Symposium Title: Understanding Down Syndrome across the Lifespan: Cognition, Brain, and Genes

Chair: Hana D’Souza\textsuperscript{1,2,3} & Kate Hughes\textsuperscript{4}

Discussant: Jamie Edgin\textsuperscript{4}

Overview: Down syndrome (DS) is caused by the presence of an additional chromosome 21 and is the most common known genetic cause of intellectual disability. Although large individual differences exist in the DS phenotype, a widely accepted profile of DS has been established. In addition to general intellectual disability falling within the mild to severe range, the profile includes particular difficulties in verbal working memory, motor ability, auditory processing, and expressive language, and relative strengths in visuospatial processing, receptive language, and some aspects of social functioning. This profile is not the direct result of genes but their probabilistic atypical modulation of complex developmental processes. The DS pattern of strengths and weaknesses gradually emerges through interactions between various factors at multiple levels of description over development. The aim of the symposium is to examine DS across the lifespan and levels of description. At the cognitive level, the first presentation will use a deferred imitation task to investigate how episodic memory changes across the lifespan in people with DS. At the brain level, the second presentation will map brain development from early childhood to young adulthood in DS. At the genetic level, the third presentation will consider how genetic variance might explain variability within cognitive outcomes of individuals with DS across the lifespan. Together, these presentations highlight the importance of understanding the DS phenotype across the lifespan and levels of description.

Paper 1 of 3

Paper Title: Differences in Memory Function across Age in Down Syndrome

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Introduction: Down syndrome (DS) is a genetic cause of intellectual disability resulting from the presence of a third copy of chromosome 21. One of the associated cognitive changes in DS is altered memory function. For example, many studies have found that although visuospatial working memory is appropriate in relation to children’s mental age, verbal working memory is delayed, especially at higher cognitive load levels (Lanfranchi et al., 2012). One of the most fundamental forms of memory for day-to-day living is episodic memory, or children’s ability to recall specific life episodes and the unique timing, place, and linked features of these memories. Episodic memory can be a difficult memory domain to assess, especially in a population with impaired verbal abilities. One task that has been used successfully to assess episodic memory in typical infants and toddlers, as well as atypically developing individuals, is deferred imitation (Milojevich & Lukowski, 2016). In our study, deferred imitation includes an assessment of the delayed recall of a series of three arbitrary physical actions in a set temporal sequence (i.e., using props). In this study, we examine changes in episodic memory function across aging in people with DS, and we test long-term recall (across 2 weeks) in relation to encoding manipulations on deferred imitation. Further research into these areas could be important as the DS population is at increased risk of developing Alzheimer’s disease, which also particularly affects memory function.

Methods: Participants include 20 young (6-18 years old) and 10 older (35 to 70 years old) individuals with DS. Each participant took part in a novel version of the deferred imitation task designed to manipulate encoding conditions. We designed 9 novel, three step, arbitrary sequences with toys/everyday accessible items. Following a 60 second interval during which participants were allowed to interact with the materials freely, each sequence was presented in one of three conditions. The sequence was

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either modeled (e.g., demonstrated) three times (MMM), twice followed by a 20-second pause (MMP), or twice followed by an opportunity for the participant to act out the sequence themselves (a direct “test” of the sequence; MMT). Each participant saw 3 sequences in each condition at the first visit and was then tested on recall of all sequences after a two-week delay. Other assessments included the KBIT-2 for mental age measure, verbal and visuospatial working memory assessments, and executive function measures from our NIH-Funded battery of neuropsychological tests for Intellectual Disability (e.g., the Arizona Memory Assessment for Preschoolers and Special Populations).

**Results:** Following a two-week delay, the young group showed best recall of sequences encoded in the MMM condition, whereas the older group had best recall of sequences encoded in the MMP condition. This suggests that older adults benefit from a rest period following exposure to novel information, whereas younger individuals have better long-term retrieval of episodic information that they have been exposed to repetitively. Examining the groups separately to see if immediate performance on a sequence predicted recall following a 2-week delay found there was no relationship between immediate and delayed recall in the young group, but a strong correlation in the adults. Within-group correlations also revealed some interesting relationships. In the young group, performance on the MMM condition correlated with age and inhibitory control abilities, MMT correlated with verbal and non-verbal components of the KBIT, there were no correlations with MMP. In the adult group MMM significantly correlated with non-verbal abilities specifically, MMT with executive function, and MMP with non-verbal mental age and executive function abilities. Interestingly, in the adult group, the performance in each condition correlated with each other, which was not the case in the young group.

**Discussion:** These findings suggest that the function of episodic memory changes with age in people with DS. In the young group, results support previous findings suggesting repeating information is beneficial for people with DS and more likely to result in learning. Adults had higher levels of floor performance at delay—suggesting memory is impaired overall—but when these individuals did recall temporal order of actions this occurred most frequently in the condition with only two exposures and a rest period. The finding that correlations with additional measures were overlapping and that all episodic memory conditions were associated in the adult group suggests that cognition becomes more uniform with age in DS. The uneven nature of cognition is more obvious in the younger group, where the memory measures were inter-correlated in adults. These results suggest different patterns of memory performance in younger and older individuals with Down syndrome, leading to some learning modifications which might support teaching strategies for new material.

**References/Citations:**

Paper 2 of 3

**Paper Title:** Mapping Brain Development in Pediatric DS: Novel Insights from a Cross-Sectional Analysis of Cortical Morphometry Across Age and Diagnostic Groups

**Authors:** Taralee Hamner\(^5\), Manisha Udhnani\(^5\), Jay N. Giedd\(^6\), Nancy Raitano Lee\(^5\)

**Introduction:** Although Down syndrome (DS) is often identified in utero and is the most common genetic cause of intellectual disability, very little is known about how the brain develops in youth with DS. Within the typically developing (TD) literature, research suggests that dynamic changes in brain morphometry occur during childhood and adolescence. These include decreases in gray matter (GM) volume over the course of late childhood, adolescence, and young adulthood alongside increases in white matter (WM) volume during this period (for a review see, Tamnes & Østby, 2018). This research suggests that in order to understand atypical brain development, one must examine how developmental trajectories differ for youth with neurodevelopmental disorders, such as those with DS, as opposed to examining static group differences in brain volumes between youth with neurodevelopmental disorders and TD controls. To the best of our knowledge, no longitudinal neuroimaging studies of DS exist. However, research from studies of other neurodevelopmental disorders, such as autism spectrum disorder (Wallace et al., 2010), suggests that examining how relations between brain morphometry and age vary as a function of group using a cross-sectional study design may provide clues to differences in neurodevelopmental trajectories that can be investigated in future research using a longitudinal study design. As such, the current study aimed to explore the relationship between cortical GM and WM volumes and age in youth with DS relative to TD peers in order to begin to make hypotheses about possible differences in developmental trajectories that may characterize the developing brain in youth with DS.

**Methods:** Participants included 31 youth with DS (17 female) and 45 youth with typical development (23 female) with a mean age of approximately 15 years (range 5 to 24 years) who completed structural neuroimaging as part of a larger study at the National Institute of Mental Health (Lee et al., 2016). All participants completed \(T_1\) weighted scans on a 3-T magnetic resonance imaging scanner. To examine how lobar GM and WM volumes varied as a function of age and diagnostic group, separate stepwise linear regressions were completed to predict GM and WM volume for each of the cortical lobes (totaling 8 regressions). Specifically, group was entered into Step 1, age in Step 2, and the group x age interaction term was entered in Step 3. A false discovery rate (FDR) correction was used to adjust for multiple comparisons. As a follow-up to any significant group x age interaction effects, analyses of cortical subdivisions were explored to further characterize group differences in cortical development during childhood and adolescence.

**Results:** After FDR correction (adjusted \(p\)-value = .029), significant main effects of group were revealed for the following structures: frontal GM and WM, temporal GM and WM, and both occipital and parietal WM. Significant effects of age were revealed for all lobar WM volumes as well as frontal, parietal, and occipital GM. For frontal GM, a significant group x age interaction emerged for frontal GM \(F(1,72) = 5.18, p = .02, R^2 = 0.43\), revealing a unique relationship between age and GM volume in youth with DS. Specifically, while the expected significant inverse relationship between frontal GM and age was observed for the TD group \((r = -.61, p < .001)\), this relationship was not observed in the DS group \((r = -.18; p > .3)\). Rather, there was little relation between frontal GM volume and age in the DS group. In order to explore this further, frontal cortical subdivisions (lateral frontal, medial frontal, and orbital frontal GM) were entered into regression analyses. Of these three subdivisions, an age x group interaction was observed for lateral frontal GM volume \(F(1,72) = 8.70, p = .004, R^2 = 0.42\), such that the expected inverse relationship between lateral frontal GM volume and age was observed in the TD group \((r = -.64, p < .001)\) but not the DS group \((r = -.07; p > .7)\).

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Discussion: Findings of the current cross-sectional study suggest that the trajectory of frontal lobe GM development (particularly in lateral frontal regions) in youth with DS may deviate from what is observed in TD peers. As differences in GM trajectories, particularly of frontal regions, have been associated with individual differences in intellectual functioning (Shaw et al., 2006), further developmentally focused research using a longitudinal study design is needed to begin to understand relationships between atypical neural and cognitive development in DS. Such research may provide insights into key windows of time during which interventions may be most effective at altering atypical neural trajectories in DS and possibly augmenting real world outcomes for this group.

References/Citations:


Paper 3 of 3

**Paper Title:** A Risk Gene for Dementia (APOE) Is Associated With Better Early Attentional Skills in Down Syndrome

**Authors:** Hana D'Souza1,2,3, Luke Mason2, Emma Meaburn2, Kin Y. Mok3,7, John Hardy3,7, Annette Karmiloff-Smith3,7, Denis Mareschal3,7, Michael S. C. Thomas3,7, & the LonDownS Consortium

**Introduction:** Down syndrome (DS) is the most common known genetic cause of intellectual disability and is caused by the presence of an additional chromosome 21. Individuals with DS show a much higher prevalence of Alzheimer’s disease (AD) than typically developing individuals (Wiseman et al., 2015). This is likely due to the overexpression of genes on chromosome 21, particularly the amyloid precursor protein (APP) gene which has been associated with early onset AD in the general population. However, there is still a large amount of variability in the clinical presentation and age of onset of dementia in those with DS. Some of this variability has been explained by variation in the apolipoprotein (APOE) gene on chromosome 19. The e4 allele of APOE is associated with an increased risk for AD in both the typical population and individuals with DS. Even though AD emerges over the last few decades of life, the effect of APOE on development may already be detected in infancy (Dean et al., 2014; Wright et al., 2003). In fact, studies in typically developing individuals suggest that the same e4 allele which is later in life linked to AD risk may initially provide an advantage over other variants of the gene (Wright et al., 2003). It has been hypothesized that this may particularly be the case for cognitive control (Han & Bondi, 2008). However, it is unclear whether e4 allele plays a similar role early in development in DS, where dementia risk is exacerbated.

**Methods:** Eighty children with genetically confirmed DS between 8 and 62 months of age participated in this study. APOE genotype was determined using a Thermo Fisher Scientific Taqman assay for SNPs rs7412 and rs429358 (Waltham, MA, USA). The gap-overlap task was administered using an eye-tracker to measure speed of attentional disengagement (Elsabbagh et al., 2009).

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**Results:** Twenty-three (29%) children were e4-carriers, 57 (71%) were e4-noncarriers, which reflects the distribution in the typical population. To understand the role of e4 in early development in DS, we constructed cross-sectional developmental trajectories (Thomas et al., 2009). Both e4-carriers and e4-noncarriers showed faster reaction times over development. We compared the trajectories of the two groups using ANCOVA. There was a significant difference between the intercepts (partial eta-squared = .07), indicating that the reaction times of e4-carriers were faster. There was also a trend for interaction between group and age (partial eta-squared = .04), suggesting that even though e4-carriers show an overall reaction time advantage, improvement in reaction times over development may have a steeper slope for e4-noncarriers.

**Discussion:** To our knowledge, this is the first study showing that e4 may provide an advantage in early development in DS. E4-carriers with DS showed faster reaction times compared to e4-noncarriers with DS. This is consistent with reports on young typically developing 2-year-olds when e4-carriers performed better on a standardized developmental test (Bayley Scales of Infant Development-II) than e4-noncarriers (Wright et al., 2003). Faster reaction times in the current study in e4-carriers with DS are in line with findings that e4-carriers between 2 to 25 months of age show greater white matter myelin water fraction (MWF) in later-maturing frontal white matter regions (Dean et al., 2014). Dean and colleagues (2014) also reported an attenuated relationship (shallower trajectory) between MWF and chronological age in e4-carriers compared to e4-noncarriers during the first two years of life. Our cross-sectional trajectory analysis of reaction time indicates a trend consistent with these typically developing brain findings. Understanding the differential role of APOE over development is an important step towards future intervention and towards generating a more balanced view of risk and protective factors for lifespan development in DS.

**References/Citations:**