Psychiatric Liability Genes are Linked to Oscillatory Brain Activity: A Genome-Wide Association Study

ENIGMA-EEG working group of the ENIGMA consortium (Enhancing Imaging Genetics through Meta-Analysis)
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Highlight 1: Brain activity genes are enriched with liability genes for schizophrenia and bipolar disorder

Highlight 2: Alcohol Dependence gene GABRA2 affects beta oscillations via hippocampal expression

BACKGROUND: Oscillatory activity is crucial for information processing in the brain. It has a long history as a biomarker for psychopathology and behavior. Cognitive processing depends on theta oscillations (4–8 Hz) for memory processing and alpha oscillations (~10 Hz) for functional inhibition. Oscillations additionally play a central role in cortical communication. Deviant patterns of oscillatory activity have been linked to schizophrenia [Boutros et al., 2008; Sponheim et al., 1994], attentional deficits [Clarke et al., 1998; Snyder and Hall, 2006], and substance use [Rangaswamy et al., 2002; Struve et al., 1989]. A link has been reported between GABA receptor gene alpha2 subunit (GABRA2), beta oscillations (~20 Hz), and alcohol use disorder. But otherwise, current understanding of specific genetic influences remains limited.

AIMS: 1) To perform a GWAS for oscillatory brain activity, with followup gene-based analyses (KGG). 2) To replicate findings for the link between GABRA2 and beta oscillations. 3) Check enrichment of top genes in GWAS databases (using FUMA; Watanabe et al., 2016). 4) Expression enrichment analysis (tissue specific; FUMA)

METHOD:
Subjects came from five cohorts, three population based twin family cohorts (Netherlands Twin Registry, Minnesota Twin Family Study, Brisbane Adolescent Twin Study), and two alcohol-ascertained samples (Collaborative Study on the Genetics of Alcohol Use). EEG was registered (Cz with ears or nose reference; O1/O2 against P7/P8), filtered into alpha (8 – 12 Hz) and beta (13 – 30 Hz) frequencies. Power was determined with the Fast Fourier Transform. Genetic analysis consisted of filtering on call rate, HWE, monomorph SNPs, and imputation with 1000 genomes build 37 phase 1 reference EUR. Post imputation QC INFO score, MAF, HWE. Association used Merlin, Generalized Estimating Equations or RFGLS ton o correct for family relatedness. Meta-analysis on p-values using metal. Positional gene-based testing was performed using KGG GATES with SNPs within 50kb.

Enrichment of differentially expressed genes (DEGs): DEGs are found by a t-test of gene expression RPKM in one specific tissue against all 52 others at p=0.05 in the GTex database. The top 500 genes in the gene-based analysis were significantly enriched for brain tissue DEGs (top enrichment for Amygdala, Frontal cortex and Cortex). The top500 genes in the Height GWAS (top right inset) shows a clearly different expression pattern (top enrichment in tibial nerve, tibal artery, and muscle/skeletal tissues). Additional enrichment was found for other tissues (e.g. heart tissues and whole-blood). This we attribute to remaining pleiotropy.

GENES: ~10 Hz alpha oscillations showed a range of significant genes (FDR adjusted), including PRKRG2 and 24 genes at chromosome 3p21.1 (from ALAS1 to ITIH4). METTL21C has been found in previous GWAS of brain oscillations. No genome-wide significant effects for beta oscillation GWAS were found.

Hippocampal GABRA2 expression is strongly associated with beta oscillations (p=0.0024), even when the original discovery GWAS (COGA) is excluded (p=0.0050).

S-PrediXcan calculated the association between the imputed expression of a gene in a specific tissue and alpha oscillation strength. The results showed significant association of many genes expression in hippocampus, hypothalamus, and putamen. These notably include schizophrenia liability genes GLYCCTK, GNL3 and ITH4. Further genes are immune-related genes IL18R1 and IL1RL1.

Expression in SCZ
Using S-PrediXcan and The second PGC Schizo-Phrenia GWAS we found strong association of ITH4, GLYCCTK and GNL3 in several brain tissues, including the target subcortical structures.

Table. Alpha Oscillatory genes found in the alpha oscillation S-PrediXcan analyses were extracted from the 5 prediXcan associations between imputed brain expression and Schizophrenia (PGC). P-values are reported.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>ITH4</th>
<th>GNL3</th>
<th>GLYCCTK</th>
<th>IL18R1</th>
<th>IL1RL1</th>
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</thead>
<tbody>
<tr>
<td>ACC</td>
<td>1.5E-07</td>
<td>-0.0825</td>
<td>-0.0409</td>
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<td>Caudate</td>
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<tr>
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<td>9.4E-07</td>
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<td>-0.7606</td>
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<tr>
<td>Putamen</td>
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<td>6.0E-09</td>
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<td>-0.4036</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: S-PrediXcan was not able to produce p-values for all associations. No correction for multiple tests was applied.

CONCLUSION:
- Many schizophrenia liability genes affect alpha oscillations, in line with aberrant alpha activity in the disorders. Subcortical expression of ITH4, GLYCCTK and GNL3 may mediate the effect. Additional effects of immune-related genes were found.
- GABRA2 affects beta oscillations via hippocampal expression, which completes the triad of GABA functioning, beta oscillations and alcohol use disorders.