BIOLOGICAL SEX CLASSIFICATION WITH STRUCTURAL MRI
DATA SHOWS INCREASED MISCLASSIFICATION IN
TRANSGENDER WOMAN

A PREPRINT

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ABSTRACT

Transgender individuals (TIs) show brain structural alterations that differ from their biological sex as well as their perceived gender. To substantiate evidence that the brain structure of TIs differs from male and female, we use a combined multivariate and univariate approach. Gray matter segments resulting from voxel-based morphometry preprocessing of N = 1753 cisgender (CG) healthy participants were used to train (N = 1402) and validate (20 % hold-out; N = 351) a support-vector machine classifying the biological sex. As a second validation, we classified N = 1104 patients with depression. A third validation was performed using the matched CG-sample of the transgender women (TWs) application-sample. Subsequently, the classifier was applied to N = 26 TWs. Finally, we compared brain volumes of CG-men, women and TWs-pre/post treatment (cross-sex hormone treatment) in a univariate analysis controlling for sexual orientation, age and total brain volume. The application of our biological sex classifier to the transgender sample resulted in a significantly lower true positive rate (TPR) (TPR-male = 56.0 %). The TPR did not differ between CG-individuals with (TPR-male = 86.9 %) and without depression (TPR-male = 88.5 %). The univariate analysis of the transgender application-sample revealed that TWs-pre/post treatment show brain structural differences from CG-women and CG-men in the putamen and insula, as well as the whole-brain analysis. Our results support the hypothesis that brain structure in TWs differs from brain structure of their biological sex (male) as well as their perceived gender (female). This finding substantiates evidence that TIs show specific brain structural alterations leading to a different pattern of brain structure than CG-individuals.

Keywords Neuroimaging · Machine Learning · Gender Dysphoria · Depression · Structural MRI · Brain Development

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1 Introduction

Being transgender describes the stable feeling of belonging to the opposite rather than the biological sex assigned at birth, while the term cisgender (CG) describes the feeling of coherence between biological sex and perceived gender.

Although there is an ongoing social and political debate regarding the terms and phrases used to describe gender, little is known about how a divergence between the biological sex and perceived gender emerges. A popular view is that sexual brain differentiation and body development diverge in transgender individuals (TIs) (1). Evidence for this comes from studies in female infants with congenital adrenal hyperplasia, who develop male playing behavior (2)(3). Due to prenatally circulating testosterone, the brain of such female infants is structurally organized as a male brain, while their body development is female (1)(2)(3)(4)(5).

Previous research provides extensive information on how brain structure differs as a function of biological sex. Briefly, local sex differences show higher gray matter volume in CG-men, while the volume of limbic structures is particularly increased in CG-women (6). However, sexual differentiation seems less prominent in the brain compared to physical appearance (7)(8)(9). Hence, brains cannot easily be classified into dimorphic gender categories (10).

Few ROI-based approaches have studied how brain structure of TIs differs from CG. Compared to CG-men, transgender woman (biological sex male, perceived gender female, transgender woman (TW)) show structural alterations of areas associated with body perception. Brain structures that repeatedly showed alterations across multiple studies are the putamen (11) and the insula (12). However, the alterations are highly heterogeneous in their direction and the reported studies only investigated individuals before cross-sex hormone treatment (CHT). Comparisons between TW-pre/post-CHT with CG-individuals again exhibited heterogeneous results (9)(13)(14)(15)(16)(17)(18). CHT in TW combines treatment with anti-androgens and estradiol and is associated with region-specific structural alterations of the brain (19) such as local volume and cortical thickness decreases (15)(20). However, longitudinal studies are scarce and a recent large study did not find any differences between TW-pre and post-CHT (9)(16).

Next to univariate analyses, multivariate analyses offer new insights into the similarities and differences between CG and TIs (21)(22). In contrast to univariate analysis, multivariate analysis does not focus on identifying mean differences between individuals rather than recognizing the discriminative patterns within the data applicable on an individual level. This may be utilized to subdivide data into broader categories, but also to identify cases that exhibit unusual patterns and cannot be categorized easily. This approach is particularly interesting for TIs, since they perceive a disparity between their gender and their biological sex. Hence, one could assume that they represent cases that exhibit unusual data patterns, e.g. hormone levels, personality traits or brain function and structure. Recent studies also show a variety of brain-structural differences between TIs and CG-individuals. Thus, a univariate approach might not be suitable to clarify how TIs and CG-individuals differ from each other structurally. Another methodological motivation for choosing multivariate techniques is that samples of transgender individuals are usually small. Using a multivariate approach trained and validated on large samples of CG-individuals and applied to TIs allows more valid conclusions about brain structural differences between TIs and CG-individuals.

Multivariate analyses have already been used to investigate whether TIs can be separated from CG-individuals by their brain volumetric patterns (21)(22). Both studies show decreased accuracy in biological sex classification in TIs compared to CG-individuals. However, it has been recently criticized that classifiers trained with small sample sizes often lead to high accuracies, but low external validity (23). Hence, in contrast to previous studies, we trained and validated a biological sex classifier with large samples of CG-participants without any psychiatric comorbidities. We then applied the classifier to a smaller sample of TW. To ensure that observed misclassification is not caused or biased by psychiatric comorbidity, we performed a second validation of the classifier in an additional large validation-sample with MDD-patients. A third validation was performed in a matched CG sample of the TW application-sample, whose data were recorded at the same time and in the same scanner. Thus, an extensively greater generalizability is expected and therefore real-life applicability is enhanced. Our hypotheses for the multivariate analysis are:

1. The classifier trained on healthy CG-participants shows significantly worse performance when applied to a sample of TW.
2. The classifier trained on healthy CG-participants performs equally well in a validation-sample of CG-patients suffering from major depression.

Following our multivariate approach, we investigated local structural brain alterations in the putamen and the insula (24)(25)(2)(12)(11)(26). Since TW differ in brain structure from both CG-men and -women, with TW exhibiting lower volume in the putamen (12) and insula (9) than CG-men, but lower volume than CG-women (9)(27)(28), we hypothesize that

3. CG-women show lower volume in comparison to CG-men (6).
4. TW-pre and post-CHT show increased volume in comparison to CG-women.
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(5) TW-pre and post-CHT show lower volume in comparison to CG-men. Since we expect CHT to be associated with a further feminization of brain structure and hence reduced volume, we hypothesize that

(6) TW-pre-CHT show higher volume in comparison to TW-post-CHT.

Being transgender describes the stable feeling of belonging to the opposite rather than the biological sex assigned at birth, while the term CG describes the feeling of coherence between biological sex and perceived gender.

2 Materials and Method

To obtain and validate a predictor for biological sex based on structural MRI brain scans, we used three different samples, which purposes are briefly described here prior to sample characteristics: A classifier was trained on a large sample of CG-individuals without any psychiatric disorder using a cross-validation procedure. An independent subsample randomly drawn in advance, served as the first validation set, to avoid overfitting (supplementary figure A.1). To rule out that depressive symptoms influence the performance of the predictor in our TW-group, we used a second validation sample with major depressive disorder (MDD)-patients. Next, the classifier was applied to data from TW-individuals, and to a third validation group whose data were acquired at the same time and with the same scanner as the TW-sample.

2.1 Data

2.1.1 Cisgender training sample and first validation set

The data from a sample of \( N = 1753 \) CG-participants without any evidence of previous psychiatric disorders served as the basis for the training. History of psychiatric disorders was ruled out using the Structured Clinical Interview following DSM-IV criteria [29]. The participants were taken from three different cohorts: the Münster Neuroimaging Cohort (MNC, \( N = 666 \) [30]), the BiDirect study (BD, \( N = 434 \) [31]) and the FOR2107 study (\( N = 653 \) [32, 33]). Exclusion criteria for the MNC were presence or history of major internal or neurological disorder, dependence on or recent abuse of alcohol or drugs, hypertension, and general MRI contraindications. BiDirect study (BD) and FOR2107 have similar exclusion criteria; details are described in supplementary table A.1 and elsewhere [34, 32].

2.1.2 Second, clinical validation sample – patients suffering from major depressive disorder (MDD)

To exclude that potential differences in classification true positive rate (TPR) rate are due to comorbid depressive symptoms in TW, data from a clinical sample (\( N = 1404 \)) of patients diagnosed with MDD were used as second validation-sample. 450 MDD patients exhibited psychiatric comorbidities such as anxiety disorders or substance abuse. Diagnoses were again verified with the Structured Clinical Interview according to DSM-IV criteria [29]. The MDD sample consisted of \( N = 285 \) participants from the MNC, \( N = 591 \) from the BD study and \( N = 528 \) from the FOR2107 study (supplementary table A.1). Additional exclusion criteria were presence of bipolar disorder, schizoaffective disorders and schizophrenia, substance-related disorders, current benzodiazepine treatment (wash out of at least three half-lives before study participation), and recent electroconvulsive therapy. Nearly all patients were under psychopharmacological antidepressant treatment and/or received psychotherapy.

2.1.3 Application: transgender application sample including third validation sample

To test for a different classification of CG and TW, we used an independent sample of \( N = 29 \) TW. Three TW had to be excluded from our analysis due to poor image quality and artifacts. Data of TW were collected in conjunction with a set of CG-controls that serve as the third validation-sample of \( N = 19 \) CG-women and \( N = 15 \) CG-men (Transgender study (TSS)). TW were recruited during their treatment at the outpatient clinic of the department of psychiatry at the University of Münster. Before treatment and study inclusion all participants were carefully tested for chromosomal abnormalities such as Klinefelter syndrome, screened for personality disorders and other psychiatric comorbidities using the Structured Clinical Interview I and II according to DSM-IV criteria.

Data of TW and CG were recorded under equal conditions (e.g. scanner, timeframe, study protocol, investigator), ruling out possible confounding of the classifier due to scanner variability. The TW were in different treatment states, with 18 already treated with hormones (supplementary table A.2). Further details can be found in the original study [35].
2.2 Image acquisition and structural preprocessing

Image acquisition and structural preprocessing followed previously published protocols for the MNC [36, 37], the FOR2107 [33] and the BiDirect Cohort [31]. A detailed description can be found in supplementary methods B.1.

2.3 Analyses

2.3.1 Multivariate analysis

Individualized prediction of the biological sex was assessed with a support-vector classifier (SVC), implemented in the Scikit-learn toolbox [35]. CAT12 whole-brain gray matter images were used as a classifier input [39]. Gray matter images were resliced to a voxel size of $3 \times 3 \times 3$ mm$^3$, to reduce dimensionality while preserving maximal localized morphometric differences. The training process was strictly separated from the evaluation, by selecting a random validation set of $20\%$ ($N = 351$, $N_{\text{female}} = 219$, $N_{\text{male}} = 132$), which was not used during classifier training and testing. 

The remaining data set of $N = 1402$ subjects was balanced for sex with a random undersampling procedure ($N = 1218$, $N_{\text{female}} = 609$, $N_{\text{male}} = 609$), and used in a 10-fold split procedure resulting in balanced training sets of $N = 1096$ subjects in each fold. A principal-component analysis (PCA) was performed next, to further reduce the dimensionality of the data. The maximum number of principal components is limited to 1096, the number of subjects resulting from the 10-fold split. We carried out a Bayes-statistic-based hyperparameter optimization (Scikit-Optimize [40]) for the SVC, nested in the 10-fold cross-validation. The parameter search included choice of the kernel (radial basis function (RBF) or linear), the $C$ parameter ($10^{-2}$ to $10^2$, non-discrete log-scale), which influences penalties for misclassification, and the $\gamma$ parameter ($10^{-6}$ to 10, non-discrete log-sale), influencing the curvature of the decision boundary. In this iterative Bayes approach, a total of 100 parameter combinations were evaluated. Quality and classifier performance are reported by area under the ROC curve (AUC). The classifier resulting from the best combination of hyperparameters was finally determined using our first validation set, the $20\%$ drawn in advance from the original sample. To exclude potential effects of comorbid depression, this step was repeated with the sample of MDD subjects, as a second validation sample (figure 1).

The final trained and validated classifier was then applied to the application sample with TIs. To test if classification results differ between CG-men and TW (same biological sex), we applied the TPR. Since Balanced Accuracy (BACC) is a measure not applicable to one-group-only scenarios, Fisher’s exact test was used to clarify whether TPR differs statistically between samples. Interpretation of TPR is based on the hypothesis that TW belong to the category of male biological sex.

In order to achieve optimal generalization of our classifier, multiple scanners were deliberately incorporated. A specific correction for possible scanner effects was not intended. Instead, the purpose was to establish a classifier based on scanner invariant features given the large amount of training data and expected excellent classification performances. Comparison of the recognition rates between the individual scanners yielded no significant differences. Hence, an influence of the scanner on the classification results could not be detected - supporting our expectation (see supplementary table A.9). However, it should be pointed out that our data reveal a practically identical classification performance of the classifier trained on the multi-scanner training set (94.01% BACC in the first validation) to its application on the third validation-sample (CG control group of the TW-sample), using a different single scanner environment (94.03 % BACC), suggesting that the classifier learned scanner independent features driving the classification performance.

2.3.2 Univariate analysis

The methodological details of the univariate analysis can be found in supplemental methods B.2.

3 Results

3.1 Multivariate analysis

3.1.1 Cisgender training and first validation sample

The training of the classifier led to two results. The first result was the estimation of a hyperparameter set, determined with the Bayes optimization method. The hyperparameter optimization estimated an RBF kernel, $C = 27.3$ and $\gamma = 2.4 \times 10^{-5}$ for the support-vector machine (SVM) as optimal approximation for the present problem.

Based on the estimated hyperparameters, the second result was the classification outcome of the $20\%$ validation set, which provided a performance indication for the trained classifier. The Balanced Accuracy for the validation set classification was 94.01 %. The confusion matrix (supplementary table A.4) revealed that our classifier assigns the
female biological sex (TPR = 99.9 \%) more accurately than the male biological sex (TPR = 88.5 \%). These results are visualized by a ROC curve, based on the probabilities for a classification as male (supplements figure 2a), with a calculated AUC of 0.99.

### 3.1.2 MDD second validation sample

To rule out that MDD comorbidity had any influence on the classifier, we used a second validation set consisting of 1404 MDD subjects (853 CG-women, 551 CG-men). Our classifier reached a BACC of 92.06 \%, and a TPR of 86.93 \% for CG-men in this sample (supplementary table A.5). The results of the classifier, the corresponding ROC curve (supplementary figure 2b), and the AUC of 0.99 are similar to the results of the first validation set. Fisher’s exact test revealed no significant differences between the distribution of results of the first and second validation sample (supplementary table A.6).

### 3.1.3 Transgender application sample and cisgender third validation sample

The BACC for the third validation sample was 94.03 \% (CG part of the TW-sample). The TPR for CG-men was 93.3 \% and for CG-women 100.0 \% (table 1). However, the TPR for the TW was remarkably low at 56 \% (supplementary table A.4); see visualization by ROC curves (supplementary figure 2p, c). The corresponding AUC differed as a function of group between 0.99 (CG-men) and 0.95 (TW). This difference in TPR was significant, as Fisher’s exact test showed a statistically significant difference between TPR of CG-men and TW with hormone treatment (table 1). The output probabilities of the classifier are represented descriptively in figure 2 as a box plot.
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### 3.2 Univariate analysis

The region of interest analysis is summarized in table A.7 and figure 4 (see coordinates and detailed statistics there). Briefly, using rigorous alpha correction, our analysis revealed no differences between TW-post CHT and CG-women in the bilateral putamen. In the insula, TW-post CHT showed higher volume than CG-women. TW-post CHT and CG-women both showed lower volume of the insula and putamen compared to CG-men. In contrast, TW-pre CHT showed larger volume in both region of interest (ROI) analyses compared to CG-women. Interestingly, TW pre CHT also showed higher volume in the putamen compared to CG-men. TW post-CHT showed lower volume of both regions of interest compared to TW pre-CHT in both regions of interest. CG-men showed larger volume in both regions of interest compared to CG-women. Detailed results of our exploratory whole-brain analysis can be found in the supplementary table A.10. Omitting TW individuals with psychiatric comorbidities did not alter findings in general (see supplementary table A.7 and A.10). However, conclusions should be made with caution due to limited sample size.
This might encourage further investigations into the cause for increased misclassifications in TW-patients suffering from MDD. When applying the same classifier to structural MRI data of CG-participants, the SVM shows a much lower TPR, resulting in significantly more misclassifications of the biological sex of TW (male) in favor of their perceived gender (female). Moreover, the descriptive statistics of classification probabilities regarding TW (figure 2) indicate a pattern of prediction uncertainty that is not observable in CG.

Hence, our results shed light on two important aspects in biological psychiatry of TIs: 1) The impact of hormonal treatment on brain structure, 2) the separation of psychological distress (i.e. depression), hormonal treatment and trait characteristics of being a TI.

Our results replicate the finding that biological sex is increasingly misclassified in TIs, as previously described [21][22]. This might encourage further investigations into the cause for increased misclassifications in TW. Most notably and in contrast to previous studies, we could rule out that our findings are biased by comorbid depression and antidepressant medication. Given that the results of the first validation-sample of healthy CG-participants were replicated in a large clinical sample of CG-patients suffering from major depression, the classifier is reliable and robust to noise even from psychiatric disorders such as MDD and medication, which have been associated with structural brain changes [31][32].

### Table 2: Results of the univariate gray matter region of interest analysis of the insula and putamen.

| compared groups               | region of interest | side | TFCE     | p-FWE | k   | x   | y   | z   |
|-------------------------------|--------------------|------|----------|-------|-----|-----|-----|-----|
| TW-pre > TW-post              | insula             | L    | 91.50    | .012  | 76  | −38 | −3  | −12 |
|                               | R                  | 54.96 | .033    | 23    | 32  | 10  | 16  |
|                               | putamen            | L    | 466.55   | < .001| 2005| −21 | 16  | 8   |
|                               | R                  | 395.31 | < .001| 1409  | 27  | −8  | 15  |
| TW-pre > CG-women             | insula             | L    | 63.21    | < .001| 1926| −39 | 3   | 12  |
|                               | R                  | 52.58 | < .001  | 2299  | 34  | 15  | 10  |
|                               | putamen            | L    | 274.31   | < .001| 2381| −21 | 10  | 23  |
|                               | R                  | 257.58 | < .001| 2316  | 26  | −4  | 14  |
| TW-pre > CG-men               | putamen            | L    | 203.55   | < .001| 892 | −21 | 15  | 9   |
|                               | R                  | 183.13 | < .001| 576   | 28  | −3  | 15  |
| TW-post < CG-men              | insula             | L    | 38.96    | .005  | 303 | −42 | 14  | −6  |
|                               | R                  | 30.99 | .010    | 124   | 42  | −8  | 4   |
|                               | putamen            | L    | 100.64   | < .001| 1050| −14 | 9   | −2  |
|                               | R                  | 70.60 | < .001  | 1429  | 26  | 4   | −8  |
| TW-post < CG-women            | insula             | R    | 114.58   | .021  | 99  | 34  | 15  | 9   |
| CG-men > CG-women             | insula             | L    | 49.7     | < .001| 1199| −44 | 14  | −8  |
|                               | R                  | 13.07 | .004    | 48    | −44 | 14  | 8   |
|                               | putamen            | L    | 109.23   | < .001| 1789| 39  | 16  | 3   |
|                               | R                  | 81.13 | < .001  | 1972  | 26  | 4   | −8  |
|                               |                    |      | 100.11   | < .001| 1429| 26  | 4   | −8  |

Note. Table reports respective statistics of significant clusters of the group comparisons between transgender and cisgender individuals. Clusters resulted from group comparisons corrected for total intracranial volume, age and sexual orientation. For reasons of brevity no results below a threshold of k = 22 voxel have been reported.

Abbreviations:
- TW: transgender woman
- CG: cisgender
- pre/post: before/after hormone treatment
- L/R: left/right
- k: cluster size
- TFCE: Threshold-Free-Cluster-Enhancement with subsequent Family-Wise-Error-Correction.

### 4 Discussion

In the present study, we developed an SVM using hyperparameter optimization resulting in an accurate classification of biological sex based on structural MRI images. The classifier, trained on a large training set of healthy CG individuals, performed equally well in three independent validation samples of healthy CG individuals, and CG participants suffering from MDD. When applying the same classifier to structural MRI data of TW, the SVM shows a much lower TPR, resulting in significantly more misclassifications of the biological sex of TW (male) in favor of their perceived gender (female). Moreover, the descriptive statistics of classification probabilities regarding TW indicate a pattern of prediction uncertainty that is not observable in CG.
Our biological sex classifier shows a higher external validity than other biological sex classifiers. First, it has been tested on controls and MDD-patients, with high and very similar accuracy. Second, the SVM has been trained on large samples that have been collected at different sites. Hence, our SVM can be regarded as more generalizable while preserving performance and accuracy, indicating its robustness to noise.

In the present work, we focused on the first application of this SVM on TW. We observed that our SVM was increasingly inaccurate in TW, compared to healthy CG controls. The explorative analysis revealed that this inaccuracy was particularly increased in TW who had hormonal treatment.

Although our TW-pre-CHT sample size was low, we aimed to differentiate structural brain alterations between TW-pre and TW-post-CHT as well as in comparison to CG-women and -men. Our results show brain structural alterations dependent on the treatment state of TW. Volumes of the insula and putamen were larger in TW-pre-CHT than in CG-women, while TW-post-CHT showed lower volumes of the right insula compared to CG-women.

In comparison to CG-men, TW-pre-CHT showed larger volumes of the putamen, while TW-post-CHT showed lower volumes of both insula and putamen. Thus, TW independent of treatment state show brain structural alterations in our regions of interest in comparison to both, CG-men and –women.

Detailed analysis of TW-pre compared to -post-CHT revealed a less pronounced pattern of structural brain alterations in TW-post-CHT compared to CG-women. Comparing TW-pre with TW-post-CHT revealed lower volume of TW-post-CHT in both regions of interest, as well as the whole-brain analysis. This implies that CHT induces a further feminization of brain structure in TW. This result fits with previous longitudinal studies that have shown reductions of cortical thickness in TW-pre to post-CHT [26]. Structural and functional alterations of the insula have consistently been associated with TIs compared to CG-individuals [9, 12, 24, 25, 43]. The insula is associated with body and self-perception. Behaviorally, TW perceive an incoherence between their biological sex and perceived gender that is accompanied by altered insula activity in response to bodily sensations [44].
Brain structural alterations of the putamen have been associated with TW across multiple studies and independent of treatment state [12][11][13]. We examined the putamen volume across different treatment states. Our study reveals that TW-pre show a higher volume of the putamen compared to CG-men and CG-women, while TW-post show lower volume of the putamen compared to CG-men, but not to CG-women. However, it remains unknown how CHT influences these structural alterations of TW. Longitudinal examinations are required to reveal region specific structural alterations to estimate the impact of CHT of brain structure.

Our combined univariate and multivariate approach revealed associations of CHT with lower accuracy in detecting the biological sex of TW. Our results show that the brain structure of TW aligns with neither their biological sex (male) nor their perceived gender (female). This implies that there is a biological basis for being transgender and thus, destigmatizes TIs. Further, this evidence can be used in psychoeducation during treatment of gender dysphoria. The diagnosis of gender dysphoria is new to DSM-5 to allow for treatment if TIs suffers from distress due to incoherence between perceived gender and biological sex. Our results could relieve distress in transgender patients in case of the experience of guilt or shame due to the discrepancy between biological sex and perceived gender.

In line with this idea, hormonal processes, brain-structural development and the development of gender identity are intertwined [17]. Intrauterine hormones drive the development of gender identity, rather than social learning processes [45][46]. The male physical appearance is formed in the first trimester, due to effects of testosterone, and the female body develops due to the lack of androgens in this period [47]. While the maturation of reproductive organs is more or less limited to the first trimester, brain development is continuing throughout pregnancy [4][48]. Hormonal influences after the first trimester do not change the biological sex, but the experience of gender and thus might be responsible for the incoherence between biological and experienced sex. Since hormonal influences change gender perception as well as brain structure, CHT may lead to misclassifications in the TW-group after treatment. Our univariate data indeed show that CHT is associated with structural brain alterations comparing TW-pre and post-CHT to CG-individuals. A previous study showed increased misclassification of biological sex even in untreated TW [21], which we could not statistically support due to the small sample size of our untreated group (N = 8). Therefore, further studies should follow up on this effect, with higher sample sizes of untreated TW to increase power. An extension of the design with a second control group (women with hormonal treatment) should be used to clarify whether misclassification is an effect of treatment only, due to the combination of being transgender and CHT.

The present svc provides a new tool for research in biological psychiatry. Prevalence of many psychiatric disorders is often higher for one biological sex than for the other. For example, prevalence in autism is higher for biological men than for biological women. Hence, it was hypothesized that female patients with autism might be similar in their brain structure to men. A previous study that developed a biological sex classifier using structural MRI scans and applied it to patients with autism [49] indeed showed increased misclassifications of biological sex in female patients with autism. Therefore, biological sex misclassifications might point to involvement of aberrant biological sex development in the onset of such neurodevelopmental disorders. Future studies could use our trained classifier (https://photon-ai.com/model_repo/bsc_mri) to test for misclassifications in other clinical diagnoses with high gender imbalance in prevalence rates, such as eating disorders, substance use disorders, or anxiety disorders.

4.1 Limitations

Next to our training and validation strategy (visualized in figure[A.1], a variety of other strategies exist such as repeated nested k-fold cross validation (see also [22]). The latter is an adequate means of choice in the absence of external validation-samples and produces robust estimates. However, even by preserving similar classification performances, we cannot rule out that other validation strategies could result in learning other patterns and therefore influence the prediction on TW individuals. In addition, due to our small sample size of TW, replication of the prediction failure of our SVM in TIs pre and post-CHT is needed. To verify that our effect is due to hormonal treatment, larger samples and studies in transgender men (biological sex female) are needed. Future studies should further dissect effects of gender dysphoria from depression, and effects of hormonal treatment from the state of being a TI. Finally, on the basis of the present data, we cannot draw firm conclusions on why the sensitivity of our classifier is greater towards the female. Further research is needed that investigates how classification performance in CG-men and -women is associated with sex hormones.

5 Conclusion

In this study, we present a highly accurate biological sex classifier in CG-individuals that shows a significantly decreased accuracy in TIs after CHT. Our results underline that the brain structure of TIs is similar to both, the brain structure of their perceived gender and biological sex. This implies that brain structure of TW differs from both cg men and women. Based on our brain structural data, we suggest a dimensional rather than binary gender construct which will contribute to the destigmatization of TIs.
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SUPPLEMENTAL MATERIALS

Biological sex classification with structural MRI data shows increased misclassification in transgender woman

A Supplemental Tables and Figures

| Münster Neuroimaging Cohort | female | male | significance test |
|-----------------------------|--------|------|-------------------|
| HC                          | Quantity | 278 | 388 |
| Age | 36.4 (11.7) | 35.8 (12.6) | $F(1, 665) = 0.4917, p = .480$ |
| MDD                          | Quantity | 121 | 164 |
| Age | 36.4 (11.7) | 35.8 (12.6) | $F(1, 665) = 0.4917, p = .480$ |
| BDI | 23.4 (9.5) | 26.5 (10.9) | $F(1, 274) = 6.212, p = .013$ |
| HDRS-17 | 18.5 (3.8) | 19.5 (4.5) | $F(1, 187) = 2.739, p = .100$ |
| IQ (MWBT) | 111.5 (13.3) | 110.9 (14.1) | $F(1, 267) = 2.739, p = .765$ |

| BiDirect Study | female | male | significance test |
|----------------|--------|------|-------------------|
| HC                          | Quantity | 217 | 217 |
| Age | 51.3 (8.1) | 53.0 (8.0) | $F(1, 1433) = 4.481, p = .035$ |
| MDD                          | Quantity | 235 | 356 |
| Age | 48.1 (7.4) | 49.6 (7.3) | $F(1, 590) = 5.612, p = .019$ |
| HDRS-17 | 12.6 (6.8) | 14.3 (6.5) | $F(1, 557) = 10.160, p = .002$ |

| FOR2107 Study | female | male | significance test |
|----------------|--------|------|-------------------|
| HC                          | Quantity | 246 | 407 |
| Age | 32.6 (11.4) | 32.6 (13.0) | $F(1, 1562) = 0.001, p = .976$ |
| MDD                          | Quantity | 195 | 333 |
| Age | 36.6 (13.8) | 37.8 (13.4) | $F(1, 527) = 0.719, p = .397$ |
| HDRS-17 | 8.9 (6.7) | 8.5 (6.8) | $F(1, 525) = 0.414, p = .520$ |

Table A.1: Descriptive statistics of the trainings and validation samples. Table reports means and standard deviations of the individual cohorts used for the training of the support-vector machine. Significance test was a univariate ANOVA without covariates.

Abbreviations: **HC** - Healthy Control

**MDD** - major depressive disorder

**Age** - age in years
SUPPLEMENTS

Biological sex misclassification in transgender woman

A PREPRINT

Table A.2: Descriptive statistics of the application sample (transgender and cisgender individuals). Table reports means and standard deviations of the transgender individuals and controls from a similar measurement period used for the test of the support-vector machine in TW. Significance test was univariate ANOVA without covariates. From 15 out of 29 TW were requested whether they had a depressive episode and 8 from the 15 TW indicated that they had a depressive episode. Highest Education was measured according to educational attainment in numbers from 1 = special school to 6 = universal degree.

Abbreviations: TW - transgender woman
   pre/post - before/after cross-sex hormone treatment
   Age - age in years

|                  | CG men | CG women | TW pre | TW post |
|------------------|--------|----------|--------|---------|
| (N = 15)         | (N = 19) | (N = 8)  | (N = 18) |
| **Age**          | 34     | 32       | 33.9   | 33.1    |
| (8.6)            | (6.3)  | (14.1)   | (31.3) |
| **Highest**      | 4.9    | 4.8      | 5.0    | 5.1     |
| Education        | 0.9    | 0.8      | 0.0    | 0.5     |
| **significance test** |  |         |  |  |
| $F(3, 56) = 0.190, p = .991$ |  |         |  |  |

Table A.3: Results of the validation set (N = 351; N_{CGmen} = 148; N_{CGwomen} = 203). Classification results in absolute numbers and percentage of accurately identified biological sex.

Abbreviations: TPR - true positive rate (sensitivity)
            TNR - true negative rate (specificity)

|                  | female | male | Accuracy | Balanced Accuracy | Precision | Recall | F1-Score |
|------------------|--------|------|----------|-------------------|-----------|--------|----------|
| predicted group  | 202    | 17   | 94.87 %  | 94.01 %           | 99.24 %   | 88.51 %| 0.9357   |
| **TPR = 99.9 %** | (TPR = 11.5 %) | (true negative rate (TNR = 11.5 %) | |
| **TNR = 0.1 %**  | (TNR = 88.5 %) | (TPR = 88.5 %) | |

Table A.4: Results of the application set (N = 60; N_{CGmen} = 15; N_{CGwomen} = 19; N_{TW} = 26). Classification results in absolute numbers and percentage of accurately identified biological sex.

Abbreviations: TPR - true positive rate (sensitivity)
            TNR - true negative rate (specificity)
            CG - cisgender
            TW - transgender woman

The following metrics are related to the CG groups only:

|                  | female | male | Accuracy | Balanced Accuracy | F1-Score |
|------------------|--------|------|----------|-------------------|----------|
| predicted group  | 19     | 1    | 94.12 %  | 96.67 %           | 0.9655   |
| **TPR = 100.0 %** | (TPR = 6.7 %) | (TNR = 38.5 %) | |
| **TNR = 0.0 %**  | (TNR = 61.5 %) | (TPR = 61.5 %) | |

The following metrics are related to the TW group only:

|                  | female | male | Accuracy | Balanced Accuracy | F1-Score |
|------------------|--------|------|----------|-------------------|----------|
| predicted group  | 0      | 14   | 100.0 %  | 93.3 %            | 90.4 %   |
| **TPR = 0.0 %**  | (TPR = 93.3 %) | (TNR = 38.5 %) | |
| **TNR = 14 %**   | (TNR = 61.5 %) | (TPR = 61.5 %) | |
Table A.5: Results of the second validation set (N = 1404; N_male = 551; N_female = 853). Classification results in absolute numbers and percentage of accurately identified biological sex.

| group   | female | male | Accuracy  | Balanced Accuracy | Precision | Recall | F1-Score |
|---------|--------|------|-----------|-------------------|-----------|--------|----------|
| female  | 829    | 72   | 93.16 %   | 93.06 %           | 95.23 %   | 86.93 %| 0.9206   |
|         | (TPR = 97.2 %) | (TNR = 13.1 %) |          |                   |           |        |          |
| male    | 24     | 479  | 92.69 %   | 92.06 %           | 86.93 %   | 0.9206 |          |
|         | (TNR = 2.8 %) | (TPR = 86.9 %) |          |                   |           |        |          |

Abbreviations: TPR - true positive rate (sensitivity)
TNR - true negative rate (specificity)

Table A.6: Classification results in the application sample. Comparison of the distribution of classification results between the first and second validation sets, using Fisher’s exact test. (CG - cisgender)
### Table A.7: Results of the whole-brain analysis.

For reasons of brevity only significant clusters > *k* = 300 voxel are reported, we did not calculate a contrast comparing cisgender men and women. The reported significant clusters resulted from group comparisons within a full factorial model corrected for total intracranial volume, age and sexual orientation.

| compared groups | region of interest | TFCE | p-FWE  | k   | x    | y    | z    |
|-----------------|--------------------|------|--------|-----|------|------|------|
| TW-pre > TW-post | R medial cingulate cortex and caudate nucleus | 1643.35 | .005 | 15117 | 27 | -9 | 16 |
|                 | L caudate nucleus  | 1514.98 | .005 | 13228 | -22 | 18 | 12 |
|                 | L precentral and middle frontal gyrus | 766.08 | .029 | 470 | -36 | 4 | 54 |
|                 | L precuneus        | 743.23 | .29  | 651 | -14 | -56 | 52 |
|                 | L postcentral gyrus | 668.59 | .040 | 410 | -63 | -14 | 39 |
|                 | R cerebellum       | 632.84 | .045 | 505 | 48  | -54 | -27 |
|                 | R cerebellum       | 611.18 | .047 | 258 | 40  | -38 | -46 |
| TW-pre > CG-women | L precuneus, R medial cingulate Cortex, L + R lingual gyrus | 982.71 | <.001 | 108742 | 22 | -3 | 15 |
|                 | L cerebellum       | 328.77 | .003 | 4657 | -30 | -33 | -50 |
|                 | R precentral, frontal inferior gyrus | 127.46 | .041 | 360 | 62  | 16 | 27 |
| TW-post > CG-women | R calcine/lingual gyrus, precuneus | 1312.08 | <.001 | 3875 | 4 | 50 | 3 |
|                 | L cuneus, superior occipital gyrus | 605.11 | .023 | 498 | -10 | 96  | 36 |
| TW-post < CG-women | R postcentral gyrus | 1057.71 | .026 | 562 | 45  | 21 | 32 |
| TW-pre > CG-men  | L caudate nucleus, putamen, hippocampus | 745.18 | .009 | 3018 | -21 | 18 | 9 |
|                 | R caudate nucleus, putamen | 713.97 | .010 | 2336 | 28  | -4 | 16 |
|                 | R Precuneus, Mid Cingulum | 673.63 | .013 | 3185 | 8 | 28 | 39 |
|                 | L Pre-, Postcentral | 654.18 | .015 | 822 | -69 | -15 | -32 |
|                 | R Hippocampus, Parahippocampus | 567.93 | .028 | 713 | 20 | 8 | -30 |
|                 | R Calcarine, Lingual gyrus | 528.98 | .002 | 416 | 26  | -75 | 3 |
| TW-post < CG-men | L middle temporal lobe, cerebellum | 939.61 | <.001 | 111736 | 32 | -56 | -38 |
|                 | R middle temporal lobe, cerebellum | 260.12 | .016 | 628 | 57  | 6 | 12 |

**Abbreviations:**
- **TW** - transgender woman
- **CG** - cisgender
- **pre/post** - before/after cross-sex hormone treatment
- **L/R** - left/right
- **k** - cluster size
- **TFCE** - Threshold-Free-Cluster-Enhancement with subsequent Family-Wise-Error-Correction.

### Table A.8: Comorbidities of transgender individuals.

Psychiatric comorbidities were reported for 10 transgender woman.

| **Substance abuse** | **Eating Disorder** | **Obsessive-compulsive Disorder** | **Anxiety Disorder** | **Major Depressive Disorder** |
|---------------------|---------------------|----------------------------------|----------------------|-------------------------------|
| 1                   | 1                   | -                               | 1                    | 2                             |

**Abbreviations:**
- **TW** - transgender woman
- **pre/post** - before/after cross-sex hormone treatment
Table A.9: Classification results separated by scanner features and site. Table shows frequencies of correctly and incorrectly classified CG-women and –men for all validation samples that used different scanners. The third validation sample was measured with the same MRI-sequence as MNC Münster.

Abbreviations: CG - cisgender
### Table A.10: ROI analysis in the restricted transgender sample without psychiatric comorbidities. Table shows significant clusters > k = 100 voxel for reasons of brevity. Transgender individuals that showed comorbidities according to the structured clinical interview based on DSM-IV-criteria were excluded from the analysis leaving N = 6 TW-pre and N = 10 TW-post.

| ROI       | TW-pre > post | TW-pre < post | TW-pre > CG-women | TW-pre < CG-women | TW-pre > CG-men | TW-pre < CG-men | TW-post > CG-women | TW-post < CG-women | TW-post > CG-men | TW-post < CG-men | TW-post < CG-men |
|-----------|---------------|---------------|-------------------|-------------------|-----------------|-----------------|-------------------|-------------------|-----------------|-----------------|-----------------|
| Insula    | TFCE          | p-FWE         | k     | x     | y     | z     | TFCE          | p-FWE         | k     | x     | y     | z     | TFCE          | p-FWE         | k     | x     | y     | z     | TFCE          | p-FWE         | k     | x     | y     | z     | TFCE          | p-FWE         | k     | x     | y     | z     | TFCE          | p-FWE         | k     | x     | y     | z     |
| TW-pre > post | n.s.         | n.s.         | 13.70  | .002  | 643   | 40   | 20   | −8             | n.s.         | n.s.         | 121.60 | .001  | 471   | −40  | −3   | 0              | n.s.         | n.s.         | 73.19  | <.001 | 2267  | −32  | −8   | 12             | n.s.         | n.s.         | 19.90  | <.001 | 1271   | 38   | −20  | 3              | n.s.         | n.s.         | 3.18   | .001  | 620   | 46   | 22   | −4             | n.s.         | n.s.         |
| TW-pre < post | n.s.         | n.s.         | 2.14   | .014  | 107   | −24  | 21   | −15            | n.s.         | n.s.         | 121.60 | .001  | 471   | −40  | −3   | 0              | n.s.         | n.s.         | 73.19  | <.001 | 2267  | −32  | −8   | 12             | n.s.         | n.s.         | 19.90  | <.001 | 1271   | 38   | −20  | 3              | n.s.         | n.s.         | 3.18   | .001  | 620   | 46   | 22   | −4             | n.s.         | n.s.         |
| TW-pre > CG-women | 4.76  | <.001 | 1058  | 40   | 21   | 8               | n.s.         | n.s.         | 4.76  | <.001 | 1058  | 40   | 21   | 8               | n.s.         | n.s.         | 4.76  | <.001 | 1058  | 40   | 21   | 8               | n.s.         | n.s.         |
| TW-pre < CG-women | 1.11  | .001  | 479   | −33  | 26   | 4               | n.s.         | n.s.         | 1.11  | .001  | 479   | −33  | 26   | 4               | n.s.         | n.s.         | 1.11  | .001  | 479   | −33  | 26   | 4               | n.s.         | n.s.         |
| TW-pre > CG-women | 357.70 | <.001 | 524   | −40  | −8   | 2               | n.s.         | n.s.         | 357.70 | <.001 | 524   | −40  | −8   | 2               | n.s.         | n.s.         | 357.70 | <.001 | 524   | −40  | −8   | 2               | n.s.         | n.s.         |
| TW-pre < CG-women | 24.46  | <.001 | 2427  | −32  | 3    | 12              | n.s.         | n.s.         | 24.46  | <.001 | 2427  | −32  | 3    | 12              | n.s.         | n.s.         | 24.46  | <.001 | 2427  | −32  | 3    | 12              | n.s.         | n.s.         |
| TW-pre > CG-men  | 9.54   | <.001 | 1309  | 48   | −10  | 3               | n.s.         | n.s.         | 9.54   | <.001 | 1309  | 48   | −10  | 3               | n.s.         | n.s.         | 9.54   | <.001 | 1309  | 48   | −10  | 3               | n.s.         | n.s.         |
| TW-pre < CG-men  | 5.41   | <.001 | 230   | 45   | 24   | −3              | n.s.         | n.s.         | 5.41   | <.001 | 230   | 45   | 24   | −3              | n.s.         | n.s.         | 5.41   | <.001 | 230   | 45   | 24   | −3              | n.s.         | n.s.         |
| TW-post > CG-women | 2.11   | <.001 | 200   | 33   | 16   | −21             | n.s.         | n.s.         | 2.11   | <.001 | 200   | 33   | 16   | −21             | n.s.         | n.s.         | 2.11   | <.001 | 200   | 33   | 16   | −21             | n.s.         | n.s.         |
| TW-post < CG-men  | n.s.   | n.s.   | n.s.   | n.s. | n.s. | n.s.             | n.s.         | n.s.         | n.s.   | n.s.   | n.s. | n.s. | n.s.             | n.s.         | n.s.         | n.s.   | n.s.   | n.s. | n.s. | n.s.             | n.s.         | n.s.         |

**Abbreviations:**
- **TW** - transgender woman
- **CG** - cisgender
- **pre-/post** - before/after cross-sex hormone treatment
- **TFCE** - statistic of the non-parametric approach using threshold-free cluster enhancement
- **k** - clustersize
- **n.s.** - not significant, k > 100
Figure A.2: Receiver Operation Characteristics for the classification as biological sex male for CG-men in first, second and third validation sample as well transgender woman of our application sample.

Abbreviations:
- **CG**: cisgender
- **TW**: transgender woman
- **MDD**: major depressive disorder
- **AUC**: area under the ROC curve
B Supplemental Methods

B.1 Images and Structural Preprocessing

T1-weighted high-resolution anatomical images of the MNC and TSS were acquired at a 3T MRI (Gyrosan Intera 3T, Philips Medical Systems, the Netherlands) using a three-dimensional fast gradient echo sequence (turbo field echo), repetition time = 7.4 ms, echo time = 3.4 ms, flip angle = 90°, two signal averages, inversion pre-pulse every 814.5 ms, acquired over a field of view of 256 (feet-head) × 204 (anterior-posterior) × 100 mm³ (right-left), frequency encoding in feet to head direction, phase encoding in anterior-posterior and right-left direction, reconstructed to voxels of 0.5 × 0.5 × 0.5 mm³ [50, 57].

The 3D T1-weighted turbo field echo images of the BD study were collected in the same scanner with repetition time = 7.26 ms, echo time = 3.56 ms, 9° flip angle, 160 sagittal slices, matrix dimension 256 × 256, FOV = 256 × 256 mm², 2 mm slice thickness (reconstructed to 1 mm) resulting in a voxel size of 1 × 1 × 1 mm³. The FOR2107 study was conducted at two different sites [53]. In Münster, data were collected with a 3T Siemens PRISMA using 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) with repetition time = 1900 ms, echo time = 2.28 ms, inversion time = 900 ms, 8° flip angle, 192 sagittal slices, 0 mm slice gap, resulting in a voxel size of 1 × 1 × 1 mm³. In Marburg, data were collected in a 3T Siemens Magnetom Trio Tim syngo MR B17 using a 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) with repetition time = 1900 ms, echo time = 2.26 ms, inversion time = 900 ms, 9° flip angle, 176 sagittal slices, 0.5 mm slice lap, resulting in a voxel size of 1 × 1 × 1 mm³. The structural images were preprocessed using the CAT12-toolbox [59] (version r1184) in all four cohorts (MNC, FOR2107, BiDirect, TSS) following published protocols. Briefly, images were bias-corrected, tissue classified and normalized to MNI-space [50]. For the univariate analysis, images were additionally smoothed with a Gaussian kernel of 8 mm full half maximum (FWHM). Absolute threshold masking with a threshold value of 0.1 was used for all univariate second-level analyses (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf).

We carefully checked the sample for poor image quality detected by visual inspection and with the check homogeneity using covariance function implemented in CAT12.

B.2 Univariate analysis

The TSS group and matched CG controls, supplementary table A.2 were used in the univariate analysis. Statistical parametric mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, http://www.fil.ion.ucl.ac.uk/spm/) was used for univariate gray matter analysis. The putamen and insula were defined as a priori ROIs using the aal-atlas [50] implemented in the Wake Forest University Pickatlas (http://fmri.wfubmc.edu/software/PickAtlas). We investigated the relationship between groups (CG-men, -women, TW-pre and -post CHT) and gray-matter volume with an ANCOVA, with age, total intracranial volume and sexual orientation as nuisance regressors in all analyses. Sexual orientation was indicated by the participants as a continuous variable (0-100, 0 indicating homosexuality, 50 indicating bisexuality and 100 indicating heterosexuality). Participants could choose each number between 0 and 100. The terminology was chosen according to the natal biological sex of TW, i.e. homosexuality indicated sexual interest in men. We calculated a priori defined t-contrasts according to our hypothesis: CG-men > women, CG-men > TW-pre, TW-pre > CG-women, CG-men > TW-post, TW-post > CG-women and TW pre > TW post. An additional whole brain analysis further explored possible regions with volume differences between the groups. Family-wise error correction with p < .05 was used in order to correct for alpha inflation. To determine statistical significance of putative clusters in each of the two bilateral ROIs (insula, putamen) and the whole brain analysis, after applying the non-parametric approach of Threshold-Free Cluster Enhancement as implemented in the TFCE toolbox (http://dbm.neuro.uni-jena.de/tfce version 167) we conducted 5000 permutations per test.

C Supplemental Results & Discussion

Basal testosterone was significantly associated with classification as male (r = .437, p = .014) across both TW groups, while progesterone only showed a tendency towards a significant association with classification accuracy (r = .274, p = .09). Looking at TW-pre-CHT and -post-CHT separately, TW-pre CHT showed no significant association (r = .218, p = .302), while TW-post-CHT showed a tendency towards a significant association between basal testosterone concentration and classification as male (r = .392, p = .06). The classification performance was significantly associated with the amount of basal testosterone measured in TW. However, this association alone is not sufficient to draw any conclusions on the effect of CHT on classification performance, since we did not directly measure the amount of estradiol and anti-androgens that were taken. For instance, it is possible that TW-pre-CHT contain lower levels of basal testosterone without taking any medication which might also increase the feeling of incongruence between natal sex and perceived gender (for a review [17]).
D Abbreviations

AUC area under the ROC curve
BACC Balanced Accuracy
BD BiDirect study
CG cisgender
CHT cross-sex hormone treatment
HC Healthy Control
MDD major depressive disorder
MNC Münster Neuroimaging Cohort
PCA principal-component analysis
RBF radial basis function
ROI region of interest
SVC support-vector classifier
SVM support-vector machine
TI transgender individual
TNR true negative rate
TPR true positive rate
TSS Transgender study
TW transgender woman