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Genetic Correlation Between Schizophrenia and Epilepsy

Neuropathological, clinical, and epidemiological data suggest that schizophrenia and epilepsy are associated.\(^1\) Reported estimates of the prevalence of schizophrenia among people with epilepsy vary, depending on phenotypic definition, but may be around 7%.\(^7\) One hypothesis to account for this is that schizophrenia and epilepsy are associated.\(^1\) However, whether this link represents a shared etiology had not previously been clarified. Here, we have provided an initial demonstration of a significant shared liability to epilepsy of all types and 26,157 control individuals. The individual significant positive \(r_G\) for schizophrenia with focal epilepsy, although it does not survive Bonferroni correction for multiple comparisons, could be taken to suggest that it is this subtype of epilepsy driving the overall significant positive correlation.

**Results** | Results are shown in the Table. There was a positive genetic correlation between schizophrenia and epilepsy (all subtypes) of 0.22 (SE, 0.07; \(P = .001\)). The heritability for schizophrenia was 0.30 (SE, 0.02). All heritability estimates are presented on the liability scale.

**Discussion** | In this study, the LDSC regression has revealed a statistically significant positive association between schizophrenia and epilepsy (all subtypes). The individual significant positive \(r_G\) for schizophrenia with focal epilepsy, although it does not survive Bonferroni correction for multiple comparisons, could be taken to suggest that it is this subtype of epilepsy driving the overall significant positive correlation.

The value for epilepsy heritability of 0.05 calculated by LDSC here is significantly lower than values calculated previously using alternative methods.\(^6\) This is likely attributable in part to the genomic control correction applied to each constituent study of the epilepsy meta-analysis data. This biases estimates of heritability downwards without affecting the value for genetic correlation.\(^3\) The schizophrenia data set did not undergo genomic control correction and accordingly the heritability reported here is more in keeping with previously published estimates. We would also note that the complete epilepsy data set included both genetic generalized epilepsy and focal epilepsy, and the low heritability estimate could potentially be explained by heterogeneity among these cases. However, neither of these limitations is likely to produce a falsely significant positive result for genetic correlation.

The power of LDSC lies in the fact that it only requires summary statistics, rather than individual-level genotype data, to estimate trait heritability and genetic correlation. Estimations of correlation can provide insights into shared biology at the molecular level and are especially useful where environmental confounders might otherwise be thought to link 2 diseases. A link between schizophrenia and epilepsy has been the subject of interest and controversy since it was noted early in the 20th century that there was some apparent phenotypic overlap between them. However, whether this link represents a shared etiology had not previously been clarified. Here, we have provided an initial demonstration of a significant shared liability to study and the degree of sample overlap between the studies, which in this case was zero. Because sample overlap can impair the ability of this method to detect genetic correlation, we did not use the most recent Psychiatric Genetics Consortium meta-analysis of schizophrenia GWAS because this study shared some control individuals with those of the epilepsy GWAS.

**Table. Heritability of Epilepsy and Subtypes and Genetic Correlation With Schizophrenia**

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Heritability (SE)</th>
<th>Correlation With Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(r_G) (SE)</td>
<td>(P) Value</td>
</tr>
<tr>
<td>All epilepsy (n = 8696)</td>
<td>0.05 (0.01)</td>
<td>0.22 (0.07) .001</td>
</tr>
<tr>
<td>Genetic generalized epilepsy (n = 2606)</td>
<td>0.32 (0.05)</td>
<td>0.02 (0.04) .62</td>
</tr>
<tr>
<td>Focal epilepsy (n = 5310)</td>
<td>0.04 (0.03)</td>
<td>0.31 (0.15) .04</td>
</tr>
</tbody>
</table>

Abbreviation: \(r_G\), genetic correlation.

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schizophrenia and epilepsy, suggesting that the relationship between the 2 disorders occurs at the level of the genome.

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Author Contributions: Dr Vonberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Both authors.

Acquisition, analysis, or interpretation of data: Both authors.

Drafting of the manuscript: Both authors.

Critical revision of the manuscript for important intellectual content: Both authors.

Statistical analysis: Both authors.

Administrative, technical, or material support: Vonberg.

Study supervision: Bigdeli.

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OBSERVATION

A Case of Rapid Eye Movement Sleep Behavior Disorder in Parkinson Disease Treated With Sodium Oxybate

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by altered dream mentation, vocalizations, and dream enactment behavior (DEB). The motor behavior is often aggressive, resulting in potential injury to the patient or bed partner. Clonazepam and melatonin are considered standard treatments. Limited data exist on the use of alternative agents when standard medications fail. We report a case of successfully treated RBD in advanced Parkinson disease (PD) with sodium oxybate in a patient refractory to both standard and alternative pharmacologic agents.

Report of a Case  A man in his late 60s with a 15-year history of PD (Hoehn and Yahr score, 3) and 20-year history of RBD presented with worsening DEB. While the patient’s daytime motor symptoms improved following deep brain stimulation, episodes of DEB became progressively more violent, resulting in assault on his wife and self-injurious behaviors. Yelling occurred multiple times per night. Violent behaviors were reported every other night, such as punching through walls or striking furniture (Figure). Initial polysomnography demonstrated obstructive sleep apnea (OSA), with an Apnea Hypopnea Index score of 8.5. Given the mild severity of OSA, risk of interaction with continuous positive airway pressure device during DEB, and patient preference, conservative treatment was initiated.

Violent behaviors persisted despite treatment with standard agents (clonazepam and melatonin). The patient’s maximum tolerated dose of clonazepam was 1 mg, as higher doses resulted in drowsiness. The addition of melatonin, titrated to 12 mg, also failed to control symptoms. Prazosin, ramelteon, cyproheptadine, and eszopiclone were subsequently added. Despite this extensive regimen, the violent behaviors increased in frequency. One severe episode resulted in a head laceration after striking the wall, requiring emergency department evaluation with unremarkable neuroimaging. Given the persistent threat of violent, potentially fatal behaviors, a trial of sodium oxybate was initiated under supervision during polysomnography. Dosing was titrated to 2.5 g twice nightly, which was based on a case report1 and guidelines for treatment of RBD.2 Treatment with sodium oxybate resulted in complete cessation of DEB episodes for 2 months, representing a reduction from the patient’s previous frequency of nearly every other night.

Figure. Rapid Eye Movement Behavior Disorder and Violent Events

Despite removing all objects from the bedroom and laying the mattress onto the floor, the patient continued to strike out at walls and the ground, causing self-injury and damage to property during dream enactment behavior.