Original Research Article

Influence of Heart Rate Variability on abstinence-related changes in brain state in everyday drinkers

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Supplementary Material

1. Supplementary Methods

*1.1 Heart Rate Assessment and Data Processing for PBRSA Calculation*

In addition to assessment of PBRSA data collected while participants were seated (PBRSA-rest), PBRSA was also calculated on heart rate data collected following a postural shift (seated to standing; PBRSA-react). The main outcomes for PBRSA-react data were negative, and as such were excluded from discussion of primary results. Using the ECG 3-electrode set up, data was collected for 5 minutes while participants were seated comfortably, and for 2 minutes following the postural shift. CardioEdit and CardioBath Plus software were used to inspect the data and calculate heart rate as described in the paper methods. To calculate PBRSA-react scores, the average 5 minute seated PBRSA value (PBRSA-rest) was subtracted from the PBRSA recorded during the standing 2 minutes.

*1.2 Statistical Analysis and Mixed-Effects Modeling Framework*

A mixed-effects regression was used to assess the relationship between whole brain connectivity, participants’ drinking state (normal vs. abstain), continuous measure of HRV (PBRSA), and possible confounding variables [1, 2]. This framework was able to account for correlations between network connections within the individual participants and between the normal and abstained drinking states, as well as allow for the analysis of both network and non-network variables. This two-part regression models the *probability* of network connections (binary; presence vs. absence) and the *strength* of connections, if they exist. The multivariate regression captures the relationship between brain connections (probability and strength) as outcome (dependent) variables and network/non-network covariates as the independent variables. For all analyses, significant results were determined by a critical p-value < 0.05. All p-values were adjusted for multiple comparisons using the adaptive False Discovery Rate procedures detailed by Benjamini and Hochberg [3]. Analyses were conducted using the WFU\_MMNET toolbox [4], Matlab (R2016b), and SAS v9.4 software.

Figures were generated from the resulting fits of the mixed effects regression model. For visualization purposes, the upper and lower bounds of the PBRSA relationships were used in the regression equations in conjunction with the dichotomous drinking state variable to depict graphs. It should be remembered when interpreting these figures that they are intended for visualization, and that the statistical analyses are based on continuous functions that span the region between the upper and lower bounds.

*1.3 Covariates*

The primary variables of interest in this model were drinking state and HRV. Because fMRI time series data from both drinking states were included in the statistical model, a dichotomous variable was coded to differentiate the two conditions (normal drinking = 0, abstinence = 1). This allowed for the examination of the effects of drinking state between and within subjects, as well as the interaction of drinking state with network properties and other covariates. The complete model included interactions of all covariates and network features with both PBRSA-rest and PBRSA-react, but no 4-way interactions (i.e. probability/strength\* PBRSA-rest\* PBRSA-react\*network feature) were significant, and were subsequently remove from the model to focus on significant 3-way interactions.

The network topology [5] from each individual participant was summarized with standard graph theory variables computed from each node pair, including average *clustering coefficient* (local specialization), average *global efficiency* (global integration), differences in *degree* (number of connections) between each nodal pair, and overall network *modularity* (the extent to which the network subdivides into densely interconnected communities that are scarcely connected to the rest of the network) [6]. Each of these summary variables was included as covariates in the model.

Age, sex, and BMI were included in the model due to previous associations with alcohol use and HRV [7-9]. The spatial Euclidean distance and square of the spatial distance between network nodes (brain regions) were also included as confounding variables to account for participants’ inter/intra-hemispheric asymmetries [10]. These metrics were included as covariates in the model to control for any associations with network organization. Measures that capture variance in drinking behavior and alcohol exposure were entered in a secondary post hoc model as additional covariates. These included average number of drinks consumed per day when participants chose to drink, the percent of days that they reported drinking at least one serving of alcohol in the last three months (via the TLFB), and the total number of years they had been consuming alcohol.

2. Supplementary Results

*2.1 Primary Findings*

The two-part mixed-model test the hypothesis that the effects of drinking state on brain network topology are dependent on HRV, measured via PBRSA. This model separately evaluated connection strength and probability. Results for the connection strength model are presented here, and results for the connection probability model did not achieve significance for the stated hypothesis, and there were no significant interactions between PBRSA-react and drinking state. The full probability model and results for PBRSA-react are presented in the following section, covering the full model findings.

Degree, modularity, clustering coefficient, and global efficiency were included in the model as network covariates. No meaningful relationships with drinking state were found with modularity or degree. All four network features network features remained in the full model, but are only presented in the full model findings. The full model also included age, sex, and BMI to control for confounding effects. None of the demographic variables were significantly associated with connection strength. To control for differences in long vs. short distance brain connections, the spatial distance and square of the spatial distance between brain regions were included in this model. Distance variables were significant (Spatial Distance β = -0.05132, *p* < 0.0001, Spatial Distance2 β = 0.02890, *p* < 0.0001).

Two 3-way interactions were associated with the main study hypothesis. The most robust interaction from the connection strength model was between drinking state, PBRSA-rest, and clustering (β = 0.01186, *p* = 0.0004). This 3-way interaction can be visualized by examining the slope of the relationship between connection strength and clustering across drinking state and the upper and lower bounds of PBRSA-rest values (Supp. Fig. 1). At the upper bound of PBRSA-rest values large differences were found in the relationship between connection strength and clustering coefficient across drinking states, while at the lower bound only small differences were present. To understand these differences in the relationship between clustering and connection strength, we examined the strength values that would be expected for each condition at high clustering values. At the lower PBRSA-rest bound we observe weaker network connections between highly clustered nodes during abstinence compared to normal drinking, while at the upper PBRSA-rest bound we observe stronger connections between highly clustered nodes following abstinence.

Although it did not reach statistical significance, a notable corresponding trend was evident in the relationship between drinking state, PBRSA-rest, and global efficiency (β = -0.00518, *p* = 0.1087, Supp. Fig. 2). The difference in the relationship between connection strength and global efficiency change in opposite directions across drinking state between the upper and lower bounds of PBRSA-rest. At the lower bound the difference in slope increased as global efficiency increased, with greater strength at more globally efficient nodes observed in abstinence compared to normal drinking. At the upper bound the difference in slope decreased as global efficiency increased, and greater strength in highly globally efficient nodes was again observed n abstinence compared to normal drinking.

Suppl. Table 1 provides the key results for the connection strength mixed-model. There was a significant main effect of drinking state on connection strength, such that greater average connection strength was found during normal dinking compared to abstinence (β = 1.2340, *p* < 0.0001). The significant main effects of PBRSA-rest indicated that, on average, participants with higher PBRSA-rest had lower network connection strength (β = -0.00994, *p* = 0.0220). There was an interaction between drinking state and PBRSA-rest that did not reach statistical significance, but exhibited a notable positive trend (β = 0.01180, *p* = 0.0553). Clustering (β = 0.06825, *p* < 0.0001) and global efficiency (β = 0.02923, *p* < 0.0001) were both statistically significant positive predictors of connection strength. Interactions between drinking state and these network topological features were not statistically significant. There was an interaction of PBRSA-rest with clustering (β = -0.00532, *p* = 0.0004), but not with global efficiency.

*2.2 Full Findings*

Full results for the connection strength model can be found in Supp. Table 2. All four network features of interest associated significantly with connection strength. Clustering (β = 0.06825, *p* < 0.0001) and global efficiency (β = 0.02923, *p* < 0.0001) were positively associated with connection strength, while degree (β = -0.04430, *p* < 0.0001) and modularity (β = -0.01518, *p* < 0.0001) were negatively associated with connection strength. The relationship between PBRSA-react scores and connection strength approached significance (β = 0.007051, *p* < 0.0898), in the inverse direction of the relationship between connection strength and PBRSA-rest.

Significant interactions between connection strength and PBRSA-rest and react were seen with clustering (β = -0.05132, *p* = 0.0406) and global efficiency (β = -0.05132, *p* = 0.0440), although the relationship between PBRSA-rest and react was not significant. When examining the clustering relationship (Supp. Fig. 3), participants at the lower bound of PBRSA-rest but the upper-bound of PBRSA-react showed the strongest relationship between clustering and connection strength. Participants at the lower bound of PBRSA-react, both with high and low PBRSA-rest, showed similar relationships between clustering and connection strength. The weakest connections between highly clustered nodes was observed in participants at the upper bound of PBRSA-rest and react. For the global efficiency relationship (Supp. Fig. 4), participants at the lower bound of both PBRSA-rest and react, as well as those at the upper-bound of both PBRSA-rest and react showed the strongest relationship between global efficiency and connections strength. The weakest connections between highly globally efficient nodes were observed in at the upper PBRSA-rest bound, but the lower PBRSA-react bound.

Full results for the probability model can be found in Supp. Table 3. Clustering (β = 0.3214, *p* < 0.0001) and degree (β = 0.1480, *p* < 0.0001) showed significant positive associations with connection probability, while global efficiency showed a significant negative relationship with connection probability (β = -0.3050, *p* < 0.0001). Spatial Distance (β = 0.3597, *p* < 0.0001) and Spatial Distance2 (β = -0.1346, *p* < 0.0001) were significantly associated with connection probability. Drinking state was positively associated with probability (β = 0.1803, *p* < 0.0001), indicating greater average probability of connection was found during normal drinking compared to abstinence. Finally, a significant interaction was found between degree and PBRSA-rest with connection probability (β = 0.04649, *p* = 0.0389), such that the higher degree observed with greater probability of connections was even greater at higher PBRSA-rest values.

**3. Supplementary Tables and Figures**

*3.1 Supplementary Tables*

**Supplementary Table 1.** Relevant mixed-model strength results. Significant effects and interactions are bolded.

|  |  |  |  |
| --- | --- | --- | --- |
| **Effect** | **Estimate** | **Standard**  **Error** | **p-value** |
| **Drinking State** | **0.2340** | **0.004659** | **<0.0001** |
| **PBRSA-rest** | **-0.00994** | **0.004340** | **0.0220** |
| Drinking State\*PBRSA-rest | 0.01180 | 0.006157 | 0.0553 |
| **Clustering Coefficient** | **0.06825** | **0.002450** | **<0.0001** |
| **Global Efficiency** | **0.02923** | **0.002528** | **<0.0001** |
| Drinking State\*Clustering Coefficient | 0.001887 | 0.003163 | 0.5509 |
| Drinking State\*Global Efficiency | -0.00456 | 0.003046 | 0.1344 |
| **PBRSA-rest\*Clustering Coefficient** | **-0.00532** | **0.002651** | **0.0449** |
| PBRSA-rest\*Global Efficiency | 0.000041 | 0.002713 | 0.9879 |
| **Drinking State\*PBRSA-rest\*Clustering Coefficient** | **0.01186** | **0.003357** | **0.0004** |
| Drinking State\*PBRSA-rest\*Global Efficiency | -0.00518 | 0.003357 | 0.1087 |
| **Spatial Distance** | **-0.05132** | **0.001100** | **<0.0001** |
| **Spatial Distance2** | **0.02890** | **0.000537** | **<0.0001** |
| Age | -0.00116 | 0.003233 | 0.7187 |
| Sex | -0.00012 | 0.005968 | 0.9843 |
| BMI | -0.00348 | 0.003519 | 0.3221 |

**Supplementary Table 2.** Full mixed-effects model results – strength. Significant effects and interactions are bolded.

|  |  |  |  |
| --- | --- | --- | --- |
| **Effect** | **Estimate** | **Standard**  **Error** | **p-value** |
| **Drinking State** | **0.2340** | **0.004659** | **<0.0001** |
| **PBRSA-rest** | **-0.00994** | **0.004340** | **0.0220** |
| PBRSA-react | 0.007051 | 0.004156 | 0.0898 |
| **Clustering Coefficient** | **0.06825** | **0.002450** | **<0.0001** |
| **Global Efficiency** | **0.02923** | **0.002528** | **<0.0001** |
| **Degree** | **-0.04430** | **0.001256** | **<0.0001** |
| **Modularity** | **-0.01518** | **0.003053** | **<0.0001** |
| Age | -0.00116 | 0.003233 | 0.7187 |
| Sex | -0.00012 | 0.005968 | 0.9843 |
| BMI | -0.00348 | 0.003519 | 0.3221 |
| **Spatial Distance** | **-0.05132** | **0.001100** | **<0.0001** |
| **Spatial Distance2** | **0.02890** | **0.000537** | **<0.0001** |
| **Clustering Coefficient\*PBRSA-rest\*PBRSA-react** | **-0.00223** | **0.001092** | **0.0406** |
| **Global Efficiency\*PBRSA-rest\*PBRSA-react** | **0.001999** | **0.000993** | **0.0440** |
| Degree\*PBRSA-rest\* PBRSA-react | -0.00051 | 0.000561 | 0.3639 |
| Modularity\*PBRSA-rest\*PBRSA-react | -0.00570 | 0.004092 | 0.1637 |
| **Clustering Coefficient\*Drinking State\*PBRSA-rest** | **0.01186** | **0.003357** | **0.0004** |
| Global Efficiency\*Drinking State\* PBRSA-rest | -0.00518 | 0.003226 | 0.1087 |
| Degree\*Drinking State\*PBRSA-rest | -0.00120 | 0.001734 | 0.4897 |
| Modularity\*Drinking State\*PBRSA-rest | -0.00138 | 0.007352 | 0.8511 |
| Clustering Coefficient\*Drinking State\*PBRSA-react | -0.00329 | 0.003343 | 0.3245 |
| Global Efficiency\*Drinking State\*PBRSA-react | 0.002779 | 0.003215 | 0.3874 |
| Degree\*Drinking State\*PBRSA-react | 0.001632 | 0.001730 | 0.3456 |
| Modularity\*Drinking State\*PBRSA-react | -0.01339 | 0.008060 | 0.0967 |
| **Clustering Coefficient\*PBRSA-rest** | **-0.00532** | **0.002651** | **0.0449** |
| Global Efficiency\*PBRSA-rest | 0.000041 | 0.002713 | 0.9879 |
| Degree\*PBRSA-rest | -0.00049 | 0.001351 | 0.7183 |
| Modularity\*PBRSA-rest | 0.003155 | 0.003607 | 0.3817 |
| Clustering Coefficient\*PBRSA-react | 0.000271 | 0.002731 | 0.9209 |
| Global Efficiency\*PBRSA-react | 0.001526 | 0.002783 | 0.5835 |
| Degree\*PBRSA-react | -0.00154 | 0.001399 | 0.2701 |
| Modularity\*PBRSA-react | 0.006400 | 0.005891 | 0.2773 |
| Clustering Coefficient\*Drinking State | 0.001887 | 0.003163 | 0.5509 |
| Global Efficiency\* Drinking State | -0.00456 | 0.003046 | 0.1344 |
| Degree\* Drinking State | 0.000871 | 0.001643 | 0.5961 |
| Modularity\* Drinking State | -0.00044 | 0.005495 | 0.9367 |
| Drinking State\*PBRSA-rest | 0.01180 | 0.006157 | 0.0553 |
| Drinking State\*PBRSA-react | -0.00886 | 0.005583 | 0.1124 |
| PBRSA-rest\*PBRSA-react | -0.00021 | 0.002646 | 0.9366 |

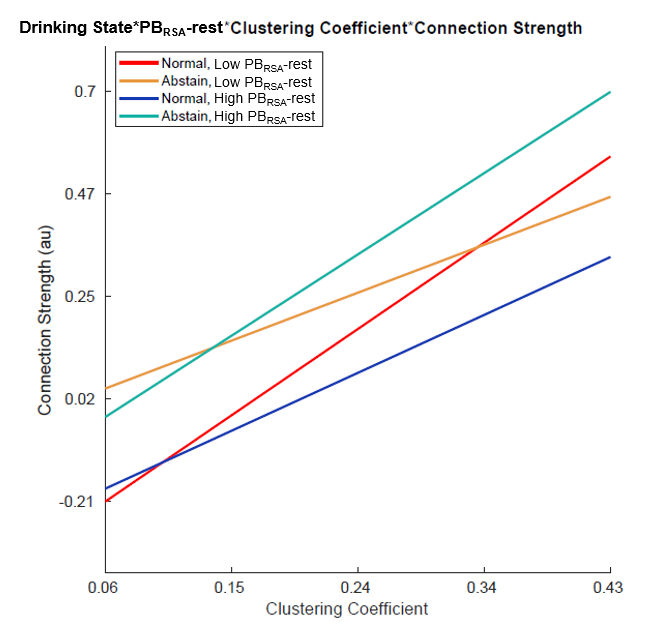
**Supplementary Table 3.** Full mixed-effects model results – probability. Significant effects and interactions are bolded.

|  |  |  |  |
| --- | --- | --- | --- |
| **Effect** | **Estimate** | **Standard**  **Error** | **p-value** |
| **Drinking State** | **0.1803** | **0.03493** | **<0.0001** |
| PBRSA-rest | 0.01808 | 0.03219 | 0.5744 |
| PBRSA-react | 0.01719 | 0.03085 | 0.5773 |
| **Clustering Coefficient** | **0.3214** | **0.03876** | **<0.0001** |
| **Global Efficiency** | **-0.3050** | **0.03331** | **<0.0001** |
| **Degree** | **0.1480** | **0.02094** | **<0.0001** |
| Modularity | -0.02212 | 0.02264 | 0.3284 |
| Age | -0.00487 | 0.02465 | 0.8433 |
| Sex | 0.05779 | 0.04574 | 0.2065 |
| BMI | -0.02645 | 0.02686 | 0.3249 |
| **Spatial Distance** | **0.3597** | **0.01672** | **<0.0001** |
| **Spatial Distance2** | **-0.1346** | **0.006994** | **<0.0001** |
| Clustering Coefficient\*PBRSA-rest\*PBRSA-react | -0.01740 | 0.01504 | 0.2474 |
| Global Efficiency\*PBRSA-rest\* PBRSA-react | 0.002055 | 0.01414 | 0.8843 |
| Degree\*PBRSA-rest\*PBRSA-react | 0.007776 | 0.01001 | 0.4373 |
| Modularity\*PBRSA-rest\*PBRSA-react | 0.02905 | 0.03159 | 0.3578 |
| Clustering Coefficient\*Drinking State\*PBRSA-rest | 0.06127 | 0.04924 | 0.2133 |
| Global Efficiency\*Drinking State\*PBRSA-rest | -0.02835 | 0.04439 | 0.5229 |
| Degree\*Drinking State\*PBRSA-rest | -0.03306 | 0.03066 | 0.2808 |
| Modularity\*Drinking State\*PBRSA-rest | -0.02421 | 0.06190 | 0.6957 |
| Clustering Coefficient\*Drinking State\*PBRSA-react | 0.01006 | 0.04920 | 0.8380 |
| Global Efficiency\*Drinking State\*PBRSA-react | -0.00360 | 0.04436 | 0.9354 |
| Degree\*Drinking State\*PBRSA-react | -0.01732 | 0.03065 | 0.5719 |
| Modularity\*Drinking State\*PBRSA-react | -0.02421 | 0.06190 | 0.6957 |
| Clustering Coefficient\*PBRSA-rest | 0.002834 | 0.04147 | 0.9455 |
| Global Efficiency\*PBRSA-rest | -0.01805 | 0.03568 | 0.6129 |
| **Degree\*PBRSA-rest** | **0.04649** | **0.02251** | **0.0389** |
| Modularity\*PBRSA-rest | -0.03168 | 0.02663 | 0.2341 |
| Clustering Coefficient\*PBRSA-react | -0.02664 | 0.04265 | 0.5323 |
| Global Efficiency\*PBRSA-react | 0.02381 | 0.03693 | 0.5190 |
| Degree\*PBRSA-react | 0.005685 | 0.02352 | 0.8090 |
| Modularity\*PBRSA-react | 0.008284 | 0.04362 | 0.8494 |
| Clustering Coefficient\*Drinking State | -0.05450 | 0.04664 | 0.2426 |
| Global Efficiency\* Drinking State | 0.04794 | 0.04207 | 0.2545 |
| Degree\* Drinking State | 0.01711 | 0.02907 | 0.5562 |
| Modularity\* Drinking State | -0.01087 | 0.04291 | 0.8000 |
| Drinking State\*PBRSA-rest | -0.03600 | 0.04742 | 0.4477 |
| Drinking State\*PBRSA-react | -0.01412 | 0.04311 | 0.7432 |
| PBRSA-rest\*PBRSA-react | 0.007958 | 0.01986 | 0.6887 |

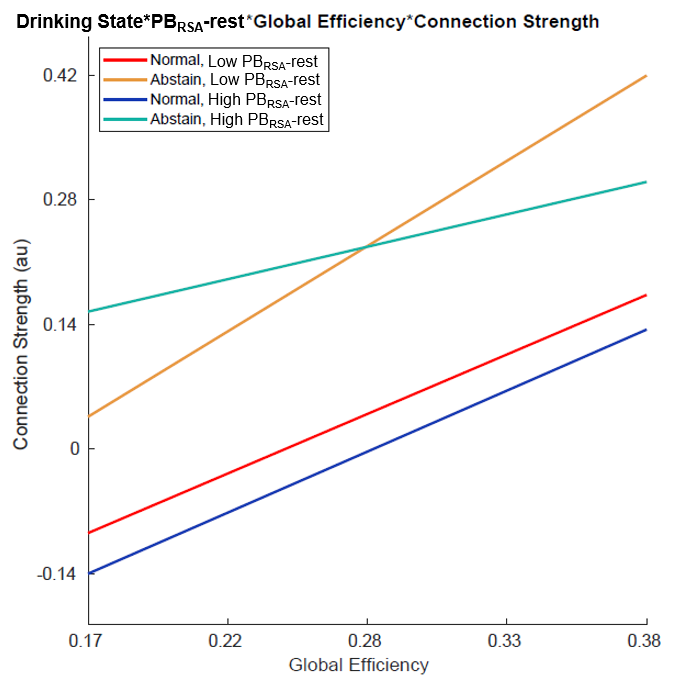
**Supplementary Table 4.** Differences in average survey responses preceding MRI scanning across drinking states.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Normal**  **Drinking** | **Abstinence** | **t-value** | **p-value** |
| **Alcohol Craving Experience (ACE) Questionnaire** | 14.1 (13.5) | 14.5 (10.9) | -0.247 | 0.806 |
| **Perceived Stress Scale (PSS)** | 30.8 (2.8) | 30.3 (2.3) | 1.404 | 0.168 |
| **State Trait Anxiety Inventory (STAI)** | 45.9 (3.9) | 45.9 (3.4) | 0.092 | 0.927 |
| **Mindful Attention Awareness Scale (MAAS)** | 7.8 (5.2) | 7.6 (5.6) | 0.272 | 0.787 |
| **Freiburg Mindfulness Scale** | 40.7 (5.6) | 41.5 (5.9) | -1.548 | 0.130 |

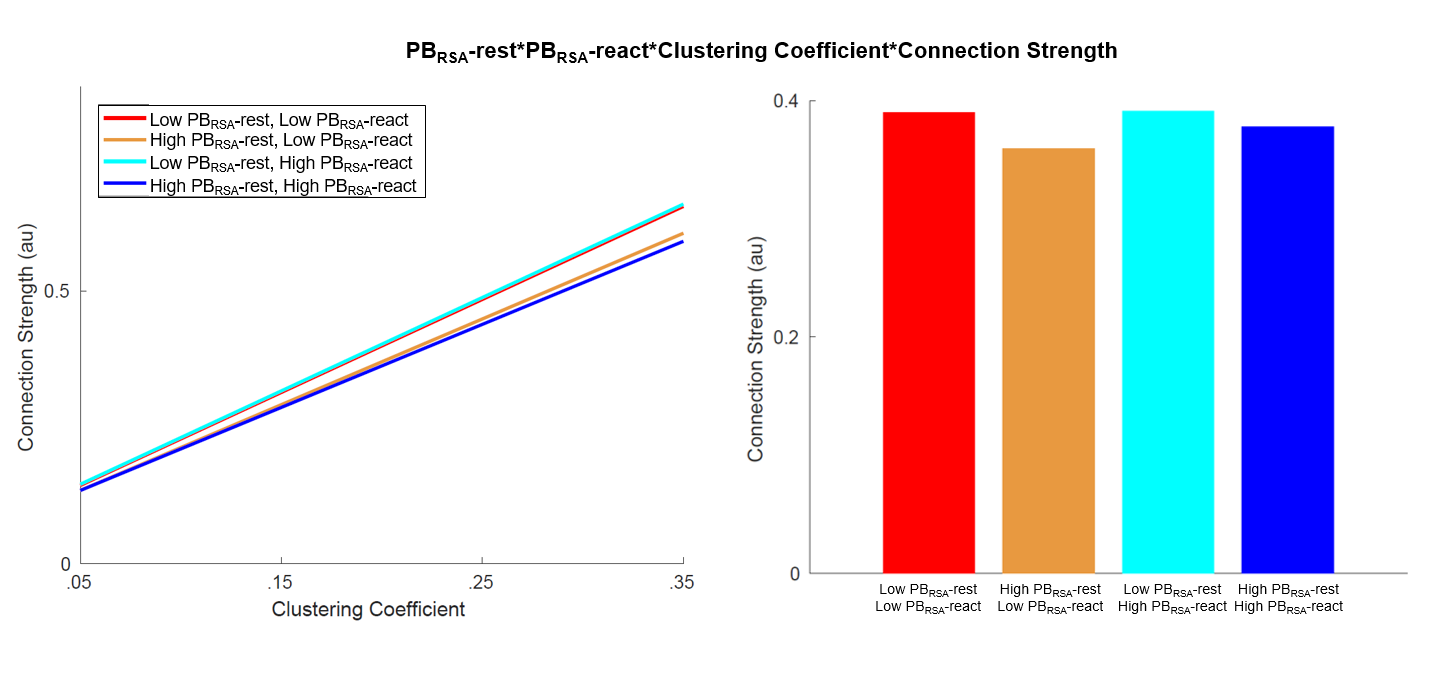
*3.2 Supplementary Figures*



**Figure 1.** Graphical representation of the relationship between connection strength and clustering coefficient across drinking states, divided by the upper and lower bounds of PBRSA-rest values, meant only for illustrative purposes. Because PBRSA is a continuous variable, the 3-way interactions form 3-dimentional planes and cannot easily be graphed. For visualization purposes, the upper and lower bounds of PBRSA-rest values were used in the regression equations in conjunction with the dichotomous drinking state variable to create this graph.



**Figure 2.** Graphical representation of the relationship between connection strength and global efficiency across drinking states, divided by PBRSA-rest values (approaching significance), meant only for illustrative purposes. Because PBRSA is a continuous variable, the 3-way interactions form 3-dimentional planes and cannot easily be graphed. For visualization purposes, the upper and lower bounds of PBRSA-rest values were used in the regression equations in conjunction with the dichotomous drinking state variable to create this graph.



**Figure 3.** Graphical representation of the relationship between connection strength and clustering coefficient when accounting for both resting and reactive PBRSA, meant only for illustrative purposes. Because PBRSA is a continuous variable, the 3-way interactions form 3-dimentional planes and cannot easily be graphed. For visualization purposes, the upper and lower bounds of PBRSA-rest and PBRSA-react values were used in the regression equations to create this graph. A depiction of the regression equation (as included in Supplementary Figures 1 and 2) as well as the slopes of the four conditions (as seen in the main body of the manuscript) are included.



**Figure 4.** Graphical representation of the relationship between connection strength and global efficiency when accounting for both resting and reactive PBRSA, meant only for illustrative purposes. Because PBRSA is a continuous variable, the 3-way interactions form 3-dimentional planes and cannot easily be graphed. For visualization purposes, the upper and lower bounds of PBRSA-rest and PBRSA-react values were used in the regression equations to create this graph. A depiction of the regression equation (as included in Supplementary Figures 1 and 2) as well as the slopes of the four conditions (as seen in the main body of the manuscript) are included.

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