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CNVs conferring risk of autism or schizophrenia affect cognition in controls

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In a small fraction of patients with schizophrenia or autism, alleles of copy-number variants (CNVs) in their genomes are probably the strongest factors contributing to the pathogenesis of the disease. These CNVs may provide an entry point for investigations into the mechanisms of brain function and dysfunction alike. They are not fully penetrant and offer an opportunity to study their effects separate from that of manifest disease. Here we show in an Icelandic sample that a few of the CNVs clearly alter fecundity (measured as the number of children by age 45). Furthermore, we use various tests of cognitive function to demonstrate that control subjects carrying the CNVs perform at a level that is between that of schizophrenia patients and population controls. The CNVs do not all affect the same cognitive domains, hence the cognitive deficits that drive or accompany the pathogenesis vary from one CNV to another. Controls carrying the chromosome 15q11.2 deletion between breakpoints 1 and 2 (15q11.2(BP1–BP2) deletion) have a history of dyslexia and dyscalculia, even after adjusting for IQ in the analysis, and the CNV only confers modest effects on other cognitive traits. The 15q11.2(BP1–BP2) deletion affects brain structure in a pattern consistent with both that observed during first-episode psychosis in schizophrenia and that of structural correlates in dyslexia.

Little information is available on whether or how rare CNVs conferring high risk of schizophrenia and/or autism affect physiologic function of otherwise normal brains. As none of these CNVs hitherto described are fully penetrant for the diseases, and both schizophrenia and autism affect cognition, we aimed to examine the possibility that the CNVs affect cognition in control carriers, those who do not suffer either disease or intellectual disability. We based our selection of CNVs on a literature search for CNVs associated with schizophrenia and/or autism ('neuropsychiatric CNVs'); this search produced 26 CNV alleles (Supplementary Table 1)[1–3]. These CNV alleles are rare, found in 0.002% to 0.2% frequency, and cumulatively in 1.16% of our sample of 101,655 genotyped subjects, representing approximately one-third of the Icelandic population (Supplementary Tables 1 and 2).

We used the subset of genotyped subjects born before 1968, without excluding patients, to examine the association of each neuropsychiatric CNV with reproductive outcome ('fecundity'), defined simply as the number of children each subject had by age 45. After correction for multiple comparisons, three neuropsychiatric CNVs were significantly associated with fecundity (Table 1). Subjects carrying the 16p11.2 deletion or the 22q11.21 duplication show reduced fecundity, with the effect in males significantly greater than in females ($P = 0.0083$ and $P = 0.029$ for the difference in effect by sex for the 16p11.2 deletion and the 22q11.21 duplication, respectively). In contrast, individuals carrying the 16p12.1 deletion have more children than do controls (Table 1). Those with deletions at 15q11.2(BP1-BP2) show a nominally significant reduction in fecundity (Table 1). Consistent with previous reports[4], schizophrenia patients show a large decrease in fecundity, with a more pronounced reduction in males ($P = 9.5 \times 10^{-25}$ for the difference in effect by sex) (Table 1).

We recruited neuropsychiatric CNV control carriers, controls carrying other CNVs not known to be associated with schizophrenia or autism ('other CNVs'), controls without large CNVs, and schizophrenia patients. All recruited subjects (Supplementary Table 2 and Supplementary Fig. 1) were administered a battery of neuropsychological tests (see Methods), the mini international neuropsychiatric interview (MINI)[5] and the general assessment of function scale (GAF)[6].

The neuropsychiatric CNVs as a class

We found that the GAF score is 0.70 standard deviations (s.d.) lower in the group of neuropsychiatric CNV control carriers than in population controls ($P = 2.2 \times 10^{-12}$). Based on MINIs, anxiety and substance abuse prevalences in the neuropsychiatric CNV control group are similar to those of controls ($P = 0.27$ and 0.36, respectively), however, depression and suicidal ideation are more common (odds ratio = 2.86, $P = 0.0017$, and odds ratio = 2.20, $P = 0.011$, respectively). The other CNVs have GAF scores 0.18 s.d. lower than population controls ($P = 0.0098$), but do not differ significantly from controls in prevalence of phenotypes assessed by the MINI ($P = 0.22$, 0.90, 0.97 and 0.097, for depression, suicidal ideation, anxiety and substance abuse, respectively).

Neurocognitive deficits, or heritable neurocognitive traits, are seen in those at risk of schizophrenia and in unaffected family members[7,8]. They typically distinguish patients with schizophrenia from controls

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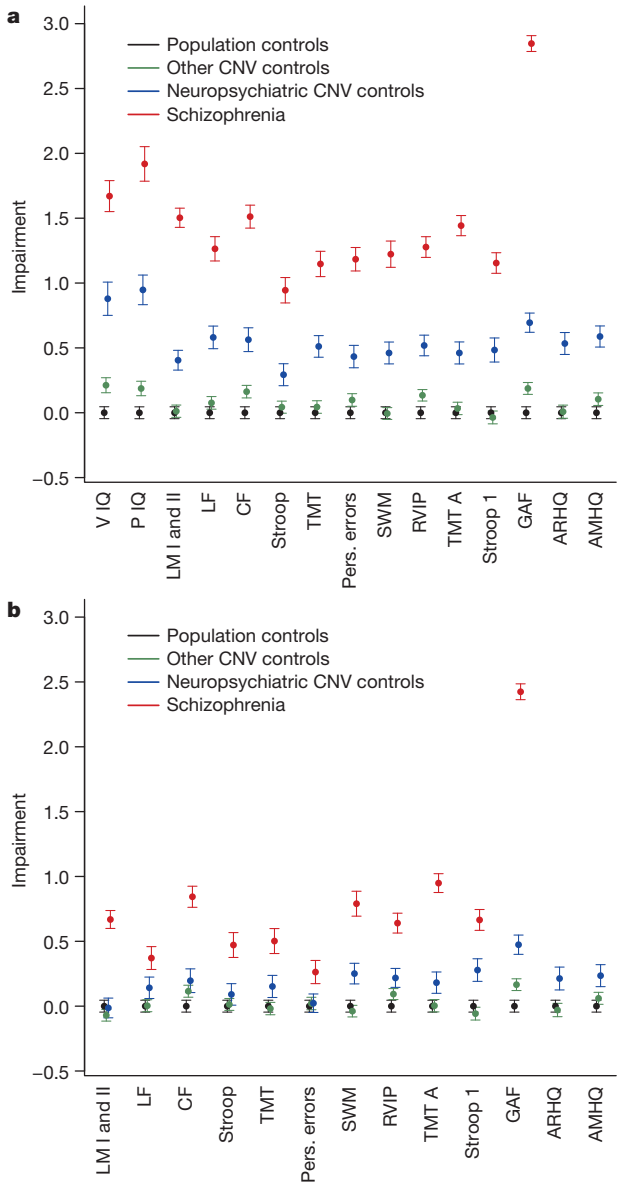
Table 1 | Fecundity of neuropsychiatric CNV carriers and schizophrenia patients based on individuals born before 1968

CNV	Carriers (male/female)	Non carriers (male/female)	Effect (male/female)	*P* value
16p11.2 del	14/13	33910/42223	0.14/0.51	1.6×10^{-12}
22q11.21 dup	25/33	33899/42203	0.60/0.90	0.00093
16p12.1 del	36	76124	1.32	0.0011
15q11.2 del	73/99	33851/42137	0.81/1.03	0.015
1q21.1 del	21	76139	0.76	0.062
15q11.2–13.1 dup	9	76151	0.69	0.11
16p13.1 dup	90	76070	0.91	0.14
16p11.2 distal del	11	76149	0.76	0.2
16p13.1 del	28	76132	0.86	0.22
17q12 dup	28	76132	1.11	0.3
2p16.3 (NRXN1) del	10	76150	0.83	0.34
16p11.2 dup	26	76134	0.89	0.35
22q11.21 del	7	76153	0.79	0.37
17p12 del	24	76136	1.08	0.48
13q31.3 (GPC6) dup	76	76084	0.96	0.55
10q11.22–23 dup	13	76147	1.08	0.62
10q11.22–23 del	12	76148	0.96	0.81
1q21.1 dup	33	76127	1.02	0.88
15q13.1 dup	17	76143	1.02	0.9
2p25.3 (MYT1L) dup	106	76054	0.99	0.91
15q13.3 all del	18	76142	1.01	0.95
Schizophrenia	306/197	33618/42039	0.21/0.54	9.5×10^{-206}

The effect is the factor by which fecundity is altered in CNV carriers or schizophrenia patients. Different effects on males and females are shown when there is a significant ($P < 0.05$) interaction between sex and either CNV or patient status. Counting both models fitted (with and without sex interaction), 42 tests were performed, thus the significance threshold for CNVs is $P = 0.0012$.



with an effect size of approximately one s.d. (ref. 9). The cognitive deficits seen in first-degree relatives of schizophrenia patients indicate that they are partly independent of the clinical state[10] and are likely to persist in psychotic patients, at least in a milder form, even if a complete remission would be achieved. All subjects were administered tests for cognitive profiling that measure functions previously shown to be impaired in schizophrenia patients, including attention, spatial working memory, logical memory, executive function, cognitive flexibility, language and processing speed (see Methods). On all tests, the schizophrenia patients performed worse than population controls (Fig. 1a and Supplementary Table 3a). The neuropsychiatric CNV control carriers performed at a level between that of schizophrenia patients and population controls, whereas the controls carrying other CNVs performed in line with population controls (Fig. 1a and Supplementary Table 3a). For all the tests, the association is much weaker when IQ is taken into account (Fig. 1b and Supplementary Table 3b). This is not surprising as the cognitive tests measure attributes that contribute to IQ.

Scores on the adult reading history questionnaire (ARHQ)[11,12] and adult mathematical history questionnaire (AMHQ) questionnaires (see Methods), designed to detect a history of reading and mathematics learning difficulties indicative of dyslexia and dyscalculia, separate the control neuropsychiatric CNV carriers from population controls with an effect of 0.50 s.d. ($P = 3.1 \times 10^{-6}$) and 0.55 s.d. ($P = 2.5 \times 10^{-7}$), respectively (Fig. 1a). ARHQ and AMHQ scores for the carriers of other CNVs are not significantly different from those of population controls ($P = 0.98$ and 0.17, respectively).

Figure 1 | Association of CNV groups with cognitive traits, GAF, ARHQ and AMHQ scores. **a**, Average standardized scores for schizophrenia patients ($n = 161$), control carriers of neuropsychiatric CNVs ($n = 167$), control carriers of other CNVs ($n = 465$) and population controls ($n = 475$). **b**, Average standardized scores after adjustment for IQ. AMHQ, adult mathematical history questionnaire; ARHQ, adult reading history questionnaire; CF, category fluency; GAF, global assessment of functioning; LF, letter fluency; LM I and II, logical memory I and II; Pers. errors, perseverative errors; P IQ, performance IQ; RVIP, rapid visual information processing; Stroop, difference in time to complete trial 3 and time to complete trial 2; Stroop 1, Stroop trial 1; SWM, spatial working memory (between-search errors for 6 boxes); TMT, TMT trail B − TMT trail A; TMT A, TMT trail A; V IQ, verbal IQ; (see Methods for further information on tests). Error bars represent s.e.m. Impairment is in s.d. units, ARHQ and AMHQ scores for the patient group are not available.

Individual neuropsychiatric CNVs

To determine whether the CNVs differ in their effects on cognition, we examined the association of individual CNVs with neurocognitive traits, GAF score and history of learning difficulties. Few control carriers could be recruited for some of the neuropsychiatric CNVs but between 5 and 47 control carriers could be evaluated for each of 11 CNVs (Supplementary Table 2). Six of the CNVs are associated with verbal and/or performance IQ with large effects (0.73–3.51 s.d. units) in the carrier controls. These are the 16p11.2 deletion and the reciprocal duplication, 17p12 deletion, 17q12 duplication, 16p12.1 deletion and 16p13.1 duplication (Table 2). The effect is also large for the 2p16.3 deletion carriers for performance IQ, although the P value is >0.005 (Supplementary Table 4a). Significant associations were also found between individual neuropsychiatric CNVs and GAF, spatial working memory (SWM), AMHQ, category fluency, letter fluency, perseverative errors and Stroop trial 1 (Table 2).

The alleles of the 16p11.2 CNV confer mirrored effects on anthropometric traits[13]. The deletion, conferring high risk of autism[14], shows the greatest impairments in the cognitive domains tested in the control carriers. The reciprocal duplication, conferring risk of schizophrenia[15] and autism[14], confers somewhat different abnormalities on the control carriers (Supplementary Table 5). Although the deletion is strongly associated with impaired verbal IQ and deficits in verbal letter and category fluency tests, in keeping with what is seen in autism, the duplication more selectively impairs the spatial working memory and executive functions that seem to be more important in the pathophysiology of schizophrenia[16].

Four neuropsychiatric CNVs, duplications at 13q31.3, 22q11.21 and 1q21.1 and a deletion at 15q11.2(BP1-BP2), show more modest (around 0.5 s.d. or less) or no effects on verbal and performance IQ (Supplementary Table 4a). Twenty-one control subjects carrying the 22q11.21 duplication were evaluated and trends were seen for impairments in all neurocognitive traits and the most significant impairment was observed in category fluency (0.97 s.d., $P = 1.4 \times 10^{-4}$) (Supplementary Table 4a). Ten control subjects carrying the 1q21.1 duplication were evaluated and not even a nominally significant effect was detected on neurocognitive traits, GAF or history of learning difficulties (Supplementary Table 4a). Forty-seven control subjects carrying the 15q11.2(BP1-BP2) deletion were evaluated, and significant associations were observed with a lower GAF score (0.66 s.d., $P = 9.9 \times 10^{-5}$), history of learning difficulties as evaluated by the ARHQ (0.70 s.d., $P = 1.9 \times 10^{-4}$) and the AMHQ (0.78 s.d., $P = 2.3 \times 10^{-5}$) (Supplementary Table 4a). Association with a lower GAF score indicates impaired functioning, possibly due to some psychological disturbance, although the number of carriers studied was too small to allow detection of association with the individual phenotypes as derived from the MINI.

When conditioned on IQ the associations with specific cognitive traits, GAF and history of learning difficulties become less significant for the 11 CNVs (Table 2 and Supplementary Table 4a). However, the association of AMHQ score with the 15q11.2(BP1-BP2) deletion remains the most significant (0.70 s.d., $P = 2.3 \times 10^{-4}$). In Fig. 2a and Supplementary Table 6 the neuropsychiatric CNV carriers are divided into those carrying the 15q11.2(BP1-BP2) and those carrying other neuropsychiatric CNVs. A clear difference in the effect of conditioning the ARHQ and AMHQ scores on IQ is observed in these two groups: in the 15q11.2(BP1-BP2) deletion group, the association with ARHQ and AMHQ scores is only slightly weakened when conditioned on IQ, whereas in the group of remaining neuropsychiatric CNV carriers (without the 15q11.2(BP1-BP2) deletion carriers) there is no longer any significant association with the history of learning difficulties after conditioning on IQ (Fig. 2b and Supplementary Table 6).

The 15q11.2(BP1-BP2) deletion has previously been shown to confer modest risk of schizophrenia[1], behavioural disturbances[17], developmental and language delay[18], and epilepsy[19]. We show that the 15q11.2(BP1-BP2) deletion has only modest impact on results of the neuropsychological tests but is still strongly associated with a history of difficulties in learning mathematics and reading (Fig. 2). IQ is only marginally lower in the controls carrying the 15q11.2(BP1-BP2) deletion than in the population controls. Using a score of greater than 0.43 on the ARHQ[11] as a surrogate for dyslexia[20], the 15q11.2(BP1-BP2) deletion is associated

Table 2 | Controls carrying different neuropsychiatric CNVs perform worse than population controls on cognitive tests, GAF and history of learning difficulties

CNV	Cognitive trait	Effect	*P*-value	Effect (adjusted for IQ)	*P*-value (adjusted for IQ)
16p11.2 del	V IQ	3.51	5.90×10^{-16}	NA	NA
17p12.del	V IQ	2.99	2.30×10^{-9}	NA	NA
16p11.2 del	LF	2.00	2.00×10^{-7}	0.61	0.14
16p11.2 del	P IQ	2.01	1.30×10^{-6}	NA	NA
16p11.2 del	CF	1.83	2.00×10^{-6}	0.58	0.16
16p11.2 del	Stroop 1	1.8	2.80×10^{-6}	1.14	0.006
16p12.1 del	V IQ	2.05	8.30×10^{-6}	NA	NA
16p13.1 dup	P IQ	1.09	9.30×10^{-6}	NA	NA
16p11.2 del	Pers. errors	1.77	2.00×10^{-5}	0.48	0.25
15q11.2 del	AMHQ	0.78	2.30×10^{-5}	0.70	0.00023
16p11.2 dup	SWM	1.72	3.20×10^{-5}	1.51	0.00025
17q12 dup	GAF	1.63	5.10×10^{-5}	1.43	0.00037
16p11.2 del	GAF	1.55	5.80×10^{-5}	0.58	0.10
17q12 dup	V IQ	1.57	8.10×10^{-5}	NA	NA
15q11.2 del	GAF	0.66	9.90×10^{-5}	0.57	0.0012
16p11.2 del	SWM	1.49	0.00011	0.45	0.27
22q11.21 dup	CF	0.97	0.00014	0.81	0.0016
15q11.2 del	ARHQ	0.7	0.00019	0.60	0.0018
17p12 del	GAF	1.67	0.00031	1.11	0.021
16p11.2 del	TMT A	1.37	0.0004	0.4	0.33
17p12 del	Stroop	1.61	0.00043	1.13	0.018
16p11.2 dup	P IQ	1.29	0.00062	NA	NA
16p11.2 dup	TMT	1.27	0.00073	0.91	0.016
17p12 del	CF	1.48	0.0012	0.62	0.2
16p12.1 del	P IQ	1.41	0.0021	NA	NA
16p13.1 dup	V IQ	0.73	0.0022	NA	NA
17q12 dup	LF	1.2	0.0026	0.78	0.051
16p12.1 del	LM I and LM II	1.25	0.0027	0.77	0.092
16p13.1 dup	SWM	0.66	0.0049	0.54	0.026

Abbreviations for the different tests are given in the supplementary text. The significance threshold for the 11 CNVs each compared for 15 tests and 13 IQ-adjusted tests is $P = 0.00016$. AMHQ, adult mathematical history questionnaire; ARHQ, adult reading history questionnaire; CF, category fluency; GAF, general assessment of function scale; LF, letter fluency; LM I and LM II, logical memory I and II; NA, not applicable; Pers errors, perseverative errors; P IQ, performance IQ; Stroop, difference in time to complete trial 3 and time to complete trial 2; Stroop 1, Stroop trial 1; SWM, spatial working memory; TMT A, TMT trail A; V IQ, verbal IQ.

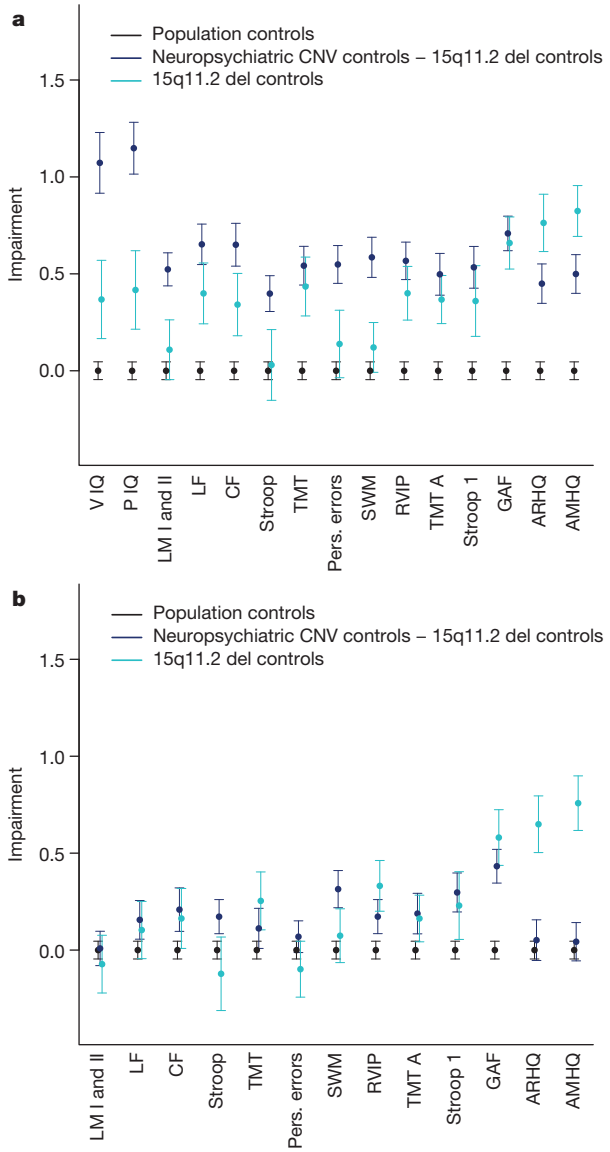


Figure 2 | Association of CNVs with cognitive traits, GAF, ARHQ and AMHQ scores. **a**, Average standardized scores for controls carrying neuropsychiatric CNVs excluding the 15q11.2(BP1-BP2) deletion carriers (blue, $n = 120$), controls carrying the15q11.2(BP1-BP2) deletion (cyan, $n = 47$) and population controls (black, $n = 475$). **b**, Average standardized scores conditioned on IQ. Error bars represent s.e.m.

with dyslexia with an odds ratio of 3.18 ($P = 0.0017$). Of three previously described ARHQ subscales, based on factor analysis[11], the ARHQ dyslexia-symptoms subscale shows the strongest association with the 15q11.2(BP1-BP2) deletion (effect = 0.71 s.d., $P = 1.4 \times 10^{-4}$, Supplementary Table 7). Based on a score of greater than 12 on the AMHQ (see Methods), the 15q11.2(BP1-BP2) deletion shows association with dyscalculia (odds ratio = 3.91, $P = 0.00011$). In 136 controls carrying the reciprocal 15q11.2(BP1-BP2) duplication the results are comparable to those of population controls on the neurocognitive tests (Supplementary Table 4a), and their GAF (0.01 s.d., $P = 0.95$), ARHQ (−0.22 s.d., $P = 0.057$) and AMHQ (0.07 s.d., $P = 0.52$) scores are also in keeping with those of population controls.

Structural MRI phenotypes

In a search for neural intermediate phenotypes, we performed structural magnetic resonance imaging (MRI) on 15 control carriers of the 15q11.2(BP1-BP2) deletion, 55 carriers of the reciprocal duplication, and 201 population controls. Given the association with schizophrenia, we focused our attention on regions defined by a recent meta-analysis of first-episode psychosis[21] (Fig. 3a). The 15q11.2(BP1-BP2) deletion carriers have a reduced volume of grey matter in the perigenual anterior cingulate cortex (pACC) (Fig. 3b) and the left insula (Fig. 3c). Furthermore, deletion carriers showed reductions in white matter of the temporal lobe bilaterally and an increase in the volume of the corpus callosum (Fig. 3d). Importantly, for both grey and white matter, 15q11.2(BP1-BP2) duplication carriers always show reciprocal changes in exactly the same regions altered in deletion carriers, providing the first demonstration of allele-dose-dependent effects of CNVs on the structure of the human brain.

The pACC is a key region for regulation of limbic activity[22] previously shown to be abnormal in schizophrenia[23]. Furthermore, the frontoinsular cortex is highly connected to the pACC, with which it forms the cortical aspects of the salience network[24], a circuitry linked to schizophrenia risk[25]. Although reduction in the volume of the temporal lobe white matter is a well-established feature of schizophrenia and is present early in the illness[26], the finding of increased callosal volume was unexpected, as patients with schizophrenia have reduced volume in this region[27]. Notably, carriers of the schizophrenia-associated 22q11.21 deletion also show increased volume of the corpus callosum[28].

The abnormalities found in the structural MRI studies also show overlap with published work on structural correlates of dyslexia and dyscalculia. In dyslexia, grey matter abnormalities in the supramarginal gyrus were prominent in a recent meta-analysis[29]. Grey matter reductions in a very similar location in pACC have also been seen in developmental dyscalculia[30]. In both cognitive developmental disorders, other regions are abnormal that are not implicated in the present study (such as left perisylvian areas in dyslexia and the intraparietal sulcus in dyscalculia), suggesting that the neuropsychological impairment seen in 15q11.2(BP1-BP2) deletion carriers may be related to specific key nodes in the networks associated with these cognitive dysfunctions.

It is of interest that the controls carrying the 15q11.2(BP1-BP2) duplication ($n = 136$) perform to a similar level as population controls on all tests of cognitive function used in this study (Supplementary Table 4a). Thus, although mirror effects on brain volume phenotypes are observed for the 15q11.2(BP1-BP2) CNV, we do not observe clear mirror effects on the ARHQ and AMHQ scores.

Conclusion

There were two main aims to this study. The first was to determine whether carriers of CNVs that predispose to schizophrenia and/or autism, who have not been diagnosed with a psychotic disorder or autism, have cognitive abnormalities that are akin to those encountered in schizophrenia. If this were the case these neuropsychiatric CNVs could be used as instruments in the study of cognitive abnormalities that characterize the disease. The results show that carriers of these CNVs show cognitive abilities in between those of normal controls and patients with schizophrenia. This raises the possibility that the difference between the patients and the control carriers may not be due to a lack of penetrance but instead to variation in expressivity of the CNVs. It also shows that the cognitive abnormalities are not necessarily consequences of the disease, and that the risk of the disease may, at least in part, be mediated through the cognitive abnormalities. These CNVs could be used to identify individuals in whom schizophrenia-like cognitive abnormalities could be studied without the confounding effects of psychosis or medications.

The second aim was to better define the cognitive abnormalities in population controls carrying CNVs associating with schizophrenia and autism; by evaluating controls carrying the neuropsychiatric CNVs we sought to learn more precisely which cognitive abnormalities put carriers at risk of developing schizophrenia. We tested the carriers primarily for those aspects of cognition that have been shown to be abnormal in schizophrenia (Fig. 1), and in all of these aspects the control carriers were found to perform somewhere between the schizophrenia patients

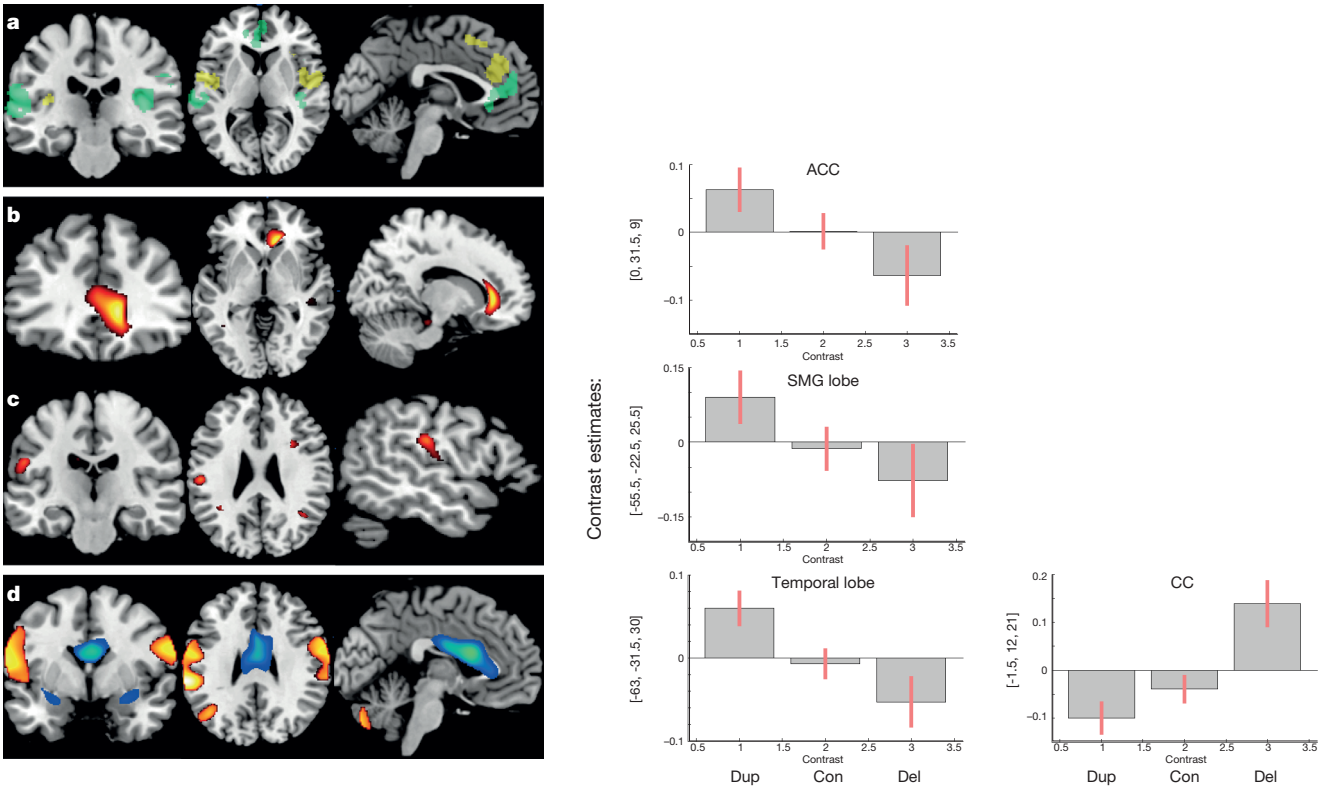


Figure 3 | Dose-dependent alterations in brain structure in 15q11.2 (BP1-BP2) CNV carriers. **a**, Regions of interest defined by a meta-analysis of first-episode psychosis in pACC and insula[21]. **b**, Grey matter alterations in perigenual anterior cingulate cortex. **c**, Grey matter alterations in insula and supramarginal gyrus (SMG). **d**, White matter alterations in left temporal lobe and corpus callosum. All data are displayed on a coronal, horizontal and sagittal section (left to right) of a structural template MRI. Maps are displayed at a threshold of $P = 0.001$ uncorrected for presentation purposes, but findings are significant at $P < 0.05$, family-wise error corrected for multiple comparisons. Right panels in **b**–**d** associate with the images to the left and show plots of contrast estimates extracted from the peak voxel in standard space (template for defining the standard space; Montreal Neuroimaging Institute). Bars represent means across subjects. Con, controls; Del, deletion; Dup, duplication. Error bars represent s.e.m.

and the population controls. When controlled for IQ, the number of tests that separate the control neuropsychiatric CNV carriers from population controls decreases substantially, which is not surprising as these tests assess functions that are components of the IQ. Of the 11 neuropsychiatric CNV alleles tested independently for association in 5 or more controls, 8 associated with a cognitive trait.

Dosage-sensitive genes at CNV loci can give rise to mirrored phenotypes for anthropometric loci including body mass index[13] and head circumference[15]. In this study we provide the first evidence that dose-dependent effects of CNVs also affect human brain structure directly. Two brain regions, with clear evidence of both structural and functional alterations early in the course of schizophrenia, show dosage effects in controls carrying the 15q11.2(BP1-BP2) deletion and its reciprocal duplication.

In this paper we demonstrate how cognitive abnormalities and changes in the structure of the brain observed in schizophrenia are also found in control carriers of CNVs that confer high risk of the disease. One of the missing pieces in our understanding of the pathogenesis of schizophrenia has been the nature of the physiologic function that is first perturbed in the disease or the perturbation of which leads to the disease. We show that carriers who have not been diagnosed with autism, intellectual disability, or schizophrenia show intermediate phenotypes in brain structure that are in good agreement with the observations in first-episode psychosis. We suggest that the work presented here lends support to the idea that the cognitive abnormalities are fundamental defects in schizophrenia as they are manifest in carriers of CNVs conferring risk of the disease who do not suffer from the disease. Furthermore, in addition to the information they may provide on disease, these CNVs provide us with an opportunity to search systematically for the biochemical foundations of the cognitive differences between the carrier and non-carrier controls.

METHODS SUMMARY

Control subjects carrying CNVs or not carrying CNVs were recruited from a large genotyped sample. Subjects aged 18 to 65 years were recruited for cognitive phenotyping. The psychologists and psychiatrists evaluating all subjects were blind to genotype. To examine fecundity, a nation-wide genealogy database was used to calculate fecundity of patients and controls carrying neuropsychiatric CNVs. The MINI[5] was used to screen the controls for psychiatric disorders, and participants' overall level of functioning and their ability to carry out activities of daily living were rated using the GAF scale[31]. Memory was assessed using the logical memory subtest from Wechsler Memory Scale III (WMS-III)[32]. Verbal fluency was assessed using the controlled oral word association test (COWAT)[33] and the category naming test[34]. The Stroop test was administered as an indicator of the ability to suppress an habitual response[35]. The trail-making test (TMT) was administered as a measure of psychomotor speed and mental flexibility[36]. As a further measure of mental flexibility, including the ability to alter cognitive sets, the Wisconsin card sorting test (WCST)[37] was administered and the ratio of perseverative errors to the number of trials administered used in our analysis. Spatial working memory and sustained attention were evaluated by the computerized CANTAB battery, using the SWM[38] and rapid visual information processing (RVIP) subtests[39], respectively. Intelligence was evaluated using the Wechsler Abbreviated Scale of Intelligence (WASI-I)[40]. For neuroimaging, MRI examinations were conducted on a 1.5 T whole body Philips Achieva scanner. High-resolution T1-weighted images were processed according to the unified segmentation model with SPM8 and Matlab 8b software. Copy-number effects were examined on a voxel-by-voxel basis with a multiple regression model using SPM8.

Online Content Any additional Methods, Extended Data display items and Source Data are available in the online version of the paper; references unique to these sections appear only in the online paper.

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METHODS

Control subjects carrying or not carrying CNVs were recruited from a large genotyped sample. Subjects aged between 18 and 65 years were recruited for cognitive phenotyping. The psychologists evaluating all subjects were blind to genotype. A nation-wide genealogy database was used to calculate the fecundity of patients and controls carrying neuropsychiatric CNVs. The mini international neuropsychiatric interview (MINI)[5] was used to screen the controls for psychiatric disorders, and participants' overall level of functioning and their ability to carry out activities of daily living were rated using the general assessment of function (GAF) Scale[31]. Memory was assessed using the logical memory subtest from Wechsler Memory Scale III (WMS-III)[32]. Verbal fluency was assessed using the controlled oral word association test (COWAT)[33] and the category naming test[34]. The Stroop test was administered as an indicator of the ability to suppress an habitual response[35]. The trail-making test (TMT) was administered as a measure of psychomotor speed and mental flexibility[36]. As a further measure of mental flexibility, including the ability to alter cognitive sets, the Wisconsin card-sorting test (WCST)[37] was administered and the ratio of perseverative errors to the number of trials administered used in our analysis. Spatial working memory and sustained attention were evaluated by the computerized CANTAB battery, using the spatial working memory (SWM)[38] and rapid visual information processing (RVP) subtests[39], respectively. Intelligence was evaluated using the Wechsler Abbreviated Scale of Intelligence (WASI-I)[40]. For neuroimaging, MRI examinations were conducted on a 1.5 T whole body Philips Achieva scanner. High-resolution T1-weighted images were processed according to the unified segmentation model with SPM8 and Matlab 8b software. Copy number effects were examined on a voxel-by-voxel basis with a multiple-regression model using SPM8.

Sample. Twenty-six CNVs conferring risk of psychiatric disorders ('neuropsychiatric CNVs'), of which most are recurrent, were identified through literature search (Supplementary Table 1). Control subjects carrying neuropsychiatric CNVs were identified from a large genotyped sample ($n = 101{,}655$). The sample had been genotyped by Illumina HumanHap (300, 370, 610, 1M, 2.5M) and Illumina Omni (670, 1M, 2.5M, Express) SNP arrays. BeadStudio (Illumina; version 2.0) was used to call genotypes, normalize signal intensity data and establish the log R ratio and B allele frequency at every SNP. Samples passing quality control were examined using PennCNV[41]. All putative neuropsychiatric CNVs and other CNVs not known to be associated with schizophrenia or autism ('other CNVs') were visually inspected using DosageMiner software (developed by deCODE genetics). The neuropsychiatric CNVs, with one exception, span more than 15 SNPs on the Illumina arrays (Supplementary Table 1).

Both the neuropsychiatric CNVs and the other CNVs are large, on average around 1.5 and 1.0 Mb, respectively. All 26 neuropsychiatric CNVs delete or duplicate exons of genes, whereas 89 of the 94 other CNVs delete or duplicate exons of genes (Supplementary Table 8).

In the sample of 101,655 genotyped subjects we identified 1,178 subjects carrying one or more of the neuropsychiatric CNVs (1.16% of the sample). Carriers aged between 18 and 65 were recruited for further phenotyping and were excluded from control groups if any of the following applied: if they were diagnosed with schizophrenia, schizoaffective or bipolar disorder; if they were diagnosed with autism, intellectual disability or developmental delay at the State Diagnostic and Counseling Centre in Iceland serving children and adolescents with a disability; if they met psychoses criteria on the MINI interview; if they were diagnosed with schizophrenia, schizoaffective, bipolar disorder, autism, intellectual disability or developmental delay according to self reports (or reports from parents); if they were using antipsychotic drugs.

Phenotyped control subjects passing the exclusion criteria were: 167 controls carrying neuropsychiatric CNVs; 465 controls carrying otherCNVs: 475 controls without large CNVs. In addition, 161 schizophrenia patients were recruited for the neuropsychological phenotyping.

Phenotyping. Encrypted identifiers of subjects were decrypted by a representative of the Icelandic Data Protection Authority and subjects were recruited to the study by a clinic overseen by the Icelandic Data Protection Authority. Psychologists and nurses phenotyping the participants were blind to genotype. Those working with the genetic data were blind to personal identifiers and could only work on the encrypted data set. Only a representative of the Data Protection Authority of Iceland holds the key for encrypting and decrypting the personal identifiers. Genotypes are only linked to encrypted identifiers. Approval for this study was obtained from the National Bioethics Committee of Iceland and the Icelandic Data Protection Authority. Written informed consent was obtained from all participants or their guardians before blood samples or phenotypic data were obtained. All sample identifiers were encrypted in accordance with the regulations of the Icelandic Data Protection Authority.

GAF[42] score was used to rate participants overall level of functioning and their ability to carry out activities of daily living. The scale was rated by the tester with respect to psychosocial, social, and occupational functioning. All participants were also interviewed using the MINI[5] edition 5.0.0. The MINI was designed as a brief structured interview for the major Axis I psychiatric disorders in ICD-10 and DSM-IV.

To assess cognitive function, logical memory I and II from the Wechsler Memory Scale (3rd edn) (WMS-III)[32] was used to assess memory. An Icelandic translation of the test was used (unstandardized). Two variables from the test were calculated; immediate memory that is the total item score immediately after the reading of story A and after both readings of story B, and delayed memory that is the total item score from both stories after 30 min delay. The average of the two scores was used in the analysis.

Verbal fluency was assessed using the COWAT[33] and the category naming test[34]; animal naming. In COWAT the subject is required to name as many words as he or she can that begin with a certain letter in one minute, the letters H and S were used in the Icelandic translation (unpublished). For the analysis a mean score of the number of words registered with each of the two letters were calculated (verbal fluency) and for category fluency the number of animals registered (category fluency).

The Stroop test[35] is a measure of selective attention and the ability to block out irrelevant stimuli. An Icelandic translation (unpublished), derived from the Golden version[43], was used in this study. In the first trial the participant is asked to read the names of colours written in black ink. In the second trial the participant has to name the colour of words written in coloured ink, and in the last (the main) trial the participant has to name the colour of the ink of a word which is actually the name of another colour. Two measures from the Stroop test were used in the analysis; the time it took to finish trial 1, and the interference score which is the difference in time to complete trial 3 minus the time for completing trial 2.

For visual scanning and mental flexibility, TMT A and B[36] were used administered. Trail A is a measure of psychomotor speed and attention and trail B is thought to be a test of flexibility of thinking. A measure of the time it took to finish trail A and a derived score of the time it took to finish trail B minus trail A was used in the analysis.

The WCST was designed to assess abstract reasoning and the ability to shift cognitive strategies in response to environmental cues[37]. A computerized version of the test was used[44]. The variable used in our analysis is per cent perseverative errors, which reflects the ratio of perseverative errors to the number of trials administered. Perseverative errors are made when participant persists in responding to the old rule after the rule has changed.

The SWM subtest from the CANTAB battery was used, which gives a measure of spatial working memory[38]. The measure used in this analysis was between-search errors for 6 boxes, which is a count of times the subject revisits a box where the token has previously been found. This is thought to rely on the long-term spatial memory system as the subject has to remember the location for some time and through interferences[45].

RVIP, a subtest from the CANTAB battery was used to access vigilance, which is the ability to sustain attention on one or more items over a period of time[39]. The main variable is A′, which is a signal detection measure of sensitivity to errors regardless of error tendency. This is a measure of the subjects ability to detect target sequences by using p(hit) and p(false). p(hit) is the probability of a hit; the proportion of correct responses that are given when a target sequence is presented on the screen. p(false) is the probability of a false alarm; the proportion of responses when there is no target sequence presented on the screen.

Intelligence quotient (IQ) was assessed using the WASI-I. The WASI-I test includes four subtests: vocabulary and similarities, both tests of verbal IQ, and matrix reasoning and block design, both tests of performance IQ[40].

The WASI-I test has been translated into Icelandic for standardization that is in progress and this study has been a part of that work. Here the healthy control group was used to make local norms by calculating the mean and s.d. for each of the age groups used in the US version of the WASI-I. *Z*-scores were then calculated for every subtest for each participant, and the mean of the subtests was transformed into an IQ score having a mean of 100 and a s.d. of 15 in the healthy control group.

A fraction of the participants were tested with an older translation of the WASI-I with two subtests, vocabulary and matrix reasoning. Thirty-nine subjects were tested using both editions of the test (with more than one year apart), and Pearson's correlation coefficient between the two measures in these subjects was 0.66. No significant effect of test type (new or old translation of WASI-I version) was found in any group included in the study.

The adult mathematical history questionnaire (AMHQ) described here is modelled after the adult reading history questionnaire (ARHQ)[12]. The AMHQ consists of six questions, each scored on a Likert-type scale ranging from 0 to 4.

The questions were: 1. Did you experience any difficulties in learning math in elementary school? 2. How was your math performance compared to your classmates in elementary school? 3. How do you rate your math skills now compared to people your age with a comparable education level? 4. Did you experience any difficulties learning the multiplication table in elementary school? 5. How much extra help did you need when learning math in elementary school? 6. What is your current attitude towards math?

The six questions were selected to assess the degree to which adults have experienced symptoms of specific disorder of arithmetical skills, or dyscalculia (F81.2), which according to the ICD-10 criteria[20], "Involves a specific impairment in arithmetical skills that is not solely explicable on the basis of general mental retardation or of inadequate schooling. The deficit concerns mastery of basic computational skills of addition, subtraction, multiplication, and division rather than of the more abstract mathematical skills involved in algebra, trigonometry, geometry, or calculus."

The score for the AMHQ scale ranges from 0 to 24 with higher scores indicating greater impairment. Internal consistency reliability ($\alpha = 0.90$) was assessed using Cronbach's α from AMHQ results of a large survey sample ($n = 2{,}757$). An exploratory factor analysis of this data set combining 28 items from ARHQ-Ice (22) and AMHQ (6) found that association with all three previously reported ARHQ subscale factors (dyslexic symptoms, current reading and memory)[11] were replicated, and all six AMHQ items had high factor loadings (≥ 0.55) on a separate fourth factor. This further confirms the internal consistency of the AMHQ scale and suggests an independence of the arithmetical disorder scale from the ARHQ total scale representing specific reading disorder or dyslexia and its three subscales[11]. Concurrent validity was assessed by comparing AMHQ scores of adults ($n = 39$) who had by formal neuropsychological evaluation been diagnosed as children with specific disorder of arithmetical skills (F81.2) and population controls without diagnosis of psychiatric or learning disorders and no learning disorder by self-report ($n = 564$). A significant difference in mean AMHQ scores was observed for these groups; that is, 17.8 (s.d. = 6.5) and 8.1 (s.d. = 5.3), respectively ($P < 0.001$).

For statistical analysis of cognitive traits, scores from each cognitive test or questionnaire were inverse normally transformed. They were then adjusted for sex, age at testing and, where indicated, IQ based on data from controls only. Final scores were shifted and scaled so that controls had a mean of 0 and a standard deviation of 1, and also arranged so that higher scores indicated greater impairment. To take the information on relatedness of the individuals into account, CNV carriers or schizophrenia patients were compared with controls using generalized least-squares regression with a variance–covariance matrix based on the kinship coefficient of each pair of individuals. Meiotic distance between neuropsychiatric CNV control carriers evaluated for cognitive traits can be found in Supplementary Table 4b.

The sample sizes obtained resulted in about 80% power to detect a difference of around 0.4 s.d. in the neuropsychiatric CNV control or schizophrenia versus population control comparisons, and about the same amount of power to detect a difference of around 0.3 s.d. for the other CNV control versus population control comparison. For the individual neuropsychiatric CNVs with the smallest sample size ($n = 5$), there was approximately 80% power to detect a difference of about 2.5 s.d.

Fecundity. deCODE genetics has built a nation-wide genealogy database for its genetic studies. The database contains information on year of birth and numbers of children of Icelanders. An encrypted version of the genealogy database was used for studying the fecundity in patient and CNV groups.

Mixed-effects Poisson generalized linear models (GLMs) were used to examine the association of fecundity with various neuropsychiatric CNVs and schizophrenia. The number of children at age 45 or older was regressed on sex, year of birth (included as factors for each 5 year birth cohort), sex-year of birth interaction (for each birth cohort factor), sibship (to account for relatedness) and the CNV or disorder of interest. All predictors were modelled as fixed effects except for sibship, which was random. A second set of models including a sex-CNV/disorder interaction term were also fit.

Neuroimaging. MRI examinations were conducted on a 1.5 T whole body Philips Achieva scanner. Scans were performed with a sagittal 3D fast T1-weighted gradient echo sequence (TR 8.6 ms, TE 4.0 ms, flip angle 8 degrees, slice thickness 1.2 mm, matrix 192 × 192, field of view 240 × 240 mm). Quality control of the MRI images consisted of a test of image homogeneity covariance and noise estimation (VBM8 toolbox; Gaser, http://dbm.neuro.uni-jena.de/author/admin/) as well as visual inspection.

For voxel-based morphometry, high-resolution T1-weighted images were processed according to the unified segmentation model[46] with SPM8 (statistical parametric mapping, Wellcome Department of Cognitive Neurology http://www.fil.ion.ucl.ac.uk/spm) and Matlab 8b software (The Mathworks). In brief, this method involves an iterated scheme of bias correction, segmentation into white matter, grey matter and cerebrospinal fluid and warping of prior images in stereotactic space to the data, which is repeated until no significant change occurs anymore. During normalization, images were interpolated to isotropic 1 × 1 × 1 mm voxels. The VBM8-toolbox extends this model with a partial volume estimation to account for partial volume effects and the application of a spatially adaptive non-local means (SANLM) filter[47] for bias correction. Normalization to stereotactic space consisted of a linear affine registration and a linear deformation corresponding to a high-dimensional DARTEL normalization[48] implemented in VBM8. The resulting probability maps were modulated, that is, intensity-corrected for local volume changes during normalization, to make them more sensitive to the distribution of grey matter and white matter volume. Modulation was limited to nonlinear warping; global differences in brain volume were thus excluded in the modulated probability maps. The modulated maps were smoothed with a 12-mm FWHM kernel.

For statistical analysis of neuroimaging data from MRI subjects carrying the 15q11.2(BP1-BP2) CNV, copy number effects at 15q11.2 (duplication > control > deletion and deletion > control > duplication) on regional brain volume were examined on a voxel-by-voxel basis with a multiple regression model using SPM8; age and gender were included as covariates of no interest.

An interaction between performance on neuropsychological tests that indicated a genetic dosage effect and copy number at 15q11.2, on regional grey matter volume was tested with a multiple regression analysis (SPM8); age and gender were included as covariates of no interest.

Effects on grey matter volume were reported as significant when whole-brain voxel-level FWE-corrected P value was less than 0.05. Additional region-of-interest (ROI) analyses were performed in the following regions found to show both functional and structural abnormalities in a recent meta-analysis of subjects with high risk of schizophrenia[21]: anterior cingulate and medial frontal cortex, and bilateral insula extending into temporal and parietal cortex. Results of these ROI analysis were considered significant at $P < 0.05$ voxel level, FWE-corrected.