Neural activity and diurnal variation of cortisol: Evidence from brain electrical tomography analysis and relevance to anhedonia

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Abstract

The medial prefrontal cortex (mPFC), hippocampus, and amygdala are implicated in the regulation of affect and physiological processes, including hypothalamic-pituitary-adrenal (HPA) axis function. Anhedonia is likely associated with dysregulation of these processes. Dense-array resting electroencephalographic and cortisol were obtained from healthy and anhedonic groups. Low-resolution electromagnetic tomography was used to compute intracerebral current density. For the control group, voxelwise analyses found a relationship between current density in beta and gamma bands and steeper cortisol slope (indicative of more adaptive HPA axis functioning) in regions of the hippocampus, parahippocampal gyrus, and mPFC. For the anhedonic group, the mPFC finding was absent. Anhedonia may be characterized by disruptions of mPFC-mediated neuroendocrine regulation, which could constitute a vulnerability to the development of stress-related disorders.

Descriptors

Electroencephalography (EEG); Anhedonia; Cortisol; Stress; Prefrontal cortex; Low resolution electromagnetic tomography (LORETA)

In recent years, there has been growing interest in the examination of the neural substrates underlying affective regulation and stress reactivity. Functional neuroimaging studies have delineated a particular neural circuit, including the mPFC, hippocampus, and the amygdala, that is critically implicated in the regulation of affect and physiological responses to biologically salient events (for reviews, see Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Phan, Wager, Taylor, & Liberzon, 2002). In particular, data from animal studies suggest that this circuit plays an important role in the regulation of hypothalamic-pituitary-adrenal (HPA) axis function. Specifically, the mPFC and the subgenual PFC are implicated in the modulation of HPA axis function by acting as a site for glucocorticoids to exert negative feedback (Diorio, Viau, & Meaney, 1993; Hurley-Gius & Neafsey, 1986; Terreberry & Neafsey, 1983). In

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addition to these prefrontal regions, the hippocampal and parahippocampal regions have been implicated in the negative-feedback effects of glucocorticoids (Sapolsky, 2000).

The diurnal pattern of cortisol secretion has been well characterized and is typified by higher morning levels that decrease throughout the day. Flattened cortisol slope, that is, an attenuated decrease throughout the day, has been found to be associated with poor health and the vulnerability toward disease progression for medical disorders (Catley, Kaell, Kirschbaum, & Stone, 2000; Matthews, Schwartz, Cohen, & Seeman, 2006; Spiegel & Giese-Davis, 2003) and psychiatric disorders (Carrion et al., 2002; Cicchetti & Rogosch, 2001; Gunnar & Vazques, 2001; Young, Haskett, Pande, Weinberg, & Watson, 1994). Relatedly, relationships have been demonstrated between diurnal patterns of cortisol and affect. Greater self-reported negative affect has been found to be associated with higher diurnal cortisol levels (Jacobs et al., 2007) as well as flatter diurnal cortisol slopes (Polk, Cohen, Doyle, Skoner, & Kirschbaum, 2005). Moreover, diurnal studies of positive affect and cortisol indicate an inverse relationship between the two measures (Jacobs et al., 2007; Steptoe, Gibson, Hamer, & Wardle, 2007; Steptoe, Wardle, & Marmot, 2005). Although the exact effects of disrupted diurnal cortisol secretion have not been determined, it appears to signal a deviation of normal HPA axis function, which is associated with pathology and affective disturbance.

Positive affect and feelings of pleasure can act as a buffer to the experience of negative affect and distress. Individuals who are impaired in this regard, that is, are anhedonic, not only experience an attenuation of positive affect but are also more vulnerable to the effects of aversive and stressful events (Meehl, 1975). Anhedonia is a prominent symptom of various psychopathological disorders, including unipolar depression and schizophrenia, and has been often associated with disease chronicity and poor treatment outcome (e.g., Spijker et al., 2004; Moos & Cronkite, 1999). Consequently, it is not surprising that this important phenotype has attracted substantial interest in both the human and animal literature (e.g., Anisman & Matheson, 2005; Hasler, Drevets, Manji, & Charney, 2004; Horan, Kring, & Blanchard, 2006). Additionally, anhedonia has been examined as a subclinical syndrome, and numerous studies have confirmed its construct validity. Particularly, psychophysiological and phenomenological data (Fitzgibbons & Simons, 1992; Gooding, Davidson, Putnam, & Tallent, 2002) confirm that anhedonia is characterized by a disruption in the reward and appetitive systems as well as, in some cases, an increased sensitivity to the presence of unpleasant stimuli and environmental challenges (for a review, see Loas, 1996). An improved understanding of the psychophysiology of anhedonia would contribute to the characterization of the relationship of the effects of negative environmental stimuli and blunted positive affect on the development and treatment of various psychopathological disorders.

Few humans studies have directly examined the neural circuits associated with the regulation of the diurnal slope function of the HPA axis. This knowledge could help identify targets for the development of treatments for stress-related illness as well as elucidate the neural mechanisms governing the stress response. Therefore, the goal of this study was to examine the association between patterns of diurnal salivary cortisol, an index of HPA function, and neural activity as indicated by current density measured by source localization of resting electroencephalographic (EEG) data using low resolution electromagnetic tomography (LORETA; Pascual-Marqui, Michel, & Lehmann, 1994; Pascual-Marqui et al., 1999). Cross-modal validation for LORETA has been provided by studies combining this algorithm with other measures of neural activation, including traditional scalp spectral EEG, functional fMRI, structural MRI, PET, and intracranial recordings (for a review, see Pizzagalli, 2007). LORETA improves the spatial resolution of EEG data, and there is initial evidence indicating incremental validity for this algorithm compared to traditional scalp spectral analyses (Pizzagalli et al., 2002; Pizzagalli, Sherwood, Henriques, & Davidson, 2005). To our knowledge, no study has examined relationships between diurnal salivary cortisol and neural activity using these

methods. We have further extended this investigation by contrasting our findings between a control group and a group with physical anhedonia. Due to the association between affect and HPA axis function, an examination of the physiological underpinnings of anhedonia may provide clues to the pathophysiology of psychiatric syndromes characterized by reduced positive affect and, thus, increased vulnerability to aversive environmental events.

In light of animal studies linking mPFC, including the orbital frontal cortes (OFC) and subgenual PFC, and hippocampal function to the regulation of glucocorticoids, we predicted that activity in the mPFC and the hippocampus would be associated with diurnal cortisol variation in a healthy population. Additionally, we predicted that the anhedonic group would demonstrate disruptions in these regulatory systems as evidenced by (1) abnormal associations between mPFC/hippocampal activity and diurnal cortisol slope and (2) flatter averaged diurnal cortisol slope and lower mPFC/hippocampal current density, that is, neural activity, compared to healthy controls. We are not predicting relationships with the amygdala, as the electrophysiological imaging method utilized in this study does not allow us to probe this region. Both groups were defined by the manifestation of psychological phenomenon, and our aim is to examine the relationship of these phenomena to biological constructs. This is critical, as both psychological and biological concepts contribute crucial and specific roles to the understanding of psychopathological symptoms (see Miller, 1996).

Methods

Participants

Participants were right-handed, English-speaking undergraduates at the University of Wisconsin who received course credit for their research participation. They completed a questionnaire comprised of all items from the Chapman Psychosis-Proneness Scales: the Perceptual Aberration Scale (Chapman, Chapman, & Raulin, 1978), the Magical Ideation Scale (Eckblad & Chapman, 1983), the Revised Social Anhedonia Scale (Eckblad, Chapman, Chapman, & Mishlove, 1982), and the revised Physical Anhedonia Scale (PAS; Chapman & Chapman, 1978) as well as the Chapman Infrequency Scale (Chapman & Chapman, 1983). The PAS score was chosen as the defining criterion for the anhedonic group, as this scale reliably detects deficits in affective functioning related to physical, that is, sensory versus interpersonal, experience (Chapman, Chapman, & Raulin, 1976). We chose this scale due to its strength in differentiating groups of individuals who exhibit distinct psychological and physiological profiles (e.g., Ferguson & Katkin, 1996; Fitzgibbons & Simons, 1992). The anhedonic group ($N = 28$) scored ≥ 2 standard deviations above the mean of the same sex group on the PAS, and they were within normal range on the other scales except the revised Social Anhedonia Scale, which is moderately correlated with the PAS. A control group ($N = 31$) consisted of individuals who scored <0.5 standard deviations above or below the same sex group mean on the PAS as well as on all of the other scales. All participants endorsed less than three items on the Chapman Infrequency Scale (Chapman & Chapman, 1983), a 13-item scale developed to screen out participants who are either responding in a random manner or demonstrating negative response biases.

There were no significant group differences in age or sex: anhedonic group mean age = 19.37 years, $SD = 2.63$, 38% female; control group mean age = 18.65 years, $SD = 0.75$, 42% female. All participants completed the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and the anhedonic group reported higher levels of depression than the control group, $t(26) = 7.21$, $p<.001$. However, the mean BDI score for the anhedonic group was 9.8 ($SD = 7.1$) and therefore well below the threshold for moderate depression, which is represented by scores within the range of 15–30. One participant in the control group had incomplete cortisol data, and 4 participants in the anhedonic group had incomplete EEG data

due to excessive artifacts. Therefore, the final groups consisted of 30 individuals in the control group and 24 individuals in the anhedonic group.

Procedure

Participants first provided informed consent consistent with institutional requirements and then received a diagnostic interview, the Structured Clinical Interview for the DSM-IV Non-Patient Version I (SCID-I; First, Gibbon, & Williams, 1997). None of the control participants met diagnostic criteria for any current or past Axis I disorder. Four members of the anhedonic group had current Axis I disorders: alcohol abuse ($n = 1$), major depression ($n = 2$), and obsessive-compulsive disorder ($n = 1$). Removing these 4 anhedonic participants from the analyses did not change the pattern or statistical significance of any of the results.

To measure cortisol levels, participants provided samples of saliva in supplied plastic tubes twice daily for 4 days. Sample collection was cued by a signal from a preprogrammed Seiko wristwatch and occurred at the same time each day: between 30 and 45 min after wakening and again 12 h later. For the morning samples, the wristwatch was programmed based on the participants' reports of their expected awakening times. This was relatively easy to do for the weekdays, as participants were able to predict morning awakening time based on their class and/or work schedules. They were instructed to leave a cortisol sample between 15 min and 45 min after awakening. If they awoke at a different time than was previously programmed into the wristwatch, they were instructed to follow the same procedure and to indicate the new time on the questionnaire booklet provided. Participants reported that they were able to comply with this procedure. The rationale behind this approach is that there is evidence that the morning awakening curve is based on time of awakening, rather than a set time for each day (Pruessner et al., 1997). Participants were instructed to avoid eating, physical activity, or drinking anything but water for 60 min before collecting each sample. The first sample was taken before breakfast and the second sample was taken after dinner and before bed. Participants were instructed to store samples in their home freezer until they delivered them to an experimenter at the end of the study. At times, participants did not have immediate freezer access; however, research has shown that salivary cortisol is stable at room temperature for as long as 30 days (Kirschbaum & Hellhammer, 1989). On days of cortisol collection, they provided information concerning illness, medication use, and amount of sleep.

Participants came into the laboratory for the electrophysiology session within 1 week of the saliva sampling. To ascertain levels of distress, participants completed questionnaires that tapped symptoms of anxiety and depression (The Mood and Anxiety Symptom Questionnaire– 90 items [MASQ]; Watson & Clark, 1991) and "trait" affect (The Positive and Negative Affect Scales–General [PANAS]; Watson, Clark, & Tellegen, 1988). These measures were given immediately after the EEG recording session.

Apparatus and Physiological Recording

Resting EEG data were collected with a Geodesic net with 128 sensors (Electrical Geodesic system; Tucker, 1993) and obtained in 8 contiguous, counterbalanced 1-min trials (4 with eyes open and 4 with eyes closed). Participants were instructed to be still, quiet, and relaxed but to stay awake. After the experimenter instructed the participant as to the type of trial, there was a brief delay before EEG recording began to avoid any contamination of the resting EEG signal.

Data were collected at a 250-Hz sampling rate with hardware filters set at 0.1–100 Hz (recording reference: Cz) and filtered offline with a 60-Hz digital notch filter. Electrooculogram (EOG) was recorded with two tin leads placed on the suborbit of the left eye and referenced to a forehead lead.

Data Reduction and Processing

Cortisol data—When returned, samples were sealed and frozen at −70°C. Cortisol was assayed using the Pantex [125]I Cortisol RIA Kit modified for saliva. The technicians performing cortisol assays were blind to group membership. The detection limit of the assay (ED_{80}) was 0.03 μg/dl (for additional details, see Smider et al., 2002). Cortisol values were *z*-transformed to identify outliers (none were detected), and a logarithmic transformation was applied. The diurnal cortisol profiles of participants who reported unusual sleeping patterns, antibiotic use, or use of oral contraceptives on the days of cortisol assessment were examined, and no unusual patterns were observed. Two women, one from each group, reported use of oral contraceptives. These data were retained in the final analyses because oral contraceptives have been reported only to affect free cortisol responses to psychosocial stress, not diurnal variation (Rohleder, Wolf, Piel, & Kirschbaum, 2003), and the data did not appear abnormal.

EEG data—Off-line, the EEG data were visually scored and edited to remove artifact. Only epochs with artifact-free data across all channels were retained. Corrupted channels were replaced using a spline interpolation (Perrin, Pernier, Bertrand, & Echallier, 1989). All available artifact-free 2048-ms EEG epochs were extracted, rederived to the average reference, and then subjected to standard spectral analyses via discrete Fourier transform (DFT) using boxcar windowing (Brillinger, 1981). Next, LORETA was used to compute the three-dimensional intracerebral current density distribution for the following eight bands: Delta (1.5–6.0 Hz), Theta (6.5–8.0 Hz), Alpha1 (8.5–10.0 Hz), Alpha2 (10.5–12.0 Hz), Beta1 (12.5–18.0 Hz), Beta2 (18.5–21.0 Hz), Beta3 (21.5–30.0 Hz), and Gamma (36.5–44 Hz). As our predictions focused on neural regions located deeply within the brain (hippocampus, parahippocampal gyrus) as well as ventral regions of the PFC, we employed this source localization technique rather than scalp EEG analyses, which are unable to reveal information regarding these regions.

Without postulating a prespecified number of generating sources, LORETA estimates location (s) of electrical source activity by assuming similar activation among neighboring neuronal sources, an assumption implemented by computing the "smoothest" of all possible activity distributions. The present implementation uses a three-shell spherical head model (Ary, Klein, & Fender, 1981) and EEG electrode coordinates derived from cross-registrations between spherical and realistic head geometry (Towle et al., 1993). Both the head model and the electrode coordinates were registered to the digitized MRI available from the Brain Imaging Centre, Montreal Neurologic Institute (MNI305; Collins, Neelin, Peters, & Evans, 1994; Evans et al., 1993). The solution space (2394 voxels; voxel size: 7 mm^3) was restricted to cortical gray matter and hippocampi, as defined by the digitized MNI probability atlases. This is a subset of the total brain volume. LORETA values represent the power, that is, squared magnitude, of the computed intracerebral current density (unit: amperes per square meter [A/m^2]). Following established procedures (Pizzagalli et al., 2001, 2004), LORETA data were intensity normalized before statistical analyses. For each band and participant, the image volume was scaled so its mean was the same as the grand mean (mean across participants). This approach emphasizes regional differences within the brain and removes participant-to-participant global variation, which is typically considered a nuisance variable. Recently, LORETA has received important cross-modal validation with other measures of neural function (Pizzagalli et al., 2004; Mulert et al., 2004; Worrell et al., 2000; Zumsteg, Friedman, Wennberg, & Wieser, 2005).

Statistical Analyses

Between-group analyses of questionnaire data—To reduce the number of comparisons, separate MANOVAs were used to analyze the subscales from the MASQ (General Distress, Mixed Symptoms; General Distress, Anxious Symptoms; Anxious Arousal;

General Distress, Depressive Symptoms; and Anhedonic Depression) and the PANAS Scales (NA and PA). Post-hoc Tukey tests were used to analyze items from statistically significant MANOVAs.

Between-group analyses of cortisol data—Cortisol slopes were computed per day from the logged cortisol levels and then averaged across all 4 days; individual levels were also averaged across all 4 days per participant. To test between-group differences in levels, a mixed-level hierarchical linear model was used (PROCMIXED in SAS) that included Time of Day (morning or evening) and Day (1–4) as fixed variables. Additionally, all the averaged variables, that is, Slope and Level, were compared between groups using independent *t* tests.

Voxelwise between-group analyses of EEG data—To examine if current density in hypothesized brain regions differed between groups, whole-brain voxelwise *t* tests were computed within each EEG band.

Voxelwise correlation analyses—For each band separately and at each voxel, a Spearman's rank correlation (rho) was computed between cortisol slope and intensity-normalized current density. To identify normative relations between resting brain activity and cortisol, coefficients were first computed for the control group. If significant correlations emerged (for $p<.01$, $|rho| \geq .47$), voxelwise Fisher's tests (Fisher, 1921) were run to assess whether these patterns of correlations were significantly different ($p<.05$) between the groups. Reported results were restricted to a priori identified regions, that is, the hippocampus and the mPFC, and clusters greater in size than 10 contiguous voxels. The size limitation was imposed in an effort to restrict interpretations to major regions of interest.

Corrections for multiple testing—To protect against multiple testing, we utilized a program designed for fMRI data (AlphaSim in the software Analysis of Functional Neuro Images [AFNI]; Cox, 1996) to determine a combination of *p*-value threshold at the individual voxel level and cluster size yielding a mapwise $p<.05$ (corrected, two-tailed; Xiong, Gao, Lancaster, & Fox, 1995). For the present study, Monte Carlo simulations were run by assuming varying degrees of spatial correlation among the LORETA data. Findings revealed that a cluster size of at least 31 voxels (i.e., 10.63 cm^3) was required for statistical significance when considering an individual voxel threshold of $p = .01$.

Laterality analyses—To formally test whether findings were specific to one hemisphere, laterality analyses were conducted. Homologous contralateral regions were identified (by reversing the *x* coordinates), and the averaged current density was calculated across all voxels within the identified cluster of interest. Spearman's rank correlations were then computed between each contralateral region and cortisol slope. Finally, the two sets of correlations, one for each hemisphere, were compared using the Meng-Rosenthal (Meng, Rosenthal, & Rubin, 1992) test for comparing dependent correlation coefficients.

Results

Between-Group Analyses of Questionnaire Data

The MANOVA for the PANAS–General (i.e. "trait" affect) was statistically significant, Wilks' Lambda $F(2,55) = 3.66$, $p<.05$. Follow-up Tukey tests indicated that the anhedonic group reported significantly more negative affect, $F(1,56) = 4.17$, $p<.05$. There was a trend for significance for the MANOVA for the MASQ, Wilks' Lambda $F(5,52) = 2.45$, $p = .06$. Follow-up Tukey tests indicated statistically significant between-group differences for General Distress, Mixed Symptoms, $F(1,56) = 8.30$, $p<.01$, Anxious Arousal, $F(1,56) = 4.09$, $p<.05$,

and Anhedonic Depression, $F(1,56) = 9.59$, $p<.01$. In all cases, the anhedonic group reported greater levels of symptomatology.

Between-Group Analyses of Cortisol Data

The mixed model examining logged cortisol levels revealed a main effect of Time of Day, $F(1,57) = 224.32$, $p<.0001$. Thus, both groups demonstrated normal diurnal patterns as evening cortisol levels were significantly lower. There were no statistically significant effects of Group or Day. All t tests for average Slope and Level were nonsignificant for both one- and two-tailed tests.

Voxelwise Between-Group Analyses of EEG Data

Using voxelwise independent t tests, current density was not significantly different between the two groups at the .01 probability level for any band using either one- or two-tailed tests.

Voxelwise Correlational Analyses

The left panel of Figure 1 shows findings from the whole-brain correlational analyses between current density and cortisol slope for the control participants (panels A–C) and the anhedonic participants (panels D–F). The right panel shows findings from the Fisher's tests assessing differences between the control and anhedonic participants (panels A–C) and the anhedonic and control participants (panels D–F) in their correlations between current density and cortisol slope. Table 1A depicts data from clusters in which control participants had significant Spearman's rho coefficients and were significantly different from the anhedonic group; Table 1B depicts data from clusters in which anhedonic participants had significant Spearman's rho coefficients that were significantly different from the control group. Significant negative coefficients indicate that current density is associated with steeper negative cortisol slope, and significant positive coefficients indicate that current density is associated with flatter cortisol slope. All findings discussed below are those which demonstrated a significantly greater correlation for one group compared to the other, as assessed by the Fisher's tests.

For the control group, significant Spearman's rho coefficients were found in two clusters. The first is in the Gamma band (Fisher's test: $z = 2.23$) and has a positive correlation with cortisol slope (Cluster 1; Figure 1A); this includes the dorsolateral prefrontal cortex (DLPFC), specifically, the inferior frontal gyrus and precentral gyrus (BAs 9 and 4/6). The second cluster is in the Beta3 (Cluster 2; Figure 1B; Fisher's test: $z = 2.43$) and Gamma (Cluster 2; Figure 1C; Fisher's test $z = 2.51$) bands and has a negative correlation with cortisol slope. This is a large cluster that includes the ventromedial PFC, the OFC, and the subgenual anterior cingulate (ACC) cortex as well as the regions of the left hippocampus and parahippocampal gyrus (BAs 11, 25, 28/37, and 47). Figure 2 depicts the scatterplot for the Beta3 band in this cluster. For Clusters 1 and 2, anhedonic participants failed to show significant correlations between current density and cortisol slope (Table 1).

A secondary analysis computed voxelwise Spearman's rho correlations for the anhedonic group. These analyses also revealed a large cluster in the hippocampal/parahippocampal region significantly correlated with cortisol slope (BAs 18, 19, 27, 29, 30, and 37) in the Beta1 (Cluster 3; Figure 1D; Fisher's test: $z = 2.12$), Beta2 (Cluster 3; Figure 1E; Fisher's test: $z = 2.50$), and Beta3 (Cluster 3; Figure 1F; Fisher's test: $z = 2.43$) band. This was also a negative correlation, but for the anhedonic group, this region was in the right posterior hippocampus. Unlike the control group, no significant correlation coefficients were found between cortisol slope and current density within any regions of the mPFC.

For these analyses, the cluster sizes are well above the threshold required for a corrected mapwise $p<.05$ level (31 voxels), with the exception of the hippocampal/parahippocampal

cluster in both the control and anhedonic groups. In the control group, there were only 25 voxels in the Gamma band; however, in a similar region, there were 75 significantly correlated voxels in the Beta3 band. In the anhedonic group, there were only 18 contiguous voxels in the Beta3 band; however, in a similar region, there were 39 significantly correlated voxels in Beta1 and 40 significantly correlated voxels in Beta2. As the Beta and Gamma bands are closely related in terms of frequency and levels of brain activation (e.g., Oakes et al., 2004), these slightly smaller clusters do not alter the overall pattern and relevance of findings.

Laterality Analyses

Within each group, regions that were identified in the voxelwise correlational analyses were tested for laterality. Only one cluster was found to be significantly and differentially associated with cortisol slope when compared to an analogous region in the contralateral hemisphere: Cluster 1 for the Gamma band for the control group (results specific to right side), $z = 2.35$, $p<.05$ (rho for the right side = .54, rho for the left side = .34). None of the analyses revealed a significant laterality difference for the clusters encompassing the hippocampus and the PFC, and there were no laterality differences within the anhedonic group.

Discussion

The primary goal of this study was to investigate relationships between resting neural activity, as measured by current density in EEG using LORETA, and diurnal cortisol slope in a group of healthy participants. These findings were then extended to a group of participants who had elevated scores on the Revised Physical Anhedonia Scale (Chapman et al., 1976). Regarding the role of the PFC, results for the control group indicate that there was a significant negative association between cortisol slope and Beta3 current density in a large region encompassing the mPFC, the subgenual PFC, and the OFC. The anhedonic group had no significant correlations within the PFC. Neural activity in the hippocampus and parahippocampal gyrus also had negative associations with cortisol slope for both the control (Beta3 and Gamma) and anhedonic (Beta1, Beta2, and Beta3) groups, although different hemispheres were involved (left for controls; right for anhedonics). In spite of these hemispheric differences, formal laterality tests revealed no significant group differences, precluding firm conclusions about laterality involving hippocampal regions.

Because activity within the Gamma and Beta bands is considered a direct index of brain activation (Bonnet & Arand, 2001; Oakes et al., 2004), the above findings suggest that greater resting neural activity in the medial and subgenual PFC, OFC, hippocampus, and parahippocampal gyri was associated with steeper negative slope of cortisol levels over the course of the day. This correlation raises the possibility that these regions may be implicated in the regulation of normal HPA axis function. Steeper cortisol slope, that is, relatively greater cortisol levels in the morning followed by a decline throughout the day, is associated with resistance to pathophysiology and thus may be an index of psychological and physiological resiliency (Gunnar & Vazquez, 2001; Young et al., 1994). These findings are consistent with animal (Diorio et al., 1993; Meaney & Aitken, 1985; Sapolsky, 2000) and human (MacLullich et al., 2006; Ottowitz et al., 2004; Sarrieau et al., 1988; Urry et al., 2006; Vermetten & Bremner, 2002) studies that associate the mPFC and the hippocampus with the regulation of neuroendocrine function. Further evidence for the role of the mPFC in HPA axis function is provided by several studies demonstrating that the acute effects of corticosteroid administration impact EEG signal by increasing right relative to left frontal activity (Schmidt, Fox, Goldberg, Smith, & Schulkin, 1999; Tops et al., 2005).

This study also revealed that Gamma activity in a region of the right DLPFC was associated with a flatter cortisol slope in the control, but not anhedonic, group. Laterality analyses revealed that this relationship was specific to the right DLPFC. This finding extends prior studies

reporting that neural activity in the right DLPFC is associated with negative affect, including clinical depression and, more specifically, withdrawal-related affects (Davidson, 1998; Davidson et al., 2002; Pizzagalli et al., 2002). Therefore, it is not surprising that this neural region would be implicated in disrupted HPA axis function. Because no association was observed between neural activity in the right DLPFC and cortisol levels for the anhedonic group, it is likely that functions normally ascribed to this region of the brain are disrupted in anhedonia. Although speculative, this disruption may represent a vulnerability toward the development of depression or other stress-related disorders characterized by increased levels of negative affect and affective dysregulation.

The mPFC and OFC regions are critically involved in an individual's ability to utilize evaluative feedback from the environment in order to rapidly and appropriately switch affective responses to seek reward and to avoid punishment (Kringelbach & Rolls, 2004; Ongur & Price, 2000; Rolls, 1996, 2000). A recent source localization human study found that among healthy participants, increased baseline activity in the mPFC was associated with the development of a stronger reward bias in response to experimental feedback (Pizzagalli, Sherwood, et al., 2005). In the present study, the anhedonic participants were selected because they demonstrated impairment in their ability to process the reward value of stimuli, which suggests a potential dysfunction in the OFC and mPFC. Contrary to our predictions, no group differences in resting mPFC or OFC activity emerged from this study. We did confirm, however, predicted relationships in healthy controls between diurnal cortisol profiles and neural activity in the mPFC, specifically the ventral medial and orbital frontal PFC. Intriguingly, this association was not observed in the subclinical anhedonic group. This lack of association in the anhedonic group raises the possibility that certain functions of this region might be disrupted in anhedonia.

The lack of group differences in resting brain activity, cortisol levels, or average diurnal slope was unexpected. One possibility is that differences in brain activity between groups may emerge by engaging participants in tasks probing reinforcement learning (e.g., Pizzagalli, Jahn, & O'Shea, 2005) or distinct aspects of reward processing (e.g., anticipation vs. consumption; Dillon et al., 2008). Further, it is notable that this is not only a sub-clinical group, but a young group (college freshmen). Although we cannot conclude that the two groups differed in these neurobiological indicators, we can speculate that, within the anhedonic group, diurnal cortisol rhythm and related functions are potentially regulated by other, less efficient and less functionally specific neural systems. Accordingly, the lack of ventromedial PFC/OFC involvement may point to a less economical regulatory mechanism that may, over time, manifest itself in the development of stress-related pathology.

Additionally, no group differences emerged in Alpha band asymmetry. Previous studies found that relatively increased left PFC activity (as measured by EEG Alpha band suppression) is associated with approach-related behavior and positive affect (Davidson, Abercrombie, Nitschke, & Putnam, 1999). Additionally, studies examining EEG Alpha band activity have found that relatively greater left PFC activity was linked to reward anticipation and individual differences in reward responsivity (Miller & Tomarken, 2001; Pizzagalli, Sherwood, et al., 2005; Sobotka, Davidson, & Senulis, 1992). Although anhedonia designates a disruption in the processing of reward cues, previous studies have not found EEG Alpha abnormalities in anhedonic subjects (Pierson, Ragot, Ripoche, & Lesevre, 1987; Simons, MacMillan, & Ireland, 1982). Moreover, prior work has examined task-related EEG activity (Miller & Tomarken, 2001; Sobotka et al., 1992) or has correlated resting EEG with task performance (Pizzagalli, Sherwood, et al., 2005) in healthy controls. In the present study, we examined two resting neurophysiological states and included anhedonic subjects. Furthermore, there is evidence that anticipatory and consummatory pleasure can be clearly distinguished in animals (Berridge & Robinson, 2003) and humans (Dillon et al., 2008; Gard, Kring, Gard, Horan, & Green, 2007; Klein, 1984). The tasks used in the above studies were designed to elicit anticipatory pleasure.

It is not clear if the classification measure we used, the PAS, taps an anticipatory or a consummatory pleasure deficit. Therefore, the lack of Alpha findings may be due to methodological and conceptual differences between the present and prior studies.

When interpreting the present findings, it is critical to bear in mind that anhedonia plays an important role in various psychiatric syndromes as well as more generally in the dysregulation of affect and stress (Davidson, Putnam, & Larson, 2000; Drevets & Raichle, 1998; Park & Holzman, 1992; Weinberger, Berman, & Zec, 1986). Although we did not directly query current stressful life circumstances or events in our samples, we did find that individuals with anhedonia reported greater levels of anxiety, trait negative affect, and depression—affect states that are characterized by associations with affective dysregulation and stress. Notably, disorders characterized by anhedonia (e.g., schizophrenia and depression) also feature disruptions in PFC functioning. The subgenual PFC, for example, has been found to be hypo-active in individuals with familial-pure depressive disorder (Drevets et al., 1997) and melancholic depressive disorder (Pizzagalli et al., 2004). As the present study highlights a link between the diurnal regulation of cortisol and resting activity in the subgenual PFC, it may be important for future studies to address whether HPA abnormalities in depression are associated with subgenual PFC dysfunction. The lack of the expected links between the mPFC and neuroendocrine activity in anhedonic subjects could indicate impairment in affective regulation systems that rely on the integration of multiple physiological and psychological systems. This impairment could compromise an individual's ability to cope with and recover from a stressor, which may in turn exacerbate or lead to the development of depression or psychopathology, more broadly.

Of note, in the present study, measures of EEG and saliva sampling did not occur on the same days. Instead, the saliva sampling occurred within the same week of the EEG session. This methodological aspect can be considered an asset of this study, as the results were statistically significant—even with a time lapse between assessments. Several studies indicate significant test–retest reliability in EEG signal (Allen, Urry, Hitt, & Coan, 2004; Corsi-Cabrera et al., 2007; Debener et al., 2000; Frund, Schadow, Busch, Korner, & Herrmann, 2007) and also when investigating EEG activity in specific neural regions for resting and task-related conditions (McEvoy, Smith, & Gevins, 2000; Neuper, Grabner, Fink, & Neubauer, 2005). Additionally, there is also evidence for strong test–retest reliability of diurnal cortisol slope if averaged over 3 days or more (Kraemer et al., 2006). In this study, cortisol slope was averaged over 4 days. Therefore, we can expect that these measures are relatively stable, and our conclusions are not affected by the intended time lapse.

We were unable to control for phase of the menstrual cycle in our female participants. However, it is unlikely that this affects the validity of our results. Although there is evidence that menstrual cycle phase influences cortisol stress reactivity in laboratory stressors (for a review, see Kajantie & Phillips, 2006), it is not clear that this would affect cortisol slope averaged over the course of presumably normal days, that is, with the absence of any directly identifiable stressor. Further, in the current study, all participants were relatively the same age. Age is an important factor when interpreting cortisol levels for both men and women, but it is particularly relevant for women because levels of estrogen vary throughout the life span. The restricted age range of the present study may allow for a more accurate measurement of diurnal cortisol, in contrast to including women during different phases of their life-time reproductive cycle.

Due to the limitations of this preliminary study, the present findings should be replicated. Although the two groups differed in their relations between resting brain activity and diurnal cortisol slope, no group differences emerged with respect to brain activation or cortisol. Additionally, statistical significance levels were corrected for multiple testing within each EEGb and but not across the eight bands. Based on a paucity of prior studies in this area, we

chose to use this compromise between Type I and II errors. Saliva sampling occurred only twice per day; a more frequent measurement of cortisol levels would have provided more fine-grained information. A further limitation is the reliance on resting measures of neural function. Recent discussions indicate that resting measures may be more indicative of purposeful, but undefined, neural activity rather than reflecting a truly inactive state (Gusnard & Raichle, 2001)—thus, potentially introducing undetermined variance. Finally, as both of the study groups were selected by specific criteria, it is unclear whether the present findings generalize to other anhedonic and healthy control groups with different characteristics, for example, those selected by different measures or demographics.

Despite these limitations, the present study identified an association between mPFC activity and diurnal change of cortisol levels in a healthy control group that was absent in a subclinical anhedonic group. Both groups demonstrated an association between hippocampal/ parahippocampal activity and cortisol slope, with a nonsignificant laterality difference between the two groups. More generally, the current study used a multilevel approach that integrates measures at different levels of analyses, including self-report measures, HPA axis function, and resting neural activity. When applied to clinical samples, this integration is expected to provide new insights into the pathophysiology of mental illnesses as well as the putative disjunctions between self-reported affective experience and physiological responses.

Acknowledgments

References

Allen JJ, Urry HL, Hitt SK, Coan JA. The stability of resting frontal electroencephalographic asymmetry in depression. Psychophysiology 2004;41:269–280. [PubMed: 15032992]

Anisman H, Matheson K. Stress, depression, and anhedonia: Caveats concerning animal models. Neuroscience and Biobehavioral Reviews 2005;29:525–546. [PubMed: 15925696]

Ary JP, Klein SA, Fender DH. Location of sources of evoked scalp potentials: Corrections for skull and scalp thicknesses. IEEE Transactions on Biomedical Engineering 1981;28:447–452. [PubMed: 7287042]

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of General Psychiatry 1961;4:561–571. [PubMed: 13688369]

Berridge KC, Robinson TE. Parsing reward. Trends in Neurosciences 2003;26:507–513. [PubMed: 12948663]

Bonnet MH, Arand DL. Impact of activity and arousal upon spectral EEG parameters. Physiology & Behavior 2001;74:291–298. [PubMed: 11714491]

Brillinger, DR. Time series: Data analysis and theory. New York: McGraw-Hill; 1981.

Carrion VG, Weems CF, Ray RD, Glaser B, Hessl D, Reiss AL. Diurnal salivary cortisol in pediatric posttraumatic stress disorder. Biological Psychiatry 2002;51:575–582. [PubMed: 11950459]

Catley D, Kaell AT, Kirschbaum C, Stone AA. A naturalistic evaluation of cortisol secretion in persons with fibromyalgia and rheumatoid arthritis. Arthritis Care and Research 2000;13:51–61. [PubMed: 11094926]

Chapman JP, Chapman LJ. Reliability and the discrimination of normal and pathological groups. Journal of Nervous and Mental Disease 1983;171:658–661. [PubMed: 6631430]

Chapman, L.; Chapman, J. Revised physical anhedonia scale. D. C. Gooding, Department of Psychology; 1202 West Johnson Street, University of Wisconsin, Madison, WI 53706: 1978.

Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. Journal of Abnormal Psychology 1976;85:374–382. [PubMed: 956504]

Chapman LJ, Chapman JP, Raulin ML. Body-image aberration in schizophrenia. Journal of Abnormal Psychology 1978;87:399–407. [PubMed: 681612]

Cicchetti D, Rogosch FA. Diverse patterns of neuroendocrine activity in maltreated children. Development and Psychopathology 2001;13:677–693. [PubMed: 11523854]

Collins D, Neelin P, Peters T, Evans A. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. Journal of Computer Assisted Tomography 1994;18:192–205. [PubMed: 8126267]

Corsi-Cabrera M, Galindo-Vilchis L, del-Rio-Portilla Y, Arce C, Ramos-Loyo J. Within-subject reliability and intersession stability of EEG power and coherent activity in women evaluated monthly over nine months. Clinical Neurophysiology 2007;118:9–21. [PubMed: 17055781]

Cox RW. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Computers and Biomedical Research 1996;29:162–173. [PubMed: 8812068]

Davidson RJ. Anterior electrophysiological asymmetries, emotion, and depression: Conceptual and methodological conundrums. Psychophysiology 1998;35:607–614. [PubMed: 9715104]

Davidson RJ, Abercrombie H, Nitschke JB, Putnam K. Regional brain function, emotion and disorders of emotion. Current Opinion in Neurobiology 1999;9:228–234. [PubMed: 10322186]

Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: Perspectives from affective neuroscience. Annual Review of Psychology 2002;53:545–574.

Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation—A possible prelude to violence. Science 2000;289:591–594. [PubMed: 10915615]

Debener S, Beauducel A, Nessler D, Brocke B, Heilemann H, et al. Is resting anterior EEG alpha asymmetry a trait marker for depression? Findings for healthy adults and clinically depressed patients. Neuropsychobiology 2000;41:31–37. [PubMed: 10629433]

Dillon DG, Holmes AJ, Jahn AL, Bogdan R, Wald LL, Pizzagalli DA. Dissociation of neural regions associated with anticipatory versus consummatory phases of incentive processing. Psychophysiology 2008;45:36–49. [PubMed: 17850241]

Diorio D, Viau V, Meaney MJ. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary- adrenal responses to stress. Journal of Neuroscience 1993;13:3839–3847. [PubMed: 8396170]

Drevets W, Price J, Simpson J, Todd R, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386:824–827. [PubMed: 9126739]

Drevets W, Raichle M. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: Implications for interactions between emotion and cognition. Cognition and Emotion 1998;12:353–385.

Eckblad M, Chapman LJ. Magical ideation as an indicator of schizotypy. Journal of Consulting and Clinical Psychology 1983;51:215–225. [PubMed: 6841765]

Eckblad, M.; Chapman, L.; Chapman, J.; Mishlove, M. The revised social anhedonia scale. 1982. Unpublished test

Evans AC, Collins DL, Mills SR, Brown ED, Kelly RL, Peters TM. 3D statistical neuroanatomical models from 305 MRI volumes. Proceedings IEEE Nuclear Science Symposium and Medical Imaging Conference 1993;95:1813–1817.

Ferguson ML, Katkin ES. Visceral perception, anhedonia, and emotion. Biological Psychology 1996;42:131–145. [PubMed: 8770375]

First, M.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). Arlington, VA: American Psychiatric Press; 1997. Clinical Version

Fisher RA. On the probable error of a coefficient of correlation deduced from a small sample. Metron 1921;1:3–32.

Fitzgibbons L, Simons RF. Affective response to color-slide stimuli in subjects with physical anhedonia: A three-systems analysis. Psychophysiology 1992;29:613–620. [PubMed: 1461952]

Frund I, Schadow J, Busch NA, Korner U, Herrmann CS. Evoked gamma oscillations in human scalp EEG are test-retest reliable. Clinical Neurophysiology 2007;118:221–227. [PubMed: 17126070]

Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: Distinctions between anticipatory and consummatory pleasure. Schizophrenia Research 2007;93:253– 260. [PubMed: 17490858]

Gooding DC, Davidson RJ, Putnam KM, Tallent KA. Normative emotion-modulated startle response in individuals at risk for schizophrenia-spectrum disorders. Schizophrenia Research 2002;57:109–120. [PubMed: 12165381]

Gunnar MR, Vazquez DM. Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. Development and Psychopathology 2001;13:515– 538. [PubMed: 11523846]

Gusnard DA, Raichle ME. Searching for a baseline: Functional imaging and the resting human brain. Nature Reviews Neuroscience 2001;2:685–694.

Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology 2004;29:1765–1781. [PubMed: 15213704]

Horan WP, Kring AM, Blanchard JJ. Anhedonia in schizophrenia: A review of assessment strategies. Schizophrenia Bulletin 2006;32:259–273. [PubMed: 16221997]

Hurley-Gius KM, Neafsey EJ. The medial frontal cortex and gastric motility: Microstimulation results and their possible significance for the overall pattern of organization of rat frontal and parietal cortex. Brain Research 1986;365:241–248. [PubMed: 3947992]

Jacobs N, Myin-Germeys I, Derom C, Delespaul P, van Os J, Nicolson NA. A momentary assessment study of the relationship between affective and adrenocortical stress responses in daily life. Biological Psychology 2007;74:60–66. [PubMed: 16942831]

Kajantie E, Phillips DI. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology 2006;31:151–178. [PubMed: 16139959]

Kirschbaum C, Hellhammer D. Response variability of salivary cortisol under psychological stimulation. Journal of Clinical Chemistry and Clinical Biochemistry 1989;27:237.

Klein, DF. Depression and anhedonia. In: Clark, DC.; Fawcett, J., editors. Anhedonia and affect deficit states. New York: PMA Publishing; 1984. p. 1-14.

Kraemer HC, Giese-Davis J, Yutsis M, O'Hara R, Neri E, Gallagher-Thompson D, et al. Design decisions to optimize reliability of daytime cortisol slopes in an older population. American Journal of Geriatric Psychiatry 2006;14:325–333. [PubMed: 16582041]

Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbito-frontal cortex: Evidence from neuroimaging and neuropsychology. Progress in Neurobiology 2004;72:341–372. [PubMed: 15157726]

Loas G. Vulnerability to depression: A model centered on anhedonia. Journal of Affective Disorders 1996;41:39–53. [PubMed: 8938204]

MacLullich AM, Ferguson KJ, Wardlaw JM, Starr JM, Deary IJ, Seckl JR. Smaller left anterior cingulate cortex volumes are associated with impaired hypothalamic-pituitary-adrenal axis regulation in healthy elderly men. Journal of Clinical Endocrinology and Metabolism 2006;91:1591–1594. [PubMed: 16464941]

Matthews K, Schwartz J, Cohen S, Seeman T. Diurnal cortisol decline is related to coronary calcification: CARDIA study. Psychosomatic Medicine 2006;68:657–661. [PubMed: 17012518]

McEvoy LK, Smith ME, Gevins A. Test-retest reliability of cognitive EEG. Clinical Neurophysiology 2000;111:457–463. [PubMed: 10699407]

Meaney MJ, Aitken DH. [3H]Dexamethasone binding in rat frontal cortex. Brain Research 1985;328:176–180. [PubMed: 3971175]

Meehl PE. Hedonic capacity: Some conjectures. Bulletin of the Menninger Clinic 1975;39:295–307. [PubMed: 1156704]

Meng X, Rosenthal R, Rubin D. Comparing correlated correlation coefficients. Psychological Bulletin 1992;111:172–175.

Miller A, Tomarken AJ. Task-dependent changes in frontal brain asymmetry: Effects of incentive cues, outcome expectancies, and motor responses. Psychophysiology 2001;38:500–511. [PubMed: 11352139]

Miller GA. How we think about cognition, emotion, and biology in psychopathology. Psychophysiology 1996;33:615–628. [PubMed: 8961782]

Moos RH, Cronkite RC. Symptom-based predictors of a 10-year chronic course of treated depression. Journal of Nervous and Mental Disease 1999;187:360–368. [PubMed: 10379723]

Mulert C, Jager L, Schmitt R, Bussfeld P, Pogarell O, Moller HJ, et al. Integration of fMRI and simultaneous EEG: Towards a comprehensive understanding of localization and time-course of brain activity in target detection. NeuroImage 2004;22:83–94. [PubMed: 15109999]

Neuper C, Grabner RH, Fink A, Neubauer AC. Long-term stability and consistency of EEG event-related (de-)synchronization across different cognitive tasks. Clinical Neurophysiology 2005;116:1681–1694. [PubMed: 15922658]

Oakes TR, Pizzagalli DA, Hendrick AM, Horras KA, Larson CL, Abercrombie HC, et al. Functional coupling of simultaneous electrical and metabolic activity in the human brain. Human Brain Mapping 2004;21:257–270. [PubMed: 15038007]

Ongur D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cerebral Cortex 2000;10:206–219. [PubMed: 10731217]

Ottowitz WE, Dougherty DD, Sirota AD, Niaura R, Rauch SL, Brown WA. Cognitive and affective probes of the HPA axis: A SPECT study. Brain and Cognition 2004;54:138–140. [PubMed: 15025037]

Park S, Holzman PS. Schizophrenics show spatial working memory deficits. Archives of General Psychiatry 1992;49:975–982. [PubMed: 1449384]

Pascual-Marqui RD, Lehmann D, Koenig T, Kochi K, Merlo MC, Hell D, et al. Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. Psychiatry Research 1999;90:169–179. [PubMed: 10466736]

Pascual-Marqui RD, Michel CM, Lehmann D. Low resolution electromagnetic tomography: A new method for localizing electrical activity in the brain. International Journal of Psychophysiology 1994;18:49–65. [PubMed: 7876038]

Perrin F, Pernier J, Bertrand O, Echallier JF. Spherical splines for scalp potential and current density mapping. Electroencephalography and Clinical Neurophysiology 1989;72:184–187. [PubMed: 2464490]

Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. NeuroImage 2002;16:331–348. [PubMed: 12030820]

Pierson A, Ragot R, Ripoche A, Lesevre N. Electrophysiological changes elicited by auditory stimuli given a positive or negative value: A study comparing anhedonic with hedonic subjects. International Journal of Psychophysiology 1987;5:107–123. [PubMed: 3610727]

Pizzagalli, DA. Electroencephalography and high-density electrophysiological source localization. In: Cacioppo, JT.; Tassinaru, LG.; Berntson, GG., editors. Handbook of psychophysiology. Vol. 3. Cambridge, UK: Cambridge University Press; 2007. p. 56-84.

Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. Biological Psychiatry 2005;57:319–327. [PubMed: 15705346]

Pizzagalli DA, Nitschke JB, Oakes TR, Hendrick AM, Horras KA, Larson CL, et al. Brain electrical tomography in depression: The importance of symptom severity, anxiety, and melancholic features. Biological Psychiatry 2002;52:73–85. [PubMed: 12113998]

Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, et al. Anterior cingulate activity as a predictor of degree of treatment response in major depression: Evidence from brain electrical tomography analysis. American Journal of Psychiatry 2001;158:405–415. [PubMed: 11229981]

Pizzagalli DA, Oakes TR, Fox AS, Chung MK, Larson CL, Abercrombie HC, et al. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Molecular Psychiatry 2004;9:393–405.

Pizzagalli DA, Sherwood RJ, Henriques JB, Davidson RJ. Frontal brain asymmetry and reward responsiveness: A source-localization study. Psychological Science 2005;16:805–813. [PubMed: 16181444]

Polk DE, Cohen S, Doyle WJ, Skoner DP, Kirschbaum C. State and trait affect as predictors of salivary cortisol in healthy adults. Psychoneuroendocrinology 2005;30:261–272. [PubMed: 15511600]

Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, von Auer K, Jobst S, et al. Free cortisol levels after awakening: A reliable biological marker for the assessment of adrenocortical activity. Life Sciences 1997;61:2539–2549. [PubMed: 9416776]

Rohleder N, Wolf JM, Piel M, Kirschbaum C. Impact of oral contraceptive use on glucocorticoid sensitivity of pro-inflammatory cytokine production after psychosocial stress. Psychoneuroendocrinology 2003;28:261–273. [PubMed: 12573295]

Rolls ET. The orbitofrontal cortex. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 1996;351:1433–1443.

Rolls ET. The orbitofrontal cortex and reward. Cerebral Cortex 2000;10:284–294. [PubMed: 10731223]

Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Archives of General Psychiatry 2000;57:925–935. [PubMed: 11015810]

Sarrieau A, Dussaillant M, Sapolsky RM, Aitken DH, Olivier A, Lal S, et al. Glucocorticoid binding sites in human temporal cortex. Brain Research 1988;442:157–160. [PubMed: 3359250]

Schmidt LA, Fox NA, Goldberg MC, Smith CC, Schulkin J. Effects of acute prednisone administration on memory, attention and emotion in healthy human adults. Psychoneuroendocrinology 1999;24:461–483. [PubMed: 10341371]

Simons RF, MacMillan FW 3rd, Ireland FB. Anticipatory pleasured deficit in subjects reporting physical anhedonia: Slow cortical evidence. Biological Psychology 1982;14:298–310. [PubMed: 7126726]

Smider NA, Essex MJ, Kalin NH, Buss KA, Klein MH, Davidson RJ, et al. Salivary cortisol as a predictor of socioemotional adjustment during kindergarten: A prospective study. Child Development 2002;73:75–92. [PubMed: 14717245]

Sobotka SS, Davidson RJ, Senulis JA. Anterior brain electrical asymmetries in response to reward and punishment. Electroencephalography and Clinical Neurophysiology 1992;83:236–247. [PubMed: 1382945]

Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. Biological Psychiatry 2003;54:269–282. [PubMed: 12893103]

Spijker J, de Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. Determinants of persistence of major depressive episodes in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Journal of Affective Disorders 2004;81:231–240. [PubMed: 15337327]

Steptoe A, Gibson EL, Hamer M, Wardle J. Neuroendocrine and cardiovascular correlates of positive affect measured by ecological momentary assessment and by questionnaire. Psychoneuroendocrinology 2007;32:56–64. [PubMed: 17157442]

Steptoe A, Wardle J, Marmot M. Positive affect and health-related neuroendocrine, cardiovascular, and inflammatory processes. Proceedings of the National Academy of Sciences, USA 2005;102:6508–6512.

Terreberry RR, Neafsey EJ. Rat medial frontal cortex: A visceral motor region with a direct projection to the solitary nucleus. Brain Research 1983;278:245–249. [PubMed: 6315155]

Tops M, Wijers AA, van Staveren ASJ, Bruin KJ, Den Boer JA, Meijman TF, et al. Acute cortisol administration modulates EEG alpha asymmetry in volunteers: Relevance to depression. Biological Psychology 2005;69:181–193. [PubMed: 15804545]

Towle VL, Bolanos J, Suarez D, Tan K, Grzeszczuk R, Levin DN, et al. The spatial location of EEG electrodes: Locating the best-fitting sphere relative to cortical anatomy. Electroencephalography and Clinical Neurophysiology 1993;86:1–6. [PubMed: 7678386]

Tucker DM. Spatial sampling of head electrical fields: The geodesic sensor net. Electroencephalography and Clinical Neurophysiology 1993;87:154–163. [PubMed: 7691542]

Urry HL, van Reekum CM, Johnstone T, Kalin NH, Thurow ME, Schaefer HS, et al. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. Journal of Neuroscience 2006;26:4415–4425. [PubMed: 16624961]

Vermetten E, Bremner JD. Circuits and systems in stress. I. Preclinical studies. Depression and Anxiety 2002;15:126–147. [PubMed: 12001181]

Watson, D.; Clark, LA. Mood and anxiety symptom questionnaire. University of Iowa; 1991. Unpublished manuscript

Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. Journal of Personality and Social Psychology 1988;54:1063–1070. [PubMed: 3397865]

Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. Archives of General Psychiatry 1986;43:114–124. [PubMed: 3947207]

Worrell GA, Lagerlund TD, Sharbrough FW, Brinkmann BH, Busacker NE, Cicora KM, et al. Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. Brain Topography 2000;12:273–282. [PubMed: 10912735]

Xiong J, Gao J, Lancaster J, Fox P. Clustered pixels analysis for functional MRI activation studies of the human brain. Human Brain Mapping 1995;3:287–301.

Young E, Haskett RGL, Pande A, Weinberg V, Watson S. Increased evening activation of the hypothalamic-pituitary-adrenal axis in depressed patients. Archives of General Psychiatry 1994;51:701–707. [PubMed: 8080346]

Zumsteg D, Friedman A, Wennberg RA, Wieser HG. Source localization of mesial temporal interictal epileptiform discharges: Correlation with intracranial foramen ovale electrode recordings. Clinical Neurophysiology 2005;116:2810–2818. [PubMed: 16253551]
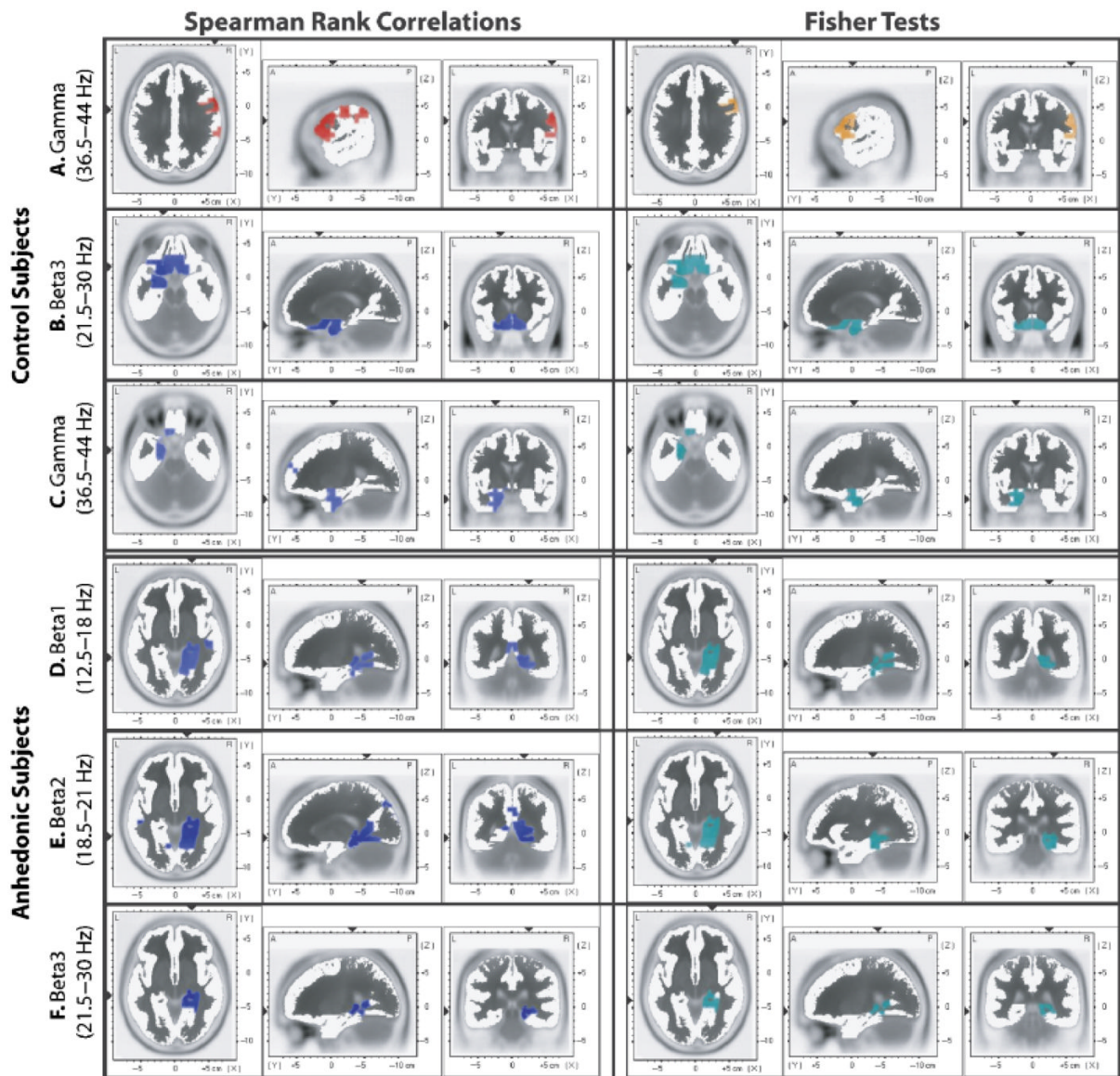
Figure 1.
Two-dimensional slices (axial, sagittal, and coronal orientations) showing thresholded (*p*<.01, |rho| ≥ .47) results of voxelwise Spearman's rho correlations between current density and cortisol slope for the target group (left column). Also shown are two-dimensional slices thresholded at *p*<.05 from Fisher's tests contrasting independent correlations between the two groups (right column). In the left column, significant negative associations are shown in blue and indicate that current density is associated with steeper diurnal cortisol decline; significant positive associations are shown in red and indicate that current density is associated with flatter cortisol slope. In the right column, orange colors denote voxels in which controls (a) had significantly more positive rho values compared to anhedonic participants. Green values denote voxels in which controls (b,c) had significantly more negative rho values or anhedonic participants (d–f) had significantly more negative rho values. Results are restricted to hypothesized regions that were predicted a priori and where clusters are greater in size than 10 contiguous voxels. a: Results for the Gamma band in the control group (left column) and control group–anhedonic group (right column) in a region in the right inferior frontal gyrus and

precentral gyrus. b,c: Results for the Beta3 (b) and the Gamma (c) bands in the control group (left column) and control group–anhedonic group (right column) in a region in a left hemisphere and medial region encompassing the hippocampus, parahippocampal gyrus, medial PFC, and OFC. d–f: Results for the Beta1 (d); Beta2 (e); and Beta3 (f) bands in the anhedonic group (left column) and anhedonic group–control group (right column) in a region in the right hippocampus and parahippocampal gyrus.
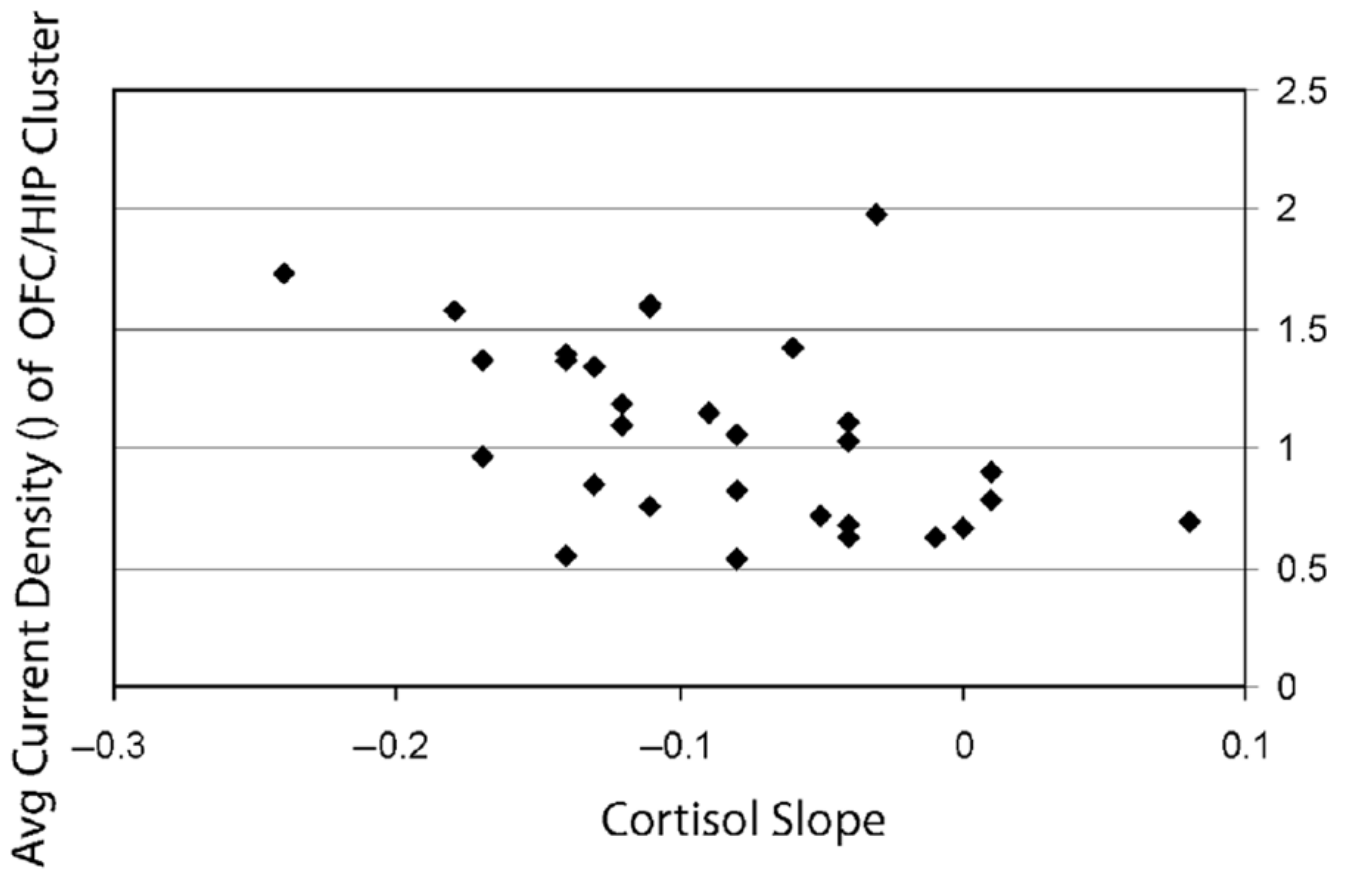
Figure 2.
Scatter plot for the control group of cortisol slope and averaged current density of Beta3
activity, normalized with the grand mean, in the OFC/HIP cluster (Cluster 2).

Table 1

Cluster Information Presented for Group and Band[a]

Cluster	Hemisphere	Rho		X	Y	ZBand	Region	Brodmann's Areas	No. voxels
		Control	Anhedonic						
A. Clusters identified in control group analysis									
1	Right	.54	.16	60	−4	29Gamma	inferior frontal gyrus; precentral gyrus	9, 6/4	30
2	Left/Medial	−.52	−.06	−17	17	−20Beta3	inferior frontal gyrus; rectal gyrus; middle frontal gyrus; parahippocampal gyrus; hippocampus	11, 25, 37, 47	75
B. Clusters identified in anhedonic group analysis									
3	Right	−.49	.09	−24	−4	−27Gamma	parahippocampal gyrus; hippocampus	28/37	25
		.11	−.57	25	−46	−6Beta1	lingual gyrus; parahippocampal gyrus; hippocampus	19, 27/30/37	39
		.14	−.51	18	−53	−6Beta2	lingual gyrus; parahippocampal gyrus; posterior cingulate	18/19, 27/30/37, 29/30	40
		.07	−.48	25	−39	−6Beta3	parahippocampal gyrus; hippocampus	19/30/37	18

[a]Coordinates are the center of the cluster; rhos are averaged across the cluster.