Reduced Lingual Volume is Associated with Deficient Working Memory in Children with Chromosome 22q11.2 Deletion Syndrome

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Chromosome 22q11.2DS

- Chromosome 22q11.2 deletion syndrome (22q11.2DS) includes DiGeorge and velocardiofacial (VCFS) syndromes.
- Occurs in between 1:2000 and 1:4000 live births via a 3Mb deletion on the long (q) arm at the 11.2 band of one copy of chromosome 22.[1]
- Broad psychiatric phenotype; 20-35% develop schizophrenia in young adulthood.[2]
- Children with chromosome 22q11.2DS exhibit a nonverbal learning disability incorporating vast spatial working memory impairment.[3]

Overview and Purpose

- Working memory relies on the ability to efficiently update and manipulate task-relevant information.[4]
- Spatial working memory impairments are well documented in individuals with 22q11.2DS.[5]
- Frontal, parietal, and temporal brain regions underpin spatial working memory processing.[6]
- Children with 22q11.2DS exhibit reduced volumes (hippocampal and thalamic) in brain regions associated with spatial working memory; also seen in patients with schizophrenia without 22q11.2DS.[7,8,9]

Hypotheses

1. Performance on working memory indices (WISC-IV WMI and Spatial WM Task) will be positively correlated.
2. Children with 22q11.2DS will do worse on measures of working memory compared to typically developing (TD) controls.
3. Impaired performance on working memory indices will be associated with smaller neural volumes associated with working memory in children with 22q11.2DS compared to TD controls.

Participants and Procedures

- Children aged 7 to 16 years; 22q11.2DS: n = 25, 9 female; mean age: 12.62 ± 2.72 years; TD: n = 36, 13 female; mean age: 11.33 ± 2.68 years
- *Computerized Spatial Working Memory (WM) Task:*

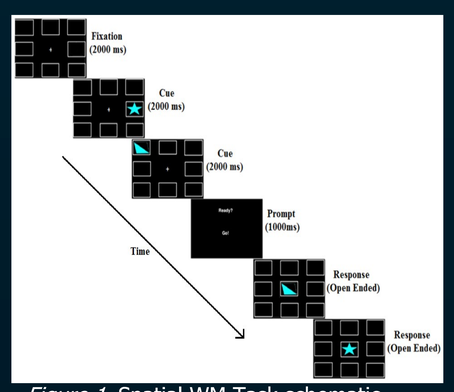


Figure 1. Spatial WM Task schematic.

- Displays a maximum of eight shapes
- Each level consists of four trials
- Correct answers provided at least 65% of the time proceeded participants to the next level.
- Score: Level . Level Accuracy (e.g. 5.23)

Participants and Procedures

- *Wechsler Intelligence Scale for Children - Fourth Edition: Working Memory Index (WISC-IV WMI)*
  - A composite score obtained from digit and picture span subtest administration.
  - Used to measure children's ability to maintain, recall, manipulate, and sequence auditory information.

MRI Data Acquisition

- A 3.0T Siemens Tim Treo scanner and 8-channel head coil were used to acquire 3D high-resolution T_1 anatomical images.
  - 176 slices, 1.0 mm thick, TR/TE = 1900/2.48 ms, 9° flip angle, 246 x 256 acquisition matrix, FOV = 100 mm.
- Raw images were imported and processed in FreeSurfer (v5.3.0) software using the 'recon-all' script.
  - The automated cortical and subcortical parcellation on structural data yields volumes for brain regions-of-interest including the lingual and parahippocampal gyri.

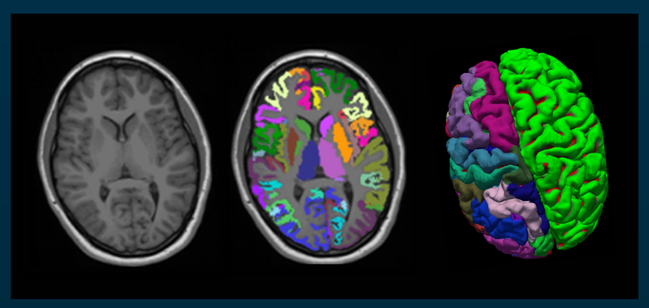
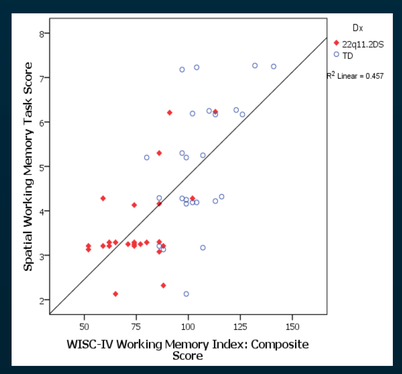


Figure 2. Example brain segmentation (L to R) Transverse sliced T1 anatomical, parcellation, and 3D reconstruction for one brain.

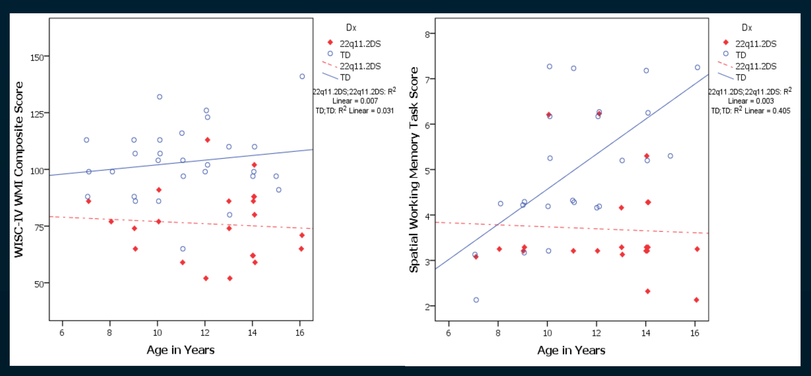
Task Results



1. Controlling for age and sex, performance on the WISC-IV WMI and Spatial WM Task are positively correlated: $r(34) = 0.72$, $p < 0.001$

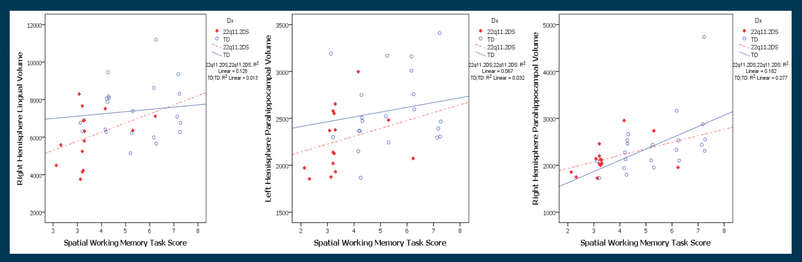
Figure 3. (left) Spatial WM Task and WISC-IV WMI correlation.

Figures 4 and 5. (below left to right) 22q11.2DS diagnosis predicts performance on WISC-IV WMI and Spatial WM Task.



2. Controlling for age and sex, diagnosis of chromosome 22q11.2DS is negatively associated with working memory performance:
   - WISC-IV WMI: $\beta = -0.64$, $t(43) = -5.31$, $p < 0.001$
   - Spatial WM Task: $\beta = -0.54$, $t(36) = -3.77$, $p = 0.001$

Imaging Results



Figures 6, 7, and 8. (above left to right) Performance on the Spatial WM Task predicts right lingual volume within kids with 22q11.2DS. Bilateral parahippocampal volumes trending in 22q11.2DS and task performance.

3. Controlling for age, sex and total grey matter volume within kids with 22q11.2DS, performance on the Spatial WM Task is positively related to lingual volume as bilateral parahippocampi approach significance:
   - Right Lingual: $\beta = 0.37$, $t(9) = 2.30$, $p < 0.05$
   - Left Parahippocampus: $\beta = 0.36$, $t(9) = 2.17$, $p = 0.06$
   - Right Parahippocampus: $\beta = 0.47$, $t(9) = 2.11$, $p = 0.06$

Summary and Implications

- Spatial WM Task performance is related to WISC-IV WMI scores.
- Working memory impairment in 22q11.2DS appears to extend into the spatial domain using a novel working memory task.
- Impaired performance on the Spatial WM Task is associated with reduced right lingual gyrus volume and trends towards reduced bilateral parahippocampal volume.
- Lingual gyri are involved in visual processing and recruited during delay periods in spatial working memory tasks.[10,11] Parahippocampal gyri are involved in spatial memory processing.[12,13] Damage to these regions and their connections to surrounding areas results in impaired spatial memory.
- Impaired memory is previously reported in 22q11.2DS, but this study is the first to identify specific brain regions associated with spatial working memory impairment.
- Disruption of working memory systems interacting with atypical brain development of brain networks that underpin autonoetic consciousness may play a role in the etiopathology of schizophrenia.
- This Spatial WM Task could be used to monitor improvement or decline of spatial working memory over time in this at-risk population.

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This project is supported by grants from the National Institute Of Mental Health (EAB 5R00MH086616-05), the University of Louisiana, and the Louisiana Board of Regents to EAB.

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