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)

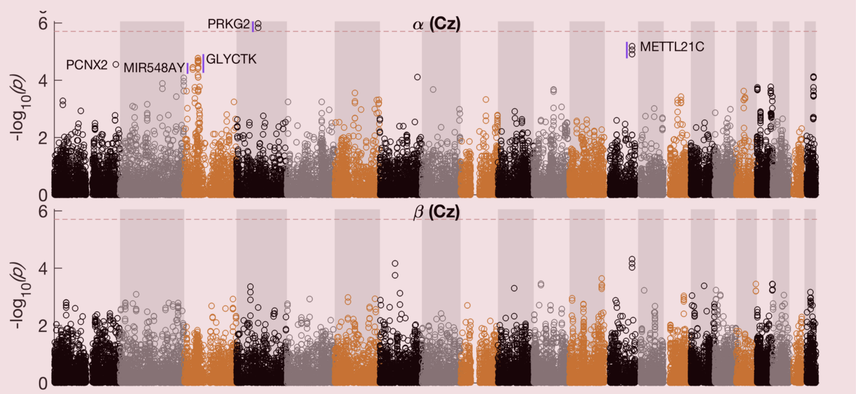
Dirk JA Smit, Margaret J Wright, Jacquelyn L Meyers, Nicholas G Martin, Yvonne YW Ho, Stephen M Malone, Jian Zhang, Scott J Burwell, David B Chorlian, Eco JC de Geus, Damiaan Denys1, Narelle K Hansell, Jouke-Jan Hottenga, Matt McGue, Catharina EM van Beijsterveldt, Neda Jahanshad, Paul M Thompson, Christopher D Whelan, Sarah E Medland, Bernice Porjesz, William G Iacono, Dorret I Boomsma

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*

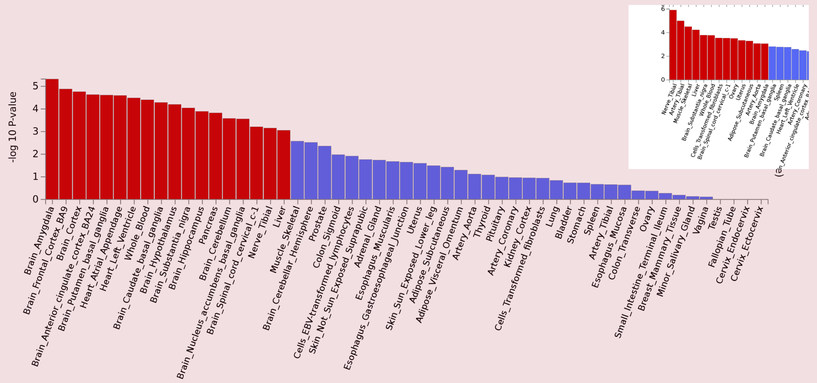
BACKGROUND: *Oscillatory activity is crucial for information processing in the brain. It has a long history as a biomarker for psychopathology and behavior. Cognitive processing depends on theta oscillations (4 – 8 Hz) for memory processing and alpha oscillations (~10 Hz) for functional inhibition. Oscillations 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 a 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 Foruier 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 50kbp.

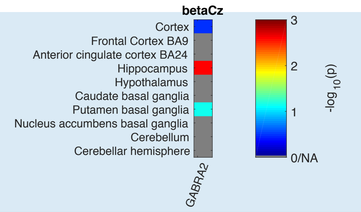


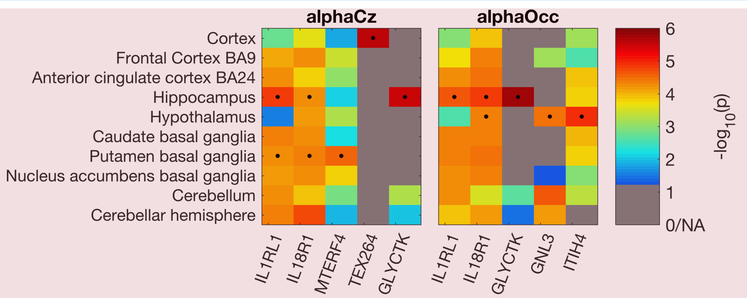
GENES: ~10 Hz alpha oscillations showed a range of significant genes (FDR adjusted), including PRKG2 and 24 genes at chromosome 3p21.1 (from ALAS1 to ITIH4). METTL21C has been found in previous GWAS of brain oscillations. No genome-wide significant effects for beta oscillation GWAS were found.



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, tibial 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.

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 *GLYCTK*, *GNL3* and *ITIH4*. 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 *ITIH4*, *GLYCTK* and *GNL3* in several brain tissues, including the target subcortical structures.

Table. Alpha Oscillatory genes' found in the alpha oscillation S-Prdixcan analyses were extracted from the S-predixcan association between imputed brain expression and Schizophrenia (PGC). P-values are reported.

	Gene				
Tissue	ITIH4	GNL3	GLYCTK	IL18R1	IL1RL1
ACC	1.9E-07	-	-	0.0625	0.4040
Caudate	8.3E-08		-	0.3954	0.3992
BA9	0.9754	0.9684	-	0.9951	0.9957
Hippocampus	6.3E-08	-	1.5E-08	0.2626	0.3727
Hypothalamus	1.5E-09	9.4E-07	-	0.4607	0.7606
Accumbens	0.0001	3.0E-05	-	0.4202	0.4988
Putamen	5.7E-08	0.0539	-	0.3988	0.4036

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 *ITIH4*, *GLYCTK* 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.