Thickness and contrast in 16p11.2 CNVs

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Introduction

Genomic studies have identified 16p11.2 copy number variants (CNV) as a risk factor for developmental disorders (Weiss, et al., 2008; Zufferey, et al., 2012). Duplications of this CNV are associated with reductions in total brain volume; deletions are associated with increases; both are associated with abnormalities in cortical and subcortical regions (Maillard, et al., 2015). The current study seeks to better characterize the cortical abnormalities using a larger sample than used in previous studies, and measures of both the thickness of the cortical gray-matter and of the gray-white intensity contrast. The two measures dissect gray-matter density, and so may provide better insight into the nature of any alterations.

Methods

The data analyzed here are from the 16p11.2 European and the Simons VIP Consortia. The European imaging data were acquired at two sites, one with a Siemens 3T TIM Trio scanner and one with a Siemens 3T Prisma Syngo. The Simons data were acquired at five sites on either a Siemens 3T TIM Trio or a 3T Philips Achieva.

This study used only T1-weighted images. These were acquired at 1x1x1mm resolution with a multi-echo MPRAGE sequence on the TIM Trios, and with a single-echo MPRAGE sequence on the other scanners. The multi-echo data were processed using the root-mean square of the intensity at each echo-time.

All data were processed with CIVET, a fully automated pipeline developed at the Montreal Neurological Institute. CIVET classifies voxels as white matter, gray matter, or cerebrospinal fluid (Tohka, et al., 2004); extracts the white-matter and pial surfaces (Kim, et al., 2005); and warps these to a common surface template (Lyttelton, et al., 2007). The thickness of the gray-matter is measured in native space at 81,924 vertices using the laplacian distance between the two surfaces. To extract the gray-white contrast measures, the intensity on the t1 was sampled 1mm inside and 1mm outside the white surface, and the ratio of the two measures was formed. Both the thickness and contrast measures were smoothed with a 20mm fwhm Gaussian kernel on the MNI-152 average surface.

These data were examined, and only data that had been successfully processed were included in the analysis. The analysis included 63 deletion carriers (21.8 yrs±13.4), 64 duplication carriers (27.8 yrs±16), and 196 (67 intra-familial, and 129 extra-familial) controls (23.9yrs±13.7). Both genders are well represented in each group.

These data were analyzed with SurfStat (Worsley, et al., 2009) using the mixed-effects model

$$M = \text{CNV} + \text{AGE} + \text{SEX} + \text{SITE} + \text{TBV} + \text{rand}(\text{FAMILY}) + \text{I} + 1$$

Group differences between deletion or duplication CNVs and controls were assessed for both thickness and contrast. Correction for multiple comparisons was done with random field theory.

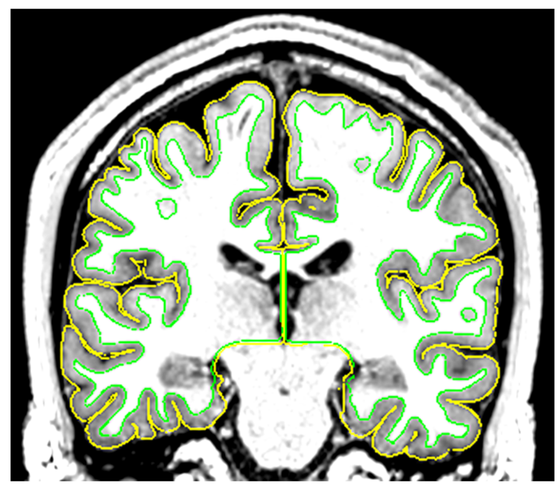

Figure 1. The CIVET surfaces.

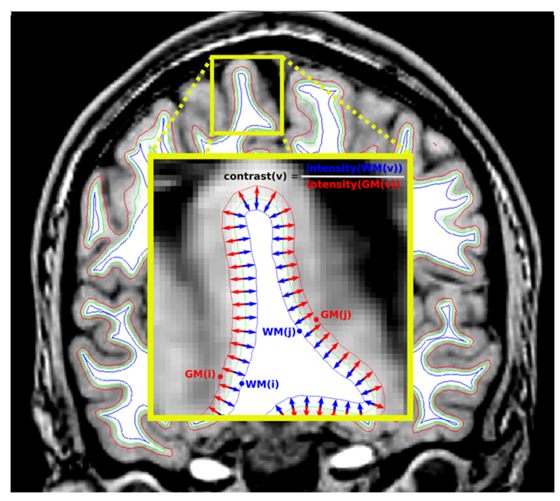

Figure 2. The method for measuring contrast.

Results

Duplications yield similar patterns of thickness and contrast: thickness is decreased in the left central sulcus and right calcarine fissure; contrast is increased in the central sulcus and medial visual areas, bilaterally, and in the left primary auditory cortex.

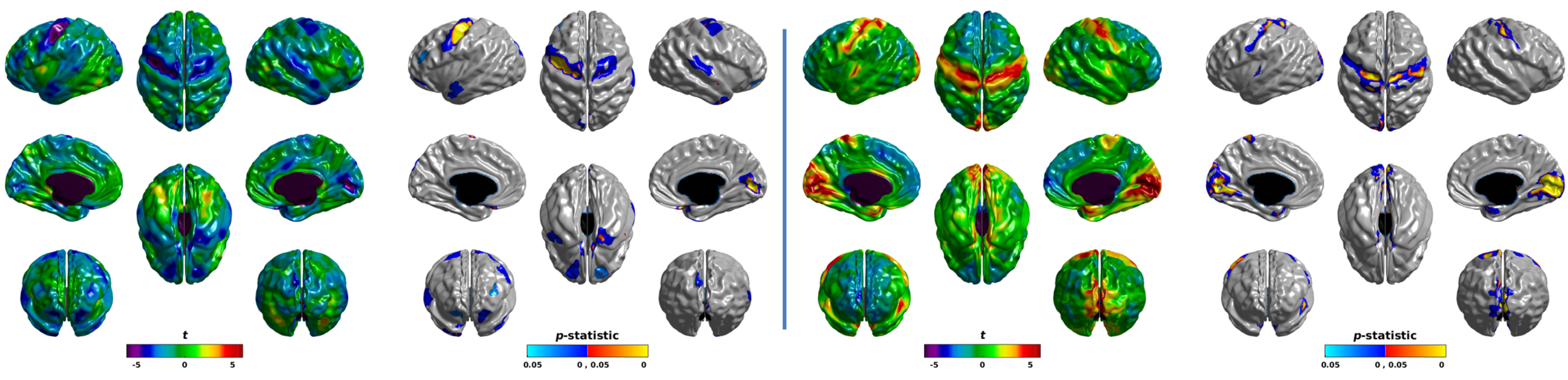

Figure 3. Thickness **(left)** and contrast **(right)** for duplication - control. The t-statistic is shown on the left; the p-statistic is shown on the right, with vertex-level significance shown in yellow-red, and cluster-level significance shown in blue-cyan. Duplication carriers show decreased thickness and increased contrast in the central sulcus, bilaterally; increased contrast in bilateral medial visual areas, and decreased thickness in the right calcarine fissure; increased contrast in the left insula; and decreased thickness at the left temporal pole.

For deletions, thickness is increased in bilateral visual areas, in the extreme posterior of the insula, bilaterally, and in the left hippocampal gyrus; contrast is decreased in broad regions of the insula and temporal lobe, bilaterally, and in Broca`s area and its right hemisphere homologue.

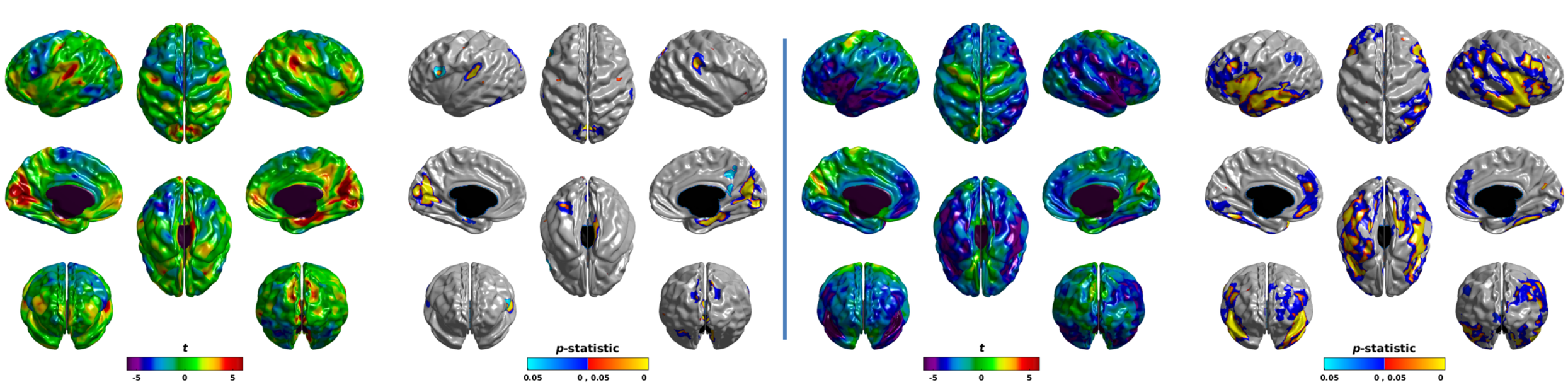

Figure 4. Thickness **(left)** and contrast **(right)** for deletion - control. The t-statistic is shown on the left; the p-statistic is shown on the right, with vertex-level significance shown in yellow-red, and cluster-level significance shown in blue-cyan. Deletion carriers show increased thickness in bilateral medial visual areas, the bilateral posterior insula, and the right medial temporal lobe; and decreased contrast in bilateral insula, bilateral temporal lobes, bilateral inferior frontal gyri, and the right lateral parietal lobe.

Conclusions

Duplications of the 16p11.2 complex yield patterns of thickness and contrast which align to localize abnormalities in regions associated with low-level sensory processing. Deletions, however, yield a pattern for thickness that partially mirrors that seen in duplications, but a pattern for contrast which implicates the bilateral insula, inferior frontal cortex, and association regions of the bilateral temporal cortices. Thus, despite the reciprocal effects on overall brain volume, 16p11.2 CNVs appear to have divergent effects on cortex, implicating distinct mechanisms.

Acknowledgements

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