**Title**: Feasibility of prefrontal measurement using fNIRS during an executive function task in Williams syndrome

**Authors**: Emma Condy1,2, Maeve Sargeant 2, Audrey Thurm2, Amir Gandjbakhche3, & Beth A. Kozel4,5

**Introduction**: Williams syndrome (WS) is a genetic condition characterized by mild-moderate intellectual disability (ID), with relatively preserved verbal ability, and notable visuospatial and executive function deficits. Due to limitations in most neuroimaging modalities, individuals with ID (including those with WS) are often excluded from neuroscientific studies, particularly those focused on functional activity. The limited neuroimaging work in WS has focused on the social and visuospatial profile and less on the attention and cognitive profile (Thom et al., 2023) despite evidence that these skills may be implicated in the former. The lack of literature is due in part to the high participant burden of traditional functional neuroimaging methods (i.e., fMRI). However, functional near-infrared spectroscopy (fNIRS) is a functional neuroimaging technique which measures changes in oxygenated and deoxygenated hemoglobin in the cerebral cortex. fNIRS affords better temporal resolution than fMRI and better spatial resolution than EEG while being more tolerant to motion artifact, portable, and quiet (Lloyd-Fox et al., 2010). For these reasons, fNIRS is a practical candidate for measuring brain activity in populations that are less likely to complete wakeful state fMRI, such as individuals with ID. The present study assessed the feasibility of using fNIRS in individuals with WS and their brain activity during an executive function task (i.e., go/no-go). If individuals with WS have greater difficulty with executive function, then we expect to see increased effort (i.e., increased oxygenated hemoglobin) in the prefrontal cortex during the no-go condition than the go condition of a go/no-go task.

**Method**: Individuals with WS (*n*=37) ages 5-66 enrolled in a natural history protocol were invited to participate in the fNIRS measurement. Control participants (*n*=21) were also recruited to match the age and sex of the WS sample. Participants were first introduced to the fNIRS device and then the 16-optode headband was centered at Fpz on their forehead. Participants then underwent a 3-minute resting state baseline. A modified go/no-go task (Smith et al., 2017) was then administered. Finally, participants repeated the 3-minute resting state measurement. Qualitative data regarding participant behavior during the fNIRS sessions documented unsuccessful attempts. fNIRS data were preprocessed using Homer 3 software. Resulting oxygenated hemoglobin values are being analyzed using a mixed effects model including participant as a random effect, and region, task (go v. no-go), group (WS vs. control), and age as fixed effects.

**Results**: Individuals with WS completed the fNIRS go/no-go task with moderate success (24; 65%). Of those that were unable to complete the fNIRS go/no-go, 6 were due to limited understanding of the go/no-go task, 3 never attempted the fNIRS measurement due to clinical judgement, 2 moved the fNIRS band during collection, 1 declined to wear the fNIRS band, and 1 attempted the task but data were invalid due to excessive talking during the session. All participants who completed the task had adequate data quality. Preliminary go/no-go task analyses suggest oxygenated hemoglobin changes were higher in the no-go compared to the go condition for both WS and control groups at right lateral prefrontal channels. There was no difference in change in oxygenated hemoglobin at other locations and age was not related to the change in oxygenated hemoglobin.

**Discussion:** The present study found fNIRS to be a viable neuroimaging method for use in individuals with WS. Notably, the primary factor determining success was understanding the cognitive task and not the fNIRS itself. In future studies, careful selection of the imaging task and practice trials are warranted to ameliorate this issue. We expect successful fNIRS rates to generalize to other populations characterized to mild-moderate ID; notably, limited feasibility has been reported in populations with severe-profound ID, namely, Angelman’s syndrome (Hagenaar et al., 2024).Additionally, preliminary results suggest that right lateral prefrontal cortex, such that individuals with WS and controls both showed heightened activity during the no-go blocks. Additional analyses relating brain activation to performance on the go/no-go task as well as resting state data are planned. Future studies investigating the potential for fNIRS in ID should consider less complex cognitive tasks and, relatedly, more flexible fNIRS systems that allow collection from regions other than the prefrontal cortex. Such studies would help determine whether fNIRS can elucidate neural activation differences in ID, a historically underrepresented diagnosis in the neuroscience literature, which stands to benefit from a functionally relevant marker of cognition for future intervention studies.

**References:**

Hagenaar, D. A., Bindels-de Heus, K. G. C. B., van Gils, M. M., van den Berg, L., ten Hoopen, L. W., Affourtit, P., Pel, J. J. M., Joosten, K. F. M., Hillegers, M. H. J., Moll, H. A., de Wit, M.-C. Y., Dieleman, G. C., & Mous, S. E. (2024). Outcome measures in Angelman syndrome. *Journal of Neurodevelopmental Disorders*, *16*, 6. https://doi.org/10.1186/s11689-024-09516-1

Lloyd-Fox, S., Blasi, A., & Elwell, C. E. (2010). Illuminating the developing brain: The past, present and future of functional near infrared spectroscopy. *Neurosci Biobehav Rev*, *34*(3), 269–284. <https://doi.org/10.1016/j.neubiorev.2009.07.008>

Smith, E., Anderson, A., Thurm, A., Shaw, P., Maeda, M., Chowdhry, F., Chernomordik, V., & Gandjbakhche, A. (2017). Prefrontal Activation During Executive Tasks Emerges Over Early Childhood: Evidence From Functional Near Infrared Spectroscopy. *Developmental Neuropsychology*, *42*(4), 253–264. https://doi.org/10.1080/87565641.2017.1318391

Thom, R. P., Canales, C., Tresvalles, M., McDougle, C. J., Hooker, J. M., Chen, Y., & Zurcher, N. R. (2023). Neuroimaging research in Williams syndrome: Beginning to bridge the gap with clinical care. *Neurosci Biobehav Rev*, *153*, 105364. https://doi.org/10.1016/j.neubiorev.2023.105364

Hofstra University, Hempstead, NY

2 National Institute of Mental Health, Bethesda, MD

3 National Institute of Child Health and Human Development, Bethesda, MD

4 Steve and Cindy Rasmussen Institute for Genomic Medicine,Nationwide Children’s Hospital, Columbus, OH

5 National Heart, Lung, & Blood Institute, Bethesda, MD