Disordered fronto-limbic interactions during emotion processing in the vulnerable brain: fMRI and Dynamic Causal Modeling applied to the study of adolescents

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Abstract

•Background: Disordered organization of cortico-limbic circuits in the brain may underlie documented social impairments in schizophrenia offspring (SCZ-Off; Philips & Seidman, 2008). Advanced techniques such as Dynamic Causal Modeling (DCM; Stephan et al., 2007) are ideally suited to understand network interactions in the brain, yet have never been applied to this important developmental question. Here, we use a combination of DCM and fMRI to investigate cortico-limbic network interactions during affective appraisal in a group of adolescent ($10 \leq$ age ≤ 20 yrs) SCZ-Off (n=19) and controls (n=24).

• Methods: All subjects provided consent or assent before performing an event-related affective appraisal task (continuously presented faces; Ekman & Oster, 1979). DCM was conducted (SPM8) on fMRI data (4.0T) using time series ($p<.05$, effects of interest) from five cortico-limbic regions (V1, FG, AMYG, DPFC, VPFC). To comprehensively address model fit, we employed 100 models per subject to explore a combination of intrinsic and modulatory interactions between regions. Finally, Bayesian model selection (Stephan et al., 2009) identified the appropriate models within and across groups.

•Results: Results of a conjunction analysis (activation to faces) in Controls and SCZ-Off show activation in both groups in our network of interest. Compared to HC, reduced intrinsic DPFC → Amygdala and VPFC → Amygdala connectivity/coupling (in 1/s) is observed in SCZ-Off. Markedly increased modulatory *inhibition* of activity in these pathways by negatively-valenced faces is observed. Conversely, in response to neutrally-valenced stimuli, SCZ-Off show exaggerated inhibition of the AMYG by the VPFC, but excitatory modulation of the dorsal pathway.

• Conclusions: Aberrant cortico-limbic responses appear to characterize the impaired affective response in adolescent SCZ-Off and may reflect a substantive disordering of this important pathway.

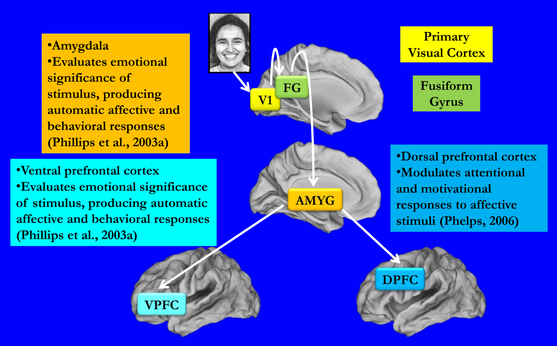
Background

•Studies suggest that interactions between fronto-limbic circuits in response to social stimuli may underlie affective appraisal and response (Phelps 2006).

•The development of fronto-limbic interactions driving affective processing continues well into adolescence (Phillips et al., 2003b), and dysmaturation may underlie affective and behavioral impairments characterizing many psychiatric disorders (Dahl 2004).

•Adolescent offspring of schizophrenic patients (SCZ-Off) demonstrate widespread developmental deficits, particularly in affective processing and social function (Philips & Seidman, 2008), yet fronto-limbic interactions in this sample are largely unknown.

•Advanced techniques, such as Dynamic Causal Modeling (DCM; Stephan et al., 2007) are ideally suited to understand network interactions in the brain. DCM allows one to infer effective connectivity from fMRI data by modeling brain activity at the neuronal level.



•Here, we present an application of DCM and fMRI to investigate the fronto-limbic network interactions during affective appraisal in a group of adolescent SCZ-Off and controls (HC), based on the model of affective processing above.

Task

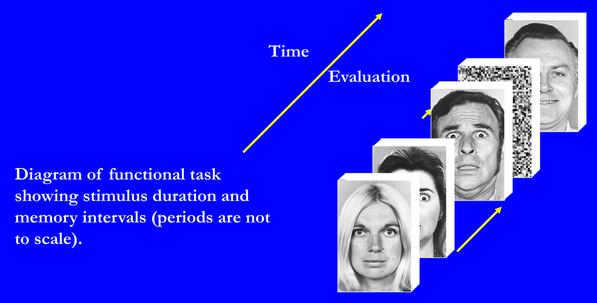


Diagram of functional task showing stimulus duration and memory intervals (periods are not to scale).

•Subjects performed a jittered (3-5s in .5s increments) fMRI event-related (Josephs & Henson, 1999) affective appraisal paradigm, during which subjects indicated if the affect signaled on a face in a given trial was the same as that on the previous trial (regardless of identity).

•Stimuli were presented (3s/stimuli) in pseudo-random order and comprised faces expressing one of three valences of emotion: negative (angry, fearful, sad), positive (happy), neutral (Ekman & Oster, 1979).

•Inverted, pixelated face images were interspersed with face stimuli and served as visual controls.

Methods: Subjects and fMRI

•HC (n=24, age range 10-19, mean age 14.7, 16 male, 8 female)

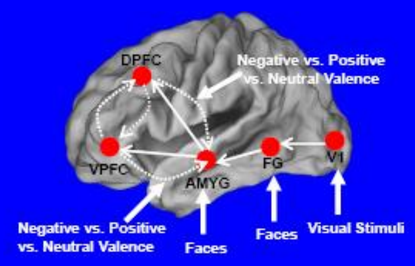
•SCZ-Off (n=19, age range 8-19, mean age 14.3, 12 male, 7 female)

•Gradient echo EPI was collected over an 11.5 minute scan time (TR = 2000ms, TE = 30ms, matrix = 64 x 64, slices = 24, FOV = 240 mm, voxel size = 3.8 x 3.8 x 4.0mm, scans = 345), using a Bruker MedSpec 4.0 T full-body scanner with an 8-channel head coil.

• MR images were preprocessed and analyzed using SPM. First level modeling in the GLM framework employed five regressors to represent sensory, cognitive and affective psychological processes relevant to the modeling: i) Visual: encoding all conditions (all faces and control stimuli) that resulted in visual stimulation, ii) Faces: trials on which a face was presented, iii) Negatively, iv) Positively and v) Neutrally-valenced faces.

•DCM was conducted using time series ($p<0.05$, effects of interest) from five cortico-limbic regions (primary visual cortex, fusiform gyrus, amygdala, dorsal prefrontal cortex, ventral prefrontal cortex)

•To comprehensively address model fit, 100 models per subject were employed to explore a combination of intrinsic and modulatory interactions between regions.



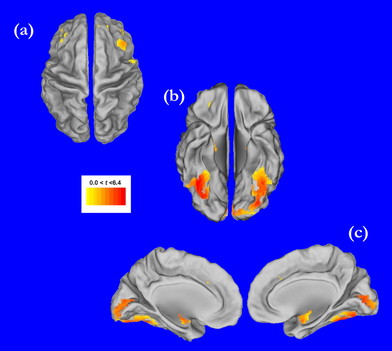
Behavioral Results

•No differences in detection sensitivity (d') were observed between HC and SCZ-Off (2.04 vs. 2.1, $p>.25$), indicating that the cognitive component of the appraisal task was not impaired in SCZ-Off.

fMRI Data: Conjunction Analysis

•First-level activation maps (Faces > Control) were submitted to a conjunction analyses (Nichols et al., 2005) to identify common substrates of activation in the ROIs.

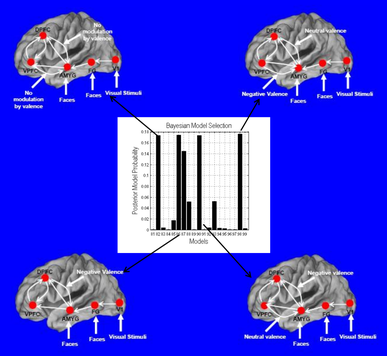
•Significant clusters ($p < .05$) are depicted on dorsal (a; bilateral DPFC), ventral (b; visual, fusiform, amygdala, and VPFC), and medial (c; amygdala, fusiform, and visual) views of the brain.



fMRI Data: DCM and BMS Analyses

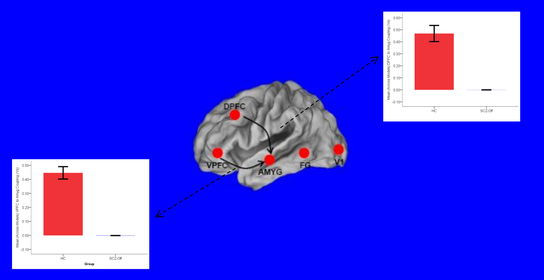
•To identify the most appropriate model(s) associated with the data, Bayesian model selection (Stephan et al., 2009) was applied across all models and all subjects.

•Optimal models across subjects; all evince reciprocal intrinsic connections between VPFC, DPFC, and AMYG and top-down modulation of AMYG by VPFC and DPFC in response to non-positively valenced stimuli.

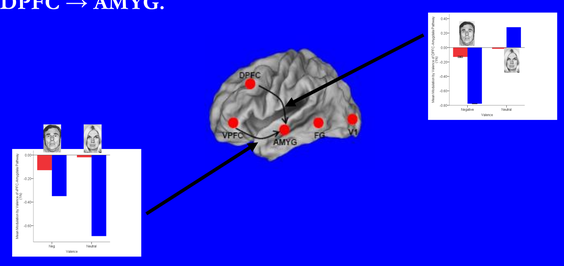


•To assess differences between HC and SCZ-Off in interactions between dorsal and ventral prefrontal cortex and amygdala, Bayesian averages of coupling estimates (Stephan et al., in press) were separately compared for *intrinsic* and *modulatory* coupling.

•Reduced intrinsic DPFC → AMYG and VPFC → AMYG connectivity/coupling (in 1/s) in SCZ-Off, relative to HC.



•For negatively-valenced faces, markedly increased modulatory *inhibition* of activity in both pathways, relative to HC; for neutrally-valenced faces, markedly increased *inhibition* of VPFC → AMYG but *excitatory* modulation of DPFC → AMYG.



Summary of Results

•DCM and BMS analyses evidence reciprocal intrinsic connections between VPFC, DPFC, and AMYG and top-down modulation of the AMYG by VPFC and DPFC in response to non-positively valenced stimuli.

•Comparison of Bayesian averages of coupling estimates demonstrate markedly reduced intrinsic coupling from the ventral and dorsal prefrontal cortex to the amygdala in SCZ-Off.

•HC demonstrate frontal inhibition of the amygdala in response to non-positively valenced stimuli.

•SCZ-Off show exaggerated inhibition of the AMYG in both pathways in response to negatively-valenced stimuli. Conversely, in response to neutrally-valenced stimuli, SCZ-Off show exaggerated inhibition of the AMYG by the VPFC, but excitatory modulation of the dorsal pathway.

Discussion

•Winning models are consistent with previously published data (Phillips et al, 2003a). Reciprocal intrinsic connections between AMYG, VPFC, and DPFC evidence the general properties of structural and functional connections hypothesized for this sub-circuit (Barbas & DeOlmos, 1990; Dahl 2004; Cunningham et al., 2002).

•Top-down modulation of AMYG by VPFC and DPFC directly evidences the necessity of frontal modulation of amygdala activity that has been proposed as central to fronto-limbic interactions (Phelps 2006).

•Group differences in intrinsic and modulatory coupling estimates suggest that aberrant fronto-limbic responses characterize impaired affective response in adolescent SCZ-Off and may reflect a substantive disordering of this important pathway.

• Behavioral results showing no group differences in cognitive appraisal (d') further indicate that impairments of SCZ-Off lie in disordered affective circuitry.

References

•Barbas H, De Olmos J. Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. J Comp Neurol. Oct 22 1990; 300(4):549-571.

•Dahl RE. Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. Ann N Y Acad Sci. Jun 2004; 1021:1-22.

•Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. J Comp Neurol. Nov 11 2002; 453(2):116-130.

•Ekman, P. and Oster, H. Facial expressions of emotion. Annual Review of Psychology. 1979; 20: 527-54.

•Josephs, O. and Henson, R.N. Event-related functional magnetic resonance imaging: modelling, inference and optimization. Philosophical transactions of the Royal Society of London, Series B, Biological Sciences. 1999; 354(1387):1215-28.

•Nichols T, Brett M, Andersson J, Wager T, Poline JB. Valid conjunction inference with the minimum statistic. Neuroimage. Apr 15 2005; 25(3):653-660.

•Phelps EA. Emotion and cognition: insights from studies of the human amygdala. Annu Rev Psychol. 2006; 57:27-53.

•Phillips, L.K. and Seidman, L.J. Emotion processing in persons at risk for schizophrenia. Schizophrenia Bulletin. 2008; 34(5): 888-903

•Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of Emotion Perception I: The Neural Basis of Normal Emotion Perception. Society of Biological Psychiatry. 2003a; 54:504-514.

•Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biological Psychiatry. 2003b; 54:515-528.

•Stephan, K.E., Harrison, L.M., Kiebel, S.J., David, O., Penny, W.D., and Friston, K.J.. Dynamic causal models of neural system dynamics:current state and future extensions. Journal of Biosciences. 2007; 32:129-144.

•Stephan, K.E., Penny, W.D., Daunizeau, J., Moran, R.J., and Friston, K.J. Bayesian model selection for group studies. NeuroImage. 2009; 46, 1004-1017.

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