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

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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 9,291 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 due to 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 over 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. This study was restricted to individuals (n = 9,932) who had completed a brain MRI scanning session and from whom MRI data was available at the outset of this study, and carried at least one SZ-CNV[13,14] or none of the 93 CNVs previously proposed to be associated with neurodevelopmental disorders[18,19] (non-CNV carriers). 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. The final sample included 49 SZ-CNVs carriers and 9,291 non-CNV carriers. Data were released to Cardiff University after application to the UK Biobank (permission under project ref 17044).

Genotyping and CNV calling and annotation

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, a call rate <96%, or Log R Ratio standard deviation>0.35 This quality control process resulted in the exclusion of 25,069 individuals (5.1%). 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].

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. 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. This method

was also applied for the 93 pathogenic CNVs that constituted exclusion criteria for our group of non-CNV (see [16] for full methods on CNV calling).

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. Additionally, to avoid the potential effect of extreme values that could have been caused by problems during data processing, outlier volumes – defined as values above or below 2.5 standard deviations from the group mean - in any of those 14 structures 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 8,828 participants in our sample and 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 of 9,340 healthy participants (9,291 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 had shown consistency of individual CNV frequencies between UK Biobank batches, and between the UK Biobank and other independent control datasets[16].

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Participant's mean age was 61.6 years (sd= 7.03, range= 45-73), with SZ-CNVs carriers being approximately 2 year older than non-carriers (mean= 63.5(sd= 5.97) and 61.6(sd= 7.03) respectively; t(47.71)= 2.26, p=.028), and fairly equally split between genders (52% female participants), with no difference in gender distribution across CNV carrying status ($Chi^2(1)= 0.65$, p>.1).

Subcortical brain volumes association with SZ-CNVs carrying status

SZ-CNVs 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 CNVs was predictive of a reduction in volume compared with non-CNV carriers. Only two subcortical structures showed no association with SZ-CNVs carrying status in either left or right hemisphere: caudate and amygdala (Table 2 and Figure 1).

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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 group, 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= -0.45, SE= 0.18, p= 0.014, p_{FDR}= 0.064), 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).

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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-CNVs 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, four of the 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 and thalamus, and left putamen and pallidum, with only the right accumbens not predicting cognitive performance (Table 3). Therefore, only the volume of these four subcortical structures were taken forward into the mediation analysis. From this analysis (Figure 2), there is a significant direct effect of SZ-CNVs carrying status over fluid intelligence (B= -0.46, p=0.002) and significant indirect effects mediated by right thalamus (B=-0.03, p=0.008) and right hippocampus (B=-0.02, p=0.033); left putamen and pallidum do not significantly mediate the association between SZ-CNVs carrying status and fluid intelligence; however, the total indirect effect of these four variables remains significant (B=-0.07, p <0.001), accounting for almost

14% (p=0.006) of the variance of the association between SZ-CNVs carrying status and fluid intelligence.

Discussion

The main aim of this study was to ascertain whether unaffected carriers of rare SZ risk variant 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 and thalamic volume to significantly mediate the association between CNV carrying status and cognitive performance, demonstrating their relevance for explaining phenotypic variance.

Concordant with our hypothesis, we found evidence for a reduced volume in SZ-CNVs 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-CNVs 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-CNVs 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 some of these subcortical structures – mainly right thalamus and hippocampus – significantly mediate the association between SZ-CNV risk and cognitive performance; in other words, part of the previously reported association between SZ-CNVs and cognition[16,32,33] is explained by the effect of these rare variants over 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 and hippocampus, or other biomarkers identified here – e.g. right accumbens – 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).

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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	0.53	100
CNV non-carriers	9,291	99.47	--
Total	9,340	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)	8727	47	-0.18	0.09	0.052	0.091
Thalamus (right)	8728	47	-0.21	0.09	0.016	***0.045***
Caudate (left)	8718	48	-0.10	0.12	0.418	0.488
Caudate (right)	8728	48	-0.08	0.12	0.502	0.540
Putamen (left)	8751	48	-0.33	0.11	0.002	***0.013***
Putamen (right)	8741	47	-0.23	0.11	0.029	0.068
Pallidum (left)	8687	46	-0.26	0.13	0.035	0.071
Pallidum (right)	8697	47	-0.36	0.12	0.003	***0.013***
Hippocampus (left)	8698	46	-0.14	0.13	0.288	0.367
Hippocampus (right)	8673	47	-0.48	0.13	<0.001	***0.002***
Amygdala (left)	8755	46	-0.03	0.14	0.828	0.827
Amygdala (right)	8741	47	-0.20	0.14	0.152	0.213
Accumbens (left)	8718	47	-0.24	0.13	0.064	0.099
Accumbens (right)	8737	48	-0.34	0.13	0.007	***0.026***

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	8401	0.09	0.02	***<0.001***
Putamen (left)		8427	0.04	0.01	***0.003***
Pallidum (right)		8370	0.03	0.01	***0.045***
Hippocampus (right)		8349	0.05	0.01	***<0.001***
Accumbens (right)		8406	0.02	0.01	0.076

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

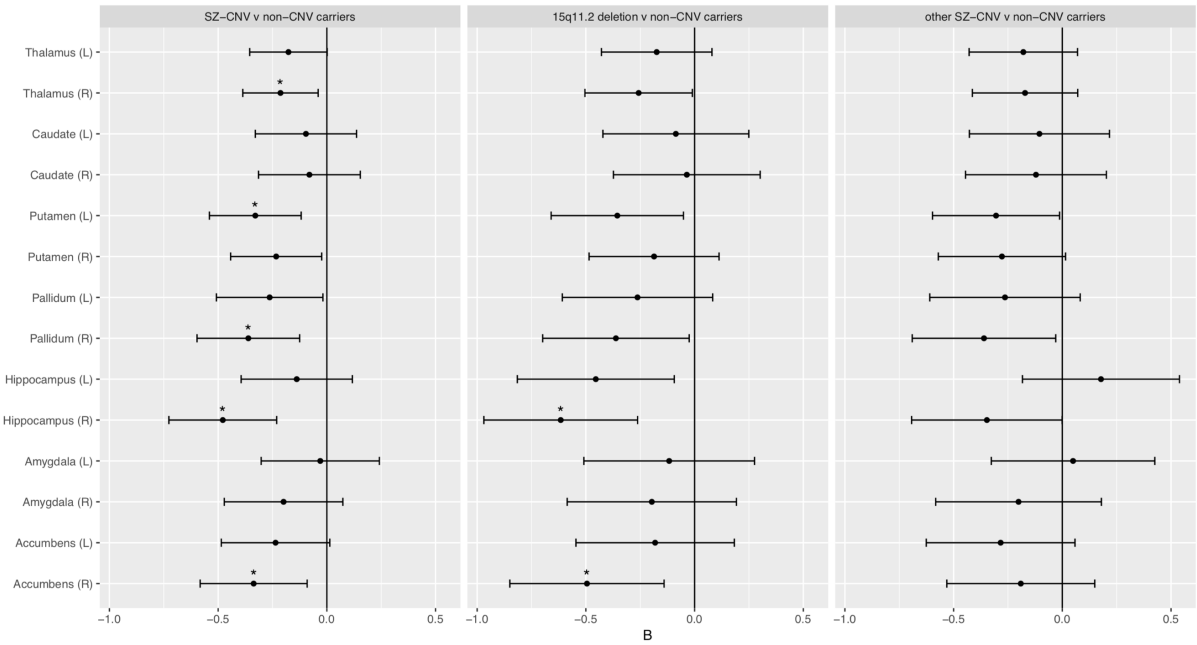

Figure 1. Differences in the volume of subcortical structures across SZ-CNV carriers v non-CNV carriers (left panel), 15q11.2 deletion v non-CNV carriers (middle panel) and other SZ-CNV than 15q11.2 deletion v non-CNV carriers (right panel). The x-axis reflects the standardised B value (z-score difference 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.

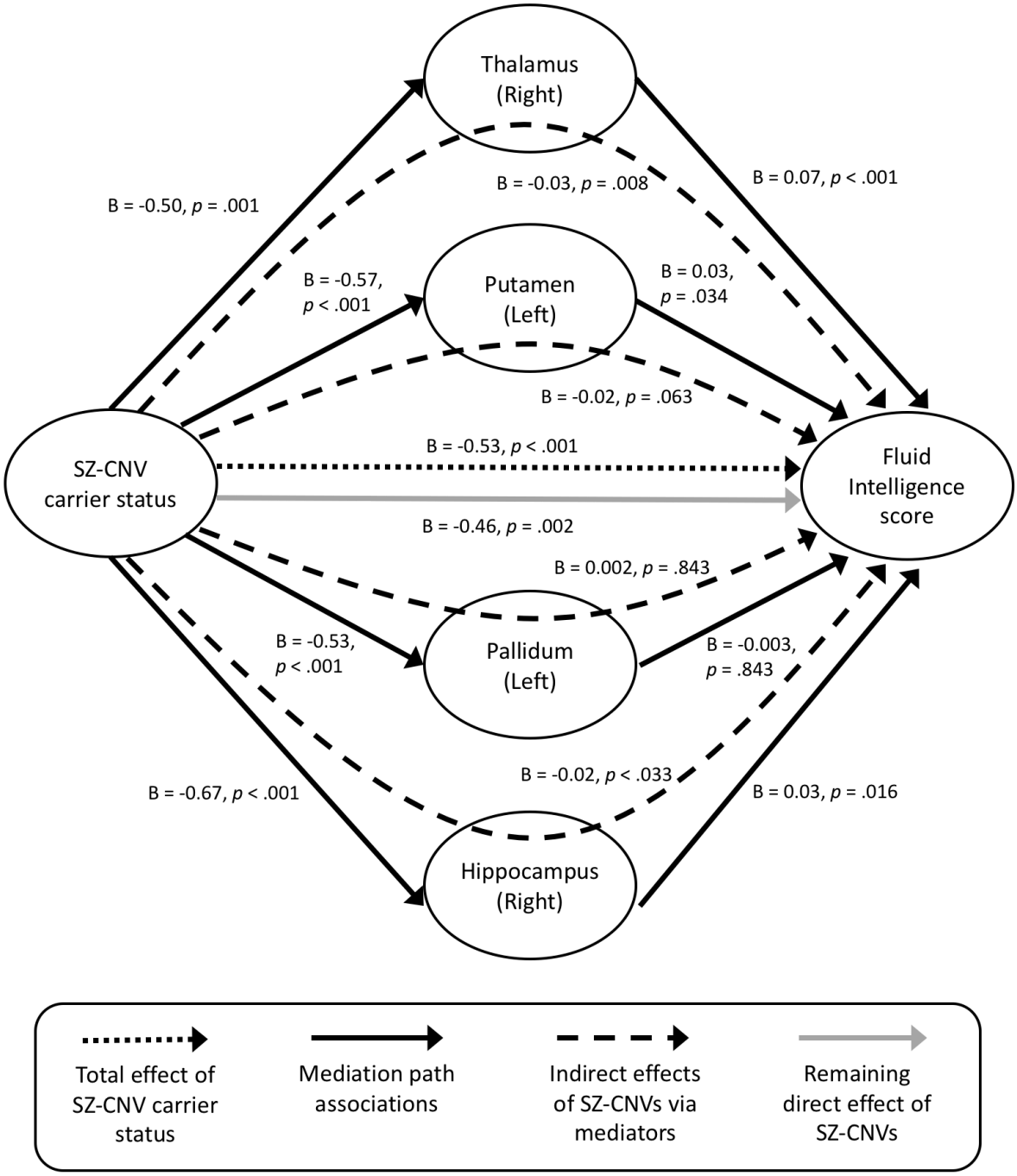

Figure 2. Results from the mediation analysis of brain volume over the association between SZ-CNV carrying status and performance in the fluid intelligence test. N= 8050 participants (44 SZ-CNV carriers v 8006 non-CNV carriers).

Supplementary material

Supplemental Table 1. List of schizophrenia associated CNVs with critical region coordinates and calling criteria

Syndrome	**Locus**	**Critical/Unique Sequence Region (hg19)**	**N Bialleleic Axiom probes**	**PSD Genes (from 685 PSD genes)**	**Calling criteria**
1q21.1 del	1q21.1	chr1:146,527,987-147,394,444	289		Size >50% of critical region
1q21.1 dup	1q21.1	chr1:146,527,987-147,394,444	289		Size >50% of critical region
NRXN1 del	2p16.3	chr2:50145643-51259674	235	*NRXN1*	Exonic deletions
3q29 del	3q29	chr3:195,720,167-197,354,826	627	*DLG1*	Size >50% of critical region
WBS dup	7q11.23	chr7:72,744,915-74,142,892	349	*STX1A*	Size >50% of critical region
15q11.2 del BP1-BP2	15q11.2	chr15:22,805,313-23,094,530	145	*CYFIP1*	Size >50% of critical region
PWS/AS dup	15q11.2q12	chr15:22,805,313-28390339	1807	*CYFIP1*	Full critical region, ~4Mbp
15q13.3 del BP4-BP5	15q13.3	chr15:31,080,645-32,462,776	466		Size >50% of critical region
16p13.11 dup	16p13.11	chr16:15,511,655-16,293,689	349	*MYH11*	Size >50% of critical region
16p12.1 del (520kb)	16p12.1	chr16:21,950,135-22,431,889	168	*UQCRC2*	Size >50% of critical region
16p11.2 dup (593kb)	16p11.2	chr16:29,650,840-30,200,773	193	*ALDOA,CORO1A,MAPK3,TAOK2*	Size >50% of critical region
22q11.2 del	22q11.2	chr22:19,037,332-21,466,726	843	*PI4KA,SEPT5*	Size >50% of critical region

Supplemental Table 2. Summary statistics from linear regression analysis of the effect of 15q11.2 deletion carrier status on the 14 subcortical brain volumes

Subcortical volume	non-CNV carriers	15q11.2del carriers	B	SE	p-value	FDR
Thalamus (left)	8727	23	-0.17	0.13	0.179	0.314
Thalamus (right)	8728	23	-0.26	0.13	0.041	0.096
Caudate (left)	8718	23	-0.09	0.17	0.615	0.662
Caudate (right)	8728	23	-0.04	0.17	0.836	0.836
Putamen (left)	8751	23	-0.36	0.16	0.022	0.077
Putamen (right)	8741	23	-0.19	0.15	0.222	0.345
Pallidum (left)	8687	23	-0.26	0.18	0.137	0.274
Pallidum (right)	8697	23	-0.36	0.17	0.035	0.096
Hippocampus (left)	8698	23	-0.45	0.18	0.014	0.064
Hippocampus (right)	8673	23	-0.62	0.18	0.001	0.009
Amygdala (left)	8755	22	-0.12	0.20	0.560	0.653
Amygdala (right)	8741	23	-0.20	0.20	0.322	0.419
Accumbens (left)	8718	22	-0.18	0.19	0.329	0.419
Accumbens (right)	8737	23	-0.50	0.18	0.006	0.044

Supplemental Table 3. Summary statistics from linear regression analysis of the effect of carrying any SZ-CNV other than 15q11.2 deletion status on the 14 subcortical brain volumes

Subcortical volume	Non-CNV carriers	non15q11.2del CNV-carriers	B	SE	p-value	FDR
Thalamus (left)	8727	24	-0.18	0.13	0.159	0.290
Thalamus (right)	8728	24	-0.17	0.12	0.166	0.290
Caudate (left)	8718	25	-0.11	0.16	0.522	0.562
Caudate (right)	8728	25	-0.12	0.17	0.463	0.541
Putamen (left)	8751	25	-0.30	0.15	0.041	0.220
Putamen (right)	8741	24	-0.28	0.15	0.063	0.220
Pallidum (left)	8687	23	-0.26	0.18	0.135	0.290
Pallidum (right)	8697	24	-0.36	0.17	0.032	0.220
Hippocampus (left)	8698	23	0.18	0.18	0.334	0.426
Hippocampus (right)	8673	24	-0.35	0.18	0.050	0.220
Amygdala (left)	8755	24	0.05	0.19	0.797	0.797
Amygdala (right)	8741	24	-0.20	0.19	0.301	0.421
Accumbens (left)	8718	25	-0.28	0.17	0.104	0.290
Accumbens (right)	8737	25	-0.19	0.17	0.272	0.421