Abstract:

In this study we aim to evaluate whether certain categories of stressors are grouped together based on whether they elicit similar behavioral and BOLD stress responses. We also seek to compare category relationships under behavioral versus fMRI analysis. Ten subjects were scanned in an fMRI while asked to rate and indicate the stress level of 60 prompts, which were divided into 4 categories of stressors: career-related, school-related, social-related, and event-related. Stress responses were evaluated through a behavioral survey and the fMRI responses of the amygdala, hippocampus, and cingulate cortex. Representational analysis was used to construct dissimilarity matrices and determine correlation of responses between stimuli categories. In the behavioral response analysis, career and school responses were found to be the most similar and career and event responses were found to be the least similar. In the analysis of various brain regions, the dissimilarity of categories differed across the brain regions examined. However, responses for social and school prompts tended to be moderately similar across all brain regions.

Introduction:

Stress is a feeling of emotional or physical tension. It can come from any event or thought that make us feel frustrated, angry, or nervous. Stress is a body's reaction to a challenge or demand. In short bursts, stress can be positive, such as when it helps us avoid danger or meet a deadline. But when stress last for a long time, it may harm your health. Because of the potential dangers and consequences of chronic stress, learning more about whether certain kinds of stress generate similar or dissimilar stress responses is significant to better understanding stress and thus leading toward methods of stress management. Because of the relevancy of stresses and experiences to college students, we found it of interest to evaluate various situations and categories of stressors and whether stress responses were similar for certain kinds of stressors.

Imaging techniques are increasingly being used to examine the neural correlates of stress and emotion processing; however, in our study we are trying to find if the stressors can be grouped together based on the neural data and if it does, how it is grouped together. For our study, Stress responses were measured by a behavioral survey and the fMRI responses of the amygdala, hippocampus, and cingulate cortex due to their involvement in the stress response [1]. In our hypothesis, we started with two types of groups that can be formed due to stress. In the former, we described stress as high or low stress and in the latter group, we divided the groups into categories – Social, School, Events, Career based on our data questions. We later realized that we are mostly grouping Career and School related questions as high stress and School and Social related questions as low stress and we thus decided to run our GLM on only one of these analysis – 4 categories

Since stress also accompanies with physiological changes like increase heart rate etc, we run the GLM to account for these changes as well. fMRI studies have demonstrated that the hemodynamic response function changes in association with stress response markers under acute psychosocial stress [2], and that brain areas such as the amygdala and hippocampus are involved in the general stress response [1].

Methods:

Participants:

We scanned 10 subjects (n=10). Nine of the ten subjects were college-aged students at Dartmouth College, with ages ranging from age 18 to age 24 and the other subject was a professor at Dartmouth College. 4 of the subjects were male. All subjects consented to being scanned. We did the GLM on all subjects and decided to remove one subject was for the further analysis due to excessive movement in all three runs (trial 1 max fd = 11.385mm, trial 2 max fd = 5.077mm, trial 3 max fd = 5.814mm). We decided to do this way so that we could capture all variations for different categories in the GLM process

Materials:

For scanning we used a 3T functional magnetic resonance imaging (fMRI) scanner at Dartmouth College. Subjects were shown the prompts for mentalization through SuperLab. Analysis was done using SPM12. The functional task involved button presses, which required the use of a Lumina box. In the scanner, participants had 4 possible buttons to press.

Procedure:

Participants were first screened for safety, then placed into the fMRI scanner. The scan consisted of 7 scans: a scout scan, an anatomical scan, a T1, 3 functional runs, and a diffusion tensor imaging scan. During the functional runs, participants were instructed to mentalize the prompt shown on the screen and indicate how stressful the stimuli was for them by pressing buttons. There were 60 prompts and 15 fixations, thus 75 stimuli in total. The prompts seen were sentences indicating a situation or experience that was likely to be common across all subjects. For the self-reporting stress options, there were

4 buttons for 4 possible levels of stress, with 1 being the minimal amount of stress and 4 being the maximal amount of stress. Each subject did three runs of the functional stress task. Each run consisted of the same prompts, however prompts were shown in different orders on each run. The scan in its entirety took around 40 minutes.

Design:

This study utilized a repeated measures design, as each subject's scan consisted of three runs. There were no controls, nor different groupings of participants. There was no blinding in this study. Each participant saw the prompts presented in the same order for each run. In other words, runs 1, 2, and 3 consisted of the same questions in the same order for each of the participants.

GLM:

Nipype and SPM12(Wellcome Department of Cognitive Neurology, London, UK) was used to perform general linear model analyses. Task conditions and covariates of no interest were convolved with a canonical hemodynamic response function (HRF) and included in a general linear model (GLM) to determine neural responses from the video to above-mentioned categories. Covariates of no interest included, a high-pass filter (128 seconds) to account for low-frequency scanner drift and a run regressor to account for differences between runs. GLM based on different groups was modeled at a subject-level and then subsequently smoothed using a 6mm FWHM isotropic gaussian kernel. Smoothed results were then submitted to second-level random-effects (RFX) analysis. A two-group t-test was performed to identify differences between **Social, Career, School and Events Categories.** Images were visualized using nilearn [8]. Self-reported stress was included as a parametric regressor

Analysis:

In this study we uncover groupings of similar stress responses using representational similarity analysis of fMRI data. Representational Similarity Analysis is a multivariate technique which compares the similarity between brain activity and a particular measure [3]. This technique was initially proposed by Nikolaus Kriegskorte in 2008, [4]. RSA mainly helps us identifying if the conceptual grouping has a neural basis i.e., are patterns of neural activity for oranges and apples more similar to each other as compared to patterns for oranges and ping-pong balls

RSA is a way to compare and contrast different brain states and quantify the space in which they are embedded. Here we compute a similarity matrix (often correlation) between patterns of neural activity for each item. Items thus next to each other must have higher similarities, as compared to items far apart [5].

The most basic type of RDM is a square symmetric matrix, indexed by the stimuli horizontally and vertically. The diagonal entries reflect comparisons between identical stimuli and are 0, by definition in this type of RDM. Each off-diagonal value indicates the dissimilarity between the activity patterns associated with two different stimuli. The dissimilarities can be interpreted as distances in the multivariate response space. RDM's can be derived from variety of sources beyond brain – activity patterns. One can also define an RDM on the basis of behavioral measures that capture the discriminability of different objects, such as judgment of dissimilarity, frequencies of confusions, or reaction times in a discrimination task. [6] We in our study, are hypothesizing about the similarity and dissimilarity between different categories of stress through the self-reported responses.

Dissimilarity matrices were constructed using representational similarity analysis (RSA) of behavioral responses and activity in the following regions: left and right amygdala, left and right hippocampus, cingulate cortex, and left and right occipital-parietal junction. The amygdala, hippocampus and cingulate cortex were chosen because of their involvement in stress. The amygdala plays a primary role in processing emotion, particularly fear and anxiety, the hippocampus is thought to regulate emotion and stress, and the cingulate cortex is likewise involved in emotional regulation and emotional memories.

Results:

RSA of behavioral responses reveals the least dissimilarity for the school and career pairing, and the greatest dissimilarity for the event and career pairing. As behavioral responses were measured on a self-reported 1-4 scale, this suggests that prompts in the school and career categories were more similarly ranked, whereas there was the greatest discrepancy in ratings across the career and event categories. In order, career and school responses were most similar, followed by social and event, school and social, career and social, and career and event.

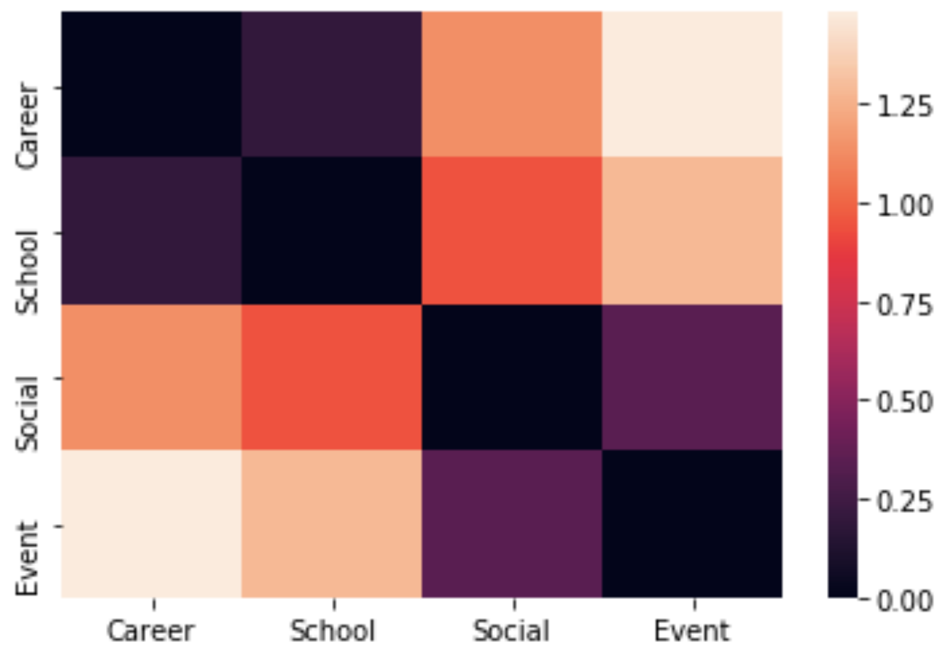
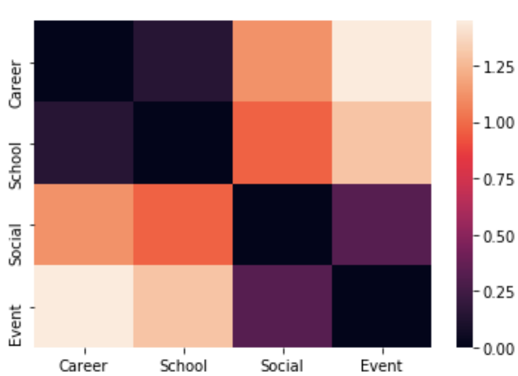
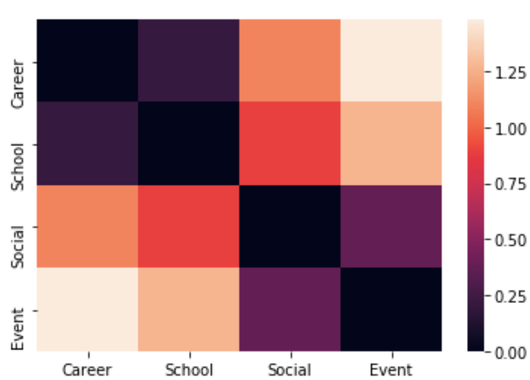


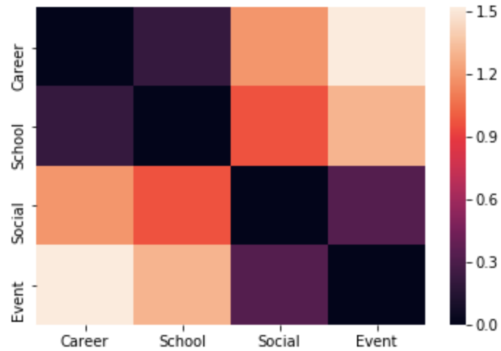
Figure 1: Behavioral Response dissimilarity matrix for career, school, social, and event categories. Average over all 10 subjects and 3 runs

We also examined whether the order of the prompts had any effect on the degree of response similarity between sets of categories. The dissimilarity matrix is largely the same for the individual orders, with the exception that the school and social category similarity is higher in the second order. This suggests that the order of the questions does not greatly affect reported response (i.e. numerical ranking).





Run 1 Run 2



Run 3

Representational dissimilarity matrices (RDMs) constructed from RSA of different brain regions were found to be varied. In both the right and left amygdala, responses to school prompts were highly correlated with responses to social prompts, and responses for school prompts were also correlated with responses for event prompts. This correlation was higher in the left amygdala in both cases. In the right amygdala, school and social categories were least dissimilar (most similar), followed by school and event, event and career, social and event, career and school, and social and career being the most dissimilar. For the left amygdala, the school and social categories were least dissimilar followed by school and event, social and event, career and social, career and school, and career and event being the most dissimilar. The career and social, and career and social pairing tended to be more dissimilar for both the right and left amygdalae. However, the social and career categories are more dissimilar in the right amygdala than the right, and there is very little correlation between career and event in the left amygdala, while some correlation is demonstrated in the right amygdala.

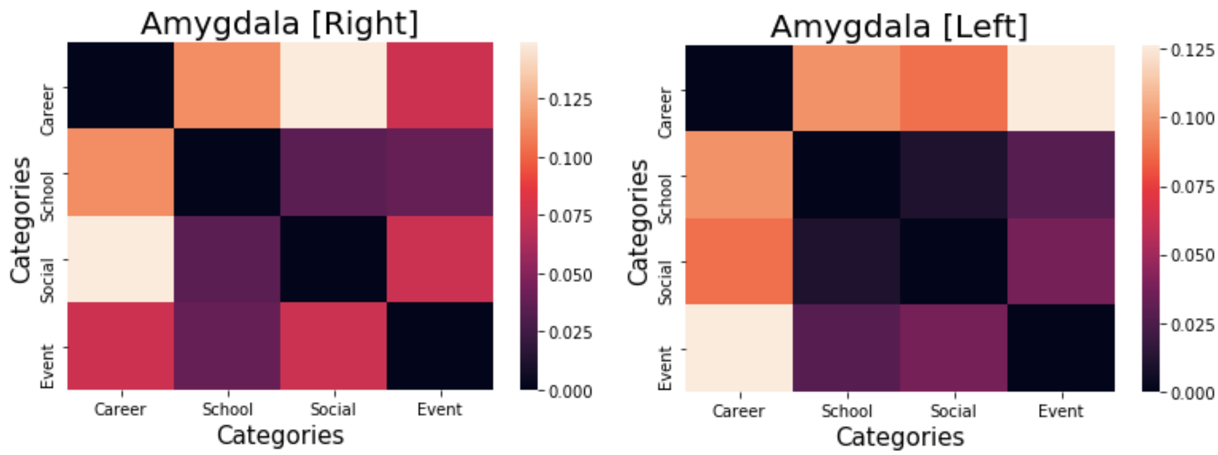


Figure 2: Dissimilarity matrices for left and right amygdala

RSA of the hippocampus shows the least dissimilarity for the social and event categories and the most dissimilarity in response for the event and career categories (left hippocampus), and career and social categories (right hippocampus). In order from least to most dissimilar, the category pairs for the left hippocampus were: social-event, school-social, career-school, school-event, career-social, and career-event. The right hippocampus is as follows: school-event, social-event, school-social, career-school, career-event, and social-career. Overall, hippocampal RDMs showed higher correlation in social and event category prompts and social and school category prompts, and low correlation between career and social prompts, and career and school prompts. Of note is the extremely strong correlation in the right hippocampus of the school and event categories. In both the amygdala and the hippocampus, school and event categories and school and social categories seemed to show low dissimilarity. This contrasts with the results of the behavioral matrix in which these two category pairs are less similar in comparison to the highly similar school and career, and social and event categories.

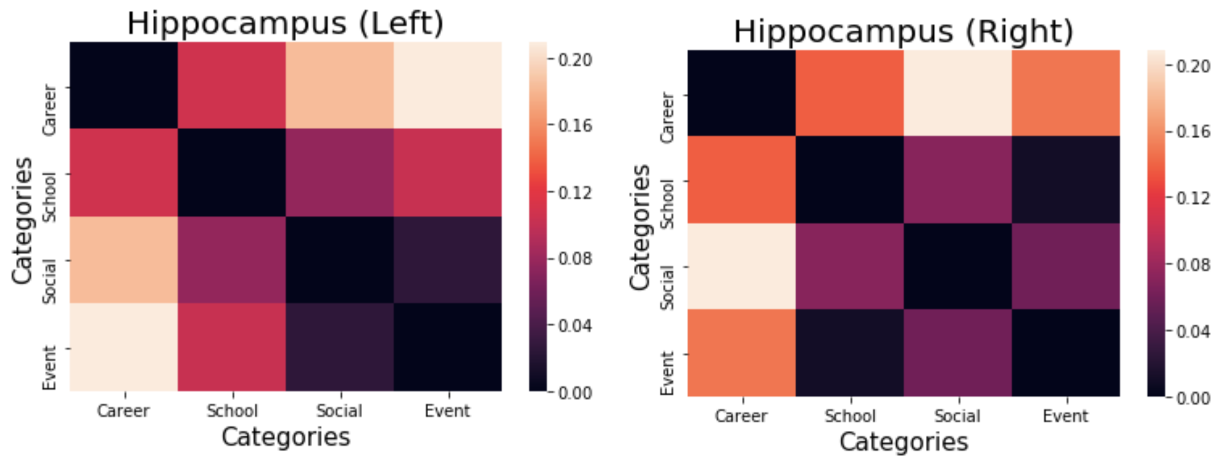


Figure 3: Dissimilarity matrices for left and right hippocampus

The dissimilarity matrix constructed from the activity of the cingulate cortex shows that responses for the school and social categories tended to be more similar (which is also generally true in the amygdala and hippocampus). However, there is an extremely low dissimilarity between the event and career categories. This is interesting as these categories were most highly correlated in self-reported stress level in the behavioral analysis. The social and event categories as well as the school and event categories appear to be fairly dissimilar, whereas social and event correlated strongly in the hippocampus and school and event categories correlated strongly in the amygdala and right hippocampus.

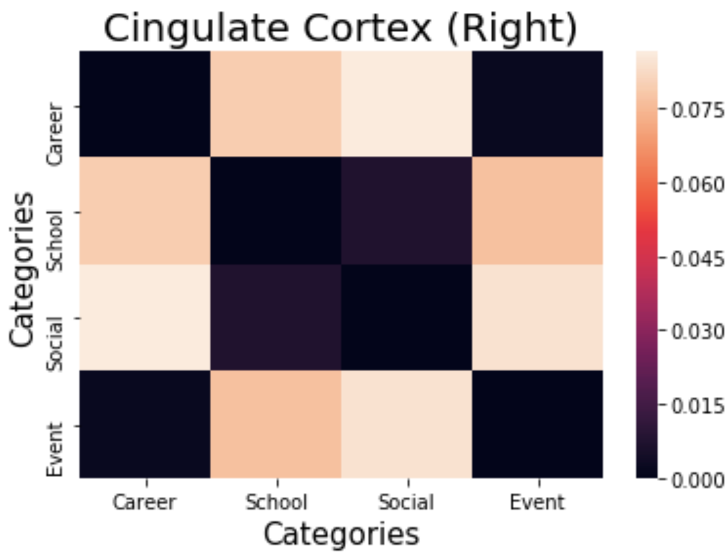


Figure 4: Dissimilarity matrix for right cingulate cortex

Overall, behavioral responses for the career and school categories were most similar (high rating of stress) and responses for career and event categories were most dissimilar (suggesting that event prompts tended to be ranked at low stress ratings). fMRI responses for school and social tended to be grouped as relatively similar across all brain regions examined, although this relationship is strongest in the right cingulate cortex and left amygdala. In contrast to the behavioral analysis, in the fMRI analysis career and school were not the relatively more similar pairings. Career and social categories were fairly dissimilar across the majority of analyses carried out.

Discussion

The dissimilarity matrix results were constructed by taking the mean of activated neural activity for all subject and all runs taken separately for each category and finding the distance between each category by taking the absolute difference and plotting it via heatmap. Since stress is a systematic and more global response that implicates multiple areas in varying ways and we mainly chose 3 regions – Amygdala, hippocampus, Cingulate cortex and see that they have different RSA's all together. Among them, cingulate cortex was the most different from the Behavioral data RSA as well as other 2 selected brain region in our study. This suggests that one source of this difference in activity could be that maybe different kinds of stress activates different brain areas differently.

Another interesting thing that we can see from our analysis that career category is the most different from all other categories. We were assuming career related stress to be similar to school stress, which we also saw it in DSM of self-reported data, but in the brain regions, career related stress proved to be quite different than all other category of stress , i.e Career stress is grouped differently, this might be because most of the subjects were students and do not have any experience and thus memory of stress related to that category. Thus, there might be a possibility that Amygdala and Hippocampus is related to episodic memory. We can also try to do the RSA by excluding the subjects that have some experience related to a job and see if that helps to strengthen our statement about episodic memory.

among the different brain regions points to the fact there is no one brain organ for stress, but that the different brain areas respond differently, and stress is a systemic and more global response that implicates multiple areas in varying ways. In addition, this suggests that one source of this difference in activity could be that different kinds of stress activate different brain areas differently. The discrepancy between the behavioral and brain response matrices is interesting because it suggests that how stressful one thinks something is may not be the same as the actual stress response in different brain areas, which leads to the question of what determines our subjective experience of stress.

In order to improve this study, the sample size could be increased, and the sample could be randomly selected to allow for generalizing to a population. If there was time, we also could have grouped brain areas into “functional regions” to examine whether activity responses would have revealed any trends for a particular function (e.g. pain).

References

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