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**Repeated cortisol administration attenuates the EEG response to buspirone in healthy volunteers: Evidence for desensitization of the 5-HT1A autoreceptor**

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**Short title:** Cortisol and somatodendritic 5-HT1A receptors

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ABSTRACT

It has previously been postulated that the therapeutic effect of antidepressants, particularly selective serotonin re-uptake inhibitors (SSRIs), is mediated by a down-regulation of somatodendritic (presynaptic) 5-HT$_{1A}$ autoreceptors with chronic treatment. Animal studies have revealed that repeated administration of corticosteroids similarly down-regulate this receptor. However, it has previously been difficult to explore if this receptor is similarly modulated in man in vivo. The objective of this study was to explore the effect of repeated administration of cortisol to healthy volunteers utilising a novel putative index of somatodendritic 5-HT$_{1A}$ autoreceptor function. This method involves the administration of the 5-HT$_{1A}$ agonist buspirone and observing the subsequent negative shift in the frequency spectrum of the electroencephalogram (EEG). Healthy male volunteers were treated with cortisol 20 mg, or placebo, orally twice daily for seven days in a double-blind random-order cross-over study. After each treatment period volunteers were administered buspirone 30 mg orally prior to EEG recordings. Following a week’s treatment with placebo, buspirone led to a negative shift in the EEG frequency spectrum as previously reported. However following treatment with cortisol, the effect of buspirone was significantly attenuated. This is consistent with corticosteroids having a similar effect on somatodendritic 5-HT$_{1A}$ autoreceptors in man as seen in rodents.

Key words: Cortisol, EEG, 5-HT$_{1A}$ receptors, buspirone
INTRODUCTION

Corticosteroid hormones (cortisol in man and corticosterone in rodents) mediate the body’s response to physical and psychological stressors. The actions of these hormones on neurotransmitter systems in the brain may impact on cognitive performance and mental health. Indeed it has long been postulated that cortisol plays an aetiological role in mood disorders (Dinan, 1994; McAllister-Williams et al., 1998). In animal studies corticosteroids have been shown to have several effects on elements of the central 5-HT neurotransmitter system including attenuation of 5-HT_{1A} receptor function. 5-HT_{1A} receptors are located both as autoreceptors on the somata and dendrites of serotonin containing neurones in the raphe nuclei and postsynaptically on cells throughout the forebrain (Burnet et al., 1995; Azmitia et al., 1996; Pasqualetti et al., 1996). Activation of somatodendritic 5-HT_{1A} autoreceptors plays a key role in determining the activity of the entire serotonergic system both in terms of firing activity (Aghajanian and VanderMaelen, 1982; McAllister-Williams and Kelly, 1995) and the release of 5-HT in terminal areas (Sharp et al., 1993). With this in mind, it is of particular interest that repeated administration of corticosteroids has been consistently shown to attenuate somatodendritic 5-HT_{1A} receptor function in rodent studies (Young et al., 1992; Young et al., 1994a; Laaris et al., 1995; McAllister-Williams et al., 2001; Man et al., 2002; McAllister-Williams et al., 1999; Fairchild et al., 2003). This effect is also seen with endogenous increases in circulating corticosteroids in response to stress (Laaris et al., 1997).

The examination of brain 5-HT receptor function in man *in vivo* is difficult. Neuroendocrine challenge test have been widely used to probe postsynaptic 5-HT_{1A} and 5-HT_{2} receptors in the hypothalamus and pituitary. The hypothermic response to 5-HT_{1A}
receptor agonists can also be used as an index of 5-HT\textsubscript{1A} receptor function and it has been shown that repeated cortisol administration to healthy volunteers attenuates the hypothermic response to buspirone (Young et al., 1994b) in line with findings in rodents. However, there is continuing controversy concerning the somatodendritic or postsynaptic location of receptors mediating this effect (Blier et al., 2002). An alternative method of assessing the functional status of the somatodendritic 5-HT\textsubscript{1A} receptor in man in vivo may be the effect of the 5-HT\textsubscript{1A} receptor agonist buspirone on the EEG frequency spectrum (McAllister-Williams and Massey, 2003).

There are consistent findings that buspirone administration to healthy humans leads to negative shift of the awake EEG frequency spectrum in man (due to an increase in theta and decrease in alpha activity) (Murasaki et al., 1989; Barbanoj et al., 1994; Holland et al., 1994; Anderer et al., 2000). Although buspirone is a relatively non-selective drug, and its systemic administration makes the localization of effects difficult, several pieces of evidence indicate that this negative shift may be mediated by somatodendritic 5-HT\textsubscript{1A} receptors. Firstly, the EEG frequency effects are mimicked by other more selective 5-HT\textsubscript{1A} partial agonists in man (Saito et al., 1993; Anderer et al., 2000) and is seen in animals following administration of buspirone as well as the highly selective full 5-HT\textsubscript{1A} receptor agonist 8-OH-DPAT (Bogdanov and Bogdanov, 1994). Secondly, source localization of the effect of buspirone using low resolution electromagnetic tomographic analysis (LORETA) demonstrates a significant increase in theta EEG activity in the hippocampus as well as neighbouring cortical areas (Anderer et al., 2000). Hippocampal theta activity is well known to be under ascending serotonergic control (Vertes, 1982). Animal studies using local application of 8-OH-DPAT into the raphe have indicated that
activation of somatodendritic 5-HT\textsubscript{1A} receptors causes a decrease in hippocampal theta (Vertes et al., 1994; Nitz and McNaughton, 1999), an effect blocked by 5-HT\textsubscript{1A} antagonists (Marrosu et al., 1996). Thirdly, a somatodendritic location for a 5-HT\textsubscript{1A} receptor mediated negative shift in the EEG frequency spectrum in man is also inferred from findings of acute administration of SSRIs causing such a shift (Saletu et al., 1986) and that pindolol mimics, rather than blocks, the effect of buspirone on the awake EEG (McAllister-Williams and Massey, 2003). Following acute administration, SSRIs increase concentrations of 5-HT in the raphe nuclei leading to somatodendritic 5-HT\textsubscript{1A} activation (Bel and Artigas, 1992); pindolol acts as a 5-HT\textsubscript{1A} antagonist at postsynaptic receptors but a partial agonist at somatodendritic receptors (Clifford et al., 1998). Taken together, these data support the hypothesis that the effect of buspirone on the EEG frequency spectrum is a potential index of somatodendritic 5-HT\textsubscript{1A} receptor function.

The aim of this study was to examine whether repeated corticosteroid administration attenuates somatodendritic 5-HT\textsubscript{1A} receptor function in man. The \textit{a priori} hypothesis was that cortisol administration would lead to an attenuation of somatodendritic 5-HT\textsubscript{1A} receptor function as indexed by a reduction in the buspirone induced negative shift in the EEG frequency spectrum.

**METHODS AND MATERIALS**

**Subjects**

Twenty four healthy male subjects aged between 18 and 33 years (mean ± SD: 24 ± 3.8) gave written informed consent to participate in the study, which had been approved by the
Newcastle and North Tyneside Local Research Ethics Committee in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects were free of significant past or present physical illness and had received no medication for at least 2 months prior to their participation. They were screened to exclude significant current, past or family history of psychiatric illness. In addition, the volunteers were all right handed, within a weight range of 70-100 kg, and had not experienced previous adverse reactions to steroids.

**Experimental procedure and medication**

Subjects were tested on two separate occasions at least three weeks apart to minimise any potential carry over effects of cortisol treatment. Prior to each testing session they were treated with hydrocortisone 20mg twice daily or placebo in a double-blind cross-over, random, balanced-order fashion over the course of the preceding week. Treatment started in the evening of "day 1" at approximately 2100 hours and finished with a 14\textsuperscript{th} dose at approximately 0800 hours on "day 8". Following their first void of urine on day 7, subjects collected their urine for 24 hours, up to and including their first void on day 8.

Subjects attended the research laboratory at 1200 hours and were given a light lunch and a drink prior to testing. They subsequently completed a short computer-based cognitive task (to assess executive function and published elsewhere (McAllister-Williams et al., 2002)). Volunteers were given free access to drinking water but were otherwise fasted during the experiment. At baseline (approximately 1300 hours) a blood sample was obtained, a number of visual analogue scales (VASs) completed, and EEG recorded with subjects sitting in front of a computer monitor with a fixation point displayed in the centre.
Following baseline measurements, buspirone 30mg was administered orally. Three further sets of measurements (VAS and EEG recording) were conducted at half hourly intervals for 90 minutes ($t = 30, 60$ and $90$ min).

**EEG recordings and analysis**

EEG recordings and analysis were as previously described (McAllister-Williams and Massey, 2003). Briefly, EEG was recorded from 29 silver/silver chloride electrodes positioned on the scalp using an elasticated cap (Easy Caps, Germany) and sited in accordance with the International 10-20 system (American Electroencephalographic Society, 1994). Further electrodes were placed on the right and left mastoid processes. All channels were recorded relative to the left mastoid. Vertical electro-occulograms (VEOG) was recorded between electrodes placed on the nazion and electrodes below the centre of each eye. Horizontal EOG (HEOG) was recorded between electrodes placed on the outer canthus of the eyes. EEG and EOG were filtered with a bandpass of $0.1 - 100$ Hz and sampled at a rate of 400 points per second. At each recording time point, subjects were instructed to keep their eyes open and to maintain their gaze on the fixation point (a red cross) displayed on a computer monitor, remain still and relaxed, and to keep their minds as blank as possible for three 3 minute periods interspersed with 30 second rest intervals between. Ten minutes of continuous EEG was acquired during this period.

A standardised EEG analysis procedure was followed using Neuroscan Scan 4.1 software (Neurosoft Inc. USA). This included blink-correction (Semlitsch et al., 1986) and a principle component analysis (PCA) to remove any visible ECG artefact. Data was algebraically re-referenced to represent recordings from average mastoid reference and...
epoched into segments 10.24 seconds long. Any epoch in which any channel, except VEOG, had a voltage deflection greater than ±75 µV was excluded. Remaining epochs underwent Fast Fourier Transformation (FFT) and were averaged together. The precision of the FFT was 0.098 Hz. Potential shifts in the EEG frequency spectrum were assessed by calculating the centroid frequency between 6 and 10.5 Hz (Anderer et al., 1993; McAllister-Williams and Massey, 2003). This standardised analysis protocol is associated with extremely high test-retest reliability (McAllister-Williams and Massey, 2003).

**Visual Analogue Scales**

Visual analogue scales (VASs) consisted of 100 mm scales on which subjects rated "depression", "drowsiness", "restlessness", "nausea" and "lightheadedness", with "the most severe possible" at one end and "not at all" at the other.

**Cortisol Assays**

Baseline blood samples were taken into EDTA tubes, centrifuged at 3,000 rpm for 10 minutes and plasma removed and stored at -20°C. Samples were analysed for cortisol using radioimmunoassay kits (Immuno Diagnostic Systems Ltd, Boldon, Tyne and Wear, UK). Intra- and inter-assay coefficients of variation for the assay were 8.1% and 8.5% respectively. Subjects collected their 24 hr urine samples into 2 litre bottles containing 5g of boric acid. The cortisol level of an aliquot of the urine was assayed using a similar radioimmunoassay to that used for the plasma samples. The intra- and inter-assay coefficients of variation were 14.0% and 12.8% respectively.

**Statistical analysis**
SPSS (version 11.0, Chicago, Illinois) was used throughout. For the analysis of the shift in EEG frequency spectrum, the change in centroid frequency, calculated between 6 and 10.5 Hz, over the 90 minutes following buspirone administration was quantified as an area under the curve (AUC) at t = 30, 60 and 90 minutes relative to that at t = 0 minutes (i.e. subtraction of the baseline extrapolated from t0) using the trapezoid method. The primary outcome measure was the AUC for data recorded at the CZ electrode only (in line with the published methodology (McAllister-Williams and Massey, 2003). The effect of pre-treatment with cortisol versus placebo on the AUC measurement was compared using a two-tailed paired t-test. ANOVA was also performed as a secondary outcome measure on the change in centroid time series data with within subject factors of “treatment” (cortisol vs placebo) and “time” (30, 60 and 90 min.). The AUC data from all 29 active electrode sites was analysed using a repeated measures ANOVA employed within subject factors of “treatment” and “electrode site”. VAS data was analysed with within subject factors of “treatment” and “time”. In addition, possible correlations between 24 hour urinary cortisol concentrations and the EEG responses to buspirone administration were assessed using the Spearman’s rank correlation coefficient.

The Kolmogorov-Smirnov test was applied to all data. This revealed no significant departure from normality of the centroid frequency, AUC values, or urinary free cortisol concentrations. VAS data did however deviate from normality as did log transformed values, though less so. All ANOVA analyses incorporated the Greenhouse-Geisser correction for inhomogeneity of covariance, with F ratios reported with corrected degrees of freedom. All values are quoted as mean ± SD.
RESULTS

Subjects

Of the 24 subjects recruited to the study, four had to withdraw during the first visit due to intolerance of the side effects of buspirone (three with lightheadedness or nausea and one vomiting). One subject with extremely low 24-hour urinary free cortisol levels following cortisol pre-treatment and was excluded from the analysis (see below for details). Data from a further two subjects were excluded due to their EEG being heavily contaminated with movement artifacts. Data for the remaining seventeen subjects are presented.

Subjects scored a mean (± SD) of 0.1 ± 0.3 on the Hamilton Depression Rating Scale (18-item; HDRS; range: 0-1) and 0.9 ± 1.3 on the Beck Depression Inventory (BDI; range: 0-4). Mean full scale IQ was estimated at 114 ± 6.5 using the National Adult Reading Test (NART; range: 100-123). Subjects weighed 82.3 ± 9.2 kg with a body mass index of 25.0 ± 2.5 (range 22.0 - 30.3).

Baseline plasma and 24 hour urinary cortisol concentrations

Urinary free cortisol concentrations were significantly increased following cortisol pre-treatment relative to placebo (cortisol: 556 ± 187 nmol/l; placebo: 240 ± 82 nmol/l; t (16) = -7.52, p < 0.001). The subject that was excluded from the analysis on the basis of their urinary cortisol concentration had a level of 61 nmol/l, which was more than two standard deviations below the group mean following cortisol pre-treatment, and substantially lower than the value observed for the same subject following placebo pre-treatment (260
nmol/L). This was the only subject who did not show an increase between the placebo and cortisol arms of the study (figure 1).

Baseline plasma cortisol concentrations prior to the administration of buspirone (at approximately 1300 hours) were not statistically different (placebo: 306 ± 23 nmol/L; cortisol: 348 ± 53 nmol/L, t(13) = -0.72, p > 0.1).

Effect of cortisol pre-treatment on buspirone EEG effects

Following placebo pre-treatment buspirone administration caused a decrease in the centroid frequency. When subjects were pre-treated with cortisol this effect of buspirone was attenuated (figure 2). The *a priori* defined primary outcome measure, the AUC for the centroid frequency for t = 30, 60 and 90 minutes relative to the value at t = 0 minutes, was significantly less negative following cortisol compared to placebo pre-treatment (-0.37 ± 14.85 vs -7.34 ± 15.93 Hz.min; t(16) = -2.14, p < 0.05). The baseline centroid frequency values at t = 0 minutes recorded at Cz did not significantly differ between the two treatment arms (8.19 ± 0.31 Hz vs 8.11 ± 0.35 Hz, placebo vs cortisol; t(16) = 1.79, p > 0.05). Repeated measures ANOVA of the change in centroid frequency from t = 0 at t = 30, 60 and 90 minutes revealed a significant main effect of cortisol versus placebo pre-treatment (F(1,16) = 4.52, p < 0.05) but there was no treatment by time interaction. To
explore if the decrease in AUC following cortisol pre-treatment simply reflected an effect of cortisol on the baseline centroid frequency rather than an effect of cortisol on the buspirone EEG response, the correlation between baseline centroid frequency and AUCs was examined (figure 3). This revealed no significant correlation between the baseline centroid frequency and AUC for the change following buspirone administration recorded after either placebo or cortisol pre-treatment, or when all data was combined.

Figure 3 near here

The topography of the effect of cortisol pre-treatment on the baseline centroid frequency was examined by conducting repeated measures ANOVA on the data from all 29 electrode sites. This revealed a trend for a main effect of cortisol pre-treatment (F(1,16 = 4.14, p < 0.1) but no treatment by site interaction. Likewise ANOVA of AUC data across the head revealed a trend for an effect of cortisol pre-treatment (F(1,16) = 3.52, p < 0.1) but again no treatment by site interaction. This suggests the effects of cortisol pre-treatment do not modulate the topography of the buspirone EEG effects.

Effect of cortisol pre-treatment on buspirone induced subjective effects

Repeated measures ANOVA of the log transformed data from individual VAS scales found no effect of pre-treatment, time or pre-treatment by time interaction for the "depressed", "drowsy" and "restless" scales, indicating a lack of effect of buspirone and cortisol pre-treatment. However, there was a significant effect of time for both the "nausea" and "lightheadedness" scales (F(2.1,31.7) = 9.10, p < 0.001 and F(2.4,36.3) = 5.27, p < 0.005 respectively) due to buspirone increasing these symptoms. Nevertheless, once again there
was no effect of cortisol pre-treatment or pre-treatment by time interaction for either of these two scales.

**DISCUSSION**

The aim of the present study was to examine the effect of repeated cortisol administration on somatodendritic 5-HT\textsubscript{1A} receptor function in healthy volunteers. Healthy young men were treated with cortisol or placebo in a cross over design and the EEG response (frequency shift) to buspirone was used as a marker of somatodendritic 5-HT\textsubscript{1A} receptor function. We found that buspirone caused a negative shift in EEG frequency spectrum and that cortisol treatment attenuated this effect. The data are consistent with the *a priori* hypothesis that repeated administration of cortisol decreases somatodendritic 5-HT\textsubscript{1A} receptor function and are consistent with data from rodent studies showing similar effects.

**The cortisol treatment paradigm**

In exploring whether alterations in corticosteroid concentrations may have an effect on somatodendritic 5-HT\textsubscript{1A} function in man, clearly the choice of cortisol administration paradigm is important. Here we used repeated administration for one week and ensured that testing was performed long enough after the last dose so that subjects were normocortisolaemic. We used 24h urinary free cortisol as a measure of the ability of cortisol administration to raise circulating cortisol. Previous studies (Young et al., 1999; McAllister-Williams and Rugg, 2002) using this paradigm of administration found 24h urinary cortisol was markedly elevated at the end of the cortisol arm of treatment relative to the placebo arm. We were also able to use this measure as an indicator of subject compliance and identified one individual who apparently had not been taking his
medication as directed. Plasma cortisol concentration immediately before testing did not differ between the two arms. This reflects the rapid clearance of cortisol between the time of the last dose (approximately 0800 hours) and the time of the first blood sample (approximately 1300 hours). The finding confirms that subjects were normocortisolaemic at the time of testing with no evidence of adrenal suppression following the cortisol pre-treatment. This suggests that the effect seen in this study does not relate to differences in cortisol concentrations at the time of assessing somatodendritic 5-HT$_{1A}$ receptor function, but rather the repeated increases over the preceding seven days.

**The Buspirone EEG Response**

In previous pilot studies as well as a published report of the effects of buspirone on the EEG frequency spectrum (McAllister-Williams and Massey, 2003) we have found that the peak effect is seen either 30 or 60 minutes post oral administration of buspirone, with the effects waning by 90 minutes. Variation is seen between individuals presumably due to variations in rates of oral absorption. Since each EEG recording requires 10 minutes of data to obtain the precision in the FFT the number of data points obtainable from subjects is limited. The primary analysis focused on the AUC for the three data points post buspirone administration to take into account inter-subject variation in time to maximal effect. The focus on a single electrode (Cz) increases the statistical power of the study. *A priori* it was determined that 16 subjects provided an 80% chance of detecting a 50% decrease with cortisol pre-treatment in the negative shift in EEG frequency at Cz with buspirone, utilising a within subject methodology.
Although the present study involved just two treatment arms and no placebo control for the effect of buspirone, we have previously observed that placebo/time alone has little effect on the EEG frequency spectrum (McAllister-Williams and Massey, 2003). Hence we are confident in ascribing the shift in frequency spectrum to the effect of buspirone over time rather than to time alone. Although the effect of buspirone in the current study was of smaller magnitude than we have previously reported (-7.34 Hz.min cf -14.73 Hz.min), the within subject design of the current study ensured sufficient statistical power to detect a significant effect of cortisol on the buspirone effect on the EEG frequency spectrum. Indeed it was noted that there was a high degree of correlation between individual’s baseline centroid frequencies ($r = 0.79$, $p < 0.001$) between the placebo and cortisol conditions, demonstrating minimal intra-subject variation over time and the robustness of the EEG measures.

The Effect of Cortisol on the Buspirone EEG Response

Repeated cortisol treatment resulted in an attenuation of the effect of buspirone on its negative shift in the EEG frequency spectrum. The effect of cortisol was observed over the whole time course of the EEG recording as evidenced by the significant decrease in AUC and the significant main effect in the time course ANOVA. The effect of cortisol was also observed over the whole scalp surface with no electrode by treatment interaction being observed. We have previously shown that the effect of buspirone is greatest at Cz but is apparent in all electrode locations.

Cortisol pre-treatment was associated with a non-significant decrease in baseline EEG centroid frequencies between 6 and 10.5 Hz, prior to the administration of buspirone. It is
possible that this could compromise the conclusion that cortisol pre-treatment led to a reduction in the shift in frequency spectrum following buspirone administration (as measured with the AUC relative to the baseline) due to a "floor effect". However, there was no correlation between baseline centroid frequencies and AUC values following placebo pre-treatment, cortisol pre-treatment, or when all the data was combined (see figure 3) as one might have expected if this was the case. It is likely that there are multiple transmitter systems that determine the level of the baseline centroid frequency beyond serotonergic ones. As a result, a down-regulation of somatodendritic 5-HT$_{1A}$ receptors following cortisol pre-treatment, may have little effect on the resting EEG frequencies unless there is activation of the system, as occurs with buspirone administration.

The finding that cortisol pre-treatment has no effect on the subjective symptoms induced by buspirone is consistent with previous data (Young et al., 1994b; Porter et al., 2002). It suggests that any effect of cortisol on the buspirone EEG response is not secondary to subjective symptoms experienced by the volunteers. Interestingly although, buspirone caused some nausea and lightheadedness as previously reported, these effects were unaltered by the cortisol pre-treatment. These data are important in providing indirect evidence that the attenuation of the EEG effect was not simply due to a cortisol-induced change in the pharmacokinetics of buspirone.

**Implications of findings**

A fundamental question is why some individuals become depressed when exposed to life stress, whereas others remain well. Serotonergic central pathways have been argued to be fundamental to mechanisms of resilience to stress (Deakin and Graeff, 1991). Effects of
cortisol on serotonergic function may be the means by which environmental factors are transduced to a change in serotonergic function. The findings of this study, supported by numerous animal investigations, suggest that repeated administration of cortisol attenuates somatodendritic 5-HT$_{1A}$ autoreceptor function, an effect similar to that seen with antidepressants in pre-clinical studies. As such it is inviting to speculate that this cortisol-5-HT interaction might be importance in mechanisms of resilience in man. Further research is required to delineate the dynamic nature of the effects of alterations in plasma cortisol on somatodendritic 5-HT$_{1A}$ autoreceptor function, and if such interactions are dysfunctional in subjects at risk of depression, it will be important to investigate whether a dysfunctional interaction predicts the development of depression in response to stress.

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**CONFLICT OF INTEREST**

None.
REFERENCES


Bogdanov NN, Bogdanov MB (1994) The role of 5-HT{sub 1A} serotonin and D{sub 2} dopamine receptors in buspirone effects on cortical electrical activity in rats. Neurosci Lett 177: 1-4


McAllister-Williams RH, Kelly JS (1995) The modulation of calcium channel currents recorded from adult rat dorsal raphe neurones by 5-HT1A receptor or direct G-protein activation. Neuropharm 34: 1491-1506


Young AH, Goodwin GM, Dick H, Fink G (1994a) Effects of glucocorticoids on 5-HT_{1A} presynaptic function in the mouse. Psychopharm 114: 360-364


FIGURE LEGENDS

**Figure 1.** Urinary free cortisol concentrations. 24 hour urinary free cortisol concentrations of subjects after placebo and cortisol pre-treatment. Individual data points for all subjects, including J017 (indicated by solid circle data point) who was excluded from all analyses as described in the text.

**Figure 2.** A. Time course of the effect of buspirone on the EEG centroid frequency measured between 6 and 10.5 Hz at the Cz electrode site following placebo and cortisol pre-treatment. Baseline, prior to buspirone administration, is indicated by time = 0 minutes. Data plotted as change from baseline. B. Bar graph of the area under the curve (AUC) for the change in centroid frequency at CZ following placebo and cortisol pre-treatment.

**Figure 3.** Correlation between baseline centroid frequency between 6 and 10.5 Hz and the AUC for the change in baseline following treatment with buspirone. Data plotted for individual subjects separately for placebo and cortisol pre-treatments. Linear regression lines plotted (GraphPad Prism V3.0) for each. No significant correlation found.
Figure 1
Figure 2

A

Change in Centroid frequency (Hz)

Time (minutes)

-0.2
-0.1
0.0
0.1
0

Placebo
Cortisol

B

AUC (Hz.min)

-12.5
-10.0
-7.5
-5.0
-2.5
0.0
2.5

Placebo
Cortisol
Figure 3

![Graph showing the relationship between Baseline Centroid Frequency (Hz) and AUC (Hz.min) with data points for Cortisol and Placebo treatments.](image-url)