

**USING MIXED EFFECTS MODELS TO COMPARE DIFFERENCES IN STRESS
REACTIVITY BETWEEN WOMEN WITH AND WITHOUT A FAMILY HISTORY OF
BREAST CANCER**

by

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ABSTRACT

Breast cancer is the leading cause of cancer death in women and affects hundreds of thousands of women and their families yearly in the United States. Having a family history of breast cancer is one of the strongest predictors of developing the disease. Previous studies have found evidence that women with a family history of breast cancer have excessive worry and intrusive thoughts about developing the disease and may react differently to stress than women who do not have a family history of breast cancer. This study uses the novel approach of measuring the activity of the autonomic nervous system to compare stress reactivity between women with and without a family history of breast cancer.

Eighty-two women with a family history of breast cancer and 140 women without a family history of breast cancer who were otherwise healthy underwent a laboratory stress test. During the test, their heart rate variability was measured as a proxy for the activity of the autonomic nervous system. Repeated measures of heart rate variability were taken at baseline, the three tasks of the stress test, and during a recovery period. The reactivity of the two groups throughout the test were compared using a mixed effects ANCOVA model. One of nine heart rate variability measures showed significant group differences. During the stress test, women with a family history of breast

cancer had significantly higher levels of parasympathetic activity than women without a family history of breast cancer.

Public Health Significance: The results of this study can be used to further our understanding of the effects of having a family history of breast cancer.

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PREFACE

I would like to express my gratitude to Dr. Robert Krafty for his guidance throughout this project and his continued support to my professional and career development. I would like to thank Dr. Dana Bovbjerg for providing me with the data, helping me to understand the clinical importance of the results of the study, and for providing constructive feedback as a member of my committee. I would also like to thank Dr. Ada Youk for being a member of my committee and for helping me throughout my career as a graduate student.

1.0 INTRODUCTION

Other than skin cancer, breast cancer is the most common cancer among women in the United States, accounting for nearly one third of new cancer diagnoses [1]. It is the leading cause of cancer death for American women [1]. In 2016, it is estimated that there will be 246,660 new cases of breast cancer and 40,860 women will die from breast cancer [3]. One of the strongest predictors for breast cancer is family history of breast cancer. Having a first degree relative, (mother, sister, or daughter), who has had breast cancer increases a woman's risk for developing the disease [4]. Multiple heritable gene mutations have been identified and linked with a higher risk of developing breast cancer. For example, the BRCA1 mutation is associated with a 60 - 80% lifetime risk of breast cancer and the BRCA2 mutation with a 40 - 60% risk [4]. It is therefore understandable that women with a family history of breast cancer have a higher than normal perceived risk for developing the disease. They also experience more worry and intrusive thoughts about it in their daily life [5]. Research efforts seek to quantify the effect of family history of breast cancer on otherwise healthy women's lives. One particular question of interest is if women with a family history of breast cancer react differently to acute stress.

A study from 2004 demonstrated that women with a family history of breast cancer had a higher rate of epinephrine excretion while at work and were more reactive to work stress. This effect was moderated by BMI, with lower BMI's being associated with a more pronounced effect [6]. The more intense reaction to stress from women with a family history of breast cancer has also

been studied in a laboratory setting. After a 15-minute laboratory stress test involving speech and math tasks, women with a family history of breast cancer demonstrated a greater increase in distress, heart rate, natural killer cell activity and natural killer cell numbers [7]. Another study used the same stress test to show significant differences in epinephrine and cortisol reactivity between women with and without family histories of breast cancer. This study found that women with a family history of breast cancer had a stronger reaction to stress [8]. The current study uses the same laboratory stress test to compare stress reactivity between women with and without a family history of breast cancer by measuring their autonomic nervous system activity.

1.1 THE AUTONOMIC NERVOUS SYSTEM AND HEART RATE VARIABILITY

The human autonomic nervous system has two branches, the sympathetic and the parasympathetic. The parasympathetic nervous system maintains internal regulation while the sympathetic nervous system drives activities such as the fight or flight impulse. The two systems exist in a dynamic balance that can change rapidly in response to the surrounding environment [9]. During a stressful event, parasympathetic activity decreases and sympathetic activity increases. This occurs to minimize energy expenditure [9]. Heart rate variability (HRV), the variation in the intervals between consecutive heart beats, can be used to measure the activity of the sympathetic and parasympathetic nervous system [10]. A 1981 study demonstrated that HRV is a “sensitive, quantitative and noninvasive” measure of the autonomic nervous system [15].

The following measures of HRV, which can be grouped into time domain and frequency domain measures, are calculated from small segments (typically two to five minutes) of an electrocardiograph (ECG) recording. Each of the QRS complexes is detected and the normal-to-

normal (NN) intervals (the intervals between adjacent QRS complexes) are determined. The QRS complex from a continuous ECG record is shown in Figure 1 [12].

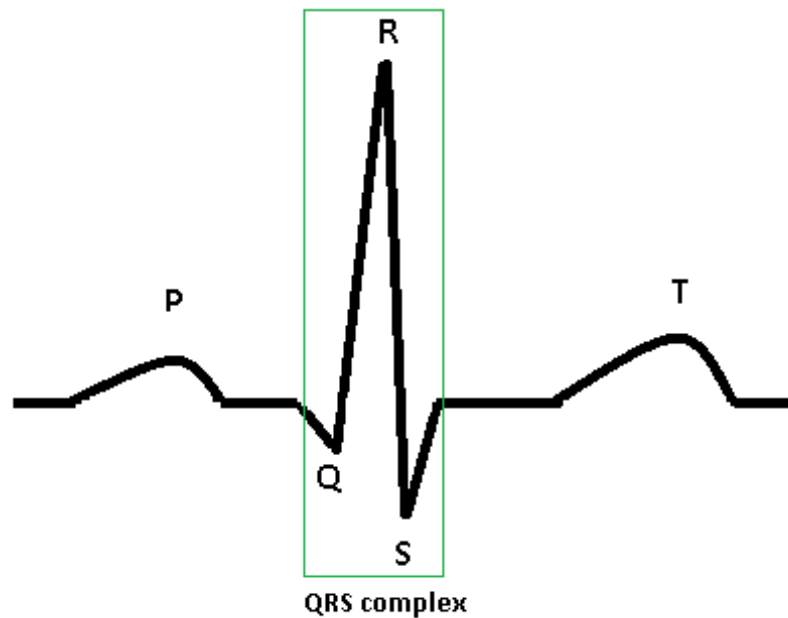


Figure 1. The QRS complex from a continuous ECG record

Time domain measures are the simplest to perform and describe aspects of the NN interval. When calculating time domain measures it is assumed that the correlation between adjacent time points is best explained by the dependence of the current value on past values [13]. The standard deviation of the NN intervals, SDNN, is a common time domain measure based on this interval. The standard deviation of the average NN interval calculated over short periods, SDANN, is another common time domain measure. Three time domain measures of short term variation, RMSSD, NN50, and pNN50, estimate high frequency variations in heart rate. RMSSD is the

square root of the mean squared difference of successive NN intervals, NN50 is the number of interval differences of successive NN intervals that are greater than 50 ms, and pNN50 is NN50 divided by the total number of NN intervals [10].

Frequency domain methods measure the power spectral density (PSD) that describes how the power, or variance, is distributed as a function of frequency [10]. The primary characteristic of interest is the periodic variations found in the data. We assume that the time series we are analyzing is composed of periodic components that appear in proportion to their underlying variances. The variance associated with each periodicity of interest is evaluated separately [13]. There are three spectral components of interest in short-term recordings lasting roughly two to five minutes. They are the very low frequency (VLF), the low frequency (LF), and high frequency (HF) components [10]. Of particular interest are the HF component of frequencies between 0.15 and 0.40 Hz and the LF component of frequencies between 0.04 and 0.15 Hz. Changes in the balance between the sympathetic and parasympathetic nervous system are reflected in the LF and HF measures. The HF component is an approximate measure of parasympathetic activity while the ratio of LF to HF power is an approximate measure of sympathetic activity [10]. During stress when parasympathetic activity decreases and sympathetic activity increases, one would expect the HF component to decrease and the ratio of LF to HF to increase. The HF power component can also be measured in normalized units (nu) which represent the relative value of HF in proportion to the total power minus the VLF component [10].

The PSD can be thought of as an analogue of the probability density function (PDF). Similar to the PDF, the PSD is a theoretical population based concept that we can only estimate by sampling data. The Fast Fourier Transformation (FFT) is a commonly used non-parametric

method of estimating the PSD using sampled data. The FFT produces consistent estimators of the HF, LF, and ratio of LF to HF denoted fftHF , fftLF and fftLFOverHF [13].

For observed data of length T , X_1, \dots, X_T , the FFT is computed at Fourier frequencies $\omega_j = j/T$ for $j = 1, \dots, T$ as

$$d_j = T^{-1/2} \sum_{t=1}^T X_t e^{2\pi i t \omega_j}$$

The square moduli of the FFTs, known as the periodogram,

$$I_j = |d_j|^2$$

are approximately independent and unbiased estimators of the power spectrum [13]. Consequently, summing periodogram values within a range of frequencies provides consistent estimators of a spectral component. Particularly, we consider

$$\text{fftHF} = \sum_{0.15T \leq j \leq 0.40T} I_j$$

$$\text{fftLF} = \sum_{0.04T \leq j \leq 0.15T} I_j,$$

which are consistent estimators of HF and LF, and $\text{fftLFOverHF} = \text{fftLF}/\text{fftHF}$, which is a consistent estimator of the ratio of power from low frequencies compared to high frequencies.

1.2 RESEARCH OBJECTIVES

This paper seeks to compare modulation of the two branches of the autonomic nervous system via HRV between healthy women with and without a family history of breast cancer. We use mixed models to compare HRV between women with and without a family history breast cancer during a common laboratory stress test. The results of the study can be used to further our understanding

of the psychological and physiological effects of having a family history of breast cancer on healthy women. Breast cancer is a huge burden in the U.S., not just for women who develop the disease but also for women who have a family history of it. Previous studies have shown the effect of a family history of breast cancer on women's immune systems and stress hormone levels. This study can help to clarify the effects of family history of breast cancer on stress reactivity of healthy women.

2.0 METHODS

Participants signed informed consent and completed a laboratory-based stress test. All participants were healthy women who either had a family history of breast cancer (FH+) or did not have a family history of breast cancer (FH-). There was a 10-minute baseline period (baseline) before the test and a 10-minute recovery session (recovery) after the stress test. During these resting periods and throughout the stress test, participants' heart rate was continuously recorded using a 3-lead ECG. The stress test was the Trier Social Stress Test (TSST), which includes speech preparation (task 1) and presentation (task 2) for 10 minutes followed by completing math problems orally in front of an evaluator and video camera for five minutes (task 3) [14].

2.1 STATISTICAL ANALYSIS

In the basic linear regression model, there is an assumption that the random errors are independent. This assumption is violated when repeated measures are taken over time from an individual. We would expect measurements taken from the same individual to be correlated. That is, measurements from the same person will be more similar to each other than measurements from different individuals. Mixed effects models allow us to specify a pattern for the correlation of measurements taken from the same subject over time. This technique provides more accurate estimates than we would get if we were to use simple linear regression. The mixed model allows estimation of group differences at each time point while taking the within-subject correlation into

account. It also makes it possible for us to assess whether there is a difference in the way in which HRV measurements change over time between the two groups.

The pattern that we specified for the correlation between an individual's measurements is compound symmetry. In compound symmetry, the correlation is the same value for any two repeated measurements taken from a given individual. The model specifications are demonstrated as follows:

$$y_{ijk} = \alpha_j + \beta_k + \gamma_{jk} + \theta_1 \cdot x_{1i} + \dots + \theta_p \cdot x_{pi} + \epsilon_{ijk}$$

where y_{ijk} is the HRV outcome value for subject i of group j (FH- or FH+) at stage k of the stress test and ϵ_{ijk} is the random error associated with this observation. We let $j = 0$ represent the FH- group and $j = 1$ represent the FH+ group. Since there were five stages of the stress test let $k = 0, 1, 2, 3, 4$ where $k = 0$ represents baseline and $k=4$ represents the recovery stage. The group effect for group j is denoted by α_j , the time (stage of stress test) effect for stage k is denoted by β_k and their interaction effect is γ_{jk} . The p covariates are x_1, \dots, x_p with corresponding coefficients $\theta_1, \dots, \theta_p$. We assume the random errors are normally distributed, $\epsilon_{ijk} \sim N(0, R_i)$, where R_i is the covariance matrix of residuals for individual i . We also assume that R_i has compound symmetry, that is, for a given individual i ,

$$R_i = \begin{pmatrix} \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 \end{pmatrix}$$

where σ^2 is the variance for each time point and $\rho\sigma^2$ is the covariance between two time points.

Here the covariances are all equal to some unspecified multiple, ρ , of the variance.

The model simplifies the construction of linear contrasts. As an example, consider the mean difference between FH+ and FH- at stage k of the stress test. This can be represented by the model as

$$(\alpha_1 - \alpha_0) + (\gamma_{1k} - \gamma_{0k}) .$$

The change from baseline to stage k for the FH- group is given by

$$(\beta_k - \beta_0) + (\gamma_{0k} - \gamma_{00}) .$$

The difference in the change from baseline to stage k between FH+ and FH- is given by

$$(\gamma_{1k} - \gamma_{10}) - (\gamma_{0k} - \gamma_{00}) .$$

We used SAS to fit this repeated measures mixed effects ANCOVA model for the data for nine HRV derived outcomes. The time domain HRV outcome measures were SDNN, SDSD, RMSSD, NN50, pNN50, and SDANN. The frequency domain measures were fftHF, fftHFnu, and fftLFOverHF.

One of the assumptions of the ANCOVA model is a normal outcome. Each of the nine HRV measures were mathematically transformed so that a histogram of their values followed an approximately normal curve. The SDNN, SDSD, RMSSD, SDANN, fftHF measurements were transformed by taking the natural log of their values plus one. One was added before taking the log because if there were any zeros then taking the log of zero would become an infinite value. The log transformation was used because these outcomes were right-skewed. The NN50 and pNN50 measures were transformed by taking the square root of their value added to 0.5. This transformation was used since these measures are based on counts occurring in a fixed interval. Finally, the fftLFOverHF measure was log transformed.

3.0 RESULTS

3.1 DESCRIPTIVE STATISTICS

All women in the study were healthy (via self-report, physical exam, and blood screening) and premenopausal. The mean age of women in the study was 33.5 years, the majority were white (76%), well educated (87%), unmarried (52%), and did not have children (65%). The 222 women in the study were divided into two groups. The first group of women reported no family history of breast cancer in a first degree relative (FH-, n=140). The second group of women reported that a first degree relative had breast cancer in the past (FH+, n=82). The women in the FH- group were shown to be significantly older than those in the FH+ group via a t-test (FH- 34.3 years \pm 7.9; FH+ 32.1 years \pm 7.0; p=0.04). T-tests revealed that there was no significant difference between the groups in BMI or baseline anxiety score (POMS). This measure was included in the mixed model as a covariate to account for any differences among subjects in their baseline level of anxiety. A chi squared test showed that race differed significantly between groups with FH- being composed of 71% white women and FH+ being 83% white women (p=0.05). Education level, marriage status, and whether or not they had children did not differ significantly between the two groups. Age and BMI have been shown to be significantly associated with HRV so these covariates were included in the mixed model [11]. Race was included in the model as a binary covariate (white or other) since it differed significantly between the two groups of interest. The final model included age, race, BMI, and baseline anxiety as covariates. A summary of socio-demographics for the two groups is presented in Table 1.

Table 1. Demographics

Characteristic	Total (n=222)	FH+ (n=82)	FH- (n=140)	P-value
Age(years), mean \pm SD	33.49 \pm 7.63	32.15 \pm 7.02	34.27 \pm 7.88	0.04
BMI(kg/m ²), mean \pm SD	26.09 \pm 5.50	25.90 \pm 5.66	26.19 \pm 5.42	0.70
Baseline Anxiety(POMS), mean \pm SD	1.95 \pm 2.22	2.04 \pm 2.28	1.89 \pm 2.19	0.64
Race(white), n(%)	168(75.68)	68(82.93)	100(71.43)	0.05
Married, n(%)	114(51.58)	45(54.88)	69(49.64)	0.45
College graduate, n(%)	194(87.39)	72(87.80)	122(87.14)	0.89
Has children, n(%)	77(34.85)	23(28.05)	54(38.85)	0.10

3.2 MIXED MODEL RESULTS

All of the HRV measures showed significant changes from baseline to each of the tasks in the TSST for both the FH- and FH+ group. The coefficients for the task effect was significant for each of the outcomes. Only one of the HRV measures, high frequency power (fftHF), showed significant group differences. The p-value associated with the interaction effect between group and stage of the stress test was <0.01. Table 2 shows the p-values associated with the three main effects for each of the HRV outcomes. Covariates were included in each of the models but their p-values are not shown. As discussed previously, each of the outcomes was transformed so that a histogram of its values appeared approximately normal.

Table 2. P-values for main effects

	Group (FH+ or FH-)	Time (stage of test)	Interaction
SDNN	0.69	<0.01	0.87
SDSD	0.58	<0.01	0.93
RMSSD	0.58	<0.01	0.93
NN50	0.05	<0.01	0.70
pNN50	0.09	<0.01	0.51
SDANN	0.98	<0.01	0.90
fftHF	0.20	<0.01	<0.01
fftHFnu	0.34	<0.01	0.57
fftLFOverHF	0.22	<0.01	0.33

*P-values from type 3 test for fixed effects

As previously discussed, fftHF and fftLFOverHF provide indirect measures of parasympathetic and sympathetic nervous system activity. To provide a complete picture of autonomic activity during the stress test, we investigated results for both fftHF and fftLFOverHF. Tables 3 and 4 give estimates for the model coefficients for these two outcomes. Age was the only significant covariate for both outcomes. Each task of the stress test was a significant predictor of the fftLF outcome. All of the tasks except task 1 were significant predictors of the fftLFOverHF outcome. For the fftHF outcome, the group by time interaction was significant for the second and third tasks. None of the interactions were significant for the fftLFOverHF outcome.

Table 3. Results of ln(fftHF) model

	Unadjusted			Adjusted		
	Coefficient	Standard Error	P-value	Coefficient	Standard Error	P-value
Intercept	6.95	0.11	<0.01	8.92	0.40	<0.01
FH-	-0.15	0.14	0.29	-0.06	0.14	0.64
Baseline	-0.76	0.05	<0.01	-0.77	0.05	<0.01
Task 1	-1.04	0.08	<0.01	-1.04	0.08	<0.01
Task 2	-1.10	0.08	<0.01	-1.11	0.09	<0.01
Task 3	-1.05	0.08	<0.01	-1.04	0.08	<0.01
FH-*baseline	0.02	0.06	0.69	0.05	0.06	0.46
FH-*task 1	-0.09	0.10	0.38	-0.09	0.10	0.37
FH-*task 2	-0.28	0.10	0.01	-0.27	0.10	0.01
FH-*task 3	-0.20	0.10	0.04	-0.21	0.10	0.03
Age				-0.05	0.01	<0.01
White				0.01	0.15	0.95
BMI				-0.02	0.01	0.17
Anxiety				0.03	0.03	0.32

*FH+ and Recovery were reference groups

Table 4. Results of ln(fftLFOverHF) model

	Unadjusted			Adjusted		
	Coefficient	Standard Error	P-value	Coefficient	Standard Error	P-value
Intercept	0.59	0.08	<0.01	0.13	0.26	0.63
FH-	-0.19	0.10	0.06	-0.19	0.10	0.06
Baseline	-0.46	0.05	<0.01	-0.46	0.05	<0.01
Task 1	0.00	0.08	1.00	-0.01	0.08	0.91
Task 2	0.39	0.08	<0.01	0.39	0.08	<0.01
Task 3	0.26	0.08	<0.01	0.25	0.08	<0.01
FH-*baseline	0.12	0.06	0.05	0.12	0.07	0.06
FH-*task 1	0.00	0.10	0.98	0.01	0.11	0.95
FH-*task 2	0.13	0.10	0.20	0.13	0.11	0.21
FH-*task 3	0.10	0.10	0.33	0.12	0.11	0.28
Age				0.01	0.01	0.02
White				-0.13	0.10	0.18
BMI				0.00	0.01	0.93
Anxiety				0.01	0.02	0.59

*FH+ and Recovery were reference groups

For both groups, fftHF was significantly lower at each of the tasks than it was at baseline. This is expected, because parasympathetic activity decreases during stress. For both groups, fftHF was significantly higher at recovery than at baseline. At baseline, the first task (speech preparation), and at recovery there was no significant difference in fftHF between the two groups. During the second task (presentation), the FH+ group had a significantly higher fftHF. The FH- group had a significantly larger decrease from baseline to tasks 2 and 3. The FH- group had a significantly larger increase in fftHF from both tasks 2 and 3 to recovery. A summary of these group differences can be seen in Table 5 and a graph of the changes in fftHF throughout the stress test for both groups can be seen in Figure 2 and Figure 3.

Table 5. Group differences (FH+ vs FH-) in ln(fftHF)

Contrast	Estimate	Standard Error	P-value
Baseline	0.02	0.13	0.89
Task 1	0.15	0.14	0.32
Task 2	0.33	0.16	0.03
Task 3	0.28	0.16	0.08
Recovery	0.06	0.14	0.64
Task 1 – baseline	0.14	0.09	0.15
Task 2 – baseline	0.31	0.09	<0.01
Task 3 – baseline	0.26	0.09	0.01
Recovery – baseline	0.05	0.06	0.46
Task 2 – task 1	0.18	0.12	0.14
Task 3 – task 1	0.12	0.12	0.32
Recovery – task 1	-0.09	0.10	0.37
Task 3 – task 2	-0.06	0.12	0.64
Recovery – task 2	-0.27	0.10	0.01
Recovery – task 3	-0.21	0.10	0.03

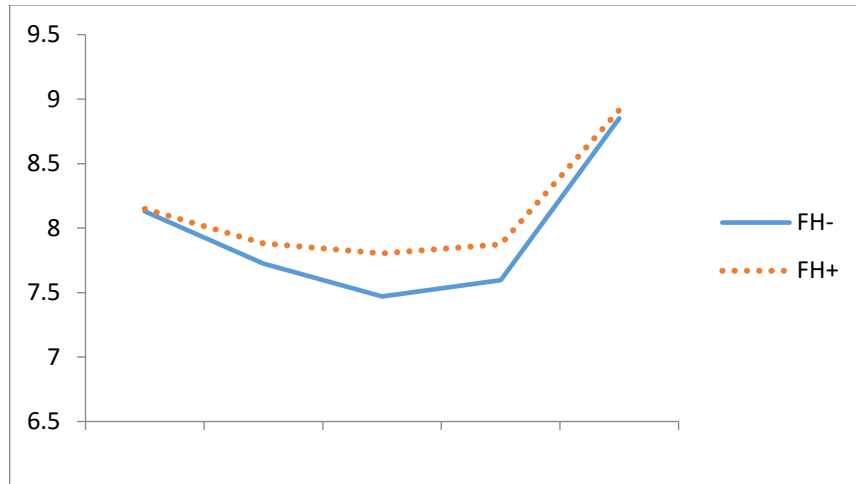


Figure 2. Mixed model estimates of ln(fftHF) over stages of stress test

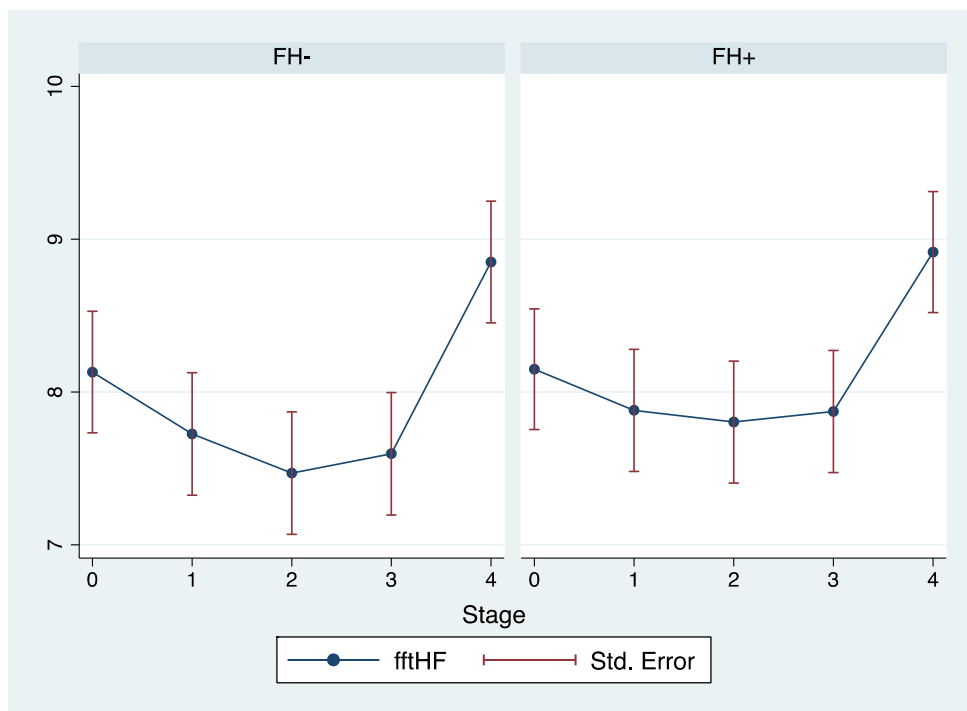


Figure 3. Mixed model estimates of ln(fftHF) over stages of stress test with standard error bars

The ratio of low frequency to high frequency (fftLFOverHF) measures sympathetic modulation. For both groups, fftLFOverHF was significantly higher at each of the tasks than it was at baseline. For both groups, fftLFOverHF was significantly higher at recovery than at baseline. There was no significant difference in fftLFOverHF between groups during baseline, each of the tasks, and recovery. There was also no significant difference in the changes in fftLFOverHF from baseline to each of the tasks and to recovery between the two groups. A summary of these group differences can be seen in Table 6 and graph of the changes in fftLFOverHF throughout the stress test for both groups is shown in Figure 4 and Figure 5.

Table 6. Group differences (FH+ vs FH-) in ln(fftLFOverHF)

Contrast	Estimate	Standard Error	P-value
Baseline	0.06	0.09	0.49
Task 1	0.18	0.12	0.15
Task 2	0.05	0.12	0.67
Task 3	0.07	0.12	0.58
Recovery	0.19	0.10	0.06
Task 1 – baseline	0.12	0.10	0.24
Task 2 – baseline	-0.01	0.10	0.92
Task 3 – baseline	0.01	0.10	0.94
Recovery – baseline	0.12	0.07	0.06
Task 2 – task 1	-0.13	0.13	0.33
Task 3 – task 1	-0.11	0.13	0.40
Recovery – task 1	0.01	0.11	0.95
Task 3 – task 2	0.02	0.13	0.90
Recovery – task 2	0.13	0.11	0.21
Recovery – task 3	0.12	0.11	0.28

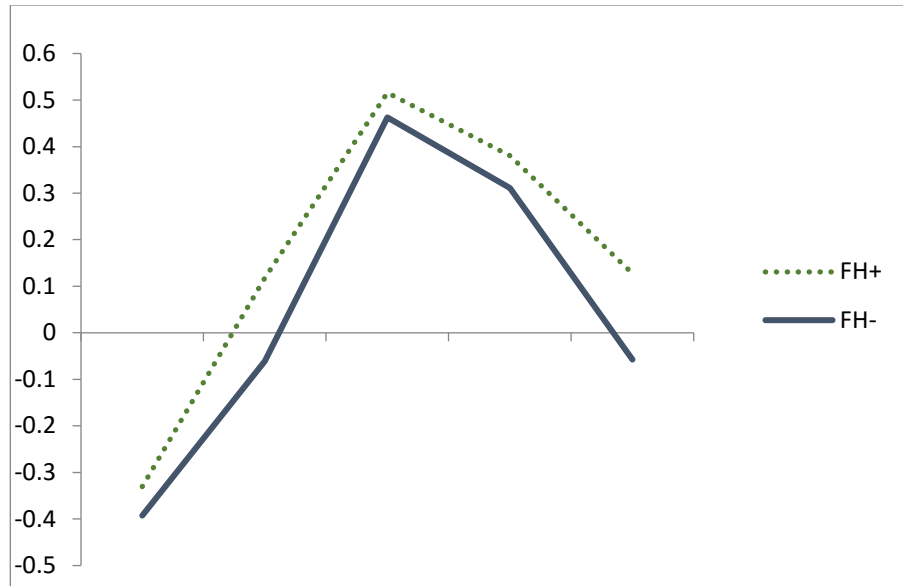


Figure 4. Mixed model estimates of $\ln(\text{fftLFOverHF})$ over stages

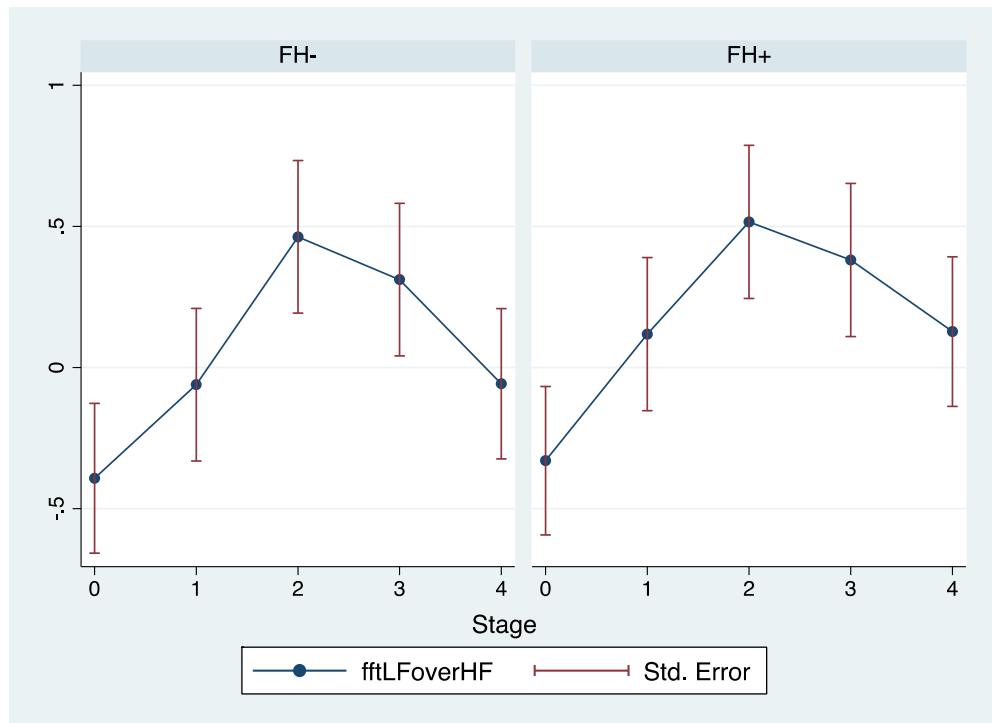


Figure 5. Mixed model estimates of $\ln(\text{fftLFOverHF})$ over stages of stress test with standard error bars

Figures 2 and 3 show that the $fftHF$ values graphed over the stages of the stress test result in a concave up parabola. From Figure 2 we can see that the curve for the FH+ groups has higher values of $fftHF$ than the curve for the FH- group. The difference between the points on the curve becomes significant only for the second task. The negative slope of the FH- curve is significantly steeper from baseline to tasks 2 and 3 and its positive slope is also significantly steeper from tasks 2 and 3 to the recovery stage.

Figures 4 and 5 show that the $fftLFOverHF$ values graphed over stages of the stress test result in a concave down parabola. While the differences between the curves is not significant, the graph shows that the FH+ curve has consistently higher values of $fftLFOverHF$.

For mixed models we assume that the residuals are normally distributed about zero and uncorrelated (that is, residuals from different subjects are not correlated). This assumption was checked and it was found that the residuals were normally distributed about zero for both the $fftHF$ and $fftLFOverHF$ outcomes. This can be seen in the plots shown in Figures 6 and 7. The residuals appear to be evenly distributed about zero and do not show a pattern or heteroscedasticity. The histograms of the residuals look like fairly close approximations of normal curves. The QQ-plots show that the residuals closely approximate a normal distribution.

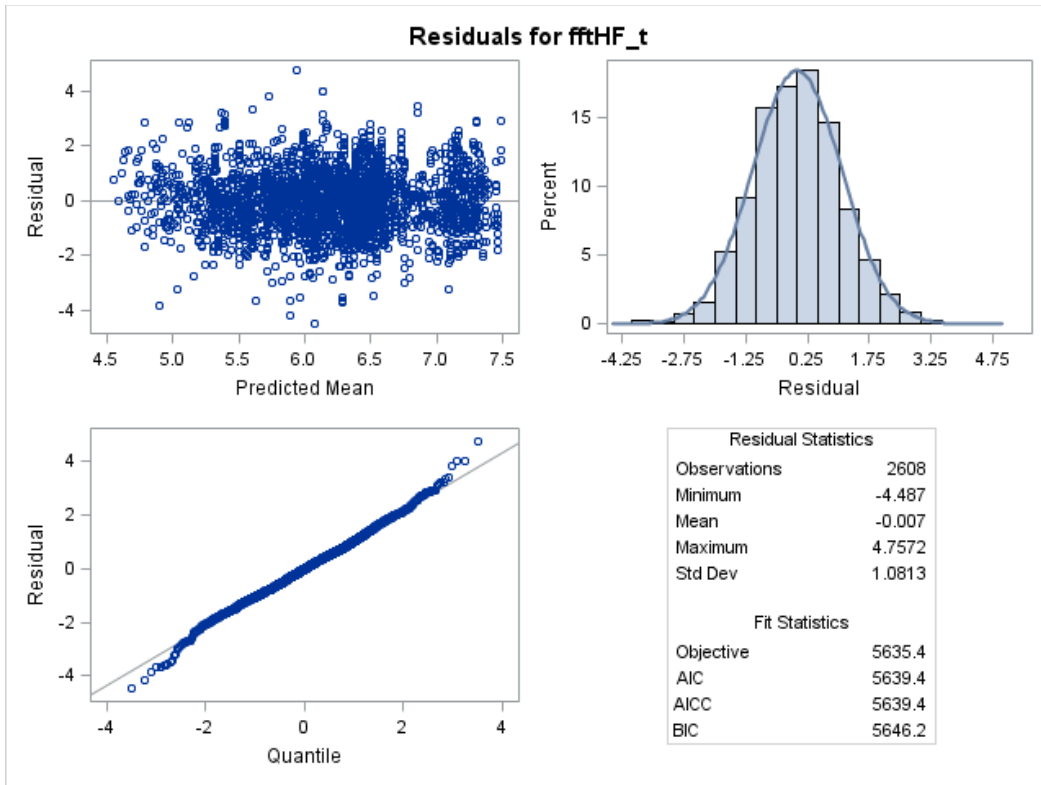


Figure 6. Residual diagnostics for $\ln(\text{fftHF})$

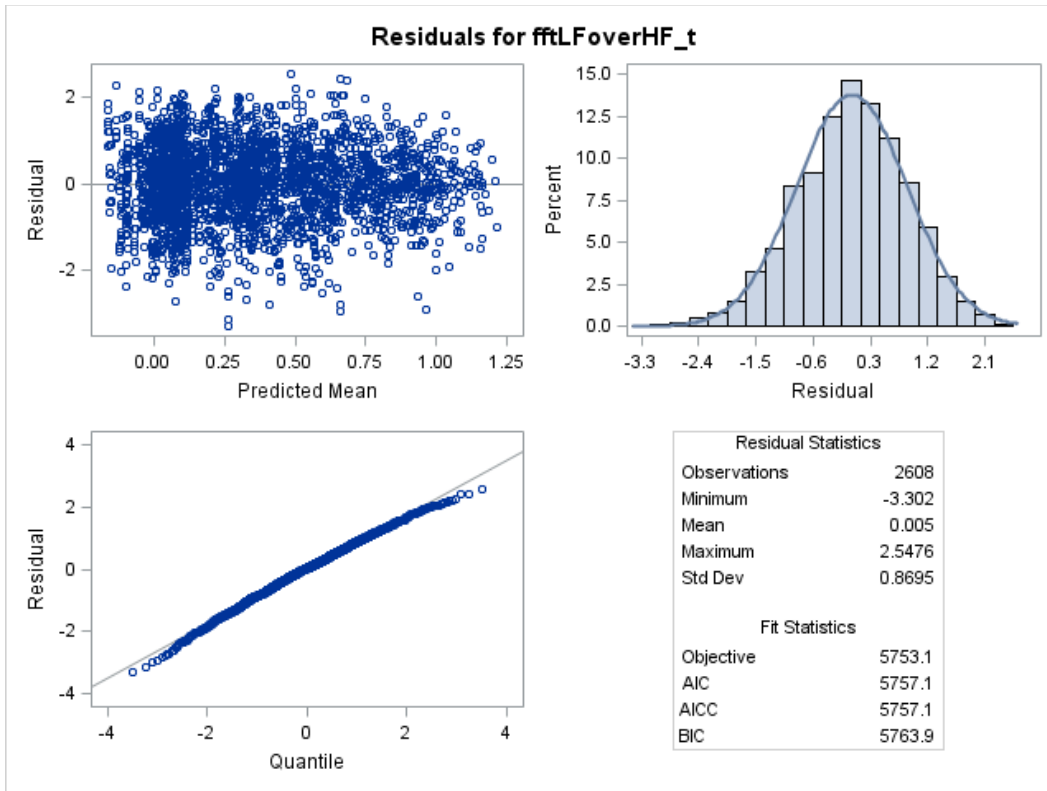


Figure 7. Residual diagnostics for $\ln(\text{LFOverHF})$

4.0 DISCUSSION

The plots of the fftHF and fftLFOverHF outcomes over time in Figures 2 through 5 coincide with the current understanding of the activity of the sympathetic and parasympathetic system. In response to stress we would expect fight or flight (sympathetic activity) to “kick in”. In order to conserve energy, the activity of the parasympathetic nervous system decreases as the sympathetic activity increases. This can be seen in the aforementioned figures since the fftHF values, which measures parasympathetic activity, decrease from baseline to the speech and verbal math activities and then increase when the tasks are over. The values of fftHF during the recovery period are higher than those at baseline. The recovery stage may be a better approximation of baseline levels since subjects may have been nervous about the test before it started. This is a possible explanation for the differences in values of fftHF between baseline and recovery for both groups.

The fftLFOverHF values, a measure of sympathetic activity, increased from baseline to the two tasks then decrease to recovery. This spike in activity was likely caused by the subject’s stress response to the TSST. The TSST has been shown to affect the stress levels of subjects in multiple other studies. For example, two different studies showed the heightened physiological response and endocrine response during the TSST for women with a family history of breast cancer [7], [8]. The mirroring of the stress exposure by the HRV measures, fftHF and fftLFOverHF , show that they are good proxies for sympathetic and parasympathetic activity.

Figures 2 and 4 both show that the estimates for women with a family history of breast cancer were above the estimates of those without a family history of breast cancer. This could mean that these women have an elevated level of activity in the two branches of their nervous

system. This result would agree with the findings of previous studies that showed that women with a family history of breast cancer reacted more severely to stress tests [7], [8].

Because there is minimal missing data and the results found in this study agree with previous findings, it is likely that we are observing a real difference in stress reactivity among women with and without a family history of breast cancer. This finding is a demonstration of one of the effects of a family history of breast cancer on women's physiology. Future work may seek to find other ways these women are different physically and psychologically.

4.1 LIMITATIONS

The study sample was relatively small and the participants were mostly young, very well educated and mainly white. This limits the generalizability of the results. Also, participants volunteered to be in the study and the flyers were placed around a university campus so this was not a true random sample of women living in the area.

APPENDIX: SAS CODE

```
dm 'log;clear;output;clear';
options nodate ls=113 ps=63 pageno=1;
footnotel 'End of Page';

libname v1 "\\Mac\Home\Desktop\Thesis";
options nofmterr;

data wsrs;
set v1.wsrs;
where haveEADSD=1; *only want people who completed the stress test;
run;

data wsrs_long; *transform data wide to long;
set wsrs;

time=1;
SDNN=SDNNs1;
SDSD=SDSDs1;
RMSSD=RMSSDs1;
NN50=NN50s1;
pNN50=pNN50s1;
SDANN=SDANNs1;
fftHF=fftHFs1;
fftHFnu=fftHFnus1;
fftLFoverHF=fftLFoverHFs1;
output;

time=2;
SDNN=SDNNs2;
SDSD=SDSDs2;
RMSSD=RMSSDs2;
NN50=NN50s2;
pNN50=pNN50s2;
SDANN=SDANNs2;
```



```
fftHF=fftHF2;  
fftHFnu=fftHFnu2;  
fftLFOverHF=fftLFOverHF2;  
output;
```

```
time=3;  
SDNN=SDNNs3;  
SDSD=SDSDs3;  
RMSSD=RMSSDs3;  
NN50=NN50s3;  
pNN50=pNN50s3;  
SDANN=SDANNs3;  
fftHF=fftHF3;  
fftHFnu=fftHFnu3;  
fftLFOverHF=fftLFOverHF3;  
output;
```

```
time=4;  
SDNN=SDNNs4;  
SDSD=SDSDs4;  
RMSSD=RMSSDs4;  
NN50=NN50s4;  
pNN50=pNN50s4;  
SDANN=SDANNs4;  
fftHF=fftHF4;  
fftHFnu=fftHFnu4;  
fftLFOverHF=fftLFOverHF4;  
output;
```

```
time=5;  
SDNN=SDNNs5;  
SDSD=SDSDs5;  
RMSSD=RMSSDs5;  
NN50=NN50s5;  
pNN50=pNN50s5;  
SDANN=SDANNs5;  
fftHF=fftHF5;  
fftHFnu=fftHFnu5;
```

```
fftLFoverHF=fftLFoverHFs5;  
output;
```

```
time=6;  
SDNN=SDNNs6;  
SDSD=SDSDs6;  
RMSSD=RMSSDs6;  
NN50=NN50s6;  
pNN50=pNN50s6;  
SDANN=SDANNs6;  
fftHF=fftHFs6;  
fftHFnu=fftHFnus6;  
fftLFoverHF=fftLFoverHFs6;  
output;
```

```
time=7;  
SDNN=SDNNs7;  
SDSD=SDSDs7;  
RMSSD=RMSSDs7;  
NN50=NN50s7;  
pNN50=pNN50s7;  
SDANN=SDANNs7;  
fftHF=fftHFs7;  
fftHFnu=fftHFnus7;  
fftLFoverHF=fftLFoverHFs7;  
output;
```

```
time=8;  
SDNN=SDNNs8;  
SDSD=SDSDs8;  
RMSSD=RMSSDs8;  
NN50=NN50s8;  
pNN50=pNN50s8;  
SDANN=SDANNs8;  
fftHF=fftHFs8;  
fftHFnu=fftHFnus8;  
fftLFoverHF=fftLFoverHFs8;  
output;
```

```
time=9;
SDNN=SDNNs9;
SDSD=SDSDs9;
RMSSD=RMSSDs9;
NN50=NN50s9;
pNN50=pNN50s9;
SDANN=SDANNs9;
fftHF=fftHFs9;
fftHFnu=fftHFnus9;
fftLFoverHF=fftLFoverHFs9;
output;

time=10;
SDNN=SDNNs10;
SDSD=SDSDs10;
RMSSD=RMSSDs10;
NN50=NN50s10;
pNN50=pNN50s10;
SDANN=SDANNs10;
fftHF=fftHFs10;
fftHFnu=fftHFnus10;
fftLFoverHF=fftLFoverHFs10;
output;

time=11;
SDNN=SDNNs11;
SDSD=SDSDs11;
RMSSD=RMSSDs11;
NN50=NN50s11;
pNN50=pNN50s11;
SDANN=SDANNs11;
fftHF=fftHFs11;
fftHFnu=fftHFnus11;
fftLFoverHF=fftLFoverHFs11;
output;

time=12;
```

```

SDNN=SDNNs12;
SDSD=SDSDs12;
RMSSD=RMSSDs12;
NN50=NN50s12;
pNN50=pNN50s12;
SDANN=SDANNs12;
fftHF=fftHFs12;
fftHFnu=fftHFnus12;
fftLFoverHF=fftLFoverHFs12;
output;

keep id time age race_bin edu_bin mar_bin kid_bin sheight sweight SBMI
SBanxietyFJohn SDNN SDSD RMSSD NN50 pNN50 SDANN fftHF fftHFnu fftLFoverHF;
run;

data wsrs_long; *transform data to get normalized outcomes;
set wsrs_long;
SDNN_t=log(SDNN+1);
SDSD_t=log(SDSD+1);
RMSSD_t=log(RMSSD+1);
NN50_t=sqrt(NN50+0.5);
pNN50_t=sqrt(pNN50+0.5);
SDANN_t=log(SDANN+1);
fftHF_t=log(fftHF+1);
fftLFoverHF_t=log(fftLFoverHF);
run;

data combine; *create stages of stress test;
set wsrs_long;
stage = 1;
if time=7 then stage=2;
if time=8 then stage=3;
if time=9 then stage=4;
if time>9 then stage=5;
run;

proc mixed data=combine; *create mixed models for each of 9 HRV outcomes;

```

```

class FHjohn stage id; *FHjohn is group variable where 1=FH+;
model SDNN_t=FHjohn stage FHjohn*stage Age race_bin SBMI SBanxiety /solution;
repeated stage/subject=id type=cs;
estimate 'mean SDNN for FH- at baseline' intercept 1 FHjohn 1 0 stage 1
FHjohn*stage 1 0/E;
estimate 'mean SDNN for FH- at task 1' intercept 1 FHjohn 1 0 stage 0 1
FHjohn*stage 0 1/E;
estimate 'mean SDNN for FH- at task 2' intercept 1 FHjohn 1 0 stage 0 0 1
FHjohn*stage 0 0 1/E;
estimate 'mean SDNN for FH- at task 3' intercept 1 FHjohn 1 0 stage 0 0 0 1
FHjohn*stage 0 0 0 1/E;
estimate 'mean SDNN for FH- at recovery' intercept 1 FHjohn 1 0 stage 0 0 0 0
1 FHjohn*stage 0 0 0 0 1/E;
estimate 'mean SDNN for FH+ at baseline' intercept 1 FHjohn 0 1 stage 1
FHjohn*stage 0 0 0 0 0 1/E;
estimate 'mean SDNN for FH+ at task 1' intercept 1 FHjohn 0 1 stage 0 1
FHjohn*stage 0 0 0 0 0 0 1/E;
estimate 'mean SDNN for FH+ at task 2' intercept 1 FHjohn 0 1 stage 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 1/E;
estimate 'mean SDNN for FH+ at task 3' intercept 1 FHjohn 0 1 stage 0 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 0 1/E;
estimate 'mean SDNN for FH+ at recovery' intercept 1 FHjohn 0 1 stage 0 0 0 0
1 FHjohn*stage 0 0 0 0 0 0 0 0 0 1/E;
estimate 'change from baseline to task 1 for FH-' stage -1 1 0 0 0
Fhjohn*stage -1 1 0 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 2 for FH-' stage -1 0 1 0 0
Fhjohn*stage -1 0 1 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 3 for FH-' stage -1 0 0 1 0
Fhjohn*stage -1 0 0 1 0 0 0 0 0 0/E;
estimate 'change from baseline to recovery for FH-' stage -1 0 0 0 1
Fhjohn*stage -1 0 0 0 1 0 0 0 0 0/E;
estimate 'change from task 1 to recovery for FH-' stage 0 1 0 0 -1
FHjohn*stage 0 1 0 0 -1 0 0 0 0 0/E;
estimate 'change from task 2 to recovery for FH-' stage 0 0 1 0 -1
FHjohn*stage 0 0 1 0 -1 0 0 0 0 0/E;
estimate 'change from task 3 to recovery for FH-' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 1 -1 0 0 0 0 0/E;
estimate 'change from baseline to task 1 for FH+' stage -1 1 0 0 0

```

```

Fhjohn*stage 0 0 0 0 0 -1 1 0 0 0 /E;
estimate 'change from baseline to task 2 for FH+' stage -1 0 1 0 0
Fhjohn*stage 0 0 0 0 0 -1 0 1 0 0 /E;
estimate 'change from baseline to task 3 for FH+' stage -1 0 0 1 0
Fhjohn*stage 0 0 0 0 0 -1 0 0 1 0 /E;
estimate 'change from baseline to recovery for FH+' stage -1 0 0 0 1
Fhjohn*stage 0 0 0 0 0 -1 0 0 0 1 /E;
estimate 'change from task 1 to recovery for FH+' stage 0 1 0 0 -1
FHjohn*stage 0 0 0 0 0 0 1 0 0 -1 /E;
estimate 'change from task 2 to recovery for FH+' stage 0 0 1 0 -1
FHjohn*stage 0 0 0 0 0 0 0 1 0 -1 /E;
estimate 'change from task 3 to recovery for FH+' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 0 0 0 0 0 1 -1 /E;
estimate 'diff SDNN for FH+/- at baseline' FHjohn -1 1 FHjohn*stage -1 0 0 0
0 1 0 0 0 0 /E;
estimate 'diff SDNN for FH+/- at task 1' FHjohn -1 1 FHjohn*stage 0 -1 0 0
0 0 1 0 0 0 /E;
estimate 'diff SDNN for FH+/- at task 2' FHjohn -1 1 FHjohn*stage 0 0 -1 0
0 0 0 1 0 0 /E;
estimate 'diff SDNN for FH+/- at task 3' FHjohn -1 1 FHjohn*stage 0 0 0 -1
0 0 0 0 1 0 /E;
estimate 'diff SDNN for FH+/- at recovery' FHjohn -1 1 FHjohn*stage 0 0 0 0 -
1 0 0 0 0 1 /E;
estimate 'diff SDNN change (task 1- baseline) for FH+/-' FHjohn*stage 1 -1 0
0 0 -1 1 0 0 0 /E;
estimate 'diff SDNN change (task 2- baseline) for FH+/-' FHjohn*stage 1 0 -1
0 0 -1 0 1 0 0 /E;
estimate 'diff SDNN change (task 3- baseline) for FH+/-' FHjohn*stage 1 0 0 -
1 0 -1 0 0 1 0 /E;
estimate 'diff SDNN change (recovery- baseline) for FH+/-' FHjohn*stage 1 0 0
0 -1 -1 0 0 0 1 /E;
estimate 'diff SDNN change (task 2- task 1) for FH+/-' FHjohn*stage 0 1 -1 0
0 0 -1 1 0 0 /E;
estimate 'diff SDNN change (task 3- task 1) for FH+/-' FHjohn*stage 0 1 0 -1
0 0 -1 0 1 0 /E;
estimate 'diff SDNN change (recovery- task 1) for FH+/-' FHjohn*stage 0 1 0 0
-1 0 -1 0 0 1 /E;
estimate 'diff SDNN change (task 3- task 2) for FH+/-' FHjohn*stage 0 0 1 -1

```

```

0 0 0 -1 1 0/E;
estimate 'diff SDNN change (recovery- task 2) for FH+/-' FHjohn*stage 0 0 1 0
-1 0 0 -1 0 1/E;
estimate 'diff SDNN change (recovery- task 3) for FH+/-' FHjohn*stage 0 0 0 1
-1 0 0 0 -1 1/E;
run;

proc mixed data=combine;
class FHjohn stage id ;
model SDSD_t=FHjohn stage FHjohn*stage Age race_bin SBMI SBanxiety /solution;
repeated stage/subject=id type=cs;
estimate 'mean SDSD for FH- at baseline' intercept 1 FHjohn 1 0 stage 1
FHjohn*stage 1 0/E;
estimate 'mean SDSD for FH- at task 1' intercept 1 FHjohn 1 0 stage 0 1
FHjohn*stage 0 1/E;
estimate 'mean SDSD for FH- at task 2' intercept 1 FHjohn 1 0 stage 0 0 1
FHjohn*stage 0 0 1/E;
estimate 'mean SDSD for FH- at task 3' intercept 1 FHjohn 1 0 stage 0 0 0 1
FHjohn*stage 0 0 0 1/E;
estimate 'mean SDSD for FH- at recovery' intercept 1 FHjohn 1 0 stage 0 0 0 0
1 FHjohn*stage 0 0 0 0 1/E;
estimate 'mean SDSD for FH+ at baseline' intercept 1 FHjohn 0 1 stage 1
FHjohn*stage 0 0 0 0 0 1/E;
estimate 'mean SDSD for FH+ at task 1' intercept 1 FHjohn 0 1 stage 0 1
FHjohn*stage 0 0 0 0 0 0 1/E;
estimate 'mean SDSD for FH+ at task 2' intercept 1 FHjohn 0 1 stage 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 1/E;
estimate 'mean SDSD for FH+ at task 3' intercept 1 FHjohn 0 1 stage 0 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 0 1/E;
estimate 'mean SDSD for FH+ at recovery' intercept 1 FHjohn 0 1 stage 0 0 0 0
1 FHjohn*stage 0 0 0 0 0 0 0 0 0 1/E;
estimate 'change from baseline to task 1 for FH-' stage -1 1 0 0 0
Fhjohn*stage -1 1 0 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 2 for FH-' stage -1 0 1 0 0
Fhjohn*stage -1 0 1 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 3 for FH-' stage -1 0 0 1 0
Fhjohn*stage -1 0 0 1 0 0 0 0 0 0/E;
estimate 'change from baseline to recovery for FH-' stage -1 0 0 0 1

```

```

Fhjohn*stage -1 0 0 0 1 0 0 0 0 0/E;
estimate 'change from task 1 to recovery for FH-' stage 0 1 0 0 -1
FHjohn*stage 0 1 0 0 -1 0 0 0 0 0/E;
estimate 'change from task 2 to recovery for FH-' stage 0 0 1 0 -1
FHjohn*stage 0 0 1 0 -1 0 0 0 0 0/E;
estimate 'change from task 3 to recovery for FH-' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 1 -1 0 0 0 0 0/E;
estimate 'change from baseline to task 1 for FH+' stage -1 1 0 0 0
Fhjohn*stage 0 0 0 0 0 -1 1 0 0 0/E;
estimate 'change from baseline to task 2 for FH+' stage -1 0 1 0 0
Fhjohn*stage 0 0 0 0 0 -1 0 1 0 0/E;
estimate 'change from baseline to task 3 for FH+' stage -1 0 0 1 0
Fhjohn*stage 0 0 0 0 0 -1 0 0 1 0/E;
estimate 'change from baseline to recovery for FH+' stage -1 0 0 0 1
Fhjohn*stage 0 0 0 0 0 -1 0 0 0 1/E;
estimate 'change from task 1 to recovery for FH+' stage 0 1 0 0 -1
FHjohn*stage 0 0 0 0 0 0 1 0 0 -1/E;
estimate 'change from task 2 to recovery for FH+' stage 0 0 1 0 -1
FHjohn*stage 0 0 0 0 0 0 0 1 0 -1/E;
estimate 'change from task 3 to recovery for FH+' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 0 0 0 0 0 1 -1/E;
estimate 'diff SDSD for FH+/- at baseline' FHjohn -1 1 FHjohn*stage -1 0 0 0
0 1 0 0 0 0 /E;
estimate 'diff SDSD for FH+/- at task 1' FHjohn -1 1 FHjohn*stage 0 -1 0 0 0
0 1 0 0 0 /E;
estimate 'diff SDSD for FH+/- at task 2' FHjohn -1 1 FHjohn*stage 0 0 -1 0 0
0 0 1 0 0 /E;
estimate 'diff SDSD for FH+/- at task 3' FHjohn -1 1 FHjohn*stage 0 0 0 -1 0
0 0 0 1 0 /E;
estimate 'diff SDSD for FH+/- at recovery' FHjohn -1 1 FHjohn*stage 0 0 0 0 -
1 0 0 0 0 1 /E;
estimate 'diff SDSD change (task 1- baseline) for FH+/-' FHjohn*stage 1 -1 0
0 0 -1 1 0 0 0 /E;
estimate 'diff SDSD change (task 2- baseline) for FH+/-' FHjohn*stage 1 0 -1
0 0 -1 0 1 0 0 /E;
estimate 'diff SDSD change (task 3- baseline) for FH+/-' FHjohn*stage 1 0 0 -
1 0 -1 0 0 1 0 /E;
estimate 'diff SDSD change (recovery- baseline) for FH+/-' FHjohn*stage 1 0 0

```



```

0 -1 -1 0 0 0 1 /E;
estimate 'diff SDS change (task 2- task 1) for FH+/-' FHjohn*stage 0 1 -1 0
0 0 -1 1 0 0 /E;
estimate 'diff SDS change (task 3- task 1) for FH+/-' FHjohn*stage 0 1 0 -1
0 0 -1 0 1 0 /E;
estimate 'diff SDS change (recovery- task 1) for FH+/-' FHjohn*stage 0 1 0 0
-1 0 -1 0 0 1 /E;
estimate 'diff SDS change (task 3- task 2) for FH+/-' FHjohn*stage 0 0 1 -1
0 0 0 -1 1 0/E;
estimate 'diff SDS change (recovery- task 2) for FH+/-' FHjohn*stage 0 0 1 0
-1 0 0 -1 0 1/E;
estimate 'diff SDS change (recovery- task 3) for FH+/-' FHjohn*stage 0 0 0 1
-1 0 0 0 -1 1/E;
run;

proc mixed data=combine;
class FHjohn stage id time;
model RMSSD_t=FHjohn stage FHjohn*stage Age race_bin SBMI SBanxiety/solution;
repeated stage/subject=id type=cs;
estimate 'mean RMSSD for FH- at baseline' intercept 1 FHjohn 1 0 stage 1
FHjohn*stage 1 0/E;
estimate 'mean RMSSD for FH- at task 1' intercept 1 FHjohn 1 0 stage 0 1
FHjohn*stage 0 1/E;
estimate 'mean RMSSD for FH- at task 2' intercept 1 FHjohn 1 0 stage 0 0 1
FHjohn*stage 0 0 1/E;
estimate 'mean RMSSD for FH- at task 3' intercept 1 FHjohn 1 0 stage 0 0 0 1
FHjohn*stage 0 0 0 1/E;
estimate 'mean RMSSD for FH- at recovery' intercept 1 FHjohn 1 0 stage 0 0 0
0 1 FHjohn*stage 0 0 0 0 1/E;
estimate 'mean RMSSD for FH+ at baseline' intercept 1 FHjohn 0 1 stage 1
FHjohn*stage 0 0 0 0 0 1/E;
estimate 'mean RMSSD for FH+ at task 1' intercept 1 FHjohn 0 1 stage 0 1
FHjohn*stage 0 0 0 0 0 0 1/E;
estimate 'mean RMSSD for FH+ at task 2' intercept 1 FHjohn 0 1 stage 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 1/E;
estimate 'mean RMSSD for FH+ at task 3' intercept 1 FHjohn 0 1 stage 0 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 0 1/E;
estimate 'mean RMSSD for FH+ at recovery' intercept 1 FHjohn 0 1 stage 0 0 0

```

```

0 1 FHjohn*stage 0 0 0 0 0 0 0 0 0 0 1/E;
estimate 'change from baseline to task 1 for FH-' stage -1 1 0 0 0
Fhjohn*stage -1 1 0 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 2 for FH-' stage -1 0 1 0 0
Fhjohn*stage -1 0 1 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 3 for FH-' stage -1 0 0 1 0
Fhjohn*stage -1 0 0 1 0 0 0 0 0 0/E;
estimate 'change from baseline to recovery for FH-' stage -1 0 0 0 1
Fhjohn*stage -1 0 0 0 1 0 0 0 0 0/E;
estimate 'change from task 1 to recovery for FH-' stage 0 1 0 0 -1
FHjohn*stage 0 1 0 0 -1 0 0 0 0 0/E;
estimate 'change from task 2 to recovery for FH-' stage 0 0 1 0 -1
FHjohn*stage 0 0 1 0 -1 0 0 0 0 0/E;
estimate 'change from task 3 to recovery for FH-' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 1 -1 0 0 0 0 0/E;
estimate 'change from baseline to task 1 for FH+' stage -1 1 0 0 0
Fhjohn*stage 0 0 0 0 0 -1 1 0 0 0/E;
estimate 'change from baseline to task 2 for FH+' stage -1 0 1 0 0
Fhjohn*stage 0 0 0 0 0 -1 0 1 0 0/E;
estimate 'change from baseline to task 3 for FH+' stage -1 0 0 1 0
Fhjohn*stage 0 0 0 0 0 -1 0 0 1 0/E;
estimate 'change from baseline to recovery for FH+' stage -1 0 0 0 1
Fhjohn*stage 0 0 0 0 0 -1 0 0 0 1/E;
estimate 'change from task 1 to recovery for FH+' stage 0 1 0 0 -1
FHjohn*stage 0 0 0 0 0 0 1 0 0 -1/E;
estimate 'change from task 2 to recovery for FH+' stage 0 0 1 0 -1
FHjohn*stage 0 0 0 0 0 0 0 1 0 -1/E;
estimate 'change from task 3 to recovery for FH+' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 0 0 0 0 0 1 -1/E;
estimate 'diff RMSSD for FH+/- at baseline' FHjohn -1 1 FHjohn*stage -1 0 0 0
0 1 0 0 0 0 /E;
estimate 'diff RMSSD for FH+/- at task 1' FHjohn -1 1 FHjohn*stage 0 -1 0 0 0
0 1 0 0 0 /E;
estimate 'diff RMSSD for FH+/- at task 2' FHjohn -1 1 FHjohn*stage 0 0 -1 0 0
0 0 1 0 0 /E;
estimate 'diff RMSSD for FH+/- at task 3' FHjohn -1 1 FHjohn*stage 0 0 0 -1 0
0 0 0 1 0 /E;
estimate 'diff RMSSD for FH+/- at recovery' FHjohn -1 1 FHjohn*stage 0 0 0 0

```

```

-1 0 0 0 0 1 /E;
estimate 'diff RMSSD change (task 1- baseline) for FH+/-' FHjohn*stage 1 -1 0
0 0 -1 1 0 0 0 /E;
estimate 'diff RMSSD change (task 2- baseline) for FH+/-' FHjohn*stage 1 0 -1
0 0 -1 0 1 0 0 /E;
estimate 'diff RMSSD change (task 3- baseline) for FH+/-' FHjohn*stage 1 0 0
-1 0 -1 0 0 1 0 /E;
estimate 'diff RMSSD change (recovery- baseline) for FH+/-' FHjohn*stage 1 0
0 0 -1 -1 0 0 0 1 /E;
estimate 'diff RMSSD change (task 2- task 1) for FH+/-' FHjohn*stage 0 1 -1 0
0 0 -1 1 0 0 /E;
estimate 'diff RMSSD change (task 3- task 1) for FH+/-' FHjohn*stage 0 1 0 -1
0 0 -1 0 1 0 /E;
estimate 'diff RMSSD change (recovery- task 1) for FH+/-' FHjohn*stage 0 1 0
0 -1 0 -1 0 0 1 /E;
estimate 'diff RMSSD change (task 3- task 2) for FH+/-' FHjohn*stage 0 0 1 -1
0 0 0 -1 1 0/E;
estimate 'diff RMSSD change (recovery- task 2) for FH+/-' FHjohn*stage 0 0 1
0 -1 0 0 -1 0 1/E;
estimate 'diff RMSSD change (recovery- task 3) for FH+/-' FHjohn*stage 0 0 0
1 -1 0 0 0 -1 1/E;
run;

```

```

proc mixed data=combine;
class FHjohn stage id time;
model NN50_t=FHjohn stage FHjohn*stage Age race_bin SBMI SBanxiety/solution;
repeated stage/subject=id type=cs;
estimate 'mean NN50 for FH- at baseline' intercept 1 FHjohn 1 0 stage 1
FHjohn*stage 1 0/E;
estimate 'mean NN50 for FH- at task 1' intercept 1 FHjohn 1 0 stage 0 1
FHjohn*stage 0 1/E;
estimate 'mean NN50 for FH- at task 2' intercept 1 FHjohn 1 0 stage 0 0 1
FHjohn*stage 0 0 1/E;
estimate 'mean NN50 for FH- at task 3' intercept 1 FHjohn 1 0 stage 0 0 0 1
FHjohn*stage 0 0 0 1/E;
estimate 'mean NN50 for FH- at recovery' intercept 1 FHjohn 1 0 stage 0 0 0 0
1 FHjohn*stage 0 0 0 0 1/E;
estimate 'mean NN50 for FH+ at baseline' intercept 1 FHjohn 0 1 stage 1

```

```

FHjohn*stage 0 0 0 0 0 1/E;
estimate 'mean NN50 for FH+ at task 1' intercept 1 FHjohn 0 1 stage 0 1
FHjohn*stage 0 0 0 0 0 0 1/E;
estimate 'mean NN50 for FH+ at task 2' intercept 1 FHjohn 0 1 stage 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 1/E;
estimate 'mean NN50 for FH+ at task 3' intercept 1 FHjohn 0 1 stage 0 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 0 1/E;
estimate 'mean NN50 for FH+ at recovery' intercept 1 FHjohn 0 1 stage 0 0 0 0
1 FHjohn*stage 0 0 0 0 0 0 0 0 0 1/E;
estimate 'change from baseline to task 1 for FH-' stage -1 1 0 0 0
Fhjohn*stage -1 1 0 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 2 for FH-' stage -1 0 1 0 0
Fhjohn*stage -1 0 1 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 3 for FH-' stage -1 0 0 1 0
Fhjohn*stage -1 0 0 1 0 0 0 0 0 0/E;
estimate 'change from baseline to recovery for FH-' stage -1 0 0 0 1
Fhjohn*stage -1 0 0 0 1 0 0 0 0 0/E;
estimate 'change from task 1 to recovery for FH-' stage 0 1 0 0 -1
FHjohn*stage 0 1 0 0 -1 0 0 0 0 0/E;
estimate 'change from task 2 to recovery for FH-' stage 0 0 1 0 -1
FHjohn*stage 0 0 1 0 -1 0 0 0 0 0/E;
estimate 'change from task 3 to recovery for FH-' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 1 -1 0 0 0 0 0/E;
estimate 'change from baseline to task 1 for FH+' stage -1 1 0 0 0
Fhjohn*stage 0 0 0 0 0 -1 1 0 0 0/E;
estimate 'change from baseline to task 2 for FH+' stage -1 0 1 0 0
Fhjohn*stage 0 0 0 0 0 -1 0 1 0 0/E;
estimate 'change from baseline to task 3 for FH+' stage -1 0 0 1 0
Fhjohn*stage 0 0 0 0 0 -1 0 0 1 0/E;
estimate 'change from baseline to recovery for FH+' stage -1 0 0 0 1
Fhjohn*stage 0 0 0 0 0 -1 0 0 0 1/E;
estimate 'change from task 1 to recovery for FH+' stage 0 1 0 0 -1
FHjohn*stage 0 0 0 0 0 0 1 0 0 -1/E;
estimate 'change from task 2 to recovery for FH+' stage 0 0 1 0 -1
FHjohn*stage 0 0 0 0 0 0 0 1 0 -1/E;
estimate 'change from task 3 to recovery for FH+' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 0 0 0 0 0 1 -1/E;
estimate 'diff NN50 for FH+/- at baseline' FHjohn -1 1 FHjohn*stage -1 0 0 0

```

```

0 1 0 0 0 0 /E;
estimate 'diff NN50 for FH+/- at task 1' FHjohn -1 1 FHjohn*stage 0 -1 0 0 0
0 1 0 0 0 /E;
estimate 'diff NN50 for FH+/- at task 2' FHjohn -1 1 FHjohn*stage 0 0 -1 0 0
0 0 1 0 0 /E;
estimate 'diff NN50 for FH+/- at task 3' FHjohn -1 1 FHjohn*stage 0 0 0 -1 0
0 0 0 1 0 /E;
estimate 'diff NN50 for FH+/- at recovery' FHjohn -1 1 FHjohn*stage 0 0 0 0 -
1 0 0 0 0 1 /E;
estimate 'diff NN50 change (task 1- baseline) for FH+/-' FHjohn*stage 1 -1 0
0 0 -1 1 0 0 0 /E;
estimate 'diff NN50 change (task 2- baseline) for FH+/-' FHjohn*stage 1 0 -1
0 0 -1 0 1 0 0 /E;
estimate 'diff NN50 change (task 3- baseline) for FH+/-' FHjohn*stage 1 0 0 -
1 0 -1 0 0 1 0 /E;
estimate 'diff NN50 change (recovery- baseline) for FH+/-' FHjohn*stage 1 0 0
0 -1 -1 0 0 0 1 /E;
estimate 'diff NN50 change (task 2- task 1) for FH+/-' FHjohn*stage 0 1 -1 0
0 0 -1 1 0 0 /E;
estimate 'diff NN50 change (task 3- task 1) for FH+/-' FHjohn*stage 0 1 0 -1
0 0 -1 0 1 0 /E;
estimate 'diff NN50 change (recovery- task 1) for FH+/-' FHjohn*stage 0 1 0 0
-1 0 -1 0 0 1 /E;
estimate 'diff NN50 change (task 3- task 2) for FH+/-' FHjohn*stage 0 0 1 -1
0 0 0 -1 1 0/E;
estimate 'diff NN50 change (recovery- task 2) for FH+/-' FHjohn*stage 0 0 1 0
-1 0 0 -1 0 1/E;
estimate 'diff NN50 change (recovery- task 3) for FH+/-' FHjohn*stage 0 0 0 1
-1 0 0 0 -1 1/E;
run;

proc mixed data=combine;
class FHjohn stage id time;
model pNN50_t=FHjohn stage FHjohn*stage Age race_bin SBMI SBAnxiety/solution;
repeated stage/subject=id type=cs;
estimate 'mean pNN50 for FH- at baseline' intercept 1 FHjohn 1 0 stage 1
FHjohn*stage 1 0/E;
estimate 'mean pNN50 for FH- at task 1' intercept 1 FHjohn 1 0 stage 0 1

```

```

FHjohn*stage 0 1/E;
estimate 'mean pNN50 for FH- at task 2' intercept 1 FHjohn 1 0 stage 0 0 1
FHjohn*stage 0 0 1/E;
estimate 'mean pNN50 for FH- at task 3' intercept 1 FHjohn 1 0 stage 0 0 0 1
FHjohn*stage 0 0 0 1/E;
estimate 'mean pNN50 for FH- at recovery' intercept 1 FHjohn 1 0 stage 0 0 0
0 1 FHjohn*stage 0 0 0 0 1/E;
estimate 'mean pNN50 for FH+ at baseline' intercept 1 FHjohn 0 1 stage 1
FHjohn*stage 0 0 0 0 0 1/E;
estimate 'mean pNN50 for FH+ at task 1' intercept 1 FHjohn 0 1 stage 0 1
FHjohn*stage 0 0 0 0 0 0 1/E;
estimate 'mean pNN50 for FH+ at task 2' intercept 1 FHjohn 0 1 stage 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 1/E;
estimate 'mean pNN50 for FH+ at task 3' intercept 1 FHjohn 0 1 stage 0 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 0 1/E;
estimate 'mean pNN50 for FH+ at recovery' intercept 1 FHjohn 0 1 stage 0 0 0
0 1 FHjohn*stage 0 0 0 0 0 0 0 0 0 1/E;
estimate 'change from baseline to task 1 for FH-' stage -1 1 0 0 0
Fhjohn*stage -1 1 0 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 2 for FH-' stage -1 0 1 0 0
Fhjohn*stage -1 0 1 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 3 for FH-' stage -1 0 0 1 0
Fhjohn*stage -1 0 0 1 0 0 0 0 0 0/E;
estimate 'change from baseline to recovery for FH-' stage -1 0 0 0 1
Fhjohn*stage -1 0 0 0 1 0 0 0 0 0/E;
estimate 'change from task 1 to recovery for FH-' stage 0 1 0 0 -1
FHjohn*stage 0 1 0 0 -1 0 0 0 0 0/E;
estimate 'change from task 2 to recovery for FH-' stage 0 0 1 0 -1
FHjohn*stage 0 0 1 0 -1 0 0 0 0 0/E;
estimate 'change from task 3 to recovery for FH-' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 1 -1 0 0 0 0 0/E;
estimate 'change from baseline to task 1 for FH+' stage -1 1 0 0 0
Fhjohn*stage 0 0 0 0 0 -1 1 0 0 0/E;
estimate 'change from baseline to task 2 for FH+' stage -1 0 1 0 0
Fhjohn*stage 0 0 0 0 0 -1 0 1 0 0/E;
estimate 'change from baseline to task 3 for FH+' stage -1 0 0 1 0
Fhjohn*stage 0 0 0 0 0 -1 0 0 1 0/E;
estimate 'change from baseline to recovery for FH+' stage -1 0 0 0 1

```

```

Fhjohn*stage 0 0 0 0 0 -1 0 0 0 1/E;
estimate 'change from task 1 to recovery for FH+' stage 0 1 0 0 -1
FHjohn*stage 0 0 0 0 0 0 1 0 0 -1/E;
estimate 'change from task 2 to recovery for FH+' stage 0 0 1 0 -1
FHjohn*stage 0 0 0 0 0 0 0 1 0 -1/E;
estimate 'change from task 3 to recovery for FH+' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 0 0 0 0 0 1 -1/E;
estimate 'diff pNN50 for FH+/- at baseline' FHjohn -1 1 FHjohn*stage -1 0 0 0
0 1 0 0 0 0 /E;
estimate 'diff pNN50 for FH+/- at task 1' FHjohn -1 1 FHjohn*stage 0 -1 0 0 0
0 1 0 0 0 /E;
estimate 'diff pNN50 for FH+/- at task 2' FHjohn -1 1 FHjohn*stage 0 0 -1 0 0
0 0 1 0 0 /E;
estimate 'diff pNN50 for FH+/- at task 3' FHjohn -1 1 FHjohn*stage 0 0 0 -1 0
0 0 0 1 0 /E;
estimate 'diff pNN50 for FH+/- at recovery' FHjohn -1 1 FHjohn*stage 0 0 0 0
-1 0 0 0 0 1 /E;
estimate 'diff pNN50 change (task 1- baseline) for FH+/-' FHjohn*stage 1 -1 0
0 0 -1 1 0 0 0 /E;
estimate 'diff pNN50 change (task 2- baseline) for FH+/-' FHjohn*stage 1 0 -1
0 0 -1 0 1 0 0 /E;
estimate 'diff pNN50 change (task 3- baseline) for FH+/-' FHjohn*stage 1 0 0
-1 0 -1 0 0 1 0 /E;
estimate 'diff pNN50 change (recovery- baseline) for FH+/-' FHjohn*stage 1 0
0 0 -1 -1 0 0 0 1 /E;
estimate 'diff pNN50 change (task 2- task 1) for FH+/-' FHjohn*stage 0 1 -1 0
0 0 -1 1 0 0 /E;
estimate 'diff pNN50 change (task 3- task 1) for FH+/-' FHjohn*stage 0 1 0 -1
0 0 -1 0 1 0 /E;
estimate 'diff pNN50 change (recovery- task 1) for FH+/-' FHjohn*stage 0 1 0
0 -1 0 -1 0 0 1 /E;
estimate 'diff pNN50 change (task 3- task 2) for FH+/-' FHjohn*stage 0 0 1 -1
0 0 0 -1 1 0/E;
estimate 'diff pNN50 change (recovery- task 2) for FH+/-' FHjohn*stage 0 0 1
0 -1 0 0 -1 0 1/E;
estimate 'diff pNN50 change (recovery- task 3) for FH+/-' FHjohn*stage 0 0 0
1 -1 0 0 0 -1 1/E;
run;

```

```

proc mixed data=combine;
class FHjohn stage id time;
model SDANN_t=FHjohn stage FHjohn*stage Age race_bin SBMI SBanxiety/solution;
repeated stage/subject=id type=cs;
estimate 'mean SDANN for FH- at baseline' intercept 1 FHjohn 1 0 stage 1
FHjohn*stage 1 0/E;
estimate 'mean SDANN for FH- at task 1' intercept 1 FHjohn 1 0 stage 0 1
FHjohn*stage 0 1/E;
estimate 'mean SDANN for FH- at task 2' intercept 1 FHjohn 1 0 stage 0 0 1
FHjohn*stage 0 0 1/E;
estimate 'mean SDANN for FH- at task 3' intercept 1 FHjohn 1 0 stage 0 0 0 1
FHjohn*stage 0 0 0 1/E;
estimate 'mean SDANN for FH- at recovery' intercept 1 FHjohn 1 0 stage 0 0 0
0 1 FHjohn*stage 0 0 0 0 1/E;
estimate 'mean SDANN for FH+ at baseline' intercept 1 FHjohn 0 1 stage 1
FHjohn*stage 0 0 0 0 0 1/E;
estimate 'mean SDANN for FH+ at task 1' intercept 1 FHjohn 0 1 stage 0 1
FHjohn*stage 0 0 0 0 0 0 1/E;
estimate 'mean SDANN for FH+ at task 2' intercept 1 FHjohn 0 1 stage 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 1/E;
estimate 'mean SDANN for FH+ at task 3' intercept 1 FHjohn 0 1 stage 0 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 0 1/E;
estimate 'mean SDANN for FH+ at recovery' intercept 1 FHjohn 0 1 stage 0 0 0
0 1 FHjohn*stage 0 0 0 0 0 0 0 0 0 1/E;
estimate 'change from baseline to task 1 for FH-' stage -1 1 0 0 0
Fhjohn*stage -1 1 0 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 2 for FH-' stage -1 0 1 0 0
Fhjohn*stage -1 0 1 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 3 for FH-' stage -1 0 0 1 0
Fhjohn*stage -1 0 0 1 0 0 0 0 0 0/E;
estimate 'change from baseline to recovery for FH-' stage -1 0 0 0 1
Fhjohn*stage -1 0 0 0 1 0 0 0 0 0/E;
estimate 'change from task 1 to recovery for FH-' stage 0 1 0 0 -1
FHjohn*stage 0 1 0 0 -1 0 0 0 0 0/E;
estimate 'change from task 2 to recovery for FH-' stage 0 0 1 0 -1
FHjohn*stage 0 0 1 0 -1 0 0 0 0 0/E;
estimate 'change from task 3 to recovery for FH-' stage 0 0 0 1 -1

```



```

FHjohn*stage 0 0 0 1 -1 0 0 0 0 0/E;
estimate 'change from baseline to task 1 for FH+' stage -1 1 0 0 0
Fhjohn*stage 0 0 0 0 0 -1 1 0 0 0/E;
estimate 'change from baseline to task 2 for FH+' stage -1 0 1 0 0
Fhjohn*stage 0 0 0 0 0 -1 0 1 0 0/E;
estimate 'change from baseline to task 3 for FH+' stage -1 0 0 1 0
Fhjohn*stage 0 0 0 0 0 -1 0 0 1 0/E;
estimate 'change from baseline to recovery for FH+' stage -1 0 0 0 1
Fhjohn*stage 0 0 0 0 0 -1 0 0 0 1/E;
estimate 'change from task 1 to recovery for FH+' stage 0 1 0 0 -1
FHjohn*stage 0 0 0 0 0 0 1 0 0 -1/E;
estimate 'change from task 2 to recovery for FH+' stage 0 0 1 0 -1
FHjohn*stage 0 0 0 0 0 0 0 1 0 -1/E;
estimate 'change from task 3 to recovery for FH+' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 0 0 0 0 0 1 -1/E;
estimate 'diff SDANN for FH+/- at baseline' FHjohn -1 1 FHjohn*stage -1 0 0 0
0 1 0 0 0 0 /E;
estimate 'diff SDANN for FH+/- at task 1' FHjohn -1 1 FHjohn*stage 0 -1 0 0 0
0 1 0 0 0 /E;
estimate 'diff SDANN for FH+/- at task 2' FHjohn -1 1 FHjohn*stage 0 0 -1 0 0
0 0 1 0 0 /E;
estimate 'diff SDANN for FH+/- at task 3' FHjohn -1 1 FHjohn*stage 0 0 0 -1 0
0 0 0 1 0 /E;
estimate 'diff SDANN for FH+/- at recovery' FHjohn -1 1 FHjohn*stage 0 0 0 0
-1 0 0 0 0 1 /E;
estimate 'diff SDANN change (task 1- baseline) for FH+/-' FHjohn*stage 1 -1 0
0 0 -1 1 0 0 0 /E;
estimate 'diff SDANN change (task 2- baseline) for FH+/-' FHjohn*stage 1 0 -1
0 0 -1 0 1 0 0 /E;
estimate 'diff SDANN change (task 3- baseline) for FH+/-' FHjohn*stage 1 0 0
-1 0 -1 0 0 1 0 /E;
estimate 'diff SDANN change (recovery- baseline) for FH+/-' FHjohn*stage 1 0
0 0 -1 -1 0 0 0 1 /E;
estimate 'diff SDANN change (task 2- task 1) for FH+/-' FHjohn*stage 0 1 -1 0
0 0 -1 1 0 0 /E;
estimate 'diff SDANN change (task 3- task 1) for FH+/-' FHjohn*stage 0 1 0 -1
0 0 -1 0 1 0 /E;
estimate 'diff SDANN change (recovery- task 1) for FH+/-' FHjohn*stage 0 1 0

```

```

0 -1 0 -1 0 0 1 /E;
estimate 'diff SDANN change (task 3- task 2) for FH+/-' FHjohn*stage 0 0 1 -1
0 0 0 -1 1 0/E;
estimate 'diff SDANN change (recovery- task 2) for FH+/-' FHjohn*stage 0 0 1
0 -1 0 0 -1 0 1/E;
estimate 'diff SDANN change (recovery- task 3) for FH+/-' FHjohn*stage 0 0 0
1 -1 0 0 0 -1 1/E;
run;

```

```

proc mixed data=combine;
class FHjohn stage id;
model fftHF_t=FHjohn stage FHjohn*stage Age race_bin SBMI SBanxiety/solution;
repeated stage/subject=id type=cs;
estimate 'mean fftHF for FH- at baseline' intercept 1 FHjohn 1 0 stage 1
FHjohn*stage 1 0/E;
estimate 'mean fftHF for FH- at task 1' intercept 1 FHjohn 1 0 stage 0 1
FHjohn*stage 0 1/E;
estimate 'mean fftHF for FH- at task 2' intercept 1 FHjohn 1 0 stage 0 0 1
FHjohn*stage 0 0 1/E;
estimate 'mean fftHF for FH- at task 3' intercept 1 FHjohn 1 0 stage 0 0 0 1
FHjohn*stage 0 0 0 1/E;
estimate 'mean fftHF for FH- at recovery' intercept 1 FHjohn 1 0 stage 0 0 0
0 1 FHjohn*stage 0 0 0 0 1/E;
estimate 'mean fftHF for FH+ at baseline' intercept 1 FHjohn 0 1 stage 1
FHjohn*stage 0 0 0 0 0 1/E;
estimate 'mean fftHF for FH+ at task 1' intercept 1 FHjohn 0 1 stage 0 1
FHjohn*stage 0 0 0 0 0 0 1/E;
estimate 'mean fftHF for FH+ at task 2' intercept 1 FHjohn 0 1 stage 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 1/E;
estimate 'mean fftHF for FH+ at task 3' intercept 1 FHjohn 0 1 stage 0 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 0 1/E;
estimate 'mean fftHF for FH+ at recovery' intercept 1 FHjohn 0 1 stage 0 0 0
0 1 FHjohn*stage 0 0 0 0 0 0 0 0 0 1/E;
estimate 'change from baseline to task 1 for FH-' stage -1 1 0 0 0
Fhjohn*stage -1 1 0 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 2 for FH-' stage -1 0 1 0 0
Fhjohn*stage -1 0 1 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 3 for FH-' stage -1 0 0 1 0

```

```

Fhjohn*stage -1 0 0 1 0 0 0 0 0 0/E;
estimate 'change from baseline to recovery for FH-' stage -1 0 0 0 1
Fhjohn*stage -1 0 0 0 1 0 0 0 0 0/E;
estimate 'change from task 1 to recovery for FH-' stage 0 1 0 0 -1
FHjohn*stage 0 1 0 0 -1 0 0 0 0 0/E;
estimate 'change from task 2 to recovery for FH-' stage 0 0 1 0 -1
FHjohn*stage 0 0 1 0 -1 0 0 0 0 0/E;
estimate 'change from task 3 to recovery for FH-' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 1 -1 0 0 0 0 0/E;
estimate 'change from baseline to task 1 for FH+' stage -1 1 0 0 0
Fhjohn*stage 0 0 0 0 0 -1 1 0 0 0/E;
estimate 'change from baseline to task 2 for FH+' stage -1 0 1 0 0
Fhjohn*stage 0 0 0 0 0 -1 0 1 0 0/E;
estimate 'change from baseline to task 3 for FH+' stage -1 0 0 1 0
Fhjohn*stage 0 0 0 0 0 -1 0 0 1 0/E;
estimate 'change from baseline to recovery for FH+' stage -1 0 0 0 1
Fhjohn*stage 0 0 0 0 0 -1 0 0 0 1/E;
estimate 'change from task 1 to recovery for FH+' stage 0 1 0 0 -1
FHjohn*stage 0 0 0 0 0 0 1 0 0 -1/E;
estimate 'change from task 2 to recovery for FH+' stage 0 0 1 0 -1
FHjohn*stage 0 0 0 0 0 0 0 1 0 -1/E;
estimate 'change from task 3 to recovery for FH+' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 0 0 0 0 0 1 -1/E;
estimate 'diff fftHF for FH+/- at baseline' FHjohn -1 1 FHjohn*stage -1 0 0 0
0 1 0 0 0 0 /E;
estimate 'diff fftHF for FH+/- at task 1' FHjohn -1 1 FHjohn*stage 0 -1 0 0 0
0 1 0 0 0 /E;
estimate 'diff fftHF for FH+/- at task 2' FHjohn -1 1 FHjohn*stage 0 0 -1 0 0
0 0 1 0 0 /E;
estimate 'diff fftHF for FH+/- at task 3' FHjohn -1 1 FHjohn*stage 0 0 0 -1 0
0 0 0 1 0 /E;
estimate 'diff fftHF for FH+/- at recovery' FHjohn -1 1 FHjohn*stage 0 0 0 0
-1 0 0 0 0 1 /E;
estimate 'diff fftHF change (task 1- baseline) for FH+/-' FHjohn*stage 1 -1 0
0 0 -1 1 0 0 0 /E;
estimate 'diff fftHF change (task 2- baseline) for FH+/-' FHjohn*stage 1 0 -1
0 0 -1 0 1 0 0 /E;
estimate 'diff fftHF change (task 3- baseline) for FH+/-' FHjohn*stage 1 0 0

```

```

-1 0 -1 0 0 1 0 /E;
estimate 'diff fftHF change (recovery- baseline) for FH+/-' FHjohn*stage 1 0
0 0 -1 -1 0 0 0 1 /E;
estimate 'diff fftHF change (task 2- task 1) for FH+/-' FHjohn*stage 0 1 -1 0
0 0 -1 1 0 0 /E;
estimate 'diff fftHF change (task 3- task 1) for FH+/-' FHjohn*stage 0 1 0 -1
0 0 -1 0 1 0 /E;
estimate 'diff fftHF change (recovery- task 1) for FH+/-' FHjohn*stage 0 1 0
0 -1 0 -1 0 0 1 /E;
estimate 'diff fftHF change (task 3- task 2) for FH+/-' FHjohn*stage 0 0 1 -1
0 0 0 -1 1 0/E;
estimate 'diff fftHF change (recovery- task 2) for FH+/-' FHjohn*stage 0 0 1
0 -1 0 0 -1 0 1/E;
estimate 'diff fftHF change (recovery- task 3) for FH+/-' FHjohn*stage 0 0 0
1 -1 0 0 0 -1 1/E;
run;

```

```

proc mixed data=combine;
class FHjohn stage id time;
model fftHFnu= FHjohn stage FHjohn*stage Age race_bin SBMI SBanxiety/solution;
repeated stage/subject=id type=cs;
estimate 'mean fftHFnu for FH- at baseline' intercept 1 FHjohn 1 0 stage 1
FHjohn*stage 1 0/E;
estimate 'mean fftHFnu for FH- at task 1' intercept 1 FHjohn 1 0 stage 0 1
FHjohn*stage 0 1/E;
estimate 'mean fftHFnu for FH- at task 2' intercept 1 FHjohn 1 0 stage 0 0 1
FHjohn*stage 0 0 1/E;
estimate 'mean fftHFnu for FH- at task 3' intercept 1 FHjohn 1 0 stage 0 0 0
1 FHjohn*stage 0 0 0 1/E;
estimate 'mean fftHFnu for FH- at recovery' intercept 1 FHjohn 1 0 stage 0 0
0 0 1 FHjohn*stage 0 0 0 0 1/E;
estimate 'mean fftHFnu for FH+ at baseline' intercept 1 FHjohn 0 1 stage 1
FHjohn*stage 0 0 0 0 0 1/E;
estimate 'mean fftHFnu for FH+ at task 1' intercept 1 FHjohn 0 1 stage 0 1
FHjohn*stage 0 0 0 0 0 0 1/E;
estimate 'mean fftHFnu for FH+ at task 2' intercept 1 FHjohn 0 1 stage 0 0 1
FHjohn*stage 0 0 0 0 0 0 0 1/E;
estimate 'mean fftHFnu for FH+ at task 3' intercept 1 FHjohn 0 1 stage 0 0 0

```

```

1 FHjohn*stage 0 0 0 0 0 0 0 0 1/E;
estimate 'mean fftHFnu for FH+ at recovery' intercept 1 FHjohn 0 1 stage 0 0
0 0 1 FHjohn*stage 0 0 0 0 0 0 0 0 1/E;
estimate 'change from baseline to task 1 for FH-' stage -1 1 0 0 0
Fhjohn*stage -1 1 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 2 for FH-' stage -1 0 1 0 0
Fhjohn*stage -1 0 1 0 0 0 0 0 0/E;
estimate 'change from baseline to task 3 for FH-' stage -1 0 0 1 0
Fhjohn*stage -1 0 0 1 0 0 0 0 0/E;
estimate 'change from baseline to recovery for FH-' stage -1 0 0 0 1
Fhjohn*stage -1 0 0 0 1 0 0 0 0/E;
estimate 'change from task 1 to recovery for FH-' stage 0 1 0 0 -1
FHjohn*stage 0 1 0 0 -1 0 0 0 0/E;
estimate 'change from task 2 to recovery for FH-' stage 0 0 1 0 -1
FHjohn*stage 0 0 1 0 -1 0 0 0 0/E;
estimate 'change from task 3 to recovery for FH-' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 1 -1 0 0 0 0/E;
estimate 'change from baseline to task 1 for FH+' stage -1 1 0 0 0
Fhjohn*stage 0 0 0 0 0 -1 1 0 0/E;
estimate 'change from baseline to task 2 for FH+' stage -1 0 1 0 0
Fhjohn*stage 0 0 0 0 0 -1 0 1 0/E;
estimate 'change from baseline to task 3 for FH+' stage -1 0 0 1 0
Fhjohn*stage 0 0 0 0 0 -1 0 0 1/E;
estimate 'change from baseline to recovery for FH+' stage -1 0 0 0 1
Fhjohn*stage 0 0 0 0 0 -1 0 0 0/E;
estimate 'change from task 1 to recovery for FH+' stage 0 1 0 0 -1
FHjohn*stage 0 0 0 0 0 0 1 0 0 -1/E;
estimate 'change from task 2 to recovery for FH+' stage 0 0 1 0 -1
FHjohn*stage 0 0 0 0 0 0 0 1 0 -1/E;
estimate 'change from task 3 to recovery for FH+' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 0 0 0 0 0 1 -1/E;
estimate 'diff fftHFnu for FH+/- at baseline' FHjohn -1 1 FHjohn*stage -1 0 0
0 0 1 0 0 0 0 /E;
estimate 'diff fftHFnu for FH+/- at task 1' FHjohn -1 1 FHjohn*stage 0 -1 0 0
0 0 1 0 0 0 /E;
estimate 'diff fftHFnu for FH+/- at task 2' FHjohn -1 1 FHjohn*stage 0 0 -1 0
0 0 0 1 0 0 /E;
estimate 'diff fftHFnu for FH+/- at task 3' FHjohn -1 1 FHjohn*stage 0 0 0 -1

```

```

0 0 0 0 1 0 /E;
estimate 'diff fftHFnu for FH+/- at recovery' FHjohn -1 1 FHjohn*stage 0 0 0
0 -1 0 0 0 0 1 /E;
estimate 'diff fftHFnu change (task 1- baseline) for FH+/-' FHjohn*stage 1 -1
0 0 0 -1 1 0 0 0 /E;
estimate 'diff fftHFnu change (task 2- baseline) for FH+/-' FHjohn*stage 1 0
-1 0 0 -1 0 1 0 0 /E;
estimate 'diff fftHFnu change (task 3- baseline) for FH+/-' FHjohn*stage 1 0
0 -1 0 -1 0 0 1 0 /E;
estimate 'diff fftHFnu change (recovery- baseline) for FH+/-' FHjohn*stage 1
0 0 0 -1 -1 0 0 0 1 /E;
estimate 'diff fftHFnu change (task 2- task 1) for FH+/-' FHjohn*stage 0 1 -1
0 0 0 -1 1 0 0 /E;
estimate 'diff fftHFnu change (task 3- task 1) for FH+/-' FHjohn*stage 0 1 0
-1 0 0 -1 0 1 0 /E;
estimate 'diff fftHFnu change (recovery- task 1) for FH+/-' FHjohn*stage 0 1
0 0 -1 0 -1 0 0 1 /E;
estimate 'diff fftHFnu change (task 3- task 2) for FH+/-' FHjohn*stage 0 0 1
-1 0 0 0 -1 1 0/E;
estimate 'diff fftHFnu change (recovery- task 2) for FH+/-' FHjohn*stage 0 0
1 0 -1 0 0 -1 0 1/E;
estimate 'diff fftHFnu change (recovery- task 3) for FH+/-' FHjohn*stage 0 0
0 1 -1 0 0 0 -1 1/E;
run;

proc mixed data=combine;
class FHjohn stage id time;
model fftLFOverHF_t=FHjohn stage FHjohn*stage Age race_bin SBMI
SBanxiety/solution;
repeated stage/subject=id type=cs;
estimate 'mean fftLFOverHF for FH- at baseline' intercept 1 FHjohn 1 0 stage
1 FHjohn*stage 1 0/E;
estimate 'mean fftLFOverHF for FH- at task 1' intercept 1 FHjohn 1 0 stage 0
1 FHjohn*stage 0 1/E;
estimate 'mean fftLFOverHF for FH- at task 2' intercept 1 FHjohn 1 0 stage 0
0 1 FHjohn*stage 0 0 1/E;
estimate 'mean fftLFOverHF for FH- at task 3' intercept 1 FHjohn 1 0 stage 0
0 0 1 FHjohn*stage 0 0 0 1/E;

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estimate 'mean fftLFoverHF for FH- at recovery' intercept 1 FHjohn 1 0 stage
0 0 0 0 1 FHjohn*stage 0 0 0 0 1/E;
estimate 'mean fftLFoverHF for FH+ at baseline' intercept 1 FHjohn 0 1 stage
1 FHjohn*stage 0 0 0 0 0 1/E;
estimate 'mean fftLFoverHF for FH+ at task 1' intercept 1 FHjohn 0 1 stage 0
1 FHjohn*stage 0 0 0 0 0 0 1/E;
estimate 'mean fftLFoverHF for FH+ at task 2' intercept 1 FHjohn 0 1 stage 0
0 1 FHjohn*stage 0 0 0 0 0 0 0 1/E;
estimate 'mean fftLFoverHF for FH+ at task 3' intercept 1 FHjohn 0 1 stage 0
0 0 1 FHjohn*stage 0 0 0 0 0 0 0 0 1/E;
estimate 'mean fftLFoverHF for FH+ at recovery' intercept 1 FHjohn 0 1 stage
0 0 0 0 1 FHjohn*stage 0 0 0 0 0 0 0 0 0 1/E;
estimate 'change from baseline to task 1 for FH-' stage -1 1 0 0 0
Fhjohn*stage -1 1 0 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 2 for FH-' stage -1 0 1 0 0
Fhjohn*stage -1 0 1 0 0 0 0 0 0 0 0/E;
estimate 'change from baseline to task 3 for FH-' stage -1 0 0 1 0
Fhjohn*stage -1 0 0 1 0 0 0 0 0 0 0/E;
estimate 'change from baseline to recovery for FH-' stage -1 0 0 0 1
Fhjohn*stage -1 0 0 0 1 0 0 0 0 0 0/E;
estimate 'change from task 1 to recovery for FH-' stage 0 1 0 0 -1
FHjohn*stage 0 1 0 0 -1 0 0 0 0 0 0/E;
estimate 'change from task 2 to recovery for FH-' stage 0 0 1 0 -1
FHjohn*stage 0 0 1 0 -1 0 0 0 0 0 0/E;
estimate 'change from task 3 to recovery for FH-' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 1 -1 0 0 0 0 0 0/E;
estimate 'change from baseline to task 1 for FH+' stage -1 1 0 0 0
Fhjohn*stage 0 0 0 0 0 -1 1 0 0 0 0/E;
estimate 'change from baseline to task 2 for FH+' stage -1 0 1 0 0
Fhjohn*stage 0 0 0 0 0 -1 0 1 0 0 0/E;
estimate 'change from baseline to task 3 for FH+' stage -1 0 0 1 0
Fhjohn*stage 0 0 0 0 0 -1 0 0 1 0 0/E;
estimate 'change from baseline to recovery for FH+' stage -1 0 0 0 1
Fhjohn*stage 0 0 0 0 0 -1 0 0 0 0 1/E;
estimate 'change from task 1 to recovery for FH+' stage 0 1 0 0 -1
FHjohn*stage 0 0 0 0 0 0 1 0 0 -1/E;
estimate 'change from task 2 to recovery for FH+' stage 0 0 1 0 -1
FHjohn*stage 0 0 0 0 0 0 0 1 0 -1/E;

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estimate 'change from task 3 to recovery for FH+' stage 0 0 0 1 -1
FHjohn*stage 0 0 0 0 0 0 0 0 1 -1/E;
estimate 'diff fftLFoverHF for FH+/- at baseline' FHjohn -1 1 FHjohn*stage -1
0 0 0 0 1 0 0 0 0 /E;
estimate 'diff fftLFoverHF for FH+/- at task 1' FHjohn -1 1 FHjohn*stage 0 -1
0 0 0 0 1 0 0 0 /E;
estimate 'diff fftLFoverHF for FH+/- at task 2' FHjohn -1 1 FHjohn*stage 0 0
-1 0 0 0 0 1 0 0 /E;
estimate 'diff fftLFoverHF for FH+/- at task 3' FHjohn -1 1 FHjohn*stage 0 0
0 -1 0 0 0 0 1 0 /E;
estimate 'diff fftLFoverHF for FH+/- at recovery' FHjohn -1 1 FHjohn*stage 0
0 0 0 -1 0 0 0 0 1 /E;
estimate 'diff fftLFoverHF change (task 1- baseline) for FH+/-'
FHjohn*stage 1 -1 0 0 0 -1 1 0 0 0 /E;
estimate 'diff fftLFoverHF change (task 2- baseline) for FH+/-'
FHjohn*stage 1 0 -1 0 0 -1 0 1 0 0 /E;
estimate 'diff fftLFoverHF change (task 3- baseline) for FH+/-'
FHjohn*stage 1 0 0 -1 0 -1 0 0 1 0 /E;
estimate 'diff fftLFoverHF change (recovery- baseline) for FH+/-'
FHjohn*stage 1 0 0 0 -1 -1 0 0 0 1 /E;
estimate 'diff fftLFoverHF change (task 2- task 1) for FH+/-'
FHjohn*stage 0 1 -1 0 0 0 -1 1 0 0 /E;
estimate 'diff fftLFoverHF change (task 3- task 1) for FH+/-'
FHjohn*stage 0 1 0 -1 0 0 -1 0 1 0 /E;
estimate 'diff fftLFoverHF change (recovery- task 1) for FH+/-'
FHjohn*stage 0 1 0 0 -1 0 -1 0 0 1 /E;
estimate 'diff fftLFoverHF change (task 3- task 2) for FH+/-'
FHjohn*stage 0 0 1 -1 0 0 0 -1 1 0/E;
estimate 'diff fftLFoverHF change (recovery- task 2) for FH+/-'
FHjohn*stage 0 0 1 0 -1 0 0 -1 0 1/E;
estimate 'diff fftLFoverHF change (recovery- task 3) for FH+/-'
FHjohn*stage 0 0 0 1 -1 0 0 0 -1 1/E;
run;

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