortisol, the cortisol negative feedback loop begins inhibiting the HPA axis and any future cortisol secretion. It takes another 20-40 minutes after peaking for cortisol levels to return to baseline (Dickerson & Kemeny, 2004; Keller-Wood et al., 1983; Kirschbaum et al., 1993; Sapolsky et al., 1985; Sapolsky et al., 2000). Thus, the response to a stress task performed during the first hour of scanning may be significantly blunted by the cortisol negative feedback loop. This inhibition of cortisol through negative feedback that results from an acute anticipatory stress response to MRI

may explain why fMRI-adapted stress tasks have not typically elicited a strong cortisol response in prior studies (Allendorfer et al., 2014; Chung et al., 2016; Dedovic, D'Aguiar, et al., 2009; Hermans et al., 2011; Root et al., 2009). Moreover, anticipatory stress elicited by scanning may have implications for other research using experimental tasks during or following fMRI. Prior work suggests elevated cortisol is associated with reduced declarative memory, increased pain perception, and altered emotional processing (Ellerbrock & May, 2015; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; Putman & Roelofs, 2011). In addition, elevated cortisol may impact neural activation patterns in multiple brain regions, particularly the amygdala, hippocampus, and prefrontal cortex (Joëls & Baram, 2009; Lovallo, Robinson, Glahn, & Fox, 2010; McEwen et al., 2015; Veer et al., 2012).

Cortisol release by the HPA axis is classified as a second wave response to stress (Joëls & Baram, 2009; Kirschbaum et al., 1993; Romero & Butler, 2007; Sapolsky et al., 2000). It can take many minutes to hours for cortisol to respond and fully recover (Dickerson & Kemeny, 2004; Joëls & Baram, 2009; Romero & Butler, 2007; Sapolsky et al., 2000). Thus, other physiological measures with greater temporal resolution than cortisol, such as heart rate and SCR, may be better suited for measuring the stress response in the scanner (Chrousos & Gold, 1992; Knight & Borden, 1979; Setz et al., 2010; Tessner et al., 2006). Elevations in heart rate and SCR are part of the first wave response to stress, which is primarily driven by fast-acting epinephrine and norepinephrine release from the sympathetic nervous system (Chrousos & Gold, 1992; Fisher, 1989; Joëls & Baram, 2009; Morilak et al., 2005; Sapolsky et al., 2000; Thoma, Kirschbaum, Wolf, & Rohleder, 2012). In contrast to the second wave, activation and recovery of heart rate and SCR occurs within seconds to a few minutes of stress exposure (Fisher, 1989; Kirschbaum et al., 1993; Popma et al., 2006; Sapolsky et al., 2000; Setz et al., 2010; Shalev, Orr, Peri, Schreiber, & Pitman, 1992). Although there was not a significant increase in cortisol following the MIST in the present study, there was a significant increase in heart rate and SCR. These findings suggest the MIST successfully induced psychosocial stress, albeit this was not reflected by cortisol. These findings are consistent with prior work demonstrating an elevation in heart rate and SCR following the MIST (Setz et al., 2010). Thus, heart rate and SCR may be viable alternatives or complementary methods for measuring the transient psychosocial stress response during fMRI.

The analyses described in the current report were not planned as part of the original, larger project from which the present data were obtained. Instead, they were added after the fact to address other research questions related to anticipatory stress in the MRI environment. Therefore, important limitations of the present study should be considered when interpreting the current findings. One limitation of the present study is that comparable measures of self-reported stress were not assessed prior to the stress tasks completed in the behavioral laboratory and MRI environment. Thus, although differences in baseline cortisol were observed, we cannot determine whether self-reported anticipatory stress shows a similar pattern. Another limitation of the present study is that the order of testing environments was not randomized due to the nature of the larger project from which these data were obtained. All participants completed the stress task in the traditional behavioral laboratory first and within the MRI environment second. Thus, we cannot definitively rule out the possibility that the difference in baseline cortisol levels (i.e. cortisol prior to the stress task in the

traditional behavioral laboratory vs MRI environment) may be due to anticipation of repeating a stress task (i.e. anticipatory sensitization) instead of anticipation of the MRI procedure. However, the cortisol elevation prior to the MRI stress task is inconsistent with prior findings of anticipatory sensitization (Boyle et al., 2016; Kirschbaum et al., 1995; Turan, 2015; Turan et al., 2015). First, prior work has demonstrated that anticipation of a repeated stress task (i.e. anticipatory sensitization) elicits a cortisol response that is smaller than the response to both the initial and repeated stress task itself (Boyle et al., 2016; Kirschbaum et al., 1995; Turan, 2015; Turan et al., 2015). In contrast, we observed a baseline elevation in cortisol prior to the stress task in the MRI environment that was equivalent to the stress response within the behavioral lab and that was larger than post-stress cortisol within the MRI environment (Figure 2). This pattern is inconsistent with prior studies that observed anticipatory sensitization (Boyle et al., 2016; Kirschbaum et al., 1995; Turan, 2015; Turan et al., 2015). Second, prior research suggests participants who produce a large cortisol response to an initial psychosocial stress task (i.e., high-responders) show greater anticipatory sensitization to future stress tasks (Turan, 2015; Turan et al., 2015). However, similar findings were not observed in the present study. Specifically, there was no relationship between cortisol reactivity to the initial stress task (i.e. in the behavioral lab) and baseline cortisol in the MRI environment. Third, prior investigations of anticipatory sensitization intentionally manipulated the procedure to elicit anticipatory stress (Turan, 2015; Turan et al., 2015). For instance, the fact that the stress task would be repeated was emphasized and participants were reminded of the procedural details of the task immediately prior to the repeated stress task to enhance anticipatory sensitization (Turan, 2015; Turan et al., 2015). However, participants in the present study were not exposed to either of the experimental manipulations used in prior anticipatory sensitization studies. Therefore, the methods used in the present study do not appear to include the critical requisite information used in prior research to elicit anticipatory sensitization of the cortisol response. Fourth, the elevated baseline cortisol observed in the present study is similar to findings in prior fMRI studies in which participants had not been exposed to a prior stress task (Allendorfer et al., 2014; Chung et al., 2016; Hermans et al., 2011; Root et al., 2009). Taken together, these studies suggest baseline cortisol is elevated in the MRI environment. In summary, the 1) exaggerated anticipatory response, 2) absence of a significant correlation between initial reactivity and anticipatory sensitization, 3) exclusion of important components of anticipatory sensitization methods, and 4) similarity of findings to other fMRI studies that did not include a prior stress task suggest the observed elevation in baseline cortisol in the MRI environment is due to anticipation of the MRI procedure and not a sensitization effect due to the repetition of a psychosocial stress task. Nonetheless, future research should counter-balance the order of testing environments to eliminate the possibility of order effects.

Conclusion

The present findings suggest research participants experience greater anticipatory stress (indexed by cortisol) prior to testing in an MRI setting than in a traditional behavioral laboratory. This finding is consistent with the view that fMRI may be perceived as a threatening procedure. Therefore, anticipation of fMRI may elicit an anticipatory cortisol response commensurate with other known stressors. Given the response and recovery time

of cortisol, anticipatory stress may disrupt the cortisol response to stress tasks performed during fMRI. Thus, elevated anticipatory stress prior to fMRI may explain why fMRI-adapted stress tasks have not consistently elicited a strong cortisol response in prior studies. Due to the impact of elevated cortisol on cognition and neural activity, anticipatory stress elicited by scanning may have broader implications for research in which experimental tasks occur during or following fMRI. Finally, the present findings suggest that additional physiological measures (e.g., heart rate and SCR) with a shorter time-course may be better suited to assess the psychosocial stress response during fMRI.

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Highlights

- Psychosocial stress studies during fMRI elicit a relatively small cortisol response

- Anticipatory stress prior to fMRI may disrupt the cortisol response during fMRI

- Anticipatory stress prior to fMRI vs traditional behavioral lab was compared

- Cortisol was greater prior to research using fMRI compared to a behavioral lab

- Anticipatory stress appears to increase cortisol prior to fMRI scanning
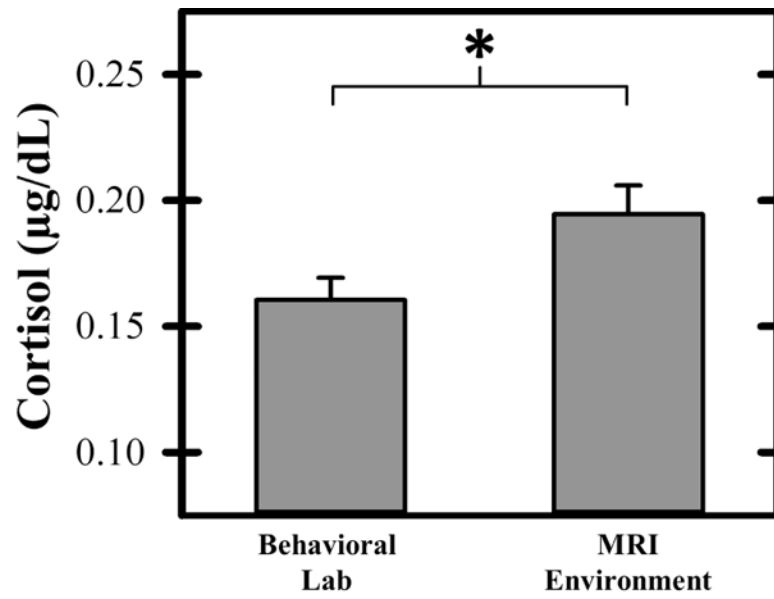
Figure 1.
Baseline cortisol samples. Baseline cortisol, used as an index of anticipatory stress, was significantly greater in the MRI environment than in the traditional behavioral laboratory. Error bars indicate standard error and asterisk denotes a significant difference.
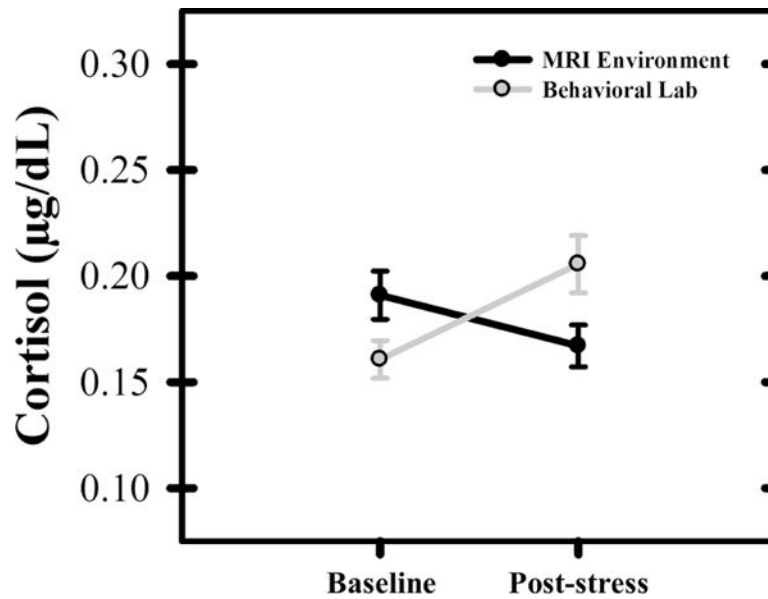
Figure 2.
Baseline and cortisol response levels in the traditional behavioral laboratory and MRI environment. Post-TSST cortisol was significantly greater than baseline in the traditional behavioral laboratory. Post-MIST cortisol was significantly lower than baseline in the MRI environment. Post-TSST cortisol was significantly greater than Post-MIST cortisol. Baseline cortisol in the MRI environment was not significantly different from Post-TSST cortisol in the traditional behavioral laboratory. These results suggest stress elicited in anticipation of fMRI is equivalent to the stress induced by traditional lab-based stress tasks. Error bars indicate standard error.
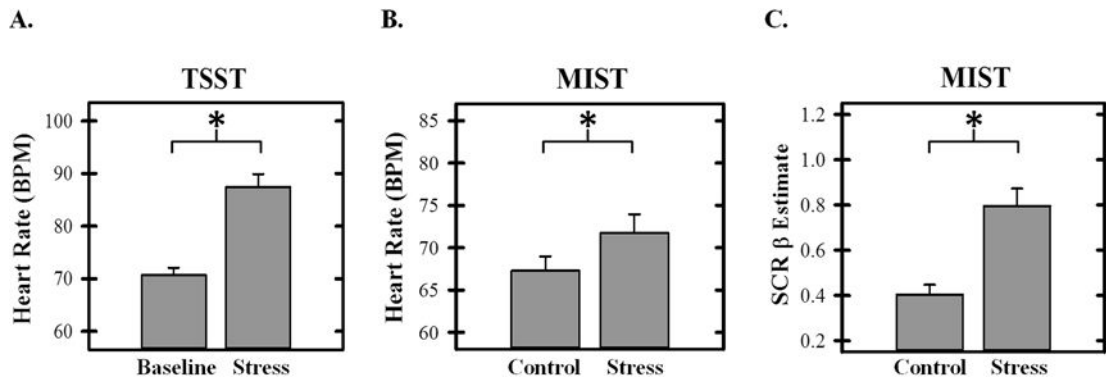
Figure 3.
Heart Rate and Skin Conductance Response (SCR). (A) Heart rate was greater during the Stress than Baseline condition of the Trier Social Stress Test (TSST). (B) Heart rate was also greater during the Stress than Control condition of the Montreal Imaging Stress Task (MIST). (C) SCR was significantly greater during the Stress than Control condition of the MIST. Error bars indicate standard error and asterisks denote a significant difference.