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SHORT COMMUNICATION

Hormonal reactivity to MRI scanning in adolescents

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Summary Magnetic resonance imaging (MRI) is a procedure that is now widely used to study emotional and cognitive processes in children and adolescents. However, the context within which brain imaging data are collected is a social context that may induce anxiety and stress. Several hormones have been shown to be responsive to environmental stressors. These stress responses may impact ability to successfully complete the procedure or collect imaging data. To investigate these issues, we measured salivary cortisol, dehydroepiandrosterone (DHEA), and testosterone in 160 adolescents during both a simulation (practice) and actual MRI. Hormones were all responsive to the MRI scan, indicating that an MRI scan itself can induce a stress response, with some hormones predicting the likelihood that an adolescent could successfully complete the scan with adequate data. The simulation scan did not hinder hormonal responses to the actual MRI. These data suggest that researchers should consider the effects of heightened hormonal reactivity to the scanning environment; adolescent's reactions to brain imaging may contribute to image data loss and may potentially influence outcome measures.

1. Hormonal reactivity to MRI scanning in adolescents

Functional and structural magnetic resonance imaging (MRI) studies of children and adolescents are becoming increasingly prominent. Brain imaging is a noninvasive procedure, yet the context within which such research occurs may be stressful. During this procedure, youth are alone in the confined space of the magnet, during which time they need to inhibit movement, are exposed to unfamiliar sounds, and are likely to be self-consciousness about their general performance. These effects may be more pronounced in children and adolescents because abilities to regulate emotion and stress are still undergoing development (Nelson et al., 2005). Emotional responses to the brain imaging environment may reduce the likelihood of obtaining valid and useable data. A previous study reported that an MRI produces an elevation in cortisol in adults (Tessner et al., 2006); no studies to date have explored this issue with youth or focused more broadly on the stress response by including other stress-related hormones. Therefore, the primary aim of this study was to examine adolescents' stress responses to an MRI environment.

To evaluate adolescents' reactions to brain imaging, we examined activation of the hypothalamic—pituitary—adrenal (HPA) axis. The HPA axis responds to uncontrollable environmental stress by releasing multiple hormones such as cortisol (Dickerson and Kemeny, 2004) and dehydroepiandrosterone

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(DHEA) from the adrenal gland (Shirtcliff et al., 2007). Additionally, the hypothalamic–pituitary–gonadal (HPG) axis interacts extensively with the HPA axis (Viau, 2002) and its end-products, such as testosterone, are also stress-responsive (Booth et al., 1989). These physiological responses are particularly relevant to functional imaging studies because stress-reactive hormones are associated with a wide variety of neural functions that are reflected in brain activity (Rubinow and Schmidt, 1996; Wolf and Kirschbaum, 1999). For example, cortisol has been shown to correlate with both deactivation in the hippocampus (Pruessner et al., 2008) and activation in the amygdala (van Stegeren et al., 2007). Activation of a stress response during imaging may also present a practical challenge in that children who are especially anxious may be unlikely to provide usable neuroimaging data. Motion artifacts are often increased in patients who are worried about the procedure (Dantendorfer et al., 1997). Therefore, we examined the relationship between stress responses to the MRI and the likelihood of unsuccessful scan outcomes due to aborted sessions or poor image quality.

Neuroimaging studies with younger participants often include a simulation (or practice) scan. This approach is based upon the intuitive idea that increased familiarity with the scanning equipment and procedures will attenuate adverse reactions (Rosenberg et al., 1997; Grey et al., 2000). Previous work found that healthy male children show no cortisol elevations during simulation scans (Corbett et al., 2006). But it is not known whether children's stress responses to a simulation scan predicts stress reactivity during an MRI. Therefore, we sought to address three questions: (1) Are stress responsive hormonal systems activated by exposure to neuroimaging procedures?; (2) If so, do stress responses to the simulation scan predict whether young participants can complete a subsequent scan successfully?; (3) Does hormonal responsivity to the simulation scan predict responsivity to the MRI scan? With regard to the third question, a positive correlation suggests that the simulation scan indeed mimicked the context of an actual scan, while a negative correlation would be consistent with the view that the simulation scan helped habituate children's stress responses.

2. Method

2.1. Participants and procedures

One hundred sixty adolescents (82 boys, 78 girls; mean age = 11 years, 2 months; range 9–14 years) were recruited from the community using flyers. Exclusion criteria included allergy or asthma medication use or failure to meet basic MRI compatibility. Study procedures were approved by the Institutional Review Board at University of Wisconsin-Madison. All participants and their parents provided informed assent and consent, respectively. This study included one laboratory visit. Additionally, participants gathered data across four days while in a home/school setting for basal hormone levels.

All laboratory visits began at the same time of day (mean = 0928 h, SD = 14 min). One hour after arrival, participants underwent a 30-min simulation scan. The simulation scanner was exact in size and structure to the MRI scanner. To orient each child with the physical and auditory features of the scanner, sound clips were played while participants practiced lying still in the scanner. Approximately 10 min later, participants completed an MRI (3.0 Tesla GE SIGNA) for approximately 1 h during which time they watched an age-appropriate movie of their choice. Participants provided saliva samples for hormone assay: (1) 1 h after laboratory arrival (mean = 1021 h, SD = 24 min), immediately before the simulation scan; (2) immediately following the simulation scan (mean = 1106 h, SD = 35 min); (3) immediately following the MRI (mean = 1218 h, SD = 38 min). Participants completed emotional state measures at each saliva collection. On basal days, participants collected their own saliva in the same method as at the laboratory using instructions for freezing, storing and mailing the samples provided at the laboratory.

2.2. Measures

2.2.1. Determination of successful vs. unsuccessful scans

Of eligible participants, a total of 18% were grouped as "unsuccessful" scans. Ten percent were unable to complete the MRI due to anxiety (5 boys, 11 girls, mean age 10.7). Eight percent completed the scan but generated unusable data for imaging analysis because of excessive head movement (7 boys, 6 girls, mean age = 10.5). Examples are shown in Fig. 1.

2.2.2. Saliva sampling

During the lab visit, three saliva samples were obtained by passive drool into 2 ml vials without stimulants. Participants had not eaten for at least an hour at the time of the first sample and were not allowed to eat or drink (except water) during the rest of the lab visit. Timing of saliva samples did not differ between participants with successful or unsuccessful MRI scans, $ps > .10$. Saliva flow rates for each time point were similar, $F(2, 151) = .06$, $p = .95$ and did not differ by MRI success, $F(1, 152) = .02$, $p = .88$. Basal days included 2 non-school days and 2 school-days. Participants were given storage containers with a time recording device in the cap (Aardex, Zug) to accurately record time of saliva collection. Average time of collection across basal days (mean = 1106 h; SD = 35 min) was slightly earlier than the laboratory collection (i.e., pre-MRI) (mean = 1123 h; SD = 15 min), $t(1, 107) = 4.99$, $p < .001$. For the basal days, timing of samples, $p = .06$, average flow rates, $p = .35$, and average time since awakening, $p = .13$, were all not significantly different between participants with successful vs. unsuccessful scans. A subset of participants did not return vials for the home days ($N = 49$) and therefore basal data was not available for these participants. This subset was no more likely to have unsuccessful scans $\chi^2(1, N = 161) = 0.94$, $p = .33$, and the general hormonal patterns of these participants during the lab day were similar to those who returned vials $ps > .14$.

2.2.3. Hormone assays

All saliva samples were stored in a −80 °C laboratory freezer. Salivary hormone assays were conducted by Madison Biodiagnostics with enzymeimmunoassays (Salimetrics, State College, PA). Sensitivity for salivary cortisol, DHEA and testosterone is .003 μg/dl, 5 pg/ml, and 1 pg/ml, respectively. The serum–saliva correlation is >.86 for the three hormones. All samples were assayed in duplicate; duplicates that varied by more than 10% were re-assayed. Samples from a particular participant were run on the same kit. Hormone values were log transformed.

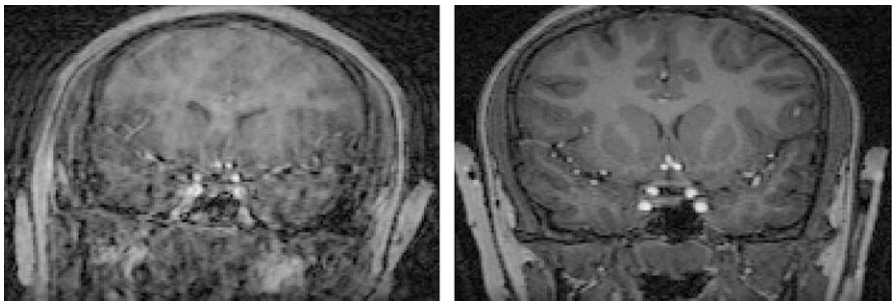

Figure 1 Movements of a few millimeters create motion artifact that distorts MRI images and confounds structural MRI analyses. Eight percent of participants were classified as ''unsuccessful'' when motion artifact during the scan prohibited reliable processing and analysis by automatic or manual processing pipelines in Statistical Parametric Mapping, FMRIB Software Library, or BRAINS2. Raw T1-scans and skull-stripped volumes were carefully examined by two researchers with extensive background in structural MRI analysis who were blind to demographic and hormonal information about participants. Inter-rater reliability between the two raters on 139 scans was strong, $\kappa = .89$. The left image shows an MRI image with excessive movement artifact rendering the image ''unsuccessful''. The right image shows a ''successful'' MRI scan.

2.2.4. Data analyses

Repeated measures ANOVAs and follow-up *t*-tests were used to test hormonal reactivities. The equal variance assumption was met for all three hormones therefore equal variance assumed *p* values were reported. Cohen's *d* was calculated for effect size. Pearson's *r* correlations were computed to test relationships between hormones.

3. Results

Our primary aim was to examine adolescents' hormonal responses to an MRI environment. All of the hormones tested rose in response to the MRI: cortisol, $F(1, 152) = 7.64$, $p < .01$, $d = .35$ DHEA, $F(1, 151) = 14.57$, $p < .001$, $d = .20$ testosterone, $F(1, 146) = 21.03$, $p < .001$, $d = .15$. There were no gender difference in reactivity for any hormone, $ps > .46$. We next tested whether stress responses during the MRI predicted aborted sessions or poor image quality. Participants with a heightened DHEA response to the MRI were more likely to have a successful scan than participants whose DHEA levels dropped during the MRI, $t(150) = 2.18$, $p = .03$. Neither cortisol, $t(151) = 1.18$, $p = .24$, nor testosterone, $t(145) = .37$, $p = .72$, differentiated participants with successful or unsuccessful scans.

We next examined whether responses to the simulation scan predicted later scan success. During the simulation scan, cortisol levels generally declined, $t(152) = 4.03$, $p < .001$, while DHEA, $t(154) = -1.02$, $p = .31$, and testosterone, $t(149) = -.23$, $p = .82$, were stable. To test whether the decline in cortisol was due to the diurnal rhythm, we compared basal hormones (at the same time of day as the post-simulation scan) to hormone levels seen in response to the simulation scan. After the simulation scan, cortisol was significantly lower than time-matched basal levels, $t(106) = -2.41$, $p < .02$, suggesting the attenuation during the simulation scan was greater than the rhythm. Further, adolescents with successful scans had the largest declines in cortisol during the simulation scan when compared with adolescents who later had unsuccessful scans, $t(151) = -2.24$, $p = .03$ (please see Fig. 2). DHEA and testosterone levels during the simulation scan were not different from basal levels, $ps > .07$. Further, neither DHEA nor testosterone changes during the simulation scan differed across adolescents with successful vs. unsuccessful scans, $ps > .09$. There was also no difference between successful and unsuccessful groups in magnitude of change between basal hormone and time-matched MRI samples, $ps > .58$. In sum, cortisol decline during the simulation scan predicted success during the actual MRI and this change in cortisol appears to be related to the experimental procedures rather than reflecting a diurnal rhythm. Hormonal responses to the simulation scan negatively correlated with hormonal responses to the MRI scan for cortisol, $r(150) = -.16$, $p < .05$, DHEA, $r(152) = -.35$, $p < .001$, and testosterone, $r(146) = -.21$, $p = .01$. Declines in each hormone during the simulation scan predicted heightened hormonal responses to the MRI.

4. Discussion

We found significant reactivity in all three hormones in response to the MRI. These data suggest that the MR imaging environment is a social environment for children and adolescents that elicits physiological responses that likely influence children's affective and cognitive functioning. Practically, hormonal responses also impacted success rates for MRI data collection. Participants with successful MRI scans had greater DHEA reactivity to the MRI compared to those with unsuccessful scans. This finding is consistent with our earlier work illustrating that DHEA is a stress responsive hormone, but differs in that DHEA responsivity to the MRI context specifically may be advantageous (Shirtcliff et al., 2007). Potentially, participants with successful scans were better able to cope with the stress of the MRI and achieve successful scans due to the anxiolytic properties of this particular hormone (Wolf and Kirschbaum, 1999).

Many researchers use simulation scanning to acclimate participants to the MRI environment, yet our results show that hormone responses to the simulation did not mirror the MRI. Simulation scanning may not adequately prepare participants for the stressful environment of an actual MRI. For all three hormones, steeper decline during the simulation scan was associated with steeper rise in hormone levels during the MRI. Consequently, researchers should not expect hormonal responses to a simulation scan to be an accurate indicator of the direction of reactivity to the MRI.

Importantly, adolescents with attenuated declines in cortisol during the simulation scan were less likely to successfully

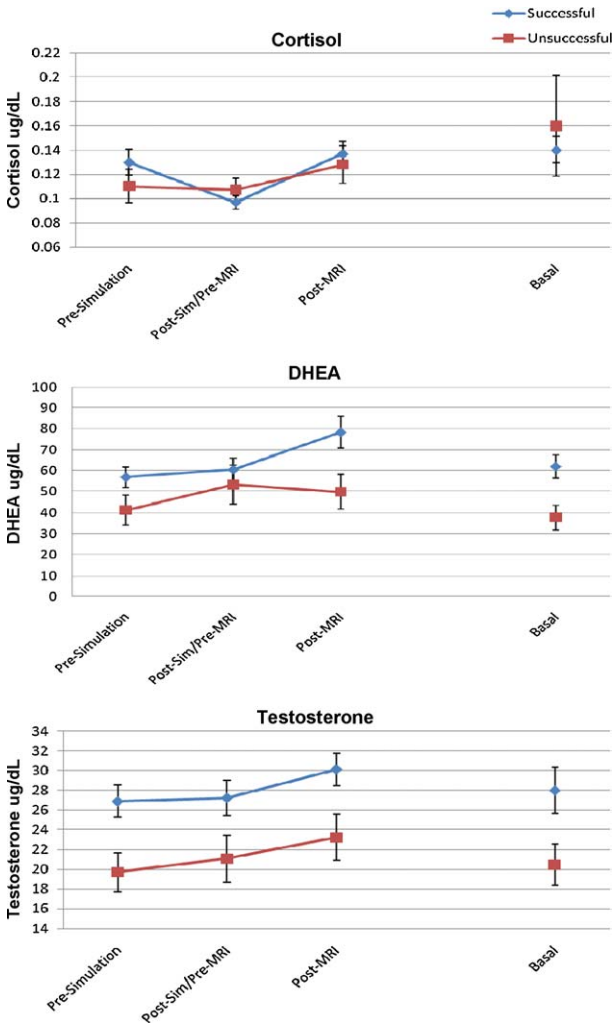

Figure 2 Trajectories of each hormone over the lab visit and basal levels from the average home/school day saliva sample. Basal samples were taken at approximately the same time of day as the post-simulation/pre-MRI sample on the lab day.

complete the MRI. Because cortisol was lower during the simulation scan than basal levels on non-scan days, it is unlikely that the cortisol decline during the simulation scan was simply due to the diurnal rhythm. This indicates that the cortisol responses to the laboratory event of a simulation scan provided the most predictive information about performance in the later laboratory event of the MRI. Given that attenuated cortisol declines can signify HPA dysfunction (Gunnar and Vazquez, 2001; Miller et al., 2007), these participants may be less able to maintain normal physiologic functioning during less severe stressors (e.g., the simulation scan) and to appropriately respond to real stressors (e.g., the actual MRI).

In interpreting these data, we note that the timing of our salivary sample collections may overlap with the start of the recovery phase during the MRI. Also, the basal samples were slightly later in the day than the post-simulation scan sample. However, the direction of our effect on cortisol levels after the simulation scan is in the opposite direction as the diurnal rhythm would predict, suggesting timing of samples does not explain the attenuation effect. Finally, basal samples were taken in a variety of environmental contexts and a subset of participants failed to return basal saliva collections, reducing our sample size for those analyses. Additionally, future research might include a group of subjects that receives no simulation scan to better understand this phenomenon.

In sum, this study suggests that changes in adolescent hormonal function may result from the salient characteristics of the MRI environment in the absence of any social or cognitive experimental manipulations. Finding that multiple hormones are responsive to the MRI indicates global hormonal activation and underscores the potential implications of a heightened physiological state on outcomes measures and brain activation patterns. Furthermore, obtaining usable imaging data from adolescent participants may be dependent on hormonal reactivities to the MRI context. Simulation scanning does not appear to eradicate these responses, but may be a useful tool for predicting a subject's later performance in an actual MRI. Researchers should consider the scanning environment as a social milieu that may influence multiple stress-related hormones.

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Conflict of interest

None declared.

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