in healthy adolescent controls (HCs), probands with a severe childhood-onset form of schizophrenia (COS), and the healthy siblings (SIBs) of COS probands. Parallel study of COS probands and their SIBs allowed us to distinguish consequences of schizophrenia risk *per se* from the consequences of active illness. We hypothesized that (i) cortical maturation in HCs would vary according to the number of higher function Val alleles (thought to result in lower synaptic DA) within fronto-temporal brain regions relevant to schizophrenia neurobiology, (ii) COS and SIB groups would both show disruption of these typical gene-brain relationships, and (iii) this disruption would be more severe in probands with COS than their SIBs.

Methods: We included a total 792 1.5T structural MRI brain scans acquired longitudinally between ages 9 and 22 years from 208 HCs (475 scans), 83 COS (192 scans), and 62 of their healthy SIBs (124 scans). A fully automated and well-validated pipeline was used to generate estimates of gray matter (GM) cortical thickness at 80,000 points (vertices) on each cortical surface, We then used mixed linear models to relate age, Val allele dosage, clinical group membership, and the interaction of these terms to CT.

Results: Increasing Val allele dose attenuated the rate of GM loss amongst HCs within dorsolateral prefrontal, medial prefrontal and superior temporal cortices that are of established relevance to the biology of schizophrenia. However, these gene-brain relationships were completely inverted amongst both COS probands and their healthy SIBs, in whom increased Val allele load (proposed to aggravate cortical deficits in schizophrenia) was associated with greater GM loss in adolescence. This disruption of the normative relationship between val158met genotype and cortical maturation was maximal in dorsolateral and medial prefrontal cortices. There was also evidence that aberrant genetic regulation of cortical development was more pronounced in COS probands than their healthy SIBs. We also found fixed GM differences according to Val allele load that were inverted in HCs (reduced GM with greater Val allele load) relative SIBS (greater GM with greater Val load).

Discussion: This is the largest longitudinal schizophrenia neuroimaging study to date, and the first to provide longitudinal evidence linking genetic variants impacting dopamine signaling to GM deficits in those at latent risk for schizophrenia, as well the accentuation of these deficits in persons symptomatic of the disorder. These findings argue that disruption of the causal pathways linking variation in DA signaling to cortical maturation indexes primary risk factors for schizophrenia rather than solely resulting from the presence of active disease. This is consistent with the novel theory that abnormalities of DA signaling and cortical anatomy that have traditionally been separately considered to indicate the presence genetic risk for schizophrenia may be causally related to one another.

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136. Prefrontal Function during Working Memory Maintenance in Unmedicated First-Episode Schizophrenia and Psychotic Bipolar Disorder

James Reilly, Anna-Maria D'Cruz, Sarah Keedy, Lisa Liu, Bruce McDonough, Peter Weiden, John Sweeney*

University of Illinois at Chicago, Chicago, IL, Univ. of IL Medical Center/Center for Cognitive Medicine, Chicago, IL

Background: A reduced ability to maintain information in working memory is an established neurocognitive deficit in schizophrenia. The specificity of this dysfunction to schizophrenia vs. psychotic bipolar disorder is unknown and is of interest given the appreciation for shared risk genes and neurobiological abnormalities between these disorders. In this study, we compared the neural substrate of working memory maintenance in untreated first-episode patients with these disorders.

Methods: We used event-related fMRI to compare patients with schizophrenia (n = 17) or psychotic bipolar disorder (n = 11) who were early in their course of illness and unmedicated at the time of testing to matched healthy individuals (n = 20) while performing an oculomotor delayed response task. This task requires maintenance of spatial location information in working memory over a 5-second delay period after which a saccade is made to the remembered location. Studies with nonhuman primates performing this task have established the relevant frontostriatal and parietal circuitry for maintaining information over delay periods. Activation among the patient and control groups during the delay period was contrasted with a passive central fixation period. Regions of interest included the middle frontal gyrus, frontal and parietal eye fields, dorsomedial thalamus and striatum.

Results: Compared to healthy individuals, schizophrenia and psychotic bipolar patients showed significant and comparable reduced activation in the middle frontal gyrus during the delay period while spatial location information was to be maintained in working memory. In contrast, only schizophrenia patients showed additional reduced activation in sensorimotor areas of frontal and parietal cortex and thalamus. No significant group differences in activation were observed in the striatum.

Discussion: Both first-episode schizophrenia and psychotic bipolar patients prior to treatment failed to activate dorsolateral prefrontal cortex while maintaining information in working memory. This finding suggests a shared prefrontal dysfunction underling working memory deficits between these disorders. For schizophrenia patients this dysfunction also included the broader thalamocortical working memory circuitry while for bipolar disorder it was restricted to prefrontal cortex.

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137. The Tryptophan Hydroxylase-2 Risk Haplotype is Associated with a Differential Pattern of Laboratory Aggression-Associated Changes in Anterior Prefrontal Cortical Activity

Daniel R. Rosell*, Erin A. Hazlett, Randall E. Newmark, Jane Zhang, Joseph Triebwasser, David Meyerson, Sophie Lazarus, Roanna Trisdorfer, Kim E. Goldstein, Marianne Goodman, Harold W. Koenigsberg, Janine D. Flory, Larry J. Siever, Monte Buchsbaum, Antonia S. New

Mt. Sinai/Bronx VA, New York, NY

Background: Evidence from our group and others has revealed that alleles of various genes of the serotonergic system exhibit a greater prevalence in patients with borderline personality disorder (BPD) compared to healthy controls, and appear to be related to the severity of various symptom dimensions of BPD. Specifically, we have described greater prevalence of the "risk" allele of the tryptophan hyroxylase-2 (THP2) gene in BPD patients relative to healthy controls. Moreover, the risk TPH2 haplotype was associated with greater aggression, affective lability, and (para)-suicidal behaviors in patients with BPD. While the means by which these risk alleles may contribute to the development of BPD is important to characterize, it is also essential to understand how the presence or absence of these risk alleles *within* BPD may effect its pathophysiology. In other words, are there genetically-determined pathophysiologic subgroups of BPD? Therefore, we set out to determine whether the TPH2 risk allele affects the neural correlates of impulsive aggression in patients with BPD. We have previously described differential patterns of prefrontal cortical activity in BPD patients with intermittent explosive disorder (IED) compared to healthy controls using a laboratory-induced model of aggression. We describe here the effect of the TPH2 risk allele on the pattern of aggression-associated changes in prefrontal cortical activity in BPD-IED patients.

Methods: We employed the Point Subtraction Aggression Paradigm (PSAP) – a validated quantitative laboratory model of impulsive

aggression – with 23 BPD-IED patients. Patients underwent positron emission tomgraphy (PET) scanning with 18-fluoro-deoxyglucose on two occasions – once with a 'provoked' and once with an 'unprovoked' version of the PSAP. Mean relative glucose metabolic rate (rGMR) was calculated for gray and white matter of cortical regions, and differences between provoked and non-provoked conditions were scored. Provoked-minus-nonprovoked rGMR scores of gray and white matter were compared as a function of genotype for the TPH2 risk allele.
Results: BPD-IED patients homozygous for the risk TPH2 allele exhibited a significantly lower gray-white matter rGMR ratio compared to those homo- or heterozygous for the non-risk TPH2 allele [$F(2,20) = 4.43$, Wilks $p = 0.025$] specifically in the anterior prefrontal cortical region.
Discussion: BPD-IED patients homozygous for the THP2 risk allele exhibited a different pattern of aggression-associated changes in metabolic activity in anterior prefrontal cortical regions compared to BPD-IED patients homo- or heterozygous for the non-risk allele. These findings may help to characterize the neural correlates of genetically-determined pathophysiologic subtypes of impuslive aggression in BPD. Such studies may lead to the identification of different pathophysiologic mechanisms that underlie the broader construct of BPD, and ultimately to greater diagnostic and therapeutic specificity for this disorder.
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138. Local vs. Focal: The Evolving Functional Neuroanatomy of the Executive System in Adolescence

TD Satterthwaite*, J Loughead, Daniel Wolf, K Ruparel, Kanchana Jagannathan, RT Garraty, Jeffery Valdez, E Yang, Mark Elliott, J Richards, Monica Calkins, H Qiu, FD Mentch, PM Sleiman, L Hermannsson, H Hakonarson, Ruben Gur, Raquel Gur

Univ of Pennsylvania, Philadelphia, PA

Background: Adolescence and early adulthood is a critical period for neurodevelopment and many neuropsychiatric disorders manifest during this period. There is evidence that frontal brain systems show the most pronounced development and dysfunction is associated with major disorders. However, linking brain-behavior measures the multiple facets of brain function requires large samples. We examined the development of the executive system with both task-based and resting-state functional magnetic resonance imaging (fMRI). This represents a preliminary report from a large ARRA NIMH study of neurodevelopmental trajectories that integrates functional and structural neuroimaging, genetic analyses, neurocognitive performance, and clinical phenotypic data.
Methods: fMRI blood oxygen level dependent (BOLD) response was examined at 3 Tesla during two functional runs in 250 subjects aged 8-21. Subjects performed a fractal n-back task with three levels of working memory load: 0-back, 1-back, and 2-back. The contrast of interest was the differential BOLD response of 2-back greater than 0-back. After standard preprocessing, the data were analyzed on a voxelwise basis across the whole brain using a bonfronni-corrected threshold of $z > 7.00$. Age was included as a covariate of interest. Additionally, the BOLD response was measured at rest for 6 minutes. Timecourses from the resting BOLD data were extracted from 19 functionally defined regions of interest (ROIs) that displayed an above-threshold response in the n-back task. To reduce spurious correlations, timecourses from the ventricles, subcortical white matter, and average whole brain signal were included as nuisance regressors. ROIs of each of these confound regressors was defined on an individual basis using segmentation algorithms. The timeseries from each ROI was correlated region by region for each subject, producing a 19x19 correlation matrix. To assess non-specific local connectivity, the timecourse from voxels within a 16 mm radius sphere around the peak of each seed region were extracted. Finally, the relationship between participant age and both inter-regional and local nonspecific connectivity was assessed.
Results: In the n-back task, 19 regions displayed a response that survived bonforonni correction. The regions (all bilateral if not midline) included the dorsal anterior cingulate, middle frontal gyrus, dorsolateral prefrontal cortex, superior parietal cortex, precuneus, frontal pole, anterior insula, thalamus, midbrain, and cerebellar crus I & crus II. Notably, all regions displayed a positive correlation with age: older subjects demonstrated greater differential recruitment within the executive function network. The resting-state data revealed a remarkably similar pattern, demonstrating greater inter-regional connectivity with age. Notably, local non-specific correlation around each seed ROI diminished with age.
Discussion: Both the task-based and resting-state data demonstrated a strong relationship with age. The resting state results suggest that during development non-specific local connectivity is lost as the brain develops more focal connectivity within a functional network. These changes may relate to the augmented working memory response seen in the n-back task during development. Taken together, these data provides convergent evidence regarding the developmental trajectory of the executive function system. Examining the relationship of this trajectory to both genotype and phenotype has the potential to elucidate neuropsychiatric symptoms as aberrations in neurodevelopment.
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139. Reduced Infralimbic and Subgenual Anterior Cingulate Cortex Volumes in Healthy and Affectively Ill Carriers of the Met Allele of the BDNF Val66Met Variant

Jonathan Savitz*, Xinmin Liu, Alexander Neumeister, Allison Nugent, Dara Cannon, Nirmala Akula, Wendy Bogers, Carlos Zarate, Dennis Charney, Francis McMahon, Wayne Drevets

LIBR, Tulsa, OK

Background: The methionine (*met*) allele of the functional val66met (rs6265) polymorphism of the brain-derived neurotrophic factor (BDNF) gene has been associated with reduced hippocampal volume, a potential endophenotye of major depressive disorder (MDD) and bipolar disorder (BD). However, the effect of rs6265 on the volume of two regions which are equally strongly implicated in mood disorders, the subgenual anterior cingulate cortex (sgACC) and the infralimbic cortex, which together make up the subcallosal gyrus, has not been measured.
Methods: High-resolution MRI (volumetric resolution ≈ 0.4 mm3) was conducted on a sample of unmedicated individuals with BD ($n = 12$), MDD ($n = 29$) and healthy controls ($n = 42$). MRI images were segmented blind to diagnosis and genotype by one rater. Data were analyzed using a two-step forced linear regression.
Results: After controlling for age, gender, handedness, diagnosis, and genetic ancestry we found no significant difference in absolute and normalized subcallosal gyrus volumes between *val/met* (combined sample, $n = 20$) heterozygotes and *val/val* homozygotes ($n = 63$) ($p > 0.5$). *Post-hoc* analyses showed no statistically significant effect of genotype for both the anterior sgACC and the IL ($p > 0.5$). There was also no association between BDNF genotype and whole brain volume ($p > 0.3$).
Discussion: Our results are not consistent with studies reporting an association between the *met* allele and volume reduction of the hippocampus and raise the possibility that the role of BDNF in