Origins of gender differences in the human brain

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Chapter 7

Summary | Samenvatting

SUMMARY

Introduction

Gender differences exist in certain aspects of human behavior, cognition, and brain structure and function (Beltz et al. 2013; Sacher et al. 2013). Identifying the factors causing these gender differences is of great importance, not only to increase our understanding of healthy brain development, but also because it can provide valuable information regarding certain neuropsychiatric disorders with a gender difference in their prevalence.

The exact factors involved in the sexual differentiation of the human brain and their relative contribution are still under investigation. Many of our ideas on this topic are based on animal research, in which hormonal and genetic manipulations have been used to create sophisticated animal models. In general, it is thought that sex hormones play a pivotal role in gender-typical brain organization during sensitive periods of neural development, e.g., prenatally, early postnatally, and during puberty, and in activating these organized tissues during adulthood.

In the last two decades, animal models have also provided evidence for sex-hormone independent effects of genes on the sex chromosomes in several aspects of neural and behavioral sex differences (Arnold and Chen 2009; Cox et al. 2014). Therefore, a new theory about the biological factors underlying sex differences has recently been formulated, proposing that sexual differentiation involves a multifactorial mechanism including sex hormone and sex chromosome effects, acting in parallel or combined (Arnold 2017). In addition, the influence of environmental factors is also acknowledged, which is particularly important to consider in humans because of the highly gendered social environment.

It is challenging to find adequate study designs to confirm findings obtained in animal research in humans. Studies in both typical and clinical populations have been performed, although each method has shown its limitations and its validity has sometimes been questioned. Regardless of these challenges, important advances have been made in our understanding of brain and behavioral sexual differentiation in humans, but many questions still remain. For example, with respect to certain gender-typed behaviors, there is converging evidence for a link with early androgens (Berenbaum and Beltz 2016). Findings from human studies on brain structure and function, however, are less consistent, and the relative contribution of sex hormones and sex chromosome genes is currently unknown.

In this thesis, (neuroimaging) studies in a rare clinical condition are described, that is, in women with complete androgen insensitivity syndrome (CAIS). Women with CAIS have a 46,XY karyotype, but a female phenotype due to nonfunctional androgen receptors (AR) caused by (a) genetic mutation(s) in the X-linked AR gene (Hughes et al. 2012). Comparisons of 46,XY women with CAIS to 46,XY control men and 46,XX control women on sexually differentiated characteristics, therefore, provide a unique opportunity to investigate the factors underlying sexual differentiation in further detail by separating sex hormone from sex

chromosome effects. The first aim of this thesis was to study the role of sex hormones versus sex chromosome genes in the sexual differentiation of human brain structure and function. Selection of neuroimaging modalities was based on previously reported gender differences. The second aim was to assess the validity of two proposed retrospective markers of early androgen exposure.

Factors involved in sexual differentiation of the human brain

In the study described in **Chapter 2**, functional magnetic resonance imaging (fMRI) scans were acquired in 30 control men, 29 control women, and 21 women with CAIS during performance of the mental rotation task (MRT), a visuospatial task known to elicit gender differences in performance and brain activity patterns. To study the factors involved in sexual differentiation of MRT-related neural activation patterns, between-group comparisons of the fMRI data were performed in brain regions of functional relevance to MRT performance. Previously reported gender differences were replicated in the control groups; neural activation in the left inferior parietal lobe was greater in control men than in control women. In women with CAIS, activation in this region was female-typical, i.e., lower than in control men, while no significant differences were observed relative to control women. These findings indicate that gender differences in mental rotation-related regional brain function are not likely to reflect direct sex chromosome gene effects, but rather reflect differences in sex hormone exposure, i.e., masculinization through androgen action and/or feminization through estrogen action. In addition, these results argue against a masculinizing role of androgens after aromatization to estrogens by activation of the estrogen receptor (ER). A role for socialization-related effects could not be ruled out, because the gender-of-rearing in women with CAIS is female.

White matter (WM) microstructure is another aspect of the human brain that has been shown to differ between men and women and can be measured using diffusion tensor imaging (DTI). Therefore, in **Chapter 3**, DTI metrics were compared between 30 control men, 30 control women, and 20 women with CAIS in order to study the relative contribution of sex hormones and sex chromosome genes to the sexual differentiation of WM microstructure. Widespread gender differences in fractional anisotropy (FA) were observed, which were in accordance with the majority of previously published studies; FA was higher in control men than in control women. FA in women with CAIS was female-typical throughout extended WM regions. Regarding the underlying DTI metrics axial (AD) and radial diffusivity (RD) in the FA gender difference regions, RD was female-typical in women with CAIS, but this effect was not significant for AD. These findings suggest that masculinizing androgen effects through the AR, feminizing estrogen effects, or both, play an important role in the sexual differentiation of WM microstructure. A subtle contribution of sex chromosome genes or masculinizing androgen effects not mediated through the AR can, however, not be ruled out for some aspects of WM microstructure related to AD.

In **Chapter 4**, regional gray matter (GM) volume was assessed with both a mass-univariate and multivariate pattern recognition (MPR) approach. Because of an international collaboration, we were able to evaluate GM data of 56 control men, 53 control women, and 34 women with CAIS. The univariate analysis showed that, in regions with a gender difference in GM volume in the control groups, GM volume in women with CAIS was female-typical in an area covering the right pre- and postcentral gyrus. Thus, these findings argue against an important role of sex chromosome genes in the sexual differentiation of GM volume in this region, and rather suggest a predominant role of sex hormones, namely androgenic masculinizing and/or estrogenic feminizing effects, or effects related to female-typical socialization. The MPR analysis demonstrated that control men and women could be automatically discriminated with high accuracy based on whole-brain spatially distributed GM volume patterns, while the classification of women with CAIS into either of the control groups was not above chance level. These findings suggest that other factors, including direct sex chromosome gene effects and/or androgen effects not mediated by the AR, are also likely to play a role in the sexual differentiation of GM volume. The relative influence of sex hormones, sex chromosome genes, and socialization might vary throughout different brain regions.

An important advantage of an MPR approach is that it can detect subtle, spatially distributed patterns in the data, with the potential to identify differences that are not detected with mass-univariate approaches. Therefore, MPR was applied to multiple structural (GM volume and FA) and functional (default mode network during the resting-state, MRT, and positive and negative affective picture task [APT]) neuroimaging modalities in **Chapter 5**. Control men and women could be accurately discriminated using the unimodal MRT, APT-positive, GM, and FA classifiers, as well as with a multimodal classifier in which these unimodal classifiers were combined. Next, the successful unimodal and multimodal classification algorithms were applied to women with CAIS. Since the significant predictive values of the GM, FA, and multimodal classifier were also reflected in the class probability values extracted from the model, these classifiers enabled the interpretation of the classification of women with CAIS. Women with CAIS were equally likely to belong to the class representing control men as to the class representing control women based on their spatially distributed patterns of GM volume, WM microstructure, and multimodal neural characteristics. These findings are suggestive of a complex, multifactorial mechanism underlying the sexual differentiation of these neural characteristics. More specifically, these findings cannot be explained by previously suggested masculinizing androgen actions through the AR, feminizing estrogen actions, and/or socialization effects alone, but indicate that genes on the sex chromosomes and/or androgen effects not mediated by the AR are likely to play a role as well.

Potential retrospective markers of early androgen exposure

In **Chapter 6**, click-evoked otoacoustic emissions (CEOAEs), which are sounds originating from the cochlea, and the 2D:4D ratio, i.e., the relative length of the 2nd to the 4th digit, were measured. Both measures show gender differences that have been hypothesized to reflect early androgen levels, although this claim has been criticized regarding the 2D:4D ratio. By assessing these measures in women with CAIS, we investigated the potential link between these measures and effective androgen exposure. Gender differences were replicated in the control groups; in control women, CEOAE amplitudes and 2D:4D ratios were larger than in control men. Women with CAIS showed a tendency towards feminine right-ear CEOAE amplitudes and significant female-typical 2D:4D ratios in the right hand, while their within-group variability in both measures was not reduced compared with the control groups. These findings indicate that gender differences in adult CEOAEs and 2D:4D ratios might reflect androgen effects to some extent, but also suggest a role for other, non-androgenic, factors. Consequently, 2D:4D ratios and CEOAEs obtained in adulthood are not recommended as retrospective markers of early androgen exposure.

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