Hypoventilation Therapy Alleviates Panic by Repeated Induction of Dyspnea

Supplemental Information

Additional information for the mixed models data analyses:

Association between level of dyspnea and next-session panic symptoms (Hypothesis 2)

The mixed model used for testing whether interoceptive exposure (dyspnea) during weekly practice exercises was predictive of panicogenic cognitions (ASI) at the next therapy session, controlling for anxiety level and PCO_2 during the weekly practice sessions, was:

$$ASI_{ij+1}=b0+b1*Dyspnea_{ij}+b2*Anxiety_{ij}+b3*PCO_{2ij}+b4*ASI_{ij}+b5*ASIpre_i+$$
$$b6*age_i+b7*gender_i+b8*diagnosisAGE_i+b9*week_{ij}+\varepsilon_{ij}$$

where $Dyspnea_{ij}$ and $Anxiety_{ij}$ were the average level of dyspnea (and anxiety) for individual i during week j, measured during the practice exercises in the week prior to the assessment of ASI at the next therapy session (ASI_{ij+1}). PCO_{2ij} was the average within-session change in PCO_2 for individual i during week j, assessed during the week prior to the assessment of ASI. ASI_{ij} was ASI level assessed at the previous therapy session. $ASIpre_i$ was the pre-treatment level of ASI for individual i, and age, gender, and age at which they were first diagnosed with panic disorder were also included as covariates. $Week_{ij}$ was also included as a covariate to control for the possibility that the variables of interest might be related to outcome merely because they are all changing over time. The covariance matrix for the errors of the repeated measures was modeled as a diagonal matrix, since that matrix was the simplest covariance matrix whose fit was not significantly worse than the model using unstructured covariance matrix. The diagonal matrix has, on its diagonal, the variances of the errors at each assessment (each week), which were significantly different across the various assessment points. No random effects were used because the model would not converge when random effects were included.

There were 4 weekly measures of dyspnea, anxiety, PCO_2, and ASI, one for each week of the practice exercises (the daily assessments of dyspnea, anxiety, and PCO_2 were averaged within each of the 4 weeks). These 4 assessments were treated as 4 repeated measures nested within individuals. Because of the repeated measurements of each parameter, these parameters were used as time-varying predictors (TVPs) of ASI over the 4 weeks. However, TVPs confound the effects of between-subjects differences in overall level of the TVP with within-subjects changes in the TVP over time (i.e., higher levels of PCO_2 might reflect higher *average* levels of PCO_2 in some cases, while being a result of higher deviations from normal in other cases) ((1) pp. 327-392, (2) pp.69-75, 25). Thus, we disaggregated the between- and within-subjects components of the TVPs into the average level of the TVP (e.g., average level of dyspnea over the 4 weeks) and the deviations each week from the average level of the TVP (e.g., the difference between a person's level of dyspnea in a particular week and their average level of dyspnea over the 4 weeks ((1) pp. 327-392, (2) pp.69-75, 25)). For example,

$$DyspneaDeviation_{ij} = Dyspnea_{ij} - DyspneaMean_i$$

where $Dyspnea_{ij}$ is the average weekly level of dyspnea for individual i at week j, $DyspneaMean_i$ is the average level of dyspnea for individual i across the 4 weeks, and $DyspneaDeviation_{ij}$ is the deviation of $Dyspnea_{ij}$ from its mean for individual i at week j. Thus, whenever a TVP would appear in a model, it is replaced by 2 predictors: its average level over the 4 assessments (a level 2 variable) and its deviation, at each assessment, from its average value across all 4 assessments. Failing to disaggregate TVPs in this way effectively assumes that the relation between the 2 disaggregated components of a TVP and the outcome are equal. Following Hoffman (1), we tested whether it was necessary to disaggregate each TVP by testing whether the model with the disaggregated TVP fit the data significantly better than the model with the non-disaggregated TVP. When the difference between the model fit of these two models was not significant, we used the simpler non-disaggregated TVP model (1).

In the model used for testing hypothesis 2, disaggregating the TVPs did not improve the model fit, so the non-disaggregated TVPs were used in this analysis.

Exploratory Analyses

Associations among within-exercise changes in dyspnea, anxiety, PCO_2, and respiratory rate

Rather than using raw change scores in these analyses, which can be distorted by regression to the mean and have high variance (3), we used residualized change scores which are not subject to regression to the mean and have lower variance (3). Residualized change scores were calculated as the residual from the OLS regression using baseline phase values of each parameter (PCO_2, respiratory rate, dyspnea, and anxiety) to predict unpaced phase values of that parameter (e.g., residualized change in PCO_2 was the residual form the OLS regression with baseline phase PCO_2 predicting unpaced phase PCO_2).

As an example of the models used in these analyses, the model for examining the concurrent relations between within-exercise change in PCO_2 and within-exercise change in anxiety, over the 4 assessments (4 weeks) of these variables, was:

$$ANXchg_{ij}=b0+b1*PCO_2chg_{ij}+b2*age_i+b3*gender_i+b4*diagnosisAGE_i+b5*week_i+\varepsilon_{ij}$$

where $ANXchg_{ij}$ and PCO_2chg_{ij} represent the within-exercise residualized change (from baseline phase to unpaced phase) in anxiety and PCO_2 for individual i during week j. The "non-disaggregated" version of PCO_2chg was used in this analysis because the model fit for the disaggregated variable was not better than the model fit for non-disaggregated PCO_2chg. The covariance matrix for the errors ε_{ij} was modeled as "unstructured" since that structure provided the best fit for the data (all simpler covariance structures resulted in models that fit the data significantly worse than the unstructured covariance matrix). Since the unstructured covariance matrix uses all the degrees of freedom in the analysis, no random effects were modeled in these analyses.

Within-exercise changes in PCO_2, respiratory rate, dyspnea, and anxiety predicting the next session's panicogenic cognitions

We used mixed models to examine whether within-exercise residualized change in PCO_2, respiratory rate, dyspnea, and anxiety during practice exercises during the week, were related to panicogenic cognitions at the therapy session at the end of that week. The model for change in PCO_2 predicting panicogenic cognitions was:

$$ASI_{ij+1}=b0+b1*PCO_2chgMEAN_i+b2*PCO_2chgDEV_{ij}+b3*ASI_{ij}+b4*ASIpre_i+$$
$$b5*age_i+b6*gender_i+b7*diagnosisAGE_i+b8*week_i+\varepsilon_{ij}$$

where ASI_{ij+1} represents ASI for individual i at therapy session j+1 (the following therapy session), while ASI_{ij} represents ASI for individual i at the prior therapy session, j. In this case, PCO_2 was disaggregated because the model with the disaggregated PCO_2 fit the data significantly better than the model that did not disaggregate PCO_2. The covariance matrix for the errors of the repeated measures was modeled as a diagonal matrix, since that was the simplest model whose fit was not significantly worse than the model using unstructured covariance matrix. No random effects were used because the model would not converge when random effects were included. This model was repeated for each of the within-exercise change parameters to determine if each predicted next session panicogenic cognitions.

Supplemental References

1. Hoffman, L (2015): *Longitudinal Analysis: Modeling Within-Person Fluctuation and Change*. New York, NY: Routledge.
2. Hedeker D, Gibbons RD (2006): *Longitudinal Data Analysis*. Hoboken, N.J.: John Wiley & Sons.
3. Tabachnick BG, Fidell LS (2013): Using Multivariate Statistics, 6th ed. Allyn & Bacon, Boston, MA.