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ORIGINAL ARTICLE

Polygenic risk has an impact on the structural plasticity of hippocampal subfields during aerobic exercise combined with cognitive remediation in multi-episode schizophrenia

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Preliminary studies suggest that, besides improving cognition, aerobic exercise might increase hippocampal volume in schizophrenia patients; however, results are not consistent. Individual mechanisms of volume changes are unknown but might be connected to the load of risk genes. Genome-wide association studies have uncovered the polygenic architecture of schizophrenia. The secondary analysis presented here aimed to determine the modulatory role of schizophrenia polygenic risk scores (PRSs) on volume changes in the total hippocampus and cornu ammonis (CA) 1, CA2/3, CA4/dentate gyrus (DG) and subiculum over time. We studied 20 multi-episode schizophrenia patients and 23 healthy controls who performed aerobic exercise (endurance training) combined with cognitive remediation for 3 months and 21 multi-episode schizophrenia patients allocated to a control intervention (table soccer) combined with cognitive remediation. Magnetic resonance imaging-based assessments were performed at baseline and after 3 months with FreeSurfer. No effects of PRSs were found on total hippocampal volume change. Subfield analyses showed that the volume changes between baseline and 3 months in the left CA4/DG were significantly influenced by PRSs in schizophrenia patients performing aerobic exercise. A larger genetic risk burden was associated with a less pronounced volume increase or a decrease in volume over the course of the exercise intervention. Results of exploratory enrichment analyses reinforced the notion of genetic risk factors modulating biological processes tightly related to synaptic ion channel activity, calcium signaling, glutamate signaling and regulation of cell morphogenesis. We hypothesize that a high polygenic risk may negatively influence neuroplasticity in CA4/DG during aerobic exercise in schizophrenia.

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INTRODUCTION

Hippocampal volume reduction is a structural hallmark of schizophrenia and reported in a series of meta-analyses in first- and multi-episode schizophrenia.[1,2] In terms of function, such structural changes in the hippocampus have been associated with cognitive deficits, especially in episodic memory, and positive and negative symptoms.[3–9] Cognitive deficits and negative symptoms are important predictors for poor social and functional outcome and major contributors to disability in schizophrenia.[10] Innovative add-on strategies are needed to enhance cognitive performance and negative symptoms, possibly by improving the plasticity of the brain.

The beneficial effects of physical activity on the brain structure, function and cognitive performance have been repeatedly reported in the healthy population.[11–14] Some of these studies provided evidence that aerobic exercise increases hippocampal volumes; this was recently confirmed by a meta-analysis.[15] However, there are also findings of no volume increase in the hippocampus[13] or even hippocampal volume decrease in the right hippocampal subfields cornu ammonis (CA)-2/3, subiculum and dentate gyrus (DG) after an intense aerobic intervention.[16] Volume loss correlated negatively with fitness improvement, indicating that decreased hippocampal volume was found mainly in those participants who did not benefit from the exercise program.[16] On the other hand, a 7-Tesla magnetic resonance imaging (MRI) study in older adults showed a prominent volume increase after physical activity in the left CA subregions of the hippocampus and a trend for volume increase in the left CA4/DG.[17] The above findings indicate that exercise may have different effects in the two hemispheres.

Meta-analyses have confirmed that aerobic exercise improves symptoms and cognition in schizophrenia patients,[18–20] although results from the literature are not fully consistent. Furthermore, findings on effects of exercise on hippocampal volume in schizophrenia are also not fully consistent. To our knowledge, the first study to investigate the effects of sustained endurance training in a small sample of multi-episode schizophrenia patients observed an increase in the hippocampal volume after 3 months of aerobic endurance training.[21] However, these findings could not be replicated in a study comparing 6 months of endurance training with occupational therapy in schizophrenia patients.[22] A subsequent study that combined 3 months of aerobic endurance

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training with cognitive remediation showed improvement in global functioning, as determined with Global Assessment of Functioning (GAF) and Social Adjustment Scale-II (SAS-II), but no significant training-related changes in the volumes of the total hippocampus and its subregions. However, voxel-based morphometry analyses found an increased volume of the left superior, middle and inferior anterior temporal gyri.[23,24] Accordingly, evaluation of the possible impact of aerobic exercise interventions on grey matter or hippocampal volume in schizophrenia raises questions about the applied type of exercise intervention; the dosage, frequency and duration; and the dose–response relationship.[25] A recent meta-analysis of exercise interventions in schizophrenia indicated that symptoms improve with a higher intensity of training.[18] Furthermore, greater amounts of exercise have been associated with larger improvements in global cognition.[19] Findings from the literature are not unequivocal, and therefore individual factors are likely to have a role in the clinical and structural responsiveness to aerobic exercise.

Studies in animal models have provided important clues to characterize at the structural, functional and molecular levels the processes mediating the effect of exercise on the hippocampus. An animal model of voluntary running in mice showed an increase in total hippocampal volume,[26] suggesting that neuroplastic restorative processes may underlie the effects of exercise in patients. In a recent combined MRI and histological study, physical exercise in mice led to an increase in gray matter volume specifically in the hippocampal DG and CA1–3 along with an increase in neurogenesis in the DG.[27] Other animal studies have shown that, in various brain regions, including the hippocampus, exercise promotes the production of neurotrophic factors, such as brain-derived neurotrophic factor.[28–30] Similar studies focusing on the DG of animals after exercise have reported increased levels of brain-derived neurotrophic factor and glutamate receptors (GluR; N-methyl-D-aspartate (NMDA) receptor, NMDA receptor NR2B subunit and GluR5) and a parallel increase in neurogenesis and long-term potentiation in this region.[31–33] Increased dendritic spine density and an earlier morphological maturation of these spines have also been reported in the DG of animals after exercise.[34,35]

As regards cognition, the exercise-induced changes seen in gene and protein expression, neurogenesis and synaptic plasticity have been associated with improvements in the performance of the studied animals in learning and memory tasks.[31,36–38] Taken together, these data fit with a model of hippocampal neurogenesis in the DG and with processes related to synaptic plasticity triggered by exercise. These models of hippocampal plasticity also provide mechanistic insight into the biological processes connecting exercise with clinical improvement in schizophrenia. In schizophrenia patients, computer-assisted cognitive remediation has been shown to exert moderate effects on certain cognitive domains, clinical symptoms and psychosocial functioning.[24] Furthermore, patients receiving this therapy demonstrated greater preservation of gray matter volume over the course of 2 years in the left hippocampus.[39]

Given the high heritability estimates of schizophrenia,[40–42] understanding the role of genetic risk variants in the modulation of the effects of exercise on disease-relevant brain structures might pave the way for identifying those patients more likely to benefit from such an intervention. Recent genome-wide association studies based on ever-increasing samples of psychiatric patients have provided outstanding results regarding the contribution of common genetic variation to schizophrenia risk.[43] More than 100 genetic risk loci have been unequivocally identified after controlling for common sources of confounding. Likewise, polygenic risk scores (PRSs), which summarize in a single risk score the effects of many single-nucleotide polymorphisms (SNPs) under an additive model, have been shown to provide a composite risk assessment with an excellent replicability across independent samples of schizophrenia patients.[43] Several studies have shown an association of schizophrenia PRSs with neurocognitive performance, such as reduced speed in emotion identification and impaired verbal reasoning, attention and working memory in young or elderly healthy volunteers.[44–47] In healthy people, schizophrenia-based PRSs have already been associated with patterns of brain activation in neurocognitive domains.[48] Likewise, in patients with chronic schizophrenia, they have been associated with the general psychopathology dimension of the Positive and Negative Syndrome Scale and anxiety in first-episode schizophrenia patients[49] and with mania,[50] underlining the clinical impact of the genetic background. Taken together, although schizophrenia PRSs currently cannot be used as a diagnostic tool in clinical settings, they hold promise for the development of a tool for predicting the outcome of schizophrenia patients.[51]

Remarkable recent evidence has shown that schizophrenia polygenic risk assessed by PRSs is negatively associated with hippocampal volumes across at-risk mental state individuals and first-episode schizophrenia patients, with lower volumes in those patients with a larger genetic burden.[52] Moreover, volumes of hippocampal subregions have been shown to be highly heritable in humans.[53] These results indicate that the individual genetic load may modulate the effects of aerobic exercise augmented with cognitive remediation on volume changes in the hippocampus and its subfields in schizophrenia patients.[24] This interaction might account for the conflicting results on the effects of aerobic exercise combined with cognitive remediation in schizophrenia, that is, the effect of the intervention may differ according to the individual genetic risk load.

Therefore, the aim of the present secondary analysis was to investigate whether schizophrenia PRSs are associated with volume changes in the total hippocampus and its subfields (CA subfields—namely CA1, CA2/3 and CA4/DG—and subiculum) in multi-episode schizophrenia patients and healthy controls after 3 months of aerobic exercise combined with cognitive remediation. Our earlier study observed no increase in the volume of the total hippocampus and its subfields after aerobic exercise.[24] According to the aforementioned evidence derived from animal model studies[27] we hypothesized that in these schizophrenia patients the PRS has a prominent impact on exercise-induced volume changes in the CA4/DG of the hippocampus. A secondary aim of the present study was to describe, based on the results of the PRS analyses, the biological processes underlying the effects of exercise on structural brain volume change.

MATERIALS AND METHODS

Participants

The sample consisted of 20 multi-episode schizophrenia patients in an aerobic exercise and cognitive remediation group, 21 multi-episode schizophrenia patients in a table soccer and cognitive remediation group (control intervention) and 23 healthy controls (who also participated in aerobic exercise and cognitive remediation). Schizophrenia patients were recruited in the Department of Psychiatry and Psychotherapy of the University Medical Center Goettingen. Healthy controls, who had no current or past mental illness, were matched for age, sex and handedness. The sample and the results on brain volumes, clinical data and cognition are described in detail elsewhere.[23,24] The study protocol was approved by the ethics committee of the University Medical Center Goettingen. All participants provided written informed consent prior to inclusion in the study. The trial is registered at www.clinicaltrials.gov (NCT01776112).

Endurance training, table soccer and cognitive remediation

The intervention lasted 3 months for all three groups and consisted of three 30-min sessions per week. The endurance training was conducted on bicycle ergometers at an individually defined intensity that was gradually increased until blood lactate concentrations of ~2 mmol/l were reached, in accordance with the continuous training method.[54] The training parameters were blood lactate concentration, heart rate and exhaustion

according to the Borg scale.[55] More details on the intervention protocol and the clinical and cognitive characterization can be found elsewhere.[23,24] The schizophrenia patients allocated to the non-endurance intervention had table soccer for the same amount of time. Blood lactate concentrations, heart rate and exhaustion were also monitored.

After 6 weeks of aerobic exercise or table soccer, all participants performed standardized cognitive remediation training with the computer-assisted training program COGPACK (software version 8.19 D/ 8.30 DE; Marker Software, Ladenburg, Germany, http://www.cogpack.de/). Patients and healthy controls completed the memory and attention tasks twice per week for 6 weeks. Each session lasted for 30 min and took place after the aerobic exercise or table soccer session.[23,24]

MRI acquisition

MRI data were acquired at baseline (V1) and after 3 months (V3) in a whole-body 3.0-Tesla MRI Scanner (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) with an eight-channel head coil. Small cushions were used between the head coil and the individuals' heads to minimize head movements. The three-dimensional anatomical images were acquired with a T1-weighted magnetization-prepared rapid gradient echo sequence with a field-of-view of 256 mm and an isotropic spatial resolution of $1.0 \times 1.0 \times 1.0$ mm^3 (repetition time = 2250 ms, echo time = 3.26 ms, inversion time = 900 ms, flip angle 9°, number of slices = 176). All images were quality-controlled by a board-certified radiologist and subsequently anonymized to blind the subjects' identities.

Image processing

Automated hippocampal segmentation was performed with the FreeSurfer version 5.3.0 software package (http://surfer.nmr.mgh.harvard.edu). The longitudinal processing stream was used for automatic subcortical segmentation, and hippocampal subfield volumes were computed from T1-weighted images.[56] An unbiased within-subject template space and image[57] was created by robust, inverse consistent registration.[58] We applied several processing steps, such as skull stripping, Talairach transforms, atlas registration and spherical surface maps. Parcellations were initialized with common information from the within-subject template, which significantly increased reliability and statistical power.[56] On the basis of the longitudinal processed images, the hippocampal total and subfield (CA1, CA2/3, CA4/DG and subiculum) volumes were computed from each participant's structural images.[59] The investigator was blinded to group allocation.

For all MRI data, we performed a correction for the individual intracranial volume (ICV) with the proportions method, in which each T1 volume is divided by the subject's ICV and multiplied by the average ICV of all subjects.[60]

Genotyping and quality control

DNA from all subjects was genotyped with the Infinium PsychArray (Illumina, San Diego, CA, USA). Quality-control steps (inclusion thresholds: SNP call rate >97%, subject call rate >95%, Hardy–Weinberg equilibrium $>10^{-6}$, heterozygosity rate within 3 s.d.'s) were performed with PLINK 1.07.[61] We calculated an identity-by-state matrix to estimate the relationship between the samples; this analysis showed that the study samples were not related.

The EIGENSOFT package (SmartPCA) was used to model ancestry differences between the study participants by using a principal component analysis based on a pruned subset of ~50 000 autosomal SNPs, after excluding regions with a high linkage disequilibrium.[62] All subjects clustered to HapMap3 Caucasian reference populations; therefore, none of them was excluded in subsequent analyses. We extracted the first two ancestry principal components to correct for the potential effects of population substructure in all analyses.

Scoring

Discovery sample: summary statistics from the most recent schizophrenia genome-wide association studies (Psychiatric Genomics Consortium), which was based on a sample of 36 989 schizophrenia patients and 113 075 healthy controls (https://www.med.unc.edu/pgc), were used to ascertain risk variants, their *P*-values and associated odds ratios.[43]

Target sample: in the sample of the present study, for each SNP contributing to the PRS the number of risk variants carried by an individual (0, 1 or 2) was multiplied by the logarithm of the odds ratio for that particular variant according to the results from the discovery sample. Scoring was based on pruning (default parameters) and thresholding (different sets of SNPs according to different *P*-value cutoffs between 0.01 and 1, with incremental 0.01 steps) and performed with PRSice.[63]

Statistical analyses of PRS effects on hippocampal volume changes in schizophrenia

For each of the imaging variables under study, the baseline values (V1) were subtracted from the values after 3 months (V3). The resulting differences were standardized. Kolmogorov–Smirnov test was used to test normality assumption. Age, sex, height, handedness and the first two ancestry principal components were used as covariates in all genetic association analyses. All analyses were performed separately for schizophrenia patients performing aerobic exercise, schizophrenia patients playing table soccer and healthy controls (who also performed aerobic exercise) in order to identify differences between the three groups. The effect of PRSs on total left and right hippocampal volume changes was ascertained by univariate linear regression. Multivariate multiple regression (dependent variables: volume changes in CA1, CA2/3, CA4/DG and subiculum) was performed separately for the left and right sides to find the optimal PRS (*P*-value threshold) with the best fit. Subsequent univariate linear regression analyses were conducted for the individual hippocampal subfields of interest by using the optimal PRS determined in the multivariate analysis. An adjustment for multiple testing was performed with the improved Bonferroni method of Simes and Hommel.[64,65]

IBM SPSS Statistics v22 was used for multivariate and univariate linear regression analyses.[66] Plots were generated in R 3.2.1 (ref. 67) with the ggplot2 package.[68] A power analysis for linear multiple regression was conducted with G*Power 3.1. Assuming a significance level of $\alpha = 0.05$, a power of 80% and four predictors (*z*-scores for relative hippocampal volume differences in CA1, CA2/3, CA4/DG and subiculum) large effects of $f^2 = 0.85$ (or $r^2 = 0.46$) can be detected with a sample size of at least $n = 20$.

Enrichment analyses

Those SNPs included within the optimal range of PRSs associated with hippocampal volume changes were annotated to genes, including 35 kb upstream and 10 kb downstream regions. The resulting list of genes (NCBI37.3) was used to perform gene ontology and pathway enrichment analyses (Gene Ontology terms, Kyoto Encyclopedia of Genes and Genomes and Reactome pathways) with the Enrichr tool (http://amp.pharm.mssm.edu/Enrichr/).[69,70]

RESULTS

Association of PRS with hippocampal volume changes

For all hippocampal volume changes, tests detected no significant deviations from normality assumption. There were no signs for nonlinear relations between PRS and hippocampal volume changes. Analyses of the total left and right hippocampal volume changes from baseline (V1) to 3 months (V3) did not show an effect of PRSs in any of the groups (Table 1). Given the significant correlations between hippocampal subfield changes in CA1, CA2/3, CA4/DG and the subiculum (Supplementary Figure 1), we performed multivariate analyses based on these hippocampal subfields. In schizophrenia patients performing aerobic exercise and cognitive remediation, the PRSs had a significant effect on individual volume change on the left side (optimal *P*-value threshold = 0.17, Wilks' Lambda = 0.343, $P = 0.031$, partial $\eta^2 = 0.660$) but not on the right (Table 2 and Supplementary Figure 2). In left subfields, univariate analyses based on the optimal *P*-value threshold of 0.17 showed a statistically significant effect in CA4/DG (corrected $P = 0.0399$, $R^2 = 0.358$), a trend in CA1 and CA2/3 subfields and no association in the subiculum (Table 2).

Multivariate analysis of schizophrenia patients in the table soccer and cognitive remediation group yielded a significant effect of PRSs on left hippocampal subfield changes (optimal *P*-value threshold = 0.14, Wilks' Lambda = 0.335, $P = 0.0465$, partial $\eta^2 = 0.664$; Table 2 and Supplementary Figure 2). However, all subsequent univariate subfield analyses were not significant (all corrected $P > 0.227$; Table 2). No significant genetic effect on right

Table 1. Association of relative volume change in total left and right hippocampus from baseline (V1) to 3 months (V3) with the optimal PRS. The optimal threshold is defined as the *P-value* cutoff point for the selection of SNPs that returns the best-fit PRS

Hippocampus	*Optimal* P-*value threshold*	*Uncorrected* P[a]	*Corrected* P[b]	R^2	*nSNPs*
Schizophrenia patients performing aerobic exercise					
Total hippocampus left	0.16	0.06868	0.1374	0.140	19 047
Total hippocampus right	0.01	0.62462	0.6246	0.018	4814
Schizophrenia patients playing table soccer					
Total hippocampus left	0.09	0.29021	0.2902	0.086	14 359
Total hippocampus right	0.09	0.04448	0.0889	0.197	14 359
Healthy controls performing aerobic exercise					
Total hippocampus left	0.07	0.21436	0.21436	0.064	12 823
Total hippocampus right	0.36	0.08038	0.16076	0.176	27 879

Abbreviations: nSNP, number of SNP included in the optimal PRS; PRS, polygenic risk score; $R^{2,}$ amount of variance explained by the respective optimal PRS in each hippocampal subfield; SNP, single-nucleotide polymorphism. [a]*P*-value not corrected for multiple testing. [b]*P*-value corrected for multiple testing according to the Simes-Hommel procedure.

Table 2. Multivariate and univariate hippocampal subfield association analyses of the volume change from baseline (V1) to 3 months (V3) with the optimal PRS

Hippocampal subfields	*Optimal* P-*value threshold*	*Uncorrected* P[a]	*Corrected* P[b]	*Partial* η^2/R^{2c}	*nSNPs*
Schizophrenia patients performing aerobic exercise					
Hippocampal subfields, multivariate left	0.17	0.03107	—	Partial $\eta^2 = 0.660$	19 597
CA1 left		0.02523	0.0508	$R^2 = 0.289$	
CA 2/3 left		0.03384	0.0677	$R^2 = 0.216$	
CA4/dentate gyrus left		0.00998	**0.0399**	$R^2 = 0.358$	
Subiculum left		0.93475	0.9347	$R^2 = 0.000$	
Hippocampal subfields, multivariate right	0.01	0.09215	—	Partial $\eta^2 = 0.554$	4814
Schizophrenia patients playing table soccer					
Hippocampal subfield multivariate left	0.14	0.04650	—	Partial $\eta^2 = 0.664$	17 859
CA1 left		0.05677	0.2271	$R^2 = 0.145$	
CA 2/3 left		0.64250	0.9724	$R^2 = 0.018$	
CA4/dentate gyrus left		0.97243	0.9724	$R^2 = 0.000$	
Subiculum left		0.45601	0.9638	$R^2 = 0.041$	
Hippocampal subfield multivariate right	0.25	0.29993	—	Partial $\eta^2 = 0.422$	23 525
Healthy controls performing aerobic exercise					
Hippocampal subfield multivariate left	0.01	0.06136	—	Partial $\eta^2 = 0.562$	4814
Hippocampal subfield multivariate right	0.02	0.17686	—	Partial $\eta^2 = 0.440$	6788

Abbreviations: Partial η^2, partial eta squared; nSNP, number of SNPs included in the optimal; PRS; polygenic risk score; R^2, amount of variance explained by the respective optimal PRS in each hippocampal subfield; SNP, single-nucleotide polymorphism. Univariate subfield analyses were only performed for those subfields and/or experimental groups of interest identified by multivariate analysis (see also Supplementary Figure 2). [a]*P*-value not corrected for multiple testing. [b]*P*-value corrected for multiple testing according to the Simes-Hommel procedure. [c]Partial η^2 for multivariate analyses, R^2 for univariate analyses. Bold value is significant as a corrected $P < 0.05$.

hippocampal subfields was observed in the multivariate analysis of this group of patients (optimal threshold = 0.25, $P = 0.300$). In the healthy control group, PRSs showed no significant effect on left (optimal threshold = 0.01, $P = 0.061$) or right (optimal threshold = 0.02, $P = 0.177$) hippocampal subfields in the multivariate analysis, thus precluding any further univariate subfield analysis in this group (Table 2).

Results of linear regression analyses of the group of schizophrenia patients performing endurance training combined with cognitive remediation that used the optimal *P*-value threshold for PRSs (0.17) as an independent variable found a correlation between a high genetic risk burden and a less pronounced volume increase or even a decrease over time in the left CA1 ($\beta = -0.541$, s.e. 0.198, 95% confidence interval (CI) = −0.957 to −0.124), left CA2/3 ($\beta = -0.523$, s.e. 0.201, 95% CI = −0.945 to −0.101) and left CA4/DG ($\beta = -608$, s.e. 0.187, 95% CI = −1.001 to −0.215; Figure 1).

We performed leave-one-patient-out analyses to estimate the effect of extreme outliers in the sample of schizophrenia patients performing endurance training. These *post hoc* analyses showed that when using a PRS *P*-value threshold of 0.17 the amount of variance explained (R^2) and the associated *P*-values fluctuated greatly in CA1 and CA2/3 regions: CA1 (R^2 range: 0.044–0.384, mean = 0.287; *P*-value range: 0.010–0.367, mean = 0.050), CA2/3 (R^2 range: 0.075–0.397, mean = 0.212; *P*-value range: 0.005–0.226, mean = 0.056). However, the leave-one-out analysis results for the CA4/DG area yielded a more stable output that did not show a large deviation from the one in the whole sample: CA4/DG (R^2 range: 0.138–0.529, mean = 0.344; *P*-value range: 0.001–0.16, mean = 0.023).

Enrichment analyses

According to the association analyses, the most consistent and stable results were obtained in the CA4/DG area in the

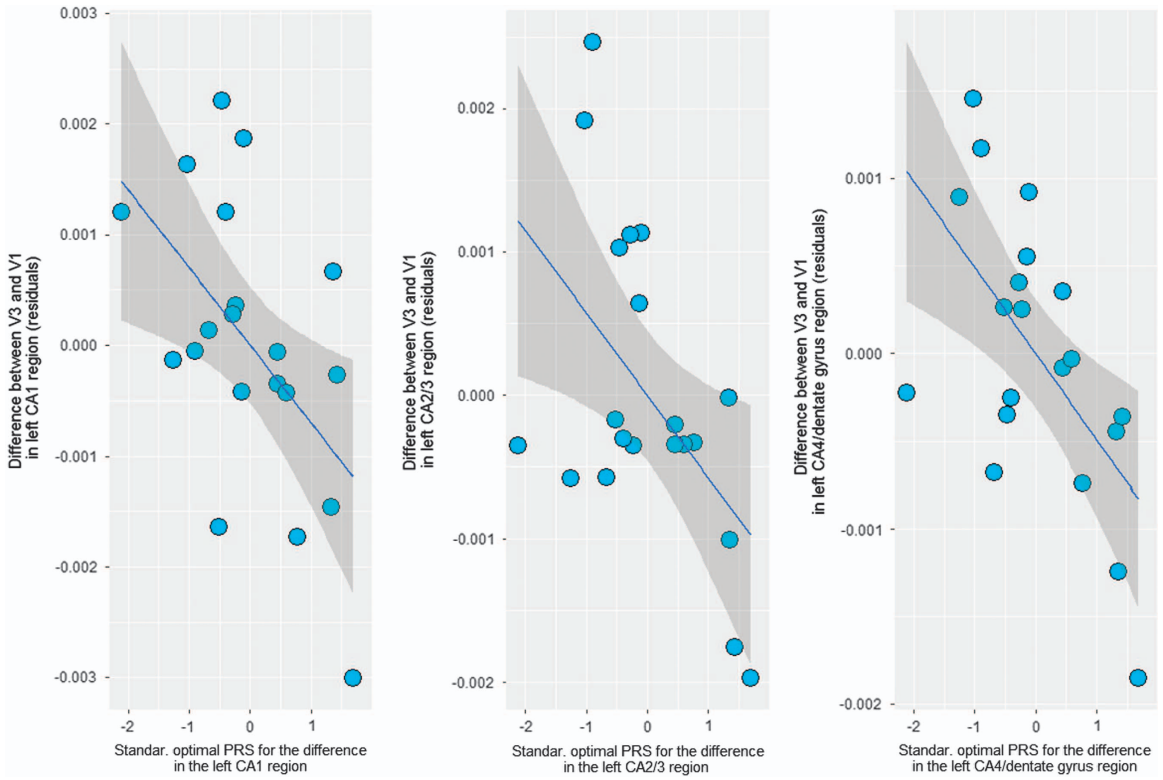

Figure 1. Scatterplot showing the relationship between the optimal schizophrenia polygenic risk score (PRS; *x* axis, standardized) and the change from baseline (V1) in the volume of the hippocampal subfields CA1 (left panel), CA2/3 (middle panel) and CA4/dentate gyrus (right panel) after 3 months of aerobic exercise (V3) (*y* axis, corrected residuals). Positive values in the *y* axis indicate a gain in volume after 3 months; positive values in the *x* axis, a higher genetic risk burden. Regression line and 95% confidence intervals are also shown.

schizophrenia group performing endurance training augmented with cognitive remediation. The leave-one-patient-out analyses also showed that in this group the optimal range of *P*-value thresholds in the PRS analyses was between 0.17 and 0.25. To capture the genetic variation driving the strongest association signal, we used the SNPs included between these optimal thresholds to generate a list of genes (where these SNPs are located) for exploratory enrichment analyses. As a result, 2250 mapped gene IDs were used for gene ontology and pathway enrichment analyses. The results (Figure 2 and Supplementary Table 1) highlighted, among other aspects, biological processes related to neuron development/differentiation, synaptic transmission, calcium transport, cell adhesion, extracellular matrix organization and cell motility/migration. With respect to cellular components/molecular function, the synapse, postsynaptic density, ion channel activity and cell adhesion terms were enriched among these genes. Analyses of Kyoto Encyclopedia of Genes and Genomes terms showed the relevance of pathways related to glutamatergic synapsis, focal adhesion and also calcium signaling. A similar analysis based on Reactome pathways observed an enrichment of pathways involved in the neuronal system, extracellular matrix organization or integrin cell surface interactions.

Association of PRS with physical fitness and clinical symptoms

We observed a correlation between the optimal PRS and the change in fitness (that is, change in Physical Working Capacity130/kg (PWC130/kg) in patients performing aerobic exercise ($r = -0.485$; *P*-value = 0.035; see Supplementary Table 2). Fitness worsened over time (V3–V1) in those patients with more genetic burden (Supplementary Figure 3). The change in PWC130/kg correlated with some volumetric changes over time, especially in the CA4/DG subfield ($r = 0.739$; *P*-value = 0.001; see Supplementary Table 3). In contrast, we did not find a correlation between PRS and clinical symptoms measured by the Positive and Negative Syndrome Scale, cognitive performance or global function (Supplementary Table 2).

DISCUSSION

To the best of our knowledge, this is the first study to ascertain the role of schizophrenia PRSs on changes in left hippocampal subfields after sustained aerobic exercise augmented with cognitive remediation. This effect was not detected in patients playing table soccer augmented with cognitive remediation, strengthening the assumption that PRSs are relevant for the effects of aerobic exercise on the brain structure. Our results indicate that a higher genetic risk burden for schizophrenia is associated with a less pronounced increase or even a decrease of left hippocampal subfield volumes over the course of the aerobic exercise intervention. In a previous study, aerobic exercise was shown to promote enlargement of hippocampal structures in schizophrenia patients, a finding that was interpreted as a regenerative process.[21] However, studies of effects of aerobic exercise on hippocampal volume and function, measured by verbal memory and working memory tasks, have produced conflicting results in schizophrenia.[18–24] Training methods, such as training intensity and the duration of the intervention, are known to influence the effects of aerobic exercise on clinical outcome.[18,71] Here we show that individual genetic risk affects the structural response to aerobic exercise augmented with cognitive remediation. Such an effect is especially prominent in the CA4/DG subregion; a similar trend is observable in the CA2/3 and CA1 subregions, but not in the total hippocampus. All these hippocampal subregions are of special interest because they have

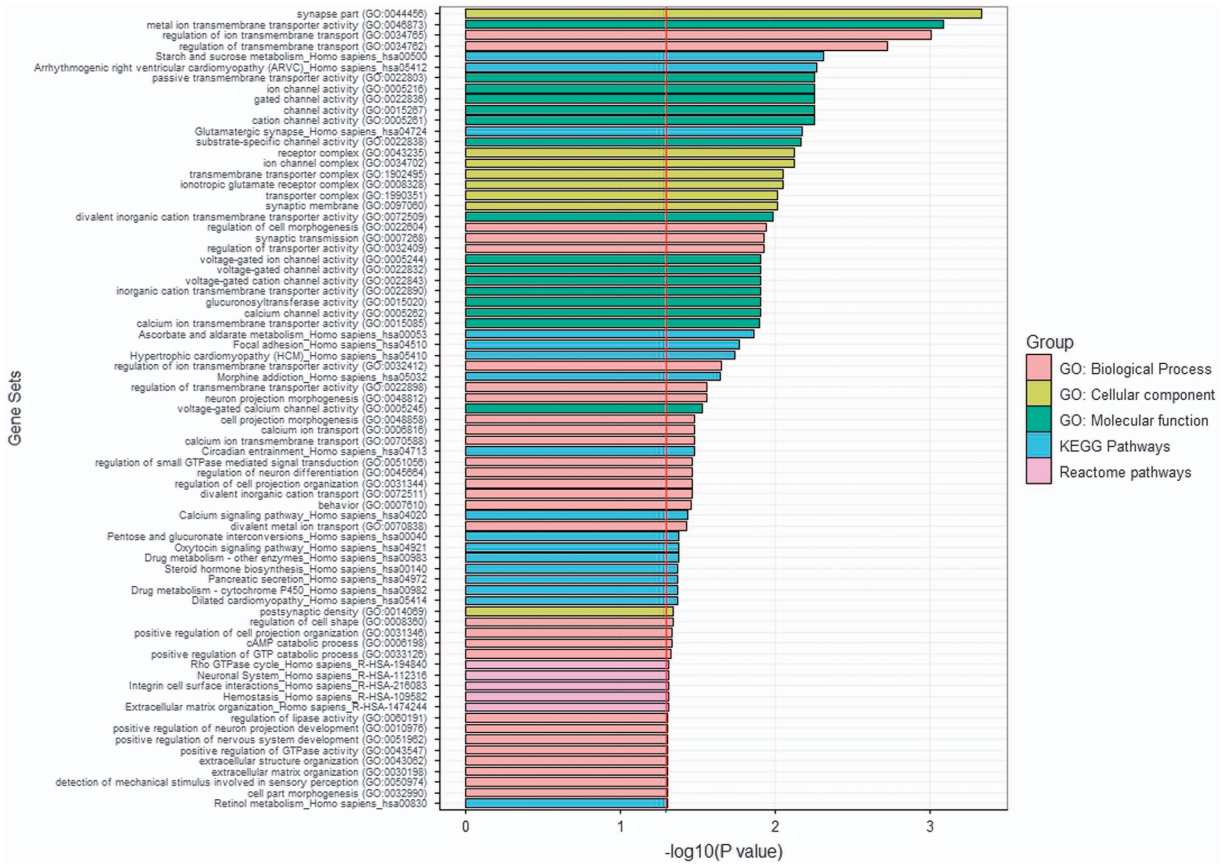

Figure 2. Results of the formal enrichment analyses summarizing the Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) or Reactome pathways enriched in this study with a Bonferroni-corrected adjusted *P*-value < 0.05. Red line: nominal significance threshold (0.05) of corrected *P*-values.

been shown to be enlarged after aerobic exercise (voluntary running) in stereological histology and MRI-based animal studies.[27,72]

Our results are in agreement with a recent study showing that a larger schizophrenia polygenic risk burden in first-episode and at-risk mental state patients correlated negatively with hippocampal volume.[52] The present study expands on these previous results by showing that in multi-episode patients PRSs also influence exercise-induced plastic processes taking place in substructures of the hippocampus. High heritabilities have been reported for both the total hippocampus[53,73] and the hippocampal subfields, including the CA4/DG region.[53,74] However, the data also suggest that a substantial proportion of variation in subcortical structures is explained by the environment (for example, physical activity, cognitive remediation) or the interaction of the environment with the individual genetic makeup. Our results support this notion by showing that the volumes of certain hippocampal subfields, especially the CA4/DG area, have different levels of responsiveness to the effect of aerobic exercise training combined with cognitive remediation, depending on the individual genetic risk burden.

We found an association between PRS and physical fitness, raising the question of the impact of risk genes on energy metabolism or somatic function (see Supplementary Tables 2 and 3). We did not find an association of PRS with global functioning, cognition or psychopathology; however, these clinical variables have higher variability than the volume of hippocampal sub-structures, and therefore large samples would be needed to detect effects on clinical symptoms. Moreover, all patients had been under stable antipsychotic treatment for at least 2 weeks before beginning the study intervention, and inclusion criteria included stabilization of disease symptoms (Positive and Negative Syndrome Scale < 75). Previous studies in schizophrenia have shown that large samples are needed to detect effects of PRSs on clinical measures.[48–50]

Exploratory enrichment analyses based on Gene Ontology terms and pathway annotations aimed to gain mechanistic insight into the biological mechanisms underlying these effects. Results point toward processes related to neuron development, neuron differentiation, cell migration and synaptic transmission. Such results, although exploratory and preliminary, are especially relevant for the interpretation of the associations we found between PRSs and volume changes in the DG area after aerobic exercise combined with cognitive remediation. The inconsistent results in schizophrenia patients may be partly due to an effect on plastic processes of other environmental factors than aerobic exercise or the individuals' genetic backgrounds, as was shown here. The DG is one of the regions in the human brain with high plasticity. It generates proliferating stem cells throughout life that differentiate to new granule neurons (neurogenesis) and integrate into brain networks.[27,75] In exercising humans, cerebral blood volume of the DG has been regarded as a measure of neurogenesis and has been shown to increase after aerobic exercise.[76] In mice, voluntary running is known to increase neurogenesis in the DG and gray matter volume in the DG and CA1–3 areas.[27] In exercising mice, neurogenesis was the best marker to explain the increase in hippocampal gray matter volume.[77] However, also other mechanisms, such as synaptic plasticity, may have a role in the volume increase induced by aerobic exercise,[34,35] and our analysis showed an enrichment on synaptic transmission and postsynaptic density terms. In the

hippocampus of schizophrenia patients, a decreased expression of synaptic proteins has been shown, especially members of the SNARE complex, including the most abundant synaptic protein, SNAP-25. Expression of SNAP-25 was related to problems related to orientation and judgement during the patients' lifetime, which could be used as a surrogate marker for cognitive disturbance in schizophrenia.[78,79] Proper function of the CA4/DG subregion is crucial for cognitive abilities, such as pattern separation,[80] and schizophrenia patients show cognitive deficits consistent with CA4/DG dysfunction.[81] In fact, in large groups of healthy subjects schizophrenia PRSs have been shown to be associated with reduced cognitive abilities in areas such as working memory, attention, social cognition and verbal reasoning across all adult age groups.[44–46,48]

Stereological post-mortem studies revealed a reduced volume of the left DG and a reduced number of granule neurons on the left side of this subregion in schizophrenia patients, pointing to disease-related pathophysiological processes.[82] These findings replicate former studies that have described such thinning.[83,84] Consistent with this finding, decreased cell proliferation in the subgranular zone of the DG has been reported and indicates a deficit of neurogenesis.[85] Moreover, a circumscribed reduction of oligodendrocyte number was revealed in the left CA4 region of the hippocampus.[82,86] In the same sample, a trend toward reduction of the density of oligodendrocyte transcription factor (Olig)1-positive cells was shown by immunohistochemistry.[87] Olig1 antibodies are known to stain precursor forms and mature oligodendrocyte populations, and Olig1 is needed for progenitor development and repair of myelin.[88] The above findings led to the hypothesis that the decreased number of oligodendrocytes in the left CA4 region indicates a disturbed regenerative process[89] and may be related to disturbed energy supply to mossy fiber axons.[90]

In summary, an increased genetic burden—as revealed by high PRSs—may affect pathways known to be involved in the pathophysiology of at least a subgroup of schizophrenia patients, lowering the beneficial effects of aerobic exercise augmented with cognitive remediation on hippocampal CA4/DG volume. However, our study also has some limitations. First, the sample size was small, and therefore the enrichment analyses have to be regarded as exploratory and the study needs to be replicated in a larger, independent sample.[91] Such a larger sample would also allow the accuracy of the relatively high R^2 estimates in the present study to be confirmed. The analyses were corrected for multiple testing by using the Simes–Hommel procedure,[64,65] and therefore the probability of a type I error was limited to $\alpha = 0.05$. Moreover, our leave-one-patient-out analyses also provided further support to the assumption that our results were not driven by potential outliers. A recent meta-analysis revealed that aerobic exercise increases hippocampal volume.[15] However, studies in schizophrenia have found different results for the effects of aerobic exercise on hippocampal structure, probably because the resolution of the acquired structural MRI data was lower and the human brain is subject to high variability in function, structure and response.[92–94] Furthermore, we did not use a randomization procedure to allocate the schizophrenia patients to the endurance training augmented with cognitive remediation or table soccer augmented with cognitive remediation group. This is an important limitation that may have resulted in a potential selection bias and baseline differences in psychopathology and dose of antipsychotic medication.[23,24] Finally, during the second intervention period from 6 weeks to 3 months, we did not include additional study arms with cognitive remediation only or with endurance training only. Therefore, we cannot conclude whether the effects of PRSs on hippocampal subfield volumes are influenced by adding cognitive remediation or are caused by aerobic exercise alone.

CONCLUSION

Understanding the genetic factors that drive clinical improvement and influence hippocampal plasticity during aerobic exercise may allow to gain mechanistic insight into the underlying processes. We hypothesize that a high polygenic risk may negatively influence neuroplastic processes in the hippocampus during aerobic exercise augmented with cognitive remediation in schizophrenia, indicating a gene × environment interaction in which the genetic load influences the effects of the intervention on neuroplastic processes. These results, based on a limited sample of individuals, need to be replicated in larger samples, ideally assessed with the same instruments and intervention protocols.

CONFLICT OF INTEREST

A Hasan has been invited to scientific meetings by Lundbeck, Janssen-Cilag and Pfizer, received a paid speakership from Desitin, Otsuka and Lundbeck, and was a member of a Roche advisory board. P Falkai has been an honorary speaker for AstraZeneca, Bristol Myers Squibb, Eli Lilly, Essex, GE Healthcare, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier and Takeda, and during the past 5 years, but not presently, has been a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly and Lundbeck. A Schmitt has been an honorary speaker for TAD Pharma and Roche, and a member of advisory boards for Roche. The remaining authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)