significantly different GFA values among the 3 groups. Posthoc between-
groups analysis showed that the non-remission group had lower GFA val-
ues in all 7 tracts than the control group; the remission group had lower
GFA values than the control group only in 4 tracts, namely the bilateral
fornices and the CFs of the bilateral temporal poles, and bilateral hippo-
campi. Compared with the remission group, the non-remission group had
lower GFA values in all 7 tracts.

Discussion: All 7 tracts that were altered in the non-remission group are
a part of the limbic system, which supports various functions, including
emotions, memory, and learning. Our results suggest that patients who had
poor outcomes to antipsychotic treatments might have more severe disrup-
tions in the limbic system. The 7 altered tracts in the non-remission group are
compatible with those reported in previous studies on white matter or
gray matter alterations. In a cross-sectional tractography-based study on
3 pairs of association fibers (i.e., the cingulum, superior longitudinal fasci-
culus, and uncinate fasciculus), Luck et al reported that compared with
patients with good outcomes, patients with poor outcomes had reduced
FA in the uncinate fasciculus and superior longitudinal fasciculus. Marques
et al performed a longitudinal study using tract-based spatial statistics and
reported that non-responders had more tracts with a significantly lower FA
than did the responders, particularly in the uncinate fasciculus and corpus
callosum. In addition to the uncinate fasciculus, we also observed reduced
fiber integrity in the bilateral fornices and the CFs of the bilateral tempo-
ral poles, bilateral hippocampi, and bilateral amygdalae; these tracts con-
nect the gray matter in the limbic system. Jääskeläinen et al revealed that a
reduction in gray matter volume in the frontal and limbic areas is associated
with overall poor outcomes. In addition, Van Haren et al reported signifi-
cantly reduced gray matter volumes in the frontal and temporal cortices of
the individuals with poor outcomes. Because the gray matter regions are
anatomically connected by the fiber tracts, gray matter reduction in the lim-
bic system might affect the interconnecting fiber tracts; this finding accords
with the findings of the present study. In conclusion, differences in the severity of white matter tract alterations in
the remission and non-remission groups might indicate biologically distinct
subgroups in schizophrenia.

T183. AUDITORY-STeady-STATE RESPONSES AND CortICAL VOLUME IN PATIENTS WITH SCHIZOPHRENIA

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Background: The 40-Hz auditory steady-state response (ASSR) probing gamma-band oscillations may reflect N-methyl-D-aspartate receptor (NMDAR) dysfunction in patients with schizophrenia (SZ). Diminished gamma oscillations are reported in SZ, although increased spontaneous gamma oscillations are also reported. We investigated the 40-Hz ASSR and its association with brain volumes and clinical symptoms of SZ.

Methods: The 40-Hz ASSR was measured using electroencephalography in 33 patients with SZ and 30 healthy controls (HCs). Four gamma oscillation components (evoked power, spontaneous oscillations (baseline and total power), and inter-trial phase coherence (ITC)) were assessed. Brain volumes were assessed using high-resolution magnetic resonance imaging and voxel-based morphometry.

Results: Patients with SZ had larger evoked and total powers and higher ITC than HCs. In HCs, evoked power showed significant positive corre-
lations with bilateral superior temporal gyrus (STG) volume. In SZ, the effect of positive symptoms on the path from evoked power to left STG vol-
ume was significantly moderated. In SZ with elevated positive symptoms,
large evoked power predicted small left STG volume, whereas large evoked power predicted large left STG volume in those with low positive symp-
toms. Increased baseline power was associated with a smaller left middle
frontal gyrus (MFG) volume in SZ, whereas increased ITC correlated with
larger MFG volume in HCs.

Discussion: Our results support the NMDAR hypofunction model of
SZ, and suggest significant involvement of the STG and MFG in gamma oscillations.

T184. BRAIN-Wide FUNCTIONAL DysCONNECTIVITY in SCHIZOPHRENIA: PARsING DiATHESIS, RESILIENCE AND THE EFFECTS OF CLINICAL EXPRESSION

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Background: The functional dysconnectivity observed from resting-state fMRI studies in schizophrenia is also seen in unaffected siblings indicating its association with the genetic diathesis of the illness. Nevertheless, when compared to patients, the extent of dysconnectivity appears to be limited both in spatial distribution and magnitude in siblings, suggesting that some of the abnormalities could be exclusively linked to the clinical expression or treatment effect rather than genetic diathesis. We investigated brain-wide functional connectivity using a graph theory approach to apportion resting-state dysconnectivity into components that represent genetic diathesis, clinical expression or treatment effect and resilience.

Methods: Resting state functional MRI data acquired from 116 subjects (28 patients with schizophrenia, 28 unaffected siblings and 60 matched healthy controls). Based on Dosenbach’s atlas applied to 6 minutes (180 time points with TR=2 s) of eyes-open resting (MRI) scan, we extracted time series of 160 functional network nodes. After constructing a 160*160 functional network, we investigated between-group differences in strength and diversity of functional connectivity and topological properties of undirected graphs constructed from thresholded correlation matrices. We also used Support Vector Machine approach to estimate the ability of functional connectivity metrics to discriminate the three groups from each other.

Results: Using ANOVA [FDR corrected p<0.05], we found 88 out of 12720 pairs of functional links to be significantly different among the three groups. 48.8% of these 88 links included nodes from the Default Mode Network (DMN), with the largest portion of these involving Salience Network/DMN connectivity (48.8%). Post-hoc t tests revealed that 62.5% of these disconnected links were associated with genetic diathesis of schizophrenia (i.e. both patients and siblings showing same direction of significant post-hoc difference compared to HC) and 21.6% were associated with clinical expres-
sion or treatment effect (i.e. patients differed from siblings and healthy con-
trols, but no difference between controls and siblings). Topologically, we observed increased degree, clustering coefficient and global efficiency but reduced local efficiency in the sibling group compared to both patients and controls, indicating a resilience (or compensation) effect. Support vector machine analysis revealed a high degree of accuracy when classifying the genetically predisposed (patients and siblings) vs. healthy controls (Area Under the Curve - AUC 0.97) or the patient groups vs. healthy controls (AUC 0.97) but not when discriminating patients vs. siblings (AUC 0.58)

Discussion: A large portion of the resting-state functional dysconnectiv-
ity seen in patients with schizophrenia represent a genetic diathesis effect. The most prominent network level disruption in this context is the dysconnec-
tivity among nodes of the default-mode and salience networks. Despite their predisposition, unaffected siblings show a pattern of resilience in the emergent connectome topology. Our findings could potentially help refine

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imaging genetics approaches currently used in the pursuit of the pathophysiology of schizophrenia.

**T185. DIFFERENTIAL ACTIVITY OF TRANSCRIBED ENHANCERS IN THE PREFRONTAL CORTEX OF 592 CASES WITH SCHIZOPHRENIA AND CONTROLS**

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**Background:** Transcription at enhancers is a widespread phenomenon, which produces so-called enhancer RNA (eRNA) and occurs in an activity-dependent manner. The role of eRNA and its utility in exploring disease-associated changes in enhancer function and the downstream coding transcripts that they regulate is however not well established. We here used transcriptomic and epigenomic data to interrogate the relationship of eRNA transcription to disease status and how genetic variants alter enhancer transcriptional activity in the human brain.

**Methods:** We combined RNA-seq data from 537 post mortem brain samples from the CommonMind Consortium with cap analysis of gene expression and enhancer identification, using the assay for transposase-accessible chromatin followed by sequencing.

**Results:** We find 118 differentially transcribed eRNAs in schizophrenia and identify schizophrenia-associated gene/eRNA co-expression modules. Perturbations of a key module are associated with the polygenic risk scores. Further, genetic variants affecting expression of 927 enhancers, which we refer to as enhancer expression quantitative loci or eeQTLs, are identified. Enhancer expression patterns are consistent across studies, including differentially expressed eRNAs and eeQTLs. Combining eeQTLs with a genome-wide association study of schizophrenia identifies a genetic variant that alters enhancer function and expression of its target gene, GOLPH3L.1

**Discussion:** Here, we expanded the scope of the CommonMind Consortium to interrogate enhancer function in schizophrenia, to examine how genetic variation affects enhancers, and to evaluate specific effects on enhancer and gene expression for previously identified schizophrenia risk variants. Our novel approach to analyzing enhancer transcription is adaptable to other large-scale, non-poly-A depleted, RNA-seq studies.

**T186. ASSOCIATION BETWEEN POLYMORPHISMS OF THE NEUREGULIN 1 (NRG1) GENE AND SCHIZOPHRENIA**

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**Background:** The dysfunction of neuregulin 1 (NRG1) is one of the plausible hypotheses for the pathogenesis of schizophrenia. The neuregulin 1 (NRG1) is located on chromosome 8p, as suggested by multiple linkage studies. The aim of this study is to clarify the contribution of polymorphisms of the neuregulin 1 (NRG1) with schizophrenia.

**Methods:** After informed consent was obtained, 100 schizophrenia patients and 100 control subjects were enrolled in this study. All subjects were administered the Diagnostic Interview for Genetic Studies (DIGS) (National Institute of Mental Health-Molecular Genetics Initiative, 1992; Nurnberger et al., 1994) by a research assistant with extensive training in this interview. Blood samples were collected in anonymously identified 10-ml Vacutainer tubes (Becton Dickinson). DNA was prepared by a modified SDS/Proteinase K procedure (Gusella et al., 1979). We genotyped polymorphism neuregulin 1 (NRG1) with the PCR-RFLP methods. The PCR products were digested by restricted enzyme.

**Results:** We observed a significant association between the polymorphism neuregulin 1 (NRG1) and the schizophrenia (Chi-Square Test P=0.0449).

**Discussion:** The NRG1 gene was originally identified as a susceptibility gene for schizophrenia by using a combination of a linkage and association approaches based on microsatellite markers and then using SNPs after microsatellite at risk haplotypes were identified. We found there is the frequency of the polymorphism of neuregulin 1 (NRG1) was significantly increased in schizophrenia patients. This allelic association suggests that the functional polymorphism neuregulin 1 (NRG1) may play a role in susceptibility to schizophrenia. Further study with larger sample sizes is required.

**T187. ALTERED DNA METHYLATION OF THE OXYTOCIN RECEPTOR GENE IS ASSOCIATED WITH SUSCEPTIBILITY TO PSYCHOSIS AND ANHEDONIA-ASOCIALITY IN FEMALES: EPIGENETIC EVIDENCE IN RECENT-ONSET SCHIZOPHRENIA AND ULTRA-HIGH RISK FOR PSYCHOSIS**

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**Background:** Oxytocin is one of the key hormones involved in human social and emotional processing. In this regard, abnormal functioning of the oxytocin system has been suggested to influence on the clinical manifestation of schizophrenia, especially negative symptoms. The aim of the present study was to investigate epigenetic modification of the oxytocin receptor gene (OXTR) and its association with negative symptoms in individuals with recent-onset schizophrenia (SCZ) and at ultra-high risk (UHR) for psychosis.

**Methods:** Sixty-four SCZ patients (< 5 years of duration of illness; 25 men, 39 women), 46 UHR individuals (27 men, 19 women), and 98 healthy controls (HCs; 46 men, 52 women) participated in the present study. DNA methylation was quantified from peripheral blood using pyrosequencing at CpG sites in OXTR intron 1 (hg19, chr3: 8,810,729–8,810,845) and exon 3 (hg19, chr3: 8,809,281–8,809,534). The severity of negative symptoms in clinical groups was measured using the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS).

**Results:** A multivariate analysis of covariance revealed significant differences in OXTR methylation between groups (F = 16.00, p < 0.001) and gender (F = 2.84, p = 0.025). Compared to HCs, both UHR and SCZ participants showed lower levels of OXTR intron 1 methylation, particularly at CpG site -934 upstream of the OXTR start codon (HCs = 47.3 ± 4.1 [mean ± SD], UHR = 38.8 ± 4.8, SCZ = 40.2 ± 5.3; F = 73.74, p < 0.001). Besides, female participants showed higher OXTR intron 1 methylation at CpG site -934 than male participants (male = 42.3 ± 6.1, female = 44.1 ± 5.8, F = 9.08, p = 0.003). Multiple linear regression analysis with clinical symptoms demonstrated that the degree of DNA methylation at CpG site -934 was significantly associated with the SANS anhedonia-asociality subscale scores in the entire group of female UHR and SCZ participants (beta = -0.44, p = 0.001).

**Discussion:** The present study demonstrated decreased OXTR methylation in both UHR and SCZ individuals compared to HCs. Furthermore, the severity of anhedonia-asociality was significantly associated with the degree of OXTR methylation in female UHR and SCZ individuals. These findings suggest that epigenetic aberration of OXTR may confer susceptibility to schizophrenia spectrum psychosis and influence the early pathogenesis of schizophrenia prior to the onset of overt psychosis, particularly in females.