Title: Characterization of Cortical Thickness in DS Is Dependent On the Control Group: Contrasting Findings from Chronological and Mental-Age Matched Peers

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Introduction: Surprisingly little is known about the developing brain in pediatric Down syndrome (DS), as there are currently 14 published structural neuroimaging studies. Of the nascent literature, cortical volume is reduced in DS compared to typically developing (TD) peers (Smigielska-Kuzia et al., 2011). However, volume is a gross measure of brain structure that may mask differences in its constituent components, thickness (CT) and surface area (SA). Research suggests that dissecting cortical volume deviations in DS into CT and SA may be particularly fruitful, as CT and SA have differing genetic etiologies and developmental trajectories (Raznahan et al., 2011) and both have been linked to individual differences in intellectual functioning in TD individuals (Shaw et al., 2006; Schnack et al., 2015). Recent research has reported increased CT and reduced SA in DS compared to TD peers matched on chronological age (CA; Lee et al., 2016). Matching youth with DS to peers based on CA is the most common practice in the neuroimaging literature. However, in psychoeducational investigations, DS is routinely compared to mental age (MA) matched peers in order to identify aspects of cognition that deviate from or appear similar to overall developmental level. Thus, the current study is an exploratory investigation that aims to examine differences in imaging findings as a function of comparison group – CA vs. MA-matched TD peers. It is hoped that this will begin to elucidate aspects of the DS neuroanatomical phenotype that are consistent with overall developmental level and aspects that may be associated with intellectual disability or DS more specifically.

Method: Participants included 31 children with DS (Mage: CA = 15.18; MA = 7.73) matched to typically developing peers on both CA (N = 42; Mage = 16.40) and MA (N=25; Mage = 7.45). Data were compiled from a larger study completed at NIMH (Lee et al., 2016). All participants completed T1 weighted scans on a 3-T magnetic resonance imaging scanner. Z-scores were created for SA and CT relative to both MA and CA controls. Two 2x2 mixed-model ANOVAs were completed. In both, the within-subjects factor was cortical component (CT vs SA) and the between-subjects factor was group (either CA or MA matched control group). Because of differences in total brain volume (TBV) between the groups, follow-up ANCOVAs were also completed with TBV covaried.

Results: Significant group-by-cortical component interactions were revealed for both the CA (F [1, 71] = 58.76, p < 0.001) and MA comparisons (F [1,54] = 22.81, p < 0.001). However, tests of simple effects revealed a different pattern of findings for the two sets of analyses. Whereas the DS group had significantly reduced SA relative to both the CA and MA groups (ps < 0.001), the DS group only differed from the CA-matched group when CT was considered (with DS having increased thickness as previously reported, p < 0.001). In contrast, CT was similar for DS and MA-matched peers (p = 0.55). ANCOVA results including TBV as a covariate yielded a similar pattern of results.

Discussion: Results suggest that the pediatric brain in DS differs from CA-matched peers on both CT and SA whereas when comparing to MA-matched peers, differences only emerge within SA but not CT. This suggests that SA deviations may reflect atypical development in excess of overall developmental level. In contrast, aberrant CT in DS may relate more to developmental level overall. These findings are consistent with the larger developmental neuroimaging literature, in which CT is known to decrease across development, a phenomenon believed to be related to synaptic pruning and contributes to cognitive maturation over the course of childhood. Thus, the paradoxically increased CT in DS is likely related to the generally slower rate of cognitive maturation that characterizes the syndrome, as a thicker cortex may be less efficient (due to excess, unneeded cortical connections). Inclusion of a MA-matched comparison group in addition to the traditional CA-matched group will be important to consider in future structural neuroimaging investigations (for an example of this in functional neuroimaging, see Jacola et al., 2014). It is our hope that the inclusion of MA comparison groups will provide novel insights into the nature of atypical brain development in DS and intellectual disability more generally.
References: