

Increased Extra-Axial Cerebrospinal Fluid Volume in Children with Angelman Syndrome: Links to Sleep Problems and Seizures

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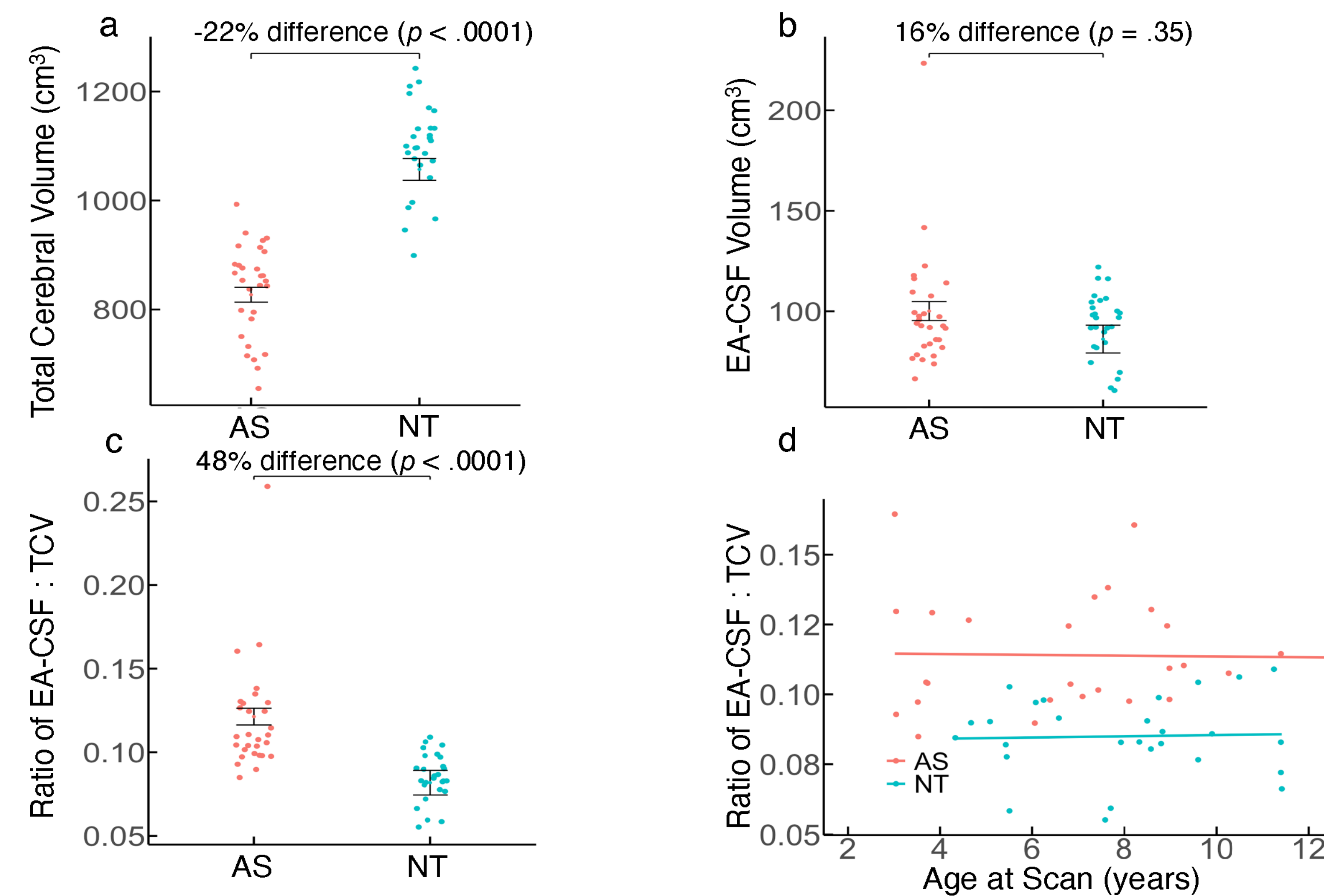
Background

- **CSF Function & Relevance:** Cerebrospinal fluid (CSF) supports brain development through waste clearance (glymphatic system) and growth factor distribution¹.
- **Motivation:** Prior research has shown elevated extra-axial CSF (EA-CSF) in individuals with autism, with higher volumes linked to clinical severity²⁻⁴. This raises the question of whether EA-CSF might be similarly altered in Angelman syndrome (AS), which shares several phenotypic features with autism, including sleep disturbances and seizures.
- **Study Objectives:** This study examined EA-CSF and total cerebral volume (TCV) in AS children compared to neurotypical (NT) controls to test whether EA-CSF is disproportionately enlarged and is associated with sleep problems and seizures.

Methods

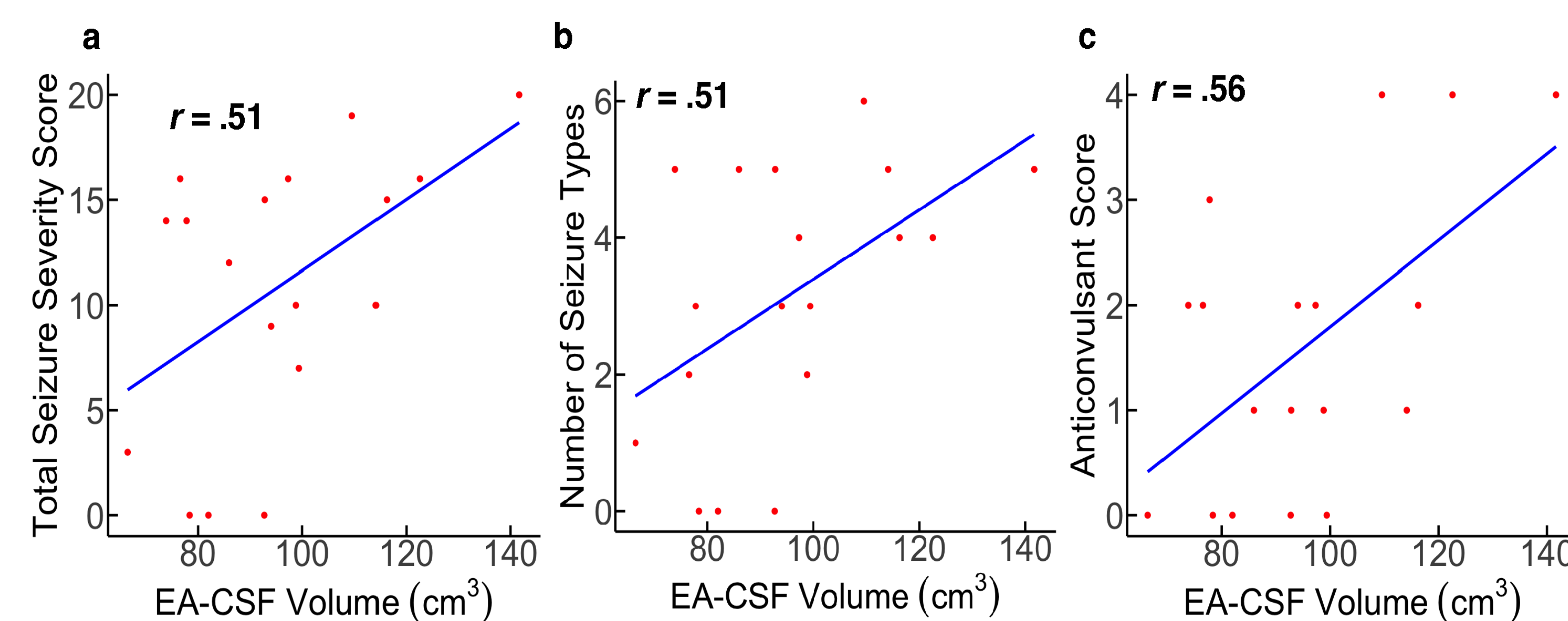
- **Participants**
 - 29 AS children (M[SD]=6.08±2.14 years); 27 NT controls (M[SD]=7.96±2.24)
 - EA-CSF TCV quantified from MRI scans (T1w & T2w) that were acquired at UNC.
- **Sleep & Seizure Measures**
 - Sleep: Children's Sleep Habits Questionnaire (CSHQ).
 - Seizures: Revised Early Childhood Epilepsy Severity Scale (E-Chess) capturing seizure types, medications, and treatment response.
- **Analysis**
 - ANCOVA for group comparisons of EA-CSF and TCV.
 - Linear regression to test associations with sleep and seizures in AS, controlling for age, sex, and time between assessments and age at scan.

Children with Angelman Syndrome Have Smaller Brain Volumes



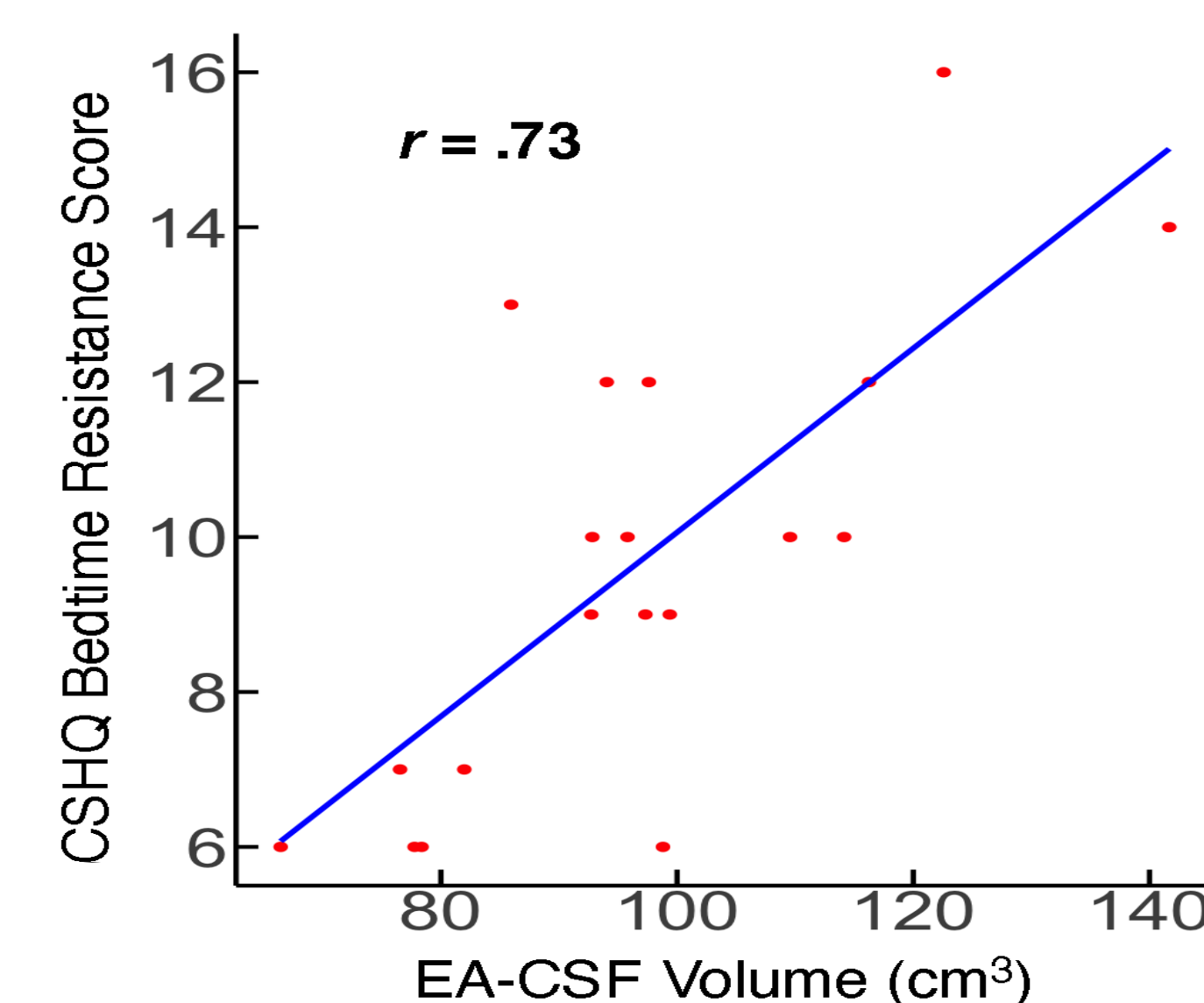
- (a) **Brain size is 22% smaller** in the AS group compared to NT ($p < .0001$, $\eta^2_{\text{group}} = 0.8$).
- (b) EA-CSF volumes between AS and NT groups are comparable ($p = 0.35$).
- (c) **The ratio of EA-CSF volume to TCV is 48% higher** in the AS group compared to NT ($p < .0001$, $\eta^2_{\text{group}} = 0.33$).
- Despite smaller brain volumes, children with AS have disproportionately increased EA-CSF volume (**consistent with children with autism**).

Extra-Axial CSF Positively Associated with Seizure Severity Metrics in Angelman Syndrome



EA-CSF volume in Angelman syndrome was positively correlated with: (a) **total seizure severity score** ($r = 0.51$); (b) **number of seizure types** ($r = 0.51$); and (c) **number of anticonvulsant used** ($r = 0.56$).

Extra-Axial CSF Positively Associated with Sleep Initiation Difficulty in Angelman Syndrome



Higher EA-CSF volumes in Angelman syndrome were associated with **greater problems with sleep initiation** (higher bedtime resistance scores; $r = 0.73$).

Discussion & Future Directions

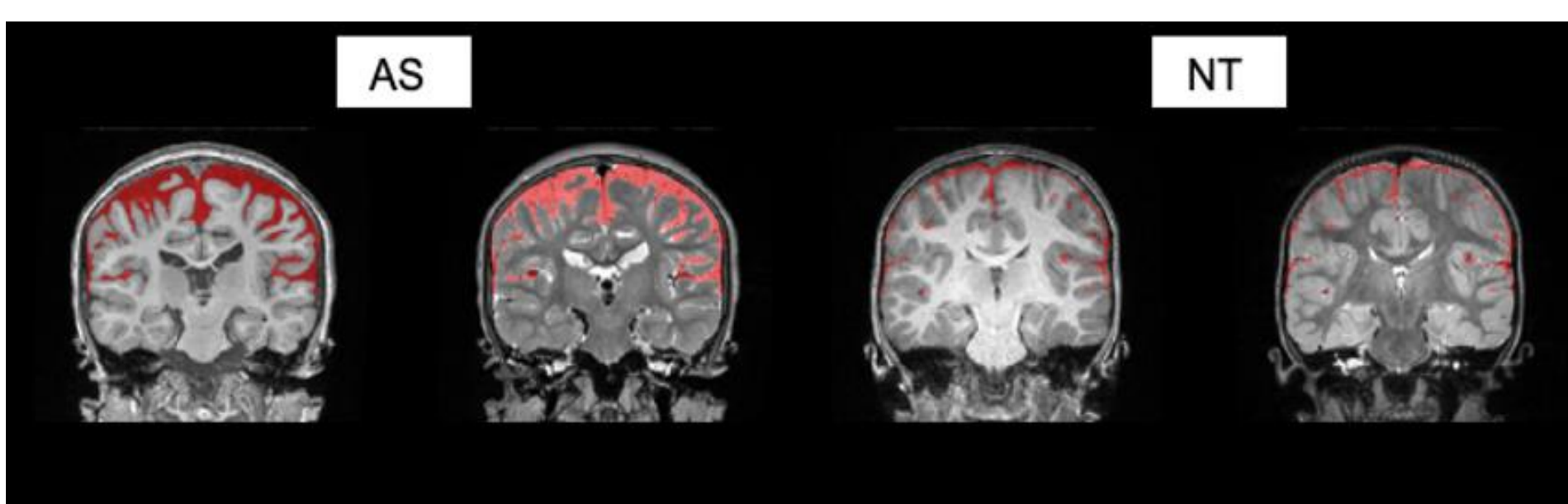
1. **Understanding CSF Dynamics in AS:** Our study reveals disproportionate increases in EA-CSF relative to brain size in children with AS, offering insights into potential disruptions in CSF circulation. Future research should explore how these alterations in CSF dynamics may impact brain waste clearance and overall neural health in AS.
2. **Investigating the Role of the Glymphatic System:** The relationship between EA-CSF and sleep disturbances in AS highlights the potential involvement of the glymphatic system, as CSF circulation is most effective during sleep. Future studies should focus on how impaired CSF flow may contribute to neuroinflammation and increased neurodevelopmental severity, paving the way for innovative therapeutic strategies.
3. **Linking CSF Dynamics to Targeted Therapies:** The study's findings raise critical questions about how disrupted CSF circulation in AS could affect the biodistribution of intrathecal therapies currently in clinical trials. Future research should explore strategies to enhance CSF flow, potentially improving the efficacy of gene-based therapies for AS.
4. **Expanding to Other Neurodevelopmental Disorders:** Given the shared characteristics between AS and other neurodevelopmental disorders, particularly autism, expanding this research to include a broader range of disorders could reveal commonalities in CSF pathology, leading to new diagnostic and therapeutic insights for early-onset neurodevelopmental conditions.

References

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Acknowledgements

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Examples of T1-weighted and T2-weighted MRI scans with extra-axial cerebrospinal fluid segmentation (EA-CSF; highlighted in red) in Angelman syndrome (AS) and neurotypical individuals in coronal view