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# The Number of Genomic Copies at the 16p11.2 Locus Modulates Language, Verbal Memory, and Inhibition

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## ABSTRACT

**BACKGROUND:** Deletions and duplications of the 16p11.2 BP4-BP5 locus are prevalent copy number variations (CNVs), highly associated with autism spectrum disorder and schizophrenia. Beyond language and global cognition, neuropsychological assessments of these two CNVs have not yet been reported.

**METHODS:** This study investigates the relationship between the number of genomic copies at the 16p11.2 locus and cognitive domains assessed in 62 deletion carriers, 44 duplication carriers, and 71 intrafamilial control subjects.

**RESULTS:** IQ is decreased in deletion and duplication carriers, but we demonstrate contrasting cognitive profiles in these reciprocal CNVs. Deletion carriers present with severe impairments of phonology and of inhibition skills beyond what is expected for their IQ level. In contrast, for verbal memory and phonology, the data may suggest that duplication carriers outperform intrafamilial control subjects with the same IQ level. This finding is reminiscent of special isolated skills as well as contrasting language performance observed in autism spectrum disorder. Some domains, such as visuospatial and working memory, are unaffected by the 16p11.2 locus beyond the effect of decreased IQ. Neuroimaging analyses reveal that measures of inhibition covary with neuroanatomic structures previously identified as sensitive to 16p11.2 CNVs.

**CONCLUSIONS:** The simultaneous study of reciprocal CNVs suggests that the 16p11.2 genomic locus modulates specific cognitive skills according to the number of genomic copies. Further research is warranted to replicate these findings and elucidate the molecular mechanisms modulating these cognitive performances.

*Keywords:* 16p11.2, ASD, Copy number variation, Inhibition, Language, Memory

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Deletions and duplications of the 16p11.2 ~600 kb breakpoints 4–5 (BP4-BP5) region are among the most frequent causes of neurodevelopmental and neuropsychiatric disorders (1–5). Although copy number variations (CNVs) are equally and frequently present in autism spectrum disorder (ASD) cohorts, only duplications are associated with schizophrenia (4). Recent studies in 16p11.2 CNV carriers demonstrated altered global cognition in deletion carriers and duplication carriers showing, respectively, up to 24-point and 15-point decreases in full-scale intelligence quotient (FSIQ) compared with intrafamilial control subjects (1,6,7). Regarding cognitive domains, language impairment in deletion carriers was reported in several case series (8,9), and specific assessments showed below-average performance in comprehension, expression, and reading skills with a 71% rate of speech and language disorder as defined in DSM-IV-TR (6,10). To our knowledge, performance of duplication carriers in specific cognitive domains has not yet been studied.

Most studies of CNVs investigated deletions and duplications separately using a case-control design; however, the simultaneous assessment of reciprocal CNVs of the same genomic region provides a unique opportunity to study how the number of genomic copies (one, two, or three) may modulate clinical phenotypes and endophenotypes. We and other authors previously showed that body mass index inversely correlates to the number of genomic copies at the 16p11.2 locus (1,9,11–13). The number of genomic copies is also negatively correlated with global brain volume (14) and associated with neuroanatomic structures involved in reward, language, and social-cognition circuits (15).

We hypothesized that specific cognitive skills correlate with the number of genomic copies of the 16p11.2 region beyond the decrease in IQ observed in both types of CNV carriers. We also explored whether this relationship is mediated by changes in brain structure. Our findings suggest that this locus modulates specific cognitive domains resulting in impaired as well as preserved or possibly enhanced skills relative to IQ in carriers of reciprocal CNVs. Neuroimaging analysis suggests that brain regions previously identified as correlating with the number of genomic copies are associated with alterations in executive functions in 16p11.2 CNV carriers.

## METHODS AND MATERIALS

### Participants

**European Cohort.** Participants were taking part in a larger research project on CNVs at the 16p11.2 locus with the aim of phenotyping a European cohort of 16p11.2 rearrangement carriers. Included in our analyses were 62 deletion carriers (37 probands/25 nonproband carriers), 44 duplication carriers (21 probands/23 nonproband carriers), and 71 intrafamilial control subjects (Table 1). Nonproband carriers are defined as relatives who carry the CNV identified through family cascade testing but who were not referred for a neurodevelopmental disorder. Inclusion criteria included presence of a recurrent 16p11.2 deletion or duplication comprising the BP4–BP5 region (29.6–30.2 Mb according to the human genome build GRCh37/hg19). Control subjects were noncarriers in the same families. Individuals <3 years old were excluded from the analyses. Also, 24 participants who were unable to perform the cognitive tasks because of low cognitive functioning were excluded (Table S1 in Supplement 1).

Additional deleterious CNVs were identified in one deletion carrier and five duplication carriers (Table S2 in Supplement 2). These participants were not removed from the analyses, but their potentially confounding effects were taken into account in a subanalysis. Deleterious CNVs were defined as 1) CNVs associated with a known recurrent genomic disorder, 2) CNVs encompassing a published critical genomic region or disrupting a gene that is a known cause of neurodevelopmental disorders, or 3) rare (<1/1000) and large (>500 kb) CNVs.

**Table 1. Sample Characteristics**

| | Deletion Carriers ($n$ = 62) | Control Subjects ($n$ = 71) | Duplication Carriers ($n$ = 44) |
|---|---|---|---|
| Age, Years, Mean ± SD (range) | 21.7 ± 15.4[a] (4.8–59) | 34 ± 15.3 (3.3–62) | 28.9 ± 16.8 (3.3–65) |
| Sex, M/F | 35/27 | 31/40 | 25/19 |
| Handedness, R/L/U | 44/11/7 | 62/6/3 | 33/9/2 |
| Inheritance, De novo/In/U | 16/26/20 | — | 8/15/21 |
| Kinship, Proband/ Nonproband Carriers | 37/25 | — | 21/23 |
| ASD, $n$ | 3 | 0 | 5 |
| Schizophrenia, $n$ | 0 | 0 | 0 |
| FSIQ, Mean ± SD | 72 ± 13.6[b] | 98 ± 15 | 75 ± 17.8[b] |
| NVIQ, Mean ± SD | 78 ± 11.7[b] | 99 ± 15.5 | 76 ± 15.3[b] |

ASD, autism spectrum disorder; F, female; FSIQ, full-scale intelligence quotient (standard score); In, inherited; L, left; M, male; NVIQ, nonverbal intelligence quotient (standard score); R, right; U, unknown/undefined.

[a]Significantly different from the control group, linear model, $p < .0001$.

[b]Significantly different from the control group, linear mixed model, all $p < .0001$.

The study was reviewed and approved by the local ethics committee, and signed consent forms were obtained from participants or legal representatives before investigation. Participants were assessed at the Lausanne University Hospital, Switzerland. Of the proband carriers, >87% were referred to the study by the clinical geneticist who had initially established the genetic diagnosis in the context of a neurodevelopmental disorder. Seven probands (four duplication carriers and three deletion carriers) were identified in the population biobank of Estonia as previously described (16), and one duplication carrier was referred for psychiatric problems. All but four participants ($n$ = 2 Asian descent and $n$ = 2 African descent) were of European descent.

**Simons Variation in Individuals Project Cohort.** For replication analyses on language, we used data from the Simons Variation in Individuals Project (VIP) cohort (http://sfari.org/resources/simons-vip), which aims at phenotyping carriers with a 16p11.2 BP4–BP5 rearrangement (Supplemental Methods and Materials in Supplement 1) (6,7).

### Cognitive Assessment

Trained neuropsychologists performed all cognitive assessments. Participants underwent age-appropriate and developmentally appropriate neuropsychological tests assessing overall cognitive functioning, fine motor skills, language, memory, and executive functions. All $Z$ scores were derived from standardized scores based on population norms provided by the testing manuals. When normative data were unavailable, we used raw scores that were adjusted for age and sex when appropriate. We specified the tasks where the latter procedure was applied. We used the following psychometric tests.

**Overall Cognitive Functioning.** The Wechsler Intelligence Scales or Wechsler Abbreviated Scale of Intelligence (17–20) was used to obtain FSIQ, nonverbal intelligence quotient (NVIQ), and verbal intelligence quotient (VIQ) when available. The FSIQ, NVIQ, and VIQ were estimated using the Differential Ability Scales–2nd Edition (21) or the Wechsler Abbreviated Scale of Intelligence in the VIP cohort.

**Fine Motor Skills.** The Purdue Pegboard test (22) (≥5 years old) assessed four conditions: dominant hand, nondominant hand, bimanual, and assembly. $Z$ scores were used as dependent variables.

**Language.** Phonological skills were assessed with nonword repetition (≥5 years old), oromotor sequences (≥3 years old), and phonological processing (≥3 years old) from the Developmental Neuropsychological Assessment battery (23). Age-adjusted raw scores were the dependent variables.

Participants ≥16 years old performed a sentence repetition task including low-frequency words. The score was the number of correct repetitions adjusted for age. Phonology in the VIP cohort was measured by the nonword repetition subtest (≥4 years old) from the Comprehensive Test of Phonological Processing (24), which is similar to the Developmental Neuropsychological Assessment nonword repetition task. Age-adjusted raw score was the dependent variable.

Lexical skills were assessed with the Wechsler Vocabulary subtest (word definition, ≥4 years old) and the Peabody Picture Vocabulary Test Revised (25) (word comprehension, ≥3 years old), semantic fluency (animal, ≥3 years old), and phonemic fluency (letter M, ≥5 years old). For word comprehension and word definition tasks, *Z* score were used as dependent variables, and age-adjusted raw scores were used for verbal fluencies.

Comprehension and verbal skills were assessed by selecting 24 items from the Test for Reception of Grammar 2 (26), syntax comprehension (≥15 years old), and the Wechsler Similarity subtest (≥7 years old). *Z* score (similarity) and age-adjusted raw scores (syntax) were used as dependent variables. Written language (≥12 years old) was assessed through a reading task (PC Robbery) (27) and a spelling task (Collective Spelling Tracking) (28). Reading fluency and reading comprehension *Z* scores were used as dependent variables; age-adjusted and sex-adjusted total raw scores were used for the spelling task.

**Memory.** Verbal short-term memory was assessed using the forward digit span task (≥6 years old) (18,19). The total age-adjusted raw score was used as the dependent variable. Verbal long-term memory was assessed using the California Verbal Learning Task (≥17 years old) (29). Two *Z* scores were used as dependent variables: number of words correctly recalled across all five learning trials (encoding) and number of words recalled after a 20-minute delay (delayed recall).

Visuospatial short-term memory was assessed using the forward spatial span task (≥6 years old) (30,31). The total age-adjusted raw score was used as the dependent variable. Visuospatial long-term memory was assessed with the Rey-Osterrieth Complex Figure test (≥5 years old) (32). For immediate and delayed (20 minutes) recalls, *Z* scores were used.

**Executive Functions.** Working memory (≥6 years old) was assessed using the backward digit span (18,19) and the backward spatial span (30,31) tasks. The total age-adjusted raw scores were used as dependent variables. Planning skills were assessed with the Tower of London test (≥7 years old) (33). *Z* scores for total correct score and total move score were used. The Stroop task (≥8 years old) (34) was used to assess verbal inhibition. A computerized version of the go/no-go task (≥7 years old) (35) was used to assess motor inhibition. In both tasks, *Z* scores for response time and number of errors adjusted for age were used as dependent variables.

## General Psychiatric and Autism Assessments

Experienced licensed psychologists and psychiatrists performed the Autism Diagnostic Interview–Revised (36) and Autism Diagnostic Observation Schedule (37) to establish a categorical diagnosis in all participants presenting with ASD symptoms. All adult carriers underwent the Diagnostic Interview for Genetic Studies to screen for major psychiatric disorders (38).

## Magnetic Resonance Imaging: Data Acquisition and Processing

We used structural magnetic resonance imaging data acquired for a previously published study (Supplemental Methods and Materials and Table S3 in Supplement 1) (14).

## Statistical Analyses

**Neuropsychological Data Analyses.** Variables derived from normative data were converted into *Z* scores for each participant (mean = 0; SD = 1) (Supplemental Methods and Materials in Supplement 1). Raw scores of variables without available normative data were systematically adjusted for age and sex where appropriate. We performed either linear or generalized regression analyses depending on data distribution. Cognitive measures were the dependent variables.

To investigate the effect of CNV on cognition, we used linear models including the following ordinal variables: deletion = 1, control = 2, duplication = 3. For contrasts between groups, we used post hoc *t* tests. Appropriate linear mixed models or generalized linear mixed models were performed taking the variable "family" as a random factor to account for correlated measures within family. We also included in the statistical design IQ, sex, and their interactions with the number of genomic copies to control for the effects of these variables. These additional covariates were kept in the final models only when the effect was significant. Results of noncarrier participants from deletion or duplication families were pooled, as they did not differ in age, sex, and cognitive performances. Selected models, estimates, and uncorrected *p* values are reported in Table 2 and Tables S4–S6 in Supplement 1.

Multiple testing correction is detailed in Supplemental Methods and Materials in Supplement 1. It takes into account all 34 cognitive tests, their level of intercorrelation, and the two post hoc contrasts (deletion carriers vs. control subjects and duplication carriers vs. control subjects). Uncorrected *p* values $\leq .001$ are considered significant, and trends are defined as $.001 < p$ values $\leq .05$. Statistical analyses were conducted using R 3.0.2 (The R Project for Statistical Computing; http://www.R-project.org/).

**Brain Structure and Behavior Correlation Analyses.** We tested whether the effects of CNVs on cognitive measures are mediated by changes observed in brain anatomy. Therefore, only cognitive measures (*Z* scores and raw scores adjusted for age and IQ) with significant differences between CNV carriers and intrafamilial control subjects were subsequently used for regression analysis with brain anatomy. The statistical design also included age, sex, and total intracranial volume as regressors. Voxel-based statistical analysis of the gray matter (GM) regional changes was assessed by creating voxelwise statistical parametric maps for the whole extent of the search volume using the general linear model and random field theory (38). Given that the number of genomic copies negatively correlates with GM volume in language and

**Table 2. Group Contrasts and Copy Number Variation Effect for Cognitive Measures Adjusting for IQ**

| | Deletion Carriers vs. Duplication Carriers | | Deletion Carriers vs. Control Subjects | | Duplication Carriers vs. Control Subjects | | Copy Number Variation | |
|---|---|---|---|---|---|---|---|---|
| Cognitive Variables | Estimate[a] (SE) | *p* Value | Estimate[b] (SE) | *p* Value | Estimate[b] (SE) | *p* Value | Estimate | *p* Value |
| Language | | | | | | | | |
| Phonological skills[c] | | | | | | | | |
| Nonword repetition (age-adjusted)[d] | 7.27 (1.88) | .0002[e] | −10.96 (1.89) | 5.2e-08[e] | −3.68 (2.08) | .078 | 4.1 | 9.9e-05[e] |
| Oromotor sequences (age-adjusted)[d] | 10.44 (2.69) | .001[e] | −13.1 (2.68) | 2.7e-06[e] | −2.68 (2.9) | .36 | 5.6 | 8e-05[e] |
| Sentence repetition (age-adjusted)[d] | .76 (.24) | .0015 | −.94 (.21) | 1.1e-05[e] | −.17 (.26) | .5 | .46 | .0001[e] |
| Lexical skills[f] | | | | | | | | |
| Word definition (*Z* score) | .48 (.19) | .01 | −.81 (.19) | 2.1e-05[e] | −.33 (.2) | .1 | .27 | .0047 |
| Comprehension and verbal skills[g] | | | | | | | | |
| Written language[h] | | | | | | | | |
| Reading fluency (*Z* score) | 1.7 (.52) | .0015 | −2.1 (.48) | 4.1e-05[e] | −.4 (.5) | .44 | .92 | .0009[e] |
| Memory | | | | | | | | |
| Verbal short-term memory | | | | | | | | |
| Forward digit span (age-adjusted)[d] | 1.54 (.4) | .0002[e] | −1.32 (.48) | .003 | .21 (.45) | .64 | .78 | .0002[e] |
| Verbal long-term memory | | | | | | | | |
| CVLT encoding (sex-adjusted *Z* score) | 1.36 (.29) | 7.2e-06[e] | −.22 (.28) | .43 | 1.14 (.3) | .0002[e] | .66 | 1.6e-05[e] |
| CVLT delayed recall (sex-adjusted *Z* score) | 1.35 (.32) | 5.9e-05[e] | −.03 (.31) | .92 | 1.31 (.34) | .0001[e] | .64 | .0001[e] |
| Visuospatial short-term and long-term memory[i] | | | | | | | | |
| Executive Functions | | | | | | | | |
| Working memory and planning[j] | | | | | | | | |
| Inhibition[k] | | | | | | | | |
| Stroop number of successes (age-adjusted)[d] | .85 (.21) | 4e-05[e] | −.78 (.17) | 3e-06[e] | .07 (.2) | .72 | .46 | 7.5e-06[e] |
| Fine Motor Skills[l] | | | | | | | | |
| Purdue dominant hand (*Z* score) | .56 (.26) | .035 | −.97 (.28) | .0009[e] | −.41 (.29) | .16 | .3 | .031 |
| Purdue nondominant hand (*Z* score) | .49 (.23) | .03 | −1.1 (.26) | 4.6e-05[e] | −.59 (.26) | .026 | .26 | .035 |

CVLT, California Verbal Learning Test.

Linear mixed models were used to account for the correlations of measures within families. When only one family member was included in the analysis, linear models were performed. Because of space constraints, cognitive variables showing no significant effect of copy number variation or no significant group differences (c, f-l; *p* values corrected) are presented in Table S5 in Supplement 1.

[a]Positive estimate: Deletion carrier score < duplication carrier score.

[b]Negative estimate: Deletion carrier or duplication carrier score < control subject score.

[c]Phonological processing.

[d]Raw score.

[e]Significant *p* value (corrected threshold, $p = .001$).

[f]Word comprehension, semantic and phonemic fluencies.

[g]Syntax comprehension and verbal reasoning.

[h]Reading comprehension and spelling.

[i]Forward spatial span and Rey-Osterrieth Complex Figure (immediate and delayed recall).

[j]Backward digit span, backward spatial span, and Tower of London (total correct and total move scores).

[k]Stroop response time, go/no-go response time, and number of successes.

[l]Purdue: bimanual and assembly conditions.

reward-related areas (14), we tested whether the behavioral deficits were associated with an increase of local GM volume. Consequently, one-tailed *t* tests were used to identify the regions whose volume showed negative correlation with the cognitive score.

We subsequently estimated the degree of overlap between brain areas correlating with behavioral scores and the previously identified regions sensitive to CNV (15). Clusters sharing both effects were obtained with a subtraction of the two statistical maps. We further examined how the number of genomic copies interacted with the brain-behavior correlation in these regions, using a multiple linear regression analysis of the summed voxel values for each group. For all whole-brain analyses, we applied a voxel-level threshold of $p < .05$ after familywise error correction for multiple comparisons. Trends were assessed by using an auxiliary uncorrected voxel threshold of $p < .001$ (39).

## RESULTS

Deletion carriers and duplication carriers showed cognitive impairment (FSIQ = 72 for deletion carriers, FSIQ = 75 for duplication carriers) compared with intrafamilial control subjects (FSIQ = 98), consistent with a larger study we recently

published (Table S4 in Supplement 1) (7). All verbal and nonverbal subtests from the Wechsler Abbreviated Scale of Intelligence equally contributed to this IQ deficit (Figure S1 in Supplement 1). To estimate the effect of the deletion and the duplication on specific cognitive domains beyond their impact on general cognition, we performed all subsequent analyses adjusting for NVIQ in verbal tasks and FSIQ otherwise (Table 2 and Table S5 in Supplement 1; see Table S6 in Supplement 1 for results not adjusted for IQ).

### 16p.11.2 Locus Modulates Phonology, Written Language, and Vocabulary

The number of genomic copies positively correlated with phonology measures such as nonword repetition ($p$ = 9.9e-05), oromotor sequences ($p$ = 8e-05), and sentence repetition ($p$ = .0001) as well as a closely related task, reading fluency ($p$ = .0009). This effect was mainly driven by the deletion carriers, who performed worse than control subjects and duplication carriers; these two latter groups did not significantly differ (Figure 1A–C). Word definition showed a similar trend ($p$ = .0047) (Table 2). Except for trends, none of the measures assessing spelling, verbal fluencies, verbal comprehension, and verbal reasoning were significantly affected by the 16p11.2 locus (Table S5 in Supplement 1).

Results from the VIP data set confirmed that the number of genomic copies correlated with performance in the nonword repetition task adjusted for NVIQ ($p$ = 9e-6). The effect was driven by both CNVs, with deletion carriers performing worse than duplication carriers and intrafamilial control subjects ($p$ = 2.7e-6 and $p$ = .002, respectively) and duplication carriers outperforming control subjects ($p$ = .016) (Figure S2 in Supplement 1).

### Verbal Short-Term and Long-Term Memory Processes Are Modulated by the Number of Genomic Copies

All verbal memory measures correlated positively with the number of genomic copies. Duplication carriers outperformed deletion carriers and control subjects in measures of verbal long-term memory after adjusting for NVIQ (Figure 1D–F). Scatter plots showing correlations between verbal long-term memory measures and NVIQ confirmed that duplication carriers scored higher than control subjects with similar NVIQ (Figure S3 in Supplement 1). Regarding verbal short-term memory, deletion carriers scored significantly worse than duplication carriers ($p$ = .0002) and control subjects (trend, $p$ = .003). The 16p11.2 locus did not significantly affect either short-term or long-term visuospatial memory.

### 16p11.2 Locus Modulates Inhibition Skills But Not Working Memory and Planning

Motor and verbal inhibition measures positively correlated to the number of genomic copies (significant for verbal inhibition, trend for motor inhibition) (Figure 1G–I). Deletion carriers who performed or tended to perform worse than control subjects and duplication carriers mainly drove this effect (Table 2). We did not observe any group differences in working memory and planning skills (Table S5 in Supplement 1).

**Fine Motor Skills.** Deletion carriers performed worse than control subjects in Purdue dominant and nondominant hand conditions, but there were no significant differences in the bimanual and assembly conditions.

**Overall Neuropsychological Profile.** To illustrate the neuropsychological profiles of deletion and duplication carriers, we summarized a sample of the cognitive tasks adjusted and unadjusted for IQ (Figure 2A, B). Carriers' data were converted into $Z$ scores relative to the intrafamilial control subjects to highlight preserved skills (performance similar to controls after adjusting for IQ), specific deficits, and enhanced performances (lower and higher performances than expected for IQ level). When adjusted for IQ levels (Figure 2A), the cognitive profile of deletion carriers showed specific deficits in language and inhibition domains, whereas there was no specific impairment in the profile of duplication carriers. The latter group showed enhanced performance in verbal long-term memory. When results were unadjusted for IQ (Figure 2B), both CNV carriers showed similar decreased performance in several tasks consistent with their overall IQ level (e.g., verbal comprehension, working memory, planning, visuospatial skills).

**ASD Diagnosis and Additional CNVs.** We considered possible confounders including a diagnosis of ASD (three deletion carriers and five duplication carriers) or the presence of additional deleterious CNVs (one deletion carrier and five duplication carriers). The analyses performed after excluding participants with additional CNVs (Table S7 in Supplement 1) and analyses excluding participants with ASD led to the same results. We also considered possible bias secondary to ascertainment for neurodevelopmental disorders, but proband carriers were not outperformed by nonproband carriers in any of the cognitive measures (Table S8 in Supplement 1). Finally, the effect of inheritance was tested. In the deletion group, performances of de novo carriers did not differ from performances of the inherited carriers (Table S9 in Supplement 1).

**Correlation With Brain Anatomy.** Whole-brain voxel-based morphometry analysis showed a positive correlation between GM volume and the verbal inhibition error rate in bilateral insula and transverse temporal gyri (Figure 3 and Table S10 in Supplement 1). Subsequent regression analyses (left cluster, $r^2$ = .14, $p$ = .007; right cluster, $r^2$ = .24, $p$ = .0003) revealed that the effect was mainly driven by deletion carriers, who showed the greatest variance (Figure 3B, C). We report a trend (uncorrected $p$ value $<$ .001 for all the clusters) for increased GM volume in the left inferior frontal gyrus, bilateral superior temporal gyri, and bilateral caudate associated with deficits in two measures related to phonology: nonword repetition and reading fluency. Measures of memory did not covary with any brain structure.

## DISCUSSION

By assessing carriers of deletion and duplication at the 16p11.2 locus and intrafamilial control subjects, our study characterizes the effect of this genomic region on several

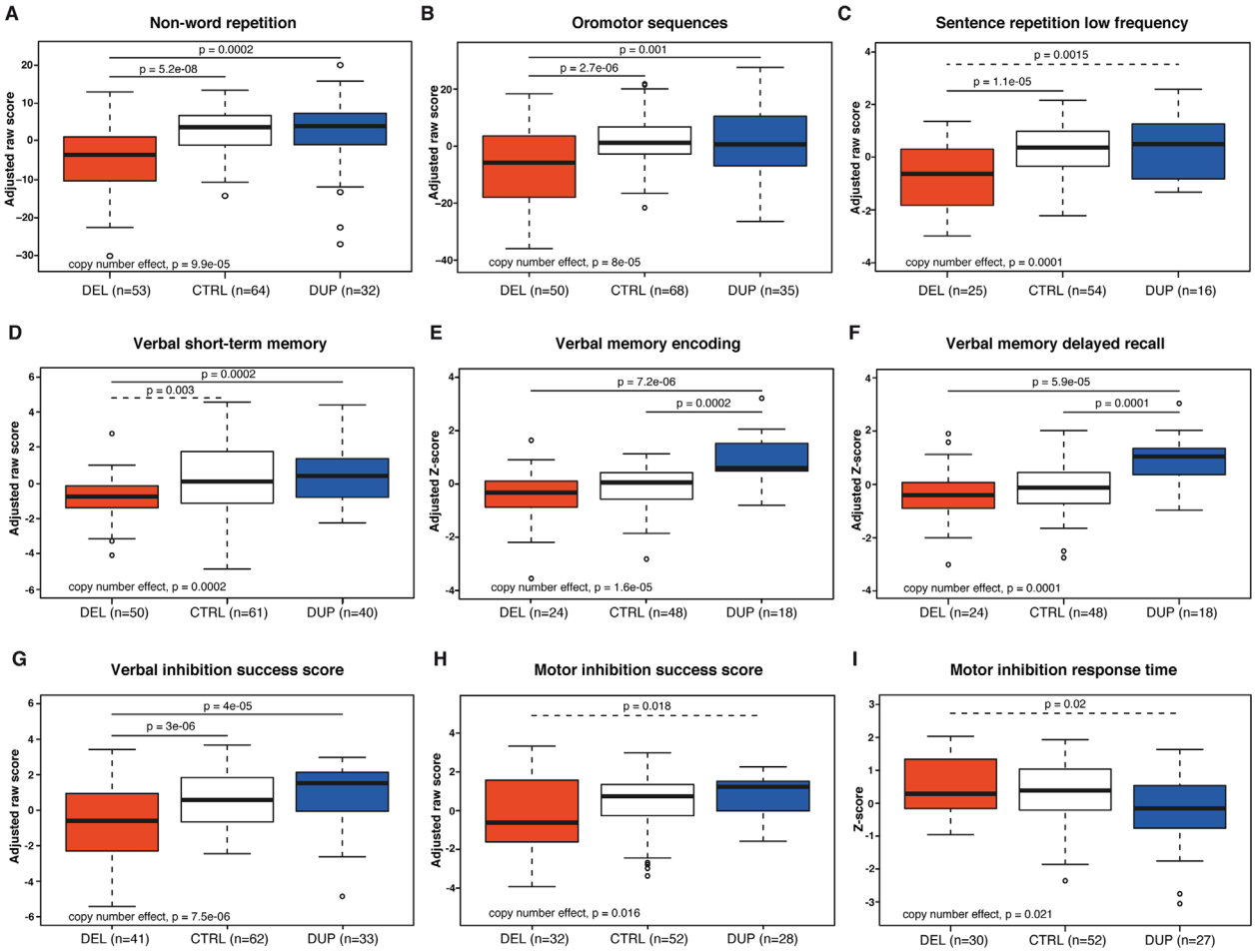


**Figure 1.** Copy number variation and group comparisons on language, memory, and executive measures. Box plots represent language measures of phonology **(A–C)**, memory **(D–F)**, and executive functions **(G–I)** in deletion carriers, duplication carriers, and intrafamilial control subjects. Higher scores translate into better performance except for panel **(I)**, where better performance is represented by a shorter response time. The bold line shows the median, and the bottom and top of the box show the 25th (quartile 1 [Q1]) and the 75th (quartile 3 [Q3]) percentile, respectively. The upper whisker ends at highest observed data value within the span from Q3 to Q3 + 1.5 times the interquartile range (Q3–Q1), and lower whisker ends at lowest observed data value within the span for Q1 to Q1 − (1.5 * interquartile range). Circles are outliers. Copy number variation effect (one, two, or three copies) and group contrasts are estimated using a linear mixed model to account for correlated measures within families **(A, B, D, G, H, I)** and a linear model when only one family member is included in the analysis **(E, F)**. A nonlinear model was required for panels **(C, G, H)**. We present *Z* scores when normative data are available in the testing manual. Otherwise, we present raw scores adjusted for age and sex when appropriate. All scores are adjusted for IQ except for panel **(I)**. Significant post hoc group comparisons (*p*-corrected threshold = .001) are represented by solid lines with exact *p* values above, and trends are represented by dashed lines with exact *p* values above. CTRL, intrafamilial control subjects; DEL, deletion carriers; DUP, duplication carriers.

cognitive domains. After adjusting for global cognition, which is decreased in both CNVs, specific cognitive functions including verbal memory, executive functions, and phonological skills show a positive correlation with the number of genomic copies. The data suggest that duplication carriers outperform intrafamilial control subjects with the same IQ for measures of verbal memory and phonology.

A recent study (40) comparing recurrent reciprocal CNVs failed to identify any correlations between cognitive functions and copy number state at the 16p11.2 BP4–BP5 and 15q11.2 BP1–BP2 loci. Either the small sample size ($n$ = 7 for 16p11.2 deletion carriers and duplication carriers, respectively) or the small effect size (for 15q11.2 BP1–BP2) could explain the lack of significant correlations between cognitive traits and copy number state.

Although linear models show that the number of genomic copies correlates with performance in several cognitive domains, our study was underpowered to demonstrate formally that deletion carriers perform worse than control subjects and control subjects perform worse than duplication carriers for a specific function. However, the results are suggestive of such a phenomenon; our analysis of phonologic skills in a larger independent data set (VIP) supports the hypothesis that, similar to other complex traits such as body mass index or brain anatomy, cognitive performances may covary with molecular mechanisms. Recent findings on 16p11.2 CNVs mouse models show enhanced memory skills on a recognition task in duplicated mice compared to wild-type animals (41). Memory processes have also been linked to

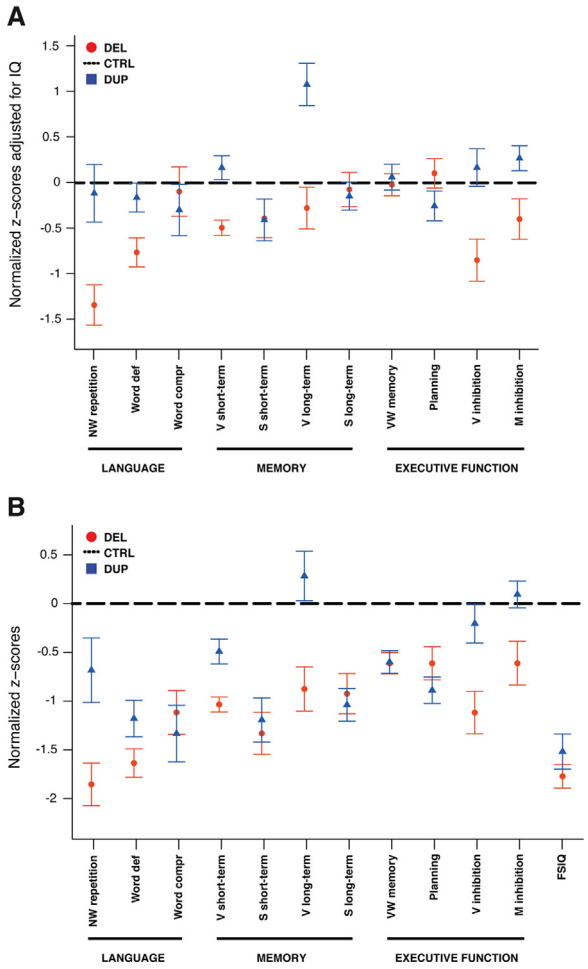


**Figure 2.** Neuropsychological profile in 16p11.2 deletion carriers and duplication carriers. IQ-adjusted **(A)** and IQ-unadjusted **(B)** neuropsychological profile of deletion carriers and duplication carriers. The y axis represents mean cognitive residual scores for deletion carriers (red circles) and duplication carriers (blue squares) converted into *Z* scores relative to the intrafamilial control subjects (black dashed line). Error bars represent SEM. When appropriate, scores are adjusted for age and sex. The x axis lists one task per subdomain with the most complete data set: NW repetition (nonword repetition), Word def (word definition), Word compr (word comprehension), V short-term (verbal short-term memory), S short-term (spatial short-term memory), V long-term (verbal long-term memory), S long-term (spatial long-term memory), VW memory (verbal working memory), Planning, V inhibition (verbal inhibition number of success), M inhibition (motor inhibition number of success), and FSIQ (full-scale intelligence quotient). CTRL, intrafamilial control subjects; DEL, deletion carriers; DUP, duplication carriers.

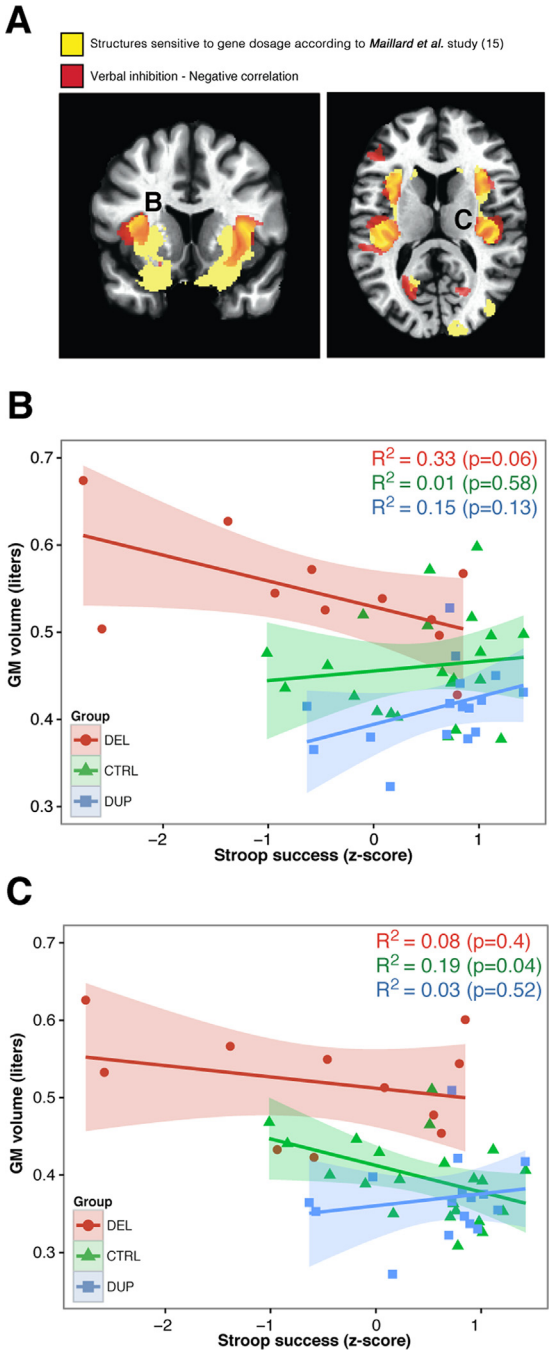


**Figure 3.** Brain structure-behavior correlation analysis between verbal inhibition score and gray matter (GM) map. **(A)** Spatial overlap between negative linear correlation with Stroop score (red) and the neuroanatomic structures previously identified as correlating to the number of genomic copies of the 16p11.2 locus (15). Overlapping clusters are represented in orange. Maps are thresholded at the $p < .05$ familywise error corrected level. Panels **(B, C)** are scatter plots showing the linear correlation between GM volume and the Stroop performance at the clusters located in the left insula **(B)** and in the right temporal gyri **(C)** in panel **(A)**. Both panels include the regression line, correlation coefficient, and *p* value for each cohort. CTRL, intrafamilial control subjects; DEL, deletion carriers; DUP, duplication carriers.

mechanisms regulating long-term synaptic potentiation and depression. These synaptic mechanisms require bursts of local protein synthesis during training and stimulation (42). Both mammalian target of rapamycin signaling and *MAPK3* signaling regulate local synaptic protein synthesis, which modulates memory performances in murine models (43,44). The expression levels of *MAPK3*, which maps within the BP4–BP5 interval, and of mammalian target of rapamycin pathway members are significantly altered in 16p11.2 CNV carriers (45). These are good candidate genes underlying or mediating the

correlation between genomic copy number and memory performances.

Deletion and duplication are strongly and equally associated with ASD, but our study shows that their cognitive profiles seem to be distinct, highlighting the heterogeneity of ASD. Our results are consistent with the results of D'Angelo *et al.* (7), who observed that the duplication is associated with a form of low-functioning ASD, whereas cognition in deletion carriers with ASD is mostly within the normal range. These results are in line with studies highlighting the potential role of the CNVs in the specific patterns of autistic symptoms (46). For example, there is a long-standing debate on whether ASD and specific language impairment arise from similar genetic bases (47). This study demonstrates that the same genomic region predisposing to ASD may or may not have a deleterious effect on structural language depending on the nature of the mutation. This dissociation between phenotypes observed in reciprocal CNVs is also corroborated by a recent study demonstrating that deletions, but not duplications, encompassing ASD genes are primarily associated with impairments in language domains (46).

Special isolated skills and cognitive strengths are also features defining subgroups of ASD (48). The 16p11.2 duplication profile is reminiscent of enhanced memory skills also reported in ASD (49,50) and may represent the first example of an ASD-related genetic predisposition leading to specific cognitive strengths compared with control subjects with the same IQ. The absence of any specific impairment beyond the IQ shortfall in duplication carriers at risk for schizophrenia echoes the nonspecific cognitive deficit pattern observed in first-episode idiopathic schizophrenia (51,52).

Our results also suggest that neuroanatomic structures previously defined on the basis of their correlation to number of genomic copies at the 16p11.2 locus (15) are associated with alterations in measures of language and verbal inhibition. These findings dovetail with previously reported structural findings positing the insula as a key player in verbal inhibitory processes (53,54) as well as the superior temporal gyrus and caudate nucleus, implicated in specific language impairment (55–57). However, larger samples are required to replicate these results and elucidate any specific association within groups. The causal relationship between genomic copies, brain structure, cognition, and behavior also remains unknown.

Increased volume of the caudate has been observed in individuals who carry *FOXP2* mutations, which is one of the few genetic forms of specific language impairment studied to date (58,59). Language deficits observed in deletion carriers are largely consistent with a previous study by Hanson *et al.* (6) reporting phonological deficits in the context of general language impairment. Other studies reported the presence of childhood apraxia of speech, although the exact characteristics of this deficit are unclear (60–62).

The present study aimed at characterizing the effect of the 16p11.2 locus on specific cognitive domains by adjusting for the effect of IQ. We are confident that our findings apply to a broad range of IQ with the exception of very low-functioning participants who were unable to perform these tasks (11% of deletion carriers and 27% of duplication carriers). It is unlikely that the exclusion of individuals with low IQ has biased our results because a much larger study showed that most deletion carriers and duplication carriers have an IQ >55. The duplication and the deletion have been associated with a decrease of approximately 16 points and 22 points of IQ, respectively (7). This finding suggests that the subgroup of very low-functioning carriers may be related to the presence of additional deleterious genetic variants, which are two to three times more frequent in 16p11.2 duplication carriers compared with deletion carriers (7). It is unknown whether low-functioning carriers represent a distinct subgroup with different profiles. Most of the probands were ascertained for neurodevelopmental disorders, which may have also biased our results. However, stratifying groups in proband and non-proband carriers does not affect any of the results. The low frequency of schizophrenia is discordant with the association reported in prior studies (4). This low frequency is likely to be due in part to the young age of our probands and the fact that most of the adults were parents, a fact that selects against a diagnosis of schizophrenia (63). Follow-up of our probands is required to estimate accurately the risk of schizophrenia in this population.

In conclusion, this study suggests that cognitive skills may be modulated by the number of genomic copies at the 16p11.2 locus in humans. Such effects are clouded by the global decrease in cognitive functioning that affects both CNVs. The strength of this study lies in the administration of an extensive cognitive test battery to both CNV carrier groups and the intrafamilial control subjects; this allowed us to assess cognitive function precisely relative to each participant's global cognitive level. Further research is warranted to elucidate the contribution of specific genes within the 16p11.2 locus by studying the relationship between expression patterns of these genes and cognitive tasks, brain anatomy, and brain function. These approaches may ultimately elucidate the molecular mechanisms that affect specifically phonological, verbal memory, and inhibition skills based on the number of genomic copies. A deeper knowledge of the cognitive strengths and weaknesses of these patients is critical for developing cognitive support strategies. Careful language assessment is recommended in deletion carriers, who might benefit from more emphasis on the use of visuospatial processes when learning. In contrast, verbal methods may improve learning strategies in duplication carriers.

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## REFERENCES

1. Zufferey F, Sherr EH, Beckmann ND, Hanson E, Maillard AM, Hippolyte L, *et al*. (2012): A 600 kb deletion syndrome at 16p11.2 leads to energy imbalance and neuropsychiatric disorders. J Med Genet 49: 660–668.
2. Cooper GM, Coe BP, Girirajan S, Rosenfeld JA, Vu TH, Baker C, *et al*. (2011): A copy number variation morbidity map of developmental delay. Nat Genet 43:838–846.
3. Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R, *et al*. (2008): Association between microdeletion and microduplication at 16p11.2 and autism. N Engl J Med 358:667–675.
4. McCarthy SE, Makarov V, Kirov G, Addington AM, McClellan J, Yoon S, *et al*. (2009): Microduplications of 16p11.2 are associated with schizophrenia. Nat Genet 41:1223–1227.
5. Green EK, Rees E, Walters JT, Smith KG, Forty L, Grozeva D, *et al*. (2015): Copy number variation in bipolar disorder [published online ahead of print Jan 6]. Mol Psychiatry.
6. Hanson E, Bernier R, Porche K, Jackson FI, Goin-Kochel RP, Snyder LG, *et al*. (2015): The cognitive and behavioral phenotype of the 16p11.2 deletion in a clinically ascertained population. Biol Psychiatry 77:785–793.
7. D'Angelo D, Lebon S, Chen Q, Martin-Brevet S, Green Snyder L, Hippolyte L, *et al*. (in press): Defining the effect of the 16p11.2 duplication on cognition, behavior, and medical comorbidities. JAMA Psychiatry.
8. Hanson E, Nasir RH, Fong A, Lian A, Hundley R, Shen Y, *et al*. (2010): Cognitive and behavioral characterization of 16p11.2 deletion syndrome. J Dev Behav Pediatr 31:649–657.
9. Shinawi M, Liu P, Kang SH, Shen J, Belmont JW, Scott DA, *et al*. (2010): Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. J Med Genet 47:332–341.
10. American Psychiatric Association (2000): Diagnostic and Statistical Manual of Mental Disorders, *4th ed text rev*. Washington, DC: American Psychiatric Association.
11. Jacquemont S, Reymond A, Zufferey F, Harewood L, Walters RG, Kutalik Z, *et al*. (2011): Mirror extreme BMI phenotypes associated with gene dosage at the chromosome 16p11.2 locus. Nature 478:97–102.
12. Bochukova EG, Huang N, Keogh J, Henning E, Purmann C, Blaszczyk K, *et al*. (2010): Large, rare chromosomal deletions associated with severe early-onset obesity. Nature 463:666–670.
13. Walters RG, Jacquemont S, Valsesia A, de Smith AJ, Martinet D, Andersson J, *et al*. (2010): A new highly penetrant form of obesity due to deletions on chromosome 16p11.2. Nature 463:671–675.
14. Qureshi AY, Mueller S, Snyder AZ, Mukherjee P, Berman JI, Roberts TP, *et al*. (2014): Opposing brain differences in 16p11.2 deletion and duplication carriers. J Neurosci 34:11199–11211.
15. Maillard AM, Ruef A, Pizzagalli F, Migliavacca E, Hippolyte L, Adaszewski S, *et al*. (2015): The 16p11.2 locus modulates brain structures common to autism, schizophrenia and obesity. Mol Psychiatry 20:140–147.
16. Männik K, Magi R, Mace A, Cole B, Guyatt AL, Shihab HA, *et al*. (2015): Copy number variations and cognitive phenotypes in unselected populations. JAMA 313:2044–2054.
17. Wechsler D (2004): WPPSI-III Echelle d'Intelligence de Wechsler pour la Période Pré-Scolaire et Primaire: Troisième édition. Paris: ECPA, Les Editions du Centre de Psychologie Appliquée.
18. Wechsler D (2005): WISC-IV Echelle d'Intelligence de Wechsler pour Enfants et Adolescents: Quatrième édition. Paris: ECPA, Les Editions du Centre de Psychologie Appliquée.
19. Wechsler D (2008): WAIS-III Echelle d'Intelligence de Wechsler pour Adultes. Paris: ECPA, Les Editions du Centre de Psychologie Appliquée.
20. Wechsler D (1999): Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: The Psychological Corporation.
21. Elliot C (2006): Differential Abilities Scale–2nd Edition (DAS-II). San Antonio, TX: The Psychological Corporation.
22. Tiffin J, Asher EJ (1948): The Purdue pegboard; norms and studies of reliability and validity. J Appl Psychol 32:234–247.
23. Korkman M, Kirk U, Kemp SL, Plaza M (2008): Nepsy, Bilan Neuropsychologique de l'enfant: Manuel. Paris: ECPA, les Éditions du Centre de Psychologie Appliquée.
24. Wagner RK, Torgesen JK, Rashotte CA (1999): Comprehensive Test of Phonological Processing. Austin, TX: Pro Ed.
25. Dunn L, Thériault-Whalen CM, Dunn L (1993): Peabody Picture Vocabulary Test–Revised. Toronto: Psycan.
26. Bishop DV (2003): Test for Reception of Grammar. London: Harcourt Assessment, Psychological Corporation.
27. Boutard C, Claire I, Gretchanovsky L (2010): Le vol du P.C. Isbergues: Editions Ortho.
28. Allal I, Cheminal-Lancelot R, Devaux M-F, Divry J, Lequette C, Maitrot C, *et al*. (2005): R.O.C.: Outil de Repérage Orthographique Collectif. Grenoble: Cogni-Sciences-IUFM Grenoble.
29. Poitrenaud J, Deweer B, Kalafat M, Van der Linden M (2007): CVLT Test d'Apprentissage et de Mémoire Verbale (California Verbal Learning Test: Adaptation Française). Paris: ECPA, Les Editions du Centre de Psychologie Appliquée.
30. Wechsler D (2001): MEM-III Echelle Clinique de Mémoire: Troisième édition. Paris: ECPA, Les Editions du Centre de Psychologie Appliquée.
31. Wechsler D, Naglieri J (2009): WNV Echelle non Verbale d'Intelligence de Wechsler. Paris: ECPA, Les Editions du Centre de Psychologie Appliquée.
32. Meyers JE, Meyers KR (1995): Rey Complexe Figure Test and Recognition Trial: Professional Manual. Odessa, FL: Psychological Assessment Resources.
33. Culbertson WC, Zillmer EA (2009): Tower of London-Drexel University, 2ème edition. Technical Manual. Toronto: Multi-Health Systems Inc.
34. Stroop JR (1935): Studies of interference in serial verbal reactions. J Exp Psychol 18:643–662.
35. Zimmermann P, Fimm B (2010): Tests d'Évaluation de l'Attention version 2.2. Herzogenrath: Vera Fimm, Psychologische Testsysteme.
36. Lord C, Rutter M, Le Couteur A (1994): Autism Diagnostic Interview–Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24:659–685.
37. Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, *et al*. (2000): The Autism Diagnostic Observation Schedule–Generic: A standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord 30:205–223.
38. Preisig M, Fenton BT, Matthey ML, Berney A, Ferrero F (1999): Diagnostic Interview for Genetic Studies (DIGS): Inter-rater and

test-retest reliability of the French version. Eur Arch Psychiatry Clin Neurosci 249:174–179.
39. Friston KJ, Tononi G, Reeke GN Jr, Sporns O, Edelman GM (1994): Value-dependent selection in the brain: Simulation in a synthetic neural model. Neuroscience 59:229–243.
40. Stefansson H, Meyer-Lindenberg A, Steinberg S, Magnusdottir B, Morgen K, Arnarsdottir S, *et al*. (2014): CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature 505:361–366.
41. Arbogast T, Ouagazzal A-M, Chevalier C, Kopanitsa M, Afinowi N, Migliavacca E, *et al*. (in press). Reciprocal effects on neurocognitive and metabolic phenotypes in mouse models of 16p11.2 deletion and duplication syndromes. PLoS Genet.
42. Rosenberg T, Gal-Ben-Ari S, Dieterich DC, Kreutz MR, Ziv NE, Gundelfinger ED, *et al*. (2014): The roles of protein expression in synaptic plasticity and memory consolidation. Front Mol Neurosci 7:86.
43. Costa-Mattioli M, Monteggia LM (2013): mTOR complexes in neurodevelopmental and neuropsychiatric disorders. Nat Neurosci 16: 1537–1543.
44. Stoica L, Zhu PJ, Huang W, Zhou H, Kozma SC, Costa-Mattioli M (2011): Selective pharmacogenetic inhibition of mammalian target of Rapamycin complex I (mTORC1) blocks long-term synaptic plasticity and memory storage. Proc Natl Acad Sci U S A 108:3791–3796.
45. Migliavacca E, Golzio C, Mannik K, Blumenthal I, Oh EC, Harewood L, *et al*. (2015): A potential contributory role for ciliary dysfunction in the 16p11.2 600 kb BP4-BP5 pathology. Am J Hum Genet 96: 784–796.
46. Merikangas AK, Segurado R, Heron EA, Anney RJ, Paterson AD, Cook EH, *et al*. (2015): The phenotypic manifestations of rare genic CNVs in autism spectrum disorder. Mol Psychiatry 20:1366–1372.
47. Lindgren KA, Folstein SE, Tomblin JB, Tager-Flusberg H (2009): Language and reading abilities of children with autism spectrum disorders and specific language impairment and their first-degree relatives. Autism Res 2:22–38.
48. Meilleur AA, Jelenic P, Mottron L (2015): Prevalence of clinically and empirically defined talents and strengths in autism. J Autism Dev Disord 45:1354–1367.
49. Jiang YV, Palm BE, DeBolt MC, Goh YS (2015): High-precision visual long-term memory in children with high-functioning autism. J Abnorm Psychol 124:447–456.
50. Mottron L, Morasse K, Belleville S (2001): A study of memory functioning in individuals with autism. J Child Psychol Psychiatry 42: 253–260.
51. Mohamed S, Paulsen JS, O'Leary D, Arndt S, Andreasen N (1999): Generalized cognitive deficits in schizophrenia: A study of first-episode patients. Arch Gen Psychiatry 56:749–754.
52. Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, *et al*. (2000): Neuropsychology of first-episode schizophrenia: Initial characterization and clinical correlates. Am J Psychiatry 157:549–559.
53. Leung HC, Skudlarski P, Gatenby JC, Peterson BS, Gore JC (2000): An event-related functional MRI study of the Stroop color word interference task. Cereb Cortex 10:552–560.
54. Derrfuss J, Brass M, Neumann J, von Cramon DY (2005): Involvement of the inferior frontal junction in cognitive control: Meta-analyses of switching and Stroop studies. Hum Brain Mapp 25:22–34.
55. Price CJ (2012): A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. Neuroimage 62:816–847.
56. Howard D, Patterson K, Wise R, Brown WD, Friston K, Weiller C, *et al*. (1992): The cortical localization of the lexicons. Positron emission tomography evidence. Brain 115(pt 6):1769–1782.
57. Giraud AL, Price CJ (2001): The constraints functional neuroimaging places on classical models of auditory word processing. J Cogn Neurosci 13:754–765.
58. Lai CS, Gerrelli D, Monaco AP, Fisher SE, Copp AJ (2003): FOXP2 expression during brain development coincides with adult sites of pathology in a severe speech and language disorder. Brain 126: 2455–2462.
59. Watkins KE, Vargha-Khadem F, Ashburner J, Passingham RE, Connelly A, Friston KJ, *et al*. (2002): MRI analysis of an inherited speech and language disorder: Structural brain abnormalities. Brain 125:465–478.
60. Fedorenko E, Morgan A, Murray E, Cardinaux A, Mei C, Tager-Flusberg H, *et al*. (2015): A highly penetrant form of childhood apraxia of speech due to deletion of 16p11.2 [published online ahead of print Jul 15]. Eur J Hum Genet.
61. Newbury DF, Mari F, Sadighi Akha E, Macdermot KD, Canitano R, Monaco AP, *et al*. (2013): Dual copy number variants involving 16p11 and 6q22 in a case of childhood apraxia of speech and pervasive developmental disorder. Eur J Hum Genet 21:361–365.
62. Raca G, Baas BS, Kirmani S, Laffin JJ, Jackson CA, Strand EA, *et al*. (2013): Childhood apraxia of speech (CAS) in two patients with 16p11.2 microdeletion syndrome. Eur J Hum Genet 21:455–459.
63. Stefansson H, Rujescu D, Cichon S, Pietilainen OP, Ingason A, Steinberg S, *et al*. (2008): Large recurrent microdeletions associated with schizophrenia. Nature 455:232–236.