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Title Page:

Rare copy number variations are associated with poorer cognition in schizophrenia

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Keywords: schizophrenia, copy number variation, cognition, schizophrenia CNV, CNV, general cognitive ability
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 (β=-0.66, 95%CI = -1.31 to -0.01) and replication samples (β=-0.91, 95%CI = -1.71 to -0.11), and after meta-analysis (β=-0.76, 95%CI=-1.26 to -0.25, p=0.003). CNVs hitting loss of function intolerant genes were associated with lower cognition (β = -0.15, 95%CI=-0.29 to -0.01, 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 schizophréniform 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 ≥ 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.
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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References


30. R Development Core Team R (2011): R: A Language and Environment for Statistical


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

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

*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

<table>
<thead>
<tr>
<th>Exploratory Schizophrenia CNV Analyses (CardiffCOGS)</th>
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<tbody>
<tr>
<td>N (SZ CNV/No SZ CNV)</td>
<td>Mean (s.d)</td>
<td>Mean (s.d)</td>
<td>P</td>
<td>B</td>
<td>95% CI</td>
<td></td>
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<td>Attention</td>
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<tr>
<td>16/866</td>
<td>-2.14 (1.23)</td>
<td>-1.38 (1.25)</td>
<td><strong>0.021</strong></td>
<td>-0.72</td>
<td>0.133 to -0.11</td>
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<td>Reasoning/Problem Solving</td>
<td>-2.17 (1.63)</td>
<td>-1.45 (1.32)</td>
<td><strong>0.043</strong></td>
<td>-0.61</td>
<td>-1.21 to -0.01</td>
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<td>Social Cognition</td>
<td>-1.46 (1.64)</td>
<td>-1.04 (1.19)</td>
<td>0.148</td>
<td>-0.43</td>
<td>-1.02 to 0.15</td>
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<td>Speed of processing</td>
<td>15/866</td>
<td>2.41 (0.93)</td>
<td>-1.87 (1.14)</td>
<td><strong>0.044</strong></td>
<td>-0.56</td>
<td>-1.10 to -0.02</td>
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<td>Verbal Learning</td>
<td>16/866</td>
<td>-2.80 (1.34)</td>
<td>-2.30 (1.55)</td>
<td>0.173</td>
<td>-0.51</td>
<td>-1.25 to 0.22</td>
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<td>Social Cognition</td>
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<td>-1.98 (1.71)</td>
<td>-1.57 (1.26)</td>
<td>0.221</td>
<td>-0.36</td>
<td>-0.95 to 0.22</td>
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<td>Working Memory</td>
<td>15/865</td>
<td>-2.44 (1.17)</td>
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<td>-0.83</td>
<td>-1.43 to -0.22</td>
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<tr>
<td>Composite</td>
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<td>-2.24 (1.4)</td>
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<tr>
<td>NART</td>
<td>16/860</td>
<td>17.56 (11.4)</td>
<td>24.50 (10.72)</td>
<td><strong>0.008</strong></td>
<td>-7.16</td>
<td>-12.44 to -1.87</td>
</tr>
<tr>
<td>SAPS Global Hallucinations (Lifetime)</td>
<td>9 / 891</td>
<td>2.67 (1.65)</td>
<td>2.8 (1.51)</td>
<td>0.770</td>
<td>-0.15</td>
<td>-1.14 to 0.85</td>
</tr>
<tr>
<td>SANS Global Alogia (Lifetime)</td>
<td>9 / 892</td>
<td>2.56 (0.73)</td>
<td>1.16 (1.46)</td>
<td><strong>0.004</strong></td>
<td>1.40</td>
<td>0.34 to 2.35</td>
</tr>
<tr>
<td>SANS Affective Flattening Lifetime</td>
<td>9 / 891</td>
<td>2.00 (1.22)</td>
<td>1.43 (1.44)</td>
<td>0.227</td>
<td>0.58</td>
<td>-0.36 to 1.53</td>
</tr>
<tr>
<td>SANS Avolition &amp; Apathy (Lifetime)</td>
<td>9 / 893</td>
<td>2.33 (1.50)</td>
<td>2.01 (1.31)</td>
<td>0.452</td>
<td>0.33</td>
<td>-0.53 to 1.20</td>
</tr>
<tr>
<td>SANS Anhedonia (Lifetime)</td>
<td>9 / 891</td>
<td>2.33 (1.58)</td>
<td>2.20 (1.45)</td>
<td>0.770</td>
<td>0.14</td>
<td>-0.81 to 1.10</td>
</tr>
<tr>
<td>SANS Positive Thought Disorder (Lifetime)</td>
<td>9 / 892</td>
<td>2.00 (1.93)</td>
<td>1.02 (1.37)</td>
<td><strong>0.032</strong></td>
<td>0.99</td>
<td>0.09 to 1.90</td>
</tr>
<tr>
<td>SANS Inappropriate Affect (Lifetime)</td>
<td>9 / 891</td>
<td>0.33 (0.7)</td>
<td>0.28 (0.79)</td>
<td>0.866</td>
<td>0.45</td>
<td>-0.48 to 0.57</td>
</tr>
<tr>
<td>Social Functioning Scale (Total Score)</td>
<td>9 / 501</td>
<td>100.8 (6.61)</td>
<td>104.3 (9.59)</td>
<td>0.301</td>
<td>-0.35</td>
<td>-9.67 to 2.96</td>
</tr>
</tbody>
</table>

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 |

*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

<table>
<thead>
<tr>
<th>GeneSet</th>
<th>Type</th>
<th>P(^a)</th>
<th>B(^a)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LoF Intolerant</td>
<td>All</td>
<td>0.048</td>
<td>-0.15</td>
<td>-0.29 to -0.001</td>
</tr>
<tr>
<td>LoF Intolerant</td>
<td>Deletions</td>
<td>0.055</td>
<td>-0.21</td>
<td>-0.42 to 0.005</td>
</tr>
<tr>
<td>LoF Intolerant</td>
<td>Duplications</td>
<td>0.513</td>
<td>-0.05</td>
<td>-0.18 to 0.09</td>
</tr>
<tr>
<td>Synapse</td>
<td>All</td>
<td>0.088</td>
<td>-0.18</td>
<td>-0.38 to 0.02</td>
</tr>
<tr>
<td>Synapse</td>
<td>Deletions</td>
<td>0.033</td>
<td>-0.22</td>
<td>-0.43 to -0.02</td>
</tr>
<tr>
<td>Synapse</td>
<td>Duplications</td>
<td>0.606</td>
<td>0.07</td>
<td>-0.20 to 0.35</td>
</tr>
</tbody>
</table>

\(^a\) 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.