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Title Page:

Rare copy number variations are associated with poorer cognition in schizophrenia

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Abstract

Background

Cognitive impairment in schizophrenia is a major contributor to poor outcomes yet its causes are poorly understood. Some rare copy number variants (CNVs) are associated with schizophrenia risk and impact cognition in healthy populations but their contribution to cognitive impairment in schizophrenia has not been investigated. We examined the effect of 12 schizophrenia CNVs on cognition in those with schizophrenia.

Methods

General cognitive ability was measured using the MATRICS composite z-score in 875 schizophrenia cases, and in a replication sample of 519 schizophrenia cases using WAIS Full-Scale IQ. Using linear regression we tested for association between cognition and schizophrenia CNV status, covarying for age and sex. In addition, we tested whether CNVs hitting genes in schizophrenia enriched gene sets (loss of function intolerant or synaptic gene sets) were associated with cognitive impairment.

Results

23 schizophrenia CNV carriers were identified. Schizophrenia CNV carriers had lower general cognitive ability than non-schizophrenia CNV carriers in discovery ($\beta=-0.66$, 95%CI = -1.31 to -0.01) and replication samples ($\beta=-0.91$, 95%CI = -1.71 to -0.11), and after meta-analysis ($\beta=-0.76$, 95%CI=-1.26 to -0.25, $p=0.003$). CNVs hitting loss of function intolerant genes were associated with lower cognition ($\beta= -0.15$, 95%CI=-0.29 to -0.001, $p=0.048$).

Conclusions

In those with schizophrenia, cognitive ability in schizophrenia CNV carriers is 0.5-1.0 standard deviations below non-CNV carriers, which may have implications for clinical

assessment and management. We also demonstrate that rare CNVs hitting genes intolerant to loss of function variation lead to more severe cognitive impairment, above and beyond the effect of known schizophrenia CNVs.

Introduction

Schizophrenia is associated with poor functioning across multiple domains of cognition including attention, processing speed, reasoning/problem solving, social cognition, verbal learning visual learning and working memory (1,2). These impairments can be indexed by a single factor representing a generalised cognitive deficit that explains the majority of cognitive impairment in schizophrenia (3). More severe cognitive impairment is associated with poorer functional outcomes (4) and remains one of the most challenging aspects of the disorder to treat (5).

A number of large, rare genetic copy number variants (CNVs) substantially increase risk of neurodevelopmental disorders including schizophrenia, autism and intellectual disability (6–8). Whilst the presentation of these disorders is markedly different, a commonality is cognitive impairment and it is plausible these CNVs may act through pathways that impact upon cognitive functioning (9). Whilst there is broad enrichment of neurodevelopmental CNVs in schizophrenia (10) only a small subset (12 ‘schizophrenia CNVs’) have been shown to be robustly associated with the disorder (7,8).

Healthy carriers of these schizophrenia CNVs, with no history of psychiatric illness, have lower mean cognitive ability by up to 1 standard deviation below population controls across multiple cognitive domains, including generalised cognition (11,12). However, the contribution of CNVs that confer increased risk for schizophrenia on cognitive functioning within schizophrenia cohorts is poorly understood, having not been studied in sufficiently powered samples.

The literature is inconsistent with respect to the contribution of rare CNV burden on cognition in schizophrenia, with varying definitions of CNV burden, including different frequency cut offs and CNV size thresholds. Yeo and colleagues reported increased burden of rare CNV deletions was correlated with lower full-scale IQ in a small schizophrenia patient cohort (13). In contrast, a study of 350 schizophrenia cases and 322 controls found no evidence of association between measures of CNV burden (number of CNVs or genes hit) and IQ (14), although relatively small CNVs were included (>50kb), and no frequency cut off was applied. It is challenging to draw substantive conclusions from these small studies and substantially larger samples and replication are required to provide robust evidence for rare CNV burden influencing cognition in schizophrenia.

To our knowledge no large studies to date have investigated whether CNVs hitting genes from particular gene-sets may be associated with cognition in schizophrenia (15,16), although one study in 161 schizophrenia patients reported no association between the number of brain-expressed genes hit by rare CNVs and cognition (17).

Using a within-case cross-sectional design, our study has two primary aims: our first aim was to investigate whether schizophrenia cases with known schizophrenia CNVs have greater impairment on measures of general cognitive ability than those without such CNVs. Our second aim was to investigate whether large, rare CNVs that hit genes in loss of function intolerant or synaptic gene sets are associated with poorer cognitive functioning.

Methods and materials

CardiffCOGS Sample

The discovery case sample comprised 875 cases from Cardiff Cognition in Schizophrenia (Cardiff COGS), a UK based sample described elsewhere (15,18). Cases were recruited from psychiatric clinics as diagnosed with schizophrenia, schizoaffective disorder or schizophreniform psychoses and interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (19). The interview was combined with a vignette summary of medical records to arrive at a best-estimate lifetime diagnosis using DSM-IV criteria by trained raters (20). Participants were aged 17 to 74 and were excluded if they had a current diagnosis of substance dependence disorder, intellectual disability or had a known diagnosis of a neurological disorder known to affect cognitive functioning.

Cognitive Assessment

Cognitive ability was measured using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (21). The MATRICS battery measures performance on seven cognitive domains (attention/vigilance, reasoning/problem solving, speed of processing, social cognition, verbal learning/memory, visual learning/memory, working memory) (1). Raw scores of MATRICS tests were standardised to z-scores based on the mean and standard deviation of 103 UK healthy controls who were recruited from the community and matched on age and sex to the case sample as we have previously described (18). Test Z-scores were converted into domain Z-scores and a composite Z-score following the MCCB manual procedures. The composite Z-score represents a measure of generalised cognition in schizophrenia compared to controls across the seven domains. To test premorbid general cognitive ability, we used raw scores

from the National Adult Reading Test (NART), where individuals are required to read and pronounce a list of 50 words (22).

Symptoms and Functioning

We also examined associations between CNV status and clinical characteristics. To measure symptoms we used the global symptom domain scores based on lifetime ratings of the SAPS (23) and SANS (24). Social functioning was measured using the total score from the Social Functioning Scale (25).

Irish sample

The replication sample comprised 679 clinically stable patients with a *DSM-IV* diagnosis of schizophrenia, schizoaffective disorder or schizophreniform psychosis from five sites across Ireland. Diagnosis was confirmed by trained psychiatrists using the *Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID)* (26). Participants were aged 18 to 65, had no history of substance abuse in the preceding 6 months, and had no previous head injury with loss of consciousness, a history of seizures or intellectual disability.

Cognitive Assessment

General cognitive ability was measured using Full-scale IQ (N=519), performance IQ (N= 526) and verbal IQ (N=673), which were derived using vocabulary, similarities, block design and matrix reasoning subtests from the Wechsler Adult Intelligence Scale, third edition (WAIS-III) (27). Control data for full scale, performance and verbal IQ were available in 322, 324 and 327 individuals respectively. IQ data in Irish cases was Z-transformed by subtracting the control IQ mean from the case IQ score and dividing by the control standard deviation (ensuring IQ scores were on the same z-transformed scale as CardiffCOGS).

Genotyping/CNV Calling

Genotyping of CardiffCOGS was performed at the Broad Institute, Cambridge, Massachusetts on the HumanOmniExpressExome-8v1 (Combo array). CNV calls were generated in 738 individuals. The Irish sample was genotyped using either the Affymetrix SNP Array 6.0 platform as part of the Wellcome Trust Case Control Consortium 2 (WTCCC2) (28) or an Illumina HumanCoreExome (+custom) SNP array at Cardiff University. Samples analysed at the Broad Institute and at Cardiff University underwent the same CNV calling procedure. Briefly, raw intensity data were processed using the Illumina Genome Studio software (v2011.1). Log R ratios (LRR) and B-allele frequencies (BAF) were generated for CNV calling. CNVs were called with the PennCNV (<http://www.openbioinformatics.org/penncnv/>) algorithm following the standard protocol adjusting for GC content. Additional QC details can be found in the supplementary text. For samples analysed by the WTCCC2, CNV calls were created using Birdseye from Birdsuite (version 1.5.5; (29)).

Analyses

Relationship between schizophrenia CNVs, CNV burden and cognitive ability

A list of 12 schizophrenia CNVs were taken from our earlier publications (8,10) (see Supplementary Table 1). Individuals were classed as having a schizophrenia CNV if they carried at least one CNV at these loci which spanned $\geq 50\%$ of the critical region or hit a critical gene. Linear regression models were used to investigate the relationship between the MATRICS composite score and schizophrenia CNV status in CardiffCOGS with age at interview and sex included as covariates. All analyses described were performed using R (version 3.2.2) (30).

The MATRICS composite score is strongly correlated with full-scale IQ (31), thus we selected that as the primary outcome measure in the Irish sample. A linear regression model was

used to investigate the relationship between Z-transformed full-scale IQ and schizophrenia CNV status in the Irish sample with age and sex included as covariates.

As both the MATRICS composite score and Z-transformed full-scale IQ were standardized on equivalent scales, we used odds ratios and standard errors from their individual regressions to perform a fixed-effects meta-analysis across the two samples using the R package “metafor” (32).

We performed exploratory analysis using the individual MATRICS domain z-scores and NART raw scores as outcomes in CardiffCOGS and Z-transformed performance and verbal IQ in the Ireland samples. Linear regression models were performed as described above.

Other exploratory CNV burden analyses were conducted to look at possible associations between rare CNV burden (total CNV length, total number of genes hit by CNVs and total number of CNVs) and general cognitive ability. All three measures of CNV burden were jointly analysed in the same linear regression, adjusted for age and sex and whether they carried a schizophrenia CNV. For each individual, total CNV length was calculated by summing the length of every CNV greater than 100kb. Total number of genes hit was derived by counting the number of times a CNV overlapped at least one base pair within the transcription start/end sequence of a gene. If an individual did not carry a CNV > 100KB, their burden scores were set as 0. We used hg19/build37 protein-coding gene coordinates from the NCBI RefSeq annotation release 105.

Relationship between loss of function intolerant / synaptic gene sets and cognition

For gene set analysis we selected two large gene-sets that are the most consistently enriched in common and rare variant schizophrenia studies (15,16); loss of function

intolerant and synaptic genes. In total, 3488 loss of function intolerant genes were used (probability of loss of function intolerant (pLI) > 0.9) as defined by the Exome Aggregation Consortium (16). 1112 synapse genes were downloaded from SynGo (33), which is the most comprehensive database of genes associated with functional roles in the synapse and derived using experimental data and expert manual curation. Linear regression modelled whether the MATRICS composite z-score was predicted by the total number of genes hit in each gene-set by a rare CNV, covarying for age, sex and total number of genes hit genome-wide by rare CNVs and whether they carried a SZ CNV.

Results

Relationship between schizophrenia CNVs, CNV burden and cognitive ability

Cognitive data were available for 15 individuals with a schizophrenia CNV and 860 individuals without a schizophrenia CNV in CardiffCOGS. Schizophrenia CNV carriers had lower MATRICS composite scores than non-carriers ($\beta=-0.66$, 95%CI = -1.31 to -0.01, $p=0.047$).

Full-scale IQ data were available in 8 cases with a schizophrenia associated CNV and 511 of those without such a CNV in the independent Irish sample. Schizophrenia CNV carriers scored nearly one standard deviation below non-carriers ($\beta=-0.91$, 95%CI= -1.71 to -0.11, $p=0.025$), replicating both the direction and magnitude of effect in CardiffCOGS.

A fixed effects meta-analysis of both samples, totalling 23 schizophrenia cases with a schizophrenia CNV versus 1371 without, demonstrates a marked cognitive impairment in those with CNVs ($\beta= -0.76$, 95%CI= -1.26 to -0.25, $p=0.003$). Full results can be seen in **Table 1 / Figure 1**. The number of individuals with each schizophrenia CNV across both samples can be found in Supplementary Table 1.

We then performed exploratory analyses in CardiffCOGS to assess whether the individual MATRICS domains or symptom measures were predicted by whether an individual carried a schizophrenia CNV. Schizophrenia CNV carriers showed greater impairment on working memory ($\beta = -0.83$, 95%CI= -1.43 to -0.22, $p=0.007$), although this effect weakens after conditioning on the MATRICS composite score ($\beta = -0.34$, 95%CI= -0.67 to 0.002, $p=0.052$). Schizophrenia CNV carriers were more impaired across all MATRICS domains, although the differences were not statistically significant (see **Table 2/Figure 1**). On the NART, a measure of premorbid IQ, there was a significant difference between schizophrenia CNV carriers and non-carriers ($\beta = -7.16$, 95%CI= -12.44 to -1.87, $p=0.008$). Schizophrenia CNV carriers had higher scores for SANS items global alogia ($\beta = 1.40$, 95%CI= 0.34 to 2.35, $p=0.004$) and positive thought disorder ($\beta = 0.99$, 95%CI= 0.09 to 1.90, $p=0.032$).

In the Irish sample, schizophrenia CNV carriers were 0.9 standard deviations below non-carriers on Verbal IQ ($\beta = -0.90$, 95%CI= -1.65 to -0.15, $p=0.019$). Effect sizes for performance IQ were in the same direction of effect however differences between the two groups were not significant. Full results can be seen in Table 2/Figure 1.

We then tested whether the MATRICS composite z-score was predicted by any measure of rare CNV burden in CardiffCOGS. There was no evidence of association between cognition and any measure of CNV burden (total number of CNVs, total CNV length or total number of genes hit; see Supplementary Table 2).

Relationship between loss of function intolerant / synaptic gene sets and cognition

We investigated whether the MATRICS composite z-score was associated with the total number of genes hit within loss of function intolerant genes (16) and synaptic gene-sets

(33). Increased numbers of loss of function (LoF) intolerant genes hit by rare CNVs were significantly associated with lower composite z-scores ($\beta = -0.15$, 95%CI= -0.29 to -0.001, $p=0.048$). Results for number of LoF intolerant genes hit by CNV deletions showed a stronger effect on cognition ($\beta = -0.21$, 95%CI= -0.42 to 0.005, $p=0.055$) whereas genes hit by CNV duplications showed a weaker effect ($\beta = -0.05$, 95%CI= -0.18 to 0.09, $p=0.513$).

The number of genes hit by CNVs within the synaptic gene-set was not significantly associated with lower composite z-score ($\beta = -0.18$, 95%CI= -0.38 to 0.02, $p=0.088$), however the number of genes hit by CNV deletions was significantly associated with lower composite z-scores ($\beta = -0.22$, 95%CI= -0.43 to -0.02, $p=0.033$), whereas CNV duplications were not (for full results see **Table 3**).

Discussion

Our first aim was to investigate whether in people with schizophrenia, cognition was impacted by carrying known schizophrenia associated CNVs. In our meta-analysis, general cognitive ability was 0.8 standard deviations lower in 23 carriers of known schizophrenia CNVs compared with 1371 schizophrenia cases without a schizophrenia CNV. These findings should be considered within the context that individuals with schizophrenia are already performing approximately 1-2.5 standard deviations below healthy controls in our samples, indicating that our case samples are somewhat more cognitively impaired than schizophrenia samples in the literature (2). Nonetheless schizophrenia CNV carriers therefore represent a small but highly impaired group of individuals within those with schizophrenia.

Exploratory analyses in CardiffCOGS showed carriers of schizophrenia CNVs performed more poorly than non-carriers in the working memory domain. In our previous publication looking at cognition in schizophrenia CNV carriers (from the population) in the UK Biobank (excluding those with a diagnosis of schizophrenia), healthy individuals with a schizophrenia CNV performed 0.4 standard deviations below non-schizophrenia CNV carriers on a working memory task, the largest effect size for any single cognitive domain (11). This complements the findings from the present study and suggests tests of working memory may be particularly sensitive to the effects of CNVs on cognition. It is also noteworthy that schizophrenia CNV carriers had lower cognitive ability than non-carriers across every measure of cognition tested across both CardiffCOGS and Irish samples. A limitation of this analysis is the number of individuals with schizophrenia CNVs is small, a result of the practical constraints of studying rare events in deeply phenotyped clinical samples. In addition, we do not expect all schizophrenia CNVs to have equivalent cognitive phenotypes, as we have and others have demonstrated in population datasets (11,12).

Premorbid deficits in cognitive ability are common before the onset of psychosis in individuals that later develop schizophrenia (34). Some patients show relative stability between premorbid and current levels of general cognitive ability whereas others experience cognitive decline (35). We found significant differences in estimated premorbid cognitive ability between schizophrenia CNV carriers and non-carriers as measured using the NART, which may indicate CNVs are exerting their effect on cognition during development rather than after illness onset, although prospectively followed up samples will be required to confirm this finding. This result is supported by the fact that our results were consistent after including age of onset in our models suggesting illness duration is not making a major contribution to the cognitive impairments we see in those with CNVs. Whilst CNV testing is not part of the routine clinical assessment or management of those with schizophrenia our

results suggest cognitive impairment could be used to prioritise patients for CNV testing, as has been shown for other neurodevelopmental clinical features (36). Conversely, and since cognition itself is not routinely measured clinically, CNV detection could alert clinicians to patients who may benefit from more intensive monitoring and management early in the course of illness (37) to avoid the functional impact of cognitive impairment (38).

Exploratory analyses were also performed investigating whether schizophrenia CNV carriers were more likely to have more severe positive, negative or disorganised symptoms, or lower social functioning scores. We observed schizophrenia CNV carriers were more likely to have higher global alogia and positive thought disorder scores, findings in keeping with the cognition results given correlations between these symptom domains, however these findings require replication in larger samples.

Our second aim was to investigate whether large, rare CNVs that hit genes in loss of function intolerant or synaptic gene sets were associated with worse cognition. We observed a significant association between CNVs hitting loss of function intolerant genes and impaired cognition. This finding was driven mainly by loss of function intolerant genes in CNV deletions which seems intuitive given deletions would best mirror the protein truncating effects of variants by which the loss of function intolerant gene set was defined (16). The effect size of number of genes hit by loss of function intolerant genes (-0.21) on cognition in schizophrenia is consistent with estimates in the general population (-0.26) (39).

These findings provide evidence that rare CNVs hitting genes that are intolerant to loss of function rare variation lead to greater cognitive impairment in those with schizophrenia, over and above the effect of known schizophrenia risk CNVs (given these were adjusted for in the analysis). We could not seek replication of this result in the Irish dataset given the availability of CNV call data and thus requires replication.

In conclusion, using the largest combined clinical schizophrenia sample to date we have found evidence that first, individuals with schizophrenia CNVs display clinically important levels of cognitive impairment. Second, rare CNV that hit gene-sets enriched for schizophrenia are associated with poorer cognition in schizophrenia. Further work to identify cognitive impairments that are specific to individual schizophrenia CNVs will be important for tailoring personalised intervention and support.

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From Cardiff

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From Ireland

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Table 1 – Schizophrenia CNV linear regression statistics in CardiffCOGS and Irish samples

	Schizophrenia CNV Analyses					
	N (SZ CNV/No SZ CNV) ^b	Mean (s.d) SZ CNV	Mean (s.d) No SZ CNV	p ^a	B ^a	95% CI
Cardiff COGS sample						
MATRICS composite z-score	15/860	-2.88 (1.3)	-2.24 (1.4)	0.047	-0.66	-1.31 to -0.01
Age (Years)		43.9 (12.2)	43.4 (11.9)	5.80x10 ⁻²⁷	-0.04	-0.04 to -0.03
Sex (Male / Female)		7 / 8	532 / 328	0.003	0.26	0.09 to 0.43
Irish Sample						
Full-Scale IQ z-score	8/511	-2.79 (0.57)	-1.86 (1.19)	0.025	-0.91	-1.71 to -0.11
Age (Years)		43.7 (9.5)	41.2 (12.4)	0.640	-1.78	-9.26 to 5.69
Sex (Male / Female)		6/2	371/140	0.942	-0.01	-0.39 to 0.19
Meta-Analysis						
Composite z-score + Full-Scale IQ z-scores	23/1371	-2.84 (1.06)	-2.10 (1.32)	0.003	-0.76	-1.26 to -0.25

^a Beta coefficient and two-tailed p-value is adjusted for age and sex

^b n refers to the number of individuals included in the model

Table 2 – Exploratory analyses of schizophrenia CNV status and MATRICS/IQ subtest domains/symptom dimensions in CardiffCOGS and Ireland samples

	Exploratory Schizophrenia CNV Analyses (CardiffCOGS)					
	N (SZ CNV/No SZ CNV)	Mean (s.d) SZ CNV	Mean (s.d) No SZ CNV	p ^a	B ^a	95% CI
Attention	16/866	-2.14 (1.23)	-1.38 (1.25)	0.021	-0.72	01.33 to -0.11
Reasoning/Problem Solving	16/866	-2.17 (1.63)	-1.45 (1.32)	0.043	-0.61	-1.21 to -0.01
Social Cognition	16/865	-1.46 (1.64)	-1.04 (1.19)	0.148	-0.43	-1.02 tp 0.15
Speed of processing	15/866	2.41 (0.93)	-1.87 (1.14)	0.044	-0.56	-1.10 to -0.02
Verbal Learning	16/866	-2.80 (1.34)	-2.30 (1.55)	0.173	-0.51	-1.25 to 0.22
Visual Learning	16/866	-1.98 (1.71)	-1.57 (1.26)	0.221	-0.36	-0.95 to 0.22
Working Memory	15/865	-2.44 (1.17)	-1.59 (1.22)	0.007	-0.83	-1.43 to -0.22
Composite	15/860	-2.88 (1.3)	-2.24 (1.4)	0.047	-0.66	-1.31 to -0.01
NART	16/860	17.56 (11.4)	24.50 (10.72)	0.008	-7.16	-12.44 to -1.87
SAPS Global Hallucinations (Lifetime)	9 / 891	2.67 (1.65)	2.8 (1.51)	0.770	-0.15	-1.14 to 0.85
SAPS Global Delusions (Lifetime)	9 / 893	3.44 (1.3)	3.20 (1.07)	0.481	0.24	-0.45 to 0.96
SANS Global Alogia (Lifetime)	9 / 892	2.56 (0.73)	1.16 (1.46)	0.004	1.40	0.34 to 2.35
SANS Affective Flattening (Lifetime)	9 / 891	2.00 (1.22)	1.43 (1.44)	0.227	0.58	-0.36 to 1.53
SANS Avolition & Apathy (Lifetime)	9 / 893	2.33 (1.50)	2.01 (1.31)	0.452	0.33	-0.53 to 1.20
SANS Anhedonia (Lifetime)	9 / 891	2.33 (1.58)	2.20 (1.45)	0.770	0.14	-0.81 to 1.10
SANS Positive Thought Disorder (Lifetime)	9 / 892	2.00 (1.93)	1.02 (1.37)	0.032	0.99	0.09 to 1.90
SANS Inappropriate Affect (Lifetime)	9 / 891	0.33 (0.7)	0.28 (0.79)	0.866	0.45	-0.48 to 0.57
Social Functioning Scale (Total Score)	9 / 501	100.8 (6.61)	104.3 (9.59)	0.301	-0.35	-9.67 to 2.96
	Exploratory Schizophrenia CNV Analyses (Ireland)					
Performance IQ Z-score	9/517	-1.99 (0.45)	-1.44 (1.00)	0.096	-0.53	-1.16 to 0.10
Verbal IQ Z-score	10/663	-2.62 (0.65)	-1.75 (1.23)	0.019	-0.90	-1.65 to -0.15

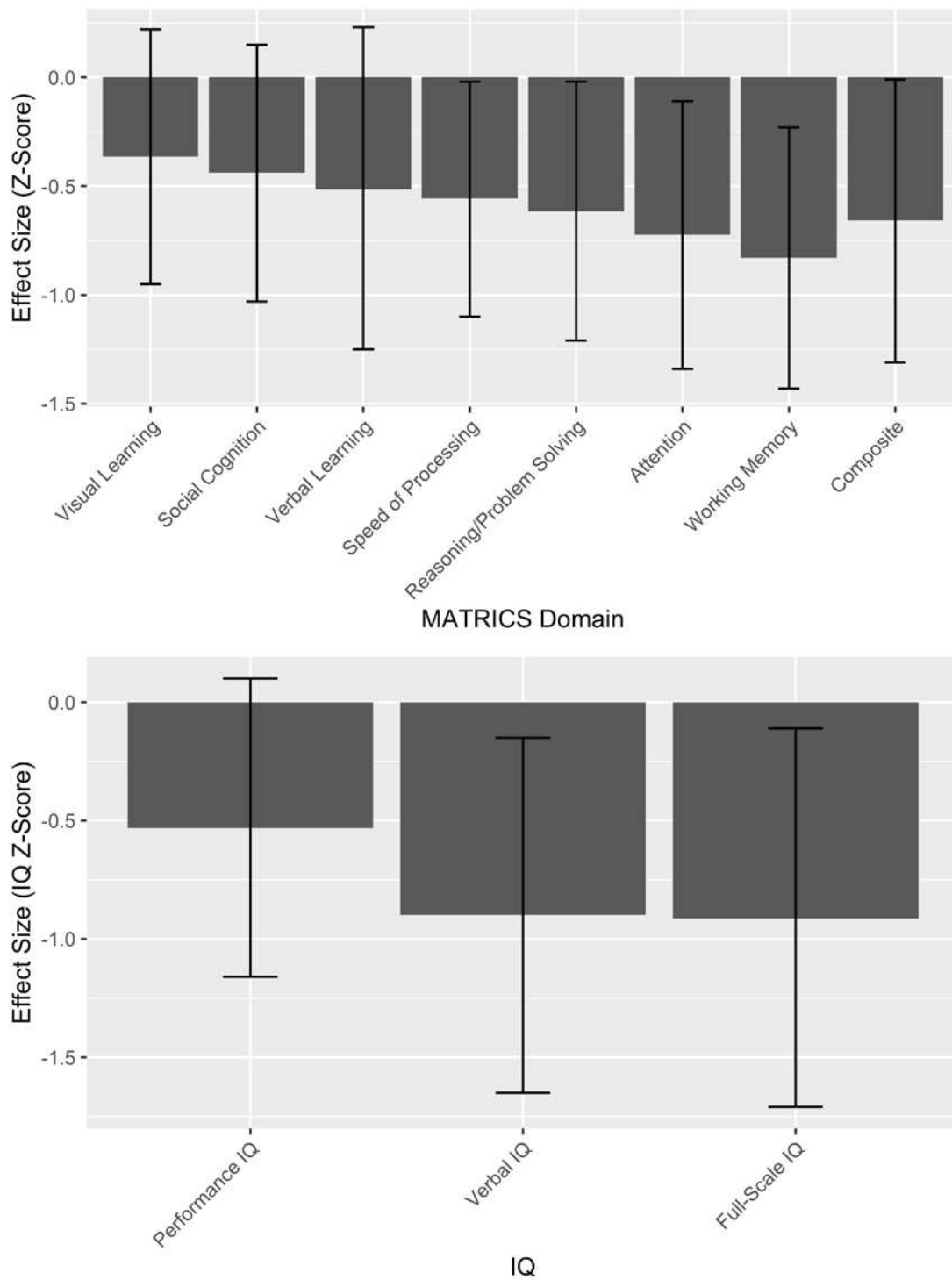
^a Beta coefficient and two-tailed p-value is adjusted for age and sex

Table 3 – Associations between the MATRICS composite z-score and number of genes hit in each gene-set

GeneSet	Type	P^a	B^a	95% CI
LoF Intolerant	All	0.048	-0.15	-0.29 to -0.001
LoF Intolerant	Deletions	0.055	-0.21	-0.42 to 0.005
LoF Intolerant	Duplications	0.513	-0.05	-0.18 to 0.09
Synapse	All	0.088	-0.18	-0.38 to 0.02
Synapse	Deletions	0.033	-0.22	-0.43 to -0.02
Synapse	Duplications	0.606	0.07	-0.20 to 0.35

^a Beta coefficient and two-tailed p-value is adjusted for age and sex, and total number of genes hit (excluding those in gene-set) and schizophrenia CNV carrier status

Figure 1 – Difference in Z-score for schizophrenia CNV carriers vs non schizophrenia CNV carriers (regression beta), lines represent the 95% confidence interval. The top figure shows difference in Z-scores in CardiffCOGS across the seven MATRICS domains and composite score (Top). The bottom figure shows differences in Z-score for three measures of IQ in Irish sample.



Rare Copy Number Variations Are Associated With Poorer Cognition in Schizophrenia

Supplemental Information

Extended Genotyping/CNV Calling Information

Sample level quality control was performed using the following QC metrics generated by PennCNV: BAF drift, LRR standard deviation, wave factor and total number of CNVs called per individual. Samples were excluded from all subsequent analyses if for any one of these metrics they represented an outlier in their source dataset. Duplicate samples were checked using identity by descent analysis in PLINK(1). Where duplicates were identified, the sample with the better QC was retained.

Raw CNVs in the same sample were joined when the distance between them was less than 50% of their combined length. CNVs were subsequently excluded if they had low probe coverage (<10), had a length of 10kb or less, overlapped with low copy repeats by more than 50% of their length, or had a probe density (calculated by dividing the size of the CNV by the number of probes covering it) greater than 20kb. CNV loci with a frequency greater than 1% were filtered out using PLINK.

The remaining rare CNVs underwent additional QC using an *in silico* median Z-score outlier method(2). This method standardises SNP probe intensities per individual across all probes, then standardises the intensity of each probe across all individuals. These QC stages help to reduce noise caused by natural fluctuations in probe intensity. The median Z-score for standardized probe intensities within a potential CNV region is used to identify real deletions and duplications, which are represented as outliers in the median Z-score distribution. Z-score histograms of CNVs with extreme Z-Scores (between -6 and -4, 2 and 4) were inspected manually using Illumina GenomeStudio v2011.1 software.

Table S1 – Overview of schizophrenia CNV carriers on CardiffCOGS and Irish samples

SZ Locus	Coordinates	MATRICES Composite Z-Score in CardiffCOGS (Diagnosis)	Z-Score Full-Scale IQ and (IQ Score) in Irish Sample (Diagnosis)
1q21.1dup	1:146527987-147394444	-1.30 (Schizophrenia) -3.68 (Schizophrenia)	N/A
<i>NRXN1</i> exonic del	2:50145643-51259674	-3.04 (Schizophrenia)	N/A
Williams-Beuren Syndrome dup	7:72744915-74142892	-4.51 (Schizophrenia)	-2.23 (85) (Schizophrenia)
15q11.2del	15:22805313-23094530	-3.03 (Schizophrenia) -1.37 (Schizophrenia) -4.30 (Schizophrenia)	N/A
16p13.11dup	16:15511655-16293689	-1.07 (Schizophrenia) -3.21 (Schizophrenia) -4.26 (Schizophrenia)	-2.61 (79) (Schizophrenia) -3.06 (72) (Schizophrenia)
16p12.1del	16:21950135-22431889	-1.12 (Schizophrenia) -1.32 (Schizophrenia)	-2.11 (87) (Schizoaffective Disorder)
16p11.2dup	16:29650840-30200773		-2.55 (80) (Schizophrenia) -2.62 (79) (Schizophrenia) -3.38 (67) (Schizophrenia)
22q11.2del	22:19037332-21466726	-3.74 (Psychosis) -3.58 (Schizophrenia) -3.63 (Schizophrenia)	N/A

Table S2 – Rare CNV burden associations predicting the MATRICES composite score

<u>CNV Burden</u>	<u>P^a</u>	<u>B^a</u>	<u>95% CI</u>
Number of CNVs	0.761	-0.02	-0.15 to 0.17
Number of genes hit	0.187	-0.02	-0.04 to 0.008
Size of CNV (KB)	0.918	-0.001	-0.01 to 0.41

^a Beta coefficient and two-tailed p-value is adjusted for age, sex and schizophrenia CNV carrier status

Table S3 – PLI Gene Count in CardiffCOGS

<u>Gene Symbol</u>	<u>EntrezID</u>	<u>PLI>0.9 Gene Count</u>
ABCC1	4363	3
ABR	29	1
ACACA	31	3
ADAMTS2	9509	1
ADCK5	203054	1
AKAP13	11214	7
ANAPC2	29882	1
ANGPT1	284	1
ANKRD28	23243	1
ANKRD34A	284615	1
ARC	23237	1
ARID5A	10865	1

ASAP1	50807	1
ATAD5	79915	1
ATG4B	23192	1
ATN1	1822	1
ATP8A2	51761	1
ATXN2L	11273	2
AUTS2	26053	1
B3GAT1	27087	1
BAZ1A	11177	1
BAZ1B	9031	1
BCL9	607	2
BCR	613	1
BIRC6	57448	5
BRIX1	55299	1
BTBD11	121551	1
CACNA1C	775	1
CACNA2D1	781	1
CANX	821	1
CCDC132	55610	1
CD19	930	2
CDC42BPB	9578	1
CDH13	1012	1
CFH	3075	2
CHD2	1106	1
CIZ1	25792	1
CLIP2	7461	1
CNTN4	152330	1
COL27A1	85301	7
CRLF3	51379	1
CTPS1	1503	1
CYC1	1537	1
CYFIP1	23191	1
DAZL	1618	1
DBN1	1627	1
DGCR8	54487	3
DLG2	1740	1
DMTF1	9988	1
DMXL1	1657	1
DNAJC2	27000	1
DNM1	1759	1
EEF1A1	1915	2
EIF3A	8661	1

EIF4B	1975	1
EPS8	2059	1
FAM135B	51059	1
FAM160B1	57700	1
FAM49B	51571	1
FAM83H	286077	1
FOXM1	2305	2
GATM	2628	1
GDF2	2658	1
GGNBP2	79893	3
GMDS	2762	1
GRIN1	2902	1
GTF2H1	2965	1
GTF2I	2969	1
GTF2IRD1	9569	1
HELLS	3070	1
HIRA	7290	3
HNF1B	6928	3
HNRNPH1	3187	1
HTR2A	3356	1
IPO11	51194	1
IQGAP1	8826	1
KANSL3	55683	1
KCNQ4	9132	1
KIAA0430	9665	3
KIAA1033	23325	1
KIF2A	3796	1
KLHL36	79786	1
KRT18	3875	1
LEO1	123169	1
LIMK1	3984	1
LINGO2	158038	7
LPCAT3	10162	1
LRRC4C	57689	1
LRRN1	57633	1
LTBP1	4052	5
MAF1	84232	1
MAML1	9794	1
MAP3K2	10746	1
MAPK3	5595	1
MAPK8	5599	1
MAZ	4150	1

MCM3AP	8888	1
MGAT4B	11282	1
MPHOSPH8	54737	1
MYH11	4629	4
NCKAP1	10787	1
NCKAP5	344148	1
NCOR1	9611	1
NCOR2	9612	1
NF1	4763	1
NFAT5	10725	1
NRXN1	9378	1
NSD1	64324	1
NUP153	9972	1
ODC1	4953	1
OTUD7A	161725	1
PAFAH1B1	5048	1
PIAS3	10401	1
PPIE	10450	2
PRKCE	5581	1
PRKG1	5592	1
PRMT8	56341	1
PSMA6	5687	1
PSMC2	5701	1
PSPC1	55269	1
PTK2	5747	1
PTPN6	5777	1
RAB11FIP4	84440	1
RAB24	53917	1
RAP1GAP2	23108	1
RB1CC1	9821	3
RBFOX2	23543	1
RBM8A	9939	1
REEP1	65055	1
RIMS2	9699	2
RMND5A	64795	1
RNF130	55819	1
RNF144A	9781	1
ROCK1	6093	1
RPL35A	6165	2
RPL8	6132	1
RPL9	6133	1
RPS10	6204	1

RRM2	6241	1
SATB1	6304	1
SCRIB	23513	1
SEMA4C	54910	1
SEMA4D	10507	1
SESN3	143686	1
SH2B1	25970	2
SIPA1L1	26037	1
SLC25A1	6576	3
SLC25A25	114789	1
SMCHD1	23347	1
SNRNP200	23020	1
SPATA13	221178	1
SQLE	6713	1
SRP54	6729	1
ST18	9705	2
STK38L	23012	1
SYNRG	11276	3
TAOK2	9344	1
TBX1	6899	3
TFDP2	7029	4
THAP4	51078	1
THSD7A	221981	1
TMOD3	29766	1
TNKS	8658	1
TNR	7143	2
TNS3	64759	1
TUBB4B	10383	1
UBAP2	55833	1
UBXN4	23190	1
UFD1L	7353	3
UNC5A	90249	1
USP10	9100	1
USP5	8078	1
USP7	7874	1
VPS35	55737	3
WBSCR22	114049	1
XKR6	286046	1
XRN1	54464	5
XYLT1	64131	1
ZC3H3	23144	1
ZDHHC8	29801	3

ZMYM2	7750	1
ZNF496	84838	1

Table S4 – Synaptic Gene Count in CardiffCOGS

Gene Symbol	EntrezID	SYNAPTIC Gene Count
ABR	29	1
ACTBL2	345651	1
ADRBK2	157	1
AKAP7	9465	1
ARC	23237	1
ARFGAP1	55738	1
ARFGAP3	26286	1
ARHGAP22	58504	1
ARHGAP39	80728	1
ATP6V1G1	9550	7
BCR	613	1
BIN1	274	1
CACNA1C	775	1
CACNA2D1	781	1
CANX	821	1
CDH13	1012	1
CHRNA4	1137	1
CHRNA7	1139	8
CLSTN2	64084	1
CNTN6	27255	1
COMT	1312	3
CRKL	1399	5
CYFIP1	23191	1
DBN1	1627	1
DGCR8	54487	3
DLG2	1740	1
DNM1	1759	1
DOC2A	8448	1
DRD5	1816	2
DVL1	1855	1
EEF1D	1936	1

EEF2K	29904	2
EIF3A	8661	1
EIF4B	1975	1
EPS8	2059	1
FZD9	8326	1
GRIN1	2902	1
HNRNPH1	3187	1
HTR2A	3356	1
LRRC4C	57689	1
LRRTM3	347731	2
MAPK3	5595	1
NCKAP1	10787	1
NF1	4763	1
NRXN1	9378	1
P2RX6	9127	5
P2RX7	5027	1
PAFAH1B1	5048	1
PARK2	5071	9
PHB2	11331	1
PRKCE	5581	1
PRR7	80758	1
PRRT2	112476	1
PTK2	5747	1
RGS14	10636	1
RIMBP3	85376	3
RIMS1	22999	1
RIMS2	9699	2
RPL35A	6165	2
RPL38	6169	2
RPL8	6132	1
RPL9	6133	1
RPS10	6204	1
RPS3A	6189	1
RTN4R	65078	3
SCRIB	23513	1
SIPA1L1	26037	1
SLC18A3	6572	1
SNAP29	9342	5
STX1A	6804	1
SYNE1	23345	1
SYT10	341359	4

TAOK2	9344	1
TNR	7143	2
TUFM	7284	2
VPS35	55737	3

Supplementary References

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