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Polygenic risk for schizophrenia and associated brain structural changes: A systematic review

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ABSTRACT

Background: Genome wide association studies (GWAS) of schizophrenia allow the generation of Polygenic Risk Scores (PRS). PRS can be used to determine the contribution to altered brain structures in this disorder, which have been well described. However, findings from studies using PRS to predict brain structural changes in schizophrenia have been inconsistent. We therefore performed a systematic review to determine the association between schizophrenia PRS and brain structure.

Methods: Following PRISMA systematic review guidelines, databases were searched for literature using key search terms. Inclusion criteria for the discovery sample required case-control schizophrenia GWAS summary statistics from European populations. The target sample was required to be of European ancestry, and have brain structure and genotype information. Quality assessment of the publications was conducted using the Mixed Methods Appraisal Tool for quantitative non-randomised studies.

Main findings: A total of seven studies were found to be eligible for review. Five studies found no significant association and two studies found a significant association of schizophrenia PRS with total brain, reduced white matter volume, and globus pallidus volume. However, the latter studies were conducted using smaller discovery ($n_{cases} = 9394$ $n_{controls} = 12{,}462$) and target samples compared to the studies with substantially larger discovery ($n_{cases} = 33{,}636$ $n_{controls} = 43{,}008$) and target samples where no association was observed. Taken together, the results suggest that schizophrenia PRS are not significantly associated with brain structural changes in this disorder.

Conclusions: The lack of significant association between schizophrenia PRS and brain structural changes may indicate that intermediate phenotypes other than brain structure should be the focus of future work. Alternatively, however, the lack of association found here may point to limitations of the current evidence-base, and so point to the need for future better powered studies.

Contents

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1. Introduction

Schizophrenia is a common, highly heritable disorder [1,2]. Although recent genome wide association studies (GWAS) have identified over 100 risk loci, each associated variant has a small effect on risk [3]. Post-GWAS measures such as polygenic risk score (PRS) are able to address the polygenic architecture of schizophrenia and quantify the common risk allele burden carried by individuals for a given disorder [4]. PRS has been successfully used to show that schizophrenia and bipolar disorder have substantial genetic overlap [4,5], as do personality traits and mood disorders [6], and depression and anxiety disorders [7,8].

In schizophrenia, altered brain structures are well described [9]. A meta-analysis of 58 studies of schizophrenia found evidence for enlarged lateral ventricles and globus pallidus, and reduced volume of amygdala, hippocampus, thalamus and caudate in this disorder [9]. The ENIGMA brain imaging consortium reported enlarged lateral ventricles and globus pallidus, and reduced amygdala, hippocampus, thalamus and accumbens in 2028 schizophrenia patients [10]. Brain structural changes have also been observed in unaffected first degree relatives of schizophrenia patients, suggesting a genetic component to these alterations [11,12]. Indeed, measures for partitioning heritability in a study on 1750 healthy individuals showed significantly enriched contribution of schizophrenia-associated genetic variants with eight brain structure traits [13]. In contrast, however, a study using linkage disequilibrium (LD) score regression to assess genetic correlations between schizophrenia and eight volumetric brain measures found no significant associations [14].

It has been suggested that PRS may be useful in determining the relationship between schizophrenia and intermediate phenotypes, such as brain structural alterations [15–17]. However, studies on the association between schizophrenia PRS and brain structural changes in this disorder have been contradictory [14,18]. We therefore undertook a systematic review of studies of genetic risk scoring for schizophrenia and brain structural changes to determine i) the association between PRS and brain structural changes in schizophrenia, and ii) what factors may contribute to these findings.

2. Methods

2.1. Database search

The review was conducted in line with the PRISMA systematic review guidelines [19]. An electronic literature search was conducted using PubMed, Scopus, EMBASE, PsycINFO, PubPsych, ISI Web of Science and WorldCat databases. The search terms included “schizophrenia”, “polygenic risk score”, “genetic risk score”, “endophenotypes” and “brain imaging” in various combinations as needed. No search restrictions were added. The review was registered on PROSPERO (ID: CRD42018084060).

2.2. Inclusion and exclusion criteria

Studies had to meet inclusion criteria for both the discovery and target sample. The discovery sample was required to comprise GWAS summary statistics from a case-control study design for schizophrenia for European populations, as there is uncertainty to how well PRS is transferred across other populations [20]. The target sample was required to 1) be of European ancestry, 2) have information on brain structure (subcortical volumes/grey and white matter volumes/total matter volumes) from magnetic resonance imaging (MRI), and 3) have genotype information from a genome-wide array. The target sample included either healthy controls from the general population, or a case-control combination. Studies were excluded if there were functional brain measures, or if PRS was performed on a subset of SNPs rather than genome wide SNPs.

2.3. Quality assessment

Quality assessment of publications found was conducted using the Mixed Methods Appraisal Tool for quantitative non-randomised studies (MMAT, http://mixedmethodsappraisaltoolpublic.pbworks.com/, Supplementary Table 1) [21]. Sample relevance, representation of the target population, appropriate measurements used, the risk of bias, and statistical analysis conducted were addressed by this tool for each of the studies included in this review. While there is no standard assessment tool for individual articles included in a PRS systematic review, we employed a checklist of criteria that are relevant for these studies (Supplementary Table 2). This ensured that all studies included in the review provided information on sample size, target cohort description, brain structural measures, genotyping platform and strength of MRI.

3. Results

3.1. Literature search

Study selection was undertaken by the first author. The initial literature search yielded a total of 1069 articles after removal of duplicates. A review of abstracts based on inclusion and exclusion criteria resulted in 64 full-text articles. This was repeated by a second reviewer and discrepancies were discussed among authors. Review of the full-text articles yielded seven final studies that were eligible for review (Fig. 1). Table 1 and Supplementary Table 3 provide a summary of each included article.

3.2. Quality assessment

Quality assessment within and between studies was validated using two separate checklists (Supplementary Tables 1, and 2). Results of all studies included in the review were of high quality. As most studies did not report standardised effect sizes, we were unable to conduct a meta-analysis and we used a narrative approach to summarize results.

3.3. Studies examining SCZ-PRS association with white matter, grey matter and total brain volume

Three out of four studies found no significant association with grey matter, white matter or total brain volume and schizophrenia PRS (SCZ-PRS) [22–24]. The study reporting a significant finding showed SCZ-PRS to be negatively associated with total brain volume (strongest $P_T < 0.006$, $p = 1.6 \times 10^{-4}$) and reduced white matter volume

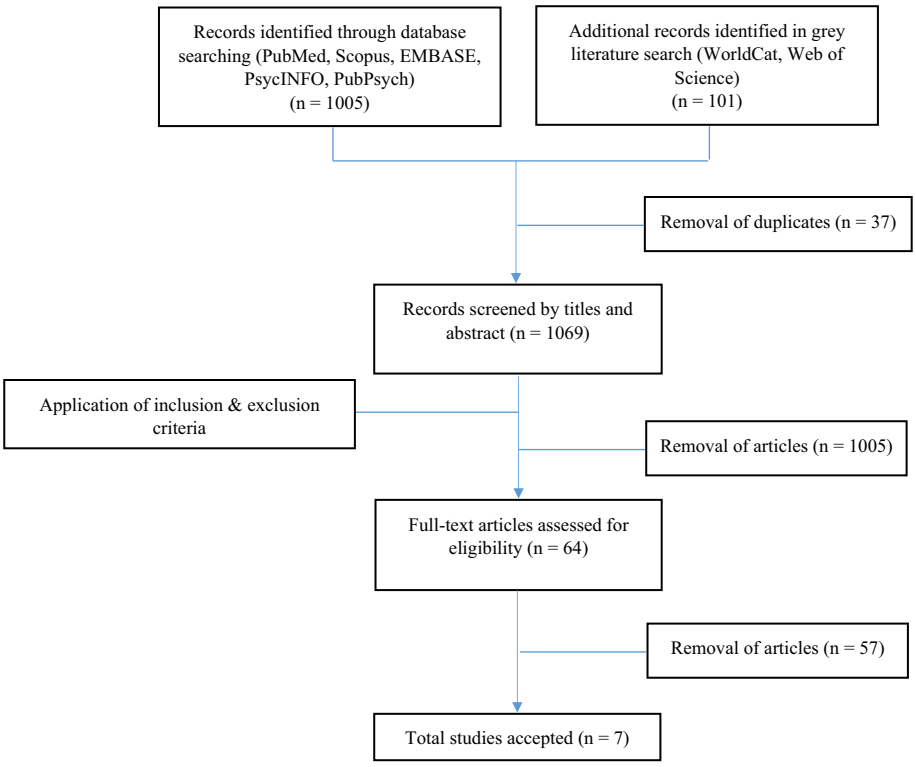

Fig. 1. Summary of methodology.

(strongest $P_T < 0.006$, $p = 8.6 \times 10^{-5}$), with approximately 5% of the variance in total brain and white matter volume explained by schizophrenia associated SNPs [17]. This study, and one of the studies with non-significant findings used smaller discovery ($n_{cases} = 8690$ $n_{controls} = 11{,}831$) and target samples ($n_{cases} = 152$ $n_{controls} = 142$ [17]; $n = 122$ [22]), compared to two of the studies with non-significant findings that had larger discovery ($n_{cases} = 33{,}636$ $n_{controls} = 43{,}008$) and target ($n = 978$, $n = 1470$) samples [23,24].

3.4. Studies examining SCZ-PRS association with specific brain regions

Three of the four studies assessing specific brain regions showed no significant association with SCZ-PRS. There was weak evidence of association with SCZ-PRS and thalamus volume in 978 subjects from the UK Biobank Imaging Study (strongest $P_T < 0.1$, $p = 0.03$ uncorrected) [23], but this was not significant after correction for multiple testing. A second study found a non-significant association between SCZ-PRS and

Table 1
A summary of the design and main findings for each study included in the systematic review.

Reference	Discovery sample			Target sample		Relevant findings
	Dataset(s)	Cases (N=)	Controls (N=)	Description	Brain regions analysed	
Terwisscha van Scheltinga et al., 2013	SCZ GWAS Consortium	8690	11,831	152 patients with SCZ and 142 healthy controls	GM, WM, TBM	• SCZ PRS was significantly associated with TB volume and reduced WM volume regardless of disease state • SCZ associated SNPs explained appx 5% of the variance in TB and WM volume
Papiol et al., 2014	SCZ GWAS Consortium	9394	12,462	122 healthy subjects	GM, WM, TBM	• SCZ PRS was not associated with any of the brain dimensions in healthy participants
Van der Auwera et al., 2015	SCZ Working Group of the PGC	33,636	43,008	1470 healthy subjects	GM, WM, TBM	• No association was observed between SCZ PRS and brain volume
Caseras et al., 2015	SCZ GWAS Consortium	9394	12,462	319 healthy subjects	Tha, Hip, Amy, GP, Cau, LVV	• SCZ PRS was significantly associated with GP volume ($p = 0.004$)
Reus et al., 2017	SCZ Working Group of the PGC	33,636	43,008	978 subjects from UK Biobank Imaging study	GM, WM, Cau, Hip, Pal, Tha, Amy, Acc, Put	• No significant associations between SCZ PRS and total GM and WM • Modest negative association between SCZ PRS and thalamus volume ($p = 0.03$, uncorrected)
Ranlund et al., 2017	SCZ Working Group of the PGC	31,658	42,022	703 patients with SCZ, 822 unaffected relatives, 2333 controls	LVV	• SCZ PRS was modestly associated with LVV, and explained 0.4% of the variance ($p = 0.063$)
Franke et al., 2016	SCZ Working Group of the PGC	33,636	43,008	11,840 subjects from the ENIGMA Consortium	Amy, Cau, Hip, Acc, Pal, Put, Tha, ICV	• No significant association was observed

SCZ, schizophrenia; GWAS, genome wide association study; Tha, thalamus; Hip, hippocampus; Amy, amygdala; Cau, caudate nucleus; GP, globus pallidus; LVV, lateral ventricular volume; Acc, nucleus accumbens; Pal, pallidum; Put, putamen; ICV, intracranial volume; GM, grey matter; WM, white matter; TBM, total brain matter; PRS, polygenic risk score.

lateral ventricular volume (strongest $P_T < 0.1$, $p = 0.063$) [25]. No association between SCZ-PRS and brain structural changes was observed in the study with the largest discovery ($n_{cases} = 33{,}636$ $n_{controls} = 43{,}008$) and target samples ($n = 11{,}840$) [14] (Table 1). SCZ-PRS was found to be significantly associated with globus pallidus volume in a sample of 319 healthy subjects (strongest $P_T < 0.001$, $p = 0.004$; Table 1) [18]. However, this study used a smaller discovery sample ($n_{cases} = 9394$ $n_{controls} = 12{,}462$) compared to the previous studies ($n_{cases} = 33{,}636$ $n_{controls} = 43{,}008$).

3.5. Effects of PRS by diagnosis

Five studies assessed the relationship between SCZ-PRS and brain structural changes in the general population [14,18,22–24]. Of these, only one study found a significant association between SCZ-PRS and globus pallidus volume, but used a smaller discovery sample [18]. Of the two studies that looked separately at cases and controls, one found a significant association with total brain volume [17]. However, this was regardless of disease state (i.e. effects were similar in patients and controls), and a smaller discovery sample was used. In the second study, individuals with schizophrenia had the highest polygenic score compared to unaffected relatives and controls [25]. However, the entire sample was used to test for an association with lateral ventricular volume, and no significant association was observed.

3.6. Study and sample characteristics

We reviewed possible factors that may have influenced the outcome of the results (Table 2). Of the seven studies, socioeconomic status and childhood experiences were controlled for in four and three studies respectively. Imputation was performed in four of seven studies, which may also affect the outcome of the results. Additional factors that were not accounted for in one or two of the studies include drug or alcohol use, history of head trauma, and education status.

4. Discussion

This is the first paper to systematically review the association between polygenic risk for schizophrenia and brain structural changes. Overall, the results presented in this systematic review suggest that SCZ-PRS is not significantly associated with brain structural changes. Two studies showed a significant association, but this was preliminary work with smaller discovery [17,18]. Larger sample sizes equates to increased study power, which maximises the likelihood that a significant finding reflects a true effect [26]. The lack of significant association noted here may suggest that future work should rather focus on intermediate phenotypes other than altered brain structure. However, the lack of association may also reflect a number of methodological issues.

First, demographic, physiological and environmental confounders affecting the target sample may have influenced findings [27]. Demographic factors that have been linked to brain functional and structural changes include increased age [28], education [29], and socio-economic status [30]. Physiological factors include a history of head trauma [31], medication [32–34], and disease duration. Environmental factors include drug or alcohol use [35,36] and childhood experiences [37,38]. Future work may benefit from including such variables in the analysis.

Table 2
Possible factors contributing to study findings.

	Variable	Number of studies with this information
Demographic	Age (mean yrs)	7/7
	Education	5/7
	Socio-Economic status	4/7
	Gender	7/7
Physiological	History of head trauma	6/7
	Medication	1/2 (NA, 5/5)
	Disease duration	1/2 (NA, 5/5)
Environmental	Childhood experiences	3/7
	Drug or alcohol use	5/7
Genotyping	Imputation performed	4/7
Imaging	Quality control	7/7

yrs, years; NA, not applicable.

Second, genotyping array platforms differed across each study and between the target and discovery samples within each study. Chip coverage may affect an association of PRS with outcomes, particularly if the target sample size is small. Imputation reduces the variability and differences in coverage and power across chips [39], facilitates meta-analysis of studies genotyped on different platforms, and is used for fine-mapping efforts [40]. Recent studies have suggested that pre-phasing data (estimating haplotypes for each individual) improves imputation accuracy [40,41]. Furthermore, imputation is improved when using the most recent reference panel available. Three studies did not use imputed datasets in the PRS analysis, which may have contributed to the findings. Consideration should be taken to select the array and imputation strategy most likely to confer maximum accuracy, coverage, and power.

A third set of confounders are those related to MRI imaging. MRI is not a direct measure of brain structure, but rather a physical-chemical measure dependent on signals related to the density of protons within tissues and their magnetic properties [42]. External factors, including drug and alcohol use, smoking, exercise, pain and hydration have been shown to influence MRI signals [43–46]. Further, a simple factor such as head motion during a scan may lead to contrasting results [42,47]. The use of different MR scanners can also contribute to confounding. Images, data acquisition and data analysis were different across studies reviewed here, and caution in the interpretation of these results is therefore warranted.

Additional key limitations of PRS studies should be emphasized. First, PRS accounts for only a small proportion of total phenotypic variance [23]. PRS predictive accuracy may be improved by enlarging the discovery cohort. Second, the variance explained by PRS is limited insofar as PRS does not capture Copy Number Variation or rare SNP contributions to variance [48,49]. Third, the proportion of variance explained by PRS may be biased by recruitment of cases and controls in proportions that do not represent that of the general population [14]. Fourth, an additive model of variant effects is assumed in PRS, which disregards the potentially more complex genetic interactions at play and may not provide proportionate weight to biologically relevant genes [27]. Furthermore, a greater understanding of the genetic similarities and differences between brain structure and schizophrenia might be found by looking at gene x environment interactions, epigenetic influences, and systems biology networks and pathways.

PRS depends on a preserved effect directionality among shared variants, which could overlook scenarios of genetic overlap with mixed directions. Other approaches, such as partitioning heritability, SNP Effect Concordance Analysis (SECA), LD score regression (LDSR) and conditional false discovery rate (cFDR) may provide additional insight on the genetic relationship between schizophrenia and brain structure [13,14,27]. A recent study using cFDR observed polygenic overlap between schizophrenia and hippocampal, putamen and intracranial volumes [50]. In addition, partitioning heritability has found associations with schizophrenia genetic risk and intracranial volume under varying SNP selection conditions [13]. However, LDSR found no significant genetic correlations between schizophrenia and eight brain volumes [14]. Future work using these various genomic approaches in conjunction with PRS in large sample sizes would add value to the understanding of the complex relationship between schizophrenia and brain structure.

The inclusion of only seven studies in this review provides limited statistical power. It may be valuable to conduct PRS on various subphenotypes of schizophrenia. It has been suggested that genetic liability can be present with regard to certain symptom domains, rather than for a specific syndrome of symptoms [51]. A study performed PRS on five

continuous dimensions of schizophrenia: positive, negative, disorganisation, mania and depression. While no difference was observed in variance explained, it would be interesting to determine associations of these PRS scores with brain structure. Also, including additional variables that could affect the association between SCZ-PRS and brain structure may be a valuable exercise. For example, a study observed that cannabis use in early adolescents moderates the association between genetic risk for schizophrenia and cortical maturation among male individuals [52]. Additional studies such as these may elucidate the polygenic association between schizophrenia and brain structure.

In order to maintain uniformity in the review process, studies were excluded if PRS was performed on a subset of SNPs rather than genome-wide SNPs. However, it may be possible that an association would be observed if pre-selected SNPs are used for the PRS calculation. A recent study generated biologically informed genetic scores based on the 108 genome-wide significant SNPs found in the most recent schizophrenia GWAS [3], hypothesizing that this might be more informative than genome-wide scores [53]. Nominal significance was observed for a cluster spanning the amygdala and parahippocampus areas, although there was little convincing evidence for additional associations.

5. Conclusions

Bearing in mind these limitations, the lack of a significant association between SCZ-PRS and brain structural alterations in this disorder found here, is noteworthy. It may be that PRS affects a range of intermediate phenotypes other than brain structure. Alternatively, this negative finding may indicate that given the many confounders in this area of research, larger studies addressing these confounders are needed. Future studies should also embrace additional techniques such as LDSR, SECA, cFDR and advanced imaging techniques to complement work on PRS.

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Declaration of interest

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