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Development of sex differences in the human brain

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ABSTRACT

Sex differences in brain anatomy have been described from early childhood through late adulthood, but without any clear consensus among studies. Here, we applied a machine learning approach to estimate 'Brain Sex' using a continuous (rather than binary) classifier in 162 boys and 185 girls aged between 5 and 18 years. Changes in the estimated sex differences over time at different age groups were subsequently calculated using a sliding window approach. We hypothesized that males and females would differ in brain structure already during childhood, but that these differences will become even more pronounced with increasing age, particularly during adolescence. Overall, the classifier achieved a good performance, with an accuracy of 80.4% and an AUC of 0.897 across all age groups. Assessing changes in the estimated sex with age revealed a growing difference between the sexes with increasing age. That is, the very large effect size of d = 1.2 which was already evident during childhood increased even further from age 11 onward, and eventually reached an effect size of d = 1.6 at age 17. Altogether these findings suggest a systematic sex difference in brain structure already during childhood, and a subsequent increase of this difference during adolescence.

1. Introduction

An ever growing interest in sex differences in the brain has resulted in a vast amount of literature on this topic (for reviews see Cosgrove et al., 2007; Giedd et al., 2012; Jancke, 2018; Lenroot & Giedd, 2010; Luders & Kurth, 2020; Luders & Toga, 2010; Sacher et al., 2013). While it remains unclear which parts of the brain differ and in what way exactly, the lack of consensus between studies does not necessarily imply that observed sex differences are spurious and incidental, or that a distinction into 'male' and 'female' brains is impossible. For example, when assessing brain patterns using multivariate machine learning techniques (instead of focusing on a specific brain feature using univariate traditional analyses), male-female distinctions have been established with classification accuracies between 69% and 93% (Anderson et al., 2019; Chekroud et al., 2016; Del Giudice et al., 2016; Rosenblatt, 2016; Tunc et al., 2016).

Importantly, sex differences in the brain do not only exist during adulthood, but are already present earlier in life (Berenbaum & Beltz, 2011, 2016; Cosgrove et al., 2007; Hines, 2010; Giedd et al., 1999, 2012; Lenroot & Giedd, 2006, 2010; Luders & Toga, 2010; Sacher et al., 2013). In fact, male and female brains have been reported to differ significantly in newborns and babies (Benavides et al., 2019; Gilmore et al., 2007), with more and more sex differences becoming evident during childhood and adolescence (Gur & Gur, 2016; Herting & Sowell, 2017; Giedd et al., 2012; Tunc et al., 2016; Vijayakumar et al., 2018). This seems to suggest that males and females might be distinguishable based on sex differences in brain anatomy already early in life, with the sex gap further widening over the years. At this point, however, the degree of such an age-dependent sex difference as well as the trajectory of the gap widening is largely unknown.

The present study was designed to assess the male-female separability in brain anatomy in the developing brain. For this purpose, a multivariate machine learning algorithm was applied in 347 healthy children and adolescents (162 boys and 185 girls) between the age of 5 and 18. Given that individual brains may show different degrees of 'maleness' or 'femaleness', we used a classifier that yielded a continuous probabilistic estimate for being male/female, rather than a binary classifier. We hypothesized that male and female brains can be distinguished with considerable accuracy already in childhood, indicating sex differences in brain structure before puberty. We furthermore expected that the

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continuous classifier would yield increasingly dissimilar estimates of sex in boys and girls in later years (thus indicating more pronounced sex differences in brain structure with increasing age). Adolescence, for example, might present itself as a period where dissimilarities in brain structure increase disproportionally due to the influence of puberty with higher levels of circulating sex hormones, which may render the brain more masculine (more feminine, respectively).

2. Methods

2.1. Subjects and image acquisition

The study included 347 subjects (162 boys; 185 girls) aged between 4.9 and 18.6 years (mean ± SD: 11.2 ± 3.8 years). All subjects were selected from the NIH Pediatric MRI Repository created by the NIH MRI Study of Normal Brain Development (https://www.bic.mni.mcgill.ca/nihpd_info/info2/index.html), which is described in detail elsewhere (Evans, 2006). Of the 432 subjects available in this repository, 56 subjects were excluded given the low resolution of their MRI images (>2mm^3) resulting from an altered scanning protocol to reduce motion. In addition, 28 subjects were excluded due to insufficient image quality and improper segmentation, and one subject was excluded because MRI-related information was missing. Informed consent was obtained from parents and adolescents, and assents were obtained from the children. All protocols and procedures were approved by the relevant Institutional Review Board at each pediatric study center and at each coordinating center (Evans, 2006); additional local ethics approval for the data analysis was obtained from the University of Auckland (UoA) ethics committee (Protocol No. 022375). T1-weighted images of the brain were obtained at six sites on 1.5 Tesla systems from General Electric (GE) or Siemens Medical Systems using a 3D T1-weighted spoiled gradient recalled (SPGR) echo sequence with the following parameters: TR = 22–25 ms, TE = 10–11 ms, excitation pulse = 30°, refocusing pulse = 180°, field of view: anterior-posterior = 256 mm; left-right = 160–180 mm (for details see Evans, 2006). On Siemens scanners the voxel size was 1 × 1 × 1 mm^3, whereas on GE scanners it was 1 × 1 × 1.5 mm^3 (Evans, 2006).

2.2. Data preprocessing

The T1-weighted images were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html). Given that the investigated population consisted of children with a mean age of 11.2 years, customized tissue probability maps in MNI space were calculated using the TOM8 Toolbox (Wilke et al., 2008). Using these customized tissue probability maps, all brain images were corrected for magnetic field inhomogeneities and tissue-classified into gray matter, white matter, and cerebrospinal fluid. The segmentation procedure was based on maximum *a posteriori* estimations (Rajapakse et al., 1997) and used a partial volume estimation algorithm (Tohka et al., 2004), a spatially adapting non-linear means denoising filter (Manjon et al., 2010), as well as a hidden Markov Random Field model (Cuadra et al., 2005). The resulting gray and white matter partitions were spatially normalized to MNI space using 12-parameter affine transformations, which effectively resulted in a correction for overall brain size, while preserving individual differences in local size and shape. Subsequently, the normalized tissue segments were smoothed using an 8 mm FWHM Gaussian Kernel, and spatial resolution was set to 8 mm (Franke et al., 2010). Finally, a principal component analysis (PCA) was performed for further data reduction using the Matlab Toolbox for Dimensionality Reduction (http://lvdmaaten.github.io/drtoolbox/), as described previously (Franke et al., 2010). To treat training and test samples separately, the loadings for the PCA were estimated from each training set prior to training the classifier and applied to the respective test set for prediction.

2.3. Estimating 'Brain Sex'

The approach is based on machine learning using Relevance Vector Regression (RVR) (Tipping, 2001) and uses 'The Spider' (https://people.kyb.tuebingen.mpg.de/spider/main.html) within MATLAB (The MathWorks, Natick, MA). It operates on the same principles as the BrainAGE framework, which is described in detail elsewhere (Franke et al., 2012, 2010). Briefly, the inputs are the voxel-wise intensities of the preprocessed gray and white matter segments after the PCA (see Section 2.2), and the output is the 'Brain Sex' estimate. 'Brain Sex' is a brain-specific number on a scale in which '0' indicates a 100% female brain and '1' indicates a 100% male brain. That is, rather than forcing a binary classification (male/female), this classifier yields a continuous probabilistic estimate of the degree of 'maleness' or 'femaleness'.[1] For example, a 'Brain Sex' estimate of '0.7' would indicate a brain that is more male than female, while a 'Brain Sex'

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[1]It must be noted that other classifiers can also be used to obtain continuous classifications. However, we intentionally chose the relevance vector machine as it has proven to be reliable and stable (Franke et al., 2012, 2010), both across a wide age range (including children) and different scanners.

estimate of '0.4' would indicate a brain that is more female than male. Training of the RVR machine and prediction of sex in the dataset was achieved using a 10-fold cross validation that was repeated nine times using different random permutations of the dataset. The resulting ten probabilistic 'Brain Sex' estimates per subject were then averaged and used as the input for the statistical analysis. The raw estimates for each sex by age are shown in the **Supplementary Figure**.

2.4. Statistical analysis

2.4.1. Classifier performance and possible effect of scanner

To assess the predictive quality of the classifier, the individual 'Brain Sex' estimates were used to calculate the receiver-operator characteristic (ROC). In addition, the individual 'Brain Sex' estimates were rounded up or down to either 1 (male) or 0 (female). This binarized classification was then assessed for classification accuracy (in reference to the real biological sex). As brain images of the study sample were acquired on different scanners, the potential effect of scanner was assessed in addition by treating the 'Brain Sex' estimates as the dependent variable, scanner as the independent variable, and sex as well as age as covariates.

2.4.2. Age-related changes of 'Brain Sex': Trajectory over the entire age span

To assess the effects of age on the 'Brain Sex' estimates, we calculated the effect size of the estimated mean sex differences at different age groups. Specifically, we employed a sliding window approach with a window length of three years to create 13 different age groups between 5 and 17 years (i.e., 1st group: 5–7 years, 2nd group: 6–8 years, 3rd group: 7–9 years, etc.). Information on the sex distribution in each 'window' is provided in the **Supplementary Table**. Subsequently, we calculated the effect size of the estimated sex difference for each of these age groups as Cohen's d using a general linear model with the 'Brain Sex' estimate as the dependent variable and the biological sex as the independent variable. In addition, based on the resulting effect sizes of the estimated sex difference for each age group, we calculated the trajectory using a non-parametric cubic smoothing spline (Fjell et al., 2010, 2013; Ziegler et al., 2012). The optimal smoothing parameter for the smoothing spline was established by calculating the adjusted R^2 for a wide range of smoothing parameters and choosing the parameter that resulted in the

maximum adjusted R^2. The point of maximum acceleration of the trajectory was determined from its second derivative.

2.4.3. Age-related changes of 'Brain Sex': Comparing the extremes of age 6 and age 17

To further assess and quantify changes in the estimated 'Brain Sex' between age 6 and age 17, we calculated the interaction between sex and the two age groups, using the 'Brain Sex' estimates as the dependent variable and the interaction between biological sex (male/female) and age group (6 years/17 years) as the independent variable. In addition, AUC and prediction accuracy were calculated for these two age groups (6 years/17 years).

3. Results

3.1. Classifier performance and possible effect of scanner

Across the entire age span, the sex classification was 80.4% accurate, and the receiver-operating characteristic of the predictions had an AUC of 0.897. These measures indicate a suitable classification performance and a reliable distinction between the sexes based on brain anatomy across the age range examined. The different scanners had no effect on the sex classification (F = 0.151, p = 0.963).

3.2. Age-related changes of 'Brain Sex': Trajectory over the entire age span

Overall, between the ages 6 and 17, the differentiation between male and female brains increased over time as indicated by the age-specific markers as well as the fitted trajectory line (Figure 1, top panel).[2] Importantly, the sex differentiation was already evident at age 6 with a very large effect size (Cohen's d = 1.2). It continued to increase over the years and peaked at age 17 (Cohen's d = 1.6). The maximum of acceleration occurred at age 11 (see green arrow).

3.3. Age-related changes of 'Brain Sex': Comparing the extremes of age 6 and age 17

When comparing the predictions between age 6 and age 17 (Figure 1, bottom panel), the increased sex difference in the older sample corresponds to a decreased overlap between predicted 'femaleness' and 'maleness'. In other words, fewer boys and girls at age 17 (Figure 1, bottom right) have a similar 'Brain Sex' estimate than at

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[2]The age range of the sample was 5–18 years but given the 'sliding window' approach, the findings are presented for age 6 (5–7 years), age 7 (6–8 years) . . . and age 17 (16–18 years).
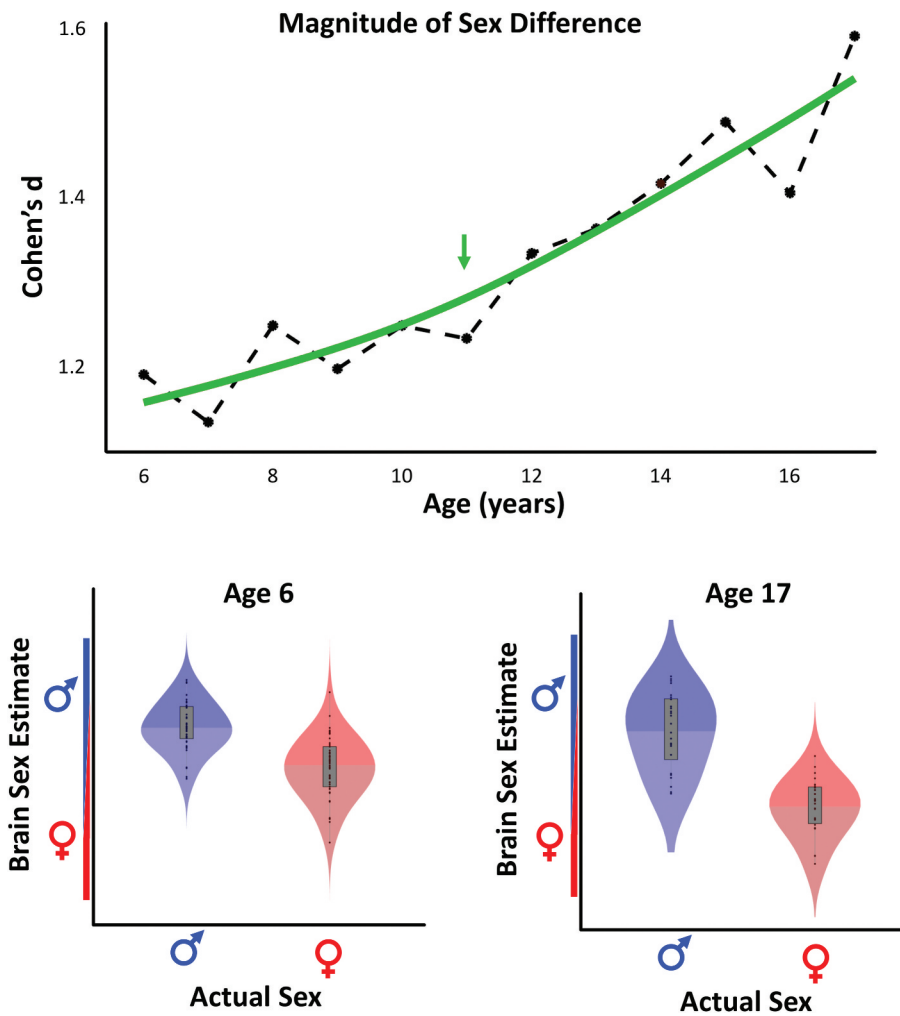
Magnitude of Sex Difference

Figure 1. Age-specific sex differences. The top graph shows the magnitude of the difference between the 'Brain Sex' estimates in boys and girls (calculated as Cohen's d) between age 6 and age 17 as markers connected by a dashed line. The fitted trajectory as determined by cubic smoothing splines is depicted in green, and the point of maximal acceleration is marked with a green arrow. The bottom graphs show the 'Brain Sex' estimates in relation to the actual sex for males (blue) and females (red) at age 6 and age 17.

age 6 (Figure 1, bottom left). This observation was confirmed by a significant interaction between sex and age (d = 0.289, T = 1.703, p = 0.045), confirming that brains of boys and girls at age 17 are less similar than at age 6. This conclusion is further supported by an increase in AUC and accuracy from age 6 (AUC = 0.86, accuracy = 79.1%) to age 17 (AUC = 0.95, accuracy = 84.6%).

Of note, this decreasing overlap between the sexes with increasing age is driven both by a shift toward the male and female extremes as well as by more homogeneous estimates, particularly in girls. Specifically, the mean 'Brain Sex' estimate for boys increased from 0.65 to 0.68, while the mean 'Brain Sex' estimate for girls decreased from 0.25 to 0.23 (with 0 being female and 1 being male). In boys, the overall range of the 'Brain Sex' estimate decreased slightly between age 6 and 17 (0.-14–1.10 vs. 0.31–1.17), whereas in girls it decreased considerably (−0.50–0.98 vs. −0.2–0.59).

4. Discussion

Using a multivariate machine learning approach, we observed a good separability between males and females based on brain anatomy. This observation replicates previous studies that reported a high accuracy in distinguishing between the sexes using machine learning (Anderson et al., 2019; Chekroud et al., 2016; Del Giudice et al., 2016; Rosenblatt, 2016; Tunc et al., 2016). Overall, the current results support the notion that male and female brains are anatomically different throughout childhood and adolescence.

4.1. Sex differences before puberty

Interestingly, the observed sex difference was already evident at the age of six, which corroborates other studies that have described sex differences in brain

structure in children, babies, and even newborns (Benavides et al., 2019; Gilmore et al., 2007; Giedd et al., 2012; Lenroot & Giedd, 2010). These findings suggest an influence of early developmental factors, such as steroid hormones. The idea that exposure to sex hormones during development has a permanent organizational effect on the brain is well-established, both in animals (Phoenix et al., 1959) and humans (for review see Berenbaum & Beltz, 2011, 2016; Hines, 2010). For example, the so-called 'organizational-activational hypothesis' (Arnold, 2009; MacLusky & Naftolin, 1981; Phoenix et al., 1959) suggests that chromosomal sex determines gonadal sex as well as the release of respective sex hormones resulting in a feminization or masculinization of the body, including the brain (McCarthy & Arnold, 2011; Phoenix et al., 1959). The outcomes of more recent studies point to more complex interrelations between brain structure, hormonal effects, gene expression and epigenetic modifications caused by environmental influences (Arnold & Burgoyne, 2004; Arnold & Chen, 2009; Carruth et al., 2002; McCarthy & Arnold, 2011; De Vries et al., 2002), but still posit that sexual differentiation begins *in utero*.

4.2. Sex differences during adolescence

While the sex difference was already evident at age 6, it increased even more during adolescence between age 11 and age 17 – a time frame that is most commonly associated with puberty (Blakemore et al., 2010). It is now generally accepted that the increase of sex hormones during puberty has activational and organizing effects on the brain, resulting in significant changes in brain structure, including sex differences, even though the results from imaging studies remain somewhat conflicting (for reviews see Arnold, 2020; Blakemore et al., 2010; Herting & Sowell, 2017; Giedd et al., 2012; Lenroot & Giedd, 2010; McCarthy & Arnold, 2011; Sisk & Foster, 2004; Sisk & Zehr, 2005; Vijayakumar et al., 2018). For example, white matter was observed to increase faster in males compared to females during puberty (De Bellis et al., 2001; Lenroot et al., 2007), but also see contrasting findings with respect to the corpus callosum in particular (Chavarria et al., 2014; Luders et al., 2010). Gray matter changes, on the other hand, are often described as following an inverted U-shape in both males and females, with the peak occurring close to the onset of puberty (Forkert et al., 2016; Giedd et al., 1999, 2012; Krongold et al., 2017; Lenroot & Giedd, 2006, 2010; Lenroot et al., 2007), but also see contrasting findings when focusing on cortical gray matter only (Mills et al., 2016; Tamnes et al., 2017; Walhovd et al., 2017). However, as the onset of puberty occurs earlier on

average in girls than in boys, gray matter changes may still follow different trajectories in both sexes (Lenroot et al., 2007). In addition, gray matter was reported to change differently in boys and girls depending on the brain region, albeit findings are not always consistent. For example, while some studies report the female hippocampus to increase in volume during puberty (Hu et al., 2013; Giedd et al., 1996; Neufang et al., 2009; Satterthwaite et al., 2014), others report it to decrease (Blanton et al., 2012; Bramen et al., 2011). Nevertheless, while single brain structures may show a considerable variance and thus at times fail to reflect sex-specific changes during puberty, the overall pattern of brain anatomy may indeed become more sexually dimorphic when assessed using a multivariate approach (Rosenblatt, 2016). In other words, the whole might be greater (aka more telling) than the sum of its parts, as also reflected in the outcomes of previous machine learning studies (Anderson et al., 2019; Chekroud et al., 2016; Del Giudice et al., 2016; Rosenblatt, 2016; Tunc et al., 2016).

4.3. Summary and implications for future research

Altogether, the current findings are in good agreement with the outcomes of prior studies and further enhance the notion that adolescence and puberty exert sex-specific effects on the brain. In the past, sex differences have been frequently assessed in a binary way. Binary views seem to imply that males and females are either fundamentally different (in the sense of a dimorphism) or not. In contrast, the current study used a continuous classifier to distinguish between boys and girls, and we observed an accurate separability between the sexes (even before the onset of puberty). This suggests that sex differences do not manifest in the form of an always and ever present clear-cut sexual dimorphism. This conclusion is also in line with current models of sexual differentiation of the brain (Arnold, 2020; Arnold & Burgoyne, 2004; Arnold & Chen, 2009; Carruth et al., 2002; McCarthy & Arnold, 2011; De Vries et al., 2002) pointing to a complex interaction between hormonal, genetic, epigenetic, as well as location- and time-specific effects that may result in a variability of 'maleness' or 'femaleness' across individuals. To better understand the driving biological mechanisms, future research, ideally longitudinal in nature, is needed to follow up on our current findings by linking measures of 'Brain Sex' to actual hormonal levels and developmental stages from early childhood to adulthood (Vijayakumar et al., 2018). Moreover, by including cognitive and behavioral measures, follow-up studies will determine whether there is a link between the degree

of male/female brain structure and (sex-typical) cognition and behavior.

Acknowledgments

Disclosure statement

Funding

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