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Original Article

Associations of schizophrenia with arrhythmic disorders and electrocardiogram traits: genetic exploration of population samples

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Background

An important contributor to the decreased life expectancy of individuals with schizophrenia is sudden cardiac death. Arrhythmic disorders may play an important role herein, but the nature of the relationship between schizophrenia and arrhythmia is unclear.

Aims

To assess shared genetic liability and potential causal effects between schizophrenia and arrhythmic disorders and electrocardiogram (ECG) traits.

Method

We leveraged summary-level data of large-scale genome-wide association studies of schizophrenia (53 386 cases, 77 258 controls), arrhythmic disorders (atrial fibrillation, 55 114 cases, 482 295 controls; Brugada syndrome, 2820 cases, 10 001 controls) and ECG traits (heart rate (variability), PR interval, QT interval, JT interval and QRS duration, $n = 46\,952–293\,051$). We examined shared genetic liability by assessing global and local genetic correlations and conducting functional annotation. Bidirectional causal relations between schizophrenia and arrhythmic disorders and ECG traits were explored using Mendelian randomisation.

Results

There was no evidence for global genetic correlation, except between schizophrenia and Brugada syndrome ($r_g = 0.14$, 95% CIs = 0.06–0.22, $P = 4.0E{-}04$). In contrast, strong positive and negative local correlations between schizophrenia and all cardiac traits were found across the genome. In the most strongly associated regions, genes related to immune and viral response mechanisms were overrepresented. Mendelian randomisation indicated that liability to schizophrenia causally increases Brugada syndrome risk (beta = 0.14, CIs = 0.03–0.25, $P = 0.009$) and heart rate during activity (beta = 0.25, CIs = 0.05–0.45, $P = 0.015$).

Conclusions

Despite little evidence for global genetic correlation, specific genomic regions and biological pathways emerged that are important for both schizophrenia and arrhythmia. The putative causal effect of liability to schizophrenia on Brugada syndrome warrants increased cardiac monitoring and early medical intervention in people with schizophrenia.

Keywords

Schizophrenia; arrhythmia; electrocardiogram; genetics; causality.

Individuals with a serious mental illness have a markedly shorter life expectancy than individuals from the general population. This life expectancy gap is especially stark for people with schizophrenia, who are expected to live, on average, 10–20 years less than individuals without mental illness.[1,2] While some of these life years lost can be attributed to manifestations of the psychological symptoms, such as suicide,[3] another important cause of premature death is cardiovascular disease.[4,5] The risk of sudden cardiac death is ~10 times higher in individuals with schizophrenia spectrum disorders compared with the general population.[6,7] Sudden cardiac death can be the result of structural disorders such as coronary artery disease, but arrhythmic disorders (electrophysiological abnormalities) also play an important role. Individuals with schizophrenia show increased rates of arrhythmia and changes on the electrocardiogram (ECG).[6,8–11] The most common arrhythmic disorder is atrial fibrillation which, over time, can lead to remodelling of the heart's ventricles and thereby make it more susceptible to ventricular fibrillation and sudden cardiac death.[12,13] Brugada syndrome, a rare arrhythmic disorder with a population prevalence of 0.05%,[14] is also more common among individuals with schizophrenia.[8,15] It is characterised by ST-segment elevation in ECG recordings and associated with an increased risk of sudden death in young adulthood.[16] While antipsychotic medication can have cardiac side-effects, its use does not (fully) explain these associations. People with schizophrenia who do not use sodium-blocking antipsychotic medication show much higher rates of ECG suspicious for Brugada syndrome than the average population, and (young) people with a first episode of psychosis already show decreased RR interval variability and increased QT interval variability (both being associated with a higher risk of sudden cardiac death).[8,17–19] Currently, it is poorly understood why schizophrenia is associated with arrhythmia, with epidemiological and clinical studies being hampered by the low prevalence of the variables of interest.

Shared genetic liability

A potential mechanism is shared genetic risk factors, such that genetic variants that convey a higher risk of developing schizophrenia also increase the risk of arrhythmia. In the most recent genome-wide association study (GWAS) of schizophrenia, some of the strongest associations were found with single nucleotide polymorphisms (SNPs) that lie in genes coding for ion channels (mainly voltage-gated calcium channels).[20] Interestingly, these are also involved in cardiac electrical function and the development

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of arrhythmia.[21] To formally assess shared genetic risk, a genetic correlation can be computed, which estimates the overlap between genetic variants that are involved in susceptibility to two traits.[22] One study found no evidence for genetic correlation between schizophrenia and a range of cardiovascular outcomes (including blood pressure, coronary artery disease, heart rate variability and heart failure[23]), while another found modest correlations between schizophrenia and cardio-metabolic traits (including lipid levels, body mass index (BMI) and coronary artery disease) but only when selecting lower-frequency genetic variants.[24] This lack of evidence for (strong) genetic correlation is striking, given that schizophrenia and cardiovascular disease are strongly correlated phenotypically. One explanation may be that genetic correlation only occurs in specific regions of the genome or in opposing directions. This would not be picked up with a global correlation as this measure aggregates associations across the entire genome into a single measure. Sophisticated methods to assess local genetic correlations[25] and the function of shared biological pathways[26] are available, but have scarcely been applied.

Causal pathways

Another potential mechanism for why schizophrenia is associated with arrhythmia is that there are causal effects. The most intuitive direction of causality is that schizophrenia increases arrhythmia risk, potentially because of the systemic effects that schizophrenia has on the body and the autonomic nervous system (which also controls the heart's electrophysiological function).[23,27] Reverse causal effects are also possible. A longitudinal study in >1 million men showed that a higher heart rate in adolescence increased the risk of developing psychosis in adulthood.[28] High heart rate could represent an early marker of psychotic disorder, but the authors speculated that it could also be a causal risk factor.[29] Mendelian randomisation mimics a randomised controlled trial (which is not feasible here) by using specific genetic variants as instrumental variables, or 'proxies', to test causal effects of a proposed risk factor ('exposure') on an outcome. With Mendelian randomisation, a subset is selected of significant genetic variants which are strongly and robustly predictive of the exposure. Because genetic variants are randomly passed on from parents to offspring, bias from confounders can be (largely) circumvented. Using Mendelian randomisation, we recently found evidence for a causal effect of liability to schizophrenia on heart failure.[23] The latest availability of large GWASs on arrhythmic disorders and ECG traits now makes it possible to comprehensively assess the causal relation of schizophrenia with arrhythmia.[20,30–34]

Study aims

In this pre-registered study (https://osf.io/fe4ms), we assess shared genetic risk factors of schizophrenia with arrhythmic disorders and ECG traits as well as specific biological pathways responsible for such shared liability, and explore potential causal effects between schizophrenia and arrhythmic disorders and ECG traits in both directions. The outcomes will help us understand why individuals with schizophrenia are at increased risk of sudden cardiac death – knowledge which is crucial to improve life expectancy in this vulnerable population.

Method

All analyses in this study were conducted with summary-level data of the largest available published GWASs, with all of the individual sites having obtained appropriate ethical approval and informed consent from participants. Levering the summary-level data, we applied various genetics-based methods displayed in Fig. 1. The primary measure of interest, schizophrenia diagnosis, was chosen because it is the psychiatric disorder linked most consistently and strongly to cardiovascular disease and mortality. Schizophrenia cases had a clinical diagnosis within the schizophrenia spectrum disorder, based on the widely accepted DSM-IV criteria.[20] Information on the measurement of the two arrhythmic disorders (atrial fibrillation[33] and Brugada syndrome[30]) and ECG traits (heart rate during activity,[35] heart rate recovery after activity,[35] heart rate variability,[34] QT interval,[31] PR,[32] JT[31] and QRS[31]) can be found in Table 1.

Global genetic correlations

To estimate genome-wide genetic correlations, we applied Linkage Disequilibrium Score regression using SNP effect estimates from the existing GWASs.[22] We first filtered the GWAS summary statistics by excluding SNPs with a minor allele frequency (MAF) < 0.01, missing values and infinite test statistic values. Next, we extracted SNPs available in the HapMap 3 reference panel. For each trait pair, genetic covariance was estimated using the slope from the regression of the product of z-scores from the two corresponding GWASs on the LD score. A global genetic correlation represents the genetic covariation between two traits based on all polygenic effects captured by the SNPs included in the GWASs. LD scores were based on the HapMap 3 reference panel (European). In order to establish whether the strength of genetic correlation varies by SNP variant frequency, for which there is some evidence,[24] we also computed MAF-stratified genetic correlations. We created strata of MAF between boundary values 0.05, 0.11, 0.22, 0.35 and 0.50, consistent with Perry et al, 2022.[24]

Local genetic correlations

We used Local Analysis of [co]Variant Association (LAVA) to assess local genetic correlations of schizophrenia with arrhythmic disorders and ECG traits.[25] A total of 2495 predefined regions across the entire genome were assessed. These regions were provided alongside the software and were created by partitioning the genome into blocks of approximately equal size (~1 Mb) while minimising LD between them. The 1000 Genomes European panel (MAF > 0.01) was used as a reference panel. Only regions that showed a highly significant univariate heritability (h^2_{SNP} $P <$ 0.0001) for both schizophrenia and the cardiac trait were tested for local genetic correlation. Per schizophrenia-cardiac trait combination, a False Discovery Rate (FDR) correction for multiple testing was applied to adjust for the number of tested regions.

Functional annotation

For regions that showed FDR-corrected evidence of a schizophrenia-cardiac trait correlation, we performed functional annotation using Functional Mapping and Annotation of GWASs (FUMA).[26] We separately investigated regions with a positive or negative genetic correlation, because enrichment in positively versus negatively associated regions would have a different interpretation. For instance, enrichment in a negative region could suggest opposing underlying biological pathways. We created lists of 'positive' and 'negative' genes for each trait pair by looking up all protein coding genes that fell within the associated regions according to the National Center for Biotechnology Information (NCBI) reference data.[36] These lists were then annotated using the FUMA GENE2FUNC module, excluding the HLA region.[26] First, we assessed with which traits these genes had previously been found to associate in the GWAS catalogue. Second, we assessed biological processes underlying the associations through Gene Ontology (GO:0050896) gene set enrichment analysis, i.e. by assessing

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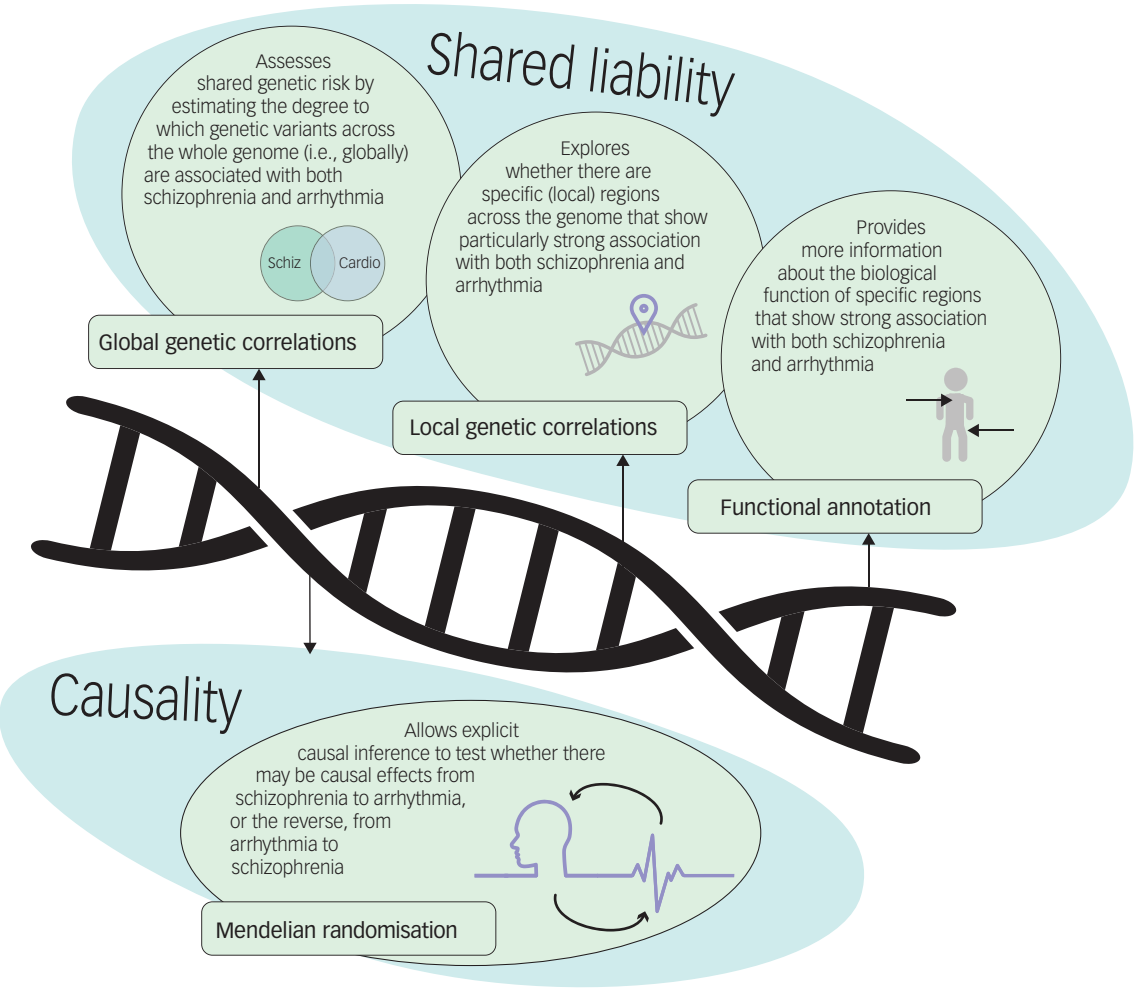

Fig. 1 Overview of the genetics-based methods that were applied to investigate the mechanisms of schizophrenia with arrhythmic disorders and ECG traits. First, we examined whether there are shared genetic risk factors between schizophrenia and arrhythmic disorders and ECG traits, by estimating global and local genetic correlations. For regions of the genome that show a correlation between schizophrenia and arrhythmia, we ran a range of functional annotation analyses to better understand the biological mechanisms involved. Subsequently, we applied bidirectional Mendelian randomisation to investigate causal associations between schizophrenia and cardiac function.

whether the genes were overrepresented in predefined gene sets. Finally, we assessed evidence for expression of these genes in the 30 available tissue types of the Genotype-Tissue Expression (GTEx) project (v8[37]) available on the FUMA platform. Specifically, we assessed whether genes in regions with a significant schizophrenia-cardiac trait association were differentially (more or less) expressed in a tissue, as compared to all the other tissues. Differential tissue expression can provide clues to the location of the biological processes driving the genetic association between schizophrenia and cardiac traits.[38] In the main results, we focus on enrichment in positively associated regions, because these showed stronger and more uniform enrichment patterns and have a more straightforward interpretation.

Causal inference with Mendelian randomisation

We applied Mendelian randomisation to assess evidence for causal effects of liability to schizophrenia on arrhythmic disorders and ECG traits, as well as of arrhythmic disorders and ECG traits on schizophrenia risk. For a Mendelian randomisation analysis to be valid, the genetic variants selected as instruments should (a) associate robustly and strongly with the exposure, (b) be independent of confounders and (c) not directly influence the outcome, except through their effect on the exposure.[39] If these assumptions are met, the causal effect of the exposure on the outcome can be estimated with inverse-variance weighted regression (IVW).[40] While IVW provides an indication of causality, it presumes that all assumptions are met, which is unlikely for complex traits. The most important source of potential bias is horizontal pleiotropy: SNPs affecting the outcome without going through the exposure. To verify results obtained from IVW, we applied five sensitivity methods. If a finding is consistent across these methods, it constitutes robust evidence for causality. Because of the inherently lower power of the sensitivity methods, some decrease in the strength of statistical evidence (but not the effect size) is expected even for a true causal effect.

The sensitivity methods we applied are: Weighted Median regression, which provides a consistent estimate of a causal effect, even when <50% of the weight of the instrument does not satisfy the Mendelian randomisation assumptions[41]; Weighted Mode regression, which can provide a consistent estimate of a causal effect if the most frequent SNP-effects are contributed by valid SNPs[42]; MR-Egger, which can explicitly test for horizontal pleiotropy by freely estimating an intercept (instead of fixing it at zero) that captures the average horizontally pleiotropic effect[43]; Mendelian randomisation pleiotropy residual sum and outlier (MR-PRESSO), which assesses horizontal pleiotropy (global test),

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Table 1 Overview of genome-wide association studies (GWASs) that were used to conduct genetics-based analytical methods

Phenotype	GWAS reference	Measurement	Sample size	h^2_{SNP}
Schizophrenia	Trubetskoy et al, 2022[20]	Cases were individuals diagnosed with a schizophrenia spectrum disorder, based on DSM-IV criteria.	53 386 cases 77 258 controls	0.21 (s.e. 0.007)
Atrial fibrillation	Roselli et al, 2018[33]	Cases were individuals diagnosed with paroxysmal or permanent atrial fibrillation, or with atrial flutter.	55 114 cases 482 295 controls	0.14 (s.e. 0.013)
Brugada syndrome	Barc et al, 2022[30]	Cases were individuals diagnosed with a type 1 Brugada electrocardiogram (ECG), defined as a coved type ST elevation at baseline (spontaneous) or after a drug challenge test, in one or more leads in the right precordial leads voltage 1 (V1) and/or voltage 2 (V2) in the standard position (fourth intercostal space) or in high positions (second or third intercostal spaces). The diagnoses were made by a cardiac electrophysiologist with expertise in Brugada syndrome.	2820 cases 10 001 controls	0.19 (s.e. 0.037)
Heart rate activity	Ramírez et al, 2018[35]	Automated heart rate measurements and ECG recordings from individuals who participated in the 'Cardio test' of the UK Biobank (UKB) study were analysed. Heart rate activity reflects heart rate measured in beats per minute during exercise (cycling).	66 811	0.15 (s.e. 0.011)
Heart rate recovery	Ramírez et al, 2018[35]	Automated heart rate measurements and ECG recordings from individuals who participated in the 'Cardio test' of the UKB study were analysed. Heart rate activity reflects heart rate measured in beats per minute 1 min post-exercise (cycling).	66 678	0.12 (s.e. 0.014)
Heart rate variability	Nolte et al, 2017[34]	The root mean square of the successive differences of inter beat intervals (RMSSD), was computed, which reflects heart rate variability.	26 523 to 46 952[a]	0.11 (s.e. 0.028)
PR interval	Ntalla et al, 2020[32]	The PR interval (in milliseconds) was determined based on ECG recordings and reflects conduction from the atria to ventricles, across specialised conduction tissues such as the atrioventricular node and the His-Purkinje system. Individuals were excluded in cases of: extreme PR interval values (320 ms), second/third degree heart block, AF on the ECG or a history of myocardial infarction or heart failure, Wolff–Parkinson–White syndrome, a pacemaker, receiving class I and class III antiarrhythmic medications, digoxin and pregnancy.	293 051	0.62[b] (s.e. 0.064)
QT interval	Young et al, 2022[31]	The QT interval (in milliseconds) was determined based on ECG recordings and represents the sum of ventricular depolarisation (QRS duration) and repolarisation (JT interval). Individuals were excluded in cases of: prevalent myocardial infarction or heart failure, pregnancy at the time of recruitment, implantation of a pacemaker or implantable cardiac defibrillator, QRS duration >120 ms, or right or left bundle branch block or atrial fibrillation on ECG.	252 977	0.17 (s.e. 0.034)
JT interval	Young et al, 2022[31]	The JT interval (in milliseconds) was determined based on ECG recordings and represents repolarisation at an organ level. Individuals were excluded in cases of: prevalent myocardial infarction or heart failure, pregnancy at the time of recruitment, implantation of a pacemaker or implantable cardiac defibrillator, QRS duration >120 ms, or right or left bundle branch block or atrial fibrillation on ECG.	252 977	0.16 (s.e. 0.031)
QRS duration	Young et al, 2022[31]	QRS duration (in milliseconds) was determined based on ECG recordings and represents ventricular depolarisation. Individuals were excluded in cases of: prevalent myocardial infarction or heart failure, pregnancy at the time of recruitment, implantation of a pacemaker or implantable cardiac defibrillator, QRS duration >120 ms, or right or left bundle branch block or AF on ECG.	252 977	0.12 (s.e. 0.014)

h^2_{SNP}, SNP-based heritability.
a. Only single nucleotide polymorphisms (SNPs) that were genome-wide significant ($P < 5E{-}08$) were analysed in the larger sample of 46 952 individuals.
b. Note that this SNP-based heritability estimate is considerably higher than what is reported in the original GWAS of Ntalla et al, 2020[32] due to a difference in the selection criteria for which SNPs to include for Linkage Disequilibrium Score Regression analysis within our own pipeline.

corrects for it by removing outliers and evaluates differences in the estimate of the causal effect before and after removal of outliers (distortion test)[44]; and Steiger filtering, which explicitly corrects for reverse causality by identifying and then excluding SNPs that explain a larger amount of variance in the outcome, compared to the exposure.[45] We also computed Cochran's Q to assess heterogeneity between SNP-estimates in each instrument, and for potentially causal findings we performed leave-one-out IVW and displayed all SNP-estimates in a funnel plot to assess (a)symmetry. To assess instrument strength, we computed the *F*-statistic ($F > 10$ is sufficiently strong). All Mendelian randomisation analyses were conducted in R (4.2.0), using the packages 'TwoSampleMR,' 'GSMR,' 'psych' and 'MR-PRESSO'.

Results

Global genetic correlations

Global genetic correlations, based on all SNPs included in the GWASs, as well as MAF-stratified genetic correlations, are presented in Supplementary Table 1 available at https://doi.org/10.1192/bjp.2024.165. Evidence for (modest) global genetic correlation ($r_g = 0.14$, 95% CIs = 0.06 to 0.21, $P = 4.0E{-}04$) was only present for schizophrenia and Brugada syndrome. When stratifying on MAF, there was some indication of stronger correlation for the lower compared with the higher MAF strata, but differences were minor.

Using Local Analysis of [co]Variant Association (LAVA), we found a picture of local correlations across the genome, both in the positive and negative direction (Fig. 2, Supplementary Table 2). After filtering on univariate heritability, between 105 and 264 regions per schizophrenia-cardiac trait combination were tested for local genetic correlation, resulting in between 20 and 60 nominally significantly associated regions per trait combination. Of particular interest are the local correlations that survived FDR-correction. For all trait combinations there were 4 (schizophrenia (SCZ)-atrial fibrillation (AF) and SCZ-heart rate variability (HRV)) to 33 (SCZ-QT) regions with significant signal after correction. For most trait pairs, there were both regions with positive and regions with negative correlation. To assess how these local correlations relate to the genome-wide significant loci of the original GWASs, we created Miami plots of the original GWAS SNP-estimates for each schizophrenia-cardiac trait pair and identified the SNPs in the local regions that showed significant correlation (Supplementary Figs. 1–10).

Functional annotation of shared genomic regions

To obtain a better understanding of the biological significance of the shared genomic regions, we performed functional annotation analysis, looking separately at genes in regions with positive or negative schizophrenia-cardiac trait associations.

The identified gene sets were found to be associated with many traits in the GWAS catalogue. Genes in regions with positive schizophrenia-QT and schizophrenia-JT associations were associated with auto-inflammatory and immune-related traits (Supplementary Fig. 11(a)). Genes in regions with negative schizophrenia-JT and schizophrenia-PR associations were mostly associated with metabolic traits (Supplementary Fig. 11(b)).

Enrichment in GO gene sets for biological processes was found mainly for genes in regions with a positive association between schizophrenia and Brugada syndrome (Supplementary Fig. 12(a) and Fig. 13). These genes were mostly related to viral response mechanisms and immune-related processes. We did not observe enrichment in the case of other trait combinations, with the exception of four terms for genes in regions that showed a negative association of schizophrenia with HR reactivity and QT duration (Supplementary Fig. 13). Including the HLA region yielded consistent results and additional enrichment in immune-related GO terms

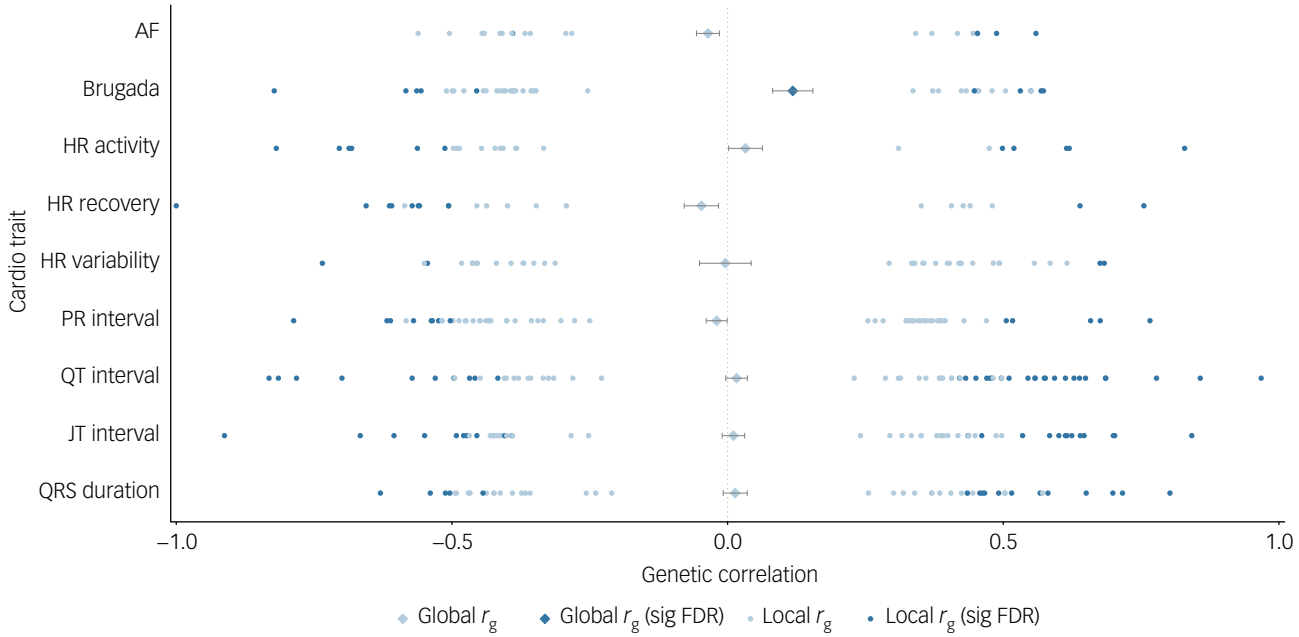

Fig. 2 Results of global and local genetic correlation analyses between schizophrenia and two arrhythmic disorders and seven ECG traits. The global genetic correlations, computed with linkage disequilibrium score regression analyses including all single nucleotide polymorphisms (SNPs) in the respective genome-wide association studies are shown as diamonds in the middle. Local significant genetic correlations for genomic regions computed with LAVA (local analysis of [co]variant association) are shown as dots, with each dot representing a region comprising a couple of thousand SNPs.

FDR, False Discovery Rate.

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for genes in positive schizophrenia-Brugada and schizophrenia-QT regions (results not shown).

Supplementary Fig. 12(b) shows differential expression across the 30 available tissue types of the Genotype-Tissue Expression (GTEx) project for positive trait pair regions (marginal $P < 0.05$). After FDR-correction, there was only one significant finding for the positive trait pair regions: genes in regions with positive associations between schizophrenia and QRS duration were upregulated (expressed at higher levels) in whole blood. This means that genes shared between schizophrenia and QRS duration are more expressed in whole blood as compared with other tissues, suggesting that a biological process within this tissue drives the association. Artery (aorta, coronary, tibial) and two brain regions were among the tissues showing marginal enrichment. For the negative trait pairs there was less differential expression, and none of the tissues survived correction for multiple testing (full results in Supplementary Fig. 14).

Causal effects between schizophrenia and arrhythmic disorders and ECG traits

Results of bidirectional Mendelian randomisation analyses between liability to schizophrenia and cardiac traits are shown in Fig. 3. There was strong evidence for a causal, increasing effect of liability to schizophrenia on Brugada syndrome risk (IVW OR = 1.15, 95% CIs = 1.03 to 1.28, $P = 0.009$), which was consistent in effect size across a range of sensitivity methods (for scatterplot, funnel plot and leave-one-out analyses, see Supplementary Figs. 15–20). The direction of causality was confirmed by Steiger. MR-Egger provided good evidence for causality (OR = 1.67, 95% CIs = 1.08 to 2.56, $P = 0.022$). While there was strong evidence for heterogeneity between the different SNP-effects (Cochran's Q, $P = 1.2E{-}04$; Supplementary Table 3), there was no indication for horizontal pleiotropy (Egger intercept = −0.03, $P = 0.104$). There was also evidence for a causal, increasing effect of liability to schizophrenia on heart rate during activity (IVW beta = 0.25, 95% CIs = 0.05 to 0.45, $P = 0.015$) consistent across sensitivity methods. Although there was weak evidence for horizontal pleiotropy (MR-Egger intercept = −0.05, 95% CIs = −0.10 to 0.00, $P = 0.073$), the MR-Egger slope still showed evidence for causality (beta = 0.97, 95% CIs = 0.23 to 1.71, $P = 0.011$). There was no evidence for causality for any other relationship.

To better understand the pathway through which schizophrenia may causally increase Brugada syndrome risk, we employed multivariable Mendelian randomisation to add each of the heart rate and

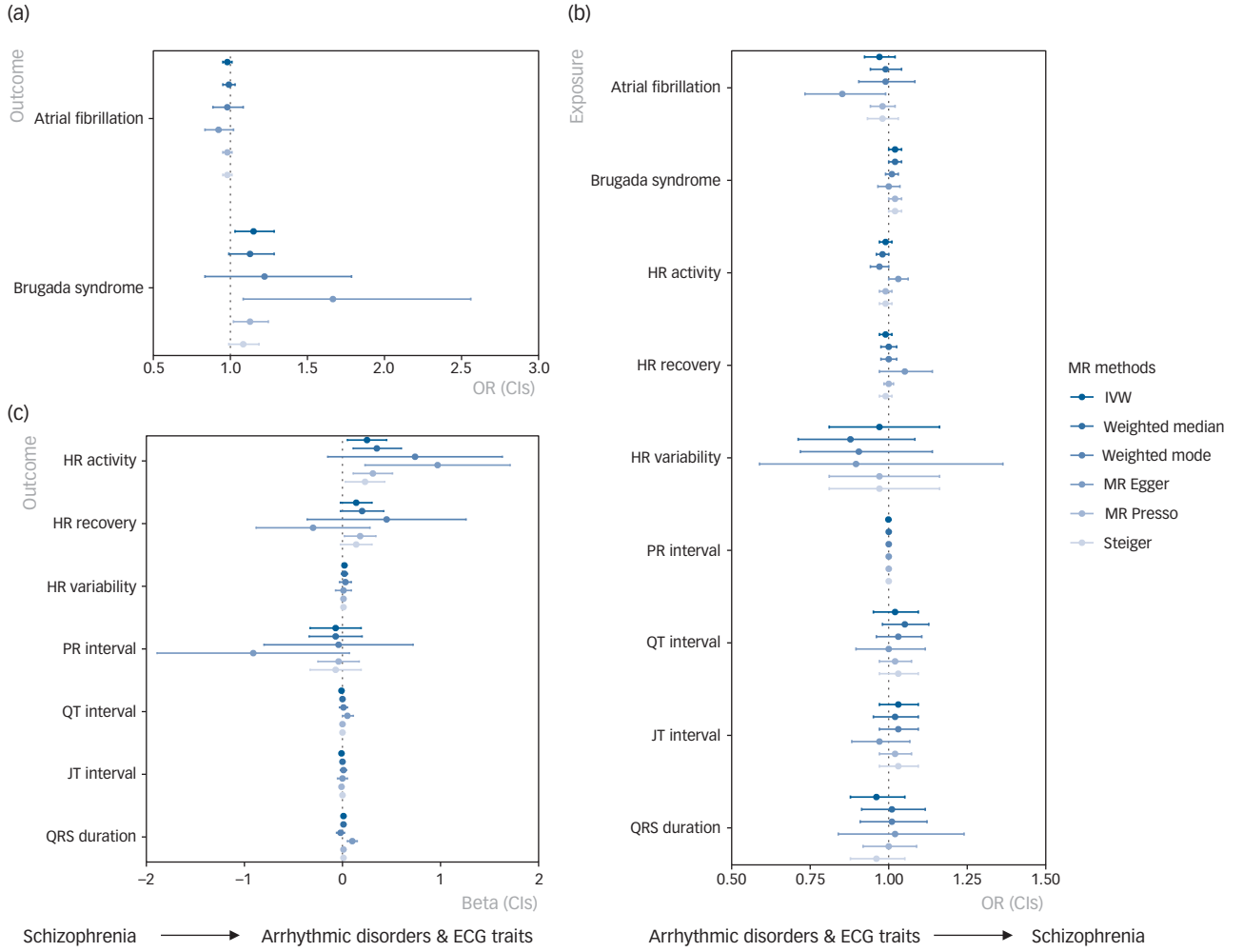

Fig. 3 Bidirectional Mendelian randomisation analyses from liability to schizophrenia to (a) arrhythmic disorders and (b) ECG traits and (c) vice versa, from arrhythmic disorders and ECG traits to schizophrenia risk.

Note that the inverse variance weighted (IVW) analysis is the main analytical method, and all other analyses should be seen as sensitivity methods to check whether any potential causal effect indicated by IVW holds (i.e. if there is a significant result for one of the sensitivity methods but not for the IVW, we would not consider that evidence for causality). MR-Egger slope indicates the estimated causal effect, while the MR-Egger intercept reflects horizontal pleiotropy (if the *P*-value for the intercept is significant, this indicates that there is horizontal pleiotropy present). The *I*-squared statistic, which assesses whether the NOME assumption was satisfied and an MR-Egger analysis can be considered reliable, ranged between acceptable to very good values (0.60 and 0.98); if *I*-squared was <0.90, Egger SIMEX (simulation extrapolation) was applied to correct for any potential bias. NOME, NO Measurement Error; OR, odds ratio; ECG, electrocardiogram.

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ECG traits. The main effect of liability to schizophrenia on Brugada syndrome stayed consistent (Supplementary Table 4), suggesting that these cardiac parameters do not drive the causal relationship.

Discussion

This study is the first to comprehensively investigate the relation of schizophrenia with arrhythmic disorders and ECG traits using advanced genetics-based methods. We found evidence for modest global genetic correlation between schizophrenia and Brugada syndrome, but no evidence for global genetic correlations between schizophrenia and eight other traits (atrial fibrillation, heart rate during activity and recovery, heart rate variability, PR interval, QT interval, JT interval and QRS duration). When considering specific regions across the genome, a pattern of widespread local genetic correlations, both negative and positive, emerged for all trait pairs. Functional annotation showed that the genes located in regions that correlated between schizophrenia and Brugada syndrome were mainly involved in immune-related processes and viral response mechanisms. Finally, Mendelian randomisation showed strong evidence for causal, increasing effects of liability to schizophrenia on Brugada syndrome and heart rate during physical activity.

The lack of evidence for (strong) global genetic correlation concurs with previous studies that found similarly low genetic correlations between schizophrenia and different cardiovascular and cardio-metabolic traits.[23,24] We did find significant correlations between schizophrenia and all cardiac traits (both positive and negative) for specific genomic regions, indicating that a global correlation overlooks important local processes by averaging out opposing effects. Functional annotation showed that the regions that correlated significantly were largely enriched in genes related to the immune system, suggesting that schizophrenia and arrhythmia share common immunological pathways. These findings are in line with an increasing body of literature suggesting a shared immunological aetiology between cardio-metabolic traits and serious mental illness, such as major depressive disorder.[46] The strongest evidence was found for regions correlating positively between schizophrenia and Brugada syndrome, which were particularly enriched for viral response pathways. This concurs with the theory that a viral infection in mothers during pregnancy increases the risk of schizophrenia in offspring.[47,48] While there is increasing evidence that systemically released autoantibodies and cytokines can have arrhythmogenic effects,[49] and one study showed that myocardial autoantibodies can be detected in individuals with Brugada syndrome,[50] the role of the immune system in the aetiology of Brugada is largely unclear and should be studied further.[51]

Another striking finding was the causal, increasing effect of liability to schizophrenia on Brugada syndrome. The pathophysiology of Brugada syndrome involves dysfunction of ion, primarily sodium, channels.[16] Interestingly, we previously showed evidence for a causal effect of liability to schizophrenia on early repolarisation, an ECG pattern which is, like Brugada, linked to increased risk of sudden cardiac death and suspected to involve ion channel dysfunction.[23] These findings indicate that schizophrenia increases the risk of such arrhythmic disorders, but the exact biological pathway remains unclear. It could be that when there is already a high liability for Brugada syndrome, an ongoing psychotic state acts as a catalyst.[52] Some people start off with normal ECG readings after which factors such as fever or metabolic disorders 'unmask' a Brugada pattern, and schizophrenia may be another such factor.[15] Dysfunction of the autonomic nervous system might play a role herein, as it is involved in schizophrenia and possibly also Brugada syndrome.[27] To assess if the effects we found may be because of antipsychotic medication use, we conducted a multivariable Mendelian randomisation analysis including QT interval (which is impacted by antipsychotic medication), and found no evidence that the effect of schizophrenia on Brugada was mediated by changes in QT. Yet, it should be acknowledged that antipsychotic medication has also been implicated in sodium channel blockade and may thus affect depolarisation, a central mechanism in Brugada syndrome.[53] Importantly, our findings suggest that systematic screening for Brugada syndrome among people with schizophrenia is warranted and should be prioritised more. Since some people with Brugada syndrome are asymptomatic, and the preventive treatment of placing an Implantable Cardioverter-Defibrillator (ICD) is invasive,[54] further research should focus on identifying individuals with Brugada syndrome who are at increased risk of sudden cardiac death. This is particularly important for those with schizophrenia, as they are already at increased risk for cardiovascular disease and mortality, even without Brugada syndrome.[55] For screening, the fact that worsening of mental illness is associated with (further) weakening of the parasympathetic system and the fact that commonly used psychotropic drugs have anticholinergic effects, both of which could mask ECG-features of Brugada, should be taken into account and necessitate careful monitoring. Clinicians that see these people should be made aware of these particular complexities, potentially through specialised educational materials.

Limitations

The current study uniquely used advanced methods and large, powerful genetic samples to study relations between (rare) complex disorders. The novel biological pathways that we report can lead to important unexplored avenues of research. Besides these important strengths, there are also limitations to consider. The serious nature of schizophrenia means that those who suffer most may not have been able to participate in research, causing selection bias, which may have led to an underestimation of the effects.[56] In addition, for cardiac diseases related to dysfunctional ion channels, (very) rare alleles play a significant role which we were not able to capture in this study. For Mendelian randomisation in particular, assortative mating, dynastic effects and residual population stratification may have caused bias, for which we were not able to correct without the availability of large family samples.[57] Another limitation is that well-powered data-sets for ancestries other than European were not available, limiting generalisability. Such bias is widespread in medical and genetics research.

In summarising, we report limited global genetic overlap, but widespread local genetic correlations of schizophrenia with arrhythmic disorders and ECG traits. We highlighted specific biological mechanisms that may be responsible for local shared aetiology, with immunological and viral response processes emerging as important candidates for follow-up research. There was highly robust evidence for a causal effect of liability to schizophrenia on Brugada syndrome, building on recent genetically informed studies that indicated effects of schizophrenia on heart failure as well as functional measures such as decreased cardiac volumes.[23,58] Overall, our findings emphasise that cardiac monitoring needs to be performed more frequently among individuals with schizophrenia than is currently done, and that treatment of both psychosis and cardiac abnormalities should be started promptly in order to decrease mortality in this vulnerable population.

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Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2024.165

Data availability

No new data were collected or created for the current study, since all analyses were based on summary-level data of existing GWASs and biobank studies. The analysis plans of the current study were pre-registered at OSF (https://osf.io/fe4ms).

Author contributions

J.L.T., C.R.B., R.T. and K.J.H.V. conceived of the initial research idea and analysis plan. J.L.T. conducted the Mendelian randomisation analyses, A.B.T. and D.J.M. conducted the genetic correlation analyses, and J. Berg and J.P. conducted the functional follow-up analyses. J.L.T. wrote and finalised the manuscript, with important contributions from all the other authors (A.B.T., D.J.M., R.T., R.R.V., D.D., J.M.V., J. Berg., J. Barc., J.P., C.R.B., K.J.H.V.). A.B.T., R.R.V., J. Berg and J.P. created the main figures in the paper, crucial to clarify the aims and results of the study. All of the authors read and reviewed the final version of the manuscript.

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Declaration of interest

None.

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