Subgenual Prefrontal Cortex Activity Predicts Individual Differences in Hypothalamic-Pituitary-Adrenal Activity Across Different Contexts

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Background: Hypothalamic-pituitary-adrenal (HPA) system activation is adaptive in response to stress, and HPA dysregulation occurs in stress-related psychopathology. It is important to understand the mechanisms that modulate HPA output, yet few studies have addressed the neural circuitry associated with HPA regulation in primates and humans. Using high-resolution F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) in rhesus monkeys, we assessed the relation between individual differences in brain activity and HPA function across multiple contexts that varied in stressfulness.

Methods: Using a logical AND conjunctions analysis, we assessed cortisol and brain metabolic activity with FDG-PET in 35 adolescent rhesus monkeys exposed to two threat and two home-cage conditions. To test the robustness of our findings, we used similar methods in an archival data set. In this data set, brain metabolic activity and cortisol were assessed in 17 adolescent male rhesus monkeys that were exposed to three stress-related contexts.

Results: Results from the two studies revealed that subgenual prefrontal cortex (PFC) metabolism (Brodmann's area 25/24) consistently predicted individual differences in plasma cortisol concentrations regardless of the context in which brain activity and cortisol were assessed.

Conclusions: These findings suggest that activation in subgenual PFC may be related to HPA output across a variety of contexts (including familiar settings and novel or threatening situations). Individuals prone to elevated subgenual PFC activity across multiple contexts may be individuals who consistently show heightened cortisol and may be at risk for stress-related HPA dysregulation.

Key Words: Cortisol, HPA, monkey, PET, stress, subgenual PFC

Cortisol, a glucocorticoid released from the adrenal cortex, is critical for survival, reflects activation of the hypothalamic-pituitary-adrenal (HPA) system and represents a primary mechanism through which emotions influence chronic disease. Persistently increased cortisol occurs in some individuals with depression (1,2) as well as in youth at risk for developing stress-related psychopathology (3). Moreover, in various chronic illnesses, increased cortisol is associated with poorer medical outcomes (4,5). Although rodent studies have examined brain mechanisms involved in HPA regulation, little is known about neural circuitry related to individual differences in primate and human cortisol concentrations.

Evidence from rodent studies points to medial prefrontal cortex (mPFC) as being important in HPA regulation and regulation of autonomic, behavioral, and emotional responses associated with stress (6–8). Of particular relevance to these functions are efferents that project from ventral PFC to subcortical and brain stem structures (9–11). Data from rodent studies indicate that dorsomedial PFC regions (prelimbic cortex) are involved in HPA inhibition, whereas ventral regions (infralimbic cortex) are involved in HPA activation (12,13). Subgenual PFC (Brodmann's area [BA] 25/24) is the primate and human cortical region most analogous to the rat infralimbic cortex (7).

Subgenual PFC is of particular interest in conceptualizing the relation between HPA overactivity and stress-related psychopathology, because this region has been the site of both structural and functional alterations in some depressed patients, as well as a successful target for treatment of severe depression (14–17). In a study in treatment-resistant depressives, deep brain stimulation decreased subgenual PFC hypermetabolism resulting in a marked reduction in depressive symptoms (18). The subgenual PFC's role as part of an "integrated pathway" for regulation of HPA is hypothesized to account partially for involvement of this region in depression (15–17,19).

To study brain circuitry associated with individual differences in HPA regulation in primates, we used data from a study aimed at establishing the relation between anxious temperament and regional brain metabolic activity (20,21). The availability of cortisol data allowed us to examine the relation between cortisol and metabolic activity in monkeys exposed to different contexts. Rhesus monkeys are an ideal species to provide insights into human HPA regulation because they share similarities with humans in HPA function, brain structure (e.g., prefrontal cortical development), and behavior (10,22). Rhesus monkeys are among the best species to investigate brain mechanisms underlying emotion regulation and psychopathology because multiple scans can be repeatedly obtained in the same individual during exposure to ethologically relevant settings (23).

Plasma cortisol and metabolic brain activity were assessed repeatedly in the same monkeys in response to four situations varying in their degree of stressfulness. Two of the conditions (separation from cagemate and introduction of a human intruder) elicit different threat-related adaptive responses, whereas the other two conditions involved assessment in the monkeys' home cages (24). Logical AND conjunction analysis (see Nichols *et al.* 2005 [25]) was used to find clusters of regional metabolic activity that correlated with cortisol concentrations across all four conditions. This logical AND conjunction analysis identifies regions where metabolism and cortisol are significantly corre-

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lated during separation from cagemate and introduction of a human intruder and home-cage alone and home-cage with cagemate; thus, excluding regions that do not show significant correlations across all conditions. To confirm these results, we used the same analytic strategy in a different data set of previously studied animals in which F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) and cortisol were collected. On the basis of rodent data suggesting that mPFC acts as a relay for limbic-cortical pathways and integrates various aspects of stress responses, we hypothesized that individual differences in mPFC activity, specifically, the subgenual PFC, would predict individual differences in cortisol concentrations across conditions.

Methods and Materials

Experiment 1

Animals and Procedures. Subjects included 35 adolescent rhesus monkeys (*Macaca mulatta*; mean [M] age ± standard deviation; 2.61 [.56]; range: 1.83–3.96; male: 12, M weight: 4.06 [.77] kg; $n = 36$, one animal excluded for refusing to leave its cage). Animals were pair-housed at the Wisconsin National Primate Center and Harlow Primate Laboratory and maintained on 12-hour light–dark cycle (lights on 6 AM). All experimental procedures were approved by the University of Wisconsin Institutional Animal Care and Use Committee (IACUC).

Animals were exposed to four conditions before FDG-PET scanning, with each condition occurring at least 1 week apart. Because the bulk of FDG uptake occurs within 30 minutes after injection (see Rilling *et al.* 2001 [26]), we designed conditions lasting 30 minutes. In the home cagemate (H-CM) condition, animals remained in their home cage with their partner for 30 minutes. In the home alone (H-ALN) condition, animals remained alone in their home cage for 30 minutes. In the no eye contact condition (NEC), animals were placed in a test cage while a human entered the room for 10 minutes, presented his profile, and avoided eye contact with the monkey while standing 2.5 miles away. The human left the test room for 5 minutes, reentered for 5 minutes, and left again for 5 minutes, then reentered for 5 minutes. This procedure was used to avoid habituation. In the alone condition (ALN), animals were placed in a foreign cage and left alone for 30 minutes. Exposure to each condition was counterbalanced: eight animals received H-ALN first, nine animals received H-CM, nine received ALN, and nine received NEC first. For each animal, all conditions were run at approximately the same time of day (minimum difference in scanning times within an individual: 4 minutes; maximum difference in scanning times: 2 hours 48 minutes). Portions of this data set have been previously described (20,21).

Cortisol. Blood was sampled by femoral venipuncture at the end of each condition, before the FDG-PET scan. Samples were obtained between 8:45 AM and 4:15 PM.

Basal cortisol was evaluated twice at intervals of at least 1 week. Baseline samples were collected in the morning between 8:00 AM and 9:30 AM.

Plasma was immediately extracted from blood by centrifugation at 4°C and frozen at −70°C until assayed. Cortisol was measured in plasma using enzyme immunoassay (Diagnostic Systems Laboratories, Webster, Texas) with intraassay variability of 6.1% and interassay variability of 6.3%. The detection limit was .125 ng. For analysis, time of day was regressed on cortisol values to remove variance associated with time of day.

Magnetic Resonance Imaging Acquisition. Structural magnetic resonance images (MRI) were used to aid in structural normalization of PET data. See Additional Methods in Supplement 1 for more information.

PET Data Acquisition and Pre-Processing. Immediately before each 30-minute condition, animals were injected with <10 mCi of FDG through a 19-gauge intravenous catheter in the saphenous vein. After the 30-minute session, blood was drawn for cortisol samples, and then monkeys were anesthetized with 15 mg/kg ketamine followed by approximately 1.5% isoflurane gas. The animal's head was positioned in a stereotaxic apparatus to maintain head positions across conditions in a P4 microPET scanner (Concorde Microsystems, Knoxville, Tennessee). PET resolution was 2-mm full width at half maximum (FWHM; volumetric resolution of approximately 2 mm^3). To facilitate across-subject comparisons, PET images were transformed into a standard space as defined by Paxinos, Huang, and Toga, 2000 (27–29).

We corrected for potential differences in PET scan intensity by applying a global scale factor to each scan. This ensured each PET image volume had the same mean-intensity value. Using standard methods, global scale factors were determined by adjusting the mean-intensity based on a whole brain region of interest (30). To compute true regional cerebral metabolic rate of glucose ($rCMR_{glu}$) values, quantitative arterial blood radioactivity measurements are required; however, obtaining these measures would have interfered with the naturalistic (awake) paradigm. Instead, we performed intensity normalization to obtain a proxy for $rCMR_{glu}$ to facilitate intersubject comparisons.

PET images were smoothed using a 4 mm FWHM Gaussian kernel to accommodate small differences in locations of functional regions across subjects (e.g., due to differences in gyral features) and increase signal-to-noise ratio (31).

Gray-matter probability (GMP) maps were created for each subject and used as a regressor in tests of FDG uptake to control for anatomical differences (32,33). See Supplement 1 for additional information.

Logical AND Conjunction Analysis. Correlations between cortisol and metabolism were performed within each condition using "fmristat" (34,35). Correlations were performed controlling for age, time of day, and anatomic differences by using the GMP map as a voxelwise covariate in our functional analyses as described in Oakes *et al.* 2007 (32).

To identify brain regions consistently correlated with cortisol levels across contexts, we performed a logical AND conjunction analysis using a minimum statistic (25). This analysis identified brain regions in which metabolism was significantly correlated with cortisol levels in each condition ($p < .05$, two-tailed uncorrected). We combined the statistical parametric maps from each condition and obtained a map revealing regions where metabolism and cortisol were significantly correlated during the NEC condition and the ALN condition and the H-ALN condition and the H-CM condition. Thus, clusters represent brain regions where metabolism and cortisol are correlated across all four conditions.

Follow-up analyses were performed by extracting mean values for each cluster of interest within each condition. Metabolic activity in the threat conditions was calculated by averaging the mean value within each region of interest for ALN and NEC conditions. Metabolic activity in the home conditions was calculated by averaging the mean glucose metabolism value within each region of interest for H-ALN and H-CM. Difference scores were created for each subject by subtracting the mean metabo-

lism value for home conditions from the mean metabolism value for threat conditions for each cluster of interest.

Experiment 2

Animals and Procedures. Data include 17 adolescent male rhesus monkeys (M age: 2.99 [.48]; range: 2.18–3.57; M weight: 4.78 [.88] kg; $n = 22$, five animals excluded from analysis due to problems with alignment in the scanner and missing cortisol data). Housing procedures were identical to those presented in Experiment 1. Experimental procedures were approved by the University of Wisconsin IACUC.

Animals were exposed to three 30-minute conditions: ALN, NEC, and stare (ST). In the ST condition, animals were placed in a test cage while an experimenter entered the room and looked directly at the animal in 10-minute increments from 2.5 miles away with a 5-minute break in which the human left the testing room. Breaks were designed to minimize habituation, thus extending the heightened sensitively to the intruder over the 30-minute FDG uptake. The NEC and ALN conditions were identical to conditions from Experiment 1. Six animals received ALN first, seven animals received ST first, and four animals received NEC first. Each condition was not performed more than once per week. Data from Experiment 2 have been described in Fox *et al.* (2005) (36) and Kalin *et al.* 2005 (23).

Cortisol. Collection, storage, and processing were identical to Experiment 1.

MRI Acquisition. Structural images were obtained for 6 of the 17 monkeys. Data collection was identical to Experiment 1.

PET Data Acquisition, Processing, and Analysis. Data collection procedures and analysis of brain metabolic activity were identical to Experiment 1 (with the exception of GMP as a covariate, which was not used). Because anatomic data were obtained for only 6 of the 17 monkeys, procedures for registration and transformation to a standard space (27) differed from Experiment 1. These methods are described in Kalin *et al.* 2005 (23). GMP maps could not be created because of the absent anatomic data.

Logical AND Conjunction Analysis. Correlations between cortisol and brain activity were performed within each condition using "fmristat" (34,35), and we statistically controlled for age and time of day. We again performed a logical AND conjunction analysis (25) using a minimum statistic ($p < .05$, one-tailed uncorrected) to determine brain regions that were related to cortisol across contexts. We combined the statistical parametric maps from each condition and obtained a map revealing regions in which metabolism and cortisol were significantly correlated during the NEC condition, the ST condition, and the ALN condition. Clusters represent brain regions where metabolism and cortisol are correlated across all three conditions.

Results

Experiment 1—Relation Between Cortisol and Regional Metabolism

Cortisol. Cortisol values, adjusted for time of day, revealed varying degrees of HPA activation in relation to the different test conditions, $F(4,136) = 37.84$, $p < .0001$ (see Figure 1A). Cortisol values (adjusted for time of day) were greater in the threat conditions (ALN and NEC) compared with the home-cage conditions (H-CM and H-ALN), $t(34) = 4.79$, $p < .001$. Cortisol values (adjusted for time of day) were greater in the home-cage conditions compared with baseline, $t(34) = 8.68$, $p < .001$. Tests on raw cortisol values also indicate significant differences across conditions (see Figure 1 and Supplement 1 for statistics).

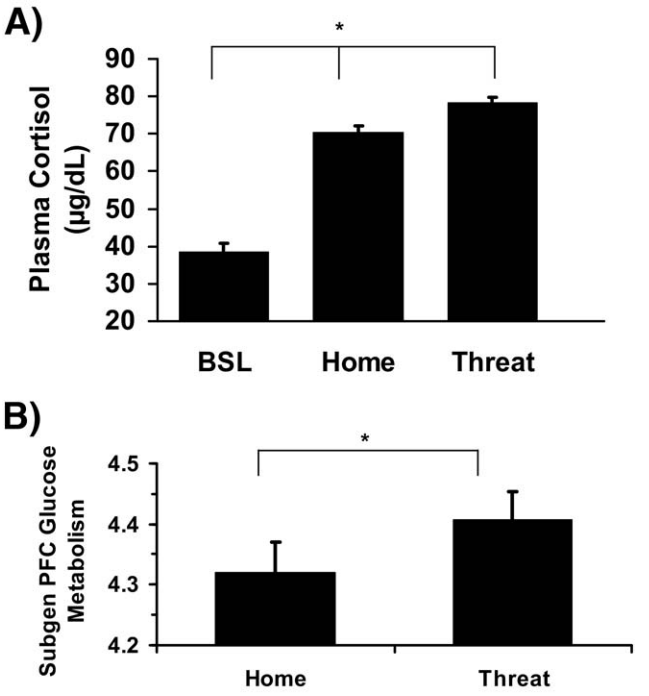

Figure 1. For Experiment 1, the two threat conditions included alone in a test cage and no eye contact. The two home-cage conditions included home alone and home with cagemate. **(A)** Both threat and home-cage conditions produced a greater cortisol response compared with baseline (BSL) morning cortisol after controlling for time of day, $ts(34) > 8.68$, $ps < .001$. Threat conditions produced a greater cortisol response compared with the home-cage conditions after controlling for time of day, $t(34) = 4.79$, $p < .001$. Differences between conditions were also significant when using raw cortisol levels, $F(4,136) = 73.97$, $p < .001$; all $ts(34) > 3.10$, $ps < .005$. Graphically, raw cortisol values are presented. **(B)** Threat conditions produced higher relative cerebral glucose metabolism in the subgenual prefrontal cortex (PFC) than home conditions, $t(34) = 3.10$, $p < .005$. Error bars represent standard error of the mean. *$p < .005$.

Consistent Correlations Between Metabolism and Cortisol. Logical AND conjunction analysis (25) revealed that metabolism in subgenual PFC and part of pregenual PFC (BA 25/24) was consistently correlated with individual differences in cortisol ($p < .05$; Figure 2, Table 1). A separate prefrontal cluster in which metabolism correlated with cortisol across conditions was identified in left orbitofrontal cortex (OFC, BA 13; Figure 2A). A region of basal forebrain including the right bed nucleus of the stria terminalis (BNST), ventral striatum, and shell and core of the nucleus accumbens (NAC) was the only other region in which metabolism positively correlated with cortisol across the four conditions (which we refer to as BNST/NAC; Figure 2B). There were no regions in which metabolism was consistently negatively correlated with cortisol.

We examined the correlation between glucose metabolism during the four test conditions with baseline cortisol sampled in the morning on nontesting days. Individual differences in baseline cortisol concentrations were significantly positively correlated with glucose metabolism in the subgenual PFC cluster during the ALN, NEC, and H-ALN conditions, $rs(33) > .35$; $ps < .05$; OFC during the ALN and NEC conditions, $rs(33) > .40$; $ps < .05$; and BNST/NAC only during the ALN condition, $r(33) > .40$; $p < .05$.

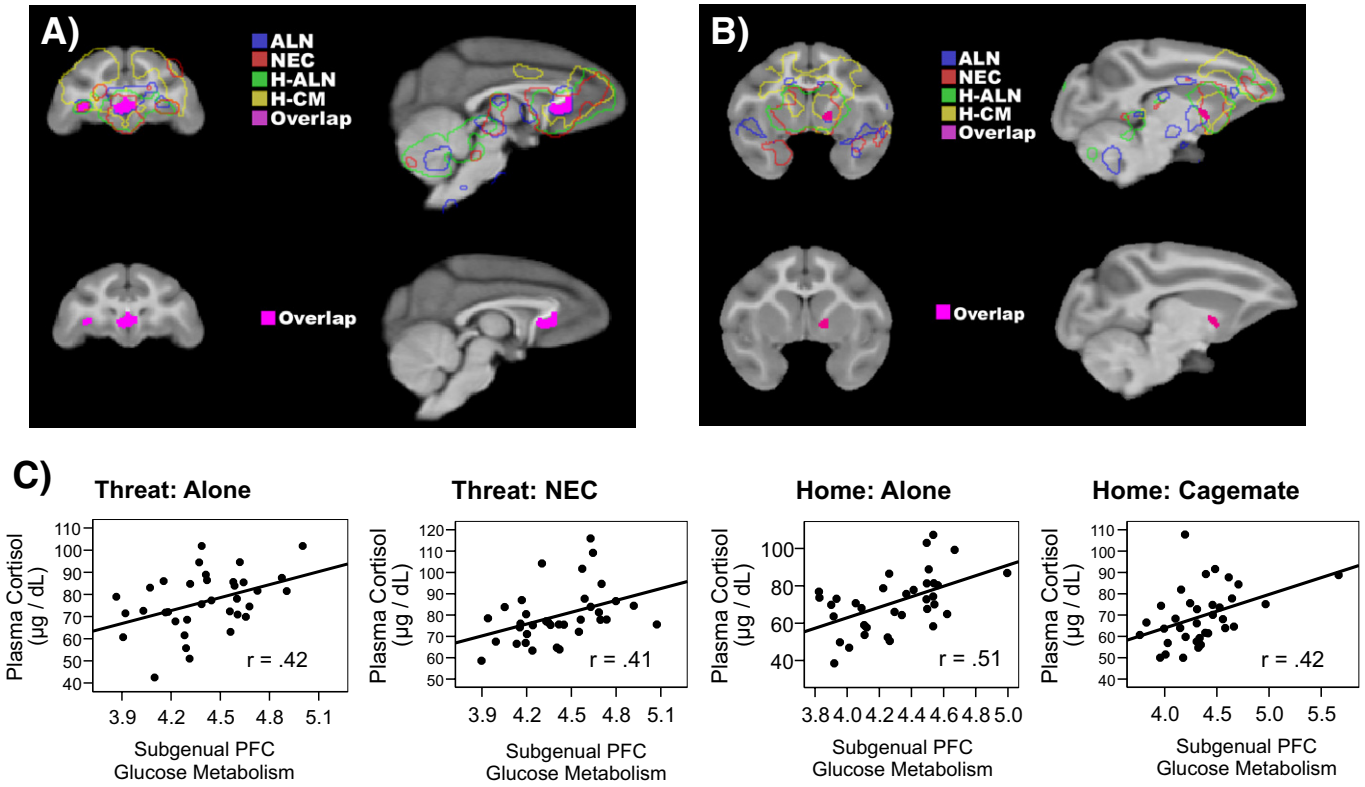

Figure 2. Correlations for Experiment 1 between glucose metabolism and cortisol across multiple contexts. **(A and B)** Upper images: correlational brain maps in which traced outlines indicate brain regions where cortisol is positively correlated with metabolism for each condition. Each color represents one of the four conditions. The solid pink areas represent the brain regions of overlap in which cortisol and glucose metabolism are correlated across all four conditions as identified using the logical and conjunction analysis. Lower images: isolated image of brain regions of overlap (solid pink). **(A)** Anterior sagittal and coronal slices depicting subgenual prefrontal cortex (PFC) and the left orbitofrontal cortex (OFC) in which cortisol correlates with glucose metabolism across all four conditions. **(B)** A more lateral, sagittal slice and more posterior, coronal slice showing the region encompassing the bed nucleus of the stria terminalis/nucleus accumbens in which cortisol correlates with metabolism in all four conditions. **(C)** Subgenual PFC: scatter plots of the relationship between metabolism in the subgenual PFC and cortisol in each of the four conditions: threat conditions—alone (ALN) and no eye contact (NEC); home-cage conditions—home alone (H-ALN) and home with cagemate (H-CM).

Condition-Related Metabolism. We compared metabolism in the threat conditions versus home-cage conditions for brain regions identified in the logical and conjunction analysis. Comparing across conditions, metabolism in subgenual PFC, OFC, and BNST/NAC (see Figure 2A for the location of these regions) revealed a similar pattern to that of cortisol. Regional metabolism during the threat conditions (NEC and ALN) was significantly higher than metabolism in the home-cage conditions (H-CM and H-ALN) in subgenual PFC, $t(34) = 3.10$, $p < .005$; Figure 1B; OFC, $t(34) = 2.96$, $p < .01$; and BNST/NAC, $t(34) = 4.82$, $p < .001$.

Follow-up correlational analyses examined the relations among subgenual PFC, OFC, and BNST/NAC metabolism. Metabolic activity was significantly correlated between subgenual PFC and OFC in all four conditions ($rs[33] = .47-.76$, $p < .01$). Metabolic activity was significantly correlated between subgenual PFC and BNST/NAC in all four conditions ($rs[33] = .52-.65$, $p < .01$). Metabolic activity was significantly correlated between OFC and BNST/NAC in one of the four conditions (H-CM: $r[33] = .45$, $p < .01$).

Table 1. Experiment 1: Brain Regions that Consistently Predict Cortisol Responses Across Contexts

Local Maxima	Hemisphere	Volume, mm^3	x	y	z
Subgenual PFC BA 24/25	midline	110	−1	10	3
OFC	left	14	−14	11	3
BNST/NAC	right	31	6	2	1

BNST/NAC, bed nucleus of the stria terminalis/nucleus accumbens; OFC, orbitofrontal cortex; PFC, prefrontal cortex.

Individual Differences between Threat and Home-Cage Conditions. To assess further the extent to which individual differences in metabolic activity predict cortisol concentrations, we computed difference scores for each subject between threat and home-cage cortisol levels, as well as difference scores between threat and home-cage regional metabolism. We correlated difference scores for metabolism for each brain region of interest and with difference scores for cortisol. This analysis demonstrated that the difference in cortisol levels between threat and home-cage conditions was significantly correlated with the difference in metabolism in the subgenual PFC, $r(33) = .53$, $p = .001$, Figure S1A in Supplement 1; OFC, $r(33) = .38$, $p < .05$, Figure S1B in Supplement 1, and BNST/NAC, $r(33) = .55$, $p = .001$, Figure S1C in Supplement 1.

Experiment 2—Analysis of Archival Data

Cortisol Data. Cortisol levels (in µg/dL) following each of the stressful conditions were greater than the baseline concentrations assessed on a different day (M: 41.94 [11.61]; $F[3,48] = 39.09$, $p < .001$) and did not significantly differ across ALN (M:

75.79 [18.10]), NEC (M: 74.10 [11.78]), and ST (M: 75.39 [16.98]) conditions $ts[16] < .54$, $ps > .60$).

Consistent Correlations between Metabolism and Cortisol. To test further the reliability of the relation between cortisol and PFC activity, we used similar methods to examine an archival data set. On the basis of the prior analyses, we hypothesized that across each of the three contexts, metabolic activity in the subgenual PFC, OFC, and BNST/NAC regions would predict individual differences in cortisol concentrations in response to the conditions. A one-tailed $p < .05$ threshold for the predicted regions was used based on the a priori directional hypothesis. Consistent with the earlier results, across the three conditions, positive correlations were found between cortisol levels and metabolic rate in a cluster overlapping with the subgenual PFC (BA 25/24; local maxima, *x*: −2, *y*: 11, *z*: 6; cluster volume = 65 mm^3). In contrast to the initial study, significant correlations between cortisol and metabolic activity were not found in the BNST/NAC or OFC regions (see Table S1 in Supplement 1 for all clusters). We did not observe significant correlations between baseline plasma cortisol levels and subgenual PFC glucose metabolism in any of the conditions in this archival data set, $rs\ (15) < .31$, $ps > .22$.

Discussion

This study provides novel data suggesting that in primates subgenual PFC is a brain area that is critically related to HPA output. By using a logical AND conjunction analysis (25), we were able to identify brain regions in which glucose metabolic rate significantly predicts cortisol in each condition and thus is consistently related to individual differences across multiple contexts. This analytic strategy allowed us to pinpoint brain regions that may act as traitlike neural regulators. The data demonstrate that individual differences in subgenual PFC metabolic rate predict cortisol levels across different contexts that vary in their degree of stressfulness. The data also show that both subgenual PFC metabolic activity and cortisol concentrations during threat conditions were greater than in the less stressful home conditions. Furthermore, analysis of the archival data confirmed the context-independent relation between subgenual PFC activity and cortisol concentrations. Taken together, these data suggest that activity in the subgenual PFC has a traitlike relationship with individual variation in cortisol levels that remains stable across threatening and nonthreatening contexts.

In primates, the subgenual PFC is linked to many brain regions that are involved in HPA regulation as well as visceral and emotional responses to stress (amygdala, BNST, hypothalamus, and periaqueductal gray) (11,37,38). Furthermore, using a similar analytic strategy in the same animals used in Experiment 1, we recently identified a network consisting of many of these regions (amygdala, hippocampus, and periaqueductal gray) that is predictive of individual differences in anxious temperament (20). In rodent studies, it has been demonstrated that during stress the infralimbic cortex (IL; the region in rodents that is most analogous to subgenual PFC in primates) (7) provides input to the basolateral amygdala (39). On the basis of rodent data, the IL is thought to influence behavior during extinction learning through indirect input (projections to intercalated amygdala neurons) to the central nucleus of the amygdala (40,41). Other studies show that lesions to the infralimbic cortex suppress stress-related corticosterone responses (13,42), elevate basal levels of corticosterone (42), prolong extinction learning to fearful stimuli (43), and alter social behavior (42). The observed relationship, across contexts, between the subgenual PFC metabolic rate and cortisol is consistent with the idea that this region is critically involved in the regulation of the HPA axis and the stress response. In conjunction with other primate and rodent data, our findings suggest that the primate subgenual PFC might represent the core of an integrated pathway for both initiation and regulation of a cortisol response.

Data from our primary study also suggest that individual differences in activity in the OFC as well as an area encompassing the BNST/NAC are associated with HPA output. Although metabolic activity between the BNST/NAC and OFC was correlated only in one of the four conditions, metabolic activity in the subgenual PFC was correlated with BNST/NAC and OFC across all four conditions. This further suggests that the subgenual PFC is part of a network of structures whose activity is related to the HPA axis. The BNST/NAC has dense projections from the mPFC which includes BA 25 (10,44). Importantly, the BNST/NAC have direct connections to the paraventricular nucleus of the hypothalamus (9,23,45). This region of the basal forebrain is thought to be part of a network that integrates endocrine, autonomic, and emotional states (46). The OFC also plays a role in regulating emotion and anxiety and is bidirectionally linked to the amygdala (47). Although the relations between cortisol and metabolism in these regions were evident in Experiment 1, they were not replicated in the analysis of the archival data and thus should be regarded with caution.

Although our findings demonstrate that greater subgenual PFC activation is related to greater cortisol secretion, the 30-minute time frame of FDG uptake (see, e.g., Rilling *et al.* 2001 [26]), along with our use of a single cortisol sample per condition, makes it difficult to interpret the specific mechanisms involved in this relationship. Because subgenual PFC provides input to the hypothalamus, amygdala, and BNST/NAC and because it is also implicated in negative feedback of the HPA system (12), it is likely that the positive relation between subgenual PFC activity, and cortisol reflects the combination of stimulatory and inhibitory processes within the HPA axis. Because of the correlational nature of our data, the possibility exists that cortisol and subgenual regional metabolism show a simultaneous increase during these contexts but share no mechanistic relationship with one another. However, rodent data provide clear evidence for a mechanistic relationship between infralimbic cortex and HPA regulation, which suggests that our correlational findings may identify in primates a region that is mechanistically related to variation in HPA output. In addition, it is notable that the primate PFC contains a wealth of glucocorticoid receptors (48), and the distribution of receptors in the PFC is affected by stress (22), further suggesting a functional relationship between these systems. The possibility also exists that the relation we observed between subgenual PFC activity and cortisol could be due to the effects of cortisol on brain metabolic activity. Future work should continue to address the causal nature of this relationship and provide data with increased sensitivity to detect time profiles of these responses.

Another potential limitation is our inability to confidently address sex-related differences in these samples. Our sample from Experiment 2 contained only male monkeys, and our sample for Experiment 1 contained an insufficient number of males ($n = 12$) and females ($n = 23$) to address sex-related differences.

It has been suggested that depression is partly due to alterations in stress-related systems (16). Studies in some depressed patients demonstrate altered regulation of the HPA axis (49). Other studies point to increased subgenual PFC activity associated with the pathophysiology of depression (18), and recent

human neuroimaging studies support the involvement of the subgenual PFC in HPA regulation during stressful contexts (50). The findings presented in this study provide a link between individual differences in subgenual PFC and HPA activity and may be important in understanding the basis of psychopathology related to dysregulation of the stress response. Future work should examine whether individuals with elevations in subgenual PFC activity across multiple contexts are at risk for stress-related HPA dysregulation and psychopathology.

In summary, this study used multiple contexts, varying in their degree of stressfulness, to elucidate relations between regional brain metabolism and HPA activity in primates. Heightened subgenual PFC glucose metabolism consistently predicted higher cortisol levels across contexts that varied in their degree of stressfulness. The findings point to a role for the primate subgenual PFC as a possible traitlike neural regulator of HPA activity. These data linking subgenual PFC to HPA function may be particularly relevant to understanding mechanisms associated with the pathophysiology of stress-related psychopathology in which both subgenual function and HPA function can be dysregulated.

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