Poster Abstracts for the 13th Imaging Genetics Conference

February 13th, 2017
A1. MeQTL driven analysis of epigenetic effects on functional brain connectivity in schizophrenia

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Aim of Investigation- Schizophrenia (SZ) is a complex mental disorder with estimated heritability of ~80%. Beyond genetic variation, DNA methylation, one of major epigenetic markers has also been increasingly recognized for its relevance to SZ. It has been suggested that epigenetics may integrate genetic and environmental factors in the etiopathogenesis of SZ. One of the underlying mechanisms has been hypothesized to be through genetic regulation, called methylation quantitative trait loci (meQTL) effect. In parallel, some evidence has shown the relationship of DNA methylation with brain structure, however, the study of biological mechanism linking genetic, epigenetic to brain function in SZ is still limited. In this work, we aim to perform an integrative analysis to explore how genetics relates to epigenetics and further influences brain functional network connectivity (FNC) changes in SZ.

Methods- We analyzed 100 SZ patients and 98 healthy controls from the Center for Biomedical Research Excellence study and the Glutamate and Outcome in Schizophrenia study. Saliva tissue was collected for DNA extraction and DNA methylation was measured by Illumina MethylationEPIC assay, covering over 850k CpG sites. Single nucleotide polymorphism (SNP) data were genotyped by Illumina Omin5M chip and further imputed to 1000 genomes reference panel. Resting-state functional MRI images were collected to measure FNCs in each subject. We first identified significant cis-effect of SNPs on DNA methylation (FDR<0.01) within 100k base pairs to detect meQTLs, and then matched them with the meQTLs identified on brain tissues in previous studies to obtain the common meQTLs. Functional brain networks were derived by applying a group-level spatial ICA to the preprocessed images using a high model order (number of components=100). 51 networks of interest were selected to construct FNCs. Finally, parallel ICA was applied to extract the correlated epigenetic and FNC components. Covariates age, gender, and race were adjusted prior to the analyses.

Results- We identified 2,255,339 SNP-CpG regulations (from 19314 CpG sites) shared by saliva and brain tissues with significant meQTL effects. A significant association was observed between CpG and FNC components after controlling for diagnosis (r=0.32, p=3.9×10-6). The CpG component consisted of 334 contributing CpG sites (|z|>3) nearby 127 genes, partially enriched in metabolic pathways and Aryl Hydrocarbon Receptor Signaling pathway (FDR<0.05). FNC component mainly reflected seven connections among visual, somatomotor and default mode networks and showed significant abnormalities in SZ compared to controls (3.3×10-3).

Conclusions- The study identified one SNP-regulated CpG component which significantly related to FNC changes between SZ patients and controls, showing the potential of epigenetics in affecting functional brain connectivity in SZ through genetic risks.

Acknowledgements

This work was funded by NIH grants R01EB005846 & P20GM103472.

Keywords

MeQTL, epigenetics, genotype, functional brain connectivity, Schizophrenia
A2. Imaging Genomics at NITRC

The NITRC Team

Aim of Investigation

Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) is a neuroimaging informatics knowledge environment for MR, PET/SPECT, CT, EEG/MEG, optical imaging, clinical neuroinformatics, computational neuroscience, and imaging genomics tools and resources. We encourage researchers to list their Imaging Genomics tools at the NITRC website www.nitrc.org.

Methods

Initiated in 2006 through the NIH Blueprint for Neuroscience Research, NITRC’s mission is to foster a user-friendly knowledge environment for the neuroinformatics community. In 2012, NITRC added Imaging Genomics to its broadened scientific scope. By continuing to identify existing software tools and resources valuable to this community, NITRC’s goal is to support its researchers dedicated to enhancing, adopting, distributing, and contributing to the evolution of neuroimaging analysis tools and resources.

Results

Located on the web at www.nitr.org, the Resources Registry (NITRC-R) promotes software tools and resources, vocabularies, test data, and databases, thereby extending the impact of previously funded, neuroimaging informatics contributions to a broader community. NITRC-R gives researchers greater and more efficient access to the tools and resources they need, better categorizing and organizing existing tools and resources, facilitating interactions between researchers and developers, and promoting better use through enhanced documentation and tutorials—all while directing the most recent upgrades, forums, and updates. 50 resources in the Imaging Genomics domain are currently listed on NITRC-R.

Conclusions

In summary, NITRC-R is now an established knowledge environment for the neuroimaging community where tools and resources are presented in a coherent and synergistic environment. In addition, NITRC now offers image data sharing and cloud-based computation services via NITRC-Image Repository (NITRC-IR) and NITRC Computational Environment (NITRC-CE). With its expanded scope into imaging genomics, NITRC aims to become the 'trusted source' for identification of resources in this highly active and promising domain bridging advanced neuroimaging and genomics. We encourage the imaging genomics research community to continue providing valuable resources, design and content feedback and to utilize these resources in support of data sharing requirements, software dissemination and cost-effective computational performance.

Acknowledgements

Funded by the NIH Blueprint for Neuroscience Research, NIBIB, NIDA, NIMH, and NINDS.

Keywords

Neuroimaging, genomics, neuroinformatics, tools, resources

Susan S. Kuo; Michael F. Pogue-Geile

Aim of Investigation

Despite hundreds of structural MRI studies documenting smaller brain volumes on average in schizophrenia compared to controls, none have investigated possible group differences in variances of brain volumes. Such group differences in variances may help interpret mean group differences in brain volumes and perhaps also better reflect effects of heterogeneous schizophrenia risk genes.

Methods

We performed a meta-analysis of variances for the volumes of brain structures in schizophrenia and controls from 242 magnetic resonance imaging studies comprising over 19,000 participants. We examined variance group differences in volumes of ten structures that have shown large to medium mean effect sizes (Cohen’s d effect size $\geq 0.4$) in recent meta-analyses: intracranial volume, total brain volume, total gray matter, lateral ventricles, third ventricle, frontal lobe gray matter, prefrontal lobe gray matter, temporal lobe gray matter, hippocampus, and planum temporale. We further examined variance group differences in volume of the caudate nucleus as a control structure showing no mean differences.

Results

We replicated mean group differences in brain volumes and further found that, compared to controls, individuals with schizophrenia show increased variation in intracranial volume (5%, $p=0.001$) and ventricle volumes (15-27%, $p<0.01$) but show no differences in variances of volumes for the whole brain or for specific brain tissue structures in either hemisphere. Heterogeneity across studies in variance group differences predicted variation in mean group differences in lateral ventricle volumes ($\beta=0.309$) and third ventricle volume ($\beta=0.420$). Interestingly, across studies, age was a significant predictor of variance group differences in gray matter volumes, showing positive correlations for the prefrontal lobe and negative correlations for the temporal lobe.

Conclusions

This review raises significant implications for understanding the heterogeneity in the etiology and pathophysiology of schizophrenia. Whereas ventricle volumes are more widely distributed in schizophrenia compared to controls, the distribution of brain tissue volumes may be altered in schizophrenia through skew rather than spread. These findings further highlight the importance of investigating variation in brain structure volumes that may be attributable to developmental change in schizophrenia.

Acknowledgements

This research is supported by a Doctoral Foreign Studies Award from the Canadian Institutes of Health Research (S.S.K.) and NIMH collaborative R01s MH42191, MH63480, MH60722 (M.F.P.G.).

Keywords

schizophrenia; variation; brain volume; MRI; meta-analysis
A4. Network-based Genome Wide Study of Hippocampal Imaging Phenotype in Alzheimer’s Disease to Identify Functional Interaction Modules

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Aim of Investigation

Biological network modules are a promising resource to enhance the statistical power of GWAS and improve biological interpretation for complex diseases. A majority of module identification studies employ tissue-free networks that lack phenotypic specificity. We propose a novel module identification method using a tissue-specific functional network under a machine learning framework, and demonstrate it in a hippocampal imaging genetics study.

Methods

Participants included 989 ADNI subjects. GWAS of the average hippocampal FDG-PET measure was performed to obtain 17,881 gene-level p-values, each of which was determined as the second smallest p-value from the SNPs located in 20K bp of the gene. The hippocampus-specific functional network was downloaded from GIANT (http://giant.princeton.edu/). Two network-based GWAS (NetWAS) methods were implemented to identify phenotype-relevant modules. We implemented a previously described method that applies SVMs to a network to classify the significance status of each gene based on a nominal p=0.01. Instead, we train a ridge regression (Ridge) model for the network to estimate continuous z-scores converted from the gene p-values. Genes were reprioritized according to their predicted responses (Ridge) or their distances from the hyperplane (SVM). AUC of reprioritized genes were assessed using documented AD candidates as gold standard positives. Link Clustering was employed on the top reprioritized genes to detect modules. Top GWAS findings were used to assess the enrichment of candidate modules, and identify significant ones as phenotype-relevant modules. Functional annotation was performed on the identified modules.

Results

Both Ridge and SVM yielded much denser connectivity on top NetWAS findings, and obtained higher AUCs than original GWAS. Our Ridge method outperformed the existing SVM approach, suggesting that continuous significance measures embrace valuable information ignored by the binary significance status. Focusing on 124 top predictions from Ridge, 21 modules were identified as candidates. 6 out of 21 were significantly enriched by top 50 GWAS findings. These modules were functionally annotated by GO terms like cognition, behavior, and neuromuscular process.

Conclusions

The proposed network-based GWAS methods can effectively detect densely connected modules enriched by top GWAS findings. Tissue-specific functional network can provide precise context to help explore the collective effects of genes with biologically meaningful interactions specific to the studied phenotype.

Acknowledgements- Supported in part by NIH R01 EB022574, R01 LM011360, U19 AG024904, U54 AG054345, R01 AG19771, P30 AG10133, UL1 TR001108, R01 AG 042437, R01 AG046171, R03 AG050856 and R00 LM011384; NSF IIS-1117335; DOD W81XWH-14-2-0151, W81XWH-13-1-0259, and W81XWH-12-2-0012; NCA 14132004; CTSI SPARC Program at IU. At University of Pennsylvania, the work was supported by NIH R01 LM011360, R01 LM009012, and R01 LM010098. Data used in preparation of this abstract were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), which was funded by NIH U01 AG024904.

Keywords GWAS, tissue-specific network, module identification, imaging genetics, Alzheimer’s disease
**Aims.** Age of onset and the heterogeneity of schizophrenia: A multiplex extended pedigree study

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**Aim of Investigation**—Since its inception, the schizophrenia diagnosis has been characterized by substantial heterogeneity in overall functioning and symptom severity. Earlier age of onset is a consistent predictor of poorer outcomes in multiple domains, but the causes of this association are still unknown. The aims of the current project are to 1) confirm the association between earlier age of onset and poorer functioning, and 2) to shed light on the potential effects of genetic variation on this association.

**Methods**—The current study employed a multiplex, multigenerational pedigree design with a total sample of 773 participants. For relatives with schizophrenia (N=103), phenotypic and genetic correlations were calculated between age of onset and indices of: 1) positive symptom severity; 2) negative symptom severity; 3) community functioning (as determined by marital, living, and occupational status, and a global assessment of functioning); and 4) cognitive functioning (as determined by a battery of 11 cognitive tasks).

**Results**—Preliminary analyses are consistent with prior literature indicating that earlier age of onset is associated with poorer outcomes. Specifically, the current study found significant phenotypic correlations between age of onset and negative symptom severity ($R_p = -0.196, p = 0.003$), positive symptom severity ($R_p = -0.228, p = 0.045$), community functioning ($R_p = 0.318, p = 0.009$) and cognitive functioning ($R_p = 0.295, p = 0.03$). Genetic correlations were all estimated at the upper limit (i.e., at -1.00 or 1.00), and the correlation was significant ($p = 0.007$) between age of onset and negative symptom severity. Age of onset itself was modestly heritable ($h^2 = 0.198$) (although not significant; $p = 0.277$), and stronger heritability estimates were obtained for negative symptoms ($h^2 = 0.977, p < 0.001$), positive symptoms ($h^2 = 0.853, p = 0.003$), and cognitive functioning ($h^2 = 0.810, p = 0.010$).

**Conclusions**—Results to date suggest that there are modest genetic effects on age of onset, and that these genetic effects on age of onset contribute to variation in outcome in multiple domains. The heritability of age of onset was lower than predicted by prior literature, which may have impacted our ability to detect significant genetic correlations between age of onset and the relevant outcome measures. Future research will incorporate neuroimaging data acquired during cognitive testing.

**Acknowledgements**—This work was generously supported by NIMH collaborative R01s, MH42191 (REG), MH63480 (VLN), MH60722 (LA), and the Behavioral Brain Research Training Program via the NIH (T32GM081760).

**Keywords** Schizophrenia, age of onset, heritability, cognition, symptomatology
Aim of Investigation

The aim of the current study was to examine the genetic effect of DISC1 polymorphisms (rs3738401 and rs821616) on cognitive potentials during a visual event-related potential (ERP) task in healthy controls. We also tested the association of these DISC1 polymorphisms with hippocampal volume in healthy control participants.

Methods

Using Applied Biosystems (ABI) 7500, the DISC-1 polymorphisms (rs3738401 and rs821616) were genotyped in two different samples: 1) 32 drug-free healthy controls recruited at the Centre for Addiction and Mental Health (CAMH) in Canada; 2) 80 drug-free Italian healthy controls recruited in Italy. The visual ERP task employed was an emotional Stroop task used to elicit the P300 amplitude and latency in 32 healthy controls. Moreover, magnetic resonance imaging (MRI) was used to measure the volume of the hippocampus (left and right) in 80 Italian participants.

Results

In our first sample of 32 healthy controls there was no significant difference in the genetic case-control analysis for rs3738401 and rs821616. There was no significant difference in the ERP measures of P300 peak latency for negative, neutral, and positive words. Moreover, there was no significant difference in the ERP measures of P300 amplitude for negative, neutral, and positive words. We also could not find any association between hippocampal volume and DISC1 polymorphisms in the Italian sample.

Conclusions

This is the first study to investigate the association between rs3738401 and rs8216161 in the DISC-1 gene and endogenous components of cognitive potentials in healthy controls using a visual modality. Future investigations with larger sample sizes are required to ascertain an association between DISC1 and P300 deficits present in healthy and psychiatric phenotypes.

Acknowledgements

This research was supported by a CIHR operating grant. We also would like to thank the research assistants and students involved in data collection and data entry.

Keywords

DISC1 gene, polymorphisms, ERP task, MRI
Neural Correlates of Fear Generalization and other Cognitive-Emotional Tasks, and its Moderation by Genetically Determined Risk for Panic Disorder

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Aim of Investigation

Meta-analyses of 23 SNPs associated to panic disorder (PD) performed by Howe et al. confirmed the roles of TMEM132D and COMT in panicogenesis, and found several other SNPs to be nominally significant. Previously, TMEM132D has been associated to increased amygdalar gray matter volume and to anxiety-related measures. As the exact way of how these SNPs moderate risk for PD is thus far unknown, this study aimed to investigate the differences in neural correlates of the performance of anxiety-related tasks, associated with genetic risk for PD.

Methods

160 healthy participants, aged 18-35, were measured with structural MRI, DTI, resting-state fMRI and fMRI with a test battery of five panic and anxiety-related paradigms. As overgeneralization of conditioned fear is a prominent feature of PD, the main task was a Fear Generalization paradigm. Additionally, intolerance of uncertainty and response to threat were investigated with Unpredicted Threat and Feedback Response during Time Estimation paradigms. Further cognitive-emotional aspects were examined with an Emotional Face Matching and a Colour and Emotional Stroop task. The Fear Generalization and Unpredicted Threat tasks also included electrophysiological measurements.

Results

Our main focus was on the Fear Generalization paradigm, where generalization gradients of neural activity could be seen in fear-related regions such as the anterior insula, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), caudate nucleus and parietal cortex. The Emotional Face Matching task showed robust (de)activation differences between fearful and happy faces in the frontoparietal regions and attention and default-mode networks, and weaker in the amygdala. The Unpredicted Threat paradigm revealed increased activation of the ventromedial PFC and default mode network during the safety context, and an increased insula and ventrolateral PFC activation during both a predictable and unpredictable context. Positive feedback during time-estimation resulted in strong activation of the nucleus accumbens, as well as of the rostral ACC and dorsomedial PFC, whereas both negative and uncertain feedback caused activation of the insula and the dorsal ACC. The Colour Stroop effect was noticed both in response times and in increased activation of the dorsal ACC and dorsolateral PFC. Unfortunately, no clear neuronal activation pattern could be seen between the Emotional Stroop conditions.

Conclusions

As most tasks resulted in main effects which are in line with expectations from previous reports, analyses on a genetic level are currently being performed. The strategy here is to see if there are differences in neural activity during Fear Generalization as a result of genetic risk for panic disorder. The specificity of potential genetic moderation will be investigated by examining whether the same regions are affected during other mental processes (i.e. other paradigms).

Keywords Psychiatry, Anxiety, Panic Disorder, Fear Generalization
B2. Genetic and Environmental Influences on Neonatal Cortical Thickness and Surface Area


Aim of Investigation

Genetic and environmental influences on cortical thickness (CT) and surface area (SA) are thought to vary in a complex and dynamic way across the lifespan. It is established that CT and SA are largely genetically distinct in older children, adolescents, and adults and that heritability varies across cortical regions. At these ages, various environmental factors have also been shown to have unique influences on CT and SA. Very little however is known about how genetic and environmental factors determine infant CT and SA. This represents a critical knowledge gap, especially given compelling evidence that neuropsychiatric disorders have their ultimate origin in prenatal and early postnatal development. Using structural MRI, we performed the first comprehensive assessment of genetic and environmental impacts on normal variation of neonatal SA and CT.

Methods

Structural MRI images were obtained from 805 neonates (434 twins, 371 singletons; 429 males, 376 females). Cortical surfaces were reconstructed and parcellated into 78 cortical regions of interest. CT was defined as the average value of the minimum distance from the inner to the outer surfaces and the minimum distance from the outer to the inner surfaces. SA was computed based on a geometrically central cortical surface. To investigate environmental influences, we examined whether 17 major demographic and medical history variables were associated with individual differences in neonatal CT and SA. To investigate genetic influences, we applied linear mixed effect models and calculated the proportion of total phenotypic variance explained by additive genetic factors as well as proportions due to common and unique environmental factors.

Results

Our results showed that birth weight, postnatal age at MRI, gestational age at birth, and sex were significant predictors of SA and postnatal age at MRI, paternal education, and maternal ethnicity were significant predictors of CT. Our genetic analyses revealed that additive genetic influences accounted for 78% of the observed variation in total SA and 24% to 75% of the observed variation for regional SA. Average CT and regional measures of CT were not significantly heritable.

Conclusions

Results indicate that individual variation in infant CT and SA is explained by different sets of environmental factors. Variation in neonatal SA are influenced by obstetric factors while variation in CT is influenced by socioeconomic factors. Results also indicate that additive genetic factors contribute to both global and regional SA measures in neonates. Surface area findings are consistent with heritability studies performed at later ages but the lack of genetic influences on cortical thickness is unique to the neonatal period. Overall, our results suggest that unique environmental and genetic factors distinguishing surface area and cortical thickness are likely established prior to infancy.

Acknowledgements

National Institutes of Health (MH064065, MH070890, and HD053000 to Dr. Gilmore, MH083045 to Dr. Knickmeyer, SES-1357666, DMS-1407655, UL1 RR025747-03, and MH086633-02 to Dr. Zhu, HD-003110 and EB005149-01 to Dr. Styner, MH108914 and MH107815 to Dr. Li, MH100217 to Dr. Shen, and T32 NS007431 to Ms. Jha and Ms. Bullins).

Keywords neuroimaging, brain development, cortex, heritability, neonate
**Aim of Investigation**

It has been evident from several studies that a majority of complex behaviors and psychiatric disorders have a highly heritable component. However, identifying these particular genes and understanding the neural mechanisms that relate them to specific behavioral problems remain very difficult. Here, we studied the association between genome-wide single nucleotide polymorphism (SNP) data and fMRI data from schizophrenia (SZ) patients and healthy controls by developing a parallel independent component analysis (P-ICA) framework to link dynamic connectivity to genetics.

**Methods**

Both resting state function magnetic resonance imaging (fMRI) and single nucleotide polymorphism (SNP) data were acquired from 87 HC and 61 SZ patients. After standard preprocessing, group independent component analysis (ICA) was applied to fMRI data. Next, dFNC was computed as the correlations between selected intrinsic connectivity network (ICN) time-courses using a sliding window approach. The dynamic connectivity states were then obtained using k-means clustering algorithm, and used as imaging features for P-ICA. Standard preprocessing steps were applied to the SNP data, and 1546 SNPs were pre-filtered and used as genetic features for P-ICA.

**Results**

Out of 25 dFNC and 15 SNP components, P-ICA identified one dFNC-SNP pair components with a significant correlation ($r = 0.52$, p-value $< 6.95 \times 10^{-9}$). We analyzed the group-wise loading parameter of the significantly associated components, and both loading parameters were lower in SZ group (for dFNC loading, $p=0.008$; for SNP loading, $p=0.243$). We also computed the correlations between the polygenic risk scores and both dFNC and SNP components’ loadings. The correlation between the risk scores and dFNC loadings was -0.2561 (p-value=0.0017), whereas the correlation between the risk scores and SNP loadings was -0.5401 (p-value=1.4024×10^{-12}). Dynamic state 1 represents a state that captures strong positive connectivity within sub-cortical, visual, sensorimotor and default-mode networks’ components, and is dominated by the healthy controls in terms of occupancy rate (HC=22% and SZ=14%). The risk score analysis also confirms that, the higher the polygenic risk score is for a given subject, the less likely it is to be in state 1.

**Conclusions**

The proposed parallel ICA framework, to our best knowledge, is the first study to identify interactions between dynamic functional connectivity and genetic information. Our proposed parallel ICA framework provides evidence for genetic effects on dynamic connectivity in the human brain, and also enables the identification of genetic risk factors mediating specific dynamic states for complex brain, behavior and psychiatric disease.

**Acknowledgements**

This project was funded by the National Institutes of Health, grant numbers: P20GM103472, R01REB020407, and National Science Foundation, grant number: 1539067.

**Keywords**

dynamic functional network connectivity, independent component analysis, single nucleotide polymorphism, schizophrenia, resting-state
B4. Genome-Wide Association Analysis of Neonatal White Matter Microstructure


Aim of Investigation

The prenatal and early postnatal period represents the foundational period in the establishment of human brain connectivity as axonal fibers are organized into fascicles, oligodendrocytes proliferate and mature, and myelination begins. A better understanding of genetic influences on early white matter development could significantly advance our understanding of disorders of axon guidance as well as psychiatric conditions characterized by altered brain connectivity.

Methods

To investigate how genetic variation impacts prenatal and early postnatal white matter development, we conducted a GWAS of diffusion tensor imaging phenotypes in 472 neonates using both quantitative tractography and TBSS (tract based spatial statistics). For each method, we used factor analysis for data reduction. Factor analysis for quantitative tractography included 5 functional principle components from each of 44 fiber tracts. Factor analysis for TBSS included average FA from 17 regions of interest. The first factor from each analysis was used as the outcome in subsequent GWAS analyses.

Results

Two loci exceeded the conventional GWAS threshold of 5 x 10-8 for the TBSS factor, one on chromosome 2 (index SNP rs66556850) and one on chromosome 5 (index SNP rs7705506). The chromosome 2 locus also exceeded the conventional GWAS threshold for the tractography-based factor with the chromosome 5 locus falling just short of genome-wide significance. Genetic predisposition scores for schizophrenia and ASD were not associated with either factor. Integration of our results with data from the Philadelphia Neurodevelopmental Cohort (PNC) indicated little overlap between common variants impacting FA in infants and those impacting FA in adolescents.

Conclusions

We have identified common variants associated with neonatal white matter microstructure using a GWAS approach. The chromosome 2 locus is of particular interest as it lies within the ALK gene, a neuronal orphan receptor tyrosine kinase that plays an important role in the genesis and differentiation of the nervous system including neuronal circuit assembly. Comparison of our results to the PNC suggests that the genetic architecture of FA varies significantly across the lifespan. Variants influencing FA in infants likely reflect genetic effects on axonal organization, while variants influencing FA in adolescents likely reflect postnatal myelination.

Acknowledgements

National Institutes of Health (MH064065, MH070890, and HD053000 to Dr. Gilmore, MH083045 to Dr. Knickmeyer, SES-1357666, DMS-1407655, UL1 RR025747-03, and MH086633-02 to Dr. Zhu, HD-003110 and EB005149-01 to Dr. Styner and NS007431 to Ms. Jha).

Keywords genomics, diffusion tensor imaging, neonate, white matter
B5. Schizophrenia-Related Biological Pathways Revealed by combined Function-Structure-Genetic Components in a Large Chinese Han Population: A Replicated Multivariate Study

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Aim of Investigation

Schizophrenia (SZ) is a heritable psychiatric disorder involving abnormalities in brain function and structure. In this study, we aim to identify the co-varying brain functional-structural imaging abnormalities revealed by multivariate techniques seen in a large pure Chinese population that are closely associated with the schizophrenia-susceptible genetic sets reported by two databases: Psychiatric Genomics Consortium's SCZ2 data (p<0.001) (1) and the SzGene database (2). The identified joint patterns, which have been validated in another independent data cohort, may help reveal the underlying biological pathways necessary to better understand schizophrenia.

Methods

452 SZs and 455 age-matched healthy controls (HCs) were recruited from six different hospitals in China. Effects of site differences were examined and regressed out. We tested the association of fractional amplitude of low-frequency fluctuations (fALFF) (78420 voxels) and gray matter (GM) maps (76969 voxels) with a set of SZ-susceptible single-nucleotide polymorphisms (3717 SNPs) using parallel independent component analysis (pICA) (3,4), and validated the association of the identified joint patterns in an independent Chinese sample. The top weighted SNPs were further examined with pathway analysis tools.

Results

One linked fALFF-GM-SNP component was identified as both significantly group-discriminating (p=1.95E-17, 8.83E-24, 3.70E-10 for fMRI, sMRI and SNP respectively), and pair-wisely correlated between modalities (fALFF-GM: r=0.639, p=2.57E-25; SNP-fALFF: r=0.242, p=1.66E-13; SNP-GM: r=0.235, p=6.93E-13). The spatial maps of the identified component joint were further projected to the replication dataset (79 SZ and 92 HCs), yielding the projected loadings which were used to verify the pair-wise inter-modality associations. Significant correlations between the estimated loadings were also achieved (fALFF-GM: r=0.692, p=9.9E-26; SNP-fALFF: r=0.309, p=3.86E-05; SNP-GM: r=0.305, p=4.95E-05). The imaging components indicated SZ-related GM reduction in thalamus and temporal pole, consistent with (5,6,7), with co-occurring fALFF variations in frontal-parietal network supported by (6,8). The linked SNP component was enriched in glutamatergic synapse, dopaminergic synapse and calcium signaling pathway, revealed by ConsensusPath database (9).

Conclusions

This study extended previous works to suggest an important role of dopaminergic synapse, glutamatergic synapse and calcium signaling pathway in the genetic factor underlying a proportion of GM variations in thalamus-temporal regions and fALFF changes in frontal-parietal network in schizophrenia based on a large pure Chinese Han population.

Keywords

schizophrenia, imaging-genetic analysis, fALFF-grey matter-SNP, Chinese Han population, parallel ICA
**B6. Dose-response effect of COMTval158met genotype on modulation of activation to working memory load across the adult lifespan**

Maria A. Boylan, Karen M. Rodrigue, Kristen M. Kennedy

**Aim of Investigation**

Dopamine (DA) availability has been shown to influence cognitive processes such as working memory (WM). Moreover, both DA availability and WM decline with age. The COMTval158met polymorphism results in lower dopamine activity in the prefrontal cortex D1 receptors, with met homozygotes expressing highest and val homozygotes expressing the lowest dopamine availability. Here we examine whether and how COMT genotype influences neural activation to parametrically increasing working memory load, and if that effect varies with age in a large, healthy lifespan sample.

**Methods**

Participants included 158 healthy adults aged 20-94, (mean 52.5±19; 93 women) who completed fMRI scanning and COMT genotyping (n’s = 38 met/met; 80 val/met; 40 val/val). During scanning participants completed three runs of a blocked-design digit n-back working memory paradigm with four levels of WM load: 0-, 2-, 3-, and 4- digits back. All participants were scanned on a single 3T Philips Achieva scanner with 32-channel head coil. Prior to scanning, participants were trained on the task to ensure they understood the instructions and were able to perform the task accurately. fMRI data were preprocessed and analyzed using SPM8. We conducted a multiple regression analysis with age as a continuous variable and COMT genotype as a 3-level categorical variable on a linear contrast of difficulty across the four levels of WM load. Thus, we tested main effect of COMT group as well as COMT x Age interaction.

**Results**

We found no COMT x Age interaction, rather a main effect of COMT on modulation of activation to increasing difficulty, suggesting that COMT influence is equal across the lifespan. Modulation to difficulty differed in a dose-response manner by risk allele: met/met individuals showed greater activation of right posterior parietal cortices (PPC) than val/met individuals, and met/met individuals showed additional regions of greater activation compared to val/val beyond rPPC, including PPC and bilateral MFG. For deactivation, met/met individuals showed greater deactivation to difficulty than val/met individuals in bilateral vmPFC, and the met/met group again showed even greater deactivation differences compared to val/val individuals beyond vmPFC, including bilateral precuneus.

**Conclusions**

Modulation of activation to difficulty differs by COMT genotype, regardless of age. Individuals with predisposition to greater dopamine availability (COMT158met carriers) show greater activation in key regions of fronto-parietal cognitive control networks than those with lesser dopamine availability (val carriers), as well as greater deactivation of “default mode” regions than val carriers. These findings suggest that greater dopamine availability, afforded by the COMT polymorphism, is associated with better ability to flexibly modulate neural activation to increasing cognitive demand.

**Acknowledgements**

Supported in part by NIA grants R00 AG-36818 to KMK and R00 AG-36848 to KMR.

**Keywords** COMT, n-back, working memory, lifespan, cognitive control, dopamine
C1. Multi-modal Imaging-based Disease Progression Scores as Quantitative Phenotypes in Genome-wide Association Studies: Application to the ADNI Cohort.

Marzia A Scelsi, Miss, Marco Lorenzi, PhD, Jonathan M Schott, MD, Sebastien Ourselin, Prof, Andre Altmann, PhD, on behalf of the Alzheimer’s Disease Neuroimaging Initiative.

Aim of Investigation

Quantitative trait genome-wide association studies (GWAS) in late-onset Alzheimer's disease (AD) using imaging biomarkers have focused either on cross-sectional or on longitudinal phenotypes that are typically derived from a single imaging modality. However, AD is a complex disorder involving several different but inter-linked pathogenic pathways. To explore genetic influences on disease progression, we first generated a novel quantitative disease progression score (DPS) comprising longitudinal measures of both β-amyloid deposition and hippocampal volume. We then used the DPS as a quantitative outcome for GWAS.

Methods

Study participants were part of the AD Neuroimaging Initiative (ADNI). Hippocampal volumes were computed with FreeSurfer from T1-weighted magnetic resonance imaging (MRI) scans. Cortical Aβ42 levels were computed as standardised uptake values ratio (SUVR) from florbetapir (AV45) positron emission tomography (PET) scans, through a pipeline featuring rigid registration with the NiftyReg toolbox and segmentation with the geodesic information flow algorithm (GIF). Tracer uptakes were standardised by a reference region comprising whole cerebellum, white matter, brainstem and pons. The AD-DPS was computed by jointly modelling the long-term time evolution of bilateral hippocampal volume and cortical SUVR for 1088 individuals, using the growth models via alternating conditional expectation (GRACE) algorithm. GRACE returns the time shifts (in years) required to align the subjects’ biomarker trajectories to the population-based long-term progression curves. We used this time shift as a continuous DPS phenotype for a GWAS with 5.2 mio single nucleotide polymorphisms (SNPs) in 846 subjects with a posterior probability of being of CEU ancestry equal to or greater than 0.8. The model was corrected for sex, age at baseline PET scan, APOE4 status, and 2 principal components of population structure.

Results

Long-term progression curves for hippocampal volume and Aβ42 burden were in good agreement with proposed models of AD biomarker evolution. A genome-wide significant association with AD-DPS was found on chromosome 4 for rs3733541 (p = 9.45e-09) and variants in the flanking sequence. The linkage-disequilibrium block is ~300 Kbp upstream of the KIT gene. This association was not found when testing hippocampal volume and Aβ42 burden separately.

Conclusions

We describe the first use of a disease progression score derived from multiple imaging modalities as quantitative trait in a GWAS. The KIT gene and its ligand stem cell factor (SCF) are involved in a pathway leading to migration and differentiation of neural stem cells to sites of brain injury. Interestingly, significantly lower levels of SCF have been found in the plasma and cerebrospinal fluid of patients with early Alzheimer’s disease. If validated in future studies, this novel susceptibility locus may influence the joint occurrence of hippocampal atrophy and amyloid deposition in AD.

Acknowledgement

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI
investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. For additional details and up-to-date information, see http://www.adni-info.org. MAS acknowledges financial support by the EPSRC-funded UCL Centre for Doctoral Training in Medical Imaging (EP/L016478/1). JMS acknowledges the support of the NIHR Queen Square Dementia BRU, the NIHR UCL/H Biomedical Research Centre, Wolfson Foundation, EPSRC (EP/J020990/1), MRC (CSUB19166), ARUK (ARUK-Network 2012-6-ICE; ARUK-PG2014-1946), Brain Research Trust ((UCC14191) and European Union’s Horizon 2020 research and innovation programme (Grant 666992). SO receives funding from the EPSRC (EP/H046410/1, EP/J020990/1, EP/K005278), the MRC (MR/J01107X/1), the EU-FP7 project VPH-DARE@IT (FP7-ICT-2011-9-601055), the NIHR Biomedical Research Unit (Dementia) at UCL and the National Institute for Health Research University College London Hospitals Biomedical Research Centre (NIHR BRC UCLH/UCL High Impact Initiative- BW.mn.BRC10269). AA holds an MRC Medical Bioinformatics Career Development Fellowship, funded from award MR/L016311/1 (MRC eMedLab).

Keywords Alzheimer’s Disease; Amyloid imaging; Imaging genetics; Disease progression models.
**Aim of Investigation**

Prior research has shown that normal aging brings about regionally specific decreases in cortical thickness. Additionally, brain morphometry is partly under genetic control. Given the known vulnerability of brain structures in dopaminergic pathways, we examine the effect of two major genetic dopamine single nucleotide polymorphisms, COMT and DRD2, and their influence on cortical thickness.

**Methods**

Cortical thickness was estimated using FreeSurfer in 177 healthy participants across the lifespan aged 20-94. General linear models were conducted with each a priori proposed ROI as a dependent variable, with age, DRD2 genotype, COMT genotype, and all associated age x gene, gene x gene, and age x gene x gene interactions as independent predictors. Non-significant interaction terms (p > 0.15) were removed and the models re-run to conserve statistical power. Having both genetic dopamine polymorphisms in the model allows for the evaluation of a potential epistatic relationship between the two polymorphisms.

**Results**

We found both COMT and DRD2 polymorphisms have a significant relation to cortical thickness displaying a regionally specific pattern. Dorsolateral prefrontal cortex regions were significantly thinner in individuals with genetic predisposition to lower D1 dopamine levels (COMTval carriers) than their counterparts, beyond the effects of age. In contrast, parietal and cingulate cortices were significantly associated with both COMT val status and dopamine D2 status.

**Conclusions**

These findings suggest that aging of prefrontal cortex is under more selective genetic influence, whereas non-prefrontal regions of the dopaminergic system are under wider genetic influence from both D1 and D2 dopamine receptors.

**Acknowledgement**

Research supported in part by NIA grants R00 AG-36818 and R00 AG-36848, and foundation awards from Dallas BvB and AWARE.

**Keywords**

COMT, DRD2, Cortical Thickness, Aging
C3. Differential effect of APOE ε4 carrier status on BOLD activation to cognitive difficulty in healthy aging

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Aim of Investigation

Prior research has shown that healthy aging alters the brain’s ability to respond to cognitive challenge. However, the mechanisms that underlie these functional differences with aging are poorly understood. The current study sought to examine the impact of genetic risk for Alzheimer’s disease on the differences in functional brain activation with aging.

Methods

A demographically matched sample of APOE ε4- and APOE ε4+ subjects (age 20-86, total n = 62), performed a distance judgment task with three levels of difficulty. Voxel-wise multiple regression with age, APOE group, and their interaction as predictors of fMRI BOLD response was conducted in the hardest vs. easiest levels of the task.

Results

Results indicated that bilateral precuneus response to cognitive challenge differed by APOE group. Specifically, APOE ε4 carriers decreased modulation with increasing age while non-carriers increased modulation with increasing age. Importantly, decreased modulation in precuneus in ε4 carriers negatively tracked task accuracy on the fMRI task as well as delayed associative memory, tested outside the scanner.

Conclusions

Findings suggest that even in healthy aging, carrying an APOE ε4 allele is associated with decreased ability to modulate brain activation to difficulty, and is associated with poorer cognition. Altered modulation in ε4 carriers may stem from reduced neural efficiency or a general reduction of resources, leading to a compensatory response earlier in the lifespan as compared to non-carriers.

Acknowledgements

Research supported by NIA grants R00 AG-036818 and R00 AG - 036848.

Keywords

Aging, APOE, fMRI
Aim of Investigation

Sirtuin (SIRT) genes are nicotinamide adenine dinucleotide (NAD+) -dependent deacetylases, which are thought to underlie the beneficial effects of calorie restriction, longevity, and protect against neurodegeneration. SIRT1, a regulator of cellular metabolism, may influence neuronal structure affecting cognitive function. The influence of SIRT1 genetic mutations on clinical, cognitive and neurobiological indices have yet to be characterized in humans. This study aims to provide insight into how missense mutants in the SIRT1 gene influence clinical, biological, and neurocognitive indices in aged human subjects.

Methods

Using data from 756 subjects from the Alzheimer’s disease Neuroimaging Initiative (ADNI) cohort, 20 functional variants in SIRT1 located on chromosome 10q21.3 were extracted from Illumina Human610-Quad BeadChip data after imputation using ShapeIt/Impute2. Linear mixed modeling in SPSS 24 tested main effects of variants on neurocognitive and biological data. Outcome variables included white matter hyper-intensity burden, markers of inflammation, global cognition and biomarkers of metabolism. Finally, voxel-wise regression on 404 subjects with imaging data gauged genetic variant associations with baseline glucose metabolism, and regional gray matter volume. Covariates included age, gender, education, and baseline Alzheimer’s disease diagnosis.

Results

Association analyses of SIRT1 polymorphisms are described in Table 1. One polymorphism, rs10822733 located at Chromosome 10:67912470, modified plasma insulin (F=8.498, P<0.001, Figure 1A), glucose (F=15.366, P<0.001, Figure 1B), White Matter Hyperintensity burden (F=7.428, P=0.001, Figure 1C), and Executive Function (F=1.350, P=0.018, Figure 1D). Voxel-wise analyses revealed minor allele carriers showed decreased glucose metabolism and grey matter volume in the hippocampus and PFC (Figure 2).

Conclusions

This is the first study to demonstrate in humans that functional variation in the SIRT1 gene influences brain structure and biological indices that may underlie cognitive function and neurodegeneration. This study supports the protective role of SIRT1 as a modulator of brain structure and function in humans, where missense mutations result in detrimental outcomes. Future investigation of Sirtuins will elucidate their role in the aging process, potentially highlighting novel pathways for therapeutic targets to treat age-related neurodegenerative diseases and promote successful aging.

Acknowledgements

This study was funded by Iowa State University and NIH AG047282. Neither funding source had any involvement in the report. Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Keywords

Sirtuin, Metabolism, Cognition, Grey Matter