The Effect of Controllability on Context Dependent Granger Causality in Snake Phobia fMRI Data at 400-ms Resolution.

McFarlin, D.R., Kerr, D.L., Green, D.E., Nitschke J.B.
University of Wisconsin, Waisman Laboratory for Brain Imaging and Behavior

Granger causality utilizes lagged time series of one or more variables to determine those that are useful in predicting future values of one or more variables. A context dependent multivariate granger causality analysis was performed, with 400 ms resolution time series of fMRI BOLD response. Time series from 13 anatomically defined regions of interest (ROIs) that are known to be important in anxiety, were extracted from 39 snake phobic subjects and 17 non-phobic subjects. The regions investigated were the pregenual anterior cingulate cortex (ACC), and bilateral subgenual ACC, supragenual ACC, anterior insular cortices, dorsal amygdalae, ventral amygdalae, and hippocampi. The directional causal effective connectivity between these ROIs was modeled in different contexts, separated by trial types, allowing complete alteration of connectivity between different contexts. Trials begin with presentation of a cue to indicate the nature of the stimulus—valence, arousal, disgust, and fear—counterbalanced across condition and with and without controllability, both within and between groups.

Participants
The 39 snake phobic participants (15 females, mean age 21.8, range 18-46) and 17 non-phobic participants (17 females, mean age 26.8, range 19-46) were right handed and neurologically healthy. Participants were absent of all clinical disorders as assessed by the Structured Clinical Interview for the DSM-IV. Informed consent in accordance with rules set by the University of Wisconsin at Madison Human Studies Committee was obtained from all participants prior to the experiment.

Stimuli
The stimuli consisted of 3-disgust, fish, and snake videos (24 each). Each video was standardized for several psychological attributes (e.g., arousal, contrast, scene complexity and movement of the stimuli) across sessions prior to the study. Physical attributes such as brightness, contrast, scene complexity and movement of the stimuli were equalized. Videos were presented to participants in the scanner using custom written software on the head coil of a 3.0 Tesla GE SIGNA Scanner (TR=2 s).

Experimental Paradigm
Participants were administered several anxiety and phobia questionnaires, followed by a mock scanner session during which they practiced the experimental task. Each trial began with an anticipation period signaled by a cue. A 1.2 second presentation of a “Stop” preceded fish videos, and an “S” preceded snake videos. Subjects were instructed at the onset of the study that they would be receiving these videos. Uncontrollability was indicated by the color of the anticipation cue. A blue cue indicated a controllable trial, and a yellow cue indicated an uncontrollable trial. When a subject had a controllable trial, if reaction time (RT) was fast enough to a target square that they chose to look at after a variable delay, they received a fixation cross rather than the video. Otherwise, they received the video. A success rate of approximately 50% was achieved with online monitoring of RT in DMN. Similarly, half of the uncontrollable trials were followed by a video. Of the 72 total video trials, 36 were rated as uncontrollable and the other half were considered as controllable. The experiment was conducted in blocks of 24 trials each, with one Likert online rating about the nature of the stimulus—valence, arousal, disgust, and fear—counterbalanced across condition.

Fourier interpolation at the voxel level was an effective method for investigating ROI interactions at rates closer to those known to occur physiologically. The increased time resolution resulted in a five fold increase in the number of between group differences compared to a more stringent multiple comparison threshold. The reduced amount of time per condition, and the more stringent multiple comparison correction required for context dependent Granger causality, make testing every possible between group differences ineffective. Context dependent Granger causality analysis for between group differences is best used to investigate which context is driving an interaction found at the general level.

Conclusions
1) The inhibitory effect of right hippocampus on right supragenual ACC in phobic subjects at 4 s is significantly different from non-phobic subjects. Context dependent connectivity analysis found this difference is most significant in uncontrollable trials with snake videos.
2) Increasing time resolution with interpolation at the voxel level is an effective method for investigating ROI interactions at rates closer to those known to occur physiologically. The increased time resolution resulted in a five fold increase in the number of between group differences compared to a more stringent multiple comparison threshold.

400 to 3200 ms Granger causality networks of 17 non-phobic control subjects, 19 snake phobic subjects, and the significant differences between groups. Red indicates a positive Granger causality (increased activity in one region leads to increased activity increase in region B, 2 s seconds later). Blue indicates a negative Granger causality (decreased activity in region A causes decrease in region B, 2 s seconds later). Line thickness indicates the strength of the path coefficients, white lines indicate no significant level of significance. In the difference networks a red line indicates a non-phobic subjects have significantly greater than the phobic subjects. A blue line indicates a significantly greater effect in the phobic subjects. APN (1-3) shows the graph testing every possible between group differences ineffective. Context dependent Granger causality analysis found the difference in left hippocampus to right insula connectivity at 2900 ms is significant in controllable trials with snake videos. Context dependent connectivity analysis found this difference is most significant in uncontrollable trials with snake videos.

Acknowledgments

References

Supported by NIMH (R01-MH74847, K08-MH63984, and K02-MH082130) Society for Neuroscience 2009 Chicago