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"The effects of hormone replacement therapy on reactive aggression, self-aggression/depression and aggression inhibition in gender dysphoria – a retrospective study"

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Abstract

Background and Study aim

Aggression is a hugely heterogeneous term and research on its relationship to sex steroid hormones has delivered inconsistent results so far. The inclusion of gender dysphoric people receiving hormone replacement therapy in a study design holds the great potential of observing the influence of drastically changing hormone levels on certain biological and/or psychological conditions in human beings. Therefore, this retrospective study aims to shed some light on the association between sex steroid hormones and reactive/impulsive aggression, self-aggression/depression, and aggression inhibition.

Materials and Methods

The overall study sample (n = 69) consisted of four groups, which were measured at two time points (before the start of hormone replacement therapy and at least 4 months into it): trans*men (n = 25), trans*women (n = 17), cis*men (n = 11) and cis*women (n = 16). All participants were asked to fill out a questionnaire measuring aggression levels (*Fragebogen zur Erfassung von Aggressivitätsfaktoren* (FAF); Hampel & Selg 1975) at both time points. Additionally, hormone levels were analyzed. Data analysis was conducted using IBM SPSS Statistics 24.

Results

Reactive/impulsive aggression scores increased significantly in trans*men between the two measured time points. Additionally, evidence was found that this increase might be a result of the exogenous administration of testosterone. Before the start of hormone replacement therapy, the transgender sample showed higher scores in self-aggression/depression as well as in aggression inhibition than cisgender people. Four months into the treatment, no difference was found in either self-aggression/depression or aggression inhibition between those two groups anymore. Interestingly, indications were found that the rise of estradiol levels in trans*women might have a protective effect on mental health, as correlations by trend were found between increases in this hormone and decreases in self-aggression and depression.

Conclusion

This longitudinal treatment study confirmed previous cross-sectional findings, which indicate that testosterone is associated with reactive/impulsive aggression. The exact mechanisms

behind this finding remain, however, unclear. Testosterone levels in an estimated biological male range cannot be the only explanation, as cis*men, who showed similar testosterone levels as trans*men at the second analyzed time point, do not report elevated aggression scores. Furthermore, higher scores on the self-aggression/depression scale for gender dysphoric people suggest a social and/or psychological cause, as there was no correlation with any analyzed hormones. As there is no longer a difference on the self-aggression/depression scale between the transgender and the cisgender sample at least 4 months into hormone replacement treatment, this gender affirming process might have a positive impact on trans*individuals lives and well-being. Further research which focuses on a possible protective effect of estradiol on mental health, must be conducted.

Zusammenfassung

Hintergrund und Ziel

Aggression ist ein sehr heterogener Begriff und bisherige Forschung zur Beziehung zwischen diesem Konstrukt und Geschlechtshormonen hat widersprüchliche Ergebnisse geliefert. Eine Stichprobe mit Personen, denen Gender Dysphorie diagnostiziert wurde, in ein Studiendesign aufzunehmen, birgt das große Potenzial, den Einfluss von sich drastisch verändernden Hormonlevels auf bestimmte biologische und/oder psychologische Gegebenheiten im Menschen zu untersuchen. Daher ist das Ziel dieser retrospektiven Studie, zum Verständnis über die Verbindung zwischen Geschlechtshormonen und reaktiver/impulsiver Aggression, sowie Selbstaggression/Depression und Aggressionshemmung beizutragen.

Materialien und Methoden

Die Gesamtstichprobe (n = 69) bestand aus vier Gruppen, die zu zwei verschiedenen Zeitpunkten (vor Beginn der Hormonersatztherapie und mindestens vier Monate nach deren Start) untersucht wurden: Trans*Männer (n = 25), Trans*Frauen (n = 17), Cis*Männer (n = 11) und Cis*Frauen (n = 16). Zu beiden Zeitpunkten wurde von allen Personen der *Fragebogen zur Erfassung von Aggressivitätsfaktoren* (FAF) (Hampel & Selg 1975) ausgefüllt. Zusätzlich wurden Hormonlevels analysiert. Die Datenanalyse wurde mit Hilfe des Statistikprogramms IBM SPSS Statistics 24 durchgeführt.

Resultate

Reaktive/Impulsive Aggressionsskalen nahmen lediglich bei Trans*Männern zwischen den beiden analysierten Zeitpunkten zu. Zusätzlich wurden Indikatoren gefunden, die darauf hindeuten, dass dieses Ergebnis womöglich auf die exogene Administration von Testosteron zurückgeführt werden kann. Vor Beginn der Hormonersatztherapie zeigte die Transgender-Stichprobe sowohl höhere Selbstaggressions-/Depressionswerte, als auch höhere Aggressionshemmung. Vier Monate nach Behandlungsbeginn waren diese Unterschiede nicht mehr nachweisbar. Interessanterweise wurden Hinweise dafür gefunden, dass der Estradiol-Anstieg bei Trans*Frauen einen schützenden Effekt auf ihre mentale Gesundheit haben könnte, da eine tendenziell signifikante Korrelation zwischen der Zunahme dieses Hormones und der Abnahme von Selbstaggression und Depression konstatiert werden konnte.

Diskussion

Diese Masterarbeit bestätigt vorhergegangene Studienergebnisse, die besagen, dass eine Verbindung zwischen Testosteron und reaktiver/impulsiver Aggression vorliegen könnte. Die exakten Mechanismen hinter diesem Resultat bleiben jedoch unklar. Testosteronlevels in einem biologisch männlichen Wertebereich können nicht die einzige Erklärung sein, da Cis*Männer, die bei beiden Zeitpunkten in diesem liegen, kein erhöhtes Aggressionspotenzial erkennen lassen. Zusätzlich kann angenommen werden, dass erhöhte Selbstaggressions-/Depressionswerte in der Transgender-Stichprobe vor Beginn der Hormonersatztherapie auf soziale und/oder psychologische Einflussgrößen zurückgeführt werden können, da keine Korrelation mit den analysierten Hormonwerten vorlag. Da es bei dieser Aggressionskategorie beim zweiten Zeitpunkt keinen Unterschied zwischen der Transgender- und der Cisgender-Stichprobe mehr gab, kann davon ausgegangen werden, dass die Hormonersatztherapie als ein Schritt im Genderaffirmationsprozess einen positiven Einfluss auf das Wohlbefinden von Trans*Individuen hat. Weitere Untersuchungen, die einen möglichen schützenden Effekt von Estradiol auf die mentale Gesundheit fokussieren, sollten zukünftig durchgeführt werden.

1 Introduction

This master's thesis aims to contribute to a better understanding of the effects of hormone replacement therapy on reactive/impulsive aggression[1], self-aggression/depression and aggression inhibition in gender dysphoric people. As physical transformations due to exogenous administered sex steroid hormones have already been well examined, the focus of this study lies on possible changes of the psychological construct of aggression in its different facets. It is important to shed light on each specific step in the gender affirmation process in order to give detailed information to clinicians, scientists and, above all, to directly affected gender dysphoric individuals.

Including gender dysphoric people, who are undergoing hormone replacement therapy, into a study design offers great advantages and potential. The influence of drastically changing hormone levels on certain biological or psychological phenomena can be observed directly in human beings, which is usually not the case in cisgender people because of ethical reasons.

Furthermore, this master's thesis serves as an interface between natural science and the humanities. There is a need to conduct interdisciplinary research in order to receive a comprehensive clinical and scientific understanding of gender dysphoria: "[T]he key challenge for gender researchers is to understand the ways in which biological predispositions become enacted through the social environment. This requires designs in which both biological and social processes are considered equally." (Berenbaum, Blakemore & Beltz 2011: 818).

The second chapter of this study illustrates relevant topics related to gender dysphoria – mainly from a medical point of view: terminology, epidemiology, etiology, comorbidity, diagnosis, and hormone replacement therapy as one part of the gender affirmation process.

The aim of the third chapter is to outline an elaborated theoretical introduction into the main and most widely acknowledged concepts of aggression as well as major experimental study results on the association between sex steroid hormones and aggression.

After the background information, study aim, protocol and hypotheses will be explained, followed by a sixth chapter, in which used materials and methods will be described more precisely. Study results and limitations will be presented and discussed in the following chapters and conclusive thoughts will be given to complete the thesis.

[1] In this study also often referred to as 'total aggression' as it is the sum of the constructs spontaneous aggression, irritability and reactive aggression in the used questionnaire (*Fragebogen zur Erfassung von Aggressivitätsfaktoren* (FAF), Hampel & Selg 1975).

2 Gender Dysphoria

2.1 Terminology

"... there are no clear and concise definitions. definitions are always a choice that includes in- and exclusion of ideas, concepts, even ways of living, existences ..."

(Baumgartinger 2017: 40)

Terminology in the field of gender nonconformity and gender dysphoria is rapidly evoloving (Coleman et al. 2012; Wylie et al. 2014). There are no universally established and finite classifications (Dargie, Blair, Pukall & Coyle 2014; Wentling, Windsor, Schilt & Lucal 2008). The following discussed definitions of field-related terms, which are in most cases widely accepted, but in some controversially discussed, are chosen only for the purpose of this document. It is acknowledged that in different communities, cultures and contexts a different understanding may prevail and that transgender people are a diverse group with various choices in self-identification. The usage of terms in this study follows the main criteria and claim of inclusion, and therefore an asterisk (*)[2], which symbolizes and represents the variety of trans*forms and -*lives (Baumgartinger 2017), is added most of the times.

In order to convey a basic understanding of transgender-related definitions, a brief historical overview of the evolvement of today's frequently used terms is given as follows. Before the 1950s the term *sex* was either used to describe men and women or sexual desire. During the same time period, *gender* was either used to refer to linguistic and grammatical gender or to sexuality between men and women (Muehlenhard & Peterson 2011). John Money, Joan Hampson and John Hampson (1955a; 1955b; 1957) were the first in the field of psychology to distinguish between a person's *sex* and *gender*. In their definition, *sex* describes physical characteristics, such as hormone values, chromosomes and gonadal sex as well as sex assignment and rearing. *Gender* is mostly used in the meaning of *gender role* or *gender identity*, which are concepts referring to a person's psychological characteristics (Muehlenhard & Peterson 2011). They provide following definition of *gender role*:

[2] The asterisk originates from computer sciences. The myth says that the usage of the asterisk in trans* was inspired by search engine functions in the Internet, in order to be most inclusive: "When you add an asterisk to the end of a search term, you're telling your computer to search for whatever you typed, plus any characters after." (Bussell 2012).

> *"[A]ll those things that a person says or does to disclose himself or herself as having the status of boy or man, girl or woman, respectively. It includes, but is not restricted to sexuality in the sense of eroticism. Gender role is appraised in relation to the following: general mannerisms, deportment and demeanor; play preferences and recreational interests; spontaneous topics of talk in unprompted conversation and casual comment; content of dreams, daydreams and fantasies; replies to oblique inquiries and projective tests; evidence of erotic practices and, finally, the person's own replies to direct inquiry."* (Money et al. 1955a: 302)

The distinction between *sex* and *gender* is still used today, although it has been greatly questioned from time to time, mostly by feminist scientists. Judith Butler, for example, challenged in her book *Gender Trouble* (1990) the assumptions of *sex* merely being given, being represented by a binary system only and representing objectively recognizable biological characteristics of an individual rather than also being socially and culturally constructed:

> *"Does sex have a history? Does each sex have a different history, or histories? Is there a history of how the duality of sex was established, a genealogy that might expose the binary options as a variable construction? Are the ostensibly natural facts of sex discursively produced by various scientific discourses in the service of other political and social interests? If the immutable character of sex is contested, perhaps this construct called 'sex' is as culturally constructed as gender; indeed, perhaps it was always already gender, with the consequence that the distinction between sex and gender turns out to be no distinction at all."* (Butler 2011, original 1990: 9f.)

Other researchers have also challenged either the assumption of *sex* as a given characteristic and emphasized its social construction (Rosenblum and Travis 2003) or the dichotomy of the category *sex* being represented by only male and female (Denmark, Rabinowitz & Sechzer 2016; Etaugh and Bridges 2017).

Most researchers in the field of medicine and psychology, however, use definitions of *sex* and *gender* similar to those suggested by Money and his colleagues, although there are many different interpretations of the terms. As this master's thesis mainly focuses on the medical and psychological side of gender dysphoria, working definitions of those fields will also be used in this study.

Therefore, *sex* in general will be defined as biological criteria for classification as female or male, such as chromosomal, hormonal, anatomical, and physiological aspects (Lorber & Moore 2007; Rosenblum and Travis 2003). It must, however, be emphasized that these criteria have to be understood as a result of social construction and the male-female binary

dichotomy of this definition is only justified in the specific context of the present study, as it focuses on the gender affirmation of either a male of a female identity. Furthermore, in this document, *sex assigned at birth* (sex listed on the birth certificate) replaces the term *biological sex,* which is focused on the individual's biological status (chromosomal, hormonal, gonadal, and genital) (Winter et al. 2016), because, particularly referring to transgender people, it seems more respectful and accurate as individuals are either identified as 'male' or 'female' at birth (Carabez et al. 2015) only by their external anatomy (genital appearance) (Transgender Equality Network Ireland n.d).

In this paper, *gender* will be defined as the psychological traits of masculinity, femininity or a non-binary group which develop through culture and socialization. In contrast to *sex*, which denotes biological or anatomical characteristics, *gender* points to social, psychological, or behavioral ones (definition on the basis of Rider 2005). Especially in societies with a strong emphasis on a binary male-female understanding of *gende*r, this term often comprises socioculturally contructed expectations and stereotypes ascribed to maleness and femaleness (Denmark et al. 2016; Etaugh & Bridges 2017; Markwick 2016; Unger 1979). *Gender stereotypes* are the result of cultural, societal, and time-dependent beliefs that people have about the characteristics mainly men and women should have and how they should act. If individuals (e.g. transgender people) do not fulfill those standards, they might face discrimination, hostility and rejection (Winter et al. 2016). Living up and fulfilling these prescriptions leads to performing those socially expected roles and to *doing gender*. These *gender roles/expressions/presentations* generally refer to the various ways in which individuals show their gender: through appearance, mannerism, clothing/style, behavior, interests, speech patterns, social interactions, etc. These expressions are often influenced by society, culture, and resultant gender stereotypes, as mentioned before (Fenway Health 2010; Markwick 2016; O'Neil, McWhirter & Cerezo 2008; Transgender Equality Network Ireland n.d.; Winter et al. 2016). *Doing gender* is conceptualized as "a routine accomplishment embedded in everyday interaction" (West & Zimmerman 1987: 125). The performative nature of *gender* is also emphasized by Butler: "[G]ender proves to be performative – that is, constituting the identity it is purported to be. In this sense, gender is always a doing […]." (ibid. 2011: 34, original 1990).

Gender identity describes the personal and subjective feeling of belonging to and self-identifying as male, female or a non-binary group. This identity does not have to correspond with the sex assigned at birth (Eckstrand, Ng & Potter 2016; Human Rights Campaign 2017;

Winter et al. 2016). People who identify with their sex assigned at birth are referred to as *cis*people* (and related expressions) or *non-gender-variant people (NGV)* (Carabez, Pellegrini, Mankovitz, Eliason & Scott 2015; Markwick 2016). Nowadays, the term *cisgender person* is preferred to *non-transgender* or *non-gender-variant people* because transgender people are not singled out as differing from 'normal and/or natural standards' (Fenway Health 2010). *Gender nonconformity/incongruence/variance* generally describes the gap between an individual's own experience of gender identity and the sex category assigned at birth. Furthermore, they can refer to gender expressions that do not conform to societal normative expectations (Coleman et al. 2012; Reisner, Radix & Deutsch 2016a; Winter et al. 2016). There are various ways to express nonconforming gender identities, for example *bigender* (more than one gender), *agender* (no gender), *genderfluid* (the feeling that gender fluctuates or is undefinable) (Eckstrand et al. 2016). *Genderqueer* includes all persons who do not self-identify within the traditional binary classification system of men and women (Transgender Equality Network Ireland n.d.). One study found that this term is the most commonly endorsed expression by people who do not identify with their sex assigned at birth (Kuper, Nussbaum & Mustanski 2012).

The following terms are more narrowly related to the field of gender dysphoria.

Gender Identity Disorder (GID) was used as a diagnosis in the DSM-IV-TR when a person has "(1) a strong and persistent cross-gender identification and (2) persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex, and the disturbance (3) is not concurrent with physical intersex[3] condition and (4) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning" (American Psychiatric Association 2000). The term *GID* was later removed and replaced by the term *Gender Dysphoria* to eliminate the negative connotation and possible resulting stigmatizing of the word *disorder* (Fenway Health 2010). *Gender dysphoria (GD)* is defined by the Diagnostic Statistical Manual of Mental Disorders - 5 (DSM-5) as "(1) a marked incongruence between one's experienced/expressed gender and assigned gender, of at least six months' duration, (2) [which] is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning." (American

[3] I*ntersexuality* and *disorders of sex development (DSD)* describe conditions in which the genitalia are atypically developed in relation to chromosomes or gonads. Both expressions have been strongly contested (Coleman et al. 2012; Transgender Equality Network Ireland n.d).

Psychiatric Association 2013: 452 f.). In this definition discomfort or distress is emphasized (Winter et al. 2016).

The discussions surrounding the term *transsexual* are often very controversial, heated and even offensive to many people (Fenway Health 2010). It is important to emphasize that this term does not imply any indication of sexual orientation. It is used to describe individuals who identify with gender roles, expectations and expressions 'opposite' to the sex assigned to them at birth (O'Neil et al. 2008) and therefore the term perpetuates a binary view of gender (Transgender Equality Network Ireland n.d.). They may or may not seek hormone replacement therapy and/or gender affirmation surgery (Markwick 2016). *Transgender* serves as an umbrella term which includes individuals whose gender identity, gender expression or anatomy does not correspond with their sex assigned at birth and more generally with (mainly Western) traditionally and stereotypically cultural and societal norms of the binary gender categories man and woman[4] (Carabez et al. 2015; Maguen, Shipherd & Harris 2005; Markwick 2016; O'Neil et al. 2008). There is no finite understanding of these terms: particularly the term *trans*(people/person)* is more broadly defined, also including for example intersex people, while some groups define the transgender terms more narrowly by excluding certain individuals, for example *true transsexuals*[5] (Fenway Health 2010; GayAlliance 2015).

*Trans*man* or *transgender man* refers to a person whose sex assigned at birth is female but who identifies and/or presents as male; *trans*woman* or *transgender woman* refers to a person whose sex assigned at birth is male but who identifies and/or presents as female (Winter 2012). Those persons may or may not seek gender affirming medical treatment (Markwick 2016). A person who identifies as belonging to the category *Female-to-Male (FtM)* shows the characteristics of trans*men, one who identifies as belonging to the category *Male-to-Female (MtF)* shows the characteristics of trans*women. Both usually have received or are in the process of receiving gender affirming medical treatment. Those expressions, however, are rejected by some transgender people because they see its focus on the transitioning process from one gender to the other, which they deny (Fenway Health 2010).

[4] The seemingly including term *transgender* has, however, also been criticized widely, mainly in the trans*community (for detailed information see: Rawson & Williams 2014).

[5] In older writings, the term *true transsexuals* referred only to individuals who have changed or are in the process of changing their sex assigned at birth to correspond with their individually felt and experienced gender identity (Fenway Health 2010).

Transition generally describes the process that individuals go through as they adopt certain characteristics (e.g. gender expression, physical appearance) aligned with their gender identity. Most people prefer the term *gender affirmation* or *gender confirmation*, because they lay emphasis on the fact that they have always had the gender they identify with and they do not transition from one gender identity to another (Fenway Health 2010). Usually, *gender affirmation* is a time consuming process, in which various changes might occur: social gender affirmation (e.g. change of name, preferred pronoun is introduced, 'coming out' to family, friends, co-workers, etc.), psychological gender affirmation (e.g. felt gender is validated and respected, internalized stigma and transphobia is resisted), medical gender affirmation (e.g. pubertal blockers, hormone replacement therapy, gender confirmation surgery), legal gender affirmation (e.g. legal name change, legal gender marker change, new identification documents), and gender role/expression affirmation (e.g. interests/activities, change of appearance: style, dress, hair, etc.) (Coleman et al. 2012; Reisner et al. 2016a; Transgender Equality Network Ireland n.d.; Winter et al. 2016). All of these changes – especially medical gender affirmation – can, but most not necessarily occur.

Hormone Replacement Therapy (HRT)[6] describes the process of taking hormones which alter secondary sex characteristics towards the desired physical appearance (Transgender Equality Network Ireland n.d).

Today, the terms *sex reassignment surgery (SRS)* and *sex realignment surgery (SRS)* have broadly been replaced by *gender affirmation surgery (GAS)* and *gender confirmation surgery (GCS)*, as they better represent the experiences of gender dysphoric people. *GCS* and *GAS* describe various procedures which alter an individual's physical appearance (primary and/or secondary sex characteristics) in order to align their bodies with their gender identities (Coleman et al. 2012; Fenway Health 2010; Transgender Equality Network Ireland n.d.).

[6] *HRT* will be discussed in greater detail in chapter 2.5.

2.2 Epidemiology

Statistics on the estimated prevalence of gender dysphoria differ widely due to various factors, such as cultural differences (e.g. stigmatization, definition of gender-nonconforming people, the (in)visibility of this phenomenon in each country's scientific field/ the mere existence of epidemiology studies/ the mere occupation of science with this phenomenon) (Coleman et al. 2012; Jobson, Theron, Kim & Kaggwa 2012), the focus on easily accessible individuals (e.g. transgender people affected by gender dysphoria seeking professional GA-related care) (Reisner et al. 2016b; Zucker & Lawrence 2009), definition of *transgender* and related terms and resulting inclusion criteria (e.g. HRT, GCS/GAS, consultation of a specialized center, etc.) (Coleman et al. 2012; Collin, Reisner, Tangpricha & Goodman 2016; Deutsch 2016; Gates 2011; Meier & Labuski 2013), and data collection methodology (Coleman et al. 2012; Gates 2011; Zucker 2017). Therefore, different data sets cannot be directly compared, and the number of reported cases are considered to be minimum estimates (Coleman et al. 2012; Olyslager & Conway 2007; Zucker 2017), even though recent studies suggest an increase in gender dysphoric and transgender self-identified people during the last few decades (Zucker 2017; Zucker, Lawrence & Kreukels 2016). Considering clinic-based studies only, gender dysphoria can still be considered a rare and uncommon diagnosis, although people affected by this phenomenon become more and more visible (e.g. general in public, in professional health care and science circles and in the mass media, especially TV, cinema, websites, blogs, online discussion groups, etc.) (Bouman, de Vries & T'Sjoen 2016a; Zucker 2017; Zucker & Lawrence 2009).

By applying alternative statistical methods, it is possible to estimate population-based prevalence numbers which state an increase of 10- to 100-fold compared to previously reported clinic-based studies (Deutsch 2016; Meerwijk & Sevelius 2017; Olyslager & Conway 2007). In a meta-regression of population-based probability samples, Meerwijk and Sevelius (2017) estimated a prevalence of 390 transgender persons per 100,000 adults in the US in 2016, which is significantly higher than all the clinical-based studies to this date and according to many scholars and professionals more realistic (ibid. 2017).

The following table is a summary of the three most recent review articles (Arcelus et al. 2015, Collin et al. 2016 and Zucker 2017), supplemented by two reviews focusing solely on studies estimating the gender-nonconforming prevalence through population-based samples (Deutsch 2016 and Meerwijk & Sevelius 2017). This overview excludes the prevalence of transgender status in children, because firstly, this study focuses on an adult and adolescent population

only and secondly, the definition of gender dysphoria for children is different to the one for adults and adolescents. The studies are ranked by the year of publication so that changes over time are visible. Together, those reviews analyze almost 40 articles, which span over 47 years and were conducted in more than 20 countries. Besides the shown prevalence and the MtF:FtM ratio, the importance of the *case definition* and the *sample* section must be emphasized. As Collin et al. (2016) stated, prevalence data depends significantly on the included participants, e.g. on inclusion criteria (ibid. 2016). Articles which focused on transgender persons requesting or receiving gender affirmation therapy estimate a prevalence of 9.2 transgender persons per 100,000 adults (trans*women: 12.5, trans*men: 5.1). Those with focus on transgender-specific diagnoses 6.8 per 100,000 (trans*women: 5.8, trans*men: 2.5) and studies operating with the inclusion criteria *transgender identity* show a highly significant prevalence-increase to 871.2 per 100,000 (trans*women: 846.2, trans*men: 1557.5) (ibid. 2016). The sample section gives information whether the study was conducted with a clinic-based or a population-based sample. As stated previously, the advantages of the population-based sample strategy outweigh those of the clinic-based one (Deutsch 2016; Meerwijk & Sevelius 2017).

Table 1: Prevalence of gender dysphoria in adolescents and adults

Reference	Year of public-cation	Time period studied	Country	Case definition	Prevalence (per 100,000)			MtF:FtM ratio	Sample
					total	MtF	FtM		
Pauly	1968	n/a	USA	Request for SRS	0.40	1	0.25	4:1	Clinic-based
Wålinder	1968	n/a	Sweden	"transsexual" diagnosis	1.42	1	0.25	2.8:1	Clinic-based
Wålinder	1971	1967-1970	Sweden	"transsexual" diagnosis	0.45	0.44	0.44	1:1	Clinic-based
Hoening & Kenna	1974	1958-68	England and Wales	"transsexual" diagnosis	1.92	2.94	0.92	3.2:1	Clinic-based
Ross, Wålinder, Lundströ & Thuwe	1981	1979-1981	Australia	"transsexual" diagnosis	2.40	4.16	0.66	6.1:1	Clinic-based
O'Gorman	1982	1968-1982	Northern Ireland	"transsexual" diagnosis	1.92	2.85	1	2.85:1	Clinic-based
Eklund, Gooren & Bezemer	1988	1976-1980	The Netherlands	Receipt of HRT	1.22	2.22	0.5	3:1	Clinic-based
		1976-1983	The Netherlands	Receipt of HRT	1.58	3.84	1	3:1	Clinic-based
		1976-1986	The Netherlands	Receipt of HRT	2.77	5.55	1.85	3:1	Clinic-based
Godlewski	1988	1974-1978	Poland	"transsexual" diagnosis	n/a	n/a	n/a	1:5.5	Clinic-based
Tsoi	1988	until 1986	Singapore	Request for SRS	23.60	35.2	12	3:1	Clinic-based
Bakker, Kesteren, Gooren & Bezemer	1993	1976-1990	The Netherlands	Receipt of HRT	4.42	8.4	3.28	2.5:1	Clinic-based
Stefansson, Lindal, Björnsson & Guômundsdóttir	1994	1931-1986	Iceland	"transsexual" diagnosis	100	n/a	n/a	n/a	Clinic-based
Landén, Wålinder & Lundström	1996	1972-1996	Sweden	Request for SRS	3.42	4.03	2.83	1.4:1	Clinic-based
Van Kesteren, Gooren & Megens	1996	1975-1992	The Netherlands	Receipt of HRT	8.05	12.11	4.3	3:1	Clinic-based

Reference	Year of public-cation	Time period studied	Country	Case definition	Prevalence (per 100,000)			MtF:FtM ratio	Sample
Weitze & Osburg	1996	1981-1990	West Germany	"transsexual" diagnosis	2.10	2.38	0.96	2.3:1	Clinic-based
Wilson, Sharp & Carr	1999	1998	Scotland	GD	4.79	7.82	1.92	4:1	Clinic-based
Garrels et al.	2000	1964-1998	Germany	"transsexual" diagnosis	n/a	n/a	n/a	1.2:1 (last 4 years)	Clinic-based
Olsson & Möller	2003	1972-2002	Sweden	Request for SRS	5.91	7.34	4.54	1.61:1	Clinic-based
Esteva et al.	2006	1999-2004	Spain (Andalucía)	GID diagnosis	n/a	10.3	6.5	1.64:1	Clinic-based
Gómez-Gil et al.	2006	1996-2004	Spain (Cataluña)	ICD-10 F64.0 (transsexualism)	3.88	4.75	2.07	2.6:1	Clinic-based
De Cuypere et al.	2007	1985-2006	Belgium	SRS receipt	4.28	7.75	2.95	2.43:1	Clinic-based
Okabe et al.	2008	1997-2005	Japan	DSM-IV GID	n/a	0.9	n/a	1.5:1	Clinic-based
Veale	2008	2008	New Zealand	Self-identity as transgender	15.7	27.5	4.4	6:1	Population-based
Vujovic, Popovic, Sbutega-Milosevic, Djordjevic & Gooren	2009	1987-2006	Serbia	Request for SRS	2.25	2.23	2.27	1:1	Clinic-based
Almeida, Johnson, Corliss, Molnar & Azrael	2009	2006	USA	Self-reported transgender and/or gender-nonconforming status	1647	n/a	n/a	n/a	Population-based
Ahmadzad-Asl et al.	2010	2002-2009	Iran	GID diagnosis DSM-IV-TR	0.7	0.69	0.74	0.96:1	Clinic-based
Lai, Chiu, Gadow, Gau & Hwu	2010	2003/04	Taiwan	Self-reported gender dysphoria	4500	1900	7300	1:3	Population-based
Caldarera & Pfäfflin	2011	1992-2008	Italy	SRS receipt	0.9	1.5	0.4	3.39:1	Clinic-based
Gates	2011	2003-2009	USA (California)	Self-identity as transgender	100	n/a	n/a	n/a	Population-based
Baba et al.	2011	2003-2010	Japan	GID diagnosis ICD-10 and DSM-IV	n/a	3.97	8.2	1:2	Clinic-based

Reference	Year of public-cation	Time period studied	Country	Case definition	Prevalence (per 100,000)			MtF:FtM ratio	Sample
Conron, Scott, Stowell & Landers	2012	2007-2009	USA (Massachusetts)	Self-identity as transgender	500	n/a	n/a	n/a	Population-based
Esteva et al.	2012	1999-2011	Spain	Request for SRS	10.0	n/a	n/a	1.9:1	Clinic-based
Blosnich et al.	2013	2002	USA (VA system)	ICD-9 codes 302.85 (GID) or 302.6 (GID NOS)	12.5	n/a	n/a	n/a	Clinic-based
		2011	USA	ICD-9 codes 302.85 (GID) or 302.6 (GID NOS)	22.9	n/a	n/a	n/a	Clinic-based
Clark et al.	2014	2012	New Zealand	Self-identity as transgender	1175	n/a	n/a	n/a	Population-based
Dhejne, Öberg, Arver & Landén	2014	1960-2010	Sweden	Request (and receipt) of SRS	16.67	11.57	6.64	1.6:1	Clinic-based
Judge, O'Donovan, Callaghan, Gaoatswe & O'Shea	2014	2005-2014	Ireland	DSM-IV GID DSM-V GD	6.77	9.84	3.61	2.7:1	Clinic-based
Kauth et al.	2014	2006-2013	USA (VA system)	ICD-9 codes 302.85 (GID), 302.6 (GID NOS), 302.5 (transsexualism)	32.9	n/a	n/a	n/a	Clinic-based
Kuyper & Wijsen	2014	2013	The Netherlands	Self-reported gender dysphoria	n/a	600	200	3:1	Population-based
Reisner et al.	2014	2010	USA	Self-identity as transgender	330	380	310	n/a	Population-based
van Caenegem et al.	2015	2011-2012	Belgium (Flanders)	Self-reported "Gender nonconformity"	722	671	552	1.2:1	Population-based

Table adapted from Arcelus et al. (2015), Zucker 2017, Collin et al. (2016), Deutsch (2016), and Meerwijk & Sevelius (2017).

Legend: n/a = not applicable, SRS = sex reassignment/realignment surgery, HRT = hormone replacement therapy, GD = gender dysphoria, GID = gender identity disorder, VA = veterans affairs, GID NOS = gender identity disorder not otherwise specified

Prevalence in clinic-based studies ranges from 0.40 (Pauly 1968) to 32.9 (Kauth et al. 2014) and in one exception up to 100 (Stefansson et al. 1994) transgender persons per 100,000 adults. Compared to population-based studies, in which the minimum prevalence is estimated at 100 (Gates 2011) transgender persons per 100,000 adults (with one exception: 15.7, Veale 2008) and the highest number at 1647 (Almeida et al. 2009), the big gap between those two analysis methods becomes clear. It can also be seen that the numbers of population-based studies are on the rise: there were no such studies before 2008 and since then about half of them are based on population sampling (Almeida et al. 2009; Clark et al. 2014; Conron et al. 2012; Gates 2011; Kuyper & Wjisen 2014; Lai et al. 2010; Reisner et al. 2014; Van Caenegem et al. 2015; Veale 2008). Overall, table 1 also shows the previously stated prevalence-increase over the years. Furthermore the table shows the different ratios of trans*women to trans*men, reaching from 1.2:1 (Garrels et al. 2000; Van Caenegem et al. 2015) to 6.1:1 (Ross et al. 1981). In almost all presented studies, except for four in which more trans*men were reported (Ahmadzad-Asl et al. 2010; Esteva et al. 2012; Godlewski 1988; Lai et al. 2010) trans*women seem to be more common. However, almost all authors reported that they included more assigned males in their study, which might also explain the larger prevalence of trans*women found in most studies. Two studies found an even ratio of 1:1 (Vujovic et al. 2009; Wålinder 1971).

2.3 Etiology

Gender identity is a complex construct and to this day there is no solid evidence of consistent etiologic processes in the development of gender dysphoria. Therefore, different theories must be considered: behavioral, environmental/cultural, psychosocial and biological causes have been identified to play a role in the development of gender identity in general and specifically of gender dysphoria, though most evidence originates from the field of biology (e.g. genetic, endocrinal, and neuroanatomical factors) (Saraswat, Weinand & Safer 2015). So far, causal aspects have been studied separately, an investigation of a possible nature – nurture interaction, though recognized, is lacking (Steensma, Kreukels, de Vries, & Cohen-Kettenis 2013; Winter et al. 2016). The analysis of biological explanations for gender dysphoria must, however, be viewed as critical and highly controversial. On the one hand, the focus on biological explanations of gender dysphoria may help to increase acceptance and understanding of transgender individuals as they show that gender identity is not a choice (Olson-Kennedy et al. 2016). On the other hand, critical voices raising concern about possible biologistic generalizations of socio-cultural concepts, such as gender, cannot be ignored

(Westbrook & Schilt 2014). Therefore, the following studies and their results must be handled cautiously. Another important aspect to consider is that the following findings can only be regarded as correlates; they do not imply a causal relationship between transgenderism/gender dysphoria and other categories, such as behavior, environment, culture, biology, psychosociology, etc.

2.3.1 Behavioral correlates

It is assumed that if preschool children diagnosed with (extreme) gender dysphoria show a high degree of atypical gender behavior, gender dysphoria persistence into adolescence and/or adulthood may be more likely (Drummond, Bradley, Peterson-Badali & Zucker 2008; Wallien & Cohen-Kettenis 2008). This is not to say that gender dysphoria in childhood automatically leads to remaining gender dysphoria: outcome studies show that about 15% of children diagnosed with GD remain gender dysphoric during their lifespan (Steensma, Biemond, de Boer & Cohen-Kettenis 2011), which emphasizes the probability of previous findings.

2.3.2 Environmental/cultural correlates

The fraternal birth order effect (Zucker et al. 1997) describes the phenomenon in adult transgender women to be born later than their male siblings and to have more brothers than sisters. Furthermore, the odds that a trans*woman is sexually attracted to men increase by as much as 40% for each older brother, whereas having older sisters does not influence these odds (Green 2000a). These studies also show a common cultural mechanism in this aspect of transgenderism (or the closest equivalents in non-Western cultures), as studies from Western societies (Canada/The Netherlands (Zucker et al. 1997), Canada (Blanchard & Sheridan 1992), The Netherlands (Blanchard, Zucker, Cohen-Kettenis, Gooren & Bailey 1996), England (Green 2000a), Spain (Gómez-Gil et al. 2011)), Singapore (Tsoi, Kok & Long 1977), Polynesia (Poasa, Blanchard & Zucker 2004; VanderLaan & Vasey 2011; Vasey & VanderLaan 2007), and South Korea (Zucker, Blanchard, Kim, Pae & Lee 2007) were conducted. Those findings could also be replicated in an early-onset gender dysphoric children and adolescent population in the Netherlands (Schagen, Delemarre-van de Waal, Blanchard & Cohen-Kettenis 2012). There is no proven explanation for the described phenomena[7]. Furthermore, it is important to look at transgenderism in the context of each

[7] The most commonly used explanation is the maternal immune hypothesis which suggests that the mother's immune system recognizes male-specific molecules when being pregnant with or giving birth to a male baby. As a reaction to these foreign molecules it produces anti-male antibodies. These

culture individually. Many Asian countries, for example, do not have the same (binary) gender distinctions as the West does (Elischberger, Glazier, Hill & Verduzco-Baker 2018). This may influence a community's acceptance that an individual's male or female status is not rigid, but can change over one's lifetime. Therefore, many gender dysphoric people are transitioning and living more openly in a social and cultural context, in which they can usually find practical information and social and/or emotional support (Winter 2009). It is, however, important to remark, that transgender lives in societies, which officially acknowledge a third gender category, should not be romanticized. More than often, they face extreme social exclusion as well as physical, verbal and sexual abuse, like the hijra in Bangladesh (Khan et al. 2009).

2.3.3 Psychosocial correlates

Older literature mainly focused on psychosocial factors as the main or even the only basis for gender nonconforming behavior and gender dysphoria. Aspects such as a symbiotically intense relationship between mothers and sons (Stoller 1974; Stoller 1976; Stoller 1994), separation anxiety and fear of loss (Coates, Friedman & Wolfe 1991; Coates & Person 1985), parental absence (Stoller 1974; Stoller 1976; Stoller 1994), parental psychological characteristics and/or problems (Zucker & Bradley 1995), traumatic experiences (Meyer & Dupkin 1985) and parental tolerance or reinforcement of gender nonconforming behavior (Green 1974; Green 1987) were considered to be reasons for the development of gender dysphoria. To this date no solid supporting evidence for these theories has been found (e.g. Stevens, Golombok, Beveridge & Study Team 2002; Wallien & Cohen-Kettenis 2008). More recent theories take multiple and cumulative factors into consideration, such as the psychodynamic theory of Zucker and Bradley (1995), in which general child and environmental/parental factors play a key role in promoting the development of gender dysphoria during critical periods in early childhood. Especially parental psychopathology, family (dys)function and children's insecurity and/or anxiousness are believed to enhance a child's uncertainty regarding the own gender identity (ibid. 1995). These hypotheses have been tested several times, resulting in ambiguous outcomes (e.g. Cohen-Kettenis, Owen, Kaijser, Bradley & Zucker 2003; Marantz & Coates 1991; Rekers, Mead, Rosen & Brigham 1983; Wallien & Cohen-Kettenis 2008). The majority of studies focus on gender dysphoria development in children. As gender identity starts to develop very early in childhood (Egan &

Y-linked minor histocompatibility antigens (H-Y antigens) are believed to affect the fetal brain (Blanchard 2001).

Perry 2001; Martin, Ruble & Szkrybalo 2002) retrospective studies focusing on psychosocial factors which may contribute to the development of this phenomenon in adults should be interpreted with caution (Zucker et al. 2016).

2.3.4 Biological correlates

Research into possible biological causes of gender dysphoria covers different areas: endocrinology with a strong emphasis on prenatal hormones, genetics, and neuroanatomy, which will be discussed as follows.

Genetics

There is only limited literature on the genetic basis of transgenderism, but the interest in these biological mechanisms, besides the role of prenatal exposure to gonadal hormones, is increasing (Ngun, Ghahramani, Sánchez, Bocklandt & Vilain 2011). Two larger studies focusing on the relatives of transgender persons suggest a higher chance of developing or already having gender dysphoria for siblings of people affected by this phenomenon than the general population (Green 2000b; Gómez-Gil 2010). Furthermore, the probability is higher for brothers than sisters of transgender persons and for siblings of trans*women than trans*men (Gómez-Gil 2010). There is also some indication of parent-child pairs concordant for gender dysphoria (Green 2000b). The increased likelihood for gender dysphoria development in families with at least one member already being gender dysphoric is also emphasized by twin studies, which have the potential to disentangle the roles of genetic and environmental influences in gender dysphoria development (Gómez-Gil 2010). There is a strong heritability among twins with transgender identity (Bailey, Dunne & Martin 2000; Coolidge, Thede & Young 2002). Furthermore, monozygotic twins are more likely to be susceptible for transgenderism than dizygotic twins (Heylens et al. 2012; Knoblauch, Busjahn & Wegener 2007; Sadeghi & Fakhrai 2000; Van Beijsterveldt, Hudziak & Boomsma 2006; Veale, Clarke & Lomax 2010). Although the potential contribution of genetic factors to transgender identity development is supported by this literature, there is also some contradictory indication (Segal 2006). The discordant transgender identity prevalence among monozygotic twins is still higher than for those who are concordant (Saraswat et al. 2015) and so far it is not possible to separate genetic from environmental influences due to study design flaws (Ngun et al. 2011). Overall, the exact role of genetic factors in the development of gender identity and transgenderism remains unclear and needs further study (Steensma et al. 2013).

A few studies found associations between polymorphisms in genes related to sex steroid receptors or sex steroid metabolism and transgenderism, but results are very inconsistent (Steensma et al. 2013). It was reported that trans*women differed from controls with respect to the mean length of the estrogen receptor beta gene (ERβ) repeat polymorphism, although most transgender results were still within normal range (Henningsson et al. 2005). Another study failed to replicate these results, but instead found some indication for a greater likelihood for reduced androgen sensitivity in trans*women as they differed on the androgen receptor gene (AR) (Hare et al. 2009). Again, another study with a larger sample could not confirm those findings (Fernández et al. 2014a). There was a link to polymorphism of the ERβ gene in trans*men (Fernández et al. 2014b). Furthermore, polymorphisms in the aromatase or CYP17 gene which influences the metabolism of sex hormones and is associated with elevated plasma levels of both estrogen and testosterone (T)[8] (Veale et al. 2010) was carried by more trans*men than female controls (Bentz et al. 2008). A recent study found that allele and genotype frequencies of the Estrogen Receptor α Gene (ESR1) for the polymorphism *Xba*I differed significantly between trans*men and cis*female controls (Cortés-Cortés et al. 2017). There were no detectable genetic variants on the sex-determining region of the Y-gene (SRY) (Hengstschläger et al. 2003) and no polymorphism association in the gene coding for 5-alpha reductase in transgender samples (Bentz et al. 2008). Contrary to the results described so far, another study found no association between sex steroid receptor genes and transgender identity at all (Ujike et al. 2009). Veale et al (2010) emphasize that care is needed in interpreting findings of positive genetic studies: though statistically significant, a large proportion of cisgender people also show these gene patterns and many transgender persons do not (ibid. 2010). Furthermore, the analyzed samples in the above reported studies were of relatively small sizes (Saraswat et al. 2015). Therefore, it can only be concluded that the likelihood of a transgender identity is increased by genetic determinants of hormones (Veale et al. 2010).

Prenatal hormones

Sexual differentiation is generally ascribed to exposure of androgenic hormones in the fetus (Bocklandt & Vilain 2007). If male-typical prenatal androgen levels are present during pregnancy, masculine phenotypes are the result, if this is not the case, feminine phenotypes occur (Zucker et al. 2016). Evidence strongly points to sex-atypical androgen levels among

[8] Testosterone is a sex steroid hormone of the androgen group secreted by the hypothalamic-pituitary-gonadal axis (Denson, Mehta & Tan 2013). Through various intermediate steps, it is derived from cholesterol in a process called steroidogenesis (Waterman & Keeney 1992).

persons with gender-variant identities (Nelson 2005) which influence the brain and lead to atypical sexual differentiation (Garcia-Falgueras & Swaab 2010). Since time windows for sexual differentiation of the genital (first two months of pregnancy) and for the brain (second half of the pregnancy) are not overlapping, they can be influenced separately and therefore exposure to atypical levels of prenatal hormones may influence the brain but not the body and in extreme cases lead to gender dysphoria (Bao & Swaab 2011; Garcia-Falgueras & Swaab 2010; Zucker et al. 2016). Persons who are assigned females at birth but who were exposed to male-typical prenatal androgen levels are more likely to be gender dysphoric (Veale et al. 2010). Females affected by congenital adrenal hyperplasia (CAH), an inherited disorder in which the adrenal gland produce excessive amounts of androgens, show an increased, albeit modest probability and a higher prevalence of gender dysphoria than the general population (Dessens, Slijper & Drop 2005; Meyer-Bahlburg, Dolezal, Baker, Ehrhardt & New 2006; Zucker et al. 1996) and a reduced satisfaction with the assigned female sex at birth (Hines, Brook & Conway 2004). Despite the replicated evidence of the association between gender dysphoria and CAH, prenatal androgenization should be understood as a predisposition for developing a male gender identity, not a determinant since the vast majority of assigned females suffering from CAH identify with this category (Berenbaum & Bailey 2003; Dessens et al. 2005; Zucker et al. 1996) and since there are also trans*men without a history of prenatal androgen exposure (Gooren 2006). Furthermore, trans*women develop a female identity despite a prenatal androgen exposure (Gooren & Cohen-Kettenis 1991). Trans*men show an increased prevalence in the hyperandrogenic disorder polycystic ovarian syndrome (PCOS) (Baba et al. 2006), in most cases resulting in hyperandrogenemia (Alexiou et al. 2017; Mueller et al. 2008).

Neuroanatomy

The above mentioned theory which purports that sexual differentiation of the genitals and of the brain take place at different time zones during pregnancy and can therefore be influenced independently (Bao & Swaab 2011; Garcia-Falgueras & Swaab 2010; Zucker et al. 2016), is also supported by neuroanatomical and functional imaging studies. These studies aim to find out whether the brains of gender dysphoric persons show more resemblance to their experienced gender identity than their assigned sex at birth (Kreukels & Guillamon 2016; Zucker et al. 2016). Conducting such research, it is important to state whether brain dimorphic structures originate from hormonal or genetic factors, or both (McCarthy, Arnold, Ball, Blaustein & De Vries 2012). Furthermore, it must be considered that environmental factors

(e.g. nutrition, stress, abuse) may also have an influence on brain structure and function (Wachs, Georgieff, Cusick & McEwen 2014).

a) Neuroanatomical correlates

Researchers found a sexually dimorphic nucleus (SDN) in the preoptic area (POA) of the human hypothalamus. In men, this nucleus is larger and contains more cells than in the female brain (Swaab & Fliers 1985). This region is believed to play a role in the neural control of endocrine functions (Hofman & Swaab 1989). Furthermore, sexually dimorphic structures were found in the central subdivision of the bed nucleus of the stria terminalis (BSTc) of the hypothalamus in size as well as in neuron numbers (Kruijver et al. 2000; Zhou, Hofman, Gooren & Swaab 1995). Neither one of these structures was influenced by alterations in hormone levels during adulthood. Comparing the BSTc of a transgender and a cisgender sample, studies found that the number of neurons in the trans*women's brain was similar to those in cis*women and the one in trans*men similar to cis*men's brain. These findings support the theory that a neurobiological basis might be an explanation for gender dysphoria (Kruijver et al. 2000; Zhou, Hofman, Gooren & Swaab 1995). Contrary to this argumentation stands the fact that sex dimorphic structures in the BSTc only start to develop until well into adulthood (Chung, De Vries & Swaab 2002), but for the vast majority of transgender persons, feelings of gender dysphoria begin early in childhood (Gooren 2006). Another aspect that must be considered is evidence suggesting that childhood environmental and psychosocial factors, such as stress and abuse, influence brain structure, including the hypothalamus (Kaufman, Plotsky, Nemeroff & Charney 2000; Teicher, Tomoda & Andersen 2006). So far, it is not clear what functional implications these dimorphic structures in the BSTc might have (Gooren 2006). However, it is interesting that this region expresses androgen, estrogen and progesterone receptors and that there seems to be an association between this hypothalamic structure and the regulation of female reproductive and maternal behavior in animals (Swaab, Chung, Kruijver, Hofman & Hestiantoro 2003).

Another hypothalamic structure with sexually dimorphic characteristics that has been found is the interstitial nucleus of the anterior hypothalamus nuclei 3 (INAH-3) (Byne et al. 2001). Postmortem examinations of transgender persons' brains support these findings: their INAH-3 neuron volume matched that of their gender identity and not their birth-assigned sex (Garcia-Falgueras & Swaab 2008). This has also found to be true in the corpus collosum at the midsaggital plane (Yokota, Kawamura & Kameya 2006).

There is also some indication that the hypothalamic microstructure of trans*men shows neuroplastic adaptations towards male proportions during HRT. Significant decreases in the mean diffusity in the lateral hypothalamus were significantly associated with increases in T levels due to HRT (Kranz et al. 2017).

Volumes in gray matter tissue, which mainly consists of neuronal cell bodies, were largely concordant between non-androphilic[9] trans*women and cis*men (Luders et al. 2009; Savic & Arver 2011). Gray matter volumes in several cortical regions in androphilic trans*women however were reportedly higher than in cis*women and trans*men (Simon et al. 2013). Overall, trans*women also showed similar cortical thickness (CTh) to cis*women (Zubiaurre-Elorza et al. 2012) and higher CTh than control men (Luders et al. 2012).

In white matter structure, which mainly contains myelinated nerve fibers (Zucker et al. 2016), non-androphilic trans*women differed significantly from control men and control women (Rametti et al. 2011). Similarly, another study showed that mean diffusivity values in both non-androphilic and androphilic trans*women were increased compared to cis*men and significantly decreased mean diffusivity values in trans*men compared to control women (Kranz et al. 2014). A structural connectivity study found decreased hemispheric connectivity ratio in subcortical/limbic regions in trans*women compared to both cis*males and cis*females, which seemed to be related to an increased interhemispheric lobar connectivity. Compared to cis*men, cis*women and trans*women, trans*men showed decreased intra-hemispheric connectivity between the right subcortical/limbic and right frontal and temporal lobes (Hahn et al. 2014).

[9] Commonly, description of sexual orientation of gender dysphoric people is complex (Galupo, Henise & Mercer 2016). Due to frequent misuse, it must be emphasized that *sexual orientation* is not the same as *gender identity* and distinct from other gender-related terms such as gender expression, etc (Transgender Equality Network Ireland n.d.; Winter et al. 2016). *Sexual orientation* refers to an individual's physical/sexual, emotional or romantic attraction to another person's gender (Carabez et al. 2015). In gender dysphoric people, it is often used with reference to an individual's natal sex, resulting in the use of the terms homo- and heterosexual (Smith, Junger, Derntl & Habel 2015). This understanding must be seen as highly controversial as it does not reflect the person's own gender-identification. Therefore, the terms *(exclusive) androphilia* and *(exclusive) gynephilia* are often preferred in scientific research. *Androphilia* describes the sexual attraction to adult males (cisgender men), whereas *gynephilia* means being sexually attracted to adult females (cisgender women) (Nuttbrock & Hwhang 2016; VanderLaan, Vokey & Vasey 2013; Vasey & VanderLaan 2007). There is the option to add the expression *exclusive* to both terms when only attracted to cisgender men or women (Hwahng & Nuttbrock 2014).

b) Functional imaging

While smelling odorous steroids, untreated non-androphilic trans*women showed a female-like hypothalamic activation pattern (Berglund, Lindström, Dhejne-Helmy & Savic 2007).

Brain patterns expressed by both trans*women and trans*men while viewing erotic and non-erotic interactions of male-female couples are associated with dimorphic genital representation (tegmental area) and social exclusion, conflict monitoring and punishment adjustment (anterior cingulate cortex) and therefore could be considered as a brain signature of the psychosocial distress accompanying gender dysphoria (Ku et al. 2013). Furthermore, trans*women showed brain response patterns similar to cis*women while viewing erotic videos (Gizewski et al. 2009).

As cis*men and -women differ in voice gender perception (Junger et al. 2013), there is evidence that transgender persons might have an intermediate position between those two groups: Neural activation in trans*women's brain during perception of female and male voices differed from both cis*male and -female control groups (Junger et al. 2014).

Differences in trans*women's and control male's brain activation were also shown during a visuospatial task (e.g. mental rotation). They remained stable during HRT (Schöning et al. 2010).

There was no significant brain activation difference found between gender dysphoric persons and control groups in verbal fluency tasks (Soleman et al. 2013).

During positive affective image processing, brain activation of trans*men differed from those of cis*women (Soleman et al. 2014).

Furthermore, asymmetry in the serotonin transporter system, which influences affective state underlying brain functions, responsible e.g. for emotional processing, was found: cis*men show – in contrast to trans*women and cis*women – a strong rightward serotonin transporter asymmetry in the midcingulate cortex, which indicates that NGV trans*women and cis*women lack masculinization in this brain region (Kranz et al. 2014).

Additionally, it was found that untreated trans*women compared to trans*men and both cis*men and cis*women showed different network patterns in an area related to empathy (e.g. emotion recognition, -description, and -contagion) and that those patterns assimilated over the course of gender affirmation (Spies et al. 2016).

2.3.5 Comorbidity

Although strong evidence exist showing that transgender persons worldwide are particularly prone to adverse health and disease outcomes, these burdens remain understudied. Especially studies focusing on possible underlying causal mechanisms, such as the impact of stigma, violence, discrimination and prejudice, are scarce (Reisner et al. 2016a). In a recent review article Reisner et al. (2016b) summarized 116 studies published between 2008 and 2014, which delivered 981 unique health-related datapoints. Their findings of an increased interest in transgender health during the last two examined years are illustrated in the following figure (ibid. 2016b).

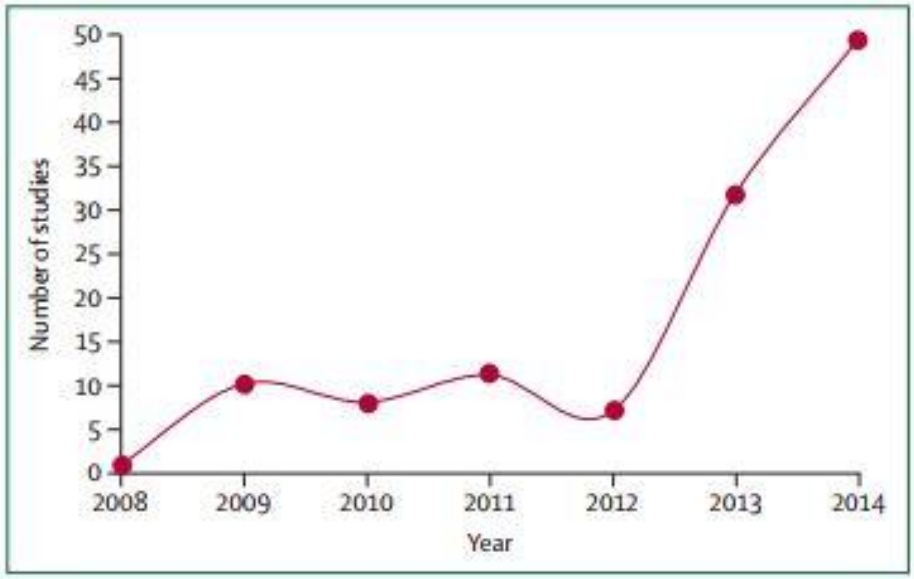

Figure 1: Number of studies on transgender health over the years
Source: Reisner et al. (2016b: 427), reprinted with permission from Elsevier

Overall, they found six health-related outcome categories after summing up the unique datapoints covered by the examined studies: mental health, sexual and reproductive health, substance use and abuse, violence/victimization, stigma/discrimination and general health (ibid. 2016b).

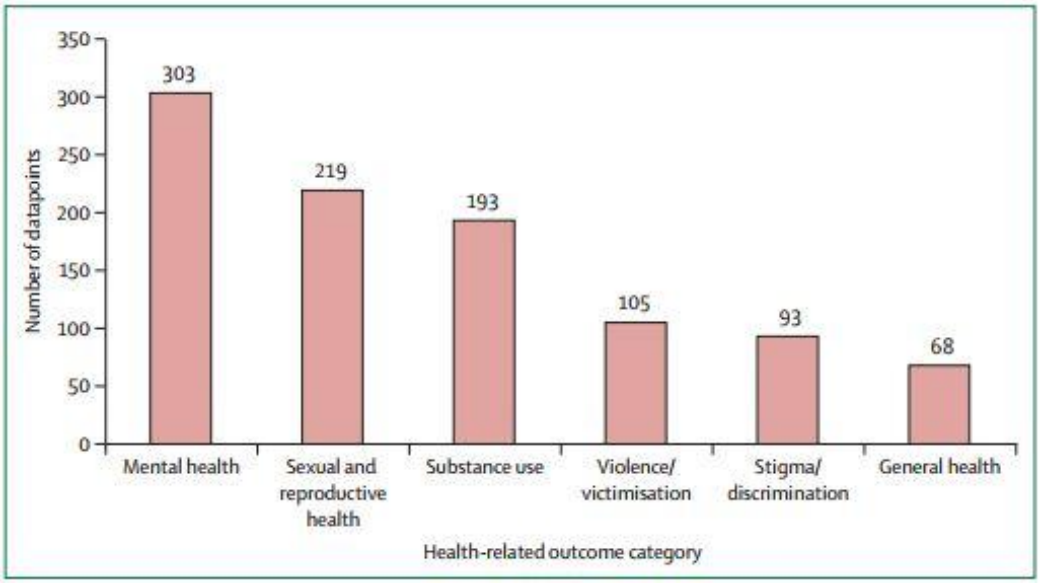

Figure 2: Number of datapoints of health-related outcome categories in studies with focus on transgender health

Source: Reisner et al. (2016b: 428), reprinted with permission from Elsevier

Mental health

Most research regarding transgender health is focused on mental issues, particularly on mood disorders, suicidal and non-suicidal self-injury (NSSI) and anxiety disorders. Although expected prevalence rates are very high (lifetime prevalence of up to 70%) (Heylens et al. 2014), gender dysphoria is not necessarily associated with comorbid psychopathology and often seen as an isolated phenomenon (Cole, O'boyle, Emory & Meyer III 1997; Hoshiai et al. 2010). Estimated prevalence rates for depression among the transgender population are high: 64% in trans*women and 63% in trans*men (Reisner et al. 2016a). A recent study found a high association between attention-deficit/hyperactivity disorder and gender dysphoria (Yildirim, Perdahli Fis, Yazkan Akgul & Ayaz 2017). In their review comprising 31 studies, Marshall et al. (2016) showed that gender dysphoric persons have a greater prevalence of NSSI and suicidality (suicidal thoughts, suicide attempts and suicide rates) than the general population. Furthermore, it was often reported that trans*men did have a higher risk for NSSI behavior (Marshall, Claes, Bouman, Witcomb & Arcelus 2016). Family rejection was associated with suicide attempts (Klein & Golub 2016). Although findings indicate that NSSI and suicidality rates decrease in progressed gender affirmation stages, they are, particularly in the case of suicidality and suicide rates, significantly higher than in the cisgender population. The authors suggest that older age and possible epiphenomenon such as loneliness, lack of social support and victimization, may act as a risk factor for this finding (Marshall et al.

2016). Another review by Jones et al. (2016) found that transgender people showed a high prevalence of body dissatisfaction, which seems to be a major risk factor for adverse health outcomes related to greater distress and which may cause eating disorders, mainly to suppress typical body characteristics of their gender assigned at birth (Jones, Haycraft, Murjan & Arcelus 2016). Cultural influences were also found to play a major role in regarding eating disorders and risky body change behavior: Trans*women often want to fulfill the western body ideal of thinness, trans*men mainly drive for muscularity (ibid. 2016). It was found that trans*women attached importance especially to voice and hair, whereas trans*men were more concerned about posture and muscularity (Van de Grift et al. 2016). The transition process may play a role in improving body image and consequently increasing body satisfaction (Jones et al. 2016). Van Der Miesen et al. (2016) showed in their review article a frequent co-occurrence of gender dysphoria and autism spectrum disorder (ASD), with up to 20% of clinic-assessed gender dysphoric persons showing characteristics in the clinical range of ASD (Van Der Miesen, Hurley & De Vries 2016). To date, there is no coherent explanation for this phenomenon (ibid. 2016). One study showed that personality disorders (PD), such as paranoid PD, avoidant PDs, and comorbid PDs, are more common among transgender persons, and especially in trans*women, than the cis*population (Duišin et al. 2014). Furthermore, a study conducted in Spain found evidence of a strong association between gender dysphoria and social anxiety disorder (Bergero-Miguel et al. 2016). Although there is great evidence that transgender persons are especially vulnerable to violence and victimization, studies focusing on the effects of related conditions like post-traumatic stress disorder are scarce (Reisner et al. 2016a). Other major mental health problems (e.g. schizophrenia, bipolar disorder) did not show a greater prevalence among transgender people than the general population (Dhejne, Van Vlerken, Heylens & Arcelus 2016). When analyzing studies focusing on mental health problems in transgender people, it is important to consider the great difference between current (38%) and lifetime prevalence (70%) of psychiatric disorders (Heylens et al. 2014). This indicates that the severity and rate of mental health problems in transgender persons may be considerably higher than shown in most present-day studies as longitudinal study designs are scarce (Dhejne et al. 2016; Reisner et al. 2016a).

In their review article, Dhjene et al. examined risk and protective factors for mental health problems in the transgender population and came to the conclusion that both an increase and reduction of psychopathology and psychiatric disorders can be influenced by a number of aspects (ibid. 2016). Although the majority of studies comparing the prevalence of psychiatric disorders between trans*men and trans*women did not find any difference, some research

evidence suggests that trans*women are more likely to experience mental health problems (ibid. 2016). Victimization mechanisms such as social stigma, prejudice, discrimination and abuse are also considered to increase the risk for psychopathology (ibid. 2016; Gooren 2011), with personal discrimination presumably having a larger effect than group stigmatization (McGarrity, Huebner & McKinnon 2013). Many transgender persons, especially in poor countries, do not have adequate health care or social services they can turn to for help. Furthermore, trans*individuals receive and/or perceive to receive little to none support from their social environment (e.g. family, friends) (De Vries, Steensma, Cohen-Kettenis, VanderLaan & Zucker 2016; Dhejne et al. 2016). Another study found associations between greater psychopathology, particularly depression, and younger age, greater body dissatisfaction, greater interpersonal problems and lower self-esteem (Bouman, Davey, Meyer, Witcomb & Arcelus 2016b).

Being in a relationship was found to operate as a protective factor against psychopathology (Dhejne et al. 2016). Furthermore, disclosure of transgender identity, social support, especially from parents, and completed medical transition also serve as protective factors, which may prevent or at least reduce psychopathology (ibid. 2016).

Sexual and reproductive health

Main health issues covered by existing literature referring to sexual and reproductive health are HIV and other sexually transmitted infections (Reisner et al. 2016b). One study found that trans*women are disproportionately more affected by those diseases than trans*men (trans*women (n = 392): 35%, trans*men (n = 123): 2%); they also showed significantly more sexual and drug-injection risk behavior than trans*men (Clements-Nolle, Marx, Guzman & Katz 2001). Other sexual and reproductive health concerns, such as non-infectious reproductive issues, fertility or pregnancy, received little to no attention from research so far (Reisner et al. 2016a).

Substance use

Studies on substance use, which may function as a coping mechanism, mainly focused on alcohol, marijuana, any other illicit drug use, and tobacco (Reisner et al. 2016a). One study found that transgender persons are exposed to more heavy episodic drinking than the general cis*population, and are at higher risk for alcohol-related suicidal ideation and sexual assaults and/or verbal threats (Coulter et al. 2015). Furthermore, family rejection was associated with

alcohol and drug abuse (Ellis, Bailey & McNeil 2015). However, overall, research focusing on substance abuse, dependence, or disorder is very scarce (Reisner et al. 2016a).

Violence and victimisation

Overall, estimated prevalence for transgender persons to experience sexual, physical, psychological/emotional, verbal or non-specified violence or victimization is 44% (Reisner et al. 2016a). These experiences act as risk factors for suicidal behavior. The transgender population is also a risk group for becoming victims of murder[10]. Exact statistics, however, are difficult to establish because many deaths may not be documented or may be misreported as murders of homosexual individuals (Winter et al. 2016).

Stigma and discrimination

Research in this area mainly examined health outcomes related to stigma and discrimination in health care (e.g. denial or postponement of care) (Reisner et al. 2016a). One qualitative study assessed transgender experiences and their perceptions of treatment quality in mental health services and gender identity clinics in the UK directly. Findings indicate that practitioners working in these facilities tend to lack knowledge about trans*issues, delay, restrict or refuse treatment to transgender persons, conduct unnecessary and intrusive questioning or show prejudicial attitudes towards this minority group, which in return may be harmful to the mental health of transgender people (Ellis et al. 2015). Outcome studies of interventions which were designed to reduce stigmatization and discrimination of transgender persons are limited (Reisner et al. 2016a).

General health

Research focusing particularly on the general health (e.g. mortality, diabetes, metabolic syndrome, cancer, etc.) of transgender people not having undergone any gender affirmation processes is lacking (Reisner et al. 2016a).

[10] For more information: The Austrian charitable organization *Transgender Europe* started the project *Trans Murder Monitoring*, which "systematically monitors, collects and analyses reports of homicides of trans and gender-diverse people worldwide" (Transgender Europe 2018) as a pilot project of their research project *Transrespect versus Transphobia Worldwide* in 2009 (Trans Respect 2018a; Trans Respect 2018b).

2.4 Diagnosis

2.4.1 Stigma versus access to care

There has been a highly controversial debate about whether variances in gender identity should remain in diagnostic manuals such as the Diagnostic Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD). On the one hand many people – especially transgender activists and some clinicians – argue that an official diagnosis of gender variant identities perpetuates stigmatizing and medicalization of nonpathological behavior (Dewey & Gesbeck 2017) and must therefore be removed (Zucker 2015). More specifically, the problem is seen in the "[…] traditional and contemporary biomedical and scientific efforts to classify, organize, and regulate sex, gender, and sexuality, as objective, universal, and stable aspects of human behavior, toward the project of rendering certain bodies 'normal' and others 'abnormal.'" (Daley & Mulé 2014: 1308). Furthermore, it is argued that the distress transgender people are experiencing, which consequently may affect their mental health and in return explain the high comorbidity rates between transgenderism and mental health issues, is nothing inherently based on the phenomenon of gender variant identity itself, but rather on societal causes (e.g. social rejection, violence (Robles et al. 2016)) (Richards et al. 2015).

On the other hand, there is the argument for retaining those diagnoses in order to maintain access to care: "[…] healthcare funding systems in many countries are set up in such a way as to make it effectively impossible to assist trans people with hormones and surgeries if they do not have a diagnosis which relates to those interventions." (Richards et al. 2015: 310). That this practice is not an unbudgeable system is shown firstly through historic examples in which certain conditions had a formal diagnosis to provide access to care (e.g. menopause) and are now considered normal, non-pathological life events (Drescher 2015). Secondly, in countries such as France, Denmark, Argentina, and Malta a psychiatric diagnosis of a gender variant identity is not a requirement for access to healthcare services and legal recognition (Davy 2015). But as those countries are still the exception to this day the dilemma remains: Should scientific knowledge of diagnostic validity or the necessitiy of a utilitarian approach be central to diagnostic processes and can these two practices even be seen separately (Bolton 2016; Frances 2016; Ghaemi 2016; Hengartner & Lehmann 2017; Jablensky 2016; Phillips 2016; Wakefield 2016)? As there is no definitive answer to these questions for now and unlikely ever will be, the authors of the DSM and the ICD decided to retain diagnoses of gender

variant identities in these manuals. Perhaps the best compromise for now is to proceed as Arlene Istar Lev (2013) proposes:

> *"I encourage everyone to practice your therapy as if there was no DSM-5 diagnosis for Gender Dysphoria, and at the same time I caution you to be very conscious of the reality of gender dysphoria."* (ibid. 2013: 295)

The two diagnostic manuals DSM and ICD will be discussed as follows, because they are the main resources for diagnostic criteria for gender variances used in scientific studies and clinical practice today.

2.4.2 Gender Dysphoria in the Diagnostic Statistical Manual of Mental Disorders (DSM)

Historical development

The following table gives a brief overview showing the changes made to the diagnosis of gender dysphoria and its significance in the DSM since it was first introduced in 1952.

Table 2: Overview of the historical evolvement of the gender dysphoria diagnosis

Year	DSM Edition	Diagnosis term	Parent catergory	Categorial changes	Definition and significance
1952	I	n/a	n/a	n/a	n/a
1968	II	Transvestitism	Sexual deviations	n/a	n/a
1980	III	Transsexualism Gender identity disorder of childhood (GIDC)	Psychosexual disorders	Two diagnostic categories appear	Transsexualism: persistent sense of discomfort with one's anatomic sex, desire to remove one's genitals, and living as the desired sex for at least two years. GIDC: persistent that one is the other sex, onset before puberty, and emphasis on the performative aspects of gender nonconformity (e.g. dress, play, affect) for males. → Recognition of the phenomenon

Year	DSM Edition	Diagnosis term	Parent catergory	Categorial changes	Definition and significance
1987	III-TR	Gender identity disorder of childhood Gender identity disorder of adolescence and adulthood, nontranssexual type (GIDDANT)	Disorders usually first evident in infancy, childhood, or adolescence	Reclassi-fication	GIDDANT: persistent sense of discomfort with one's natal sex and living as the desired sex for at least two years. → Expands access to nonsurgical gender therapies → Separation between gender and sexuality, but classification of gender nonconformity as a disorder itself → Focus on performative aspects of gender nonconformity for girls → Emphasis on symptom onset in childhood
1994	IV	Gender identity disorder (GID) in adolescents or adults Gender identity disorder (GID) in children	Sexual and gender identity disorders	Introduction of the category GID and reclassification under sexual disorders	GID: gender identity disordered people present significant distress or impairment. → Early distinction between diagnosing gender variation and diagnosing the stress caused by gender variation.
2000	IV-TR	Gender identity disorder in adolescents or adults Gender identity disorder in children	Sexual and gender identity disorders	Auto-gynephilia is added as a subtype of GID.	Autogynephilia: either a fetishistic obsession with oneself as a woman or internalized homophobia as the main motivation to undergo gender-related surgeries. → Limiting access to gender-related treatments and stigmatizing

Year	DSM Edition	Diagnosis term	Parent catergory	Categorial changes	Definition and significance
2013	5	Gender dysphoria in adolescents or adults Gender dysphoria in children	Gender dysphoria	Gender dysphoria (GD) replaces GID and is removed from the section on Sexual Dysfunction and Paraphilic Disorders.	→ Attempt to depathologize transgender by shifting focus to the distress associated with current physical sex characteristics or with birth-assigned gender roles, not the experience of gender incongruence itself. → No longer labeled a disorder; however, it remains listed in the DSM and its criteria is still used to secure gender-related therapies.

Table adapted from Drescher (2016) and Winters (2005)

Legend: n/a = not applicable, GD = gender dysphoria, GID = gender identity disorder, GIDC = gender identity disorder in children/of childhood, GIDDANT = gender identity disorder of adolescent and adulthood, nontranssexual type

From Gender Identity Disorder (DSM-IV) to Gender Dysphoria (DSM-5)

The following tables show the diagnostic criteria for gender identity disorder in the DSM-IV, TR (American Psychiatric Association 2000) and for gender dysphoria in the DSM-5 (American Psychiatric Association 2013).

DSM-IV, TR: Diagnostic criteria for Gender Identity Disorders

Table 3: Diagnostic criteria for GID in the DSM-IV, TR

Criterion A: A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex).
In children the disturbance is manifested by four (or more) of the following: 1. Repeatedly stated desire to be, or insistence that he or she is, the other sex 2. In boys, preference for cross-dressing[11] or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing 3. Strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex 4. Intense desire to participate in the stereotypical games and pastimes of the other sex 5. Strong preference for playmates of the other sex.
In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex
Criterion B: Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex.

[11] *Crossdressing* (formerly *transvestism*) generally describes individuals who usually have no desire to change their anatomical appearance, but may wear clothing, accessories, jewelry, make-up, hair styles, etc. not stereotypically or traditionally associated with their sex assigned at birth (Fenway Health 2010). There are various reasons for crossdressing such as artistic/creative expression, performance (e.g. drag queen/king), erotic enjoyment, to express femininity/masculinity, etc. (Transgender Equality Network Ireland n.d).

In children, the disturbance is manifested by any of the following: in boys, assertion that his penis or testes are disgusting or will disappear or assertion that it would be better not to have a penis, or aversion toward rough-and-tumble play and rejection of stereotypically male toys, games, and activities; in girls, rejection of urinating in a sitting position, assertion that she has or will grow a penis, or assertion that she does not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing.
In adolescents and adults, the disturbance is manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g. request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex.
Criterion C: The disturbance is not concurrent with a physical intersex condition
Criterion D: The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Source: DSM-IV, TR (Amercian Psychiatric Association 2000); reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (Copyright 2000). American Psychiatric Association.

DSM-5: Diagnostic criteria for Gender Dysphoria

Table 4: Diagnostic criteria for GD in the DSM-5

Criteria for gender dysphoria in children
A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least six months' duration, as manifested by at least six of the following (one of which must be Criterion A1):
1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender)
2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing
3. A strong preference for cross-gender roles in make-believe play or fantasy play
4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender

5. A strong preference for playmates of the other gender
6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities
7. A strong dislike of one's sexual anatomy
8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender
B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.
Specify if: with a disorder of sex development
Criteria for gender dysphoria in adolescents and adults
A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least six months' duration, as manifested by at least two of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
3. A strong desire for the primary and/or secondary sex characteristics of the other gender
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender)
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)
B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning
Specify if: with a disorder of sex development

Specify if: posttransition, the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g. penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female)

Source: DSM-5 (American Psychiatric Association (2013); reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association.

As mentioned before, a few substantial changes have been made to the formerly established and practiced diagnosis of gender identity disorder (GID; American Psychiatric Association 1994) in the fifth edition of the DSM (Eckstrand et al. 2016), some of which will be discussed as follows. First and foremost, the label 'disorder' was deleted and replaced by 'dysphoria', what was and is believed to help reduce stigmatizing. For the authors of the GID sub-work group of the DSM-5 it was also important to put emphasis on the distress gender dysphoric people are experiencing with the assigned gender at birth (Smith et al. 2015; Zucker 2015), which was put in the DSM-5 as a diagnostic criterion: "The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning." (American Psychiatric Association 2013: 453). This means that not all gender variant persons feel psychological strain due to the difference between their chosen and their assigned gender identity. As gender dysphoria is neither a sexual dysfunction nor a paraphilia, it was removed from these often stigmatizing categories under which it was previously subsumed and constitutes a new chapter of its own in the DSM-5 (Drescher 2014; Smith et al. 2015). The definition of gender dysphoria also changed: in DSM-IV-TR GID is described as a *cross-gender identification* (American Psychiatric Association 2000) which implies a strictly binary gender identity concept (Zucker 2015). The DSM-5 tries to avoid this two-gender classification system by describing gender dysphoria as "[a] marked incongruence between one's experienced/expressed gender and assigned gender […]" (American Psychiatric Association 2013: 452). One significant change was the diagnostic criteria for gender dysphoria in children, which became more narrow and conservative. With that adjustment the authors hoped to avoid false diagnoses and make it possible to clearly distinguish between gender dysphoria and normative variation (Drescher 2014; Zucker 2015). The specification *with a disorder of sex development* (DSD) (American Psychiatric Association 1994) was included in the diagnosis criteria because the relationship between GD and DSD remains

unclear to this day: there are both differences and similarities between gender dysphoric people with and without DSD (Zucker 2015). The specifier *sexual attraction* as described in the DSM-IV-TR was deleted as it does not affect symptom expression per se and treatment protocols are also not influenced by it significantly. To avoid any precipitous diagnoses of GD a 6-month duration criterion was introduced (ibid. 2015). Because gender dysphoric people continue treatment (e.g. HRT, surgery, psychotherapy) after transition but diagnosis criteria do not apply to them anymore, the *posttransition specifier* was added for gender dysphoric adolescents and adults (ibid. 2015).

2.4.3 Transsexualism in the 10th edition of the International Classification of Diseases (ICD-10**)**

ICD-10 (F64): Diagnostic criteria for Gender Identity Disorders

The following table shows the currently accepted classification and definition of Gender Identity Disorders in the ICD-10 (World Health Organization 1992).

Table 5: Diagnostic criteria for GID in the ICD-10

F64 GENDER IDENTITY DISORDERS
F64.0 Transsexualism
A. Desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make one's body as congruent as possible with one's preferred sex through surgery and hormonal treatment.
B. Presence of the transsexual identity for at least two years persistently.
C. Not a symptom of another mental disorder, such as schizophrenia, or associated with chromosome abnormality.
F64.1 Dual-role transvestism
A. Wearing clothes of the opposite sex in order to experience temporarily membership of the opposite sex.
B. Absence of any sexual motivation for the cross-dressing.
C. Absence of any desire to change permanently into the opposite sex.
F64.2 Gender identity disorder of childhood
For females:

A. Persistent and intense distress about being a girl, and a stated desire to be a boy (not merely a desire for any perceived cultural advantages from being a boy), or insistence that she is a boy.
B. Either (1) or (2): (1) Persistent marked aversion to normative feminine clothing and insistence on wearing stereotypical masculine clothing, e.g. boys' underwear and other accessories. (2) Persistent repudiation of female anatomic structures, as evidenced by at least one of the following: (a) an assertion that she has, or will grow, a penis (b) rejection of urinating in a sitting position (c) assertion that she does not want to grow breasts or menstruate
C. The girl has not yet reached puberty.
D. The disorder must have been present for at least six months.
For males:
A. Persistent and intense distress about being a boy and an intense desire to be a girl or, more rarely, insistence that he is a girl.
B. Either (1) or (2): (1) Preoccupation with female stereotypical activities, as shown by a preference for either cross-dressing or simulating female attire, or by an intense desire to participate in the games and pastimes of girls and rejection of male stereotypic toys, games and activities. (2) Persistent repudiation of male anatomic structures, as indicated by at least one of the following repeated assertions: (a) that he will grow up to become a woman (not merely in role) (b) that his penis or testes are disgusting or will disappear (c) that it would be better not to have a penis or testes.
C. The boy has not yet reached puberty.
D. The disorder must have been present for at least six months.

Source: ICD-10 (World Health Organization 1992); reprinted with permission from World Health Organization

From ICD-10 to ICD-11: proposed changes

The World Health Organization (WHO) is in the process of revising the tenth version of the International Classification of Disease and Related Health Problems (ICD-10), which was introduced in 1990. It is expected that the ICD-11 will be approved by the World Health Assembly in 2018 (Beek et al. 2017; Reed et al. 2016). Proposed changes in the section of gender identity disorders are particularly based on circumstantial and societal developments (e.g. advances in clinical practice and research, shifts in social attitudes and in laws, policies and human rights standards) (Reed et al. 2016).

After controversial discussions, the ICD working group has recommended that gender identity disorders should be retained in the ICD-11 in order to facilitate access to care (Beek et al. 2016; Drescher 2014). However, it should be moved out of the section on mental and behavioral disorders to reduce stigmatizing (Drescher 2014). It is proposed that this phenomenon should alternatively be treated as a unique medical condition in a chapter of its own, included in a new chapter on sexual disorders and sexual health containing both pathological and nonpathological conditions or become a medical or surgical diagnosis. The latter bears the problem that not all trans*people want to undergo surgery or any kind of medical gender affirmation at all (ibid. 2014). One study asked transgender people, their relatives/partners and health care providers directly for their opinion on the proposed changes recommended for the ICD-11. 88% of trans*people agreed that the diagnosis should be retained in the revised version, while 7.2% said that it should be removed entirely (for Gender Incongruence of Childhood: 33.6% of trans*people want it retained, 42.9% want it removed) (Beek et al. 2016; Beek et al. 2017). Another important aspect is the replacement of the terms Transsexualism (ICD-10, F64.0) and Gender Identity Disorder of Childhood (ICD-10, F64.2) with Gender Incongruence (GI) of Adolescence and Adulthood and GI of Childhood (Drescher 2014), which is largely seen as an improvement in the transgender community (63%) (Beek et al. 2016; Beek et al. 2017). The authors also try to avoid binary and naturalistic terms such as *opposite sex* and *anatomic sex*, replacing them with expressions such as *experienced gender* and *assigned sex* (Reed et al. 2016). In contrast to the DSM-5, the diagnosis of gender incongruence in the proposed version of the ICD-11 does not require distress or functional impairment experienced by transgender people as a criterion, although acknowledging the significant impact these commonly associated features may have on transgender lives. Furthermore, the diagnosis of gender incongruence requires a duration of several months and is therefore reduced from two years in the ICD-10 (ibid. 2016). The

following features, as presented by Reed et al. (2016), are included in the proposed diagnostic requirements for gender incongruence of adolescence and adulthood and at least two of them must be fulfilled:

> "a) a strong dislike or discomfort with primary or secondary sex characteristics due to their incongruity with the experienced gender
>
> b) a strong desire to be rid of some or all of one's primary or secondary sex characteristics (or, in adolescence, anticipated secondary sex characteristics)
>
> c) a strong desire to have the primary or secondary characteristics of the experienced gender
>
> d) a strong desire to be treated (to live and be accepted as) a person of the experienced gender." (ibid. 2016: 211)

In order to avoid any false diagnoses, the proposed criteria for GI of childhood in the ICD-11 are stricter than in the ICD-10 (ibid. 2016).

2.5 Clinical Management: Gender Affirmation/Confirmation Treatment

It is important to consider that gender affirmation is not a single process, but includes multiple domains, such as social (e.g. social support, acceptance and use of preferred pronoun or name, being accepted in one's desired gender role), medical (e.g. HRT, surgery), and legal (e.g. change of biological sex on legal documents, legal name change) (Glynn et al. 2016). This chapter focuses on the medical domain, and more specifically on HRT. The two major goals of HRT are to suppress endogenous hormone production which is determined by the individual's biological sex and to reach and maintain sex hormone levels within the normal range of the person's gender (Hembree et al. 2009). Suggested therapy for adult trans*women primarily includes estrogen, anti-androgens and possibly progestins. Estrogens induce physical feminization (e.g. breast growth, body fat distribution), reduce libido and erections and possibly lighten mood. Anti-androgens are believed to specifically discourage further male body hair growth. Progestins may be applied to augment estrogen-induced breast development and to exert psychological effects, such as the maintenance of libido. Adult trans*men primarily receive T during HRT. Intended effects of T therapy include body masculinization, lowering of voice pitch and intensified male body and facial hair growth (Levy, Crown & Reid 2003). It is important to avoid supraphysiological levels of estrogen in trans*women as they increase the risk for liver dysfunction, venous thromboembolic disease,

and development of high blood pressure. Adverse outcomes may also include breast cancer, coronary artery disease and severe migraine headaches. Possible risks increased by supraphysiological levels of T in trans*men include liver dysfunction, breast or uterine cancer, high blood pressure, erythrocytosis, salt retention, excessive weight gain, excessive or cystic acne (Hembree et al. 2009; Levy et al. 2003). Therefore, several follow-up and monitoring assessments are recommended: hormone levels, body-mass index, blood pressure, liver enzymes, serum levels of lipids, bone mineral density, breast cancer screening, prostate cancer screening, uterine cancer screening, etc. (Gooren 2011; Hembree et al. 2009). Although medical supervision should be provided throughout the treatment, it must be emphasized that HRT is considered a safe treatment, as one extensive literature review comprising 1881 scientific articles covering almost 50 years of research showed (Weinand & Safer 2015). However, there is a need for additional long-term follow-up research (Asscheman, Giltay, Megens, van Trotsenburg & Gooren 2011; Meriggiola & Berra 2012; Tangpricha 2015; Weinand & Safer 2015). Furthermore, it is crucial to weigh up benefits and possible adverse effects of HRT. Although studies examining the outcomes of HRT on the quality of life and psychological well-being often show experimental weaknesses, their results suggest that HRT significantly improves both aspects in transgender persons (Costa & Colizzi 2016; Knoblauch et al. 2007; Murad et al. 2010; White Hughto & Reisner 2016).

3 Aggression

3.1 Classic categorizations

Aggression is a very heterogeneous and complex construct. In the past, there have been several attempts to categorize aggression. Two commonly used classifications in scientific research are on the one hand the distinction between impulsive and instrumental aggression and on the other hand the reactive - proactive dichotomy. Impulsive aggression is mainly associated with spontaneous aggressive responses to a perceived provocation or threat, whereas instrumental (also: premeditated, Siever 2008) aggression mainly refers to goal-oriented aggressive behavior. It is important to emphasize that these two kinds of aggressive behavior are not mutually exclusive. Related to the impulsive - instrumental dichotomy is the reactive - proactive distinction of aggression. Taken together, reactive and proactive aggressive behavior is believed to represent a total aggression level. Due to their highly intercorrelated and coexisting character, these two constructs cannot be strictly separated. Reactive aggression is often accompanied by feelings such as hostility and anger and can be seen as an answer to perceived provocation or frustration, with the goal to suppress or prevent negative feelings. Proactive aggression on the other hand cannot be seen as a response to perceived provocation, but as goal-oriented behavior (e.g. to gain a reward, status, power, social dominance), and is therefore not necessarily accompanied by negative feelings such as rage or anger (Rosell & Siever 2015).

3.2 Neuroanatomy of aggression

Research studying the underlying neurobiological structures and functions of mainly reactive and impulsive aggression has largely focused on the amygdala, limbic prefrontal regions (particularly the orbitofrontal (OFC) and anterior cingulate cortex (ACC)), the hypothalamus, and the striatum, as these structures are involved in impulse control, emotional processing, and affective decision making. A few structural studies report consistent findings of an inverse association between left and right whole amygdalae volumes and aggression (Bobes et al. 2012; Matthies et al. 2012; Pardini, Raine, Erickson & Loeber 2014). In many studies, the amygdala has been analyzed as a unitary structure, but to better understand the connection between amygdala structure/function and aggression, recent studies have begun to look specifically at its functional subdivisions. They found that especially left dorsal amygdala activity was negatively correlated with aggression levels (Bobes et al. 2012; Gopal et al. 2013). Functional studies using Positron Emission Tomography **(**PET) and functional

Magnetic Resonance Imaging (fMRI) found that amygdala activity may be more enhanced and labile in individuals with pathological forms of aggression than in controls (Coccaro, McCloskey, Fitzgerald & Phan 2007; New et al. 2009). Another fMRI study found that aggressive compared to non-aggressive participants reacted with amygdala hyperactivity after seeing fearful and – to an even larger extent – neutral faces (Bobes et al. 2012). As they generate state representations and coordinated emotional, cognitive and behavioral responses – what includes aggressive behavior –, both the OFC and the ACC contribute to the integration of cognitive, sensory, and emotional processes. In these, the OFC is mainly associated with sensory functions (Rosell & Siever 2015), emotion evaluation and the regulation of top-down control, the ACC with determining responses or actions to certain stimuli (Carré et al. 2017). Furthermore, there are some indications that a connective circuitry between the prefrontal cortex (PFC), to which the OFC and ACC belong, and the amygdala is involved in the neurobiology of aggression (Rosell & Siever 2015). The circuitry of the OFC, the ACC and the amygdala is being viewed as the underlying core element of emotion regulation. Depending on the situational context, emotion regulation determines the intensity, length, content and quality of emotional experience in order to respond adequately to current needs or long-term goals (Coccaro, Sripada, Yanowitch & Phan 2011). It has been argued that impulsive aggression may occur as a result of a deficit in emotion regulation processes, and therefore in these connections. This hypothesis is supported by findings which indicate that individuals with clinically high levels of impulsive aggression show decreased function in this circuit (Davidson, Putnam & Larson 2000).

The hypothalamus is a small, but very complex and anatomically heterogenous brain structure. It is responsible for a wide range of physiological processes, such as vegetative and endocrinological functions, but also high-order social behavior, including aggression. Especially the posterior hypothalamic region is strongly associated with aggressive behavior (Barbosa et al. 2017). In the 1970s many lesional radiofrequency surgeries of the posterior hypothalamus were therefore performed on patients showing extensive aggressive behavior. Today, these procedures are not executed any more, especially because of the possibility of misuse. Instead, deep brain stimulations of the posterior hypothalamus are done to treat highly aggressive people (Rizzi et al. 2017). Interestingly, the hypothalamus is a crucial link in endocrinological processes: when behavior-specific areas are active, hormonal responses (e.g. sex steroid hormones) are either facilitated or inhibited, what, in return, may play a role in regulating behavioral responses (Kruk et al. 1998).

The striatum, as it integrates cortical input, is an important part in the process of appropriate response decision (e.g. cognitive, motor, emotional). Especially the ventral and dorsomedial structures of the striatum are believed to play a crucial role in aggression, because they are involved in motivated, goal-directed and value-based processes (Rosell & Siever 2015).

3.3 Neurochemistry of aggression

Numerous hormones, neuropeptides and neurotransmitters (e.g. dopamine, norepinephrine, acetylcholine, glutamatergic/gabaminergic systems, oxytocin, vasopressin) are believed to play crucial roles in aggressive behavior (Rosell & Siever 2015; Siever 2008). Serotonin is a good example of how neuroanatomy and neurochemistry are connected: serotonin stimulates the PFC regions OFC and ACC and therefore deficiencies in serotonergic innervation may result in impulsive aggression (Siever 2008). A detailed description of the exact role of the above-mentioned substances, is, however, beyond the scope of this study (for an elaborate review see Siever 2008).

The following review of current research will summarize studies examining the effects of T on aggression, as it is administered during hormone replacement therapy (HRT). The majority of studies have focused on the role of T in aggressive behavior, whereas there is a vast lack of research focusing on a potential role of estradiol (E)[12].

3.4 Testosterone and aggression

3.4.1 Testosterone and its relationship to neural mechanisms associated with aggressive behavior

As in the above-mentioned example of the connection between neuroanatomy and neurochemistry in the case of OFC/ACC and serotonin, any effects of T must be viewed in regard to its neuroanatomical relations: The amygdala as well as parahippocampal regions with their high density of androgen receptors are key targets for T-specific effects (Heany, van Honk, Stein & Brooks 2016; Nguyen et al. 2016). Furthermore, it was found that the circuitry between amygdala and PFC-structures, which is responsible for affect and impulse regulation, may have mediating effects on the association between T and aggression (Nguyen et al. 2016). T was found to increase responsiveness in these areas of social aggression

[12] Estradiol is a sex steroid hormone and belongs to the group of estrogens (Hall, Couse & Korach 2001). To put it very shortly, it is derived from cholesterol, which undergoes various intermediate steps, including the conversion to testosterone, to be converted into estradiol by aromatase, an enzyme responsible for the transformation of androgens into estrogens (Hanukoglu 1992; Miller & Auchus 2011).

(Hermans, Ramsey, van Honk 2008). It is, however, debatable how exactly T affects neural mechanisms because several factors (e.g. developmental stages, gender, sex, social environment, other circulating hormones, genetic profiles), which may influence the relationship between them, have not frequently been considered in studies to date (Heany et al. 2016).

The connection between T and aggression was originally examined in animals. In some species a direct causal link was found (Carré & Archer 2018). Many commonly cited theories state that T directly affects social behaviors in humans, such as aggression. On the contrary, many studies have discovered little or no associations at all. These inconsistent results have mainly been attributed to methodological weaknesses of studies (Mehta & Prasad 2015). There are, however, other plausible considerations which object to the idea of a direct causal link between T and aggression in human beings. First of all, context variables play an important role: Increased T levels are often a result of winning in competitive situations (Carré & Archer 2018). Secondly, there is controversial data whether rising T levels in puberty lead to increased aggression and if positive associations are found, they are mostly weak (ibid. 2018). Thirdly, the administration of exogenous T also delivered controversial data: some found no effects at all, others found an association between aggression and higher activity in brain regions associated with aggression (ibid. 2018). There might also be other moderating variables which influence the link between T and aggression: cyclic fluctuations of T, other hormones, biological sex, age, past experience, stress, circadian rhythm, etc. (Book, Starzyk & Quinsey 2011). The most common theories which might explain these contradictory research results and experimental study designs which are important for this master's thesis will be discussed in the following.

3.4.2 The dual-hormone hypothesis

A more novel theory indicates that T does not have a direct effect on social behavior, but more of an indirect one: It was found T and cortisol[13] are both involved in aggression processes. The dual-hormone hypothesis states that (mainly social) aggression and T concentrations are positively correlated when cortisol levels are low (Mehta & Prasad 2015; Montoya, Terburg, Bos & van Honk 2012). This may be particularly true for the domain of dominance behavior (e.g. leadership/power, competition, gaining and maintaining high status positions in social hierarchies) (Henry, Sattizahn, Norman, Beilock & Maestripieri 2017;

[13] Cortisol is a glucocorticoid hormone released by the hypothalamic-pituitary-adrenal axis, often as a response to physical or psychological stress (Denson, Mehta & Tan 2013).

Mehta & Josephs 2010), but also other phenomena, such as aggression/violent crime (T and aggression/violent crime are positively related only when cortisol levels are low) (Dabbs, Jurkovich & Frady 1991; Popma et al. 2007), psychopathic personality traits (T levels correlate positively with psychopathy within men when cortisol levels are high, but negatively when they are low) (Welker, Lozoya, Campbell, Neumann & Carré 2014), empathy (high T levels are related to lower self-reported empathy only when cortisol levels are low) (Zilioli, Ponzi, Henry & Maestripieri 2015), and risk-taking (T levels and risk-taking behavior are positively related only when cortisol levels are low) (Mehta, Welker, Zilioli & Carré 2015). Interestingly, it was found that high T levels may actually result in decreased dominance behavior when cortisol levels are also high (Mehta & Josephs 2010). Although this hypothesis is a very appealing explanation, some studies found no significant dual-hormone interaction in antisocial/aggressive behavior (Cote, McCormick, Geniole, Renn & MacAulay 2013; Geniole, Busseri & McCormick 2013; Mazur & Booth 2014; Salvador, Martinez-Sanchis, Simon & Brain 1999). Furthermore, even if significant results are found, the exact relationship between T, cortisol and status-seeking behaviors remains uncertain, as various variables, such as pathological personality dimensions, individual difference factors or context factors associated with social status (e.g. victory-defeat, social inclusion-exclusion), seem to have an impact on it (Geniole, Bird, Ruddick & Carré 2017; Mehta et al. 2015; Pfattheicher 2017; Rosell & Siever 2015).

3.4.3 Biosocial theories

The challenge hypothesis

The link between T levels and aggression in humans explained by the challenge hypothesis is mostly based on two studies: the original proposal of the challenge hypothesis postulated for monogamous birds by Wingfield, Hegner, Dufty and Ball (1990) and its application to wild chimpanzees (Muller & Wrangham 2004). Originally, the challenge hypothesis states that T levels rise to a moderate level in male birds at the beginning of each breeding season. If competitive situations for reproduction occur, T levels will rise and consequently enhance aggressive behavior. Therefore, the rise and fall of T and aggression levels is highly context specific (Archer 2006). Muller and Wrangham (2004) applied this hypothesis to wild chimpanzees, which are, contrary to the examined birds, neither monogamous nor seasonal breeders. They found that T level increases were highly associated with reproductive aggression throughout the entire year. As physiological costs for a constantly high androgen production are significant (e.g. immunosuppression, increased energetic costs, increased risk

for physical injury/death (Wingfield, Jacobs & Hillgarth 1997; Wingfield, Lynn & Soma 2001)) adaptive cost-benefit mechanisms monitor these boosts so that they only occur in challenging situations. Furthermore, the authors also found a positive correlation between status, aggressive behavior and T levels. Due to these results, they indicate that the challenge hypothesis may be applicable to humans as well (Muller &Wrangham 2004). Indeed, there is strong evidence supporting the challenge hypothesis in humans today (Wingfield 2017). It was, amongst other things, found that elevated T levels in men are associated with sexual stimuli, competition, aggression, dominance and status-maintaining behavior, individual characteristics (e.g. high T men were described as stable extroverts) and risk-taking behavior. Furthermore, studies also indicate similar results of increased T levels in challenging situations for women (Archer 2006).

The Biosocial Model of Status and the winner-loser effect

The Biosocial Model of Status originally proposed by Mazur (1976, 1985) argues that high or rising T levels are reciprocally associated with a higher tendency towards dominant behavior in face-to-face interactions[14] in order to maintain high ranks in social hierarchies. Low T levels are associated with deferent individuals of low ranks, who show submissive behavior to avoid further status loss. Mazur specifically states that the model is proposed for men as well as for women, although the relationship between status rank and T in the latter group is poorly investigated (ibid. 1985). Mazur distinguishes between constant status signs (e.g. age, wealth, sex, family lineage, physical strength, health and – to a certain degree – reputation) and controllable ones (e.g. posture, physical threats, relaxed or nervous behavior, language[15] etc.), which can be used to create the impression of being either a dominant or a deferent person and which are the focus of his theory (ibid.1985). According to this theory, T levels rise after winning a competition and decrease after losing (in recent literature often referred to as *the winner-loser effect*). However, a more recent study, which investigated the possible mediating role of contextual factors found a reverse winner-loser effect in a female sample: it was found that T levels significantly increased after losing a competition, especially when the loss was surprising for the defeated individual (Zilioli, Mehta & Watson 2014). The authors explained this contradictory result with the status instability hypothesis: an unstable low rank position –

[14] In a more recent publication Mazur clearly separates individual face-to-face encounters from formal organizational hierarchies and macro-level socioeconomic systems existing in large societies. He states that his theory solely applies to face-to-face social hierarchies (Mazur 2013).

[15] For the emphasis on language as a distinct human way of expressing status, also see Mazur, Welker & Peng (2015).

which is especially the case for narrow or surprising defeats – perpetuates the increase of T levels to activate more sufficient status-seeking behavior (ibid. 2014). Similar results were also found in another study for a male sample (Vongas & Al Hajj 2017). In a recently published comprehensive meta-analysis covering the last 35 years of research on this matter, Geniole et al. (2017) found support for the winner-loser effect, although study results were heterogeneous, which may be explained by weak study designs or the lack of considering moderating variables, such as location of competition, timing of pre-competition T sampling and clear or narrow win/loss (ibid. 2017). As the Biosocial Model of Status is mainly applied to men, and although a few studies suggest that similar mechanisms are also true for women (Zilioli & Bird 2017), further research which specifies on or includes women is needed (Casto & Prasad 2017).

3.4.4 Puberty

The 20- to 30- fold increase in T production in boys during puberty is often associated with changes in mood and behavior, such as aggression. There is, however, inconsistent evidence which supports these notions. A review article comprising 27 studies found inconclusive evidence (Duke, Balzer & Steinbeck 2014). The only included longitudinal study showed little relationship between T level increases and aggressive behavior (Halpern, Udry, Campbell & Suchindran 1993), cross-sectional studies mainly found a positive relationship between these two variables (Duke et al. 2014). Another longitudinal study did not find a positive relationship between rising T levels and aggressive behavior; in fact, there even was a tendency towards decreased aggression. However, the authors found that boys who eventually had a criminal record as adults, showed higher T levels at the age of 16 than those who did not commit any crimes. Boys who showed higher proactive and reactive aggression were also found to have higher T levels. The authors conclude that different forms of aggressive behavior might be linked to increased T depending on specific social settings (Van Bokhoven et al. 2006). Overall, no clear relationship between the rise of T and increased aggressive behavior in pubertal male adolescents can be established to this date.

3.4.5 Exogenous administration of testosterone

Single dosage administration

Research on single-dose administration of T suggests that acutely increasing T levels modulate processes (e.g. psychological, neural) involved in aggressive behavior. One recent study found that exogenous administration of T does not promote aggressive behavior on its

own, but is influenced by trait dominance and self-control variations, with men who are dominant and score low on the self-control scale showing significantly more aggressive behavior in a decision-making game, which measures aggression as a response to social provocation (Carré et al. 2017). Another study, however, failed to replicate former study results stating that single-dose administration of T is related to increased aggressive behavior: Elevated levels of T due to exogenous single-dose administration of 1000 mg T undecanoate were associated with anger-hostility, but unrelated to aggressive behavior. The authors suggest that their contradictory results might be explained by the low administered T dose in their conducted study (O'Connor, Archer & Wu 2004). A sample of healthy young women was found to respond with cardiac acceleration when shown angry faces after receiving a single dosage of T (0.5 mg). The authors explained this phenomenon with a higher proneness to aggressive and dominant behavior, as angry facial expressions serve as an indication of threat in social dominance situations (Van Honk et al. 2001). This result is in line with similar findings of which some also found a strong association between rising T levels and aggression-related neural structures (Goetz et al. 2014; Hermans et al. 2008; Van Wingen et al. 2009), suggesting that exogenous administered T increases aggressive behavior as a response to social provocation (Bos, Panksepp, Bluthé & van Honk 2012). Interestingly, another single-dose study delivered results contributing to the debate on whether aggression and dominance are promoted through conscious psychological or reflexive biological mechanisms. The authors found that T enhances aggressive and dominant behavior directly toward unconsciously perceived angry faces and therefore concluded that social-dominance behavior precedes conscious higher-order mechanisms (Terburg, Aarts & van Honk 2012). In another study with similar results, the authors concluded that T predisposes individuals to antisocial behavior as it reduces conscious detection of angry facial expressions (Van Honk & Schutter 2007). Highly interesting results were reported by another study, which focused on bargaining behavior of their female participants, who received a sublingual single-dose of T. The administration of T caused an increase in fair, conflict-reducing and efficiency-improving bargaining behavior. However, participants who believed they had received T showed increased unfair bargaining, regardless of whether they actually received the hormone or placebo. Therefore, the authors conclude, that the folk hypothesis of T being associated with unfair behavior, might have a strong impact on actions (Eisenegger, Naef, Snozzi, Heinrichs & Fehr 2010).

Long-term administration

Long-term exogenous T administration is of special interest for this study, as it is the most similar experimental procedure to the here examined HRT. T is administered for an extended time period for several reasons: in experimental settings, as an androgen replacement therapy in hypogonadal men[16], in women suffering from female androgen deficiency syndrome[17], as misuse in anabolic steroid users, as HRT in gender dysphoric people, etc. The most important study results will be discussed in the following.

Findings of long-term studies administering T to its participants delivered highly inconsistent results. One long-term study in which healthy, eugonadal participants were administered 200 mg T weekly for 8 weeks found that supraphysiological levels of T did not lead to significantly increased aggressive behavior. Interestingly, hypogonadal men, who were also included as a separate group in this study, showed high levels of negative affect (e.g. aggression, hostility, anger, or irritability) both before and during T treatment (O'Connor, Archer, Hair & Wu 2002). Another study, examining the effects of T therapy on hypogonadal men found no change in aggressiveness (Jockenhövel et al. 2009). However, in hypogonadal adolescent males T therapy increased physical aggression and aggressive impulses, but not verbal aggression or aggression inhibition (Finkelstein et al. 1997). Furthermore, in a sample of 43 men receiving 600 mg of T for 10 weeks, supraphysiological T levels did not lead to increased anger or aggression behavior (Tricker et al. 1996). These findings are consistent with another study, which also could not detect any significant increases in self-reported aggressive feelings after administering T (200 mg T enanthate for 8 weeks) to its participants (Anderson, Bancroft & Wu 1992). Although effects were not uniform in each individual, another study found, contrary to the above-mentioned, that T administration (up to 600 mg/week for 6 weeks) lead to significantly increased aggression scores (Pope, Kouri & Hudson 2000). Another study found similar results: Participants showed, after receiving gradually increasing doses of T over a period of 6 weeks (150 mg /week for two weeks, 300 mg/week for two weeks, and 600 mg/week for two weeks), significantly more aggressive responses in a social game (Kuori, Lukas, Pope & Oliva 1995).

[16] Men who suffer from hypogonadism cannot produce adequate amount of T as a result of testicular disorder (primary) or hypothalamic–pituitary–gonadal dysfunction (secondary) (Lood et al. 2017).

[17] Women who experience androgen deficiency might suffer from absent or greatly diminished libido, loss of pubic hair, decreased weight, a lack of well being and persistent fatigue or lack of energy (Bolour & Braunstein 2005).

Anabolic androgenic steroids (AAS) are a diverse class of synthetic derivatives of T and often used as performance enhancing and body image improving drugs (Onakomaiya & Henderson 2016; Piacentino et al. 2015). Originally, their administration was restricted to male elite athletes; nowadays, however, various people, including an alarmingly rising number of male adolescents take them, especially due to their easy accessibility (for a comprehensive review, see: Lumia & McGinnis 2010). Users take AAS at levels 10- to 100-fold that of therapeutic doses and also engage in 'stacking', which refers to the usage of multiple steroids simultaneously (Trenton & Currier 2005). These synthetic steroids can also play an important role in the transitioning process of trans*men who may illicitly self-administer AAS (Onakomaiya & Henderson 2016), particularly if no other option is available. Various studies confirm that AAS abuse is strongly linked to extreme mood swings, hostility, poor impulse control, unprovoked rage attacks and abnormal levels of aggression (Daly et al. 2003; for a comprehensive review see: Onakomaiya & Henderson 2016, Piacentino & Sani 2015 and Trenton & Currier 2005).

To the author's best knowledge, there are only two studies which explicitly examined how HRT effects aggression in trans*people (Slabbekoorn, Van Goozen, Gooren, Cohen-Kettenis 2001; Van Goozen, Cohen-Kettenis, Gooren, Frijda & Van de Poll 1995). Van Goozen et al. (1995) included four groups in their study: 35 trans*men, 15 trans*women, 20 cis*men, and 20 cis*women. Aggression tendencies were measured both before and at least three months after the start of HRT by questionnaire. Furthermore, trans*individuals kept a 'mood-diary' over the course of the study. The authors found no change in self-reported aggressive mood due to HRT after analyzing the diaries. By looking at the questionnaires, they found an increase in aggressive tendencies in trans*men after T replacement therapy. Interestingly however, the same effects were found in cis*women; no explanation for this phenomenon was given in the paper. Furthermore, the rise in aggression in trans*men cannot be explained by the rise of T, as the authors did not assess T levels (ibid. 1995). In a study by Slabbekoorn et al. (2001) investigating 54 trans*women and 47 trans*men undergoing HRT, it was found that both groups experienced a rise in aggressive feelings as a reaction to anger-eliciting situations after approximately 14 weeks of HRT compared to shortly before its start. The authors did not assess any hormone levels for the longitudinal part of their study, however, they analyzed T levels in a small subgroup of six trans*men during the first two weeks of HRT. They did not find an association between changing hormone levels and possible mood changes during that time. Unfortunately, no control groups were included in this study (ibid. 2001).

4 Study Aim

The main goal of this retrospective study is to examine the influence of HRT on aggression in gender dysphoric people. The focus hereby is on possible influences of T increase/decrease and E increase/decrease on three subcategories of aggression, as represented in the *Fragebogen zur Erfassung von* Aggressivitätsfaktoren (FAF) (Hampel and Selg, 1975): total aggression (as the sum of reactive aggression, spontaneous aggression and irritability), self-aggression/depression and aggression inhibition.

As described in chapter 2.4.5, there are only two studies which have investigated a possible link between the rise/fall of T and its effects on aggression in an all adult transgender sample so far. Both studies, however, show weaknesses, as they either lack a control group or hormone levels were not assessed and correlated with aggression levels. Therefore, this study tries to control these limitations by both including control groups and analyzing hormone levels.

As stated previously, no elaborate study was conducted researching possible effects of E level increase/decrease on aggression in gender dysphoric adults. Therefore, it is this study's goal to shed some light on this academic void.

The overall study sample (n = 69) consists of four groups, which were measured at two time points (time point 0 = before HRT, time point 1 = at least 4 months into HRT): trans*men (n = 25), trans*women (n = 17), cis*men (n = 11) and cis*women (n = 16). Furthermore, it is investigated whether gender identity (male, female), sex assigned at birth (male, female), and/or gender status (transgender, cisgender) have any influence on aggression before the start of hormonal treatment and/or at least four months into it. At both time points, the questionnaire *Fragebogen zur Erfassung von* Aggressivitätsfaktoren (FAF) (Hampel and Selg, 1975) was administered and hormone levels were assessed. To determine whether the administration of hormones has a direct influence on aggression changes, questionnaire score changes and changes in the hormones E (measured through total E in blood, as well as the free estradiol index (FEI)) and T (measured through total T in blood, as well as the free androgen index (FAI)) were correlated.

5 Study hypotheses

Total Aggression

There are only two studies explicitly examining the relationship between T levels and aggression in trans*men undergoing HRT. Both state that rising T levels are associated with increased aggressive behavior (Slabbekoorn et al. 2001; Van Goozen et al. 1995). Although these studies show some experimental weaknesses and other research examining the relationship between T and aggression are highly inconsistent, the author of this study believes that the following hypotheses can be drawn.

1) There will be no statistically significant differences in total aggression scores between any of the examined groups before the start of hormone replacement therapy.
2) Total Aggression levels will increase significantly in trans*men between the two examined time points.
3) Increases in total aggression levels in trans*men will significantly correlate with increases in testosterone levels.

Because HRT of trans*women consists of E as well as anti-androgens, treatments may interact and interpretations regarding a potential effect of T on total aggression may not be straight forward. Therefore, hypotheses on T effects in trans*women must remain undirectional in nature.

4) Total Aggression levels will significantly change in trans*women between the two examined time points.
5) Changes in total aggression levels in trans*women will significantly correlate with changes in testosterone levels.

As there is no sufficient research focusing on how E is involved in aggression processes, particularly on how the administration of this hormone might influence aggressive behavior, it is not possible to draw a well-grounded hypothesis concerning this matter. Therefore, analysis focusing on the association between E and aggression must be seen as explorative. The following hypothesis is therefore definded undirectional in nature:

6) Changes in total aggression levels in trans*women will significantly correlate with changes in estradiol levels.

Self-Aggression/Depression

Based on previous research which indicates a strong social component in self-aggression/depression for transgender people (De Vries et al. 2016; Dhejne et al. 2016; Gooren 2011), the following hypotheses can be drawn:

7) Self-Aggression/Depression levels will be significantly higher in the transgender sample compared to the cisgender sample at time point 0.
8) Self-Aggression/Depression levels will significantly decrease in the transgender sample between the two examined time points.
9) Increased/decreased hormone levels will not have any influence on self-aggression/depression levels in the transgender sample.

Aggression Inhibition

As there is no research on the association between either transgender status or HRT (or any hormones for that matter) and aggression inhibition, no directional hypotheses can be suggested.

10) Aggression inhibition levels will change significantly in the transgender sample due to hormone replacement therapy.

6 Materials and Methods

6.1 Study design

This project is part of a larger study entitled *Effects of sex steroid hormones on human brain function, structure and connectivity: A longitudinal study using 7 Tesla Ultrahigh-field Magnetic Resonance Imaging* that was financed by a grant awarded to Principal Investigator Assoc. Prof. PD Dr.med. R. Lanzenberger by the FWF Austrian Science Fund (P 23021, 2010– 2013) and approved by the Ethics Committee of the Medical University of Vienna, Austria (Ethics Committee No. 466/2010, http://www.univie.ac.at/ethik-kom/). Additionally, the study was performed in accordance with the Declaration of Helsinki (1964), including current revisions (World Medical Association 2008), the Austrian Arzneimittelgesetz (Bundeskanzleramt Österreich 2017), the EC-GCP guidelines (World Health Organization 2002), and the guidelines for Good Scientific Practice required at the Medical University of Vienna (Medizinische Universität Wien 2013). Participants were insured through the Department of Psychiatry in accordance with §32 of the Austrian Medicines Act. Recruitment for this longitudinal, single-blind, mono-center study started in January 2011 and ended in 2014. The participants attended five appoinments: one screening visit at which overall physical and psychiatric health was confirmed, three 3 Tesla and 7 Tesla ultrahigh-field MRI scans, which were held before treatment onset and after four weeks and four months of high-dose, long-term HRT (in control persons four weeks and four months after the first MRI scan), and a final physical examination. To avoid any ethical issues as well as decreased compliance, there was no placebo control group in the study, since the participants would have had to wait at least another three months for the start of active treatment. Participants could withdraw from the study at any time and could also be removed from the trial by the investigator if exclusion criteria were met. All participants were paid for their invested time.

This master's thesis includes data from 25 trans*women, 17 trans*men, 16 female control participants and 11 male control participants. For this study, the screening visit and the final physical examination are relevant, as not enough participants filled out the questionnaire at the first (before treatment onset), the second (4 weeks into HRT) or the third measurement (4 months into HRT) of the original study. Changes in the *Fragebogen zur Erfassung von Aggressivitätsfaktoren* (FAF) questionnaire scores were analyzed and correlated with changes in hormone levels (total testosterone, total estradiol, FAI, FEI) between the first screening visit and the last visit at least four months into HRT in order to assess any possible influences of the treatment on aggression components.

6.2 Procedure

Written informed consent was obtained from all participants prior to inclusion. The screening visit served to establish suitability and included the Structured Clinical Interview for DSM-IV[18] diagnosis (SCID) performed by an experienced psychiatrist to investigate possible psychiatric symptoms, a standard physical examination, a blood pressure reading, an electrocardiogram (ECG) and blood sampling of routine parameters. Additionally, a urine drug test was carried out as well as a urine pregnancy test for all assigned females at birth at the screening visit and on the day of the first fMRI measurement. Participants were asked to fill out several questionnaires including the FAF to measure different components. After the three fMRI measurement visits all participants completed a final visit, involving a physical examination and check-up of blood routine parameters. Blood samples were drawn on all five visits to monitor health and changes in hormonal levels. Participants received financial compensation for their invested time.

6.3 Participants

69 persons took part in this study. Transgender persons were recruited through the Unit for Gender Dysphoria (OÄ.in Dr.in Ulrike Kaufmann, MD) at the Department of Obstetrics and Gynecology of the General Hospital in Vienna, before starting HRT. 25 trans*men 19 to 35 years of age (mean age ± SD = 26.0 ± 6.0 years) and 17 trans*women 20 to 39 years of age (mean age ± SD = 29.5 ± 7.0 years) took part in this study. Furthermore, 16 female controls 20 to 39 years of age (mean age ± SD = 29.5 ± 7.0 years) and 11 male controls 20 to 39 years of age (mean age ± SD = 29.5 ± 7.0 years) were recruited by means of a flyer to participate in this study.

[18] As the main study *Effects of sex steroid hormones on human brain function, structure and connectivity: A longitudinal study using 7 Tesla Ultrahigh-field Magnetic Resonance Imaging* had already started in 2010, the DSM-IV was still used for this study instead of the 2013 introduced DSM-5.

6.3.1 Inclusion criteria

The following criteria were used to determine suitability of potential participants for this project:

Table 6: Inclusion criteria

Inclusion criteria
General physical health based on history, physical examination, ECG, laboratory screening
Willingness and competence to sign informed consent forms
18 -50 years of age
Applies only to transgender participants: DSM-IV diagnosis of Gender Identity Disorder (DSM-IV: 302.85; ICD-10: F64.0) by a structured clinical interview (SCID)

6.3.2 Exclusion criteria

Fulfilling one of the following criteria, the respective person was excluded from this study:

Table 7: Exclusion criteria

Exclusion criteria
Severe neurological or internal disease
Abnormal results in routine laboratory screening or general physical examination
Chronic or continuous medication intake
Steroid hormone treatment within 2 months of inclusion (including hormonal contraception and phytohormones)
Treatment with psychopharmacological medication
Current drug abuse (determined using a urine drug screening test at the screening visit)
Pregnancy (determined using a urine pregnancy test at the screening visit and at the first MRI scan)
Failure to comply with the study protocol or to follow the instructions of the investigating team
Lack of MRI suitability, intracorporeal metal (including all metal implants and stainless steel grafts excluding dental amalgam implants), severe claustrophobia
Applies only to control participants: no psychiatric or mental disorder, (assessed by the German version of the structured interview of DSM-IV (SCID), the Hamilton Anxiety scale (HAMA) and the Hamilton Depression rating scale (HAMD))

6.4 Hormone Replacement Therapy

Transgender participants received HRT in line with protocols routinely implemented at the Department of Obstetrics and Gynecology, Unit for Gender Identity Disorder (OÄ.in Dr.in Ulrike Kaufmann, MD) at the Medical University of Vienna. Trans*men obtained either 1000 mg T undecanoate (Nebido®, 4ml vial, intramuscular) every 12 weeks or 50 mg T (Testogel® 50mg/5g bag, transdermal) per day. If menstruation still occurred, they additionally received either 2-3 tablets lynestrenol (Orgametril® 5mg tablets, oral) per day or 1 tablet desogestrel (Cerazette® 75µg tablet, oral) per day. Trans*women recieved 50 mg cyproterone acetate (Androcur® 50 mg tablet, oral) per day. Additionally, trans*women, received 4 mg E hemihydrate (Estrofem® 2 mg tablets, oral) per day. Alternatively, 0.75-1.5mg (1-2 hubs) E could be administered (Estro-Gel® 0.75mg/1.25mg, transdermal). In case of extensive hair loss trans*women received 2.5mg alpha-5-reductase-inhibitor Finasterid (Actavis®/Arcana® /Aurobindo® 5mg tablets, oral) every second day. Both trans*men and *women were additionally offered a GNRH analogue in some cases: either triptorelin acetate 105µg (Decapeptyl® 0.1mg prefilled syringe, s.c.) daily, triptorelin acetate 4.12mg (Decapeptyl® 172mg powder for suspension for injection s.c. or i.m.) every month or 11.25mg leuprorelin acetate (Trenantone® 130mg powder for suspension for injection s.c.) every three months.

6.5 Questionnaire for measuring factors of aggression

The *Fragebogen zur Erfassung von Aggressivitätsfaktoren* (FAF) used by Hampel and Selg (1975) is a self-administered questionnaire, which measures five components of aggressive behavior through 66 items: spontaneous aggression (19 items), reactive aggression (13 items), irritability (13 items), self-aggression/depression (11 items) and aggression inhibition (10 items). A total aggression score, which indicates the willingness to show aggression outwardly, can be determined by adding up the scores of the first three factors.

Persons who score high on the spontaneous aggression scale describe themselves as high tempered and to show sadistic tendencies such as verbal, physical or fantasized aggression against animals and/or other human beings. Those with low scores characterize themselves as self-controlled and calm. In most cases reactive aggressions are socially sanctioned, with high scores indicating a distinct assertiveness while maintaining a conformist basic attitude, low scores meaning disaffirmation of aggressive behavior. High irritability scores reflect a deficit in emotion-regulation, a low frustration tolerance and increased impulsivity and anger (Hampel & Selg 1975; Heubrock & Petermann 2008). The following example-questions,

which are taken directly from the questionnaire and translated from German by the author of this master's thesis, are components of the total aggression scale (Hampel & Selg 1975)[19]:

	true	
When I get really angry, it's possible that I might slap someone.	yes	no
I'm easily agitated when offended.	yes	no
There is often disagreement between myself and others.	yes	no
When I'm angry, I say horrible things.	yes	no
I remember having been so furious that I took the next best thing and tore it apart or smashed it.	yes	no

The self-aggression/depression scale includes self-reproaches, depression, distrust and a suicidal tendency. Persons with high scores express dissatisfaction and a negative attitude towards life in general (Hampel & Selg 1975; Heubrock & Petermann 2008). The following example-questions, which are taken directly from the questionnaire and translated from German by the author of this master's thesis, are components of the self-aggression/depression scale (Hampel & Selg 1975)[20]:

[19] Original questions in German (Hampel & Selg 1975):
Wenn ich wirklich wütend werde, bin ich in der Lage, jemandem eine runterzuhauen.
(stimmt: ja – nein)
Ich bin leicht aus der Ruhe gebracht, wenn ich angegriffen werde.
(stimmt: ja – nein)
Zwischen anderen und mir gibt es oft Meinungsverschiedenheiten.
(stimmt: ja – nein)
Wenn ich wütend bin, sage ich Ungehöriges.
(stimmt: ja – nein)
Ich kann mich erinnern, mal so zornig gewesen zu sein, dass ich das nächstbeste Ding nahm und es zerriss oder zerschlug.
(stimmt: ja – nein)

[20] Original questions in German (Hampel & Selg 1975):
Ich tue vieles, was ich hinterher bereue.
(stimmt: ja – nein)
Manchmal bin ich bedrückt, ohne dass ich recht weiß, warum.

	true	
I do a lot of things which I regret afterwards.	yes	no
Sometimes I feel depressed without really knowing why.	yes	no
Considering all the sorrow in this world, one can only wish to never have been born in the first place.	yes	no
I often feel that I'm not leading a proper lifestyle.	yes	no
I've seriously considered suicide before.	yes	no

Aggression inhibition can be seen as the antagonist to the spontaneous aggression scale. It is defined as the knowledge about socially accepted norms and values, which means that persons with very high scores tend to overthink and put a lot of pressure on their social conscience, whereas people with very low scores might act unethically or ruthless in social situations (Hampel & Selg 1975; Heubrock & Petermann 2008). The following example-questions, which are taken directly from the questionnaire and translated from German by the author of this master's thesis, are components of the aggression inhibition scale (Hampel & Selg 1975)[21]:

(stimmt: ja – nein)
Bedenkt man alles Leid auf dieser Erde, so kann man eigentlich nur wünschen, nicht geboren zu sein.
(stimmt: ja – nein)
Ich fühle oft, dass ich nicht den richtigen Lebenswandel führe.
(stimmt: ja – nein)
Ich habe schon mal ernstlich an Selbstmord gedacht.
(stimmt: ja – nein)

[21] Original questions in German (Hampel & Selg 1975):
Ich kann mir keinen triftigen Grund dafür denken, dass man jemanden schlagen muss.
(stimmt: ja – nein)
Wenn ich etwas Unrechtes tue, straft mich mein Gewissen heftig.
(stimmt: ja – nein)
Lieber gebe ich mal in einem Punkt nach, als dass ich mich darüber streite.
(stimmt: ja – nein)

	true	
I cannot think of any good reason to hit someone.	yes	no
If I act wrongly, I get a very bad conscience.	yes	no
Most of the time I prefer giving in rather than fighting.	yes	no

Furthermore, the questionnaire contains 10 items which belong to an openness control scale and one warm-up question. Respondents are asked to choose whether a statement applies to them or not. The Cronbach's Alpha values for each scale quantifying aggressive behavior, ranging from .65 to .85, indicate acceptable internal consistency at the least. The FAF's theoretical basis follows aggressive behavior models originated from the field of psychology of learning (Hampel & Selg 1975).

6.6 Statistical Analysis

For statistical data analysis IBM SPSS Statistics 24 was used. Four different group categories and their subgroups were included in the analysis: sex assigned at birth (male, female), gender identity (male, female), gender status (transgender, cisgender), and individual groups (trans*men, trans*women, cis*men, cis*women). Hormone levels (T and E) and questionnaire results were analyzed for each group at two different time points: before HRT and at least 4 months into HRT. Furthermore, changes over these two timepoints were examined. To estimate free (non-protein-bound, bioavailable) T and E, the free androgen index (FAI), which is the molar ratio of total testosterone/sex hormone binding globulin (SHBG) and the free estradiol index (FEI), which is the the molar ratio of estradiol/SHBG, were calculated (Huang et al. 2007; Rexrode et al. 2003). As the questionnaire data is not normally distributed (examined with skewness and kurtosis values, Kolmogorov-Smirnov test, Shapiro-Wilk test, histogram and Q-Q-diagram) and the sample size is not large enough, non-parametric testing was performed. Median and range were calculated for each of these variables. To show hormone changes within each individual group between the two different time points, the Wilcoxon-Signed Rank test was used. To compare two groups at one time point, the Mann-Whitney-U test was applied. The Wilcoxon-Signed Rank test was used to

compare results of the same group at the two different time points. The Kruskal-Wallis test was performed for the category 'individual groups', as it consists of more than two subgroups. The two-tailed level of significance was 0.05 for all FAF questions. Post-hoc pairwise comparisons were computed and Bonferroni corrected[22] for multiple comparisons ($p < 0.0018$). Furthermore, effect sizes of significant results were calculated in order to estimate the explanatory power of the examined variable. Changes in hormone levels and changes in aggression scores were correlated (Spearman's rank order correlation) to show any possible relationship between them.

[22] The Bonferroni correction is used to adjust probability values when several dependent or independent statistical tests are carried out on a single data set. It is necessary because the risk of identifying at least one significant result due to chance (type I error), increases as more hypotheses are tested.

7 Results

7.1 Hormones

Table 8 shows the mean and standard deviations for testosterone, free androgen index (FAI), estradiol and free estrogen index (FEI), for all four individual groups at the different measurements.

Table 8: Hormone levels before and at least 4 months into HRT

	Estradiol (pg/ml) Time Point 0	Estradiol (pg/ml) Time Point 1	FEI (nmol/l) Time Point 0	FEI (nmol/l) Time Point 1	Testosterone (ng/ml) Time Point 0	Testosterone (ng/ml) Time Point 1	FAI (nmol/l) Time Point 0	FAI (nmol/l) Time Point 1
Trans*men	140.9 ± 113.4	77.7 ± 74.3	0.9052 ± 0.83326	0.7660 ± 0.53991	0.37 ± 0.18	5.28 ± 2.11	2.4888 ± 1.94583	58.1916 ± 48.23618
Trans*women	40.7 ± 42.1	108 ± 97.7	0.4671 ± 0.55437	0.6747 ± 0.59391	4.95 ± 1.4	1.03 ± 2.23	46.3476 ± 14.99508	8.1265 ± 17.65455
Cis*men	24.3 ± 8.1	25.5 ± 11.9	0.2627 ± 0.09056	0.2700 ± 0.08258	5.37 ± 1.36	5.62 ± 2.26	55.1518 ± 13.26008	55.5564 ± 16.45089
Cis*women	108.1 ± 126.9	109.6 ± 111.7	0.6419 ± 0.80224	0.6187 ± 0.45247	0.31 ± 0.16	0.29 ± 0.11	1.9681 ± 1.60957	1.8631 ± 1.15327

Analyzed hormone levels (E, FEI, T, FAI) did neither change in cis*women nor cis*men between timepoint 0 and timepoint 1. E decreased significantly ($p = .014$), whereas T and FAI increased significantly (both: $p < .001$) in trans*men between timepoint 0 and timepoint 1. FEI decreased, but not significantly between the two time points in this group. In trans*women, E and FEI increased significantly (E: $p = .002$; FEI: $p = .031$), T and FAI decreased significantly (T: $p = .001$; FAI: $p < .001$) within the same time frame.

7.2 Aggression

Table 9 shows the median and range for total aggression, self-aggression/depression and aggression inhibition for all groups including their subcategories at the two different time points.

Table 9: Aggression Scores before and at least 4 months into HRT

Total Aggression	Sample Size	Time Point 0	Time Point 1
Sex assigned at birth			
Male	28	4.50 ± 16	4.00 ± 18
Female	41	6.00 ± 26	22.00 ± 39
Gender identity			
Male	36	4.50 ± 26	22.00 ± 40
Female	33	6.00 ± 19	5.00 ± 24
Gender status category			
Transgender	42	5.00 ± 26	19.50 ± 40
Cisgender	27	6.00 ± 19	5.00 ± 24
Group			
Trans*men	25	5.00 ± 26	25.00 ± 22
Trans*women	17	5.00 ± 16	3.00 ± 18
Cis*men	11	4.00 ± 11	4.00 ± 12
Cis*women	16	6.00 ± 19	5.00 ± 23
Self-Aggression/Depression	Sample Size	Time Point 0	Time Point 1
Sex assigned at birth			
Male	28	2.00 ± 10	2.00 ± 10
Female	41	2.00 ± 10	2.00 ± 9

Self-Aggression/Depression	Sample Size	Time Point 0	Time Point 1
Gender identity			
Male	36	1.00 ± 10	1.50 ± 9
Female	33	2.00 ± 10	2.00 ± 10
Gender status category			
Transgender	42	2.00 ± 10	2.00 ± 10
Cisgender	27	1.00 ± 7	1.00 ± 7
Group			
Trans*men	25	2.00 ± 10	2.00 ± 9
Trans*women	17	3.00 ± 10	3.00 ± 10
Cis*men	11	1.00 ± 6	1.00 ± 6
Cis*women	16	2.00 ± 7	1.50 ± 7
Aggression Inhibition	Sample Size	Time Point 0	Time Point 1
Sex assigned at birth			
Male	28	4.00 ± 8	5.00 ± 10
Female	41	4.00 ± 8	4.00 ± 10
Gender identity			
Male	36	4.00 ± 8	4.00 ± 10
Female	33	4.00 ± 8	4.00 ± 10
Gender status category			
Transgender	42	5.00 ± 9	4.00 ± 10
Cisgender	27	3.00 ± 7	4.00 ± 10
Group			
Trans*men	25	5.00 ± 8	4.00 ± 10
Trans*women	17	5.00 ± 8	5.00 ± 10
Cis*men	11	3.00 ± 3	4.00 ± 4
Cis*women	16	2.50 ± 7	4.00 ± 10

All significant results, their Bonferroni correction and effect size are shown in table 10.

Table 10: Overview of significant results, Bonferroni correction[23] and effect sizes

Comparison				Comparison		Test	Significance ($p < 0.05$)	Effect Size ($r = \frac{Z^2}{N-1}$)
Group 1	**Group 2**	**Group 3**	**Group 4**	**Time Point 0**	**Time Point 1**			
Total Aggression								
Assigned females at birth	Assigned males at birth				X	Mann-Whitney-U	$p < 0.001$*	r = 0.35 → medium
Assigned females at birth				X	X	Wilcoxon-Signed-Ranks	$p < 0.001$*	r = 0.51 → large
Gender identity female	Gender identity male				X	Mann-Whitney-U	$p < 0.001$*	r = 0.32 → medium
Gender identity male				X	X	Wilcoxon-Signed-Ranks	$p < 0.001$*	r = 0.57 → large
Transgender	Cisgender				X	Mann-Whitney-U	$p < 0.001$*	r = 0.20 → small
Transgender				X	X	Wilcoxon-Signed-Ranks	$p < 0.001$*	r = 0.44 → medium
Trans*men	Trans*women	Cis*men	Cis*women		X	Kruskal-Wallis	$p < 0.001$*	r = 0.68 → large
Trans*men				X	X	Wilcoxon-Signed-Ranks	$p < 0.001$*	r = 0.79 → large
Self-Aggression/Depression								
Transgender	Cisgender			X		Mann-Whitney-U	p = .036	r = 0.065 → small
Aggression Inhibition								
Transgender	Cisgender			X		Mann-Whitney-U	p = .026	r = 0.073 → small

[23] All results which remained significant after the Bonferroni correction are marked with *.

7.2.1 Total Aggression

While there was no difference in the total aggression score between assigned females at birth and assigned males at birth at time point 0, assigned females at birth scored significantly higher on the same scale than assigned males at birth at time point 1 (figure 3). The effect size is considered medium strong with r = .35. This was due to an increase in total aggression score in trans*males, as can be seen in figure 10. Furthermore, total aggression scores of assigned females at birth at time point 1 are significantly higher than those of time point 0 (large effect size: r = .51) (figure 4).

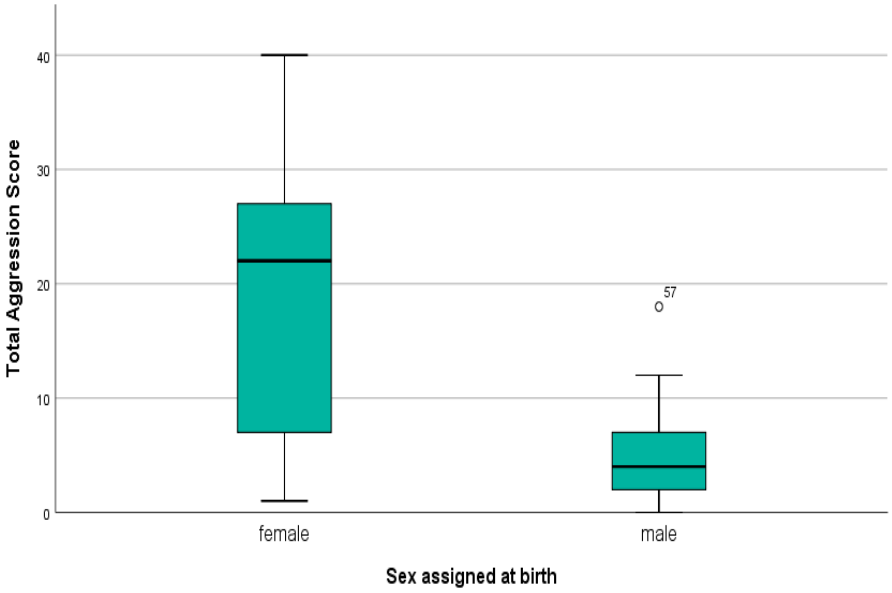

Figure 3: Total aggression scores for sex assigned at birth at time point 1

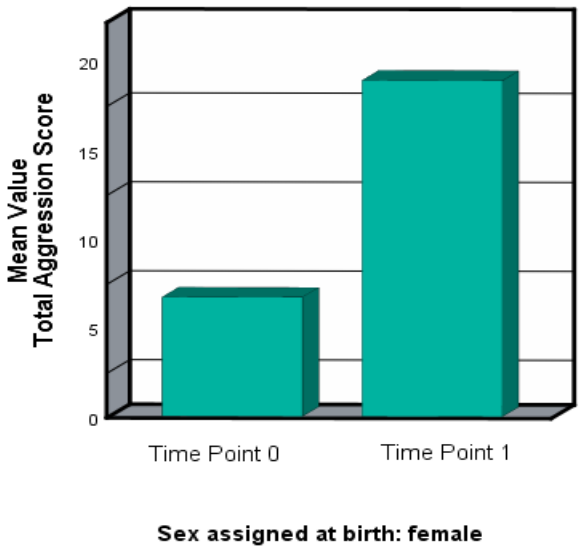

Figure 4: Change of total aggression scores for females assigned at birth between two time points

Persons with a male gender identity have a significantly higher total aggression score than individuals with a female gender identity at time point 1 (medium effect size: r = .32) (figure 5), whereas there is no difference in this scale between these two groups at time point 0. Furthermore, total aggression scores of male gender identity at time point 1 are significantly higher than those of time point 0 (figure 6). This result is with an effect size of 0.57 quite large.

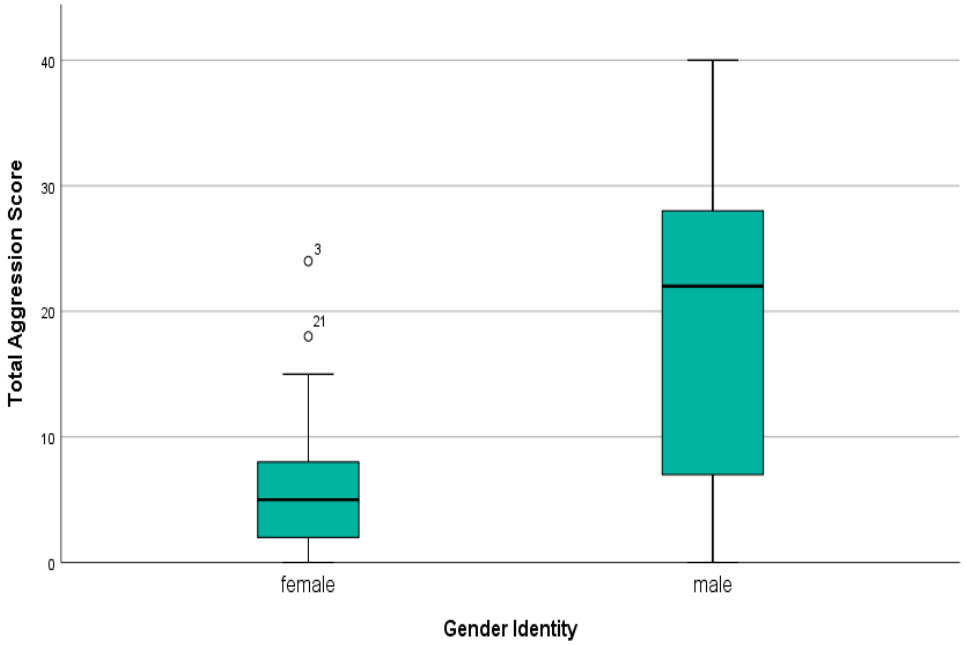

Figure 5: Total aggression scores for gender identity at time point 1

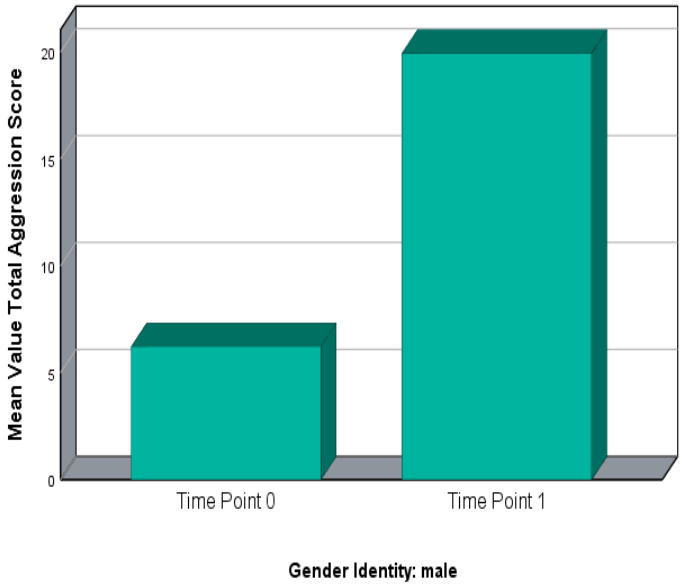

Figure 6: Change of total aggression scores for male gender identity between two time points

There were no significant differences between the transgender sample and the cisgender sample in the total aggression score at time point 0, however, they differed significantly at time point 1 (figure 7). Furthermore, the transgender sample showed significantly higher scores at time point 1 compared to time point 0, whereas the cisgender sample scores do not differ between these time points (figure 7).

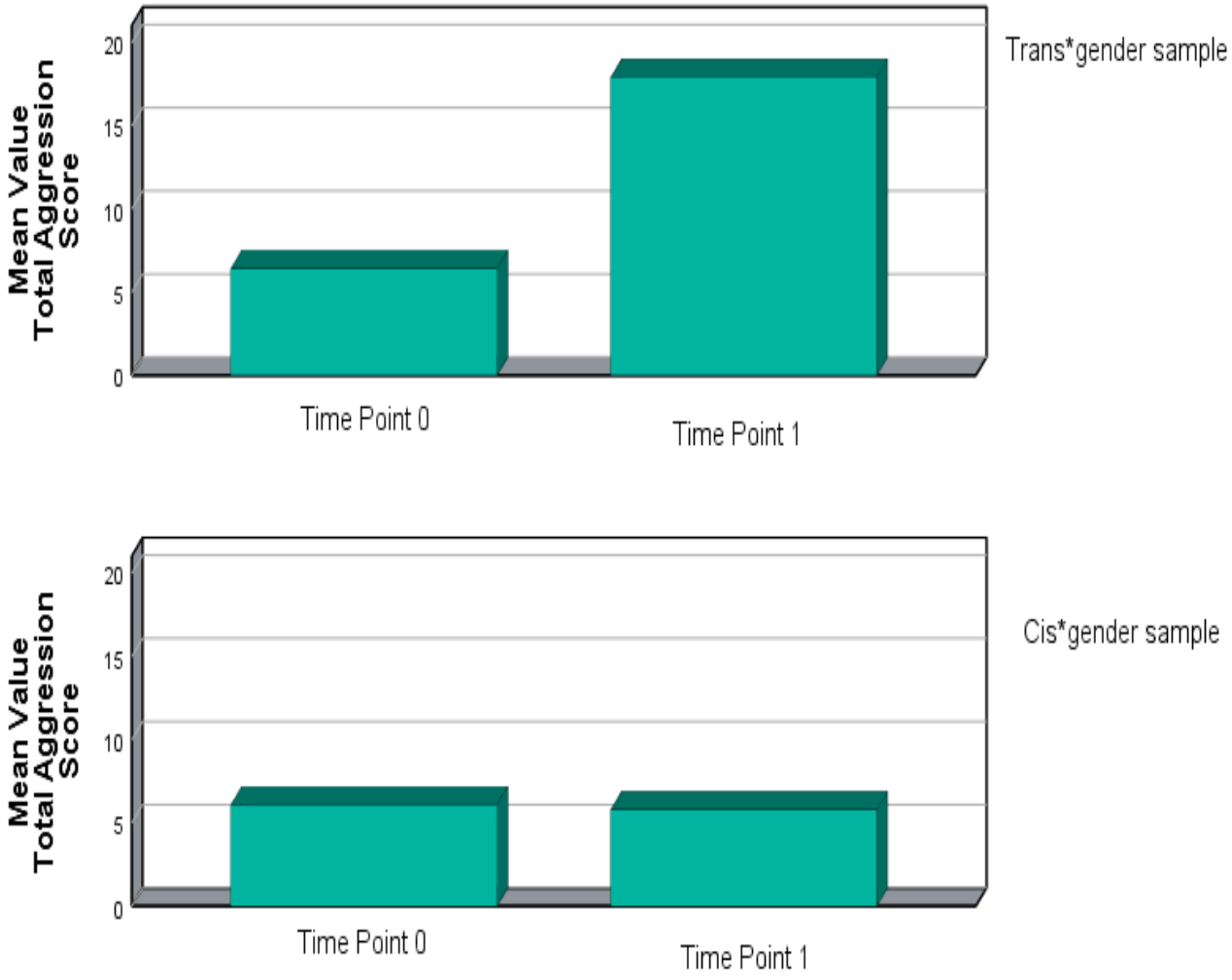

Figure 7: Comparison of total aggression scores between the transgender and the cisgender sample at time point 0, time point 1 and between both time points

There are no significant differences between the analyzed groups (cis*women, cis*men, trans*women, trans*men) at time point 0 (figure 8), however, they differ significantly at time point 1 (figure 9). Looking at each group individually, median values of the total aggression score in trans*men are significantly higher at time point 1 than time point 0 (figure 10). This finding is backed up by the strong effect size of r = .79. In trans*women, a decrease in total aggression scores can be noticed, however, it is not significant. Total aggression scores do not differ between these two time points in any of the cis*groups.

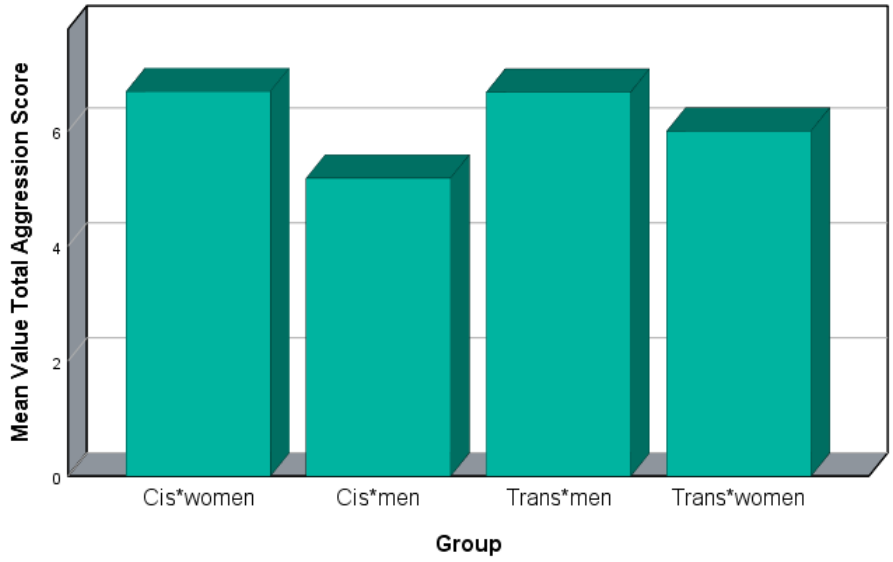

Figure 8: Total aggression scores in each group before HRT

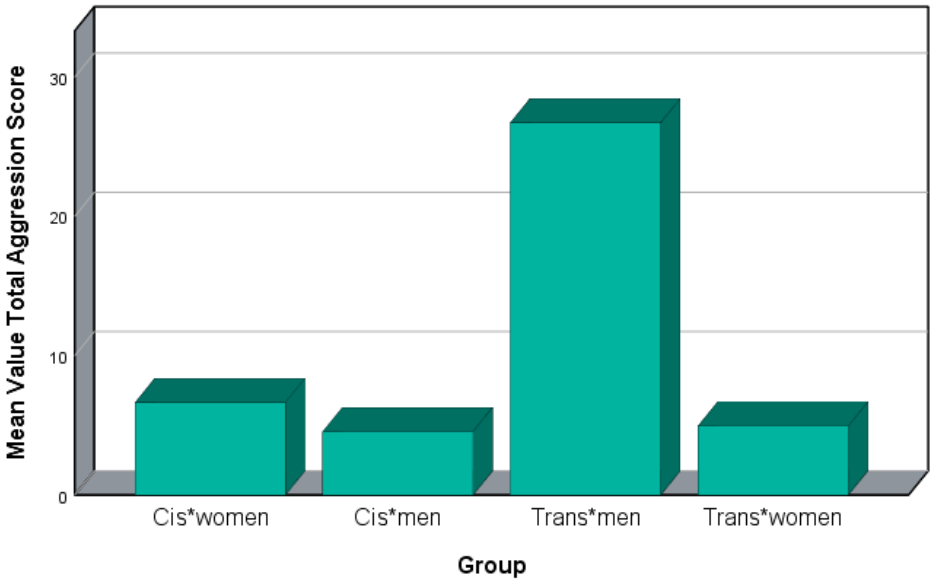

Figure 9: Total aggression scores in each group at least 4 months into HRT

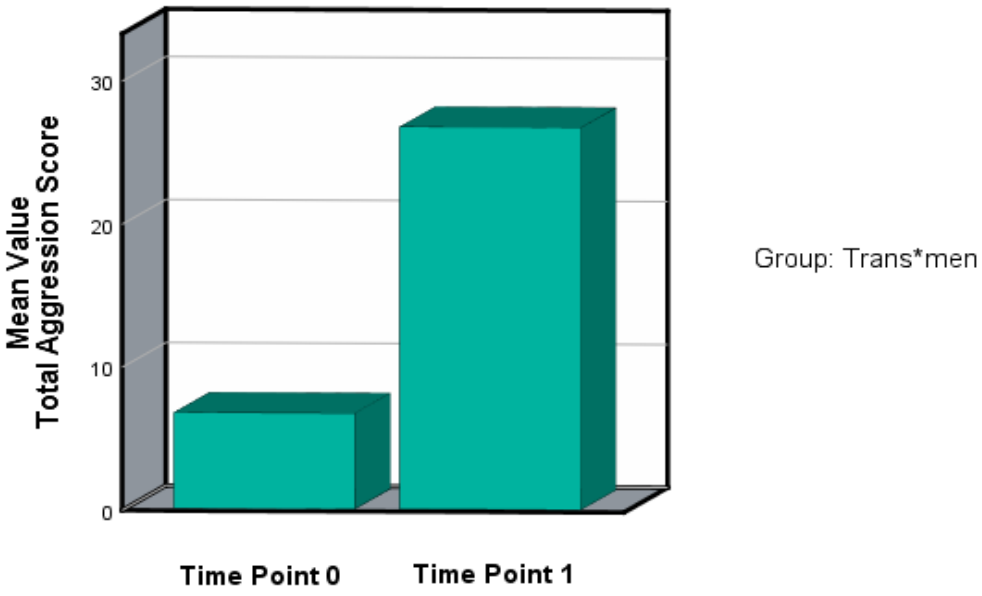

Figure 10: Total aggression scores in trans*men before HRT and at least 4 months into it

7.2.2 Self-Aggression/Depression

No significant differences were found for the categories sex assigned at birth, gender identity or individual group, neither at one time point or between two time points.

Self-Aggression/Depression scores are significantly higher for the transgender sample than the cisgender sample at time point 0 (figure 11), but not time point 1. However, Bonferroni correction shows that this significance cannot be held. Therefore, only a tendency for transgender individuals to have a higher self-aggression/depression score than the cisgender sample can be stated. This difference vanished at time point 1, although the decrease of self-aggression/depression in the transgender sample was not significant.

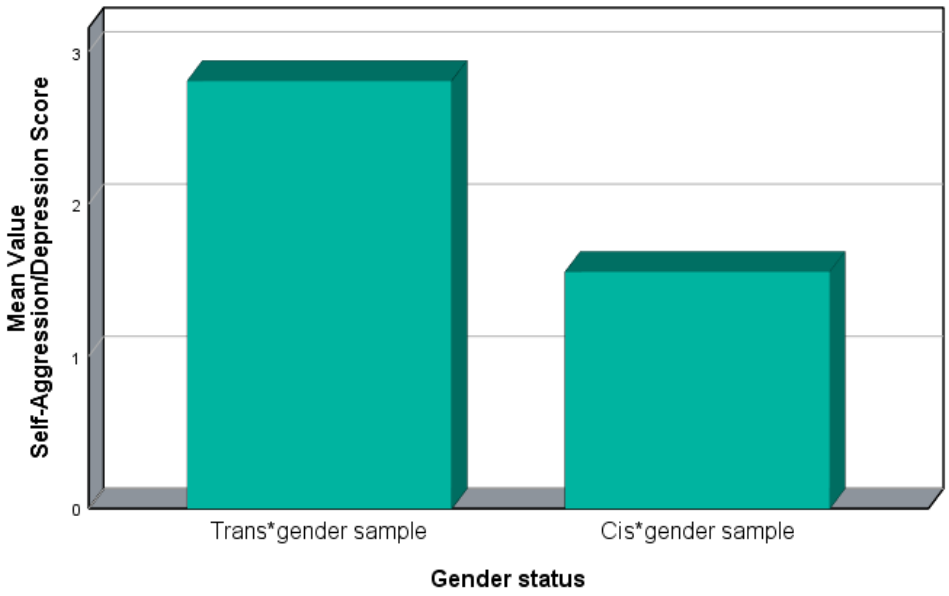

Figure 11: Self-Aggression/Depression scores for gender status before the start of HRT

There is no significant difference between groups, although statistics show a tendency for trans*women to reach the highest scores on this scale at time point 0 (p = .061) (figure 12).

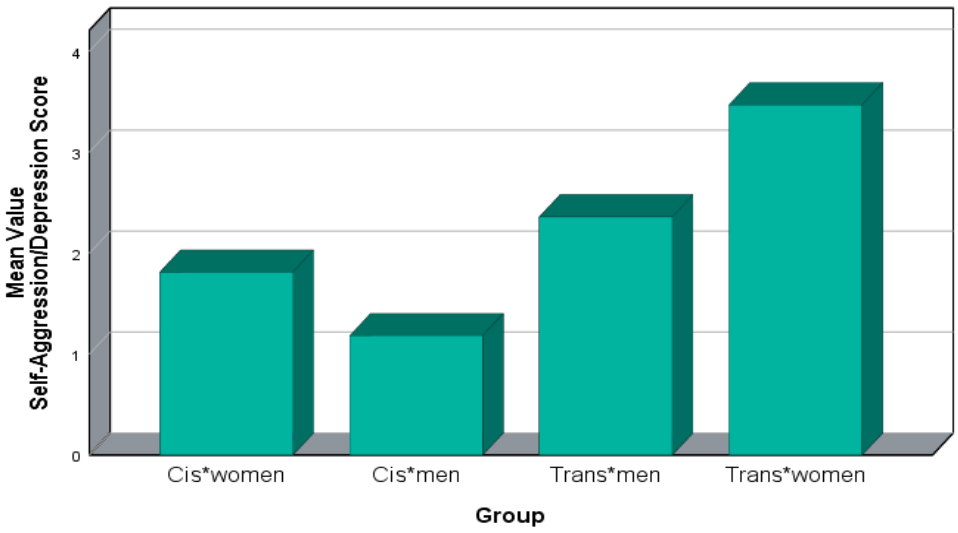

Figure 12: Self-Aggression/Depression scores for each group before the start of HRT

7.2.3 Aggression inhibition

No significant differences were found for the categories sex assigned at birth, gender identity or individual group, neither at one time point or between two time points.

Aggression inhibition scores were, however, significantly higher for the transgender sample compared with the cisgender sample at time point 0 (figure 13), but not at time point 1. Again, this observation must be seen as a trend after Bonferroni correction.

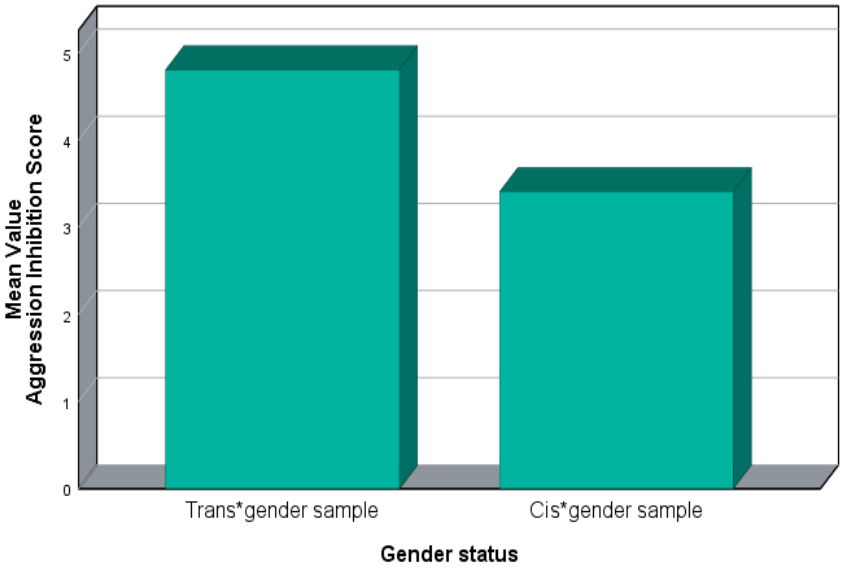

Figure 13: Aggression inhibition scores for gender status before the start of HRT

7.3 Correlation values between hormone changes and aggression score changes

The following tables in each sub-chapter show correlation values and significance levels[24] between hormonal changes (FAI changes, T changes, FEI changes, E changes) and aggression score changes (total aggression score changes, self-aggression/depression score changes, aggression inhibition score changes) between the two measured time points. As hormones did not change in the cisgender group and are therefore not necessary for this overview, these values were left out.

7.3.1 Correlation between hormonal changes and total aggression score changes

Table 11: Correlation values between hormonal changes and total aggression score changes

Total Aggression Change	Sample Size	FAI change		Testosterone change		FEI change		Estradiol change	
		r	p	r	p	r	p	r	p
Sex assigned at birth									
Male	28	.229	.242	.082	.679	-.224	.251	.123	.532
Female	41	.662*	< 0.001	.657*	< 0.001	.007	.964	-.135	.401
Gender identity									
Male	36	.460*	.005	.546*	.001	-.020	.907	-.242	.155
Female	33	.233	.192	.214	.231	.194	.278	.502*	.003
Gender status category									
Transgender	42	.695*	< 0.001	.636*	< 0.001	-.156	.324	-.394*	.010
Group									
Trans*men	25	-.068	.764	-.043	.840	-.005	.982	.052	.805
Trans*women	17	.392	.119	-.110	.674	-.173	.506	.396	.116

Legend: r = correlation, p = significance

Total aggression score changes correlated positively and significantly with FAI changes and T changes in three groups: assigned females at birth, persons with male gender identity and the transgender group. In assigned females at birth (figure 14) and the transgender group (figure 15), correlations were high.

[24] All significant results are marked with *.

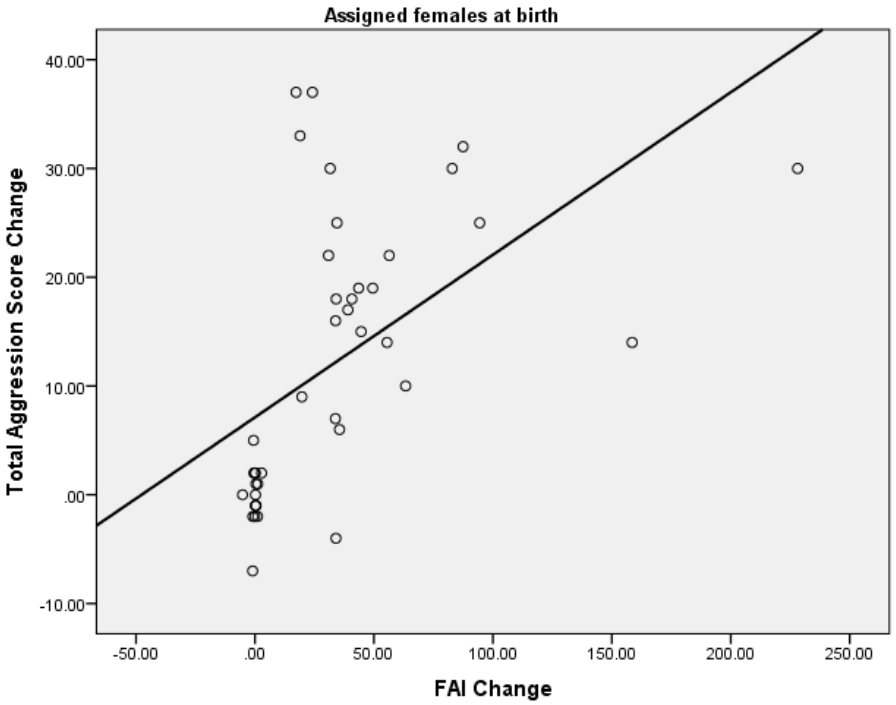

Figure 14: Correlation between total aggression score changes and FAI level changes in assigned females at birth

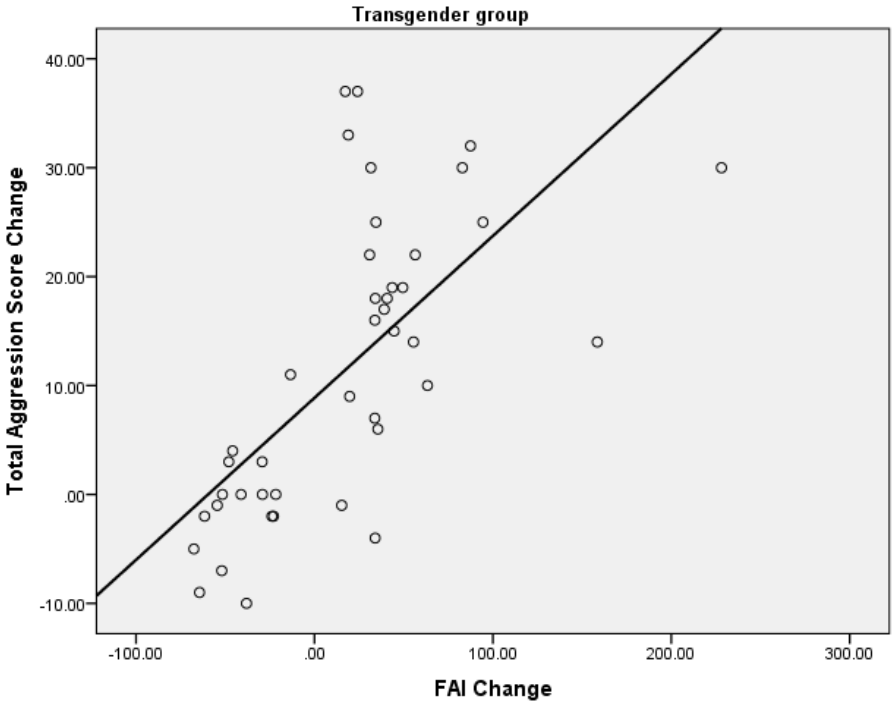

Figure 15: Correlation between total aggression score changes and FAI level changes in the transgender group

T change correlations with total aggression score changes were also high in the male gender identity group (figure 16), with FAI changes in a medium range (figure 17).

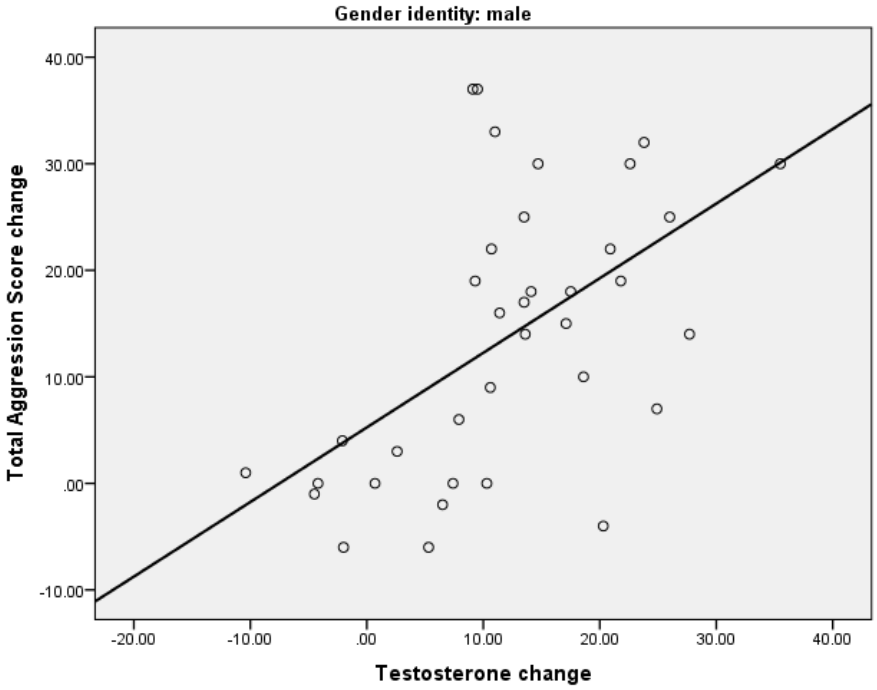

Figure 16: Correlation between total aggression score changes and testosterone level changes in male gender identity

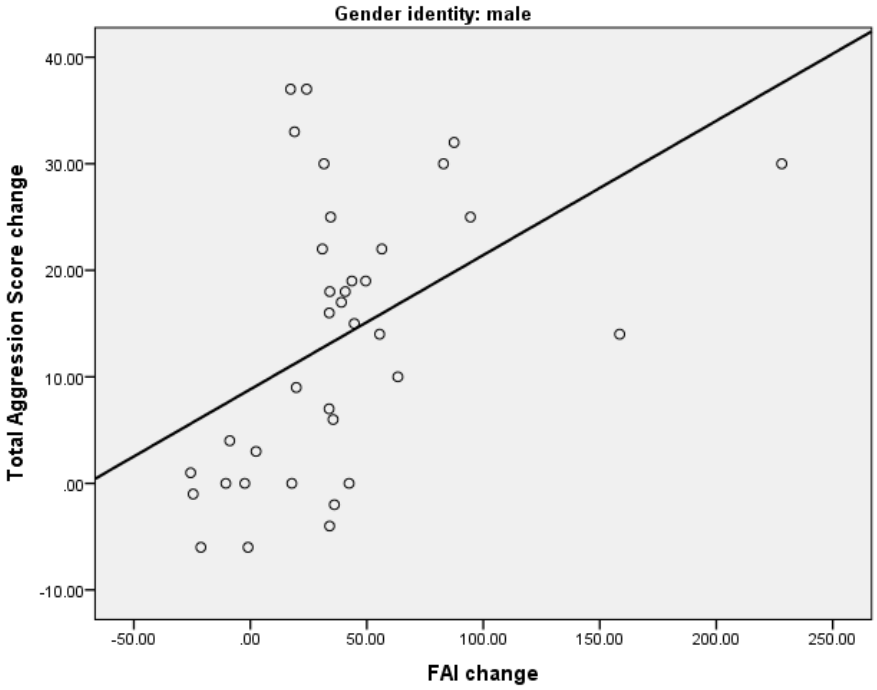

Figure 17: Correlation between total aggression score changes and FAI level changes in male gender identity

E changes and total aggression scores changes correlated positively and highly significant on a medium level in people with a female gender identity (figure 18). However, after splitting the group in cis*women (figure 19) and trans*women (figure 20), only cis*women showed the same pattern.

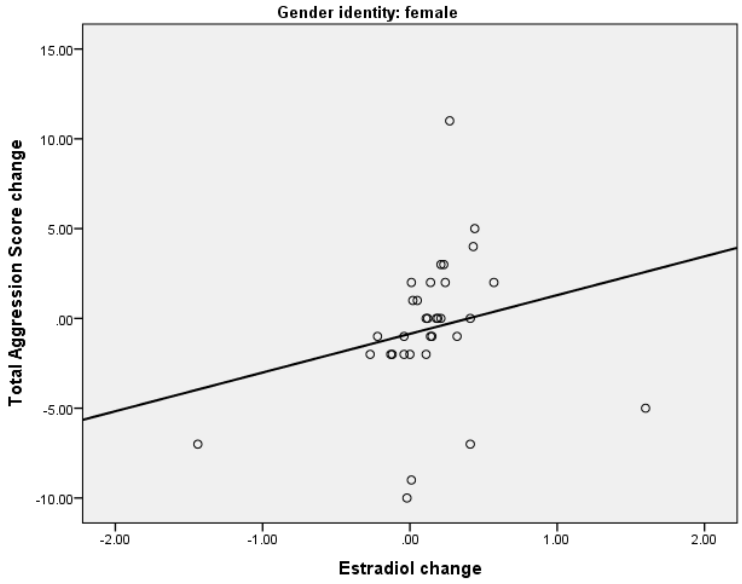

Figure 18: Correlation between total aggression score changes and estradiol level changes in female gender identity

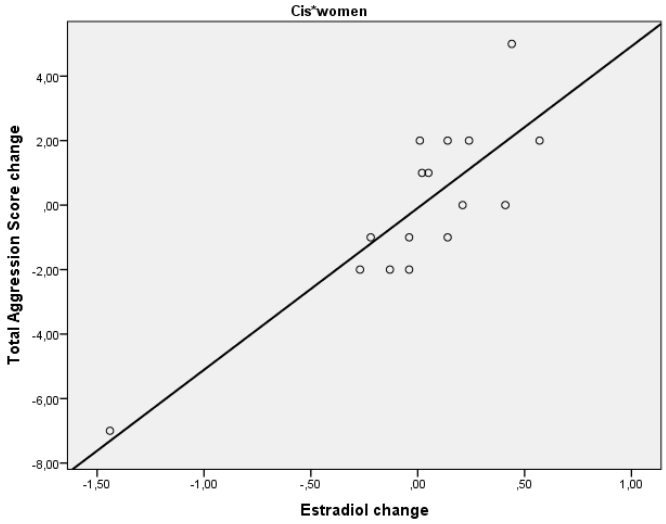

Figure 19: Correlation between total aggression score changes and estradiol level changes in cis*women

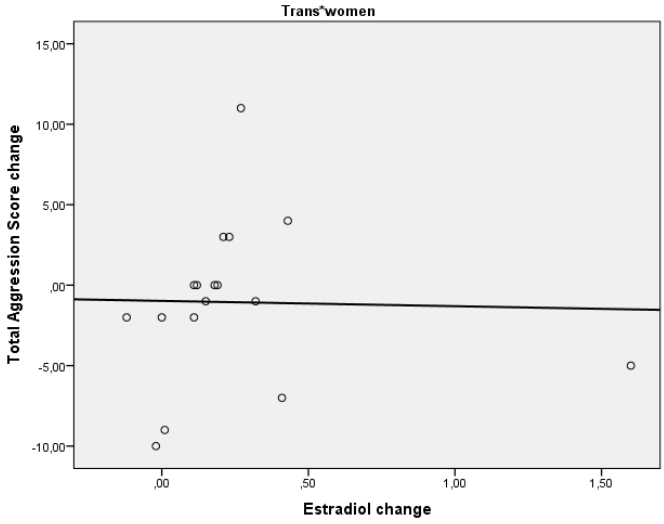

Figure 20: Correlation between total aggression score changes and estradiol level changes in trans*women

Furthermore, E changes correlated negatively and highly significant with total aggression score changes on a medium level in the transgender group (figure 21).

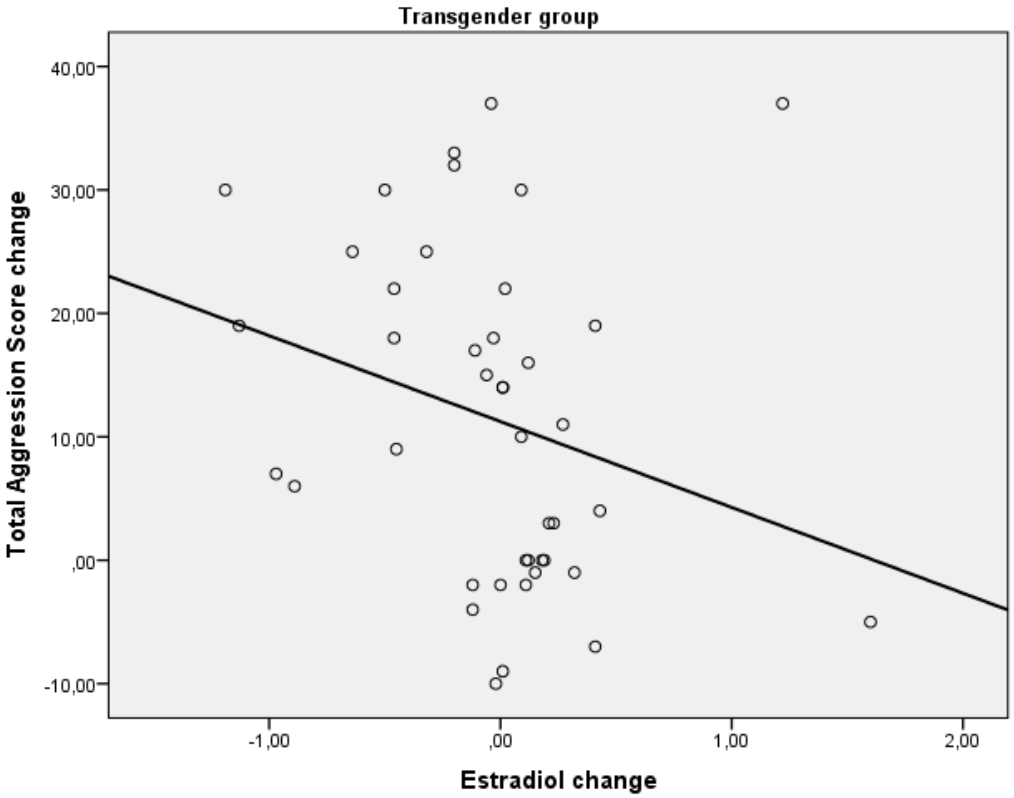

Figure 21: Correlation between total aggression score changes and estradiol level changes in the transgender group

In all other constellations (including trans*men and -*women as separate subgroups), no, or at least no significant correlation was detected.

7.3.2 Correlation between hormonal changes and self-aggression/depression score changes

Table 12: Correlation values between hormonal changes and self-aggression/depression score changes

Self-Aggression/Depression Change	Sample Size	FAI change		Testosterone change		FEI change		Estradiol change	
		r	p	r	p	r	p	r	p
Sex assigned at birth									
Male	28	.220	.261	.184	.350	-.369	.053	-.022	.913
Female	41	-.190	.235	-.208	.192	.207	.194	.253	.110
Gender identity									
Male	36	-.164	.339	-.198	.248	.102	.555	.162	.346
Female	33	.355*	.042	.284	.110	-.073	.684	.151	.400
Gender status category									
Transgender	42	.047	.770	.002	.991	-.075	.637	.130	.413
Group									
Trans*men	25	.046	.826	-.007	.972	.123	.557	.161	.442
Trans*women	17	.242	.350	.023	.931	-.432	.084	.225	.385

Legend: r = correlation, p = significance

On a medium level, FAI changes and self-aggression/depression score changes correlated positively in people with a female gender identity (figure 22). After splitting this group in cis*women (figure 23) and trans*women (figure 24), the same tendency could be shown in both subgroups and to an even larger extent in the trans*women group than the cis*women sample, although it did not remain significant.

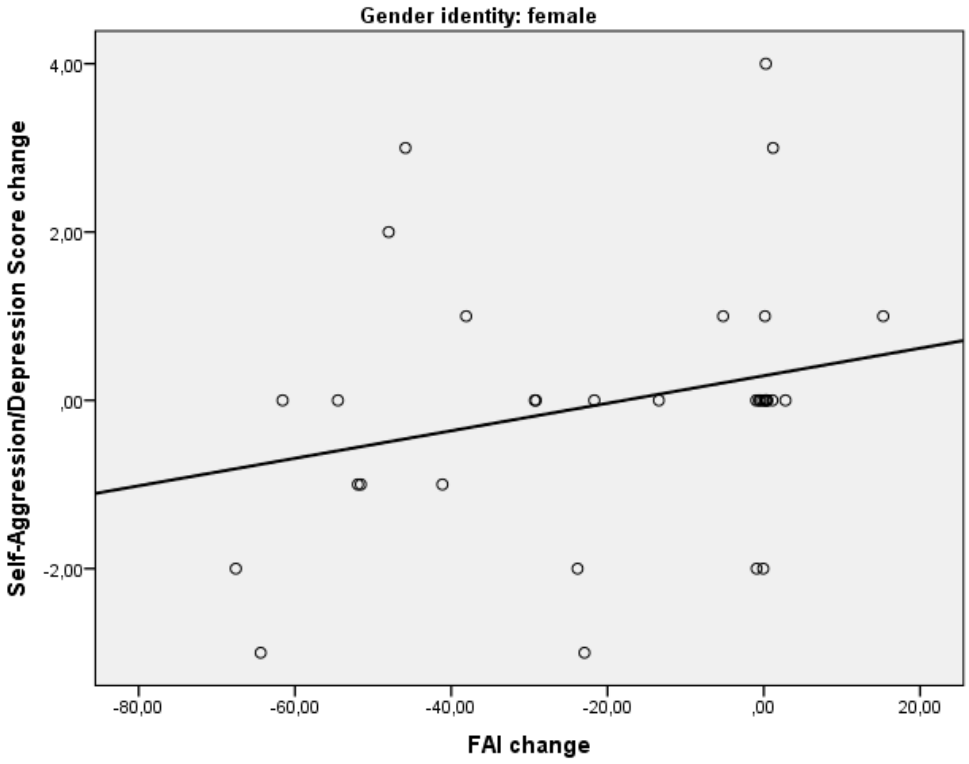

Figure 22: Correlation between self-aggression/depression score changes and FAI level changes in female gender identity

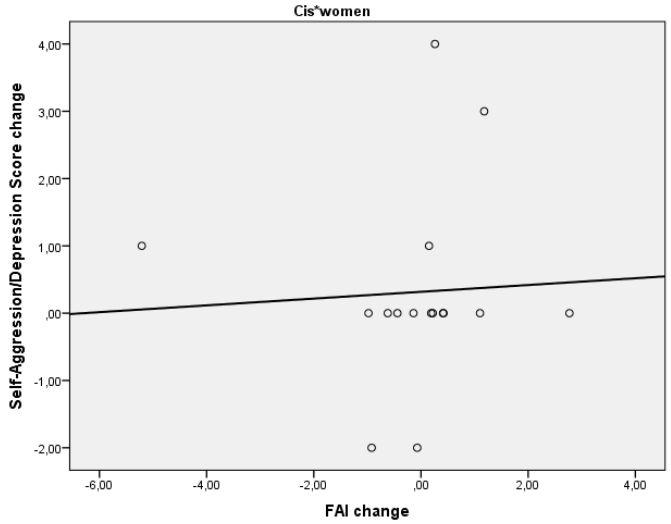

Figure 23: Correlation between self-aggression/depression score changes and FAI level changes in cis*women

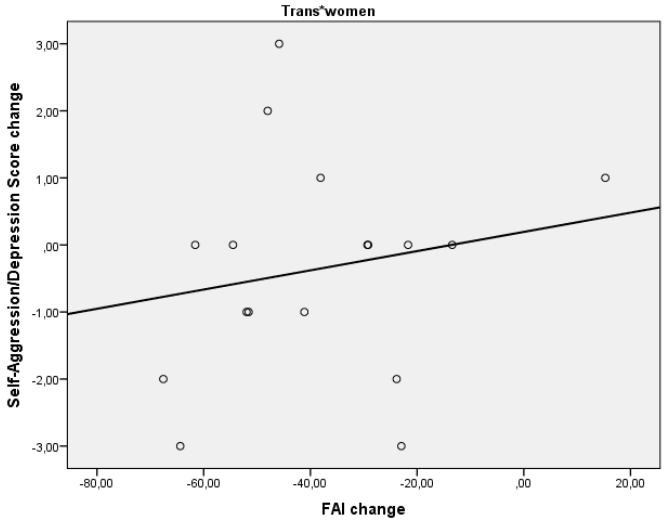

Figure 24: Correlation between self-aggression/depression score changes and FAI level changes in trans*women

Furthermore, a strong tendency towards a significant negative correlation within a medium range could be found between FEI changes and self-aggression/depression score changes in both assigned males at birth (figure 25) and trans*women (figure 26).

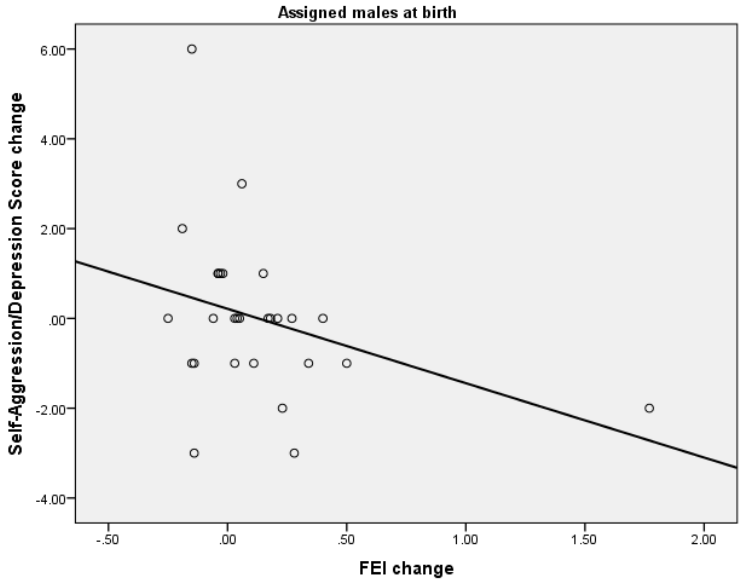

Figure 25: Correlation between self-aggression/depression score changes and FEI level changes in assigned males at birth

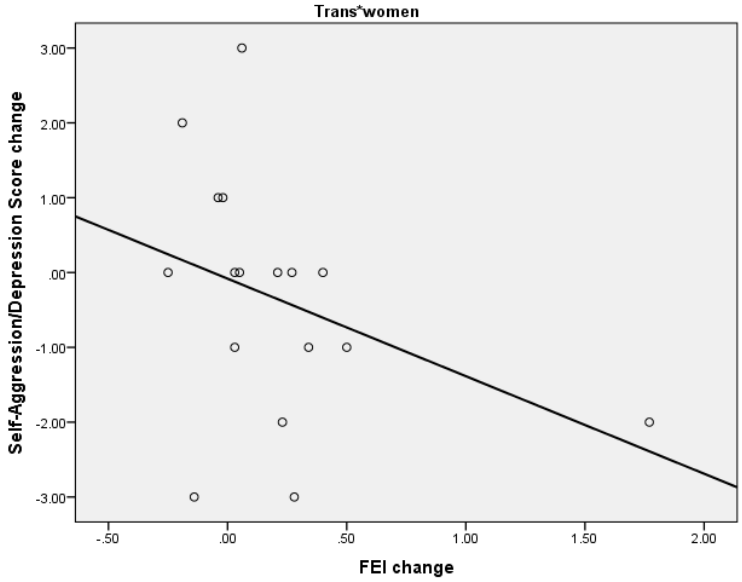

Figure 26: Correlation between self-aggression/depression score changes and FEI level changes in trans*women

In all other constellations no significant correlation could be detected.

7.3.3 Correlation between hormonal changes and aggression inhibition score changes

Table 13: Correlation values between hormonal changes and aggression inhibition score changes

Aggression Inhibition Change	Sample Size	FAI change		Testosterone change		FEI change		Estradiol change	
		r	p	r	p	r	p	r	p
Sex assigned at birth									
Male	28	.242	.215	.075	.705	.142	.472	.004	.983
Female	41	-.124	.440	-.099	.538	-.089	.581	.030	.850
Gender identity									
Male	36	.086	.618	.062	.719	-.094	.585	.022	.897
Female	33	.144	.423	-.004	.983	.012	.949	-.054	.766
Gender status category									
Transgender	42	.072	.649	.044	.780	-.131	.408	-.078	.624
Group									
Trans*men	25	.341	.095	.407*	.044	-.197	.346	-.144	.492
Trans*women	17	-.139	.595	-.430	.085	.073	.782	.048	.856

Legend: r = correlation, p = significance

T changes correlated significantly positively with aggression inhibition score changes in trans*men on a medium level (figure 27). However, FAI changes did not.

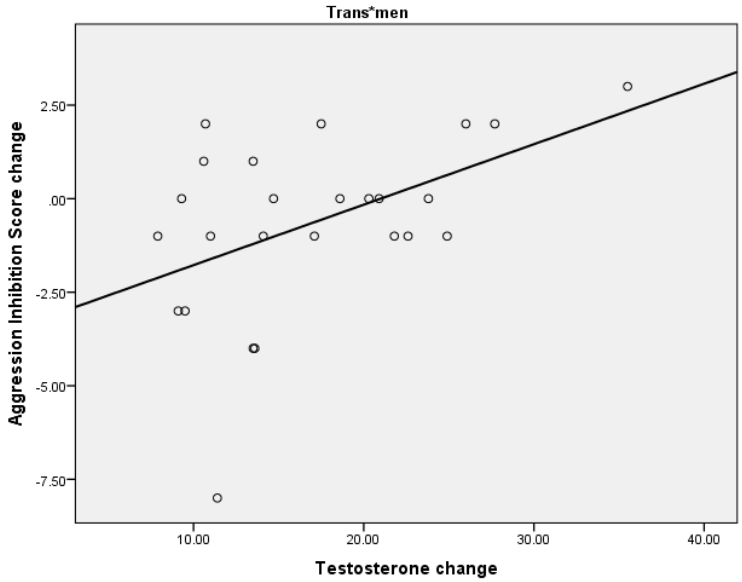

Figure 27: Correlation between aggression inhibition score changes and testosterone level changes in trans*men

A tendency towards significant negative correlation could be found between T level changes and aggression inhibiton score changes in trans*women (figure 28).

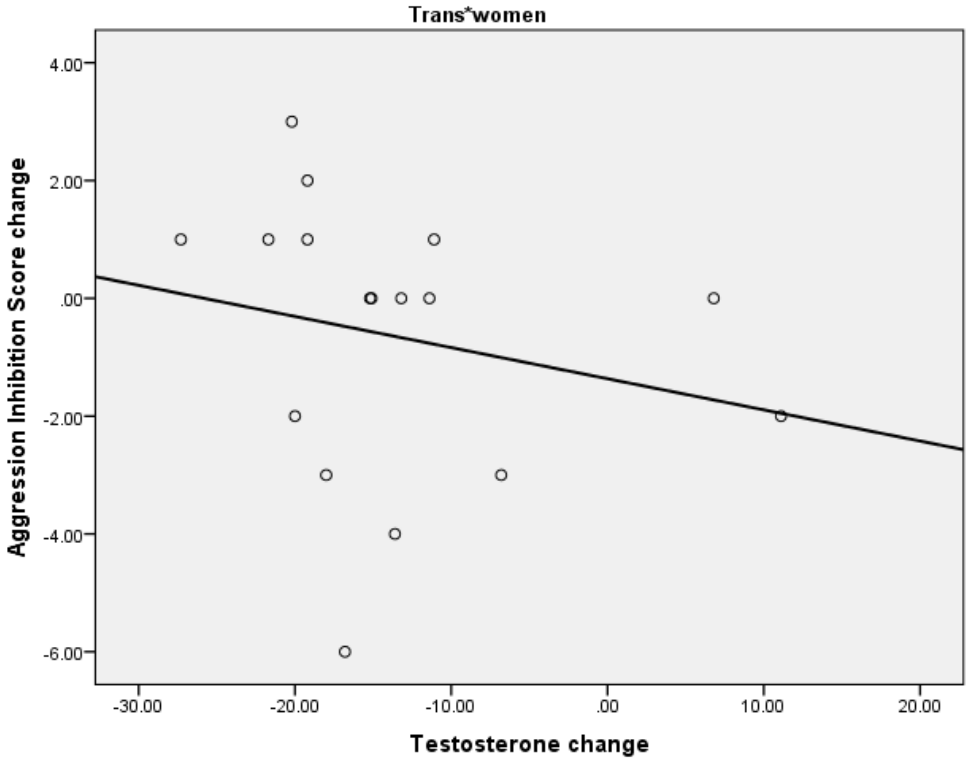

Figure 28: Correlation between aggression inhibition score changes and testosterone level changes in trans*women

In all other constellations no significant correlation could be detected.

8 Discussion

The purpose of this study was to investigate if HRT has an influence on total aggression, self-aggression/depression and aggression inhibition in gender dysphoric people. Furthermore, it was examined whether the belonging to a certain group (sex assigned at birth, gender identity, trans- or cisgender, trans*men/trans*women/cis*men/cis*women) itself has an impact on these aggression constructs.

8.1 Hormones

Levels of hormones changed greatly in transgender people during the course of this study. Before the start of HRT, individuals with a female sex assigned at birth showed similar levels of E and T (also of FEI and FAI). The same is true for people assigned males at birth. Therefore, trans*men and cis*women, as well as trans*women and cis*men had similar hormone levels at time point 0. As predicted, these hormone levels did not change significantly for cisgender individuals between the two measured time points. There were slight fluctuations which can be explained by physiological circumstances, such as menstruation in cis*women (Sanders, Warner, Backstrom & Bancroft 1983). However, at least four months into HRT, hormone levels changed drastically in trans*individuals: In trans*men E decreased significantly, whereas T levels increased significantly. FEI levels did decrease, but not significantly. This may be explained by the peripheral aromatization of produced T into E (Simpson 2002). Trans*women's hormone levels in- and decreased according to HRT protocol: There was a significant decline in T and FAI, and a significant increase in E and FEI. Overall, it can be concluded that HRT was successful in trans*individuals.

8.2 Aggression

The following discussion will include both aggression score changes and their correlation values with hormonal changes.

8.2.1 Total Aggression

Before the start of HRT all groups had similar aggression levels. Therefore the data corroborates the first hypothesis of this thesis *"There will be no statistically significant differences in total aggression scores between any of the examined groups before the start of hormone replacement therapy"*.

In accordance with previous studies (Slabbekoorn et al. 2001; Van Goozen et al. 1995), trans*men showed a drastic increase in aggression levels, with significantly higher values four months into HRT compared to any other group (trans*women, cis*men, cis*women). As the strong effect size of this result shows, almost 80% of this variance of aggression levels between trans*men and the other three groups can be explained by belonging to this subcategory. Consequently, this result supports the second hypothesis *"Total Aggression levels will increase significantly in trans*men between the two examined time points"*. Although there was no significant positive correlation between total aggression score changes and T or FAI level changes in trans*men, HRT might still be an explanation for increased total aggression. First of all, a highly significant, positive correlation between total aggression score changes and FAI/T level changes was found in assigned females at birth, persons with male gender identity and the transgender group. All three groups are linked by one subgroup, which belongs to all of them: trans*men. Secondly, a significant positive correlation could be shown between T levels and total aggression scores at time point 1 ($r = 0.313$, $p = .036$), but not at time point 0. The same is true for FAI levels and total aggression scores, as shown in figure 29 (time point 1: $r = 0.381$, $p = .001$). As the greatest FAI/T change happened in trans*men, it is likely that the changes in this group had a significant impact on these results.

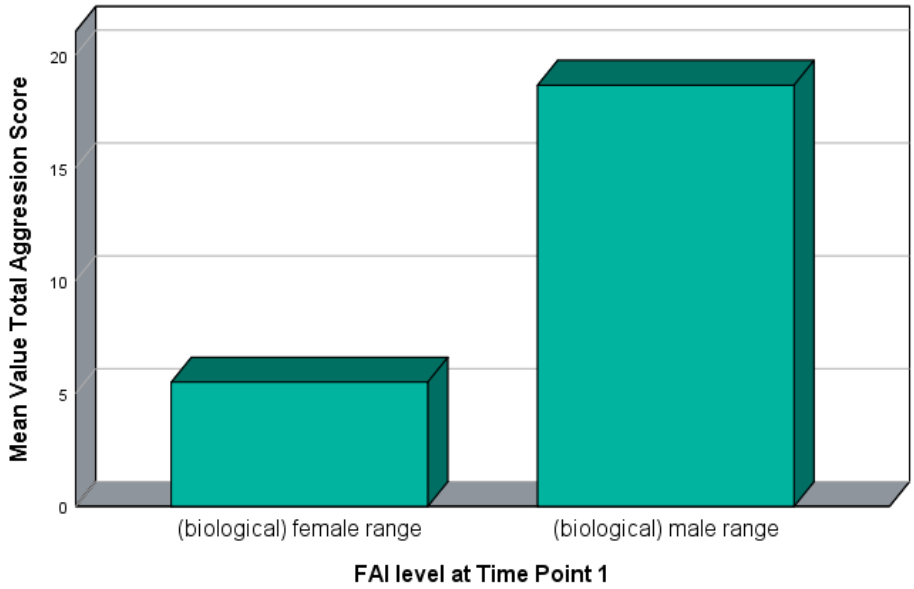

Figure 29: Total aggression scores for FAI ranges at time point 1

Thirdly, the small number of included participants in the trans*men group might be responsible that no significant correlation could be found.

Another explanation for the rise in total aggression and the lack of its positive correlation with T/FAI changes, may be found in the above mentioned study by Eisenegger et al. (2010). They found that solely the belief of having received T lead to an increase in unfair bargaining behavior in participants (ibid. 2010). Therefore, trans*men in this study might have acted upon a conception about higher levels of T rising aggression.

As a consequence of the present data, the third hypothesis *"Increases in total aggression levels in trans*men will significantly correlate with increases in testosterone levels"* must be falsified. However, further research must be conducted, as there are plenty of indications that a rise in T levels plays a significant role in aggression increases after all.

Additionally, it is important to emphasize that high T levels alone cannot explain the rise in aggression, as cis*men show similar high hormonal levels but do not have elevated aggression scores. Furthermore, although trans*women's aggression scores did decrease, it was not on a significant level, while their T levels did significantly drop.

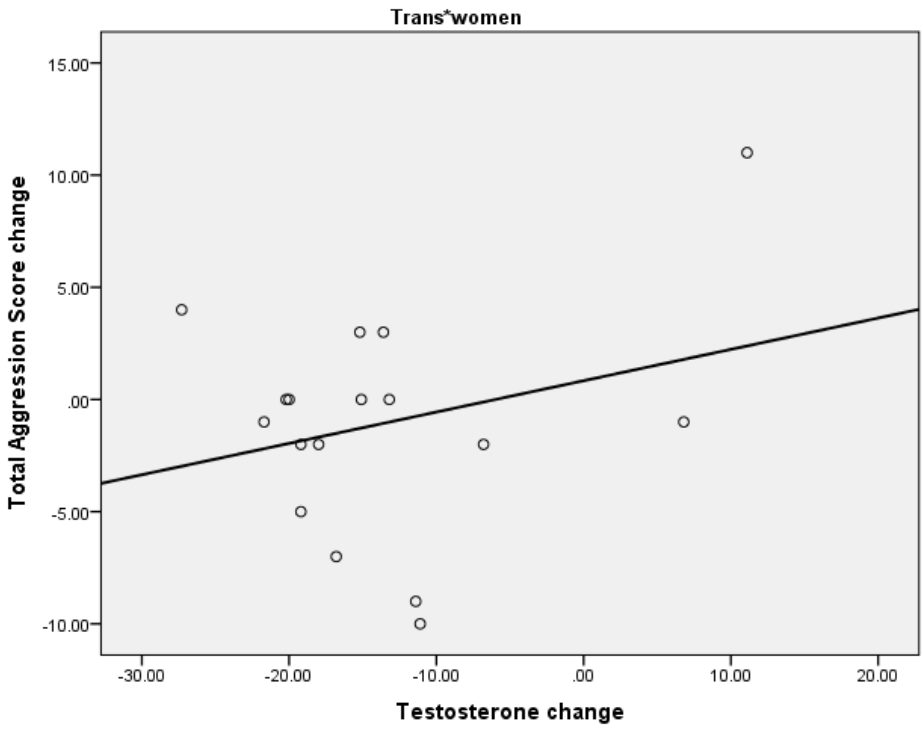

Figure 30: Correlation between total aggression score changes and testosterone level changes in trans*women

The results of this study may be comparable to the rise of reactive aggression in adolescent boys, whose T levels increase due to puberty (Mazur et al. 2015) and the long-term use of anabolic androgenic steroids, which was consistently found to also be associated with

elevated aggression levels (Daly et al. 2003). Therefore, it is assumed that higher aggressive behavior is not a direct consequence of high T levels, but rather of the increase of this steroid hormone itself.

Interestingly, E changes and total aggression scores changes correlated positively and highly significant in people with a female gender identity. As figures 19 and 20 however show, these results can only be detected in the cis*women sample and not in trans*women after splitting the group. As there was no significant E change in cis*women, this result can be neglected.

Considering the above mentioned data interpretation, hypotheses four *"Total Aggression levels will significantly change in trans*women between the two examined time points",* five *"Changes in total aggression levels in trans*women will significantly correlate with changes in testosterone levels",* and six *"Changes in total aggression levels in trans*women will significantly correlate with changes in estradiol levels"* must be rejected.

Furthermore, it was discovered that greater positive E level changes lead to decreased total aggression scores in the transgender sample. The conclusion that higher E levels might lead to lower total aggression scores could be drawn. However, after looking at the correlation values between E level changes and total aggression score changes in both trans*men and trans*women, this assumption must be rejected for now and further research must be conduced on this matter.

8.2.2 Self-Aggression/Depression

As predicted, self-aggression/depression scores were significantly higher in the transgender sample compared to the cisgender sample at time point 0, but not time point 1. Therefore, the seventh hypothesis *"Self-Aggression/Depression levels will be significantly higher in the transgender sample compared to the cisgender sample at time point 0"* is corroborated by the data. This finding is in line with current research, which suggests that prevalence rates for depression, non-suicidal self-injury and suicidality (suicidal thoughts, suicide attempts and suicide rates) are higher in transgender individuals, who have not yet started any gender affirmation processes, than in the general public (Marshall et al. 2016; Reisner et al. 2016a). These increased adverse phenomena are mainly seen as a result of negative social circumstances, such as the lack of support by family and friends, stigma and discrimination (De Vries et al. 2016; Dhejne et al. 2016; Gooren 2011). Furthermore, it was found that the gender affirmation process itself serves as a protective factor as it reduces these events.

Therefore, literature suggests that it might also decrease the probability of depression, non-suicidal self-injury and suicidality (Dhejne et al. 2016).

Interestingly, there was a strong tendency for trans*women to reach the highest self-aggression/depression scores. This is only partly in line with research, as one review article suggests that trans*women are more likely to experience mental health problems (Dhejne et al. 2016), another, however, reports that trans*men are at higher risk of non-suicidal self-injury (Marshall et al. 2016). Therefore, more research is needed to better understand this phenomenon.

The eight hypothesis *"Self-Aggression/Depression levels will significantly decrease in the transgender sample between the two examined time points"* cannot be corroborated by the data, as self-aggression/depression levels did indeed decrease, but not significantly. It is argued that four months into HRT may not be long enough to significantly improve these scores. Therefore, it would be interesting to investigate whether these constructs change significantly when the gender affirmation process is even more advanced.

Interestingly, positive correlation between changes in FAI levels and those in self-aggression/depression scores was found in persons with a female gender identity. This might indicate that a decrease in FAI levels in trans*women due to HRT leads to an decrease of self-aggression/depression tendencies. However, after splitting the group and looking at the data of both groups (cis*women and trans*women) separately, this effect could not be replicated on a significant level.

Highly interesting is the finding of a strong tendency towards a significant negative correlation between FEI changes and self-aggression/depression score changes in both assigned males at birth and trans*women, who also belong to the first group. This result indicates that increases in E due to HRT in trans*women might lead to lower self-aggression and depression; therefore it could be argued that higher levels of E might have a protective effect on mental health. The results are, however, not significant, which might be a result of a small sample size.

Hypothesis number nine *"There will be no statistically significant influence of increased/decreased hormone levels on self-aggression/depression levels in the transgender sample"* may therefore be carefully kept for now. This finding is also in line with research literature, which emphasizes a strong social component in self-aggression/depression for transgender people. It can, however, not be concluded that hormone administration does not have any impact on either self-aggression or depression in transgender individuals at all, as further research, especially focusing on a probable protective effect of E, must be conducted.

8.2.3 Aggression Inhibition

It was found that aggression inhibition scores were significantly higher in the transgender sample compared to the cisgender one before treatment onset, but not four months into it. Although scores decreased in the transgender sample between the two time points, these changes were not significant. Therefore, hypothesis number 10 *"Aggression inhibition levels will change significantly in the transgender sample due to hormone replacement therapy"* cannot be corroborated by the data. These findings are very interesting, as there is no research related to this aggression subcategory for gender dysphoric people so far. A possible explanation may be found in the definition of aggression inhibition. It is defined as the knowledge about socially accepted norms and values. High scores suggest overthinking and putting a lot of pressure on one's social conscience. Very low scores might be an indication for ruthless or unethical behavior in social situations (Hampel & Selg 1975; Heubrock & Petermann 2008). As transgender people are very often confronted with difficult social situations (e.g. stigma, discrimination, violence) (Reisner et al. 2016a; Winter et al. 2016) it is assumed that they are very aware of the perception society has of them and some social norms they might challenge. As gender affirmation proceeds and their bodies change according to the desired gender, they might feel that they "better fit" into society and social norms. However, due to lack of research, this proposed explanation is just conjectural.

Furthermore, it is very interesting that changes in T levels and the ones in aggression inhibition scores correlated positively in trans*men and by trend negatively in trans*women. This indicates that the rise in T levels due to HRT actually leads to an increased aggression inhibition score in trans*men and the decrease in T levels to a fall of aggression inhibition in trans*women, which is contradictory to the statement made above. This discrepancy cannot be explained.

8.3 Limitations

There are several limitations to this study, which may have an influence on the results.

First of all, although the overall sample size (n = 69) is comparable to other studies (Slabbekoorn et al. 2001; Van Goozen et al. 1995), the size of the subgroups varies strongly (trans*men: 25, trans*women: 17, cis*men: 11, cis*women: 16). Accordingly, less powerful non-parametric statistical analysis had to be utilized to reduce this deficit.

Secondly, it would have been interesting to use two control samples: one consisting of cisgender people and additionally, one with trans*individuals who do not desire HRT. That way, differences between trans- and cisgender people could have still been assessed, but additionally, one control sample (trans*individuals) and the experimental group would have been more similar at the starting point.

Unfortunately, not enough participants filled out the questionnaire on aggression at the first, second and third measurement of the original study (shortly before treatment onset, 4 weeks and 4 months into HRT) and therefore, these time points could not be analyzed. This would have been a great advantage, as a change over time in hormone levels and aggression scores could have been observed more closely. Additionally, the completion of the questionnaire shortly after the first hormone administration could have delivered interesting results when being compared to findings of experimental single-dose administration studies.

Furthermore, other key factors which may influence aggressive behavior, such as social upbringing, educational background, previous aggressive behavior, social environment, adverse life events during the course of HRT, etc., were not considered.

9 Conclusion

This study confirmed major results of the two already existing examinations (Slabbekoorn et al. 2001; Van Goozen et al. 1995) of the effects of HRT on reactive aggression in gender dysphoric people. In comparison, however, the great advantages of this investigation are the included control groups and especially the assessment, analysis and correlation of sex steroid hormones.

Therefore it was possible to show that first of all, HRT did proceed in the predicted way and secondly, trans*men showed higher total aggression scores four month into the treatment. There are strong indications that this phenomenon might be linked to the rise of T, however, no significant results could be found. Therefore, further research must be conducted on this matter.

Furthermore, higher self-aggression/depression scores in the transgender group compared to the cisgender one before the start of HRT might indicate an impact of social variables, such as stigma, discrimination, violence, etc. As social variables were however not conducted in this study, this explanation must remain hypothetical.

One major contribution to research is the finding that the administration and therefore the rise in E levels might have a positive effect on mental health. Strong tendencies were found for a decrease in self-aggression and depression as FAI levels (and therefore E) rose in trans*women. This result is especially important, as the effects of exogenous administered E have not been studied sufficiently enough so far. Furthermore, it may also have a great impact on the process of HRT. Therefore, further research with a larger sample of both trans*men and trans*women must be conducted.

Additional research is necessary to explain the elevated scores in aggression inhibition in the examined transgender sample compared to the cisgender sample before treatment onset.

Although this study may be regarded as a first step to better understand aggression in gender dysphoric people and the influence of HRT on this psychological construct, further research, which includes and analyses both biological and social variables, is necessary.

10 Abbreviations

AAS	anabolic androgenic steroids
ACC	anterior cingulate cortex
AR	androgen receptor gene
ASD	autism spectrum disorder
BSTc	bed nucleus of the stria terminalis
CAH	congenital adrenal hyperplasia
CTh	cortical thickness
DSD	disorders of sex development
DSM	Diagnostic Statistical Manual of Mental Disorders
E	estradiol
ECG	electrocardiogram
ERβ	estrogen receptor beta gene
ESR1	estrogen receptor α gene
FAF	Fragebogen zur Erfassung von Aggressivitätsfaktoren
FAI	Free Androgen Index
FEI	Free Estradiol Index
fMRI	functional Magnetic Resonance Imaging
FtM	Female-to-Male
GAS	gender affirmation surgery
GIDDANT	gender identity disorder of adolescent and adulthood, nontranssexual type
GCS	gender confirmation surgery
GI	gender incongruence
GD	gender dysphoria
GID	gender identity disorder
GID NOS	gender identity disorder not otherwise specified
GIDC	gender identity disorder in children/of childhood
HRT	hormone replacement therapy
i.m.	intramuscular
ICD	International Classification of Diseases and Related Health Problems
INAH-3	interstitial nucleus of the anterior hypothalamus nuclei 3

MtF	Male-to-Female
n/a	not applicable
NGV	non-gender-variant
NSSI	non-suicidal self-injury
OFC	orbitofrontal cingulate cortex
PCOS	polycystic ovarian syndrome
PD	personality disorders
PET	*Positron Emission Tomography*
PFC	*prefrontal cortex*
s.c.	subcutaneous
SCID	Structured Clinical Interview for DSM-IV diagnosis
SRS	sex reassignment surgery sex realignment surgery
SRY	sex-determining region of the Y-gene
T	testosterone
VA	veterans affairs
WHO	World Health Organization

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12 Supplements

12.1 Figures: Hormone level changes

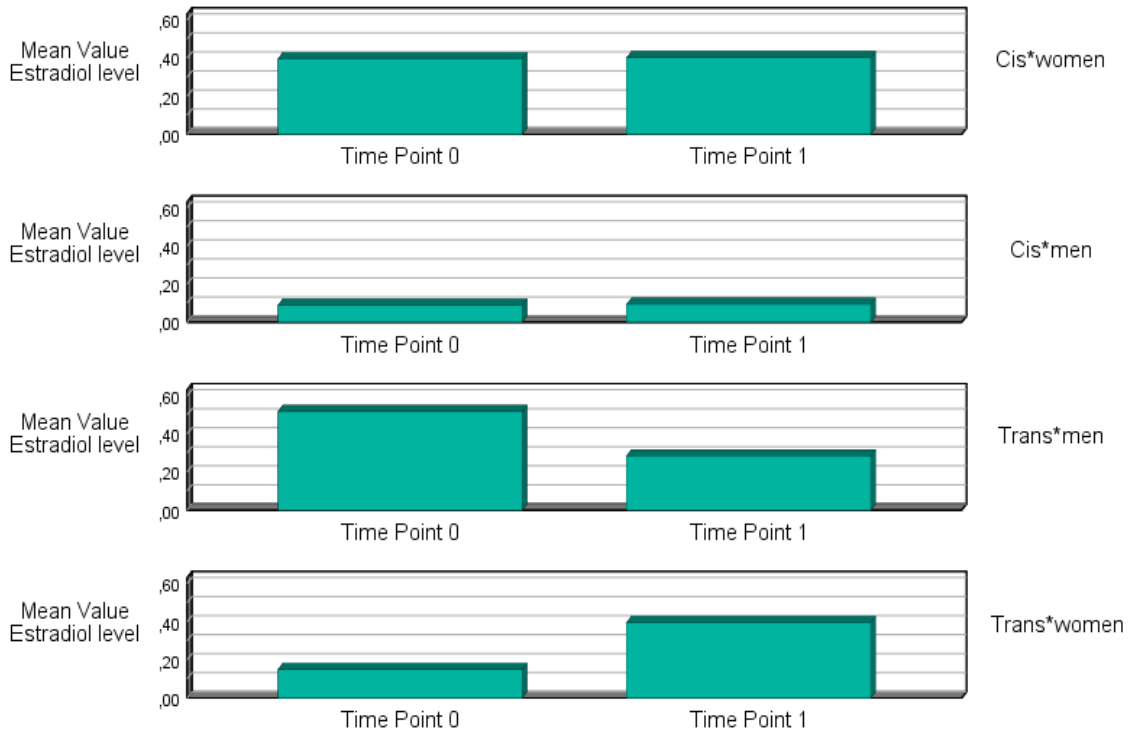

Figure 31: Estradiol levels per group at both time points

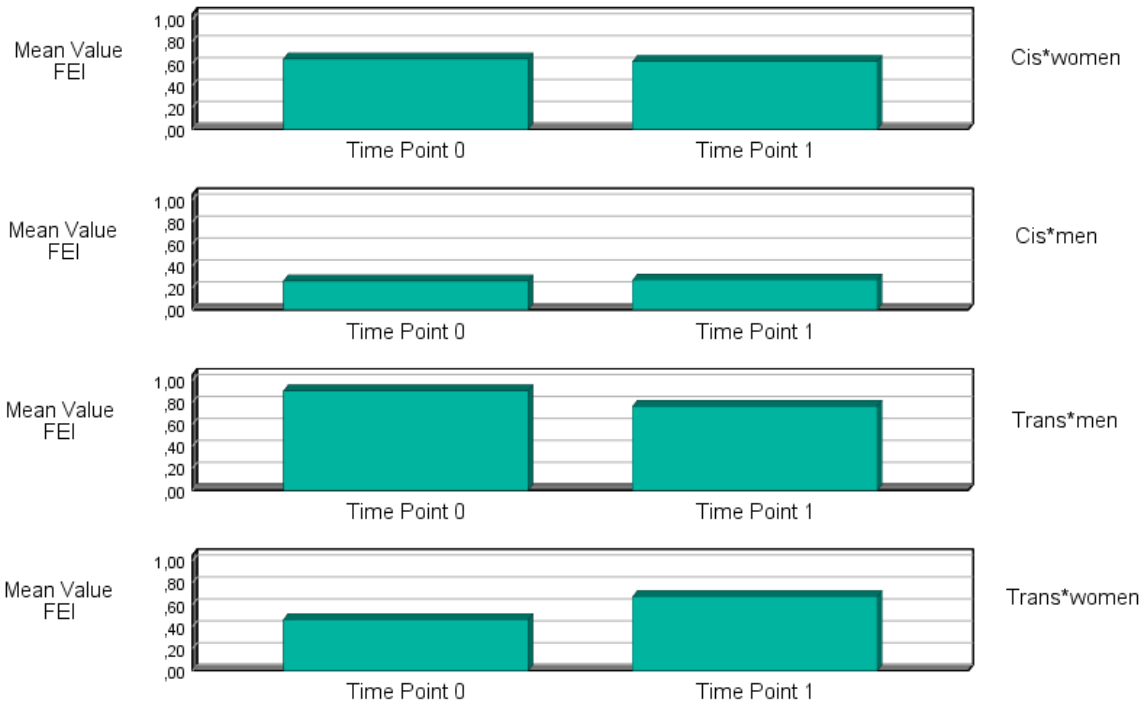

Figure 32: FEI levels per group at both time points

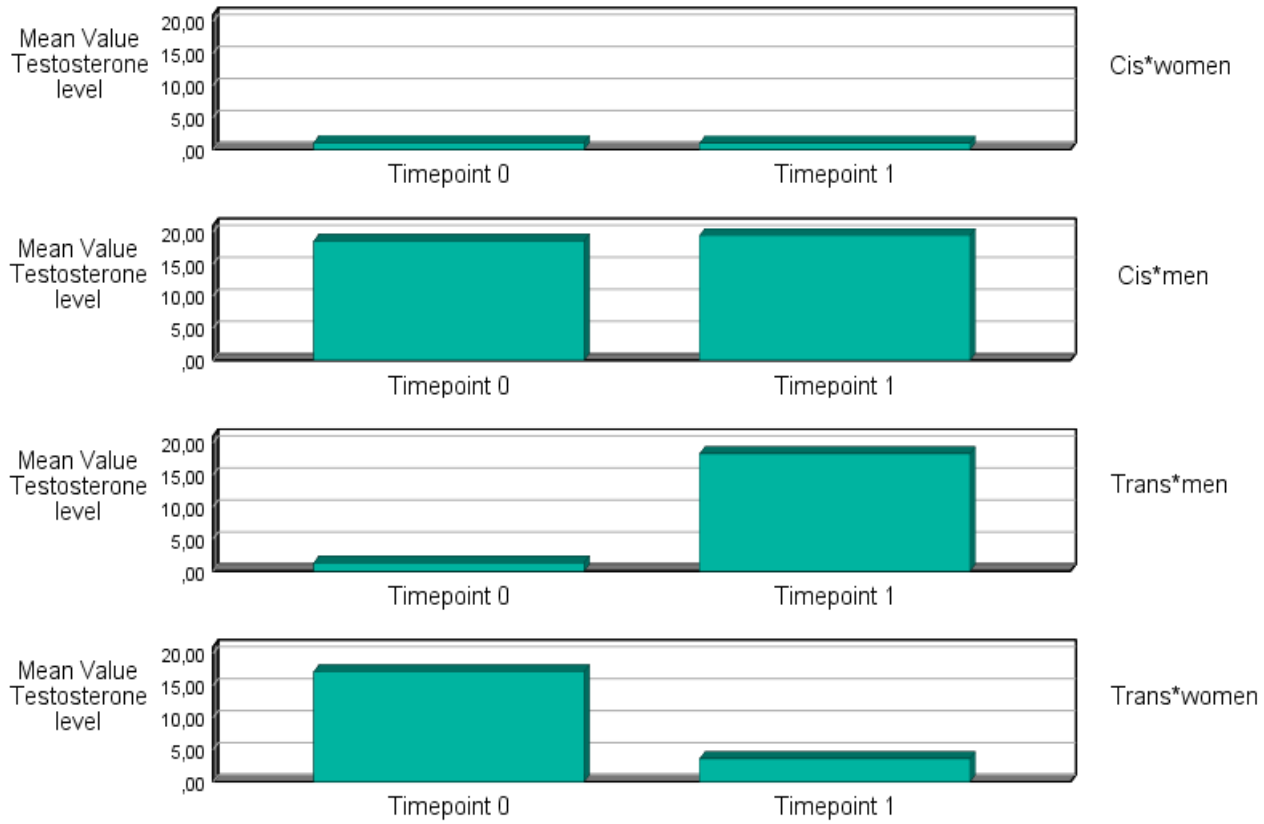

Figure 33: Testosterone levels per group at both time points

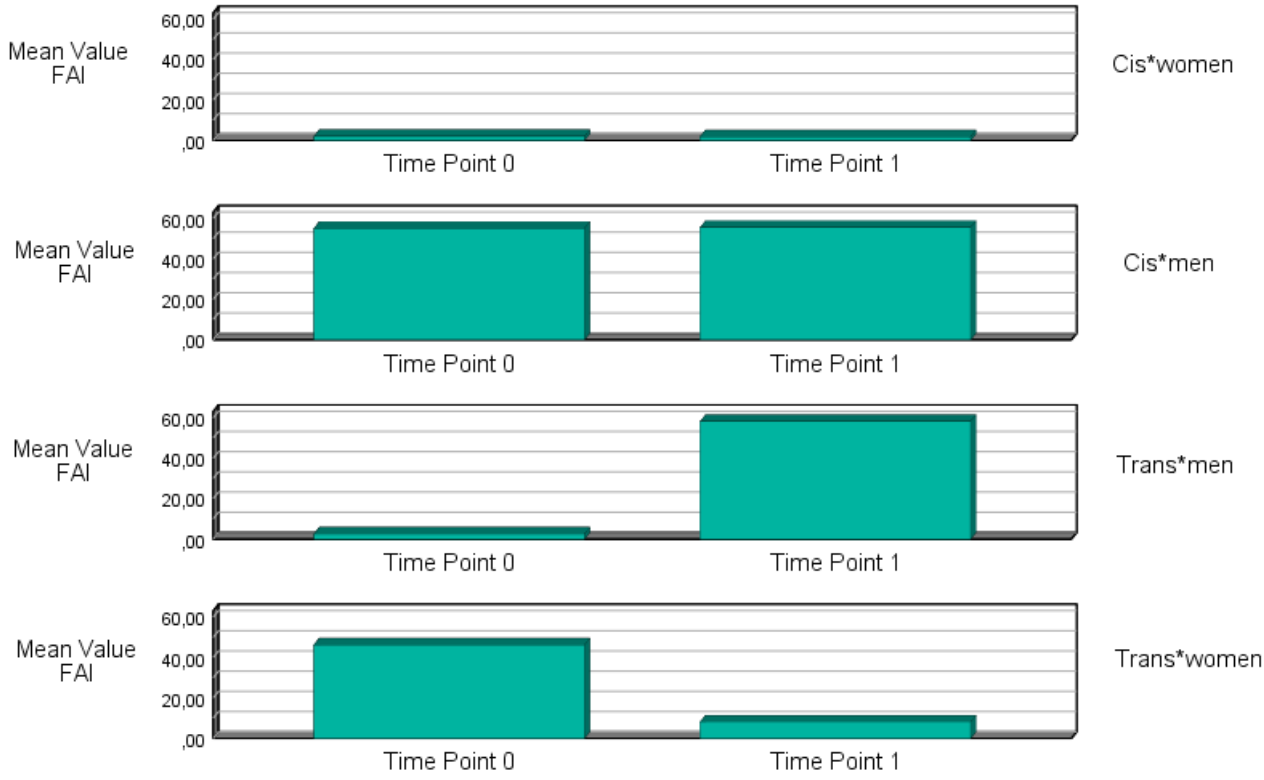

Figure 34: FAI levels per group at both time points

12.2 Tables and Figures

Tables

Figures