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Development of subcortical volumes across adolescence in males and females: A multisample study of longitudinal changes

Megan M. Herting [a,*], Cory Johnson [a], Kathryn L. Mills [b], Nandita Vijayakumar [b], Meg Dennison [c], Chang Liu [a], Anne-Lise Goddings [d], Ronald E. Dahl [e], Elizabeth R. Sowell [f], Sarah Whittle [g], Nicholas B. Allen [b], Christian K. Tamnes [h]

[a] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[b] Department of Psychology, University of Oregon, Eugene, OR, USA
[c] Phoenix Australia: Centre for Posttraumatic Mental Health, Department of Psychiatry, The University of Melbourne, Melbourne, Australia
[d] Institute of Child Health, University College London, London, UK
[e] Institute of Human Development, University of California Berkeley, Berkeley, CA, USA
[f] Department of Pediatrics, Keck School of Medicine, University of Southern California, Children's Hospital Los Angeles, Los Angeles, CA, USA
[g] Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Melbourne, Australia
[h] Department of Psychology, University of Oslo, Oslo, Norway

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ABSTRACT

The developmental patterns of subcortical brain volumes in males and females observed in previous studies have been inconsistent. To help resolve these discrepancies, we examined developmental trajectories using three independent longitudinal samples of participants in the age-span of 8–22 years (total 216 participants and 467 scans). These datasets, including *Pittsburgh* (PIT; University of Pittsburgh, USA), *NeuroCognitive Development* (NCD; University of Oslo, Norway), and *Orygen Adolescent Development Study* (OADS; The University of Melbourne, Australia), span three countries and were analyzed together and in parallel using mixed-effects modeling with both generalized additive models and general linear models. For all regions and across all samples, males were found to have significantly larger volumes as compared to females, and significant sex differences were seen in age trajectories over time. However, direct comparison of sample trajectories and sex differences identified within samples were not consistent. The trajectories for the amygdala, putamen, and nucleus accumbens were most consistent between the three samples. Our results suggest that even after using similar preprocessing and analytic techniques, additional factors, such as image acquisition or sample composition may contribute to some of the discrepancies in sex specific patterns in subcortical brain changes across adolescence, and highlight region-specific variations in congruency of developmental trajectories.

Introduction

Developmental patterns of brain morphology, and sex differences in this structural variation, exist due to both global and local maturational changes (Sowell et al., 2004; Tamnes et al., 2013; Erus et al., 2015; Giedd et al., 2015; Narvacan et al., 2017). Determining when and how sex differences emerge in the developing brain is essential to understanding differential risk for disease, especially psychopathology (Kessler et al., 1993; Kessler et al., 2005), as well as life-long sex differences in various cognitive and behavioral traits (Choudhury et al., 2006; Rose and Rudolph, 2006; Roalf et al., 2014; Gur and Gur, 2016). For example, late childhood and adolescence is a time period when many forms of psychopathology begin to emerge and do so in a sex-specific fashion, with disproportionate increases in rates of anxiety and depression seen in girls and a higher prevalence of externalizing behaviors and substance use disorders in boys (Kessler et al., 2005; Kuhn, 2015). Given that structural and functional abnormalities in subcortical regions have been associated with these various mental health problems, it is thought that plausible sex differences in the development of subcortical structures may be pertinent to explaining sex differences in onset, prevalence, and progression of mental health disorders (Paus et al., 2008; Gogtay and Thompson, 2010; Shaw et al., 2010). As such, a number of sex differences have been reported in structural magnetic resonance imaging (MRI) growth trajectories of subcortical structures. However, developmental

* Corresponding author. Department of Preventive Medicine, University of Southern California, 2001 N Soto, Los Angeles, CA 90032, USA.
E-mail address: herting@usc.edu (M.M. Herting).

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patterns observed in these structures have been inconsistent across studies, and there has yet to be a consensus as to how these patterns differ between sexes (Sowell et al., 2002; Lenroot et al., 2007; Ostby et al., 2009; Dennison et al., 2013; Wierenga et al., 2014; Narvacan et al., 2017).

To date, studies have reported discrepant findings including growth versus reduction of the thalamus and basal ganglia beginning in late childhood, as well as stability versus continuing growth of the amygdala and hippocampus across adolescence (Giedd et al., 1996; Sowell et al., 2002; Ostby et al., 2009; Koolschijn and Crone, 2013; Wierenga et al., 2014). Similarly, reported sex differences in these trajectories remain variable. From a study design perspective, it is believed that longitudinal studies that are able to better account for both within- and between-individual differences over time may help to improve our understanding of cross-sectional findings that focus on mean group differences between the sexes (Crone and Elzinga, 2015). As such, longitudinal MRI studies using raw volumes (uncorrected for whole brain size or other allometric scaling) consistently show larger volumes in males as compared to females (i.e. main effects) (Dennison et al., 2013; Raznahan et al., 2014; Wierenga et al., 2014; Narvacan et al., 2017). However, findings are less clear in terms of sex differences in the trajectories (i.e. slopes) of development seen across childhood and adolescence. Based on using raw volume estimates (i.e. trajectories reported without including allometric scaling), some studies report sex differences in neurodevelopmental trajectories of subcortical regions (Dennison et al., 2013; Goddings et al., 2014; Raznahan et al., 2014), whereas other studies find no difference between the sexes (Wierenga et al., 2014; Narvacan et al., 2017).

These discrepant observations in studies of subcortical volume development and sex differences in these patterns may be due to a number of factors, including cohort effects inherent to the sample, variation in study design, image acquisition and preprocessing, and/or statistical modeling approaches. In terms of image processing, dissimilarities have been reported in the absolute volume estimates as well as in the reliability of subcortical brain structures across different freely available automated segmentation software (Morey et al., 2010; Makowski et al., 2017). In addition, software packages vary in their methodology for processing longitudinal scans. For example, FreeSurfer's longitudinal pipeline includes creating an unbiased within-subject template space to help reduce random variation and improve the sensitivity of detecting changes over time (Reuter et al., 2012). Recently, a longitudinal cortical thickness pipeline has also been developed as part of the ANTs software (Tustison et al., Unpublished). To our knowledge, other commonly used software packages for structural analysis (e.g. CIVET (Zijdenbos et al., 2002), MAGeT (Chakravarty et al., 2013), and FSL (Zhang et al., 2001)) do not account for within-subject variance in a similar fashion during the preprocessing stream. Beyond software, differences in quality control (QC) procedures utilized across studies may also impact the results (Ducharme et al., 2016).

From a statistical perspective, the inclusion of covariates and/or statistical model vary widely by study and may impact results (Vijayakumar et al., 2017). For example, during statistical testing the inclusion of a 'global' or 'allometric' covariate to account for *between subject* differences in body size or weight (Sanfilipo et al., 2004) may directly influence sex differences that are identified (Lenroot et al., 2007; Dennison et al., 2013). Moreover, despite sex differences in allometric variables (i.e. whole brain or intracranial volume), recent findings suggest that the variability of anatomical volumes are not equal between the sexes (males show larger variance expressed at both upper and lower extremities of the distributions) (Wierenga et al., 2017), allometric covariates follow non-linear developmental patterns from childhood to adulthood (Mills et al., 2016; Reardon et al., 2016), and regions including the thalamus, striatum, and pallidum show hypoallometric scaling with whole brain size (i.e. volumes become proportionately smaller with increasing head size) (Reardon et al., 2016). Moreover, the inclusion of an allometric term may be redundant when examining longitudinal change using hierarchical modeling, as each subject receives its own intercept and slope (Crone and Elzinga, 2015). Thus, the *between-subject* variance due to individual differences in head size is captured at the individual level; allowing for better characterization of changes in regional volume estimates over time.

Study results may vary based on the type of statistical analytic techniques employed. Although longitudinal studies have typically used linear mixed effect modeling (LME) to describe age-related changes, the model terms are diverse (Vijayakumar et al., 2017). For example, studies have differed in their modeling approach, including use of polynomial terms (e.g. quadratic or cubic), model selection strategy (e.g. top-down or likelihood indices), testing males and females separately and/or including sex as an interaction term, as well as the inclusion of other confounding factors (Ruigrok et al., 2014). Moreover, while LME including polynomial terms remains a popular approach, polynomials are rather restrictive, whereas other modeling techniques, such as general additive modeling (GAMM), may allow for a more flexible fit of a curve to the data. Specifically, GAMM replaces the linear slope parameters with 'smooth' functions to find the optimal functional form between the predictor and response (Jones and Almond, 1992). Given the existing discrepancies in the existing literature and the vast array of methodology (including software, QC procedures, and model terms) utilized between studies, there remains an important gap in our knowledge regarding the reproducibility of possible sex differences in subcortical neurodevelopmental trajectories across childhood and adolescence.

The goal of the current study was to utilize identical image processing and analysis methods in three independent longitudinal neuroimaging samples to describe the development of subcortical volumes (uncorrected/no allometric scaling) for males and females from late childhood into young adulthood. This study is part of an international collaboration project intended to improve the reliability and efficiency of neurodevelopmental research by simultaneously analyzing multiple existing neuroimaging datasets (Mills et al., 2016; Tamnes et al., 2017). By keeping longitudinal preprocessing methods, QC procedures, and statistical methods constant across samples, we can assess and interpret the potential impact of sample and acquisition differences on brain development patterns in males and females. Moreover, given inherent study design differences between the longitudinal samples (e.g. age ranges and scan follow-up), we explored age and age by sex relationships in each sample using both the more flexible general additive modeling (GAMM) approach as well as the more common general mixed-effects modeling (LME). Because LME is the most commonly used approach in longitudinal MRI studies (Vijayakumar et al., 2017), LME estimates in the current study were included in order to help directly compare our results with those reported in previous studies. Thus, we aimed to examine the consistency and reproducibility of neurodevelopmental change for subcortical gray matter regions, including the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens in males and females.

Materials and methods

Participants

This study analyzed data from typically developing youth from three separate cohorts collected utilizing longitudinal designs at three separate sites in independent research projects: *Pittsburgh* (PIT; University of Pittsburgh, USA), *NeuroCognitive Development* (NCD; University of Oslo, Norway), and *Orygen Adolescent Development Study* (OADS; The University of Melbourne, Australia). Each project was approved by their respective local review board and informed consent/assent was obtained from parents and children prior to data collection. In order to best account for within-subject variance, only participants with $\geq$2 scans from each cohort were included in analyses. Details regarding participant recruitment in each project have been previously described (Yap et al., 2011; Tamnes et al., 2013; Herting et al., 2014). By study design, all