Schizophrenia Research 212 (2019) 225–228

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Effects of a neurodevelopmental genes based polygenic risk score for schizophrenia and single gene variants on brain structure in non-clinical subjects: A preliminary report

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ARTICLE INFO

Article history:
Received 12 December 2018
Received in revised form
27 May 2019
Accepted 30 July 2019
Available online 6 August 2019

Keywords:
Schizophrenia
Voxel-based morphometry
Cortical thickness
Gyrification
Polygenic risk score
Neurodevelopment

ABSTRACT

We tested whether a polygenic risk score integrating the effects of genes affecting neurodevelopment is associated to brain structural variation in healthy subjects.

We acquired magnetic resonance imaging and genetic data of 167 healthy adults and computed a neurodevelopmental polygenic risk score (nPRS). We correlated the nPRS with local gyrification, cortical thickness and grey matter density and explored effects of single nucleotide polymorphisms included in the score.

We did not find significant correlations of this nPRS with either measure. Individuals with the risk allele at rs11139497 show increases in cortical thickness ($p < 0.05$, FWE corrected) of the left superior temporal gyrus.

1. Introduction

Schizophrenia is a severe psychiatric disorder with an adolescent or early adult age onset (Kessler et al., 2007; Takahashi et al., 2000). Heritability estimates for schizophrenia range from 65 to 80% (Hilker et al., 2018; Wray and Gottesman, 2012). The impact of genetic factors on brain structure in schizophrenia has repeatedly been shown (Brans et al., 2008; Cooper et al., 2014).

Polygenic risk scores (PRS) are based on the association of multiple common genomic variations with their respective increases in the probability of expressing a phenotype. They represent the cumulative genetic risk associated with common variation. A large-scale genome-wide association study (GWAS) has identified 128 common single nucleotide polymorphisms (SNPs) to be associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). These results were even extended with associations for 179 SNPs in 145 loci (Pardinas et al., 2018). Studies have tried to associate this cumulative SNP-related risk to brain structure. These studies have not provided conclusive evidence (Liu et al., 2016; Reus et al., 2017; Van der Auwera et al., 2015).

One reason for the lack of associations might be that overall PRS scores integrate the risk not only across multiple risk genes, but also effects on different biological pathways. This “biologically informed” approach has so far not demonstrated significant associations between PRS and brain structure (Van der Auwera et al., 2017) when only applying a voxel-based approach. Nevertheless, the neurodevelopmental pathway seems a plausible target for examination as the involved genes relate to early effects, setting a trajectory that may affect the entire lifespan. There is abundant research showing neurodevelopmental aspects to be most prominent to schizophrenia (de Haan and Bakker, 2004; Rapoport et al., 2012).

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https://doi.org/10.1016/j.schres.2019.07.061
0920-9964/

We tested whether a pathway-specific risk score, integrating those variants related to neurodevelopment, would be associated with structural variation in areas linked to schizophrenia. We used cortical thickness and gyrification as well as grey matter volume (for comparison with previous VBM studies) to test this hypothesis.

To further deconstruct the impact of the selected SNPs upon the nPRS, we additionally analysed each SNP individually.

2. Methods

We included 167 healthy subjects (87 females, 80 males, mean age 29.97 years at recruitment). Subjects underwent structural T1 MRI using an MPRAGE-sequence and a blood sample of all subjects was attained.

DNA extraction and genome-wide genotyping were conducted using the high-throughput genotyping platform at the Department of Genomics at the Life and Brain Center at the University of Bonn, Germany. DNA was extracted from whole venous blood samples and all individuals were genome-wide genotyped using the Illumina's Infinium PsychArray.

Quality control and imputation was performed according to standards of the PGC (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) as described in the respective Supplementary materials.

The regions included in the neurodevelopmental PRS (nPRS) were centred around the SNPs listed below and thus included the following loci: FXR1, SATB2, PODXL, BCL11B, TLE1, TLE3 and FAM5b. We determined a neurodevelopmental polygenic risk score (nPRS) for our subjects using the publicly available LD-clumped PGC data for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) with 35,476 cases and 46,839 controls by multiplying the natural logarithms of the odds ratio for schizophrenia of each polymorphism by the imputation probability for the risk allele in each individual. The attained values were summed over each subject resulting in an individual nPRS-value for further analysis. We used a p-value threshold of $p < 0.05$ as cut-off, thus including 202 SNPs. In an additional nPRS-analysis, we applied a stricter $p < 10^{-6}$ threshold thus limiting the number of included SNPs to the 8 SNPs discussed below. nPRS-analysis included all 167 subjects.

The genotype for the SNPs chr3_180594593_I (closest gene FXR1), rs9841616 (FXR1), rs6704641 (SATB2), rs7801375 (PODXL), rs2693698 (BCL11B), rs11139497 (TLE1), rs12148337 (TLE3) and rs6670165 (FAM5b), all of which were reported to influence the odds ratio for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), was retrieved from the genome-wide dataset for PRS analysis.

Data for chr3_180594593_I (FXR1) genotype was unavailable for 11 subjects. For rs9841616 (FXR1) and rs11139497 (TLE1), one result each was unattainable. These were subsequently excluded from morphometric analysis of the specific SNPs.

We used the CAT12 toolbox (Computational Anatomy Toolbox 12; Christian Gaser, Structural Brain Mapping Group, Jena University Hospital, Jena, Germany; http://dbm.neuro.uni-jena.de/cat/), implemented in SPM12 software (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). We used default settings (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) unless stated otherwise.

In the present study, we use a parallel approach by analysing surface-based measures (cortical thickness and gyrification) as well as grey matter volume.

We performed a cortical thickness analysis using the surface estimation pipeline in CAT12. This uses a projection-based thickness approach, extracting central surface maps and cortical thickness estimates (Dahnke et al., 2013). Gyrification maps of both hemispheres were estimated using the absolute mean curvature approach (Luders et al., 2006).

Using modulated normalised grey matter (GM) maps, we tested the hypothesis of regional grey matter volume (GMV) differences. We used an 8 mm FWHM smoothing kernel for VBM data.

The statistical analysis to test correlation between nPRS and surface-based measures included age at recruitment and sex as confounding variables, while grey matter volume analysis additionally included correction for Total intracranial volume (TIV) to correct for head size and volume. In both cases, we applied a peak-level threshold of $p < 0.05$ with family-wise error (FWE) correction. Exploratory analyses were performed in cases of negative findings at $p < 0.1$ (peak level) with FWE. We used an absolute threshold of 0.1 for the analysis.

Additionally, we created a general linear model for each SNP included in the nPRS. Carriers and non-carriers of the respective risk allele were grouped and tested via a two-sample t-test. We applied a $p < 0.05$ (FWE) threshold. Additionally, we report on trends ($p < 0.1$, FWE).

3. Results

Analysis for a nPRS (both $p < 0.05$ and $p < 10^{-6}$ GWAS thresholds) yielded no statistically significant results in the VBM or SBM paradigm. Exploratory analysis ($p < 0.1$ FWE) did not show trend level correlations.

When analysing the dataset on an individual SNP-level, carriers of the risk allele rs11139497 (TLE1) showed significantly ($p < 0.05$ FWE) elevated cortical thickness in the left upper temporal gyrus (see Fig. 1). Analysis of the other SNPs included in the nPRS did not

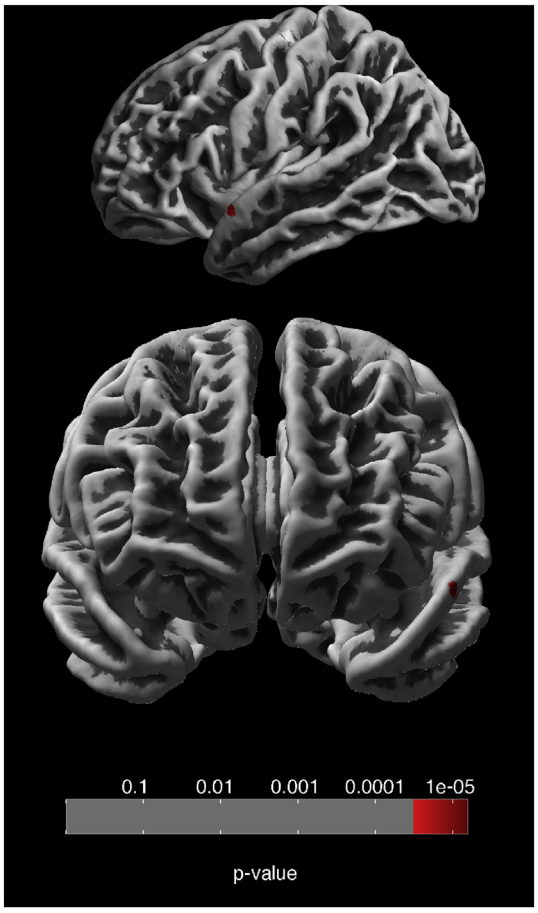

Fig. 1. Increased cortical thickness in the left superior temporal gyrus in carriers of the A-allele in rs11139497 is highlighted in red colour ($p < 0.05$ FWE-corrected). Results are projected on a central surface. Score indicates uncorrected p-value. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Summary of cortical thickness and gyrification results of individual SNP analyses. OR = odds ratio; CI = Confidence interval; FWE = Family wise error.

	Cortical thickness			Gyrification	
SNP	rs11139497	rs12148337	rs6704641	rs12148337	rs9841616
Closest gene	TLE1	TLE3	SATb2	TLE3	FXR1
Wild allele	T	C	A	C	T
Risk allele	A	T	G	T	A
OR for Sz (95% CI)	1.069 (1.045–1.093)	1.060 (1.038–1.081)	1.081 (1.053–1.110)	1.060 (1.038–1.081)	0.925 (0.900–0.951)
Effect in risk carriers	Increase	Decrease	Decrease	Increase	Increase
Max. intensity vertex (mm)	−56 7 −12	−38 12 −4	8 −43 7	−49 −28 −29	43 −33 12
p-Value (FWE corr.)	0.031	0.099	0.056	0.062	0.081
Cluster size k	26	3	1	26	9
Effect size D at max	0.73	0.66	0.69	0.73	0.721
Pearson's R at max	0.347	0.319	0.332	0.347	0.342

find significant changes. However, in exploratory analysis, carriers of the risk allele at rs12148337 (TLE3) displayed a trend ($p < 0.1$ FWE) of reduced cortical thickness in the left anterior insular cortex as well as a trend of increased gyrification in the left inferior temporal gyrus. Furthermore, gyrification in the right supramarginal gyrus in carriers of the risk allele at rs9841616 (FXR 1) was reduced and carriers of the risk allele at rs6704641 (SATB2) showed a reduction of cortical thickness in the right posterior cingulate gyrus. Note that some of the findings only comprise very small clusters. See Table 1 for a conclusive list of our findings.

4. Discussion

In this study, we investigated the effect of a nPRS as well each single variant contributing to this score, on the variation of brain structure in healthy humans. While these results provide a first evidence linking rs11139497 (TLE1) to increases of cortical thickness in the upper left temporal gyrus, the larger part of our analysis of a nPRS failed to identify an association with either local brain volumes or surface-based morphometric parameters.

Each SNP in this study only carries a fraction of an individuals' risk of schizophrenia with odds ratios ranging from 0.9 (thus representing a protective allele) to 1.1 (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) (see Table 1).

As our study did not provide evidence of an association between the nPRS and brain morphological changes, possible limitations must be considered. First, the nature of the analysed variants is not well known. More detailed knowledge of their expression patterns might illuminate which regions of interest or point in time to focus on.

Furthermore, our sample was limited in size, making it underpowered for smaller effect sizes, while lack of a replication sample calls for further studies to replicate our negative finding on neurodevelopmental PRS.

In addition, we need to consider that these associations might be different in a patient sample, where epistatic effects and other factors might reveal an impact on brain structure.

Carriers of the risk allele at rs11139497 SNP showed elevated cortical thickness in the left superior temporal gyrus when compared to non-carriers. The superior temporal gyrus is often implicated as a focus of pathologic processes in schizophrenia (Kasai et al., 2003; Sun et al., 2009) and has been linked to the generation of hallucinations.

Especially GMV, which has been extensively studied in schizophrenia, seems to be unaffected by a nPRS and, opposed to cortical thickness and gyrification index, does not show any trend level correlations to the SNPs included in this study.

Effects of the nPRS and SNPs seem too subtle to be detected with current MRI paradigms and correction for multiple comparisons. While functional effects of PRS have been described in an fMRI paradigm (Erk et al., 2017), structural correlates of nPRS-SNPs might be present only on a microscopic and histological level without modifying the macroscopic level accessible by structural MRI.

Contributors

R.S. and I.N. designed the study. I.N., F.D. and M.M.N. obtained funding. F.D., S.H.-H. and M.M.N. conducted the genetic analysis, S.R. and S.A. developed and calculated the nPRS. R.S. and C.G. conducted statistical and morphometric analyses. I.N., R.S. and B.B. contributed to interpretation of data. R.S. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Role of funding source

The authors confirm that the funding sources had no role in the design, data analysis, or interpretation of the study.

Declaration of Competing Interest

The authors declare that there are no potential conflicts of interest.

Acknowledgments

We thank our colleagues at the Department of Psychiatry and Psychotherapy, Jena University Hospital, for their help in initial recruitment and scanning of subjects, especially Kerstin Langbein and Maren Dietzek, as well as the student research assistants contributing to this. We also thank Prof. Heinrich Sauer for his support. Parts of this work were supported by grants of the IZKF Jena (Interdisziplinäres Zentrum für Klinische Forschung) to R.S. and B.B. as well as the Friedrich Schiller University Jena and the European Union (to I.N.; EUTwinsS project, grant number MRTN-CT-2006-035987) and Young Scientist grant of the Friedrich Schiller University Jena (to I.N.; grant DRM 210070/87). Further funding was received by M.M.N. and F.D. from the German Federal Ministry of Education and Research (BMBF) through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under the auspices of the e:Med Programme (grant 01ZX1314A to M.M.N. and F.D.).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.07.061.

References

Brans, R.G., van Haren, N.E., van Baal, G.C., Schnack, H.G., Kahn, R.S., Hulshoff Pol, H.E., 2008. Heritability of changes in brain volume over time in twin pairs discordant for schizophrenia. Arch. Gen. Psychiatry 65 (11), 1259–1268.

Cooper, D., Barker, V., Radua, J., Fusar-Poli, P., Lawrie, S.M., 2014. Multimodal voxel-based meta-analysis of structural and functional magnetic resonance imaging studies in those at elevated genetic risk of developing schizophrenia. Psychiatry Res. 221 (1), 69–77.

Dahnke, R., Yotter, R.A., Gaser, C., 2013. Cortical thickness and central surface estimation. Neuroimage 65, 336–348.

de Haan, L., Bakker, J.M., 2004. Overview of neuropathological theories of schizophrenia: from degeneration to progressive developmental disorder. Psychopathology 37 (1), 1–7.

Erk, S., Mohnke, S., Ripke, S., Lett, T.A., Veer, I.M., Wackerhagen, C., Grimm, O., Romanczuk-Seiferth, N., Degenhardt, F., Tost, H., Mattheisen, M., Muhleisen, T.W., Charlet, K., Skarabis, N., Kiefer, F., Cichon, S., Witt, S.H., Nothen, M.M., Rietschel, M., Heinz, A., Meyer-Lindenberg, A., Walter, H., 2017. Functional neuroimaging effects of recently discovered genetic risk loci for schizophrenia and polygenic risk profile in five RDoC subdomains. Transl. Psychiatry 7 (1), e997.

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T.M., Nordentoft, M., Glenthoj, B., 2018. Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish Twin Register. Biol. Psychiatry 83 (6), 492–498.

Kasai, K., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Lee, C.U., Ciszewski, A.A., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003. Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. Am. J. Psychiatry 160 (1), 156–164.

Kessler, R.C., Amminger, G.P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., Ustun, T.B., 2007. Age of onset of mental disorders: a review of recent literature. Curr. Opin. Psychiatry 20 (4), 359–364.

Liu, B., Zhang, X., Cui, Y., Qin, W., Tao, Y., Li, J., Yu, C., Jiang, T., 2017. Polygenic risk for schizophrenia influences cortical gyrification in 2 independent general populations. Schizophr. Bull. 43 (3), 673–680.

Luders, E., Thompson, P.M., Narr, K.L., Toga, A.W., Jancke, L., Gaser, C., 2006. A curvature-based approach to estimate local gyrification on the cortical surface. Neuroimage 29 (4), 1224–1230.

Pardinas, A.F., Holmans, P., Pocklington, A.J., Escott-Price, V., Ripke, S., Carrera, N., Legge, S.E., Bishop, S., Cameron, D., Hamshere, M.L., Han, J., Hubbard, L., Lynham, A., Mantripragada, K., Rees, E., MacCabe, J.H., McCarroll, S.A., Baune, B.T., Breen, G., Byrne, E.M., Dannlowski, U., Eley, T.C., Hayward, C., Martin, N.G., McIntosh, A.M., Plomin, R., Porteous, D.J., Wray, N.R., Caballero, A., Geschwind, D.H., Huckins, L.M., Ruderfer, D.M., Santiago, E., Sklar, P., Stahl, E.A., Won, H., Agerbo, E., Als, T.D., Andreassen, O.A., Baekvad-Hansen, M., Mortensen, P.B., Pedersen, C.B., Borglum, A.D., Bybjerg-Grauholm, J., Djurovic, S., Durmishi, N., Pedersen, M.G., Golimbet, V., Grove, J., Hougaard, D.M., Mattheisen, M., Molden, E., Mors, O., Nordentoft, M., Pejovic-Milovancevic, M., Sigurdsson, E., Silagadze, T., Hansen, C.S., Stefansson, K., Stefansson, H., Steinberg, S., Tosato, S., Werge, T., GERAD1 Consortium, CRESTAR Consortium, Collier, D.A., Rujescu, D., Kirov, G., Owen, M.J., O'Donovan, M.C., Walters, J.T.R., 2018. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat. Genet. 50 (3), 381–389.

Rapoport, J.L., Giedd, J.N., Gogtay, N., 2012. Neurodevelopmental model of schizophrenia: update 2012. Mol. Psychiatry 17 (12), 1228–1238.

Reus, L.M., Shen, X., Gibson, J., Wigmore, E., Ligthart, L., Adams, M.J., Davies, G., Cox, S.R., Hagenaars, S.P., Bastin, M.E., Deary, I.J., Whalley, H.C., McIntosh, A.M., 2017. Association of polygenic risk for major psychiatric illness with subcortical volumes and white matter integrity in UK Biobank. Sci. Rep. 7, 42140.

Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511 (7510), 421–427.

Sun, J., Maller, J.J., Guo, L., Fitzgerald, P.B., 2009. Superior temporal gyrus volume change in schizophrenia: a review on region of interest volumetric studies. Brain Res. Rev. 61 (1), 14–32.

Takahashi, S., Matsuura, M., Tanabe, E., Yara, K., Nonaka, K., Fukura, Y., Kikuchi, M., Kojima, T., 2000. Age at onset of schizophrenia: gender differences and influence of temporal socioeconomic change. Psychiatry Clin. Neurosci. 54 (2), 153–156.

Van der Auwera, S., Wittfeld, K., Homuth, G., Teumer, A., Hegenscheid, K., Grabe, H.J., 2015. No association between polygenic risk for schizophrenia and brain volume in the general population. Biol. Psychiatry 78 (11), e41–e42.

Van der Auwera, S., Wittfeld, K., Shumskaya, E., Bralten, J., Zwiers, M.P., Onnink, A.M., Usberti, N., Hertel, J., Volzke, H., Volker, U., Hosten, N., Franke, B., Grabe, H.J., 2017. Predicting brain structure in population-based samples with biologically informed genetic scores for schizophrenia. Am. J. Med. Genet. B Neuropsychiatr. Genet. 174 (3), 324–332.

Wray, N.R., Gottesman, I.I., 2012. Using summary data from the Danish national registers to estimate heritabilities for schizophrenia, bipolar disorder, and major depressive disorder. Front. Genet. 3, 118.