Brain Imaging, development and cognition

or

What does MRI brain imaging tell us about structural alterations associated with the velo-cardio-facial syndrome cognitive and psychiatric phenotype?

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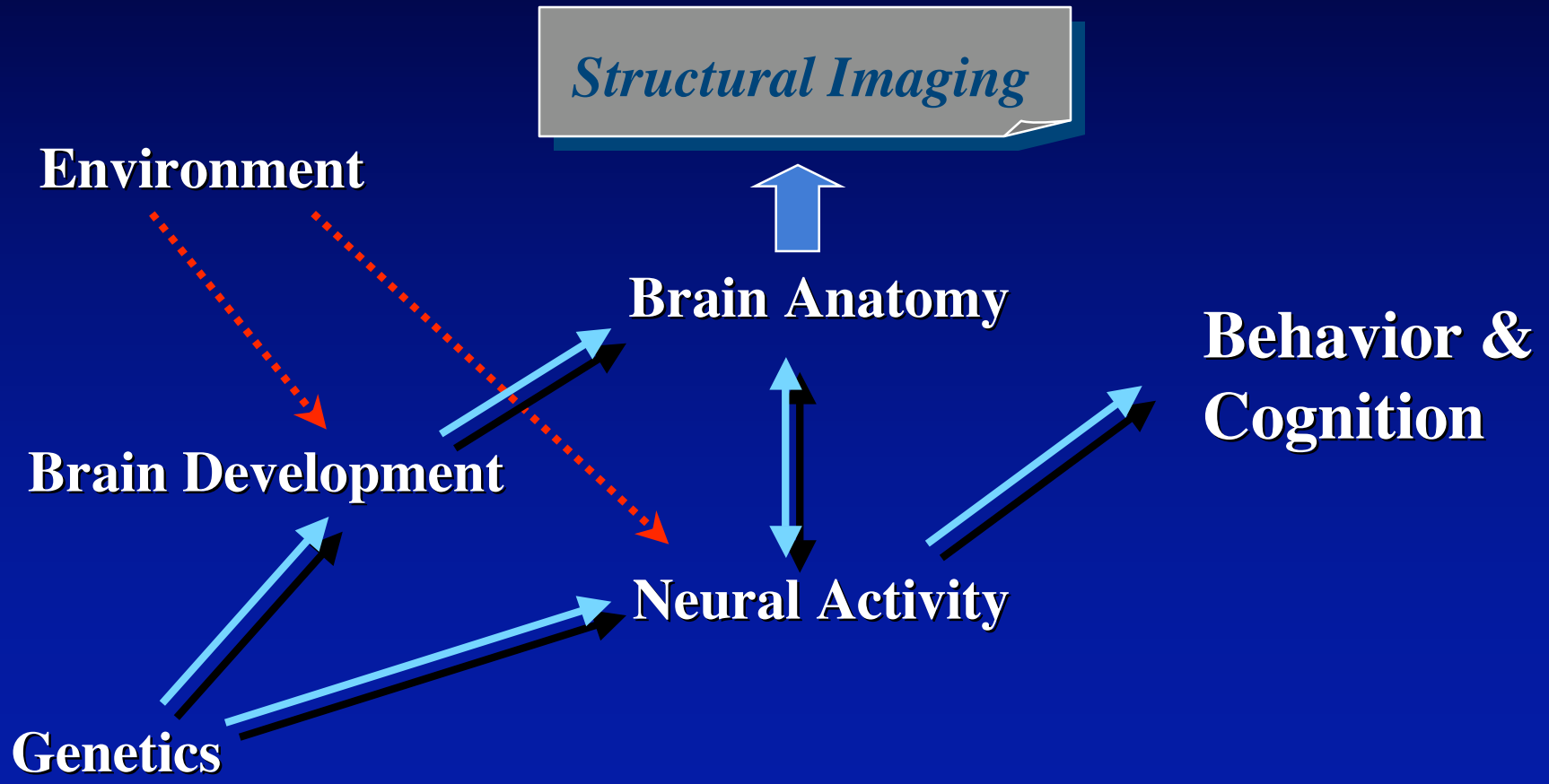
Research Model

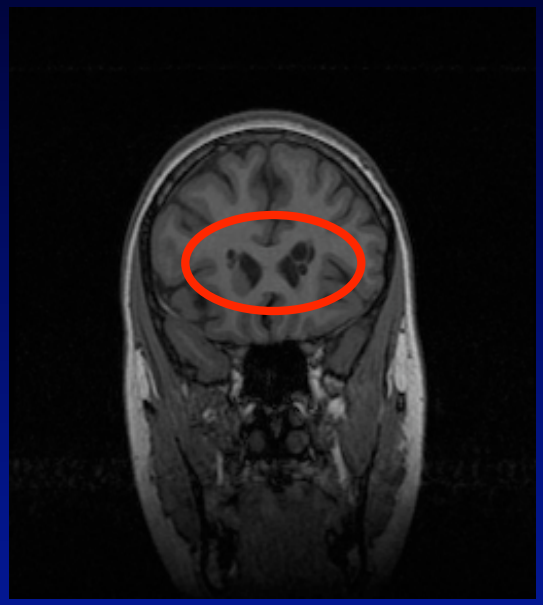


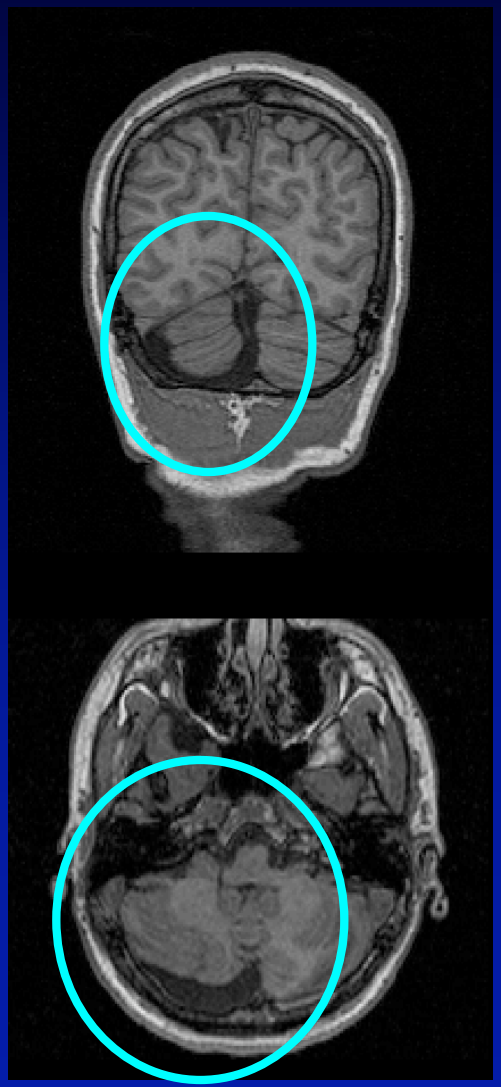
Structural Brain Imaging of VCFS

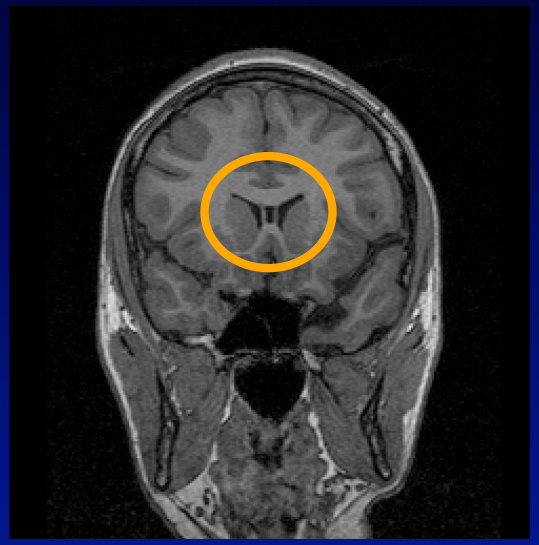
Aims and Goals

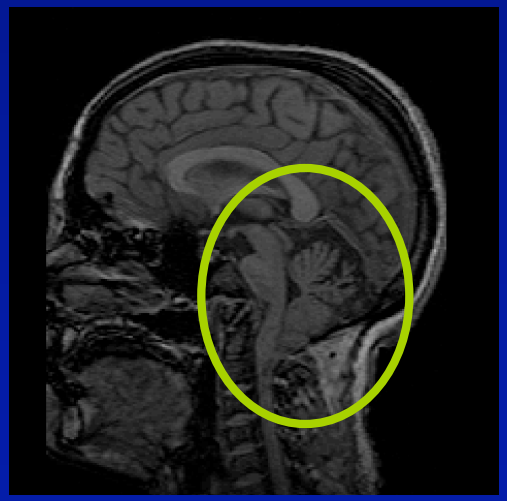
- Better definition of the syndrome
- Markers of cognitive impairment
- Markers for increased risk of psychiatric problems
- Using VCFS as a model to better understand interaction among genetic, brain, behavioral, and environmental factors in neuropsychiatric disorders

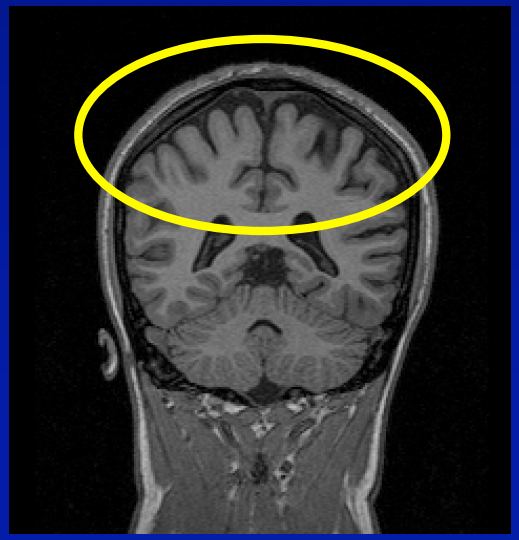
Qualitative Brain Imaging in VCFS









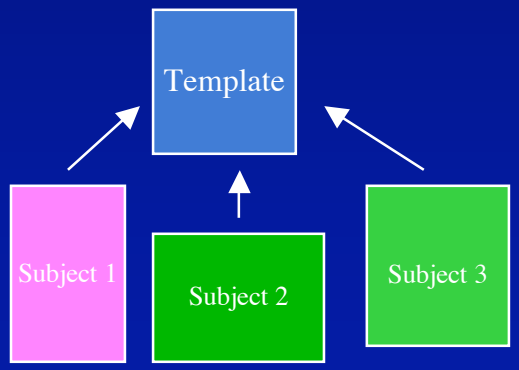


Brain Regions of Interest Suggested by Previous Quantitative Brain Imaging Research in VCFS

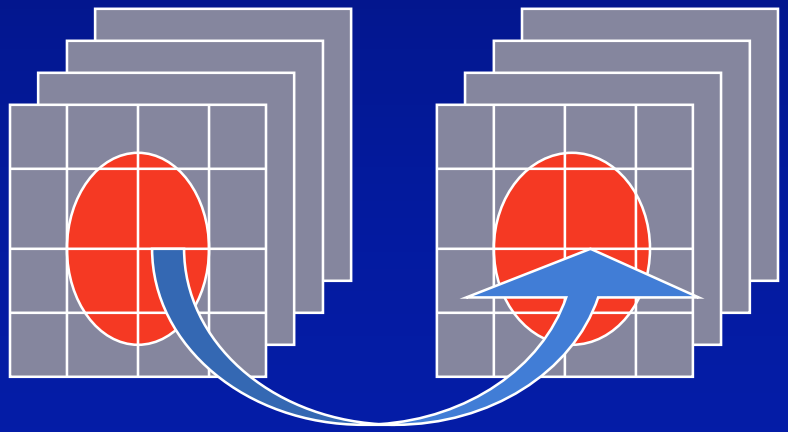
- Alteration of gray and white matter tissue (Eliez et al., Kates et al., Chow et al.)
- Relative increase/preserved frontal lobes in children and adolescents (Eliez et al.) but possible decrease as affected individuals reach adulthood (Van Amelsvoort et al.)
- Decrease of parietal lobe (Eliez et al., Kates et al.), cerebellum, and vermis (Eliez et al.)
- Increased caudate (Eliez et al.)
- Accelerated decrease of total gray matter, temporal lobes gray matter and hippocampus with age (Eliez et al.)
- DTI studies showed alteration of the superior longitudinal fasciculus, the fronto-temporal white matter track and the extreme capsule (Barnea-Goraly et al.)

Methods

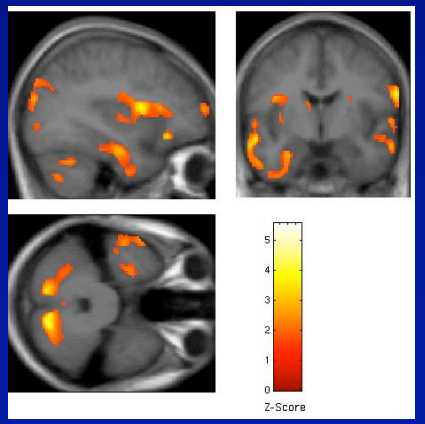
- 124 1.5mm slices coronal 3D MRI
- BrainImage© for semi-automated image processing analysis and quantification
- Manual definition of specific brain subregions to supplement semi-automated procedure
- SPM2 for voxel-by-voxel type morphometry



1) Normalization on a common template



2) t-test comparaisons

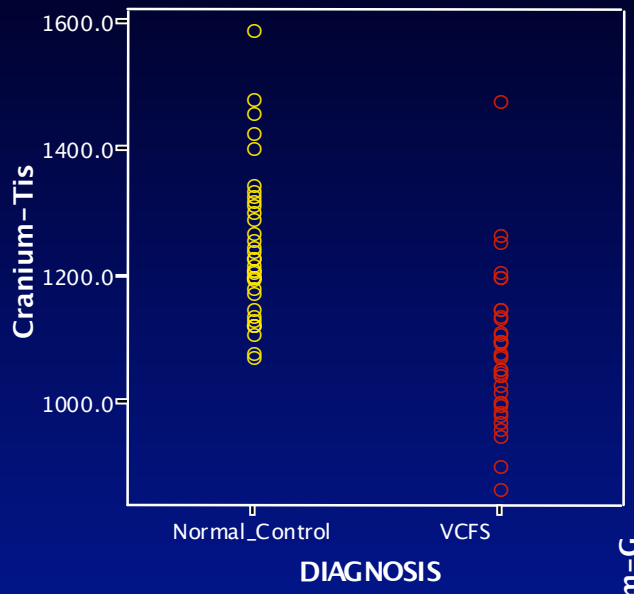


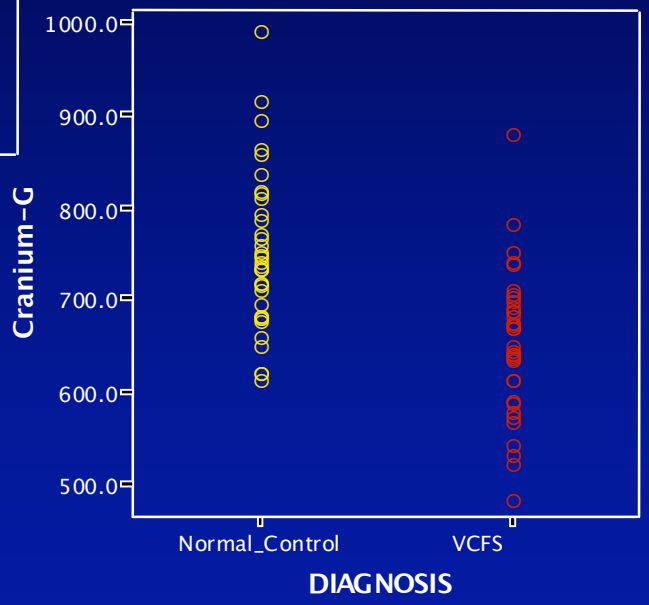
3) Correction for the number of tests

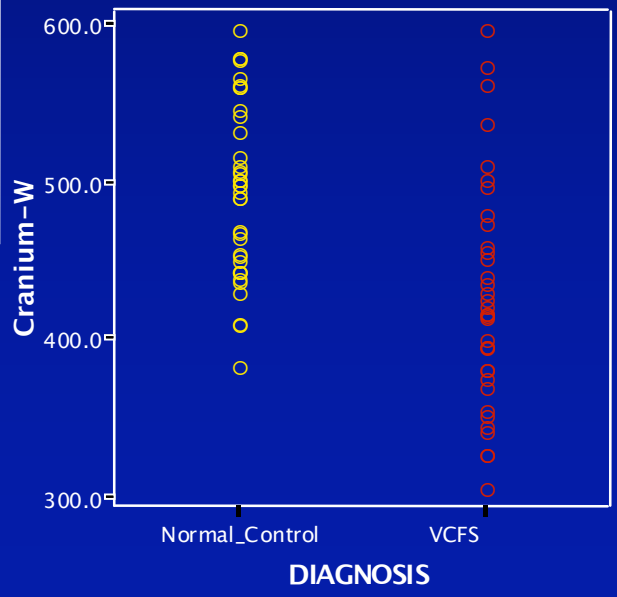
Subjects

- New independent sample of individuals participating in our research program ongoing in Geneva
- Children and adults with confirmed velo-cardio-facial syndrome and microdeletion on chromosome 22q11.2
- Typically developing control subjects (n=37) were matched for age and gender with individuals with VCFS (n=37)
- The subjects (22 females and 15 males controls; 26F/11M VCFS) ranged in age from 6.1 to 39.7 years (control: m=14.2, s=8.2; VCFS: m=16.2, s=8.9)
- Mean FSIQ for VCFS was 70.5±12.1 and 110.3 ±13.6 for controls

Volumetric Differences for Tissue

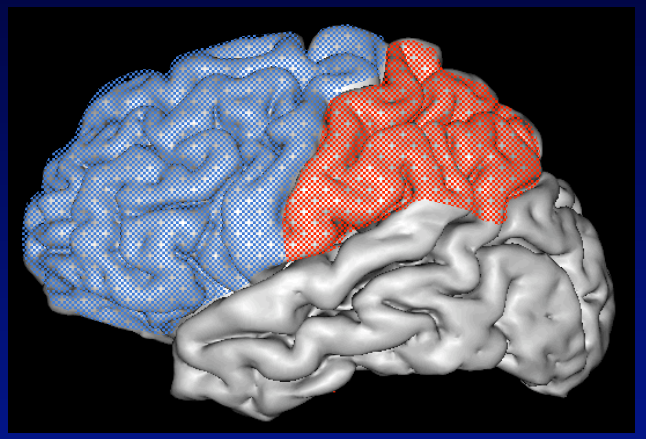






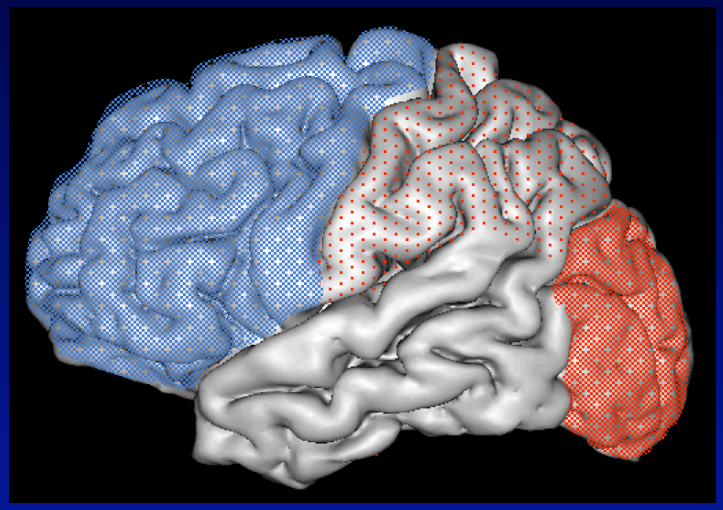
Volumetric differences for lobar gray matter

	DIAGNOSIS	Mean	Std. Deviation
Frontal Lobe-G	Control	226.449	27.7170
	VCFS	204.910	27.3134
Parietal Lobe-G	Control	157.495	18.7417
	VCFS	130.347	17.2801
Temporal Lobe-G	Control	146.312	18.3392
	VCFS	128.171	17.7999
Occipital Lobe-G	Control	75.047	16.6655
	VCFS	60.154	13.0828
Cerebellum-G	Control	82.485	12.6459
	VCFS	72.971	14.4101



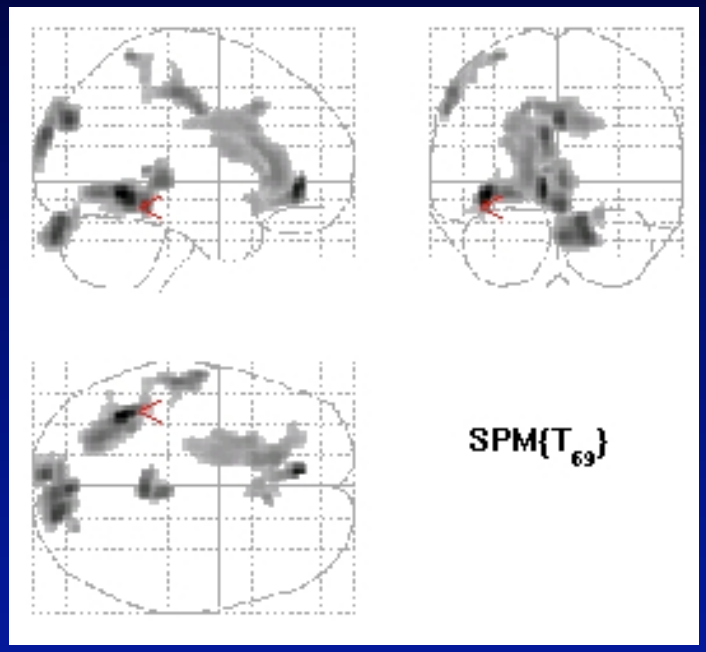
- After adjusting for differences in gray matter between groups
  - Frontal lobe is larger in VCFS
  - Parietal lobe is smaller in VCFS (Left and right)
  - No differences for temporal lobe or occipital lobe
  - No differences in cerebellar gray (total cerebellar tissue = G+W is reduced)

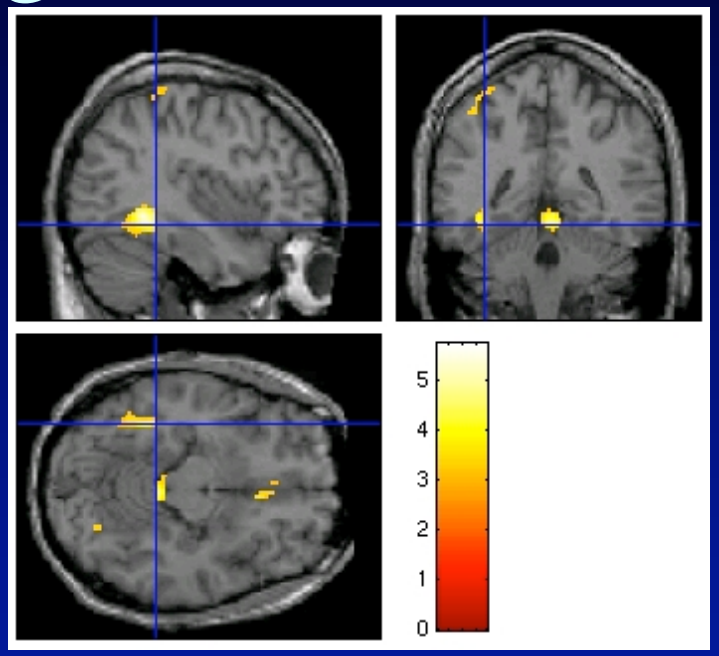
Volumetric differences for lobar and cerebellum white matter



- Relative increase of frontal white matter tissue in VCFS
- Decreased occipital white matter and white matter parietal lobe in VCFS
- Gradient of severity of the reduction from back to front: occipital more affected then parietal. Frontal lobe preserved

Changes of gray matter density with age





- Voxel-by-voxel methods (hight and extent treshold p>.01) revealed accelerated decrease in VCFS in the:
  - Left parietal lobe: working memory and arithmetic reasoning
  - Anterior/frontal part of the cingulate gyrus: attentional network and regulation of emotions
  - Vermis
  - Left fusiform gyrus: face recognition and social cognition

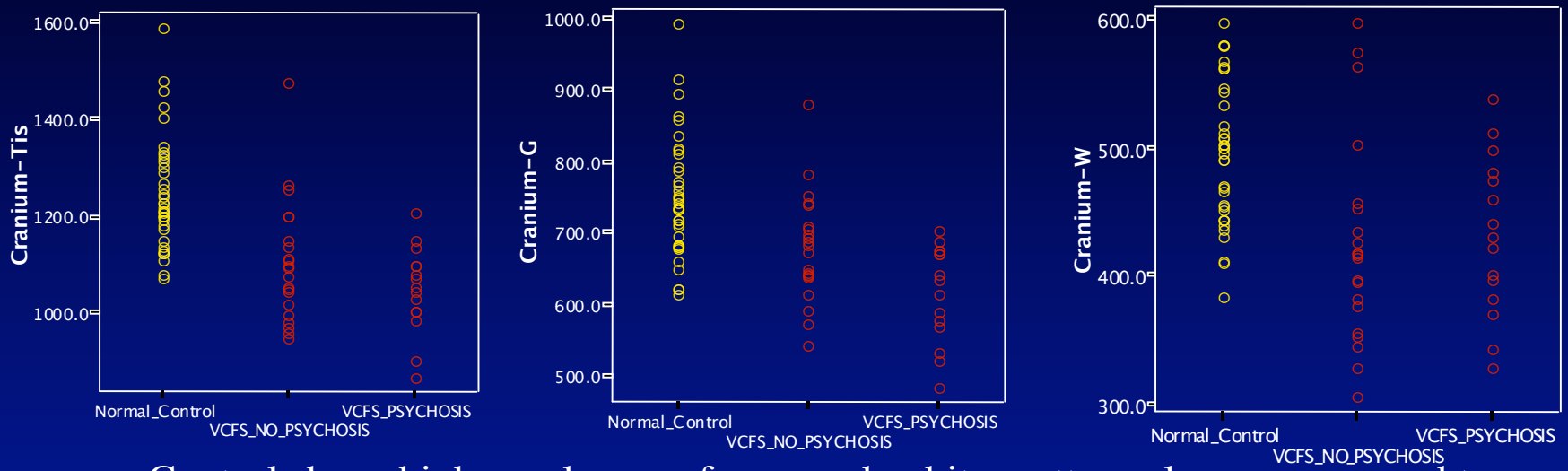
How do individuals with VCFS AND psychosis differ from controls or from individuals with VCFS without psychosis ?

Preliminary analyses

Subjects

- Children and adults with VCFS were assessed using standardized clinical assessment
  - DICA for children and adolescents (<18 y/old) and SCID for adults
  - Interview with the parents and evaluation of the child
- For the following analyses, individuals are labeled "psychotic" if they present either delusions or hallucinations, or both
- Thirty-seven typically developing control subjects (14.2 ± 8.2 y/old; 6.1 to 39.7) are compared to 21 individuals with VCFS without psychosis (13.8±9.3 y/old ranging 6.1 to 37.4; 15F/6M, FSIQ 72 ±11.5) and 15 individuals with VCFS (19.5 ±7.3; 9.7 to 32.5; 11F/4M, FSIQ 64 ±11). The age difference was not significant in our sample (p=.0926)

Tissue differences

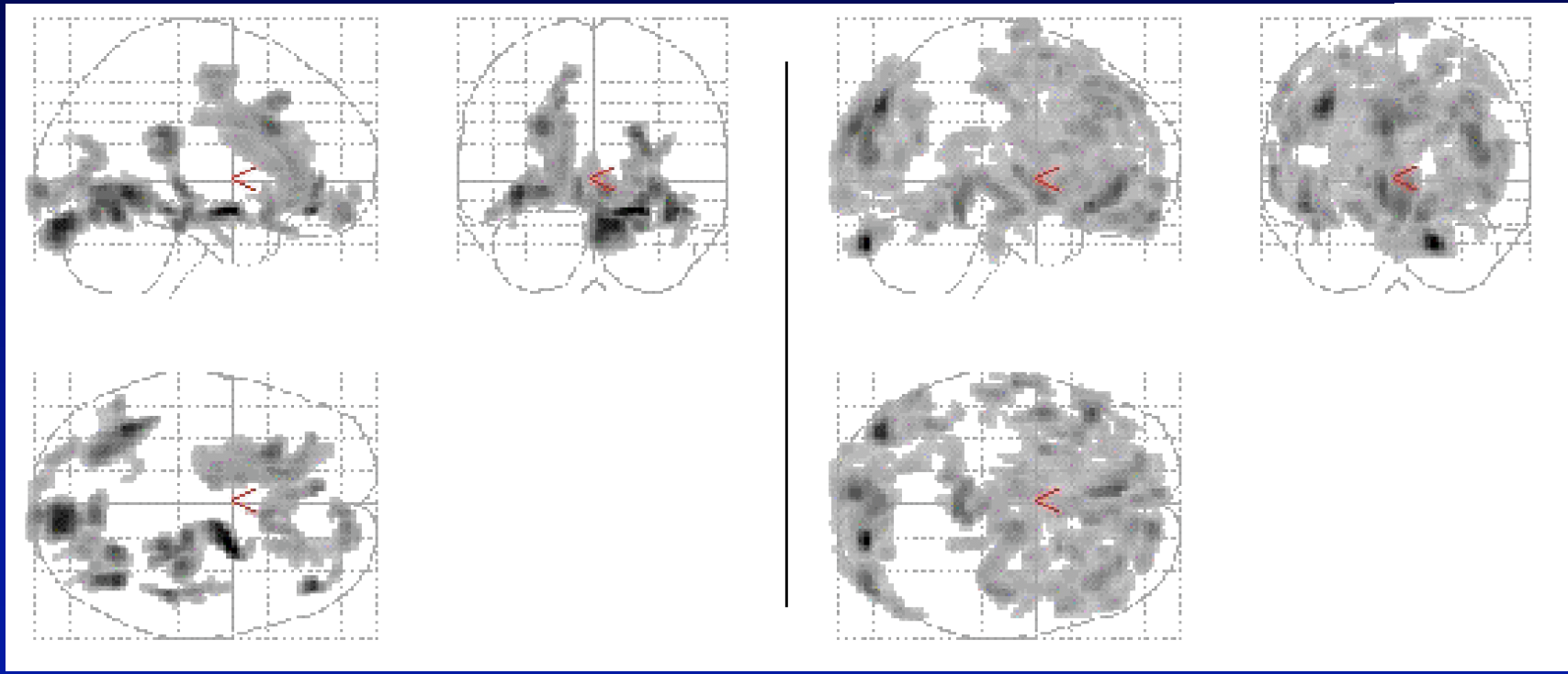


- Controls have higher volumes of gray and white matter volumes compared to both, individuals with VCFS and psychosis or individuals with VCFS without psychosis

- Individuals with psychosis have less gray matter volumes than individuals with VCFS without psychosis, even after co-varying/adjusting for age

- However, we do not observe any difference at a lobar level after adjusting for total gray matter volume. This result suggests that individuals with psychosis have an **overall** decrease of gray matter tissue that is NOT confined to a specific region of the brain

Changes of gray matter density with age



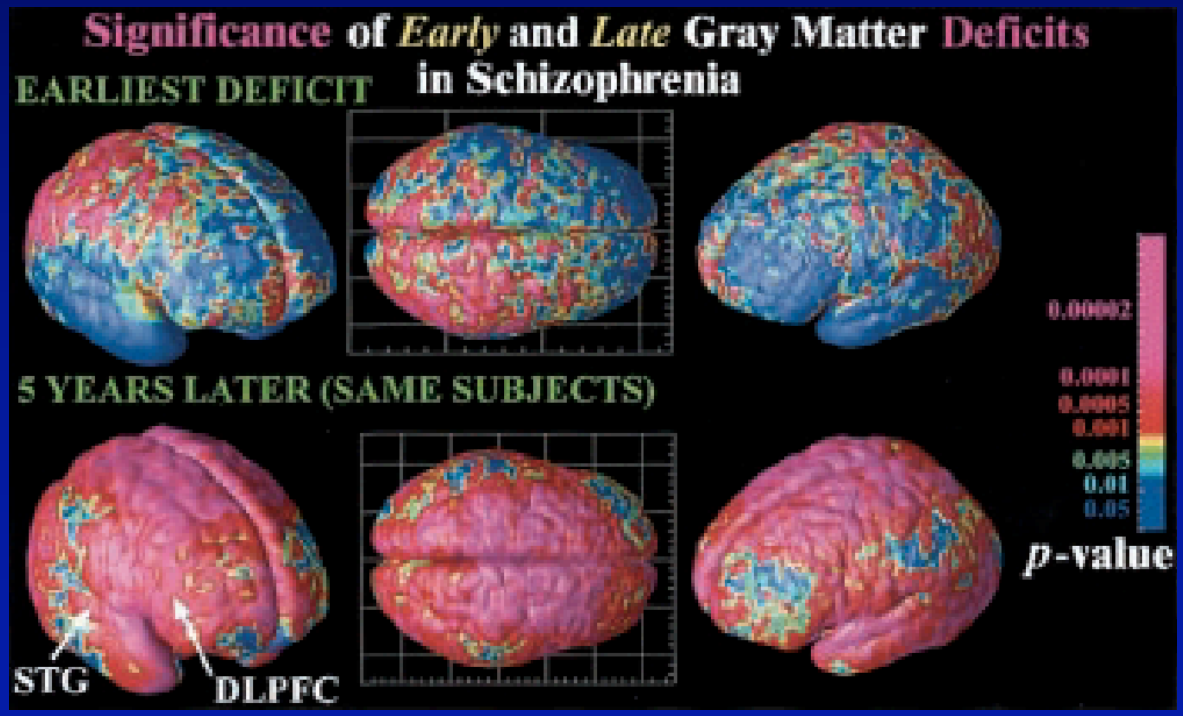
Gray matter decrease with age in individuals with VCFS **without** psychosis compared to controls

Gray matter decrease with age in individuals with VCFS **with** psychosis compared to controls

How do our findings relate to schizophrenia ?

Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia

Paul M. Thompson*†, Christine Vidal*, Jay N. Giedd‡, Peter Gochman‡, Jonathan Blumenthal‡, Robert Nicolson‡, Arthur W. Toga*, and Judith L. Rapoport‡



Conclusion

- There is a reproducible pattern of brain volume differences in VCFS compared to controls
- In VCFS with psychosis, reduction of gray matter density observed with age encompasses large areas including frontal cortex, temporal region and the parieto-occipital juncture
- It is noticeable that, even in a genetically homogeneous subtype of psychosis like VCFS, changes with age are likely to affect several lobar structures. Reductions are not limited to a single lobe or gyral structure
- The gene(s) missing in VCFS that is crucially involved in the onset of schizophrenia in the specific VCFS population, is probably expressed (or is mediating expression of secondary target genes) in most of the cortical gray matter
- Differential brain development patterns between individuals with VCFS with and without psychosis will probably affect their cognitive phenotype profile differentially

Acknowledgements

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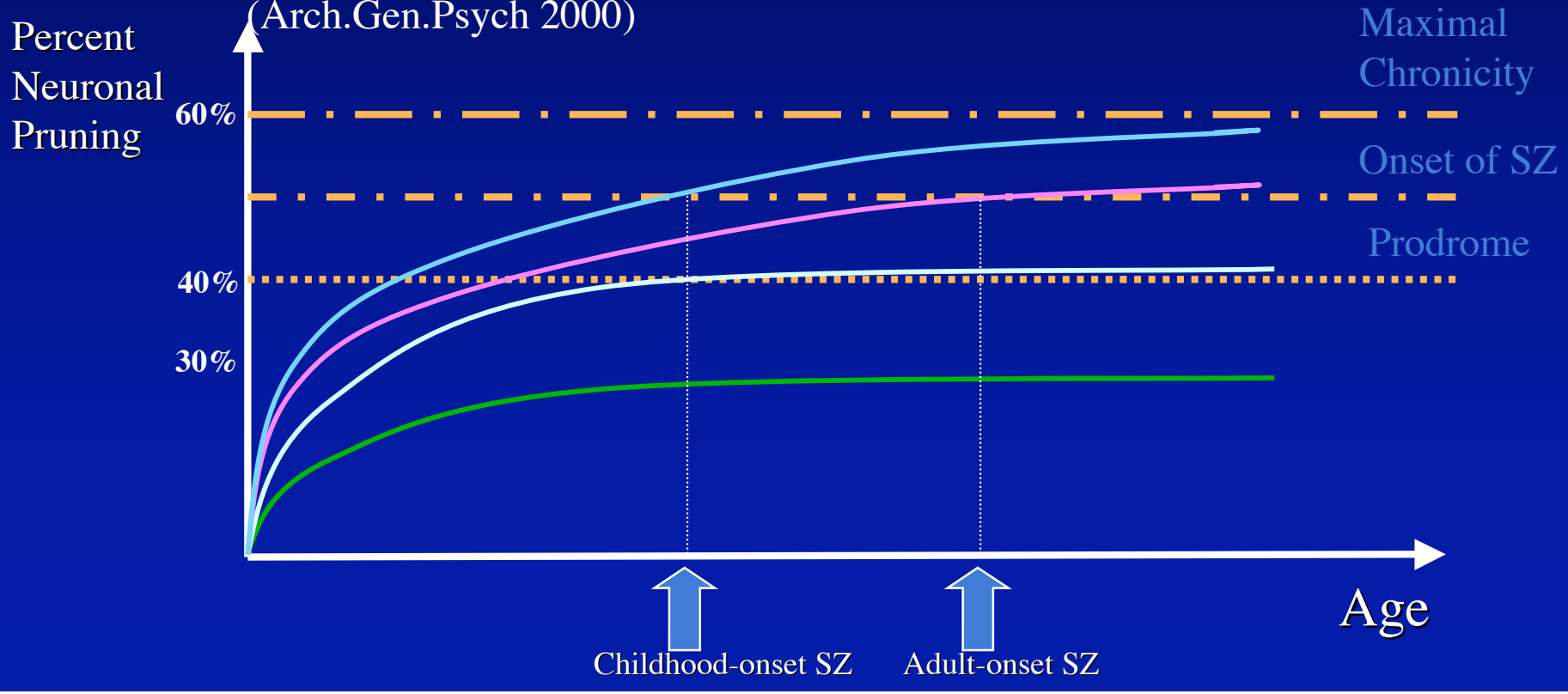
How do the Developmental Findings Relate to Schizophrenia?

- Reduced gray matter volume in first episode schizophrenia (Gur et al. & Zipursky et al. 1999)
- Progressive cortical gray reduction in childhood-onset schizophrenia (Rapoport et al., 1999)
- Model of increased neuronal pruning by McGlashan et al. (Arch.Gen.Psych 2000)



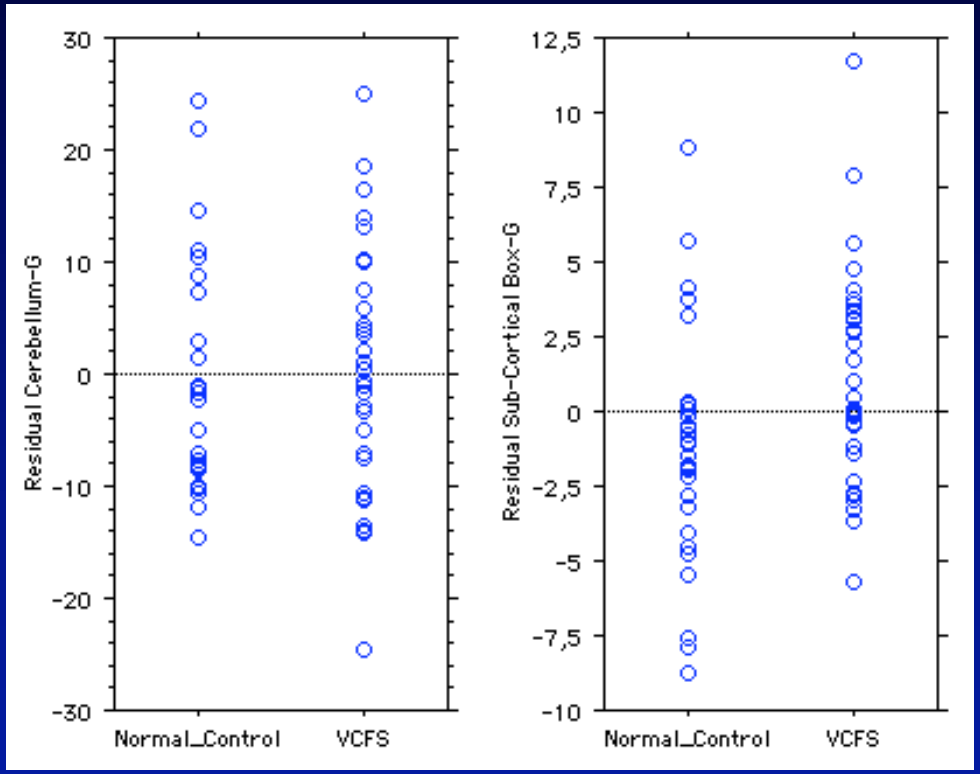
Factors Modulating Gray Matter Volumes in VCFS

- Modulation of gray matter volumes could be a major risk factor for SZ in VCFS
- Evidences from the literature that parental origin of the deletion has an impact on cognitive development (Ryan 1997, Swillen 1997)
- Imprinting could be this factor

Brain Regions of Interest Suggested by Previous Research

- Specific cognitive profile:
  - Language → Frontal, temporo-parietal regions, cerebellum
  - Arithmetic and visuo-spatial deficits → Parietal lobes
- Specific neuro-behavioral phenotype:
  - Schizophrenia → Frontal, temporal lobes, ventricles
  - ADHD → Cerebellum hemispheres and vermis, corpus callosum, basal ganglia
  - Autism or autistic features → Posterior vermis

Volumetric differences for cerebellum and subcortical gray matter



- No differences for cerebellum gray
- Relative increase in subcortical gray matter

VCFS, Brain Development and Cognition

- 11% overall brain volume decrease
- Frontal and Subcortical Grey is preserved/enlarged
  - Only borderline to mild mental retardation as opposed to other disorders with microcephaly (e.g. Rett or Williams)
- Parietal Grey reduction
  - Verbal working memory and long term memory consolidation (Smith & Jonides 1998)
  - Semantic processing of words. Inf. Parietal most common site of lesion producing conduction aphasia
  - Arithmetic
- Cerebellum reduction
  - Involved in several higher order cognitive process like language or time perception

Lobar differences for gray matter