

# A combined VBM and DTI investigation of brain structure and connectivity in 22q11 Deletion Syndrome

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**Background:** 22q11 deletion syndrome (22q11DS) is a common microdeletion syndrome associated with increased psychopathology, particularly schizophrenia in adulthood (Murphy et al, 1999). Our previous research into diminished frontal mismatch negativity potentials indicated an abnormality which could be ascribed to impaired fronto-temporal connectivity (Baker et al, 2005). We hypothesised that focal neural abnormalities associated with impaired connectivity would be present in the 22q11DS group.

**Methods:** 16 young adults with 22q11DS, mean age 18.2 years (SD = 2.2 years) were compared to 31 age matched controls, of whom a subset (11) were age and IQ matched. A neuropsychological battery was administered to all subjects, which comprised tests of IQ, verbal and spatial memory, expressive language, and executive functioning. Structural brain alterations in young adults with 22q11DS and their neuropsychological correlates were assessed using voxel based morphometry (VBM (Ashburner and Friston, 2000)) of 3D MRI (1.5T) scans, using SPM2. Scans were normalised to the standard T1 template in SPM2, using a 12 parameter Affine transformation. Normalised images were segmented and then smoothed with a 12mm FWHM gaussian filter. Diffusion weighted (DWI) scans were also acquired on 40 subjects, (at 3T) using a single-shot diffusion weighted echo-planar imaging sequence, and diffusion indices including Fractional Anisotropy (FA) which were calculated in matlab 6.5. Normalisation of the diffusion scans was achieved by co-registering the non-diffusion weighted ('b = 0') image collected as part of the DWI acquisition to the subjects' T1 weighted scan, and then normalising the latter to the T1 template in SPM2. The final normalisation parameters were then applied to the FA maps, which were then smoothed using an 8 mm FWHM filter and masked with the average white matter template to constrain analysis to white matter regions.

**Results:** Global volume differences existed between the groups, with total Grey matter (GM) volume in 22q11DS reduced by 11.2%, while total White matter (WM) volume was reduced by 14.6% when compared to the combined control groups. An inverse relationship existed between GM and WM volume and IQ in the VCFS group only ( $r^2 = 0.33$ ).

**Grey Matter:** (Fig. 1). GM density was reduced in a number of areas, including a large cluster of cingulate cortex that extended posteriorly to the parahippocampal gyrus. Bilateral reductions of the superior temporal gyri that extended inferiorly in the right hemisphere, were also seen ( $p < 0.05$ , corrected for Family Wise Error (FWE)). Uncorrected maps at  $p < 0.001$ , showed additional GM reductions in a small cluster in the middle frontal gyrus, and in two clusters in the occipital lobe.

Increased GM concentration was seen in the insula extending to the postcentral gyrus (FWE  $p < 0.05$ ). Uncorrected maps at  $p < 0.001$  identified increased GM bilaterally in a large number of frontal clusters, including clusters in the superior, middle and inferior frontal cortices. Areas of increased grey matter density were also present bilaterally in the parietal lobes, and in the postcentral and inferior parietal cortices.

**White Matter:** (Fig. 2). Reduced WM concentration in 22q11DS was seen bilaterally in the middle frontal gyrus which extended into more superior areas (FWE  $p < 0.05$ ). At  $p < 0.001$  (uncorrected), significant WM reductions were also seen, principally surrounding the ventricles in extra-nuclear white matter, and also in several clusters frontally.

Increased WM density in 22q11DS was also detected in areas posterior to the corpus callosum, extending into the parietal lobe.

**Fractional anisotropy:** (Fig. 3). Data from the DTI showed decreased FA in tracts in the temporal lobe and inferior frontal gyri. However unexpected increases in FA were also detected, in a large area potentially corresponding to a number of frontal tracts.

**Conclusions:** Areas of specific grey and white matter abnormalities were identified in 22q11DS, which persisted after accounting for differences in IQ. Preliminary DTI data provide evidence of disrupted white matter coherence in fronto-temporal areas, although further work is needed to identify the role of global and local grey and white matter loss that may have caused tracts to be located in anatomically different areas in the 22q11DS group. Differences in brain structure and abnormalities in neural connectivity may underlie the cognitive profile and increased psychopathology seen in 22q11DS.

Statistical Parametric maps,  $p < 0.001$  (uncorrected)

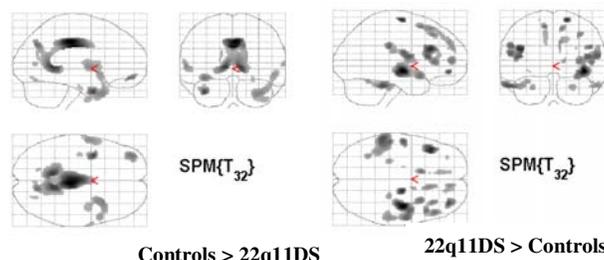


Fig. 1. Grey Matter VBM

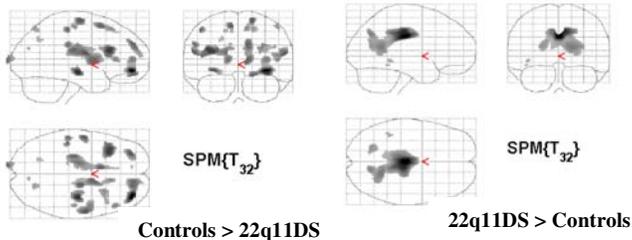


Fig. 2. White Matter VBM

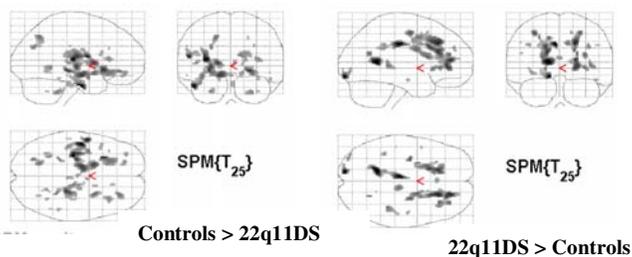


Fig. 3. Fractional Anisotropy

**References:** Baker et al, 2005. COMT Val108/158 Met modifies mismatch negativity and cognitive function in 22q11 deletion syndrome. *Biol Psychiatry* 58, 23-31  
Murphy et al, 1999. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry*. 56. 940-5.