Brain gene expression-informed analysis identifies retinoid receptor targets in suicidal thoughts and behaviours

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BACKGROUND

- Suicidal thoughts and behaviours (STBs) – comprising suicidal ideation (SI) and suicidal behaviour (SB, including suicide attempt/SA and death by suicide) – are major transdiagnostic public health concern.
- STBs show significant SNP-based heritability (h^2_{SNP} = 3-6.7%) and are linked to altered brain morphology.
- Still, little is known about how STB-associated genetic variants act on brain tissue-specific gene regulation and molecular pathways.

AIM

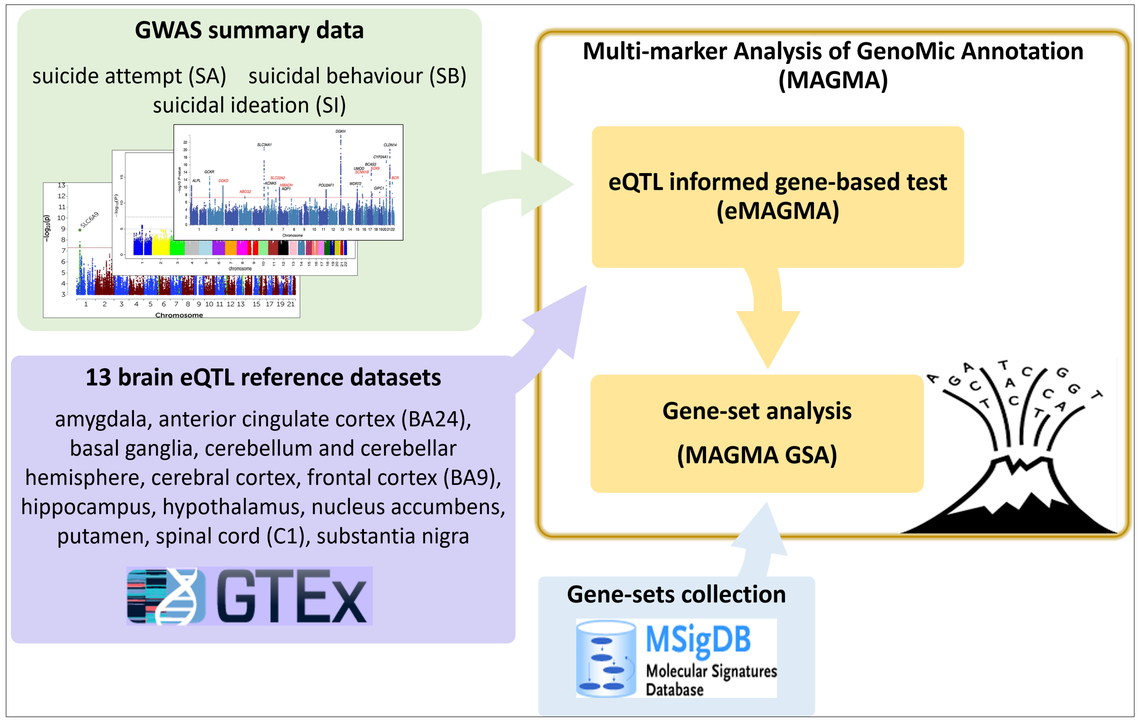
Test whether STBs' genetic liability is enriched in tissue-specific gene expression, using expression quantitative-trait loci **(eQTL)-informed gene and gene-set enrichment analyses**.

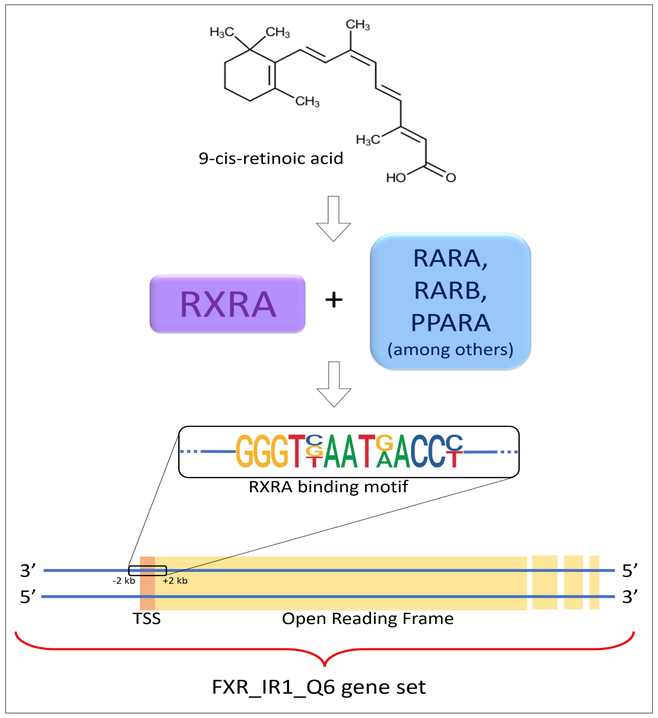
MATERIAL & METHODS

- Summary statistics for SB, SA and SI from the largest published STB GWAS.
- eQTL-informed gene-based association testing (eMAGMA) across 13 GTEx brain-tissue reference datasets (amygdala, anterior cingulate cortex (BA24), basal ganglia, cerebellum, cerebellar hemisphere, cerebral cortex, frontal cortex (BA9), hippocampus, hypothalamus, nucleus accumbens, putamen, spinal cord (C1), and substantia nigra)
- Gene-set analysis (MAGMA GSA) on mapped genes using the Molecular Signatures Database (MSigDB).

WHY eQTL-INFORMED MAPPING?

Standard gene mapping links variants nearest gene. eMAGMA instead uses eQTLs to link each variant to the gene(s) whose expression it actually regulates in a given tissue, giving a mechanistically grounded, tissue-specific picture of genetic risk.





RESULTS

- After multiple testing correction, 2 to 43 significant eGenes per trait-tissue pair were identified, resulting in 126 unique genes across the 13 brain tissues.
- SB and SA showed the broadest signal (SB 11-43; SA 7-37) vs. SI (2-13); largest gene counts were found for cerebellum, cerebellar hemisphere, cerebral cortex, BA9 and nucleus accumbens.
- SB/SA also implicated striatal regions (caudate, putamen); SI additionally mapped to hippocampus and anterior cingulate cortex.
- GSA identified 14 significant unique gene sets involving immune-related pathways, major histocompatibility complex region sets, and the chr3p21 cytoband.
- Seven pairs (involving SA/SB and hypothalamus, BA9, BA24, and C1) were enriched for the ***FXR_IR1_Q6*** gene set, which collects genes harbouring a Retinoid X Receptor (RXR) Alpha transcription factor binding site

CONCLUSIONS

- STBs are enriched in brain-expressed genes across multiple brain regions - **frontostriatal**, **corticolimbic** and **cerebellar** - consistent with neuroimaging findings.
- **Immune-related pathways** and **RXR-alpha transcriptional targets** emerged as candidate mechanisms
- RXR nuclear receptors mediate the biological effects of retinoids, involved in brain development, dendritic spine formation, and microglial activity. Altered retinoid signalling has previously been linked to psychiatric disorders, and prolonged exposure to retinoid drugs has been associated with reduced suicidal behaviours.
- Although these findings do not establish causality, they nominate immune-related and retinoid signalling as candidate pathways for future mechanistic studies.

NEXT STEPS

- Colocalization analyses
- Effector-gene prioritisation
- Brain co-expression integration
- Drug-target Mendelian randomisation

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The authors have no conflicts of interest to disclose.

Suicide ECNP Network

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