# fMRI and dynamic causal modeling reveal inefficient and imbalanced network interactions in developmentally vulnerable adolescents

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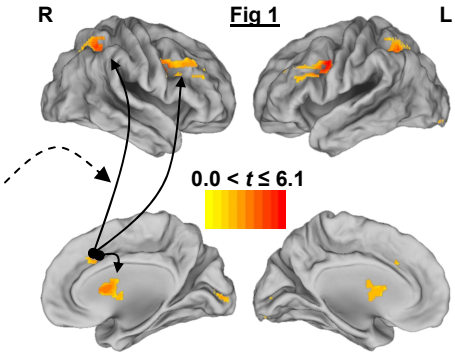
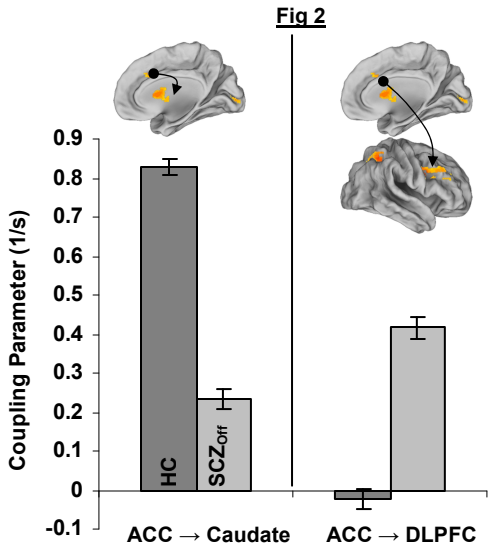
Introduction. Healthy development is characterized by increased optimization of cortical and sub-cortical structural and anatomical networks[1], resulting in an integrated and efficient "connectome"[2,3]. Conversely, developmental disorders or vulnerabilities are likely to impact the modal organizational structure of cortical and sub-cortical networks. Resultant impairment can be expressed in functional disconnections between brain regions during simple sensori-motor tasks[4], or inefficient responses of regions during complex processing [5,6]. Evaluating interactions between network constituents in "closed" neural networks using *a priori* dynamic causal models (DCM) of network interactions[7] may provide a rich framework within which to assess the impact of developmental vulnerabilities. In such a framework, emergent imbalances in network interactions in the vulnerable brain may reveal inefficiently increased control by regions such as the anterior cingulate cortex(ACC)[8] on some heteromodal cortical regions, but decreased coupling with other regions. Here we used a combination of fMRI and DCM to assess differences in ACC control of cortical and sub-cortical regions during sustained attention in adolescent offspring of schizophrenia patients ($SCZ_{Off}$) and controls with no family history of psychosis (HC). $SCZ_{Off}$ are an important group in whom to investigate emergent vulnerabilities in brain development; they at increased risk for psychiatric disorders[9], and studies indicate impaired functioning of critical domains such as sustained attention and working memory[10].




Methods. HC (n=23; mean age:14.6 yrs; range:10-19 yrs) and $SCZ_{Off}$ (n=19; mean age:14 yrs; range:8-19 yrs) participated. Gradient echo EPI images were collected using a Bruker 4T (Siemens Syngo console, TR: 2s, TE: 30ms, matrix: 64x64, 24 slices, voxels: 3.8x3.8x4.0 mm). Subjects performed a version of the continuous performance task during which 3 digit numbers were presented in rapid sequence (display time:100ms; SOA: 1000ms) for 120 s epochs. Subjects indicated with a key press when consecutive numbers were identical. Images were preprocessed in SPM5 using established methods including detrending, motion correction, normalization and smoothing. DCM was conducted on time series from five regions of interest involved in sustained attention and control. These were the ACC, the dorsolateral prefrontal cortex (DLPFC), the superior parietal cortex, the caudate nucleus and primary visual cortex[11]. DCM estimates parameters of a reasonably simple neural network so that predicted BOLD signals correspond to the observed BOLD signals. Parameter estimates corresponding to rate constants (1/s) are calculated using a bilinear differential equation that solves for 3 matrices: intrinsic connection strengths of the system's between regions; task dependent modulation of intrinsic connections, and driving inputs to the system[12].




Results. Surface projections (Fig 1) of conjunction analyses depict common activation in HC and $SCZ_{Off}$ in the five regions of interest during sustained attention (relative to rest epochs; $p_{FWE}$<.05). Solid lines are modeled intrinsic efferent connections from the ACC to the caudate, DLPFC and parietal regions; dashed lines are modulatory effects of attention on the ACC to parietal pathway. Mean parameter estimates of intrinsic connection strengths (solid lines in Fig 1) from DCM are depicted in Fig 2 (error bars are ± sem). $SCZ_{Off}$ showed significantly reduced ACC-Caudate coupling, $t_{40}$=12.21, $p$<.001, but aberrantly increased ACC-DLPFC coupling, $t_{40}$=8.44, $p$<.001. Differences in task dependent (attention related) modulation of the ACC-parietal pathway (dotted line in Fig 1) were also observed; $SCZ_{Off}$ demonstrated increased attention related modulation of this pathway than controls, $t_{40}$=32.75, $p$<.001 (not shown).

Discussion. The role of control mechanisms increases significantly through adolescence and is critical to the functional integration of complex tasks. Here we demonstrate complex imbalances and inefficiencies in the interaction between control and other regions in adolescents with developmental vulnerabilities. Thus, reduced ACC-Caudate coupling may reflect significant impairments in cortico-striatal loops critical for neural transmission underlying sustained attention[11]. By contrast, increased ACC-DLPFC coupling and modulation of the ACC-Parietal pathway may reflect inefficiently increased demand for control by regions involved in attention maintenance and shifts[13]. The combination of fMRI and DCM may significantly enhance understanding of normal and abnormal brain development and organization through adolescence.

References. 1. O. Sporns *et al.*, *Cereb Cortex* **10**, 127 (2000). 2. T. Paus, *Trends Cogn Sci* **9**, 60 (2005). 3. K. Zhang, T. J. Sejnowski, *Proc Natl Acad Sci USA* **97**, 5621 (2000). 4. S. H. Mostofsky *et al.*, *Brain* (in press, 2009). 5. M. A. Sheridan *et al.*, *J Am Acad Child Adol Psychiatry* **46**, 1357 (2007). 6. J. H. Callicott *et al.*, *Am J Psychiatry* **160**, 709 (2003). 7. K. E. Stephan, *J. Anat.* **205**, 443 (2004). 8. T. Paus, *Nat Rev Neurosci* **2**, 417 (2001). 9. V. A. Diwadkar *et al.*, *Curr Psychiatry Reports* **6**, 296 (2004). 10. V. A. Diwadkar *et al.*, *CNS Spectrums* **6**, 899 (2001). 11. S. N. Haber *et al.*, *Brain Res Bull* **78**, 69 (2009). 12. K. E. Stephan *et al.*, *J Biosci* **32**, 129 (2007). 13. M. Corbetta *et al.*, *Science* **270** (1995).