Effect of Short Term Use of NO on Neurotransmitter and Cortisol Levels in PTSD

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PURPOSE

- To determine the impact of 8 sessions of neurofeedback training using NO, V. 2, on levels of key neurotransmitters and adrenal hormones
- Serotonin, dopamine, norepinephrine, epinephrine, glycine, β-PEA, GABA, glutamate, histamine, DHEA and cortisol

Study Design

- Exploratory; no previous research on topic fond
- Convenience sample of 25 client/subjects were recruited
- All had acute, chronic PTSD based on self-report & observed symptoms and history of trauma
- Ages-18-64; 3 males, 14 females; variable use of psychotropic meds; all in psychotherapy
- Levels of neurotransmitters and a 4 point sample of diurnal cortisol were measured via urine and saliva specimens before and after 8 sessions of neurofeedback training using NeuOptimal V.2
- Samples from 8 subjects were not used (overly diluted urine) and drop out
- Complete data from 17 subjects were tabulated and analyzed

Neuronal Communication is Chemical and Electrical

- Info is relayed from neuron to neuron by both electrical and chemical stimulation.
- "We can not separate chemicals and electricity or chemical synapses and electrical synapses.
  - …in adults, electrical synapses are able to alter hard-wired networks of neurons…[and] neuroplasticity [is] triggered by the chemical synapses (Jon Lief, MD).
- A neuron receives an electrical stimulation, which triggers a chemical message via release of NTs into the synapse, this crosses the synapses and creates an electrical potential. Repeat.
- In this manner, information is transmitted to the target tissues, thoughts occur, muscles contract, hormones are released.

Literature Review

- Mistreatment of children can cause adult depression if there is additional stress later. These depressions… have high inflammatory markers .
- These adults have changes in the hypothalamus-pituitary-adrenal function and autonomic stress responses.
- *"Trauma victims have corticoid hormone abnormalities."*
- *The receptors in the hippocampus have epigenetic tags related to inflammation and increase inflammation activity based on stress.*
- *When stress occurs in the present, they had more than twice the interleukin levels in response.*" (Jon Lief, MD)
- Some lymphocytes secrete dopamine and are affected by dopamine.
- Cytokines can affect dopamine, serotonin and glutamine (NeuroScience, Inc.)

- “…neurotransmitter receptors are found on many vital immune cells—T cells, dendritic cells, and macrophages. Many immune cells in the blood signal with many traditional neurotransmitter blurring the categories further.” Jon Lief, MD

- “Adrenergics and glucocorticoids, along with serotonin and other moieties*, affect immune, chemical and structural responses to produce short- and long-term effects that we recognize as sequelae of PTSD.” Sherin et l

- Individuals who currently suffer from PTSD demonstrate upregulated immune responses, Sherin, et al

- *Moiety-A functional group is a **moiety** that participates in similar chemical reactions in most molecules that contain it. In turn the parts of the group are termed **moieties**.

Sympathetic Nervous System Messengers

NEUROTRANSMITTERS

Inhibitory

- Serotonin
- GABA
- Glycine

Excitatory

- Dopamine → Norepinephrine (80% released by brain)
- Epinephrine
- β-PEA
- Glutamate
- Histamine

HORMONES

- Cortisol
- DHEA

Aggregate Analysis Statistical Methods

- Mean, standard deviation (SD), median (50^{th} percentile; parametric), standard error (SE), lower/upper 95^{th} parametric percentiles
- Pooled standard deviation (SD_{pooled}), and effect size (Cohen's δ; see following slide) were all calculated in excel.
- Statistical significance was calculated and determined by either:
- ANOVA Fisher's LSD test for cortisol time points; threshold for significance (α)set at <0.05
- Student's Paired T-test for DHEA and all neurotransmitters
- Graphical representations of data were plotted

Effect Size

- Cortisol-reduced
- Morning-Medium
- Noon-Medium
- Midday-Low
- Evening-Medium

- Dopamine, serotonin, glutamate, histamine-reduced-, Small

- GABA, glycine, PEA, epinephrine, norepinephrine, histamine-extremely low

Aggregate Analysis Statistical Methods

Effect size

- Effect size is a quantitative measure of the strength of a phenomenon. Effect size emphasizes the size of the difference rather than confounding this with sample size.
- Effect size (ES) was determined by calculating Cohen's δ

Cohen, Jacob (1988). Statistical Power Analysis for the Behavioral Sciences.

$$\delta = \frac{(\tilde{x}_1 - \tilde{x}_2)}{SD_{pooled}}$$

$$SD_{pooled} = \sqrt{\frac{[(n_1-1)\sigma_1{}^2 + (n_2-1)\sigma_2{}^2]}{(n_1 + n_2 - 2)}}$$

1=Pretreated Value; 2=Treated Value; $\tilde{x}$=Mean; σ=Standard Deviation

- A δ value between ±0.2–0.5 was considered to be a small effect, ±0.5–0.8 was considered to be a medium effect, and a value greater than +0.8 or less than −0.8 was considered to be a large effect

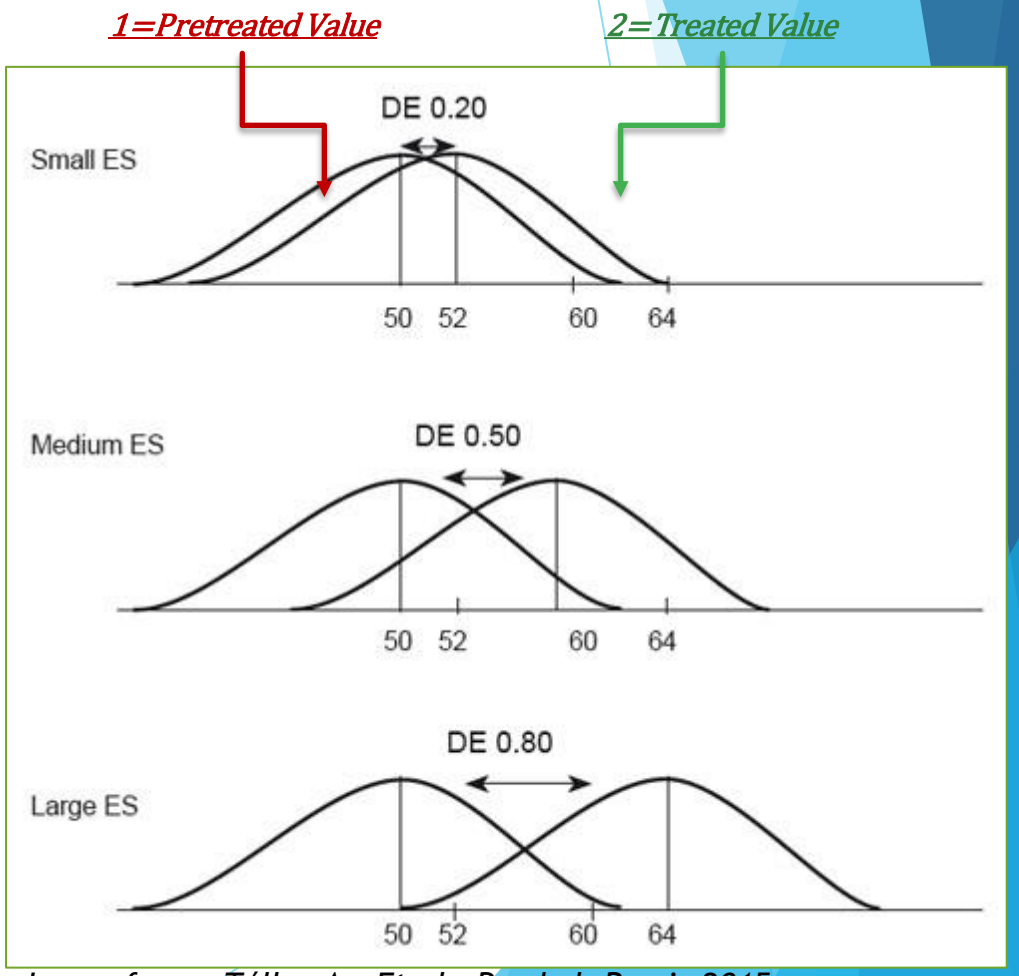


Image from: Téllez A., Et al., Psychol. Russia 2015

Aggregate Analysis Conclusion

- As cortisol is integral in the methylation of catecholamines, such as norepinephrine to epinephrine. Where a reduction in cortisol may translate to a reduction of epinephrine.
  - *However, the urinary neurotransmitters measured are of second morning urine (10 am) and do not correspond with the diurnal time-points of the salivary cortisol (7 am, noon, 5 pm, 10 pm).*
- The reduction of cortisol in the morning may also make it difficult for some individuals to wake fully in the morning.
- Conversely, the reduction of cortisol in the evening and night samples, could make it easier to fall asleep and stay asleep for individuals of whom were initially high in cortisol.

Cortisol

- released in response to stress /low blood-glucose
- increases blood sugar
- metabolism of fat, protein, and carbohydrates.
- decreases bone formation
- acute stress may reflect an enhancement of the immune response, and chronic stress may reflect a suppression of the immune response" Sherin, et al

- There is a general decrease in inflammatory molecules. Chiefly, cortisol is reduced with a trend towards the reduction of some inflammatory neurotransmitters.
- The reduction of cortisol in the morning may make it difficult for some individuals to wake fully in the morning. However, the reduction of cortisol in the evening and night samples, could make it easier to fall asleep and stay asleep for individuals were initially high in cortisol.

Dopamine and Inflammation

- Dopamine (DA…also functions as an important molecule bridging the nervous and immune systems (Basu and Dasgupta, 2000; Beck et al., 2004; Sarkar et al., 2010).
- DA receptors are present in almost all immune cell subpopulations (Sarkar et al., 2010).
- Acting on its receptors, DA or agonists for DA receptors have been reported to modulate the activation, proliferation, and cytokine production in immune cells (Basu and Dasgupta, 2000; Sarkar et al., 2010; Torres-Rosas et al., 2014).
- In addition, dopamine D2 receptor (DRD2) knockout mice show remarkable inflammatory response in CNS, suggesting that DA and its downstream signaling has an antinflammatory function

Serotonin and Inflammation

- These results suggest that the clients in this study may benefit by achieving a better quality of sleep and reduced inflammations.
- The reduced inflammation may lead to a reduced capacity for oxidative stress as well. (when free radicals damage all components of the cell, including proteins, lipids, and DNA, leading to ahost of serious psychological and physical problems).

Limitations

- Sample size and method-convenience, small, no formal screening criteria, variability of age, imbalanced gender representation
- Limited number of NO sessions
- Assessment of clinical progress was not relevant to study objective and was too sensitive to extrinsic factors
- Variable use of psychotropic medications may have confounded results Several subject/clients had very high ever]ls of pre-baseline serotonin due to polypharmacy

Implications

- Effect of neurofeedback training using NeurOptimal on cortisol and NT as markets of inflammation in people with PTSD suggests the utility of replicating and extending this study with a larger sample and possibly additional groups.
- This exploratory study elucidates methodological issues that can be addressed in future studies.
- Impact of adaptogens on cortisol dysregulation have been demonstrated clinically and in limited research; studies evaluatating the combined use of adaptogens and NO may be useful.
- Case studies of the most and least effected client/subjects pending.

Implications (Cont.)

- Effect of NF training using NO on cortisol and NT levels as markers of inflammation in people with PTSD suggests the utility of extending and replicating the study with a larger study and using a longer course of training

- There may be advantages to using a non-clinical population in terms of admission criteria-formal PTSD screening, use of psychotropics, objective evaluation of behavioral and other changes, and drop outs

Glutamate and Inflammation

Aggregate Analysis Observations

Hormones

- Cortisol
  - Loss in mean cortisol levels in the morning, midday, and night collections
  - Effects were medium for all three time-points ($\delta < -0.5$)
  - The only statistical significance was found in morning and midday ($p < 0.05$)
- DHEA
  - No effect or statistical significance was found after treatment of the group as a whole was measured

Neurotransmitters

- The group as a whole measured no statistical significance with any of the Neurotransmitters after treatment
- The group as a whole measured no effect size for norepinephrine, epinephrine, glycine, β-PEA, or GABA after treatment
- There were small losses after treatment, with measuring effect sizes $\delta < -0.2$ in dopamine, serotonin, glutamate, and histamine
  - Without statistical significance associated with the small effect sizes, this may be considered as a possible trend

Aggregate Analysis Conclusion

There is a general decrease in inflammatory molecules. Chiefly, cortisol is reduced with a trend towards the reduction of some inflammatory neurotransmitters.

- As cortisol is integral in the methylation of catecholamines, such as norepinephrine to epinephrine. Where a reduction in cortisol may translate to a reduction of epinephrine.
  - *However, the urinary neurotransmitters measured are of second morning urine and do not correspond with the diurnal time-points of the salivary cortisol.*
- The reduction of cortisol in the morning may also make it difficult for some individuals to wake fully in the morning.
- Conversely, the reduction of cortisol in the evening and night samples, could make it easier to fall asleep and stay asleep for individuals of whom were initially high in cortisol.

These results suggest that the patients in this study may benefit by achieving a better quality sleep and reduced inflammation. The reduction in inflammation may lead to a reduced capacity for oxidative stress as well.

Limitations

- Study is exploratory in nature, several methodological issues such as frequency and number of sessions, use of medications, missed sessions due to illness/weather, cost of tests, access to additional funding
- Sample size and sampling-non-random, high variability of age, use of psychotropic meds
- Several client/subjects had very high pre-baseline levels of serotonin secondary to polypharmacy
- Subjective clinical assessments too sensitive to extrinsic factors

Implications

- Effect of neurofeedback training on cortisol levels suggests utility of replicating and extending this study with a larger sample and possibly additional groups
- This pilot/exploratory study elucidates methodological issues that can be addressed in future studies
- Case studies of the most and least effected client/subjects pending

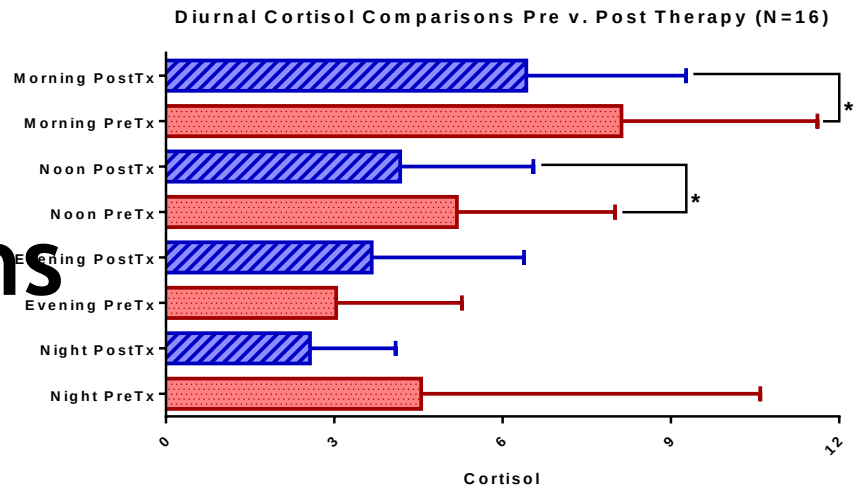
Aggregate Analysis Statistical Data

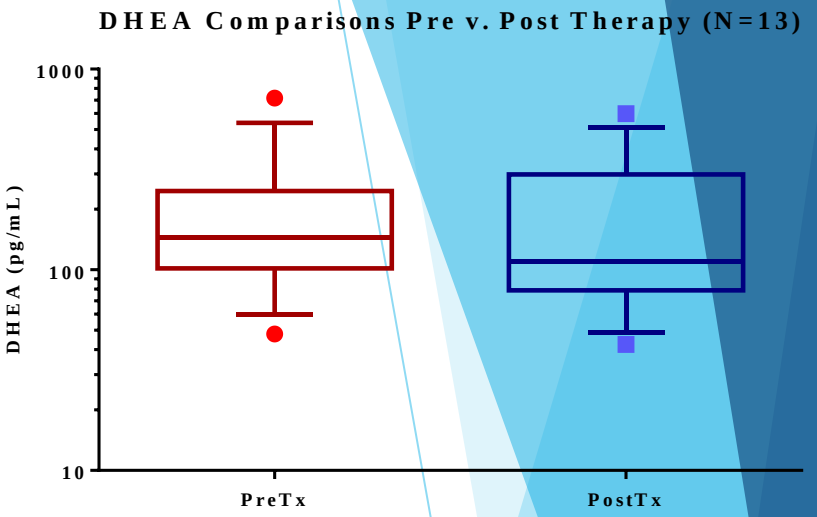
		Cortisol (µg/mL)				DHEA	Epinephrine	Norepinephrine	Dopamine	Serotonin	Glutamate	Glycine	β-PEA	Histamine	GABA
		Morning	Midday	Evening	Night	(pg/mL)	(µg/g Cr)	(µg/g Cr)	(µg/g Cr)	(µg/g Cr)	(µmol/g Cr)	(µmol/g Cr)	(nmol/g Cr)	(µg/g Cr)	(µmol/g Cr)
Pre-Tx	N	16	16	16	16	13	17	17	17	17	17	17	16	17	17
	Mean	8.12	5.19	3.03	4.55	200.31	3.71	34.22	167.08	117.33	25.54	1497.91	32.79	25.96	5.66
	SD	3.49	2.82	2.24	6.05	170.70	6.09	10.10	30.59	48.35	8.64	824.38	16.14	22.43	4.10
	Median	7.95	4.40	2.50	2.25	144.50	2.00	31.80	175.50	109.30	26.50	1538.00	28.40	23.60	4.80
	SE	0.87	0.70	0.56	1.51	47.35	1.48	2.45	7.42	11.73	2.10	199.94	4.04	5.44	0.99
	Lower 95%	3.30	2.18	1.28	0.89	56.99	0.94	20.66	109.64	52.80	11.14	510.28	17.26	12.04	2.72
	Upper 95%	15.26	11.44	8.49	19.24	583.42	18.93	52.82	216.62	220.38	40.02	3038.06	70.24	78.52	15.90
Post-Tx	N	16	16	16	16	13	17	17	17	17	15	17	16	17	17
	Mean	6.43	4.18	3.67	2.57	189.65	4.42	34.45	157.64	110.60	23.46	1419.32	31.54	20.69	5.22
	SD	2.85	2.37	2.71	1.53	163.57	7.42	15.80	48.47	46.29	14.90	660.52	15.35	6.77	3.56
	Median	5.50	3.60	2.65	2.35	109.60	2.15	34.90	141.00	95.30	20.90	1267.70	28.45	21.10	4.30
	SE	0.71	0.59	0.68	0.38	45.37	1.80	3.83	11.76	11.23	3.85	160.20	3.84	1.64	0.86
	Lower 95%	3.29	2.14	1.44	1.38	47.03	1.02	10.32	97.26	62.16	9.81	684.12	10.94	11.14	2.92
	Upper 95%	12.69	10.08	10.19	6.21	534.29	22.56	63.72	233.94	213.22	58.92	2728.88	63.80	34.64	13.86
	SD_{pooled}	2.18	1.78	1.70	3.02	113.57	4.66	9.09	27.80	32.47	8.20	512.41	10.78	11.37	2.63
	p Value◊,ǂ	0.04	0.03	0.13	0.20	0.55	0.77	0.95	0.46	0.66	0.66	0.66	0.73	0.27	0.21
	Cohen's δ	-0.78	-0.57	0.37	-0.66	-0.09	0.15	0.02	-0.34	-0.21	-0.25	-0.15	-0.12	-0.46	-0.17
	Effect Size	Med	Med	Sm	Med	≠	≠	≠	Sm	Sm	Sm	≠	≠	Sm	≠

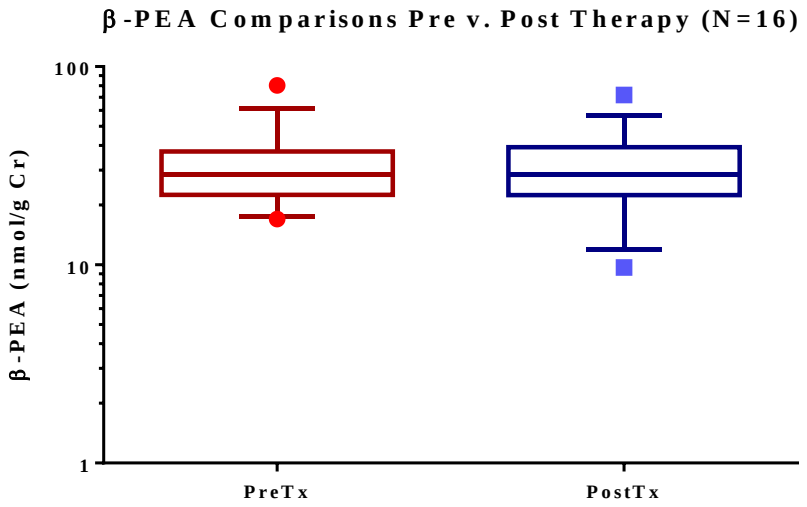
◊: Fisher's LSD test for Cortisol

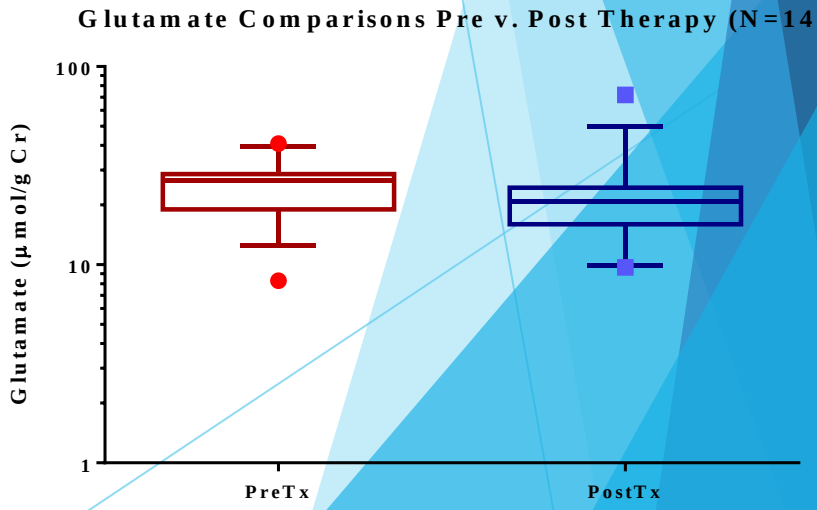
ǂ: Paired t-Test

Aggregate Analysis Graphical Representations









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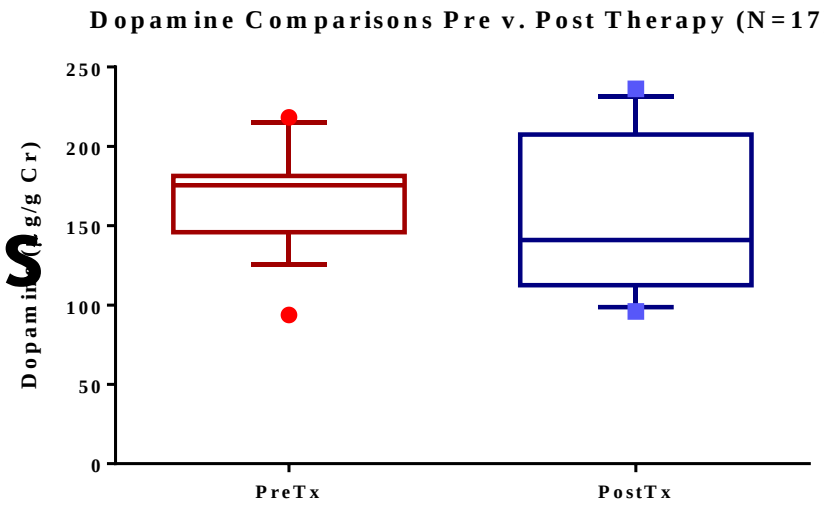

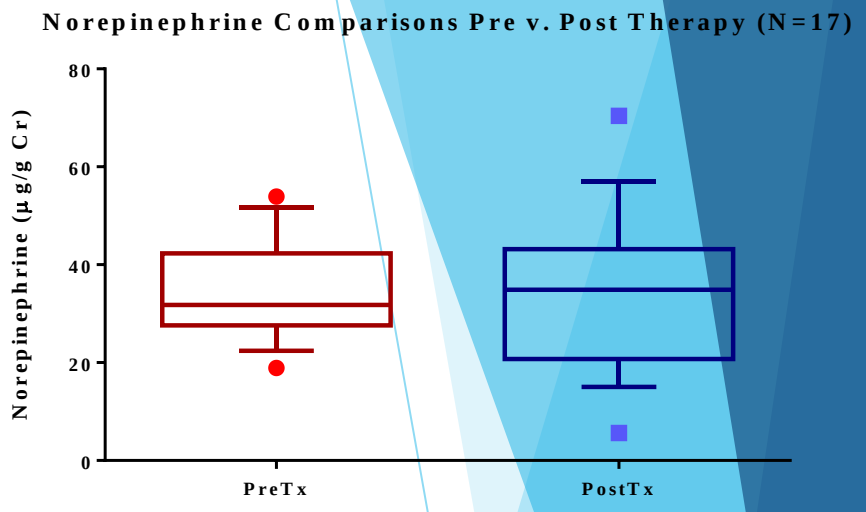

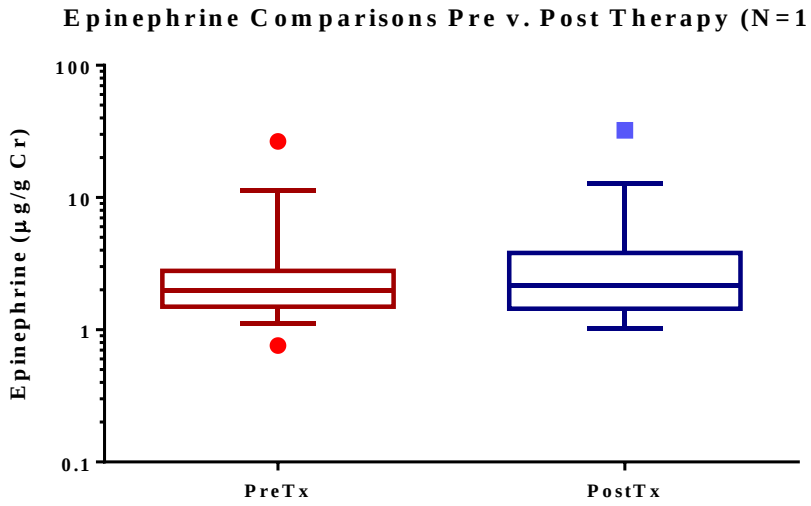

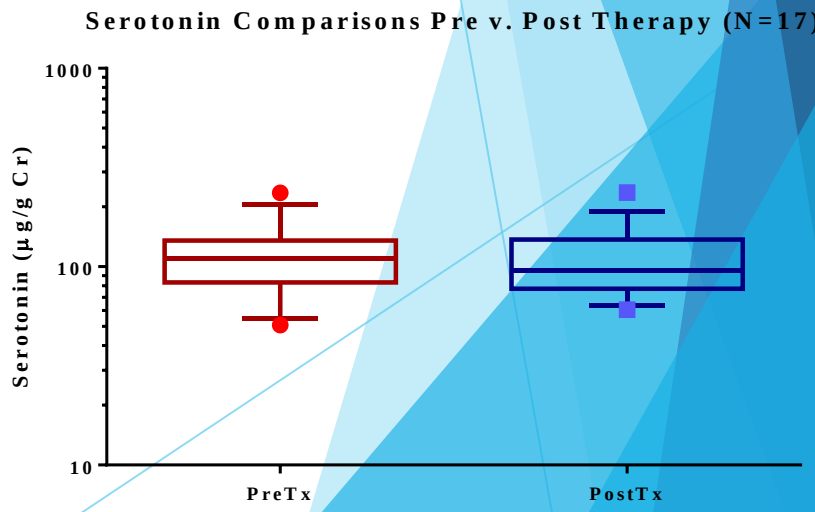

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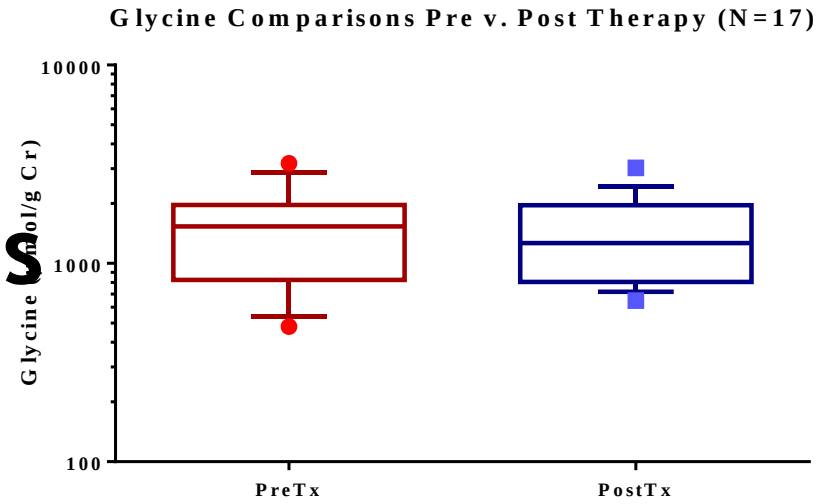
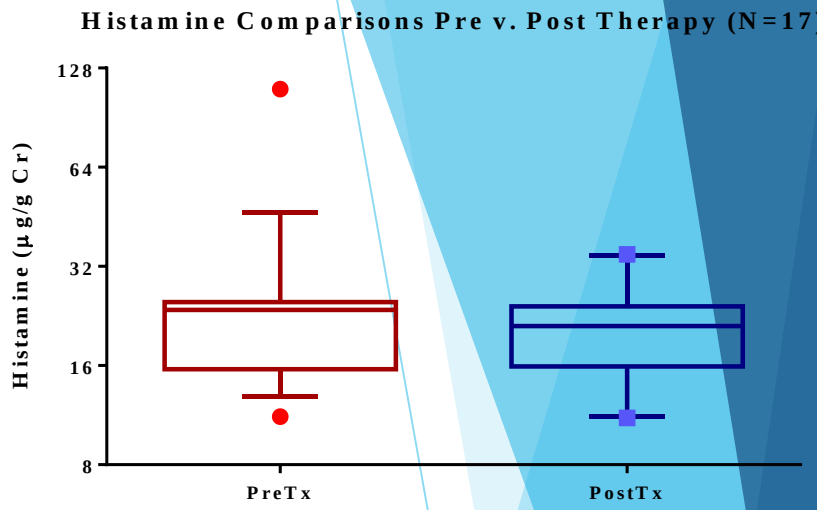
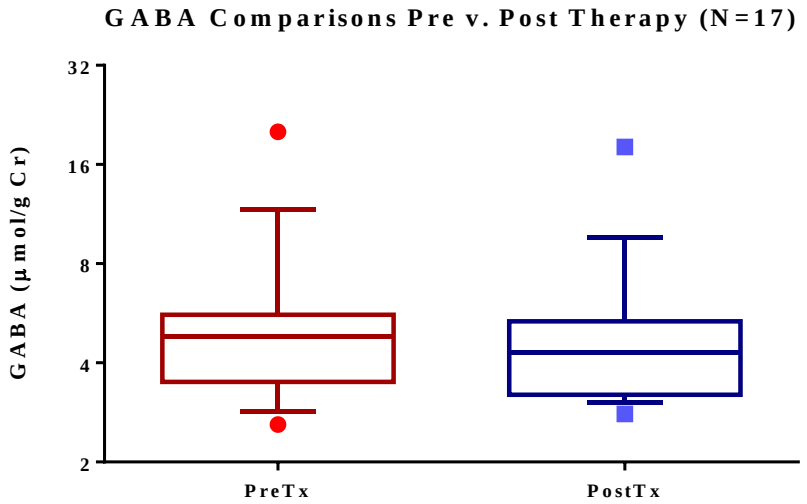
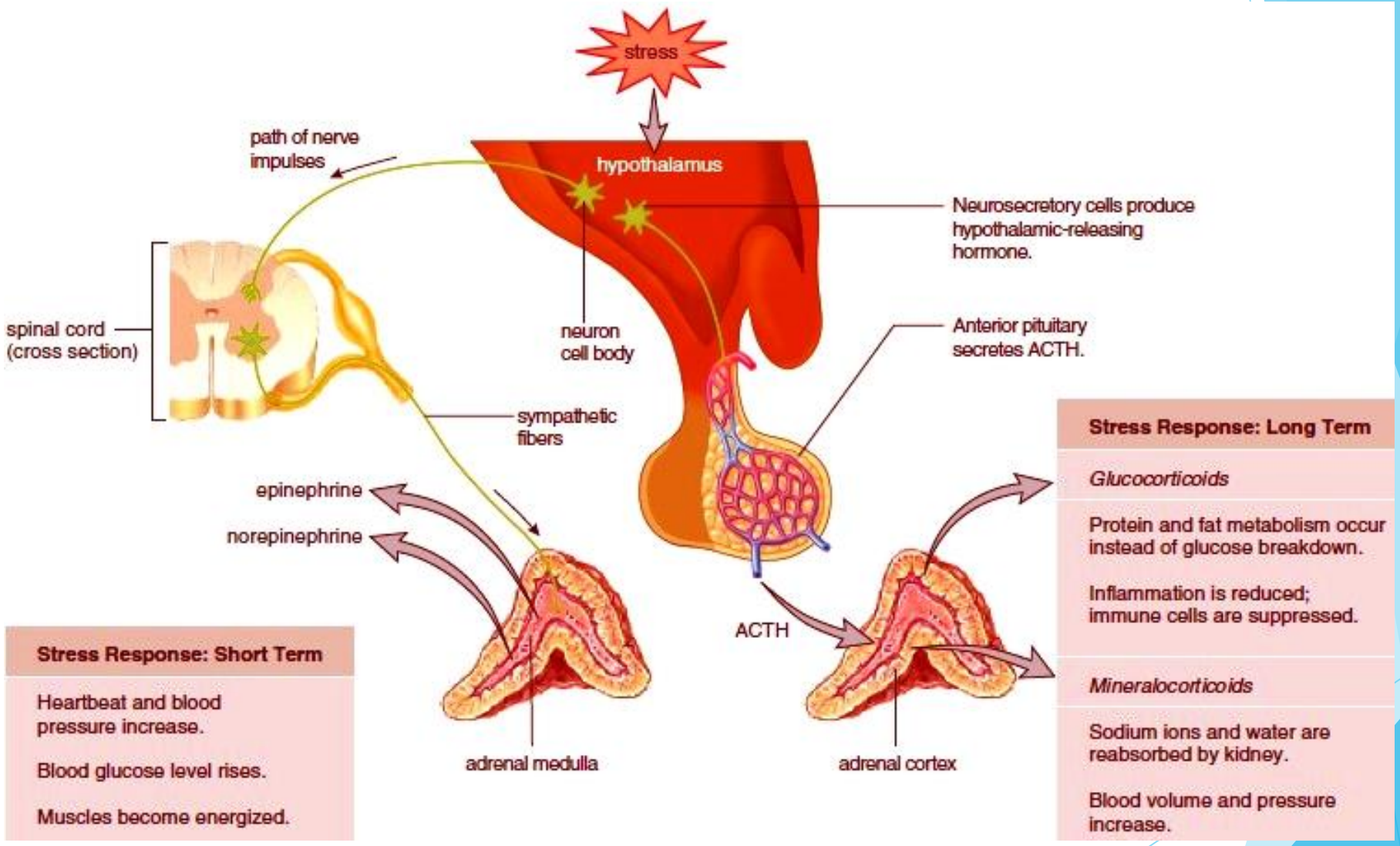








Source: Figure 10.8, http://encyclopedia.lubopitko-bg.com/AdrenalGlands.html, accessed 14/12/17

Individual Analysis

Individual Analysis Notes

- Evaluated Patients with both Pre and Post Treatment (Tx) Samples
  - Patients: 1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 17, 24, 26, 31, 32
- Evaluated patients with a single and double Post Tx sample periods
- Did not analyze patients without Post Tx sample
  - Patients: 16, 18-21, 25, 28, 30
- Patients that had NO sample
  - Patients: 2, 7, 22, 23, 27
- Patients 15 & 29 had failed samples both Pre and Post Tx and were not analyzed
- Example graphical representations were made of patients 3, 9, 11, 13. The only reasoning of this was due to the fact that these patients had multiple post treatment sample submissions

Individual Analysis Statistical Methods

- Days of treatment (Tx), Percent Difference, Standard Deviation(σ), Percent Coefficient of Variation (CV) were all calculated in Excel
- CV is the ratio of the standard deviation to the mean. Where It shows the extent of variability in relation to the mean of the comparison being made.
- Graphical representations of data were plotted with GraphPad Prism (v.6.07)

$$Days\ of\ Tx = Date_2 - Date_1$$

$$Difference = \left(\frac{(Value_2 - Value_1)}{Value_1}\right) \times 100\%$$

$$CV = \left(\frac{\sigma_{1,2}}{\tilde{X}_{1,2}}\right) \times 100\%$$

1=Pretreated Value; 2=Treated Value; $\tilde{x}$=Mean; σ =Standard Deviation

Individual Analysis Statistical Data

Patient ID	Days of Tx	Cortisol-Morning			Cortisol-Midday			Cortisol-Evening			Cortisol-Night		
		Diff.	σ	CV	Diff.	σ	CV	Diff.	σ	CV	Diff.	σ	CV
1	60	-57%	3.3	56%	22%	0.3	14%	42%	0.6	25%	-32%	0.4	27%
3	81	-21%	2.6	25%	-39%	1.7	41%	141%	1.7	77%	-51%	1.9	58%
3	104	-2%	2.8	18%	197%	3.5	71%	-63%	0.1	5%	81%	0.4	11%
4	75	-37%	2.2	16%	-63%	3.5	48%	-14%	0.4	13%	-61%	1.6	45%
5	61	-51%	2.3	48%	33%	0.7	20%	13%	0.2	9%	-27%	0.5	22%
6	62	-12%	0.7	9%	-20%	0.6	16%	-30%	0.7	25%	-43%	1.3	39%
8	33	0%	0.0	0%	-48%	1.3	44%	17%	0.1	11%	36%	0.4	21%
9	65	140%	3.0	58%	-54%	2.6	52%	171%	1.7	65%	271%	1.3	81%
9	125	-57%	0.1	2%	-53%	3.8	91%	-42%	0.6	31%	-4%	1.3	80%
10	62	-4%	0.2	3%	11%	0.4	8%	-6%	0.1	5%	21%	0.2	14%
11	51	-31%	1.7	26%	-16%	0.4	12%	53%	0.6	30%	33%	0.3	20%
11	63	52%	0.3	4%	48%	0.6	15%	17%	0.8	40%	106%	1.5	66%
12	10	-	-	-	-	-	-	-	-	-	-	-	-
13	47	-59%	4.5	60%	4%	0.1	3%	72%	1.5	38%	32%	0.5	19%
13	83	-25%	5.3	75%	-63%	2.1	63%	-72%	1.1	49%	-62%	0.8	47%
14	77	-50%	4.0	47%	14%	0.4	9%	0%	0.0	0%	32%	0.4	19%
17	52	-38%	1.6	34%	-14%	0.3	11%	-44%	0.8	40%	16%	0.2	10%
24	69	87%	2.3	43%	-18%	0.6	14%	21%	0.4	14%	-9%	0.1	6%
26	44	-30%	1.6	25%	-6%	0.1	5%	-34%	0.9	29%	-90%	16.3	116%
31	34	8%	0.5	6%	-19%	1.3	15%	89%	3.3	43%	5%	0.3	4%
32	46	-4%	0.3	3%	-9%	0.8	6%	-1%	0.1	1%	-61%	3.8	63%

Individual Analysis Statistical Data

Patient ID	Days of Tx	DHEA			Epinephrine			Norepinephrine			Dopamine		
		Diff.	σ	CV	Diff.	σ	CV	Diff.	σ	CV	Diff.	σ	CV
1	60	-32%	32.2	26%	-29%	0.4	24%	-49%	12.7	46%	-27%	34.4	22%
3	81	-31%	49.3	30%	-47%	0.6	38%	31%	11.7	32%	25%	31.4	20%
3	104	-	-	-	925%	6.0	410%	-9%	7.2	12%	7%	43.1	22%
4	75	-16%	82.2	52%	412%	3.5	61%	45%	8.9	13%	19%	23.8	10%
5	61	-26%	14.6	21%	947%	5.1	117%	-70%	9.4	77%	7%	6.9	5%
6	62	-11%	3.8	8%	23%	0.3	15%	24%	4.7	15%	12%	11.1	8%
8	33	35%	47.4	21%	-95%	18.0	129%	7%	2.1	5%	-7%	7.1	5%
9	65	-	-	-	94%	1.5	45%	-29%	6.5	24%	-36%	45.8	31%
9	125	-51%	452.1	48%	-38%	0.3	13%	26%	2.4	8%	39%	13.9	8%
10	62	15%	10.0	10%	0%	0.0	0%	-37%	7.4	33%	-21%	25.6	16%
11	51	-21%	16.0	17%	82%	0.7	41%	-3%	0.8	2%	26%	33.2	16%
11	63	6%	12.6	13%	3589%	58.6	137%	-7%	2.8	7%	-14%	10.3	5%
12	10	-	-	-	-40%	0.9	36%	-4%	1.2	3%	-10%	11.5	8%
13	47	-40%	34.0	35%	13%	0.2	9%	18%	5.2	12%	-7%	10.1	5%
13	83	-6%	36.9	39%	159%	3.1	69%	180%	65.5	76%	93%	121.9	41%
14	77	40%	76.1	23%	-5%	0.1	4%	47%	7.8	27%	7%	9.1	5%
17	52	-20%	28.8	15%	14%	0.1	9%	44%	7.3	26%	-36%	40.2	31%
24	69	-	-	-	-7%	0.1	5%	6%	1.3	4%	-50%	76.9	47%
26	44	-	-	-	-57%	3.0	57%	-63%	22.8	65%	-38%	48.7	34%
31	34	-25%	22.7	20%	-42%	0.5	38%	-20%	4.0	16%	2%	1.5	2%
32	46	28%	52.3	17%	959%	20.7	117%	96%	18.6	46%	72%	69.9	37%

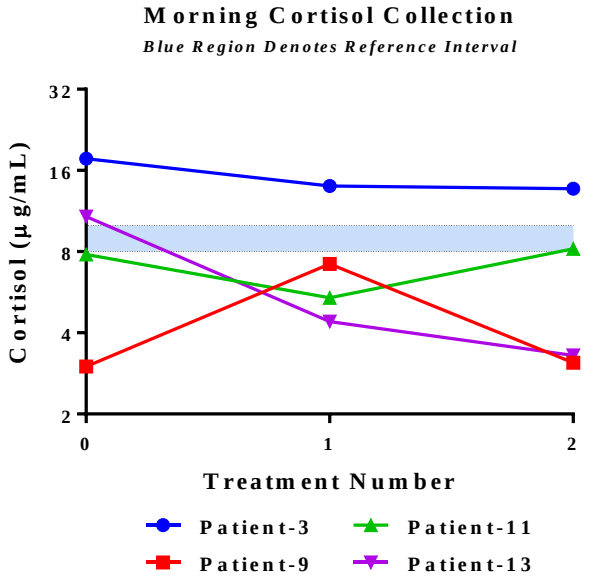
Individual Analysis Statistical Data

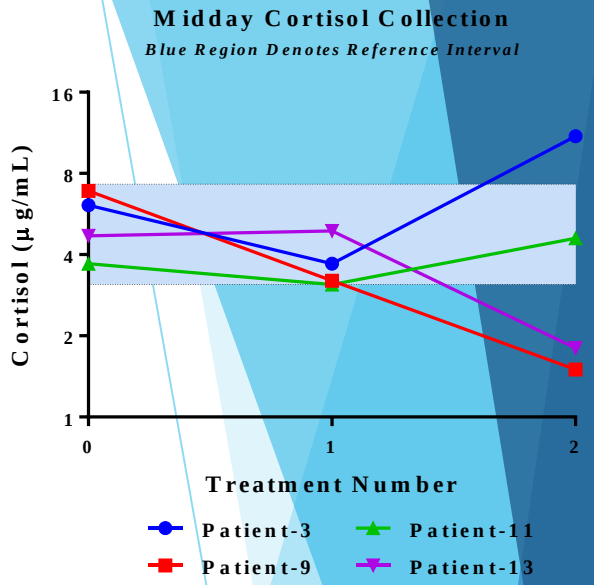
Patient ID	Days of Tx	Serotonin			Glutamate			Glycine			PEA		
		Diff.	σ	CV	Diff.	σ	CV	Diff.	σ	CV	Diff.	σ	CV
1	60	-35%	29.5	30%	-65%	13.2	68%	-48%	523.5	45%	-3%	0.6	2%
3	81	154%	60.9	90%	-14%	1.9	13%	53%	180.5	28%	0%	0.1	0%
3	104	-24%	37.1	38%	-4%	2.3	13%	-13%	115.0	19%	55%	8.6	39%
4	75	6%	6.6	5%	-31%	6.3	39%	-28%	180.9	26%	7%	1.9	7%
5	61	27%	21.6	17%	60%	9.3	33%	17%	114.8	11%	-11%	2.1	8%
6	62	-10%	10.9	8%	-13%	2.7	10%	13%	175.6	9%	26%	3.2	17%
8	33	5%	3.5	3%	58%	6.3	32%	153%	601.2	61%	-45%	5.7	41%
9	65	-73%	120.8	81%	-	-	-	-45%	784.7	41%	-	-	-
9	125	157%	49.0	24%	-38%	9.1	33%	60%	205.9	9%	-5%	1.5	3%
10	62	-23%	20.1	18%	-4%	0.7	3%	-7%	100.1	5%	-45%	17.0	41%
11	51	-7%	6.4	5%	-9%	1.4	6%	-42%	582.9	38%	75%	14.4	39%
11	63	-25%	26.2	25%	-45%	8.1	47%	38%	276.6	16%	-61%	5.9	26%
12	10	-30%	21.7	25%	-76%	22.1	87%	-28%	345.4	23%	-60%	13.7	60%
13	47	-34%	48.0	29%	-40%	10.8	35%	-16%	113.3	13%	-37%	21.3	33%
13	83	117%	59.4	25%	48%	2.8	8%	80%	350.4	29%	-	-	-
14	77	17%	9.5	11%	-28%	7.0	23%	17%	211.5	11%	9%	1.6	6%
17	52	-29%	22.0	24%	-40%	7.4	35%	-45%	894.3	41%	27%	4.0	17%
24	69	-9%	5.4	7%	-	-	-	296%	1206.3	84%	-23%	4.9	19%
26	44	9%	4.7	6%	-31%	6.2	26%	-5%	121.8	4%	15%	3.2	10%
31	34	19%	6.9	12%	55%	3.3	31%	0%	2.2	0%	33%	5.4	20%
32	46	116%	89.9	52%	284%	37.6	83%	32%	210.1	20%	53%	17.5	29%

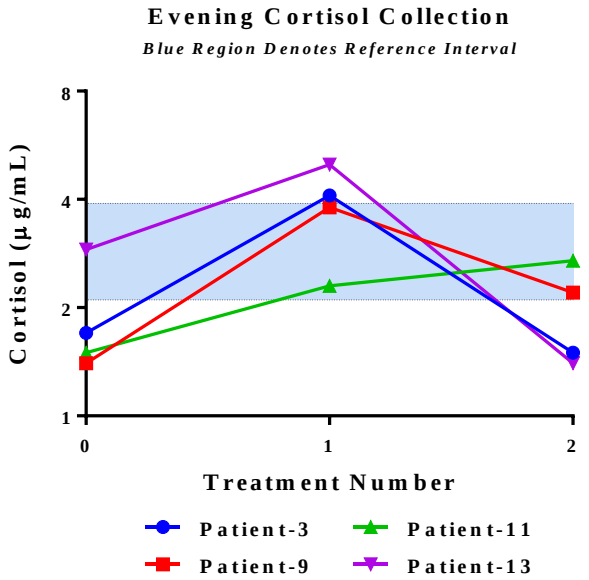
Individual Analysis Statistical Data

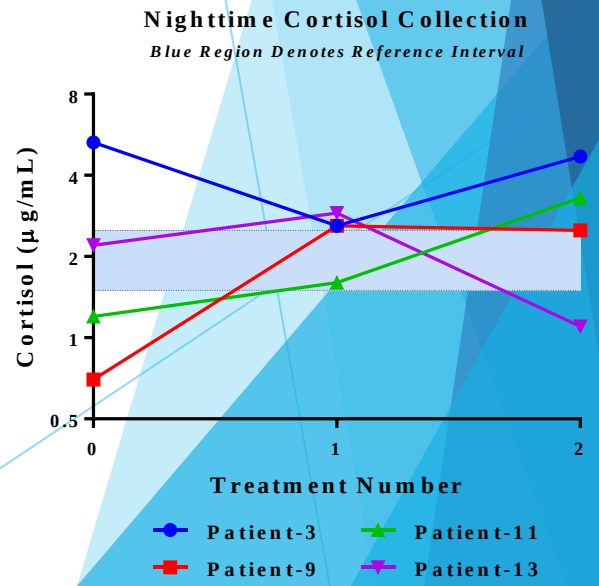
Patient ID	Days of Tx	Histamine			GABA		
		Diff.	σ	CV	Diff.	σ	CV
1	60	-11%	1.8	8%	-42%	1.4	37%
3	81	18%	1.8	10%	26%	0.6	19%
3	104	32%	5.4	37%	-23%	0.1	2%
4	75	34%	6.2	33%	47%	1.1	31%
5	61	28%	3.5	17%	17%	0.5	11%
6	62	8%	1.2	5%	18%	0.7	11%
8	33	-18%	1.8	14%	14%	0.3	9%
9	65	-36%	6.2	31%	-38%	1.3	33%
9	125	62%	0.8	3%	71%	0.2	4%
10	62	-21%	4.5	16%	-37%	1.3	32%
11	51	25%	2.3	16%	-4%	0.1	3%
11	63	-39%	2.2	19%	-7%	0.4	8%
12	10	-56%	10.2	56%	-11%	0.4	8%
13	47	-69%	53.7	74%	-42%	2.2	37%
13	83	65%	37.8	45%	198%	3.8	38%
14	77	-11%	1.9	8%	-22%	1.5	17%
17	52	-13%	1.6	9%	18%	0.5	12%
24	69	23%	3.1	15%	-10%	1.4	7%
26	44	-28%	4.9	23%	-3%	0.1	2%
31	34	57%	4.5	31%	19%	0.4	12%
32	46	2%	0.4	2%	14%	0.5	9%

Individual Analysis Graphical Representations

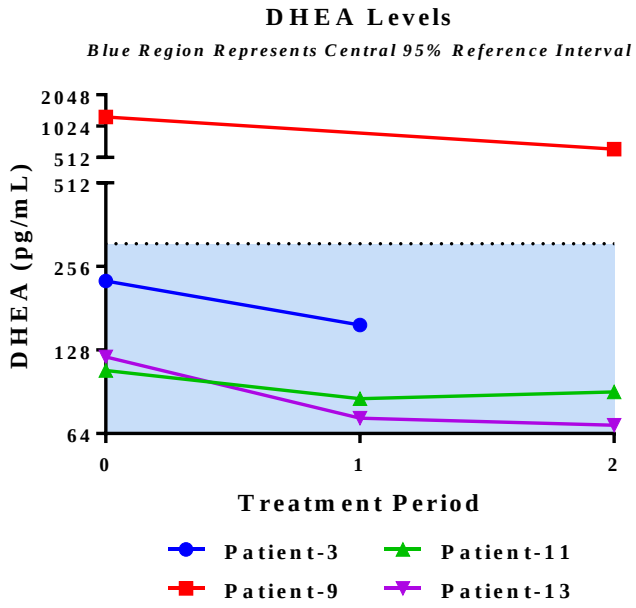


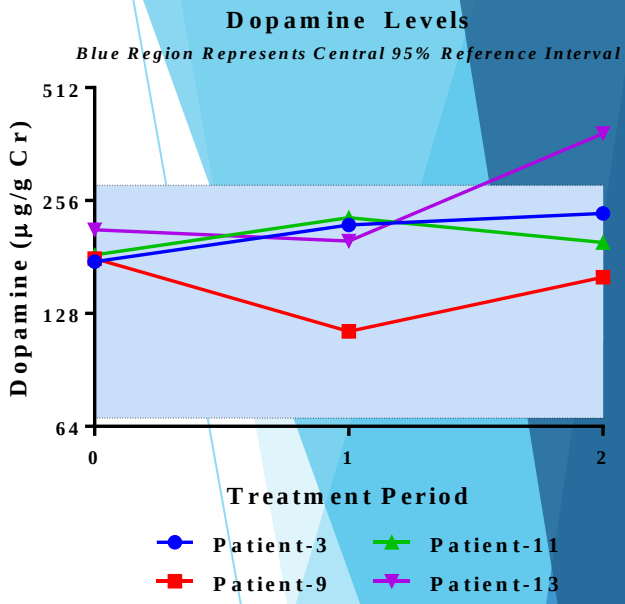


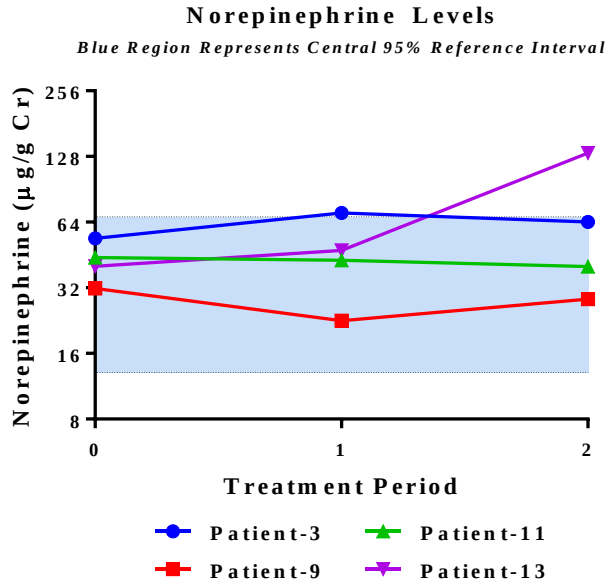


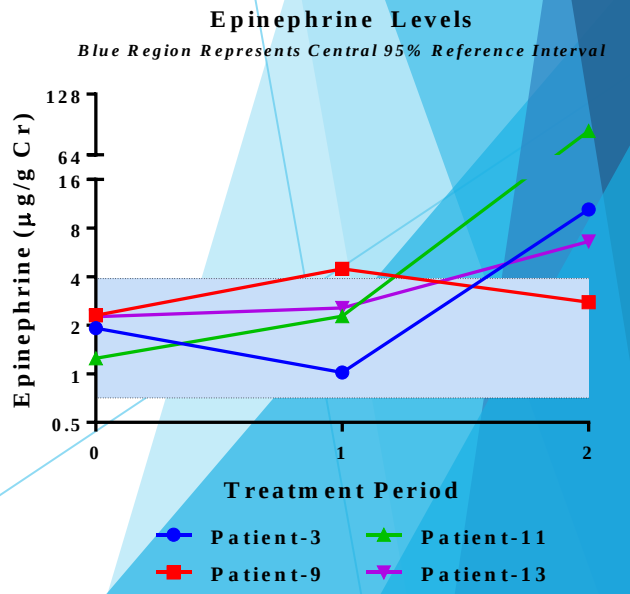


Individual Analysis Graphical Representations

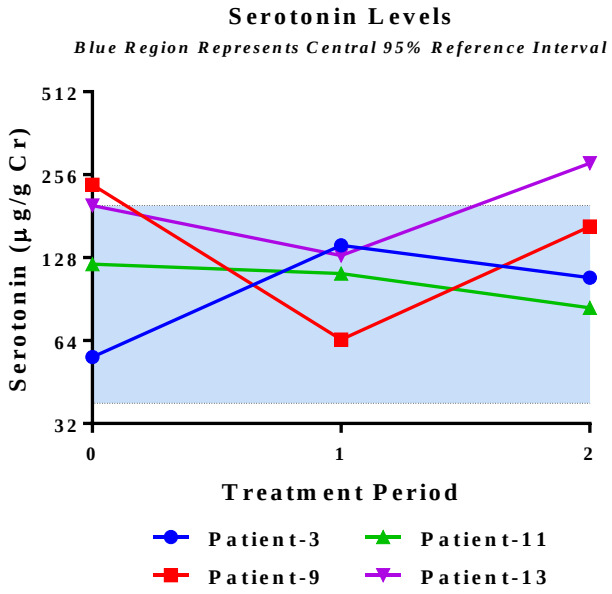


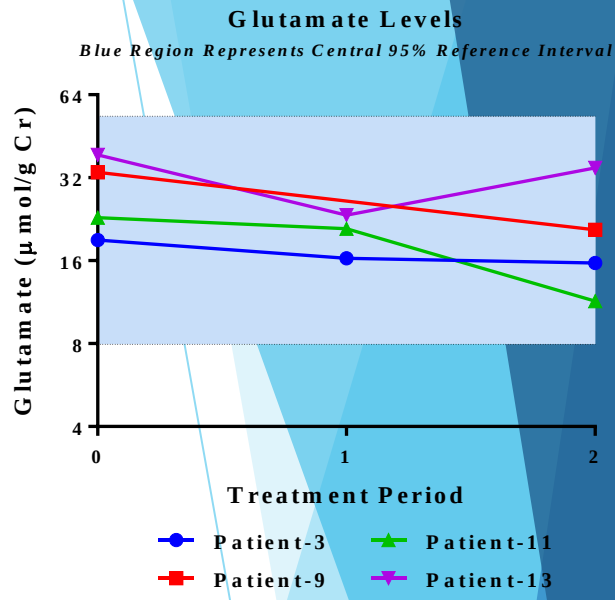


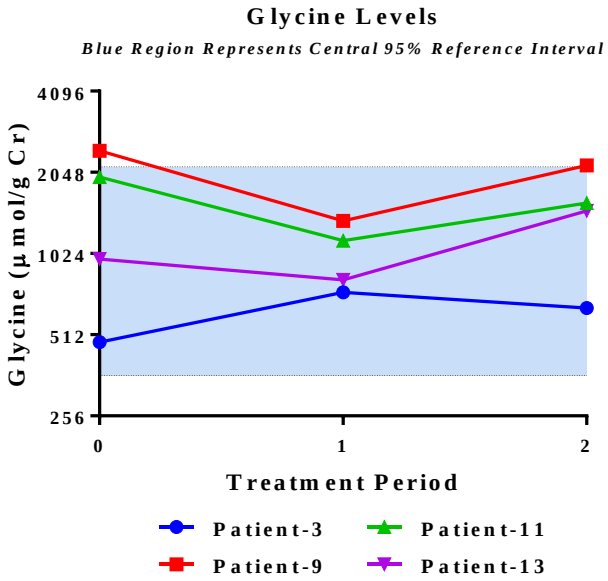


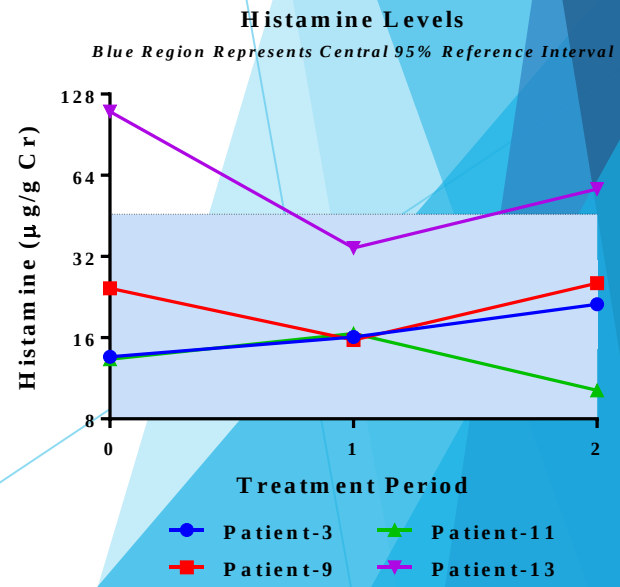


Individual Analysis Graphical Representations









Individual Analysis Graphical Representations