Schizophrenia-associated genomic copy number variants and subcortical brain volumes in the UK Biobank

Warland A[1], Kendall K[1], Rees E[1], Kirov G[1], Caseras X[1]*

[1.] MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, UK

* Corresponding Author:

Dr Xavier Caseras
MRC Centre for Neuropsychiatric Genetics and Genomics
Cardiff University
Hadyn Ellis Building, Maindy Road
Cardiff, CF24 4HQ
UK

CaserasX@cardiff.ac.uk

Abstract

Schizophrenia is a highly heritable disorder for which anatomical brain alterations have been repeatedly reported in clinical samples. Unaffected at-risk groups have also been studied in an attempt to identify brain changes that do not reflect reverse causation or treatment effects. However, no robust associations have been observed between neuroanatomical phenotypes and known genetic risk factors for SZ. We tested subcortical brain volume differences between 49 unaffected participants carrying at least one of the 12 copy number variants associated with schizophrenia in UK Biobank with 9,063 individuals who did not carry any of the 93 copy number variants reported to be pathogenic. Our results show that the carriers have reduced volume in some of the subcortical structures previously shown to be reduced in schizophrenia. Moreover, these associations partially accounted for the association between pathogenic CNVs and poor performance of tests of fluid intelligence, which is one of the features of schizophrenia.

Introduction

Schizophrenia (SZ) is a severe psychiatric disorder with a profound impact on sufferers, their families and the society in general. Around 20% of patients diagnosed with SZ experience chronic psychotic symptoms, 50% have long-term psychiatric problems, 80-90% are unemployed, and as a group they have a life expectancy 10-20 years shorter than the general population[1-4]. Despite continued research efforts, our ability to treat SZ remains very limited and no new therapeutic targets of proven efficacy have been developed for decades, with clozapine – discovered almost six decades ago – still standing as the most effective treatment for SZ[5]. To a large extent, this lack of progress is due to our poor understanding of the neurobiological underpinnings of this disorder; although recent advances in imaging have opened a window on the anatomy and function of human in-vivo brain, setting new opportunities to advance on this knowledge. Multiple case-control studies have consistently shown the existence of anatomical abnormalities in the brains of SZ patients, although restrictions in statistical power and sample representativeness have resulted in frequent discrepancies with regards to a more detailed description of these abnormalities. To overcome the limitations of smaller/circumscribed studies, large international consortia efforts – such as ENIGMA - have recently been created[6]. The ENIGMA consortium recently published their results on a sample of over 4,000 participants[7] showing a reduction in the volume of the hippocampus, thalamus, amygdala and accumbens, but increased volume in lateral ventricles and pallidum, in SZ patients relative to controls; results that were largely replicated by a parallel Asian consortium[8]. However, despite being of interest, it remains possible that these findings reflect reverse causation and/or treatment effects rather than causal neurobiological mechanisms, as they come from clinical samples.

Since SZ is a highly heritable[9] disorder, it would be expected that any potential marker of pathogenic mechanisms would also be detectable in participants at high genetic risk who are unaffected by SZ. Important advantages of this approach lie in its ability to access large samples of participants and avoid the possibility of reverse causation or treatment effects. Under this premise, a recent study probed the association between common genetic risk for SZ – i.e. polygenic score based on the latest GWAS data available[10] - and subcortical brain volumes in a large sample of over 11,000 participants[11]. However, no association between subcortical brain volumes and common genetic risk for SZ was found, calling into question whether any of the above ENIGMA findings were driven by

genetic risk. Although common risk variants collectively account for a greater proportion of the genetic liability to SZ than known rare risk variants - such as copy number variation -, individually the latter show much higher penetrance for the disorder (ranging between 2-18%)[12]. Therefore, rare risk CNVs might be better suited to capture some of the brain anatomical variability associated with SZ. Following with Franke et al study[11], here we aimed to investigate the association between genetic risk for SZ, defined as individuals carrying at least one of the 12 CNVs known to increase risk for SZ, and volume of subcortical brain structures in a large sample of ~10,000 unaffected participants from the UK Biobank project. We hypothesised that individuals carrying rare SZ-associated CNVs (SZ-CNVs) will have a smaller volume in hippocampus, thalamus, amygdala and accumbens, but larger in pallidum (volume of lateral ventricles is not currently an available measure from UK Biobank participants). We based our selection of SZ-CNVs on previously published work[13,14], which found 12 specific CNVs to be significantly associated with SZ after correction for multiple testing. Since cognitive impairment is a core feature of SZ and previous research has shown genetic overlap between IQ and SZ[15], we also aimed to examine whether the volumes of subcortical brain structures that are associated with SZ-CNVs mediate previous reports of association between these SZ-CNVs and cognitive performace[16]. Of the few cognitive measures available from scanned participants in UK Biobank, we selected Fluid Intelligence due to its strong heritability and robustness against influences from education and training[17].

Materials and Methods

Participants

This study used a subsample of participants from UK Biobank (www.ukbiobank.ac.uk), for which >500,000 participants aged 40-69 years were recruited between 2006 and 2010, performing an extensive health related assessment at baseline and obtaining different biological samples, among them DNA. All subjects provided informed consent to participate in UK Biobank projects and agreed to have their health followed over many years. Ethical approval for the study was granted by the North West Multi-Centre Ethics committee. Data were released to Cardiff University after application to the UK Biobank (permission under project ref 17044).

Based on our aim to investigate participants with no personal history of severe mental disorders that could confound any association due to reverse causation, participants were removed if they were recorded as being affected by SZ, psychosis, autism spectrum disorder (ASD), dementia or intellectual disability (ID) across any of the following three diagnosis methods: self-reported diagnosis from a doctor at any assessment visit, self-reported diagnosis by a mental health questionnaire, a discharge code for the disease from a hospital visit; or if they self-reported other than white British and Irish descent. At this stage 1,112 participants with mental disorders and 46,522 participants of non-white British and Irish descent were removed from the original sample, resulting in a sample size of n= 454,985.

Genotyping, CNV calling and CNV QC

Genotyping was performed using the Affymetrix UK BiLEVE Axiom array (807,411 probes) on an initial 50,000 participants; the remaining were genotyped using the Affymetrix UK Biobank Axiom® array (820,967 probes). The two arrays are extremely similar (with over 95% common content). Sample processing at UK Biobank is described in their documentation (https://biobank.ctsu.ox.ac.uk/crystal/docs/genotyping_sample_workflow.pdf).
CNV calling was conducted following the same procedure as described in a previous study from our group[16]. Briefly, normalised signal intensity, genotype calls and confidences were generated using ~750,000 biallelic markers that were further processed with PennCNV-Affy software[20]. Individual samples were excluded if they had >30 CNVs, a waviness factor >0.03 or <-0.03 or call rate <96%. This quality control process resulted in the further exclusion of 13,652 individuals (3.0% of the remaining sample) bringing the sample size to n= 441,333. Individual CNVs were excluded if they were covered by <10 probes or had a density coverage of less than one probe per 20,000 base pairs[16].

CNV annotation

To date, 12 CNVs have been significantly associated with SZ after correction for multiple testing[13,14] and therefore constituted the focus of this study (referred to as SZ-CNVs). A list of these 12 CNVs, and the genomic coordinates of their critical regions, can be found in Supplemental Table 1. The breakpoints of all SZ-CNVs included in our study were manually inspected to confirm that they met

our CNV calling criteria (listed in Supplemental Table 1). Briefly, we required a CNV to cover more than half of the critical interval and to include the key genes in the region (if known), or in the case of single gene CNVs the deletions to intersect at least one exon and the duplications to cover the whole gene. As a control comparison, we used individuals that carried none of the 93 pathogenic CNVs that have previously proposed to be associated with neurodevelopmental disorders[18,19] (referred to as non-CNV carriers). This criteria for defining pathogenic CNVs has been fully described in our previous publication[16].

Brain imaging data

All MRI data included in this project were collected in a single Siemens Skyra 3T scanner located at UK Biobank's recruitment centre at Stockport (UK). Details of the brain imaging protocols and quality control used by UK Biobank have been published elsewhere[21]. Briefly, this project focuses on the 14 metrics of subcortical volumes - i.e. left and right thalamus, caudate, putamen, pallidum, hippocampus, amygdala and accumbens – generated and provided by UK Biobank after applying FIRST (FMRIB's Integrated Registration and Segmentation Tool[22]) to the T1-weighted brain images. Out of the subsample that so far fulfilled our selection criteria and passed genetic QC, brain MRI data was available for 9,112 individuals at the outset of this study (n=9,067 non-CNV carriers and n=49 SZ-CNVs carriers).

To avoid the potential effect of extreme values that could have been caused by problems during data processing, outlier brain volumes – defined as values above or below 2.5 standard deviations from the group mean - in any of the above 14 subcortical brain structures considered here were removed from the analyses. After removal of outliers, all 14 volumes were normally distributed. The volume of subcortical brain volumes was then z-transformed using as reference the mean and standard deviation from the non-CNV carriers group; therefore, individual z-scores for these variables represent the deviation in standard units from the non-CNV group's mean.*Cognitive test*

During their MRI visit, participants also underwent cognitive testing, which included a measure of Fluid Intelligence (FI). The FI test included in our analyses corresponds to the total number of correct answers out of 13 verbal and numerical reasoning questions that participants were able to answer within 2 minutes. The total number of correct answers was used for our analyses. FI scores were

available for 8,694 participants that passed our CNV QC and had MRI data in our sample. These FI scores were normally distributed. As with the above brain measures, FI scores were standardised in reference to the non-CNV group mean and standard deviation.

Analyses

To investigate association between subcortical brain volumes and CNV-carrying status, regression analyses with the former as the predicted variable and the later as the predictor were run for each brain structure. In an initial step, age, gender and brain size (total grey matter + white matter volume) were entered into the model, followed by CNV-carrying status. False Discovery Rate was used to account for multiple testing.

Brain volumes significantly associated with CNV-carrying status from the above analyses were further taken into a mediation analyses, only if they were also found to be significantly associated with performance in the FI test. Multiple mediation analysis was conducted using the latent variable analysis package (lavaan)[23] for R. Age, gender and brain size were included as covariates and the covariation between mediators was also factored into the model.

Results

A final sample 9,063 non-CNV and 49 SZ-CNVs carriers were included in the analyses investigating association between CNV carrying status and volume of subcortical brain structures. Among SZ-CNVs carriers (n=49), 49% carried the most common 15q11.2 deletion CNV. Our sample did not include carriers of the rarer SZ-CNVs (see table 1 for a comprehensive list of all 12 SZ-CNVs tested and their frequency on our sample). Previous work from our group has shown consistency of individual CNV frequencies between UK Biobank batches, and between the UK Biobank and other independent control datasets[16].

---------- insert table 1 around here ----------

Participant's mean age was 61.6 years (sd= 7.04, range= 45-73), with SZ-CNV carriers being approximately 2 years older than non-carriers (mean= 63.5(sd= 5.97) and 61.6(sd= 7.04) respectively; t(47.73)= 2.26, p=.029), and fairly equally split between genders (52% female

participants), with no difference in gender distribution across CNV carrying status ($Chi^2(1)= 0.68$, $p>.1$).

Subcortical brain volumes association with SZ-CNVs carrying status

SZ-CNV carrying status was associated with 7 out of the 14 subcortical volumes tested at a nominally significant level, 5 of which survived correction for multiple testing (Table 2). In all these subcortical structures, carrying a SZ-associated CNV was predictive of a reduction in volume compared with non-CNV carriers. Only two subcortical structures showed no association with SZ-CNV carrying status in either left or right hemisphere: caudate and amygdala (Table 2 and Figure 1).

---------- insert table 2 around here ----------

To determine whether any of these effects were driven by the most frequent SZ-CNV in our sample – i.e. 15q11.2 deletion – we tested subcortical brain volumes in 15q11.2 deletion carriers vs. non-CNV carriers, and in carriers of any SZ-CNVs other than the 15q11.2 deletion vs. non-CNV carriers. Albeit the loss in statistical power due to halving the size of the CNV carriers groups, the results of these two tests replicated the above findings; with both CNV carrier groups showing the same direction of effects relative to non-carriers for all but one subcortical structure (Figure 1, supplemental tables 3 and 4). The only exception was left hippocampus, where 15q11.2 deletion carriers showed a nominally significant reduction in volume compared to non-CNV carriers ($B= -0.46$, $SE= 0.18$, $p= 0.013$, $p_{FDR}= 0.062$), whereas carriers of any other SZ-CNVs showed no-significant difference (Figure 1, supplemental tables 3 and 4). A direct comparison between 15q11.2 deletion carriers and carriers of any other SZ-CNVs showed the volume of this structure to be reduced in 15q11.2 deletion carriers compare to carriers of any other SZ-CNVs ($B= -0.58$, $SE= 0.27$, $p= 0.035$).

---------- insert figure 1 around here ----------

Mediation of subcortical volume change over the association between CNV carrier status and cognitive performance

As expected from previous research[16], performance in fluid intelligence was associated with CNV carrying status in our sample, with SZ-CNV carriers performing worse than non-CNV carriers ($B= -0.55$, $SE= 0.14$, $p< 0.001$; after controlling for age, sex and brain size). Moreover, all five brain

volumes that were significantly associated with SZ-CNV status at corrected p-value, also showed to significantly associate with fluid intelligence: right hippocampus, thalamus and accumbens, and left putamen and pallidum (Table 3). Therefore, these five subcortical structures were taken forward into the mediation analysis. From this analysis (Figure 2), there is a significant direct effect of SZ-CNV carrying status over fluid intelligence (B= -0.46, p=0.002) and a significant indirect effect mediated by the right thalamus (B=-0.04, p=0.009). Right hippocampus and left putamen show a trend towards significance (B=-0.02, p=0.063; B=-0.02, p=0.060). Right accumbens and left pallidum do not significantly mediate the association between SZ-CNVs carrying status and fluid intelligence; however, the total indirect effect of these five variables remains significant (B=-0.07, p <0.001), accounting for almost 14% (p=0.006) of the variance of the association between SZ-CNV carrying status and fluid intelligence.

Discussion

The main aim of this study was to ascertain whether unaffected carriers of rare SZ risk variants manifest similar anatomical alterations in subcortical volumes to those previously described in clinical SZ samples. Our results show this to be the case only for some of the subcortical structures included here – i.e. thalamus, hippocampus and accumbens –, whereas in others we find no association with CNV carrying status – i.e. amygdala – or even an inverse association to that previously reported in clinical research – i.e. pallidum. Importantly, we show hippocampal volume to significantly mediate the association between CNV carrying status and cognitive performance, demonstrating its relevance for explaining phenotypic variance.

Concordant with our hypothesis, we found evidence for a reduced volume in SZ-CNV carriers compared to non-CNV carriers in three of the predicted subcortical brain structures. Thalamus, accumbens and hippocampus in the right hemisphere were found to be smaller in SZ-CNV carriers after correction for multiple testing. Thalamus and accumbens in the left hemisphere showed respectively a nominally significant reduction and a trend towards significance, indicating the same direction of effect, albeit milder. Although the right hippocampus showed the strongest effect-size in our sample – almost half standard deviation difference in volume between groups -, the left hippocampus showed not even a trend towards significance at uncorrected p-threshold; suggesting clear interhemispheric differences that warrant further research. These results largely concur with

recently reported results from two independent international consortia[7,8], which showed the volumes of these three subcortical structures to be reduced in SZ patients compared to healthy controls. Moreover, subjects at high risk for SZ (i.e. first-degree relatives or prodromal participants) have also shown reductions in these same structures compared to healthy samples[24-27], with a recent meta-analysis also suggesting that hippocampal volumetric differences would be restricted to the right hemisphere[28]. All these results together provide strong support that the volume of the thalamus, the accumbens and the right hippocampus represent genetically moderated premorbid risk markers for SZ.

Contrary to our hypotheses, we found reduced volume in the pallidum in SZ-CNV carriers rather than increased volume, as we predicted on the basis of the consortia results alluded to above[7,8], and no group differences in the volume of the amygdala - either left or right. A previous study from our group[29] showed a negative association between volume in the pallidum and risk for psychosis based on common variants in healthy volunteers, again opposing the results obtained from clinical samples. Like then, it can be argued here that results obtained from clinical groups can conceal the effects of illness related factors such use of antipsychotic drugs[30], and these could explain the differences between results from clinical and at risk but otherwise healthy samples. In any case, our results indicate that previous volumetric differences observed in pallidum and amygdala between patients and healthy controls are more likely to be a consequence of disorder status than a premorbid genetic marker of SZ. Future longitudinal studies following at risk populations into disorder development would be helpful in establishing the temporal sequence and potential causes of these anatomical changes.

Due to a sample size limitation, we were not able to study the potential separated effects of each individual SZ-CNV included in our study; however, we examined the differential effects of the most frequent CNV in our sample – 15q11.2 deletion – against the rest of SZ-CNVs tested as a group. Overall, the pattern of results was very similar between 15q11.2 deletion and the remaining SZ-CNVs, indicating a lack of CNV specificity over the volume of subcortical brain structures, suggestive of a common pathobiological effect for SZ related rare genetic variants. However, for the left hippocampus, carriers of the 15q11.2 deletion showed reduced volume compared to healthy controls – albeit this did not survive correction for multiple testing –, whereas carriers of any of the other SZ-

CNVs showed no reduction even at nominal level. In a direct comparison between these two SZ-CNVs carrier groups, the volume of the left hippocampus showed to be reduced in 15q11.2 deletion carriers compared with the carriers of any of the other SZ-CNVs. This suggests that the left hippocampus could be the subcortical brain structure most susceptible to variation due to the causal mechanisms for SZ linked to rare genetic variation. If confirmed, this would help to inform a potential characterization of phenotypic subtypes of SZ; in a similar manner to a recent study which showed that hippocampal volume – taken bilaterally - characterizes subtypes of SZ patients classified on the basis of cognitive decline[31]. However, the reduction in statistical power which resulted from dividing our sample into two CNV-carrier subgroups calls for caution when interpreting the above results. Therefore, further research in this area is warranted.

Finally, we investigated the impact of the above associations on a cognitive phenotype – i.e. score in fluid intelligence. Significant associations between SZ genetic factors and brain biomarkers are of interest if they can translate or modulate clinical phenotypes, since those have more potential to inform patients stratification and research into new treatment interventions. The results from our mediation analysis indicate that the volume of the five subcortical structures found to significantly differ between non-CNV and SZ-CNV carriers explain a significant proportion of the association between CNV carrying status and fluid intelligence, with the volume of the right thalamus showing the strongest effect. Therefore, part of the previously reported association between SZ-CNVs and cognition[16,32,33] is explained by the effect of rare variants on brain anatomy and its subsequent translation into cognitive performance. Our results do not exclude, though, that many other variables not accounted for in our study could also mediate this association between genetic risk and cognition; or that the right thalamus, or any of the other biomarkers identified here, could also mediate other CNV-phenotypic associations relevant for SZ, such as anhedonia.

It is important to note some of the limitations of this study. Despite this constituting, to our knowledge, the largest dataset containing CNVs and MRI data ever analysed, the number of CNV carriers still limits the power of our analytical approaches. The fact that these genetic variants are by nature rare – i.e. infrequent – and highly penetrant, resulted in less than 50 healthy carriers from an initial sample of ~10,000 participants. The UK Biobank project, though, continues to acquire data and has set a target of ~100,000 scanned/genotyped participants to be completed within the next few years. This final

sample will certainly improve our ability to explore genetic-biomarker-phenotypic associations, as well as providing replication samples for the results presented here. Also, despite the wealth of the UK Biobank data, phenotypic variables relevant for SZ or psychiatry in general are limited, which restricts its potential in this area of research. Finally, it is also important to note that the nature of recruitment in UK Biobank – volunteers put themselves forwards to be scanned – makes this resource not truly representative of the general population[34], though it is difficult to see how this could resulted in type I error in the present study.

In summary, previous unsuccessful attempts to associate common genetic risk with the volume of subcortical brain structures[11,35] resulted in the assumption that these biomarkers could not associate with genetic risk for schizophrenia. Here we prove this assumption to be wrong. From our results, genetic risk for schizophrenia - at least from the risk conferred by CNVs as opposed to common variants - is significantly associated with anatomical brain markers, and we also show this association to be relevant by virtue of mediating the correlation between genetic risk and a core clinical phenotype (i.e. cognitive performance).

References

1. Barbato, A. Psychiatry in transition: outcomes of mental health policy shift in Italy. Aust N Z J Psychiatry. **32**, 673-679 (1998).

2. Kooyman, I., Dean, K., Harvey, S., Walsh, E. Outcomes of public concern in schizophrenia. Br J Psychiatry Suppl. **194**, s29-s36 (2007).

3. Marwaha, S., Johnson, S. Schizophrenia and employment – a review. Soc Psychiatry Psychiatr Epidemiol. **39**, 337-349 (2004).

4. Chesney, E., Goodwin, G.M., Fazel, S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry. **13**, 153-160 (2014).

5. Siskind, D., McCartney, L., Goldschlager, R., Kisely, S. Clozapine v. first- second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry. **209**, 385-392 (2016).

6. Thompson, P.M., et al. The ENIGMA Consortium: large-scale collaborative analyses of neuroimaging and genetic data. Brain Imaging Behav. **8**, 153-182.

7. Van Erp, T.G., et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol Psychiatry. **21**, 547-553 (2016).

8. Okada, N., et al. Abnormal asymmetries in subcortical brain volume in schizophrenia. Mol Psychiatry. **21**, 1460-1466 (2016).

9. Hilker, R., et al. Heritability of schizophrenia and schizophrenia spectrum based on the Nationwide Danish Twin Register. Biol Psychiatry. **83**, 492-498 (2018).

10. Schizophrenia Working group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated loci. Nature. **511**, 421-427 (2014).

11. Franke, B., et al. Genetic influences on schizophrenia and subcortical brain volumes: large-scale proof of concept. Nat Neuroscience, **19**, 420-431 (2016).

12. Kirov, G., et al. The penetrance of copy number variations for schizophrenia and developmental delay. Biological Psychiatry. **75**, 378-385 (2014).

13. Levinson, D.F., et al. Copy number variants in schizophrenia: confirmation of five previous findings and new evidence for 3q29 microdeletions and VIPR2 duplications. Am J Psychiatry. **168**, 302-316 (2011).

14. Rees, E., et al. Analysis of copy number variations at 15 schizophrenia-associated loci. Br J Psychiatry. **204**, 108-114 (2014).

15. Hubbard, L., et al. Evidence of common genetic overlap between schizophrenia and cognition. Schziphr Bull. **42**, 832-842.

16. Kendall, K.M., et al. Cognitive performance among carriers of pathogenic copy number variants: analysis of 152,000 UK Biobank subjects. Biol Psychiatry. **82**, 103-110 (2016).

17. Gray, J.R., Thompson, P.M. Neurobiology of intelligence: science and ethics. Nat Rev Neurosci. **5**, 471-482.

18. Coe, B.P., et al. Refining analyses of copy number variation identifies specific genes associated with developmental delay. Nat Genet. **46**, 1063-1071 (2014).

19. Dittwald, P., et al. NAHR-mediated copy-number variants in a clinical population: mechanistic insights into both genomic disorders and Mendelizing traits. Genome Res. **23**, 1395-1409 (2013).

20. Wang, K. et al. PennCNV: An integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. Genome Res. **17**, 1665-1674 (2007).

21. Alfaro-Almagro, F., et al. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage, **166**, 400-424 (2018).

22. Patenaude, B., Smith, S., Kennedy, D., Jenkinson, M. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage. **56**, 907-922 (2011).

23. Rosseel, Y. lavaan: An R Package for Structural Equation Modelling. J Stat Softw. **48**, 1-36 (2012).

24. Harrisberger, F., et al. Alterations in the hippocampus and thalamus in individuals at high risk for psychosis. NPJ Schizoprenia, 16033; doi:10.1038/npjschz.2016.33. (2016).

25. Ivleva, E.I., et al. Gray matter volume as an intermediate phenotype for psychosis: bipolar-schizophrenia network on intermediate phenotypes (B-SNIP). Am J Psychiatry. **170**, 1285-1296 (2013).

26. Seidman, L.J., et al. Thalamic and amygdala-hippocampal volume reductions in first-degree relatives of patients with schizophrenia: an MRI-based morphometric analysis. Biol Psychiatry. **46**, 941-954 (1999).

27. Cooper, D., Barker, V., Radua, J., Fusar-Poli, P., Lawrie, S.M. 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**, 69-77 (2014).

28. Walter, A., et al. Hippocampal volume in subjects at clinical high-risk for psychosis: A systematic review and meta-analysis. Neurosci Biobehav Rev. **71**, 680-690 (2016).

29. Caseras, X., Tansey, K.E., Foley, S., Linden, D. Association between genetic risk scoring for schizophrenia and bipolar disorder with regional subcortical volumes. Transl Psychiatry. **5**, e692 doi:10.1038/tp.2015.195 (2015).

30. Navari, S., Dazzan, P. Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med. **39**, 1763-1777 (2009).

31. Weinberg, D., et al. Cognitive subtypes of schizophrenia characterized by differential brain volumetric reductions and cognitive decline. JAMA Psychiatry. **73**, 1251-1259 (2016).

32. Stefansson, H., et al. CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature. **505**, 361-366 (2014).

33. Männik, K., et al. Copy number variations and cognitive phenotypes in unselected populations. JAMA. **313**, 2044-2054 (2015).

34. Fry, A., et al. Comparison of sociodemographic and healthy-related characteristics of UK Bionbank participants with those of the general population. Am J Epidemiol. **186**, 1026-1034 (2017).

35. Reus, L.M., et al. Association of polygenic risk for major psychiatric illness with subcortical volumes and white matter integrity in UK Biobank. http://dx.doi.org/10.1101/080283.

Table 1. List of schizophrenia-associated CNVs and their prevalence (%) in our sample

CNV	n	Prevalence (%) in the sample	Prevalence (%) among carriers
1q21.1del	4	0.04	8.16
1q21.1dup	6	0.07	12.25
NRXN1del	2	0.02	4.08
3q29del	--	--	--
WBS_dup	--	--	--
15q11.2del	24	0.26	48.98
PWS_dup	--	--	--
15q13.3del	--	--	--
16p13.11dup	9	0.10	18.37
16p12.1del	2	0.02	4.08
16p11.2dup	2	0.02	4.08
22q11.2del	--	--	--
SZ-CNV carriers	49	0.54	100
CNV non-carriers	9,063	99.46	--
Total	9,112	100	--

Table 2. Summary statistics from linear regression analysis of the effect of SZ-CNV carrier status on the 14 subcortical brain volumes

Subcortical volume	$N_{non\text{-}carriers}$	$N_{carriers}$	B	SE	p	p_{fdr}
Thalamus (left)	8511	47	-0.18	0.09	0.052	0.091
Thalamus (right)	8515	47	-0.21	0.09	0.016	***0.046***
Caudate (left)	8501	48	-0.10	0.12	0.420	0.490
Caudate (right)	8514	48	-0.08	0.12	0.511	0.551
Putamen (left)	8535	48	-0.33	0.11	0.002	***0.013***
Putamen (right)	8525	47	-0.23	0.11	0.028	0.066
Pallidum (left)	8472	46	-0.26	0.12	0.036	0.071
Pallidum (right)	8480	47	-0.36	0.12	0.003	***0.013***
Hippocampus (left)	8484	46	-0.14	0.13	0.281	0.358
Hippocampus (right)	8460	47	-0.48	0.13	<0.001	***0.002***
Amygdala (left)	8540	46	-0.03	0.14	0.827	0.827
Amygdala (right)	8526	47	-0.20	0.14	0.155	0.217
Accumbens (left)	8505	47	-0.24	0.13	0.065	0.101
Accumbens (right)	8519	48	-0.34	0.13	0.007	***0.025***

In all the cases, results after controlling for the effects of age, sex and brain size. $N_{subgroup}$= number of observations in subgroup, this number changes on the basis of QC for each brain subcortical volume measure; B = difference from CNV non-carriers in z-scores; SE = standard error; p= nominal p-value; p_{fdr} = false discovery rate corrected p-values.

Table 3. Summary statistics from linear regression analysis of the effect of the volume of subcortical structures associated with SZ-CNV carrying status on the performance (correct responses) in the fluid intelligence test.

Subcortical volume	Cognitive test	n	B	SE	p
Thalamus (right)	Fluid intelligence	8202	0.09	0.02	***<0.001***
Putamen (left)		8225	0.04	0.01	***0.004***
Pallidum (right)		8167	0.03	0.01	***0.032***
Hippocampus (right)		8149	0.05	0.01	***<0.001***
Accumbens (right)		8202	0.02	0.01	***0.050***

In all the cases, results after controlling for age, sex and brain size.

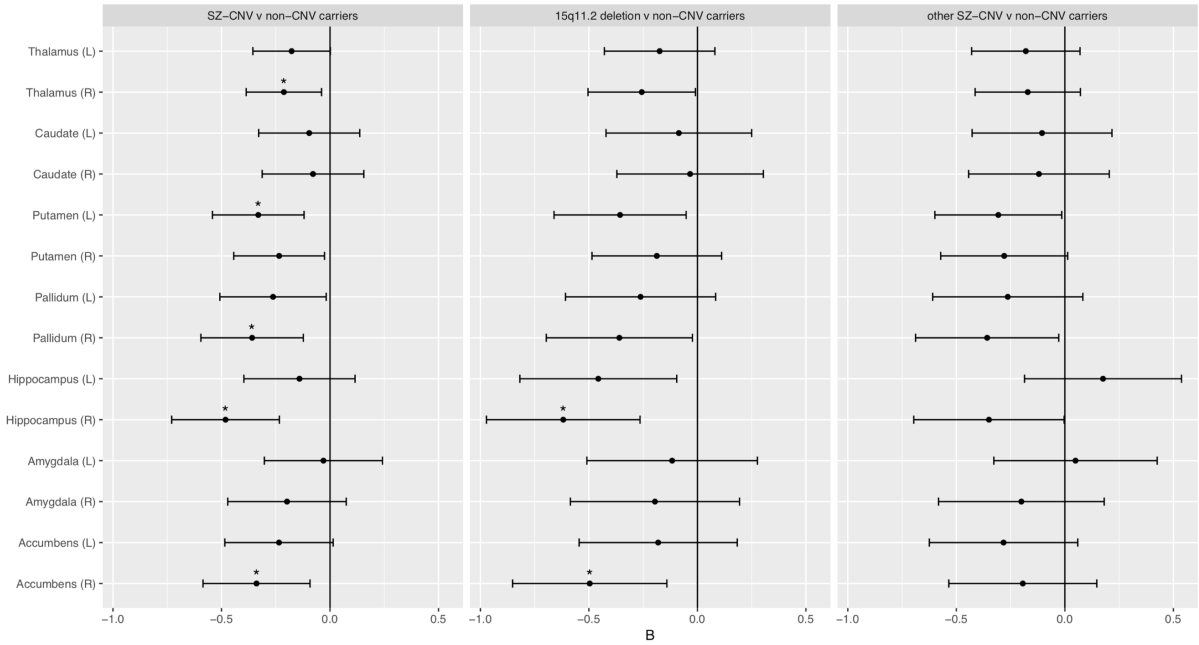

Figure 1. Differences in the volume of subcortical structures across SZ-CNV carriers v non-CNV carriers (left panel), 15q11.2 deletion v non-CNV carriers (middle panel) and other SZ-CNV than 15q11.2 deletion v non-CNV carriers (right panel). The x-axis reflects the standardised B value (z-score difference between groups, negative values indicate reduced volume in CNV carriers). Error bars indicate 95% confidence interval. Asterisks indicate differences that survive false discovery rate correction for multiple comparison.

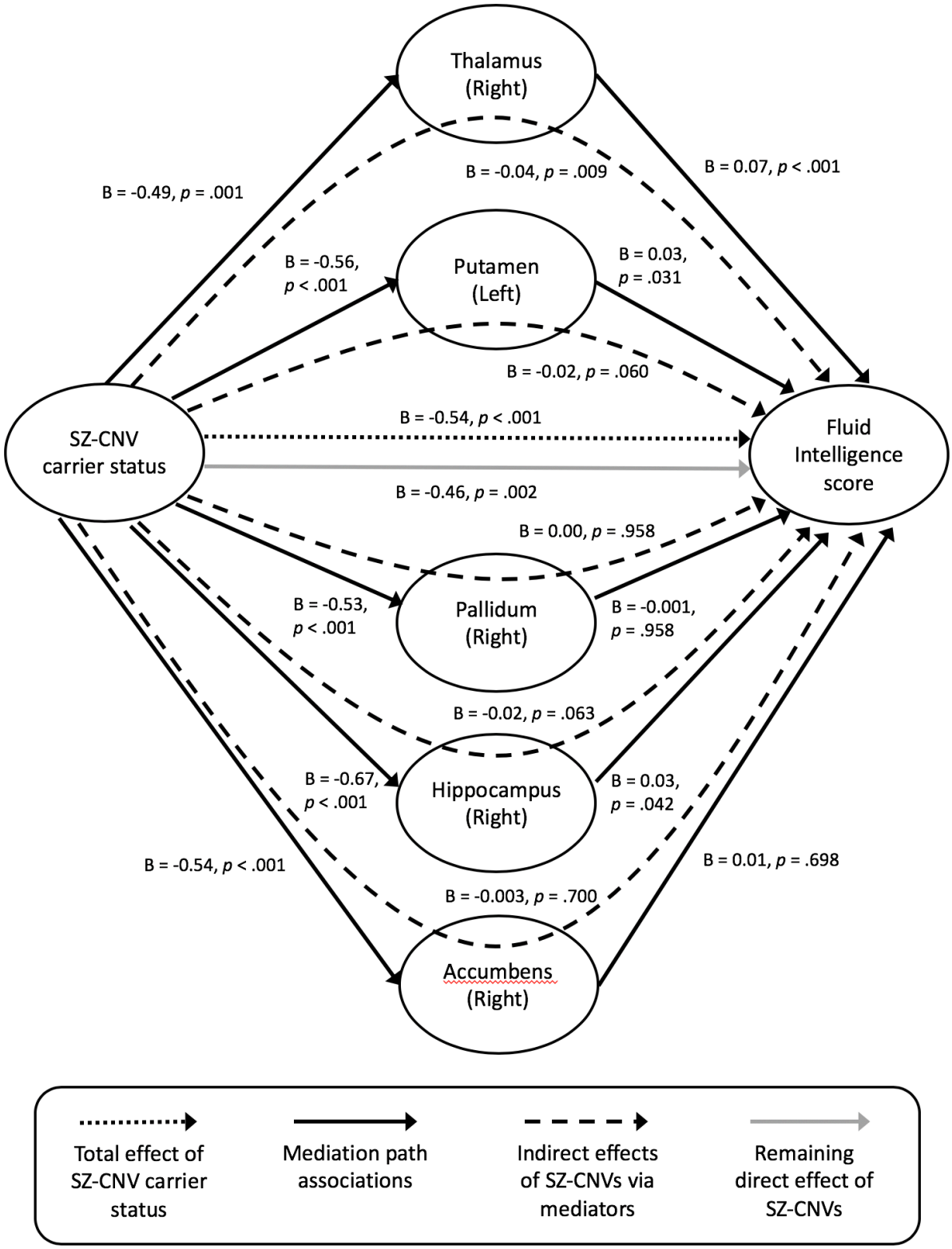

Figure 2. Results from the mediation analysis of brain volume over the association between SZ-CNV carrying status and performance in the fluid intelligence test. N= 7768 participants (44 SZ-CNV carriers v 7724 non-CNV carriers).