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# Hormone and gender dependent differences in empathy

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unter der Anleitung von

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**Diploma Thesis**

# Hormone and gender dependent differences in empathy

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# Summary

**INTRODUCTION**: In recent years research has begun to examine links between biology (e.g., endocrinology), personality and social behavior (e.g., dominance, bonding..). In over a century of animal research, results have shown that variation in hormone levels influences a variety of social behaviors. Several interactions enjoy growing popularity in scientific research, such as the link between testosterone and aggression or estrogen and affiliative behavior, etc. New approaches, such as single, exogenous hormone administration promote fast knowledge gain, but few studies investigate the modulatory effect that middle to long-term hormone treatment exerts on behavior, especially on empathy skills.

**AIM:** The principal assumption of this study was that endocrinological therapy has a psychological effect; Or more precisely, that estrogen and testosterone exert specific effects on our empathizing abilities, as we demonstrated on female controls (FC), male controls (MC), male-to-female (MtF) and female-to-male transsexuals (FtM).

**MATERIAL AND METHODS**: 23 FtM aged 18-43 years (24.6 ± 6 years, mean ± SD) and 21 MtF aged 18-45 years (32.1 ± 8.3 years, mean ± SD) took part in this study. The control group consisted of 35 FC aged 18-40 years (age 25 ± 6 years, mean ± SD) and 29 MC aged 18-47(age 32.1 ± 8.3 years, mean ± SD). In this study we analyzed hormone plasma levels on three different points in time together with methods of psychological assessment (self-reports: Emotion Contagion Scale, Bermond-Vost Alexithymia Questionnaire and Interpersonal Reactivity Index).

**RESULTS**: In this study we confirmed earlier findings by showing that FC obtained better outcomes than MC in empathy scales. Further, we found that the female gender (FC and MtF) was predictive for better empathy performance in the Interpersonal Reactivity Index. The overview of this scale demonstrated the effect of hormone therapy: Two different cross hormone therapies provoked two opposite performances in transsexual participants, while a lack of drug intervention in the control group resulted in steady outcomes. We found that before treatment testosterone had a dampening effect in FtM on affect intensity and on emotional susceptibility. Diametrically opposite, MtF increased the intensity and expressiveness of emotions, especially of love and happiness contagion during cross-sex hormone administration. In contradiction with current literature, FtM, after one month of testosterone treatment, showed a better emotional outcome if their testosterone level were high. These results may be due to unanticipated short-term psychological adjustments at the beginning of transition. Secondly, it seemed that high estrogen plasma level predicted a worse emotionalizing performance in female identity gendered individuals. However, low estrogen levels appeared to be associated with an overall increase of the extend to which someone is able to define his own arousal states. Furthermore, contrary to our expectations, the degree to which someone can or is inclined to describe or communicate about his emotional reactions is positively related to testosterone in MtF. Moreover, our findings suggest that elevated levels of estrogen and testosterone prevent fear contagion possibly through that mechanism these hormones exert their anxiolytic effects on humans.

It thus seemed that high estrogen levels decreased the faculty of imagination whereas high testosterone was predictive for increasing the faculty of imagination. Lastly, it seemed that MtF improved significantly in their analyzing skills during the four months of treatment. The reason might be that hormone treatment had a modifying effect on the extent to which MtF were looking for explanations for their emotional reactions.

**CONCLUSIONS**: With this study we provided evidence that hormones do have an effect on certain aspects of empathy; we found a treatment specific effect over time and a correlation between individual hormones plasma levels and specific facets of empathy. We were able to confirm some findings of previous studies, we demonstrated interesting new correlations and we provided an overview over human empathic abilities in relation to the steroid hormones estrogen and testosterone.

# Zusammenfassung:

**EINLEITUNG:** In den letzten Jahren verstärkte sich der interdisziplinäre Ansatz in der Wissenschaft was dazu geführt hat, dass vermehrt Zusammenhänge zwischen Biologie (Endokrinologie), Persönlichkeit und sozialem Verhalten (Dominanz, Bonding etc.) zu aufstrebenden Forschungsfeldern herangewachsen sind. Nach über einem Jahrhundert Tierforschung, wurde belegt, dass Varianzen in Hormonspiegeln im Blut eine Reihe an sozialen Verhaltensweisen beeinflussen. Einige dieser Interaktionen erfreuen sich regen Interesses und sind im Scheinwerferlicht der aktuellen Forschung, wie zum Beispiel das Zusammenspiel von Testosteron mit Aggression / Dominanz und Östrogen mit affiliativem und fürsorglichem Verhalten. Neue Herangehensweisen, wie die einmalige, exogene Hormonzufuhr tragen zu unserem ständig wachsenden Wissenskorpus bei, allerdings ist wenig über die modulierenden Langzeithormoneffekte auf das menschliche Verhalten, vor allem unser Einfühlungsvermögen, bekannt.

**ZIEL:** Die zugrundeliegende Hypothese dieser Arbeit beläuft sich auf die Annahme, dass gegengeschlechtliche Hormontherapien einen Einfluss auf das Sozialverhalten des Menschen haben; genauer gesagt, dass sowohl Testosteron als auch Östrogen einen regulierenden Effekt auf unser Empathie-Vermögen besitzt. Diese Hypothese wird an weiblichen Kontrollprobanden(FC), an männlichen Kontrollprobanden(MC), an Frau-zu-Mann Transsexuellen (FtM) und an Mann-zu-Frau Transsexuellen (MtF) verifiziert.

**METHODIK:** Dreiundzwanzig FtM im Alter von 24,6 ± 6 Jahren und einundzwanzig MtF im Alter von 32,1 ± 8,3 Jahren nahmen an dieser Studie teil. Die Kontrollgruppe bestand aus fünfunddreißig kaukasischen FC im Alter von 25 ± 6 und aus neunundzwanzig kaukasischen MC im Alter von 32,1 ± 8,3. Im Zuge dieser Studie wurden zu 3 distinkten Zeitpunkten die Hormonblutspiegel zusammen mit psychologischen Verfahren analysiert (Selbstbeurteilungsbögen: emotion contagion scale-D, Bermond-Vost Alexithymia Questionnaire und Saarbrücker Persönnlichkeitsfragebogen).

**RESULTATE:** In dieser Studie gelang es frühere wissenschaftliche Ergebnisse zu bestätigen, unter anderem, dass FC bessere Resultate als MC in Empathie Fragebögen erzielen. Weiters war das weibliche Gender (FC und MtF) voraussagend für eine bessere Leistung im Saarbrücker Persönlichkeits-Fragebogen. Die Übersicht dieses Fragebogens bestätigte den Effekt der Hormontherapie: bei transsexuellen Probanden führten zwei unterschiedliche Therapien zu zwei gegensätzlichen Resultaten in diesem Empathie-Fragebogen, während keine Hormoneinnahme zu gleichbleibenden Resultaten führte. Wir konnten aufzeigen, dass vor Therapiebeginn, Testosteron eine dämpfende Wirkung auf die Affektintensität bei FtM hatte. Im Gegensatz dazu erschienen MtF emotionaler und ihre Liebes- und Glücks-Ansteckungsfähigkeit nahm über die Zeit zu. Im jähen Gegensatz zur aktuellen Literatur stand die Tatsache, dass FtM mit hohen Testosteronspiegel nach einem Monat Therapie besser in ihrer Emotionalisierungsfähigkeit wurden. Ein Erklärungsansatz dieser Resultate mag eine unübliche kurzzeitige psychische Anpassung nach Beginn der gegengeschlechtlichen Hormontherapie sein.

Zweitens scheinen hohe Östrogenspiegel eine schlechtere Emotionalisierungsfähigkeit zu bedingen bei Menschen mit weiblichem Gender. Weiters konnte gezeigt werden, dass eine Assoziation zwischen niedrigen Östrogenplasmaspiegel und einer besseren Identifizierungsgabe besteht. Gegensätzlich zu unseren Erwartungen, scheint der Grad zu welchem jemand dazu tendiert seine Gefühle zu verbalisieren, positiv mit Testosteron zu korrelieren in MtF. Zudem lassen unsere Resultate vermuten, dass hohe Östrogen- und Testosteronspiegel vor Angstansteckung schützen. Vielleicht entfalten diese Hormone ihren anxiolytischen Effekt durch diesen Mechanismus. Überraschenderweise verringert Östrogen die Imagination und Testosteron scheint die Fantasie Fähigkeit zu stimulieren. Zuletzt konnte gezeigte werden, dass MtF über die Zeit signifikant besser in ihren analytischen Fähigkeiten geworden sind. Ein Grund dafür könnte sein, dass die Hormontherapie ihren Wunsch nach Erklärungsmodellen für ihre emotionalen Reaktionen gestärkt hat.

**SCHLUSSFOLGERUNG:** Diese Studie belegt, dass Hormone einen modulierenden Einfluss auf das Empathie-Vermögen haben, zunächst da wir einen Behandlungs-spezifischen Effekt über die Zeit feststellen konnten und zweitens weil Korrelationen zwischen individuellen Hormonspiegeln und spezifischen Facetten des Einfühlungsvermögens gezeigt werden konnten. Unsere Ergebnisse stimmten größtenteils mit früheren Forschungsergebnissen überein. Erweiternd wurden auch neue und unerwartete Hormon-Empathie Korrelationen gefunden, welche Denkanstöße für zukünftige Forschung liefern.

# Introduction

For this thesis, a detailed theoretic part was imperative. In order to prevent an imprecise and vague use of the term *empathy* and to demarcate it from other related concepts, the first part of this thesis was dedicated to the discussion of this notion. Understanding these concepts is essential for knowing what the different questionnaires are assessing. In a second phase, the term transsexualism will be defined. MtF and FtM transsexuals are the main study population evaluated in this thesis, therefore being familiar with what gender dysphoria means is an integral part of this work. Being aware of the framework conditions of transsexuals might help interpreting the results and seeing them in connection to a larger picture. The last chapter of the theoretic part consisted of an overview of the effects of estrogen and testosterone on the human behavior. Starting with a general overview, we narrow down to the specific effects of cross hormone therapy and to the specific effect that these hormones have on human behaviors, like aggression, fear, social recognition, empathy, etc.

The theoretic part was followed by the study protocol. Thanks to the extensive synopsis, it was possible to disentangle different aspects of empathy in transsexual women/men and ciswomen/men, assessed through questionnaires. Further, it was possible to put the different notions of empathy in relation to each other and to demonstrate correlations with hormones. After the result presentation, we broadened the discussion and deepened it. To close this thesis, we presented a concise conclusion.

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# A) THEORETIC PART

## I. Empathy

### 1-1. Theoretical approach

> It is only by empathy that we know the existence of psychic life other than our own.
> — Freud (1926, p. 104)

Empathy is integral to our identity as humans. Darwin already noticed that emotions are not only perceived by oneself but that they are contagious[1] and we have been accustomed to describing humans as "social animals". The unique gift of the inner representation of feelings, thoughts and the general mental state of another person is commonly known as empathy.
A variety of partially contradicting definitions of empathy have been constructed. Empathy is an umbrella term for behaviors that are intended to describe human's ability for feeling into another person. To clarify empathy and its related concepts, an overview based on Daniel Baton's article from 2009[2] will be given, together with a brief description of the etymology of the word 'empathy.'

### 1-2. Historical background

The Greek word *ἐμπάθεια* (*empatheia*) "passion, state of emotion," from *ἐν* (*en*), "in, at" + *πάθος* (*pathos*), "passion", "suffering", was translated into German by the philosopher Rudolf Lotze in 1858.[3]
„Einfühlung"(from ein "in" + Fühlung "feeling", = feeling into something) was interpreted as a new procedure for humans to understand inanimate objects, animals or humans by 'placing ourselves into them' (sich mitlebend ... versetzen).[4] Robert Vischer[5] introduced the term in 1873 in the field of esthetics and art.[6] With the term, he referred to the empathic engagement of humans with a piece of art. These reactions could range from physical responses, that are generated by the observation of art to understand emotions of represented others or even imitate the observed actions of others in paintings, sculptures etc.[7]
Theodor Lipps transferred 1903 „Einfühlungs-Vermögen" from the vocabulary of the psychology of aesthetic experience into a term characterizing the relation between observer and artwork, being the first one to put a focus on intersubjectivity and inner imitation (Innere Nachahmung) of others emotions.[8] He perceived that when watching an acrobat walking on a suspended wire, „I feel myself so inside of him" ( "Ich fühle mich so in ihm" ).[8] We can also mention here that Freud's (1921) understanding of empathy rooted in Lipps comprehension of the term.[9] Titchener translated 1909 „Einfühlung" in the English word empathy.[10]

## 1-3. Definition of Empathy

As mentioned previously, the concept of empathy is difficult to describe. The following two questions will be discussed in accordance with Batson´s classification from "These things called empathy: eight related but distinct phenomena"[2]:
First: "How do we know another person's thoughts and feelings?"
Second: "How do we respond to other person's thoughts and feelings?"

### 1-3-1 How do we know another person's thoughts and feelings?

*Adopting the posture or matching the neural responses of an observed other*

| **SYNONYM** | **AUTHOR, YEAR** |
|---|---|
| **Imitation** | Lipps 1903[8] |
| | Titchener 1909[10] |
| | Meltzoff & More 1997[11] |
| **Chameleon effect** or **mimicry** | Hatfield 1994[12] |
| **Facial empathy** | Gordon 1995[13] |
| **Motor mimicry** | Dimberg, Thunberg & Elmehed 2000[14] |
| | Hoffman 2000[15] |
| **Motor empathy** | Hatfield, Cacioppo & Rapson 1994[12] |

Lipps was the first one to define empathy as the ability to adopt the posture of others.[8] Among psychologists', terms such as "mimicry", "motor mimicry" and the "chameleon effect" stood for an innate and non-conscious reaction to imitate other people's facial expressions, postures, vocalizations and movements. A number of behavioral and electromygraphic studies validate the phenomenon that the observation of other's facial expressions elicits unconscious facial reactions in one's own face.[14,16] This might foster relationships, meliorate interactions and increase social bonding.[17,18]
Whether there is a correlation between the potency of one's mimicry reaction and the extent to which a person is empathic, remains controversial.
While some studies found a concordance,[17,19] others found no match between the extent of subject's disposition for empathy and the intensity of facial mimicry.[20,21] While the matching of posture is often interpreted as a basis for our empathic capabilities, the concept is particularly controversial when applied to aspects of empathy that are

exclusive to humans. For instance, humans may use memory and general knowledge to deduce others feelings and thoughts[22,23] or use communication as a tool of mutual understanding.[2] Through language you cannot only communicate in present states, but also through time and space.[24]

*Coming to feel as another person feels*

| **SYNONYM** | **AUTHOR, YEAR** |
|---|---|
| **Empathy** | Common dictionary definition |
| **Sympathy** | Hume 1740/1896[25] |
| | Smith 1759/1853[26] |
| **Emotional contagion** | Hatfield, Cacioppo & Rapson 1994[12] |
| **Affective empathy** | Zahn-Waxler, Robinson & Emde 1992[27] |
| **Automatic emotional empathy** | Hodges & Wegner 1997[28] |
| **Primitive empathy** | Hatfield, Cacioppo & Rapson 2009[16] |

Sharing the same feelings with another person, not only predicts the tendency to match other people's emotion, but also to "catch" them.[12,29] Compared with the idea of adopting others postures (1-3-1), sharing feelings always involves an affective and emotional component. As the perception of the emotion expressed by the other and someone's own experience of the same emotion occurs outside of awareness, we are not able to distinguish whether the source of our experience lies in our self or in the other.[30-32] For this reason the phenomenon is seen by some researchers as a precursor of empathy.[16] This continuous and non-conscious "feeling as another person feels" occurs through different non-verbal communicative channels like body language,[33] vocal expressions[34] and facial expressions.[35] Scientists working with this concept often add value to this term by emphasizing the fact that the feelings don't need to be the same, but can be experienced by each individual slightly differently.[15]
In this study we will define this capacity as emotional contagion. This ability is of particular interest because it covers the basic empathic reaction of catching and imitating other person's emotions. It is quantified by the emotional contagion scale and records five basic emotions. Of special focus will be the anger and the fear contagion, which are, based on current research results, promising subscales for showing a gender difference.

*Intuiting or projecting oneself into another person's situation*

| **SYNONYM** | **AUTHOR, YEAR** |
|---|---|
| **Einfühlung' (engl: empathy)** | Lipps 1903[8] |
| **Empath** | Titchener 1909[10] |
| **Aesthetic empathy** | Wispé 1968[36] |

The concepts described above are historical relics of the word "empathy" and are no longer used. Nevertheless Batson differentiates between "the projection of oneself into another's situation", which comes from the field of aesthetic experience, and "the process of imagining oneself in the other's situation (2-1-5)" which comes from an interpersonal background. The first is used to describe feelings in relation to works of art (see 1-2. Historical background). This differentiation is used in this thesis because it underlines the different origins and usages of the term.

*Imagining how another is thinking and feeling*

| **SYNONYM** | **AUTHOR, YEAR** |
|---|---|
| **Psychological empathy** | Wispé 1968[36] |
| **Imagine him** | Stotland 1969[37] |
| **Empathic attentional set** | Barrett-Lennard 1981[38] |
| **Imagine other perspective** | Batson 1991[39] |
| **Empathic accuracy** | Ickes 1993[40] |
| **Empathy or projection** | Adolphs 1999[41] |
| **Empathy or perspective taking** | Ruby & Decety 2004[42] |

When attempting to feel what another individual is specifically feeling, emotions can be based on either statements and actions or on one's knowledge resulting from evaluation of the other person (Character, experience etc.).[2]
The person adopts a so-called imagine-other perspective, where the focus is directed on the internal state of the other person and where no confusion between self and other occurs. Choosing this perspective promotes feelings like empathic concern and it

fosters altruistic behavior.[43,44] Barrett-Lennard empathizes the fact that one's own sensitivity is crucial for imagining what somebody else is experiencing.[38]
Ickes and his colleagues focused on the ability to infer what is going through the mind of another person by accurately guessing others' thoughts and feelings.[40]
This ability is quantified and assessed in this study by the perspective-taking scale of the Interpersonal Reactivity Index.

*Imagining how one would think and feel in the other's place*

| **SYNONYM** | **AUTHOR, YEAR** |
|---|---|
| **Changing places in fancy** | Smith 1759/1853[26] |
| **Role taking** or **empathy** | Mead 1934[45] |
| **Perspective taking** or **decentering** | Piaget 1953[46] |
| **Imagine self** | Stotland 1969[37] |
| **Cognitive empathy** | Pivinelli 1993[47] |
| **Projective empathy** or **simulation** | Darwell 1998[48] |
| **Mentalization** | Baron-Cohen 2000[49] |
| | Frith & Frith 2003[50] |
| **Theory of Mind (ToM)** | Premack & Woodruff 1978[51] |

The imagine self-perspective occurs when one explicitly puts oneself into the mental shoes of the other person. The other person's point of view is adopted and their knowledge and emotions are experienced. The capacity for self-other differentiation and cognitive appraisal seems less pronounced, a fact that predisposes for personal distress and egoistic motivations.[43,44,52]

## 1-3-2 How do we respond to other person's thoughts and feelings?

*Feeling distress at witnessing another person's suffering*

| **SYNONYM** | **AUTHOR, YEAR** |
|---|---|
| **Empathy** | Krebs 1975[53] |
| **Empathic distress** | Hoffman 1981[54] |
| **Personal distress** | Batson 1991[39] |
| **Empathic over arousal** | Decety & Lamm [32] |

Witnessing another's distress encompasses a wide spectrum of negative emotions, ranging from being upset, alarmed, worried, disturbed to troubled and the state of grieving.[55]

Emotional distress or generalized withdrawal responses are aversive, self-focused reactions to the manifestation of somebody else's negative movements, frequently leading to avoidance. The border between self and other seems less clear and the empathizer feels threatened.[30-32] That is the reason why feeling "as" the other person could prevent oneself from sensitive care taking and other oriented response because the focus is diverted to one's emotional state. Interestingly, several psychological studies have shown that language can help to develop empathy and that verbalization decreases the feeling of distress, therefore improving your personal welfare.[56,57] On the other hand Batson defends the thesis that feeling distress can also produce a helping behavior, although the main goal is not to help the person in distress but to relieve one's own distress. He called this phenomenon "egoistic motivation".[58]

In this study we summarized the negative emotions that one may experiences when seeing another person suffering "personal distress" and the Interpersonal Reactivity Index assesses this notion.

*Feeling for another person who is suffering*

| **SYNONYM** | **AUTHOR, YEAR** |
|---|---|
| **Pity** | Hume 1740/1892[25] |
| **Compassion** | Smith 1759/1853[26] |
| **Sympathic distress** | Hoffman 1981[48,54] |
| **Empathy or empathic concern** | Contemporary social psychology |
| **Sympathy** | Darwall 1988[48] |
| | Eisenberg & Strayer 1987[59] |
| | Preston & de Waal, 2002[60] |
| | Sober & Wilson 1998[61] |
| | Wispé 1986[36] |

The concept of "Feeling for another person who is suffering" means that affective changes are triggered in the observer in response to the affective state, felt or imagined, of another person.[29] Empathic concern means that one's feelings are in line with those of the other person.[58] If somebody is sad you will feel sad, if a person is happy one will feel happy too. This doesn't mean that the emotions need to be the same but that they should correspond in their general direction, either positive or negative.

Sympathy and compassion presuppose that one's feelings towards the other person are pro-social[58,62,63] but it doesn't mean that the emotions have to be isomorphic or "congruent".[62]

Feeling "for" another person could be described as a tender, warm, moved and softhearted reaction that plays a crucial role for healthy co-existence. Furthermore, it is thought to serve as a valve for sensitive care, pro-social behavior and providing the affective and motivational base for moral development.

This idea is defined as empathic concern in this study and quantified by the Interpersonal Reactivity Index.

## 1-4. Gender differences in empathy

The topic of gender differences in empathy is very controversial. Lay psychology suggests that women have a greater ability for understanding others people's thoughts and feelings than men do. However, this commonly held stereotype is underpinned by an element of truth, some studies, which mainly used questionnaires, reported that women have greater empathic ability than men.[64-68] They are also thought to have superiority in emotional competence such as understanding other's emotions.[69,70] There is evidence from research using self-report and performance based measures, that women have a better ability to identify and name their feelings than men.[71,72]

Empathy skills are primarily measured through self-report questionnaires and produce a better female performance. Due to the traditional feminine gender role, women tend to view empathic skills as a more important component of their self-concept than men do.[73,74] Women might thus be motivated to achieve better results in this domain. Some researchers believe that the cause of this gender difference in empathy is the result of motivation rather than general differences in ability of the two sexes.[75,76]

In a study by Krendl et al. the influence of such gender stereotypes on behavior as well as cerebral responses has been thoroughly demonstrated.[77] Moreover, this idea is strengthened by the fact that no systematic gender difference was found in studies that assessed physiological measures or facial-gestural measures.[70] Studies which tested empathic accuracy in a more objective way found fewer gender differences.[76] Some researchers concluded that gender differences are mostly found in situations where the subjects are aware of being evaluated on their empathic skills and in circumstances that make salient the gender role expectations in which female are supposed to display greater empathy than males.[78]
On the other hand, there are some studies which suggested that observed gender differences may not purely be the result of nurture but rather, that they may also be influenced by nature. Others suggested that the gender difference is an innate capacity because females of all ages showed a superior performance.[79,80] Newborn girls are more likely than boys to cry in response to other infants crying and hereby show a stronger emotional contagion reaction.[79] In addition, newborn girls show longer eye contact periods, spent more time looking at faces, performed better in facial recognition and showed more empathic response to distress expressed by others.[81] Another study found that four to six years old girls had significantly higher empathy scores when compared to boys.[80] Similar results were obtained for girls from seven to eleven years[82] and for adolescent girls from eleven to seventeen, who not only showed better results in empathy, [80] but also in sympathy.[83]

Furthermore, various studies on empathy from around the world, reported that women show better outcomes in empathy measurements and thus suggest that a cultural influence is unlikely.[84-86]

Sexual dimorphism in empathy is further characterized through the examination of promptness, sensitivity and accuracy in labeling and recognition of emotional facial expressions, phenomena, which are an integral part of the empathic reactions. Females outperformed men in promptness,[87] sensitivity and accuracy.[88,89]

The high perceptual sensitivity to minimal social-affective signals might be the origin of the female advantage in perceiving, identifying and responding to facial emotions.[90] First, women are better in detecting emotional stimuli of lesser saliency[91] and second, they manifest more mimicking of facial emotional expression at an automatic (unconscious) processing level compared to men and therefore understand better other persons' emotional states.[90] Interestingly, gender differences become much more apparent when facial stimuli are presented at the edge of consciousness.[89,92]
Another typical trait of empathy is the unconscious adoption of the posture or the facial expression of an observed other. Doherty et al. demonstrated that women appear to display more emotional contagion to both positive and negative expressions than men in a dyadic interaction setting concerning subjective experience and facial response.[93] The results of a study from Thunberg were consistent with the hypothesis that females are more facially reactive than males to fear relevant stimuli.[94] Other research showed that women have an advantage in decoding nonverbal information.[95]

Very little is known about the gender dependent modulation of the empathic response. An interesting study showed that empathy-related neural responses were significantly lower in males compared to females when observing an "unfair" playing person experiencing pain.[96] Further, there are some interesting studies, analysing male fans empathizing with the competitors during sport games to such a degree that they mentally project themselves into the game and experience the same hormonal surges athletes do. Their mean testosterone level increased in the fans of winning teams and on the contrary decreased in the fans of losing teams. These findings suggest that in men watching one's favourite team win or lose has physiological consequences that extend beyond changes in mood and self-esteem.[97,98] This kind of empathic engagement in male fans of sports, seems socially accepted compared to other forms of empathy, which are less part of a male self-concept.

The inability to identify and describe emotions in oneself prevents people from experiencing empathy. This personality trait is called alexithymia and its incidence is almost twice (17%) as often in men as in women (10%). Multivariate analysis showed that alexithymia was associated with male gender.[99]

Recent brain imaging studies focused on the processes underlying gender differences in empathy tasks. Despite equal performances in empathy tasks, the brain activation shows gender differences.[100]
Very few researchers have investigated the relation between empathy and gender affiliation, especially in individuals who identify with the opposite sex (transsexuals). A study by Owen-Anderson analyzed the empathic tendencies of children with gender identity disorders (GID). According to the DSM-IV-TR, GID is diagnosed when there is both ‘‘a strong and persistent cross-gender identification’’ and ‘‘evidence of persistent discomfort about one’s assigned sex or a sense of inappropriateness in the gender role of that sex’’.[101] However, no significant differences in empathy levels between boys with GID and normal control boys were found.[102]

Taken together, these findings, consisting mostly of self reported data, suggest that females may be more empathic than males,[69,70,79] in several emotional conditions but not in all, possibly as a result of motivation and gender stereotype responses.[77] In empathy-related concepts, such as emotion decoding, recognition, expression and facial

mimicry, some studies suggest that female subjects show significantly better performance than male participants.[88,89,91,95] More solid evidence suggests that the two genders may differ in the recruitment of cerebral networks.[103,104-106]

## 1-5. Medical relevance of empathy

In addition to the quest to understand the operational principles of empathy reactions operate, how they are associated with gender and how they interact with hormones, empathy has a considerable clinical impact. In some diseases a reduced ability for processing empathy reactions is an integral part of the clinical picture. It is documented that schizophrenia patients show substantial deficits in all core components of empathy,[107] especially in emotion recognition,[108,109] in the capacity to infer one's own and other person's mental states and in cognitive empathy.[110-112] These deficits in emotion processing are hallmarks of schizophrenia, with consequences not only for social functioning but also for subjective well-being.

Further, there is evidence that patients with antisocial personality disorder have difficulties in processing non-verbal emotional stimuli[113] and patients with autism spectrum disorders have impairments in cognitive and affective empathy.[114-116]

Alexithymia has been recognized as a major risk factor for a variety of psychiatric and medical disorders,[117] such as somatization,[118] hypertension,[119] chronic pain, functional dyspepsia,[120] anxiety,[121] panic disorder,[122] and depression.[121] There are many more psychiatric and somatic disorders that overlap with alexithymia, such as eating disorders,[123] traumatic brain injury[124] or substance abuse[125] just to name a few.

Reconstructing empathic skills is of primary importance in the treatment of diseases with impairments of this ability.[126] Findings about how hormones might be involved or modify these procedures could lead to new treatments. Moreover, empathy may be an interesting screening factor for anxiety, depression and burnout among health professionals in the clinical setting.[127]

Last but not least, working with transsexual patients and evaluating the effects of hormone treatment on specific domains is not only important for knowing what the positive and negative effects of these treatments are but also to create awareness in medical research for the interests of transsexual patients.

## 1-6. Social neuroscience

### 1-6-1. A neurobehavioral evolutionary perspective

Investigations of the neurobiological underpinnings of empathy showed that this phenomenon might have been an important strategy for survival and has contributed to genetic fitness.[1,128] Sharing information with conspecifics and communicating about needs, intentions and emotions could have supported survival in individuals and in the group. One can assume that social learning may also foster helping of non-kin members.[32] Mimicry may have added an important survival value, because the innate capacity of imitating postures helps to communicate and therefore fostered relationships.[32]
The evolution of empathy might lead back to mammalian maternal care,[129] but one can also find parental care in birds, fish and some reptiles.[130] Parental care is almost certainly a genetic endowment, but it is less clear if other forms of care (for siblings or non kin members) are also genetically hard wired.[131]
The evolution of executive functions, a process that serves to plan, control and regulate actions and language has been an important feature for humans to develop a more complex understanding of empathy.[132]

### 1-6-2. Two different neuronal networks

Findings from social neuroscience suggest that empathy can be divided in two different concepts: the early emotional contagion system and the more advanced cognitive perspective-taking system.[133] The boundary between these two concepts are blurry and it isn't clear if the neural systems should be seen as closed circuits or rather as interacting systems in constant exchange.[133,134]
Brain lesions or personality disorders (psychopathy) are examples of diseases and disorders associated with empathic dysfunction, which might provide evidence for the concept of two different networks.[134] On the other hand, results from a study Shamay-Tsoory et al. indicated that patients with schizophrenia[112] were significantly impaired in both cognitive and affective empathy compared to healthy control subjects and also the current state of affairs concerning the Asperger syndrome is less clear. [135]

#### *What is cognitive empathy?*

Cognitive empathy has several synonyms, such as cognitive perspective taking, theory of mind or mentalization. Earlier we defined it as "imagining how one would think and feel in someone else's place." Cognitive empathy is also defined as the ability to understand and interpret other people's thoughts, desires, goals, beliefs and intentions.[130] The empathizer is thought to use perspective-taking abilities to project

into the place of the object.[60] Brain regions activated by cognitive perspective taking include the ventromedial prefrontal regions, the superior temporal sulcus,[50,136] extending into the temporo-parietal junction[137] and the temporal pole.[32,134,138]

As an example of deficits in cognitive perspective taking we can mention ventromedial lesions and frontal damages.[134] Autistic spectrum disorders seem to be a controversial topic, some studies argue that they are linked to deficits in perspective taking only[136,139], other studies found an impairment in both cognitive and affective empathy.[135] The lack of cognitive empathy could be an explanation for their problems in communication and social interaction.[49,50]

Autism is ''the presence of markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activities and interests''.[101] The lack of cognitive empathy could be an explanation for their problems in communication and social interaction.[49,50]

*What is affective empathy?*

According to the main difference between cognitive and affective empathy is that the first one presupposes the understanding of the other and the second one involves sharing emotions, feelings or the sensory states of another person.[101]

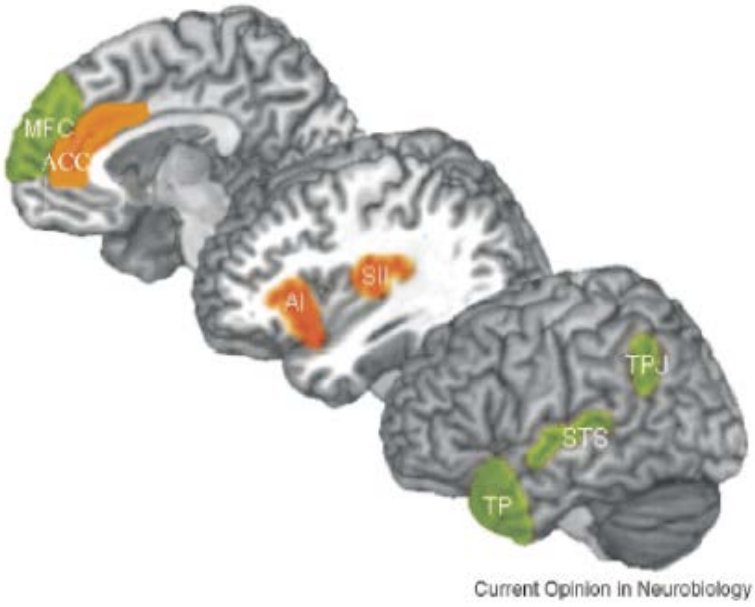
Several brain regions seem to be involved in this subjective emotional experience, such as the amygdala, the right somatosensory cortex, the right temporal pole and the insula.[23,101,140-143]
Examples of lesions, which lead to deficits in affective empathy are lesions of the left inferior frontal gyrus and atrophy in the temporal pole.[144] Also, patients with antisocial personality disorder show deficits in affective empathy.[139,144] These impairments do not show any loss in cognitive perspective taking, but do show impairments in emotion processing.[144] Individuals with Antisocial Personality Disorder are marked first by impairments in personality (self and interpersonal like Ego-centrism, absence of pro-social internal standards, lack of empathy or intimacy) and second by the presence of pathological personality traits (manipulativness, deceitfulness, callousness, hostility, irresponsibility, impulsivity, risk taking).[101]

Based of these findings some researchers concluded that two neural networks, which operate independently, mediate these two concepts.[134]

**Table 1: Two separate systems for emotional and cognitive based empathy.**
Adopted from Shamay-Tsoory et al. 2009.[134]

| Emotional Empathy | Cognitive Empathy |
|---|---|
| Simulation system<br>-Emotional contagion<br>-Empathic concern<br>-Emotion recognition | Mentalizing system and theory of mind<br>-Perspective taking<br>-Imagination<br>-Theory of mind |
| Development:<br>Infants | Development:<br>Children/ adolescents |
| Phylogenetics:<br>Rodents,Birds | Phylogenetics:<br>Chimpanzees |

**Figure 1: Schematic overview of brain regions** typically involved in understanding others on the basis of cognitive perspective taking (green) and empathy (orange); the latter measured in the domain of empathic brain responses to pain, disgust, taste, and touch. MPC, medial prefrontal cortex; ACC, anterior cingulate cortex; AI, anterior insula; SII, secondary somatosensory cortex; TP, temporal poles; STS, superior temporal sulcus; TPF, temporo-parietal junction. Taken from Hein et al. 2008 [144]




In this study, we also took into account the dichotomous classification between cognitive and affective empathy. Both the Bermond-Vorst Alexithymia Questionnaire, as well as the Interpersonal Reactivity Index measures the cognitive and the affective dimension of empathy.

### 1-6-3. Mirror neurons

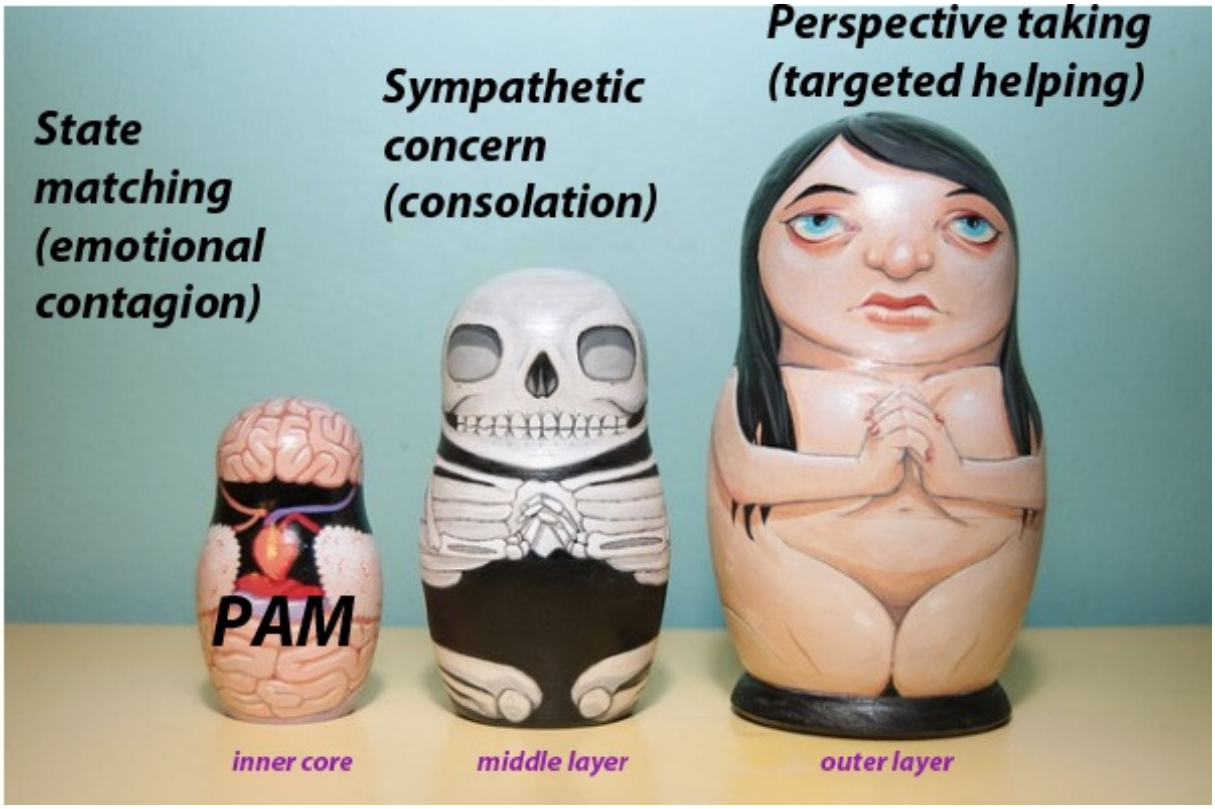
In the mid 1990´s a new class of premotor neurons was discovered in the macaque monkey'.[145] These neurons discharged when the monkey was executing an action, like grasping a nut but also discharged when the monkey was observing a goal-related action performed by another individual (monkey or human).[146,147] These neurons were called mirror neurons. Several studies have demonstrated that a mirror neuron system matching action perception and execution also exists in the human brain.[148] However it must be mentioned that evidence for their existence in humans is only indirect and relies on functional neuroimaging studies.[149]
Different functions have been attributed to mirror neurons, including action understanding, affective and cognitive empathy.[149,150] Some discoveries propose that these neurons should be understood as motor system facilitators, working by learned associations.[151] Others empathize on a connection between mirroring mechanisms and sharing emotions and sensations.[9,30]
In addition to comprehending actions, humans are able to understand the aims behind their actions and it seems that motor resonance is not a sufficient mechanism for explaining other peoples intentions.[152] Besides, neurological studies, which investigated empathy abilities in patients with brain lesions, found no evidence that lesions in regions involved in the mirror neuron system (ventral premotor, motor cortex and anterior intraparietal sulcus) led to any dysfunction in empathy, sympathy or moral reasoning.[149,153] Additional research will be necessary to determine the specific role of mirror neurons and empathy.

### 1-6-4. Perception-action model

Based on the mirror neuron hypothesis, Preston and de Waal (2002) proposed the perception-action model.[60] This model is based on the idea of a shared neural representation, where seeing or imagining another person´s emotional condition automatically activates the same condition in the viewer. The observer is simulating the other´s situation with his own neural program, thus leading to analog autonomic and somatic responses.[154]
The result is a corresponding sensorimotor, affective or mental state.[155,156] This process is not conscious but can nevertheless be controlled or inhibited.[157]
Imaging studies support evidence for common activation, aroused when experiencing disgust[143], touch[158] or pain[23] in oneself, and when perceiving the same feelings in others.

**<u>Figure 2</u>: The Russian doll model of multilayered empathy adapted from de Waal 2012**[159] (painting by Jason Levesque)

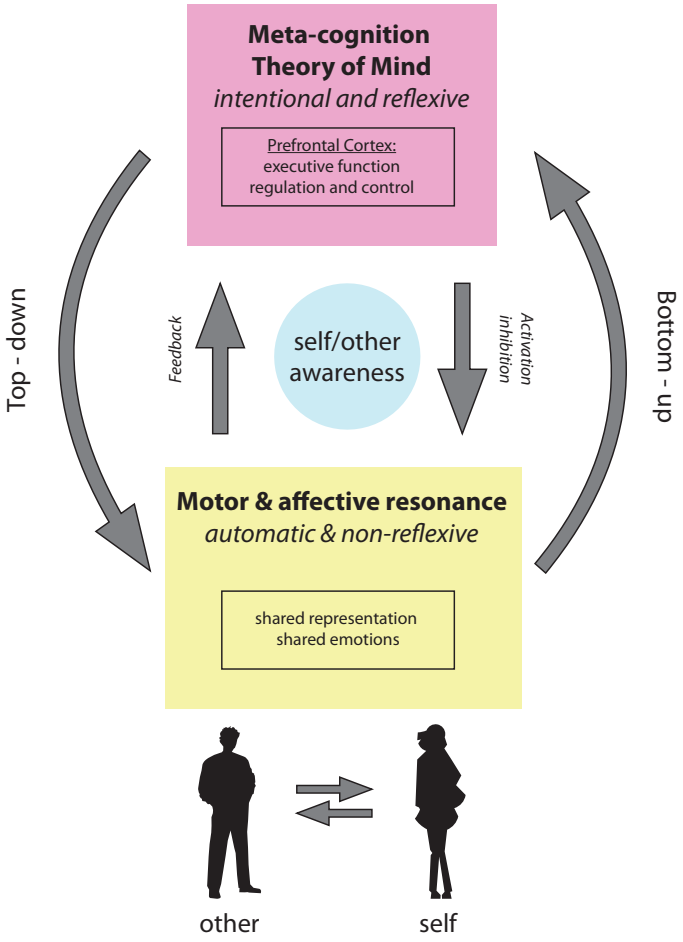
The doll's inner core consists of the innate socioaffective foundation: the perception-action mechanism (PAM) that underlies state-matching and emotional contagion.[60] Built around is the second layer, which includes sympathetic concern. The most complex outer layer includes perspective-taking capacities. A few large-brained species show all of the doll's layers, but most show only the inner ones.



## 1-6-5. Processing and modulation of empathy

*Top-down/bottom-up processes*

**Figure 3: Schematic representation of the bottom-up (matching between perception and action) and top-down (regulation and control) information processes involved in human empathy adapted from Decety 2006 [32]**




Empathy relies on automatic and unconscious bottom-up information processing: one person's first-hand emotional experience is shared between his own neural systems and the perception of this experience by another person. This meta-cognition is continuously updated by bottom-up information and, in return, modulates lower levels. Under voluntary control, individuals can regulate their response via top-down processing. Thanks to executive function resources, one can answer another person's states and needs in an appropriate way either by down regulating (i.e., reduce) or up regulating (i.e., promote) your response. This self-regulation is indispensable for flexible and tailored responses. The perceiver's empathic experience is influenced by his motivation, memories, intentions and attitudes.

# II. Transsexualism

## 2-1. Historical background

The word "transsexualism" was first introduced by Hirschfeld[160] in 1923, but it is only in 1953 that Harry Benjamin, an endocrinologist and sexologist, coined the term as we understand it today.[161] He defined transsexualism as the most extreme form of gender identity disorder, characterized by an unshakeable conviction of belonging to the opposite sex.

## 2-2. Definitions of terms

The following definitions are mainly based on *The Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People*:[162]

**Cisgender (cissexual women=ciswomen, cissexual men=cismen):** In gender studies these words are used to describe gender identities, where a person's self-perception of their gender matches their sex.[163] It is complementing the term transgender.

**Cross-dressing (transvestism):** "Wearing clothing and adopting a gender role presentation that, in a given culture, is more typical of the other sex."

**Disorders of sex development (DSD):** "Congenital conditions in which the development of chromosomal, gonadal, or anatomic sex is atypical. Some people strongly object to the "disorder" label and instead view these conditions as a matter of diversity[164] preferring the terms intersex and intersexuality."

**Female-to-male (FtM)= transsexual man** "Adjective to describe individuals assigned female at birth who are changing or who have changed their body and/or gender role from birth-assigned female to a more masculine body or role."

**Gender dysphoria:** „refers to discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics)."[165,166]

**Gender identity**: "A person's intrinsic sense of being male (a boy or a man), female (a girl or a woman), or an alternative gender (e.g., boygirl, girlboy, transgender, genderqueer, eunuch)"[167,168]

**Gender identity disorder:** "Formal diagnosis set forth by the Diagnostic Statistical Manual of Mental Disorders, 4th Edition, Text Rev. (DSM IV-TR) (American Psychiatric

Association, 2000). Gender identity disorder is characterized by a strong and persistent crossgender identification and a persistent discomfort with one's sex or sense of inappropriateness in the gender role of that sex, causing clinically significant distress or impairment in social, occupational, or other important areas of functioning."

**Gender-nonconforming**: "Adjective to describe individuals whose gender identity, role, or expression differs from what is normative for their assigned sex in a given culture and historical period."

**Gender role or expression:** "Characteristics in personality, appearance, and behavior that in a given culture and historical period are designated as masculine or feminine (that is, more typical of the male or female social role).[169] While most individuals present socially in clearly masculine or feminine gender roles, some people present in an alternative gender role such as genderqueer or specifically transgender. All people tend to incorporate both masculine and feminine characteristics in their gender expression in varying ways and to varying degrees."[170]

**Genderqueer**: "Identity label that may be used by individuals whose gender identity and/or role does not conform to a binary understanding of gender as limited to the categories of man or woman, male or female."[170]

**Male-to-female (MtF)= transsexual women:** "Adjective to describe individuals assigned male at birth who are changing or who have changed their body and/or gender role from birth-assigned male to a more feminine body or role."

**Sex:** "Sex is assigned at birth as male or female, usually based on the appearance of the external genitalia. When the external genitalia are ambiguous, other components of sex (internal genitalia, chromosomal and hormonal sex) are considered in order to assign sex.[171-173] For most people, gender identity and expression are consistent with their sex assigned at birth; for transsexual, transgender, and gendernonconforming individuals, gender identity or expression differ from their sex assigned at birth."

**Sex reassignment surgery (gender affirmation surgery)**: "Surgery to change primary and/or secondary sex characteristics to affirm a person's gender identity. Sex reassignment surgery can be an important part of medically necessary treatment to alleviate gender dysphoria."

**Transgender:** "Adjective to describe a diverse group of individuals who cross or transcend culturally defined categories of gender. The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth."[167]

**Transition:** "Period of time when individuals change from the gender role associated with their sex assigned at birth to a different gender role. For many people, this involves learning how to live socially in another gender role; for others this means finding a gender role and expression that is most comfortable for them. Transition may or may not include feminization or masculinization of the body through hormones or other medical procedures. The nature and duration of transition is variable and individualized."

**Transsexual:** "Adjective (often applied by the medical profession) to describe individuals who seek to change or who have changed their primary and/or secondary sex characteristics through feminizing or masculinizing medical interventions (hormones and/or surgery), typically accompanied by a permanent change in gender role.

## 2-3. Prevalence

Although most studies have been conducted in European countries, (Sweden,[174] the United Kingdom,[175] the Netherlands,[176-178] Germany,[179] and Belgium,[180]) and only one in Singapore,[181] it is hypothesized that cultural influences are rather small.[182] The prevalence seems to be 1 in 11,900-45,000 for male-to-female individuals and 1 in 30,400 to 200,000 for female-to-male individuals.[162,180]

## 2-4. Etiology of Gender Identity Disorders

One's gender self-awareness develops gradually during childhood, in constant interaction with parents, playmates, and the environment.[169] Most attempts to identify biological underpinnings of transsexualism in humans have investigated the effect of early biological programming; this theory hypothesized that increased androgen exposure on the brain in utero results in increased prevalence of gender dysphoria in adulthood.[183]

Prenatal androgenization seems to predispose in 50-60% of female-raised 46, XY intersexed children to a male gender identity evolvement; the rest developed a female gender identity.[184,185] On the contrary prenatal androgenization of 46, XX fetuses leads to marked masculinization of later gender-related behavior, but did not increase gender-identity confusion/dysphoria.[186-188]

Hormonal imprinting remains inexplicable, since MtF transsexuals, with an androgen exposure prenatally, still developed a female gender identity, suggesting that unknown biological mechanisms apparently may override the effects of prenatal androgens or that the specific moment in time is crucial for having an effect on gender dysphoria- it is a phase-dependant imprinting process. Gooren et al. summarize that, while prenatal androgen exposure does predispose for development of a male gender identity, this relationship is not definite.[189]

In addition a study by Bocklandt et al. showed that genetic factors may play a role in psychosexual differentiation.[190] Further support was provided from co-occurancy among twin pairs, brother-sister pairs and father-son pairs.[191,192] Genetic studies suggest that both androgen and estrogen might play a role in gender identity, because significant associations between transsexualism and the CYP17 gene (encodes 17

alpha-hydroxylase, the enzyme deficient in some congenital adrenal hyperplasia patients) were found.[193] Moreover a study by Henningson and colleagues identified a significant association between a polymorphism in the estrogen receptor beta gene and MtF transsexualism[194,195] and a study by Hare et al. found a significant association between androgen receptor gene repeat length polymorphism and MtF transsexualism.[196]

In summary, current state of knowledge does not provide satisfactory explanations for the etiology of transsexualism.

## 2-5. Diagnosis:

Gender dysphoria is a self-diagnosis with no other tests to assess it. Gender dysphoria should persist for at least two years.[197] Two senior specialists should write assessments, which involve in-depth interviews.[198] Not part of the definitions criteria is the sexual orientation, which could be, like in every other person, heterosexual, homosexual, bisexual or asexual.[199] Further, people from all social classes are equally affected.[200] An important question is if gender identity disorders are mental disorders. The DSM-IV and ICD-10 have defined transsexualism as a mental disorder. One can argue that gender dysphoric persons have a significant psychological stain. Further, the use of a formal diagnosis is advantageous by providing health insurance coverage and guiding research. On the other hand critics are justified because qualifying transsexualism, as a mental disorder is for many people a license for stigmatization and an argument for the deprivation of gender patients' civil rights.

**Table 2: ICD-10 criteria for gender identity disorders**

| **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.<br>B. Presence of the transsexual identity for at least two years persistently.<br>C. Not a symptom of another mental disorder, such as schizophrenia, or associated with chromosome abnormality. |

**Table 3: DSM-IV-TR criteria for gender identity disorders**

| | |
|---|---|
| **DSM-IV-TR**<br><br>**Diagnostic criteria for gender identity disorders** | 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:<br>(1) repeatedly stated desire to be, or insistence that he or she is, the other sex<br>(2) in boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing<br>(3) strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex<br>(4) intense desire to participate in the stereotypical games and pastimes of the other sex<br>(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.<br>B. Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex. 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 male stereotypical 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.<br>C. The disturbance is not concurrent with a physical intersex condition.<br>D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. |

*Code* based on current age:

**302.6 Gender Identity Disorder in Children**
**302.85 Gender Identity Disorder in Adolescents or Adults**

*Specify* if (for sexually mature individuals):

**Sexually Attracted to Males**
**Sexually Attracted to Females**
**Sexually Attracted to Both**
**Sexually Attracted to Neither**

## 2-6. Comorbidity

Often gender dysphoria is accompanied by psychiatric comorbidity, which could be either the consequence of the persistent gender dysphoria and the concomitant psychosocial distress (chronic minority stress) or could be unrelated.[201-204] Mental health professionals should screen for possible comorbidities, which could range from anxiety, depression, self-harm, a history of abuse and neglect, compulsivity, substance abuse, sexual concerns, personality disorders, eating disorders, psychotic disorders to autistic spectrum disorders.[205-207]

## 2-7. Treatment

The objective of treatment is to assist people in finding their gender identity and a gender role that is comfortable for them[205] and thus maximize overall psychological well-being and self-fulfillment. A study by Murad and colleagues has shown that gender dysphoria can be treated successfully.[202] The newest approach is that the treatment needs to be individualized. Not every patient needs surgery and not every patient desires hormone treatment, but some want both. Personal comfort is achieved for each person through different treatments and at a different level.[205,208]
*The Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People*[162] promulgated a variety of therapeutic options, including the following:

• **Real life experience:** This phase consists in living part time or full time in the other gender role, consistent with one's gender identity. This phase could be very difficult since the transsexuals are particularly exposed to discrimination.[197]
• **Psychotherapy:** (individual, couple, family, or group): Therapy is important for exploring one's own gender identity, role, and expression. Further, it is a good opportunity for reprocessing the negative impact of gender dysphoria or other comorbidities. Especially group therapy may enhance social and peer support.
• **Cross Hormone treatment:** The goal of hormone therapy is to feminize or masculinize the body in direction of one´s desired gender identity.
• **Surgery:** (e.g., breasts/ chest, external and/or internal genitalia, facial features, body contouring) Operations are the most invasive step targeting to change primary and/or secondary sex characteristics.

# III. Hormones

## 3-1. Background

Hippocrates, "the father of medicine," introduced the theory of humors in medicine. The idea that imbalances in body fluids are the cause for health, disease, temperament and personality traits seem far-fetched, but if one attempts to reinterpret this terminology with modern concepts of medicine, some ideas do not seem so outdated and archaic anymore. Testosterone is associated with aggression, antisocial behavior and social dominance[209] and estrogen with maternal behavior and bonding.[210-212] The black bile, the yellow bile, the phlegm and the blood might be seen in cautious analogy to the 'neurotransmitters' and 'neurohormones' of our days.
In the past investigations and research about the effects of hormones and neuropeptides on the human behavior, there had been technical and ethical limitations. Thanks to new hormone administration techniques and neuroimaging methods it was possible to investigate the regulatory effect of hormones on the social-emotional behavior.[213] It is certain that humans are less under the influence of hormones than simple organisms, but more and more research demonstrate that humans are still swayed by their endocrine system, regarding their motivations, actions, and behaviors.

## 3-2. Hormones, behavior and environment

Hormones not only influence behavior but are in turn also being affected by them. Further, environmental forces are acting in a reciprocal way on both hormones and behavior.[214] When hormones influence behavior, they do so by changing the probability of evoking behaviors, rather than provoking totally new ones. Interestingly, this system is characterized by mutual interactions, where each player influences and modulates the other.

## 3-3. Types of hormone-behavior associations

The overview of hormone-behavior associations are based on an article written by Buchanan and colleagues in 1992.[215]

### 3-3-1. Activation effects

This conceptualization refers to the rising or falling of plasma hormone levels, which results in heightened or reduced levels of moods or behaviors. As a consequence, hormone levels correlate either positive or negative with the level of mood or behavior.[215] An empirical example of this activation effect would be that higher

estrogen (E) levels involve more positive mood in girls[216] or that testosterone (T) is associated with aggression. As a side note, if hormone levels rise or fall, in other words if the hormone level varies, the resulting effects could be very different. A study by de Lignieres et al. found out that irritability and aggressiveness was induced by excessive increase of E, a pleasant feeling of well-being was linked to moderate E levels and depressive symptoms were correlated to very low plasma E level.[217]

### 3-3-2. Adjustment effects

Behavior could change as a result of a progressive deviation from the normal, accustomed hormone level.[65] As an example one can mention the fast changing of hormone levels in adolescence. A study by Brooks-Gunn et al. proved that rapidly rising E levels are associated with negative affect and depression for girls in an early stage of puberty.[218] No literature concerning short-term psychological adjustment effects of cross hormone treatment for transsexuals exists so far.

### 3-3-3 Irregularity effects

This effect describes irregular fluctuations of hormones, which lead to instability of nervous functioning, with potential implications for the mood.[215] Dennerstein et al. showed that the premenstrual syndrome was linked to several "irregularities" in the menstrual cycle.[219] In cross hormone therapy, provided that the intake is as prescribed, hormone levels are stable.

### 3-3-4. Complex interactions

Hormones are likely to interact with other biological and nonbiological factors. Individuals have a different sensitivity to hormone levels, moreover some individuals show a predisposition to certain behavior and also different context factors could modulate hormonal effects.[215]
A study by Udry demonstrated that individual sensitivity for certain behaviors, rather than T level are the determining factor for certain personality dimensions, like extroversion in girls.[220] Individuals with a predisposition towards depressive or aggressive behavior are under hormonal influence more prone to such behavior.[221-223] But these hypotheses remain controversial especially because it was not demonstrated that prior depression or aggression could predict later behavior patterns.[224]
Finally, evidence that the effect of hormones depends on contextual factors comes from Olweus et al., who showed that boys with higher T levels were only under conditions of threat, more likely to act aggressively.[225]

## 3-4. The steroid hormone Estradiol, Testosterone and the neuropetide Oxytoxin and Vasopressin

Social endocrinology research has established that hormones play an important role in social behavior. Enclosed, one can find a detailed overview of the hormones E and T and a brief overview of the neuropeptides Oxytocin (OT) and Vasopressin (AVP) and their effects on social human behavior. This overview is based on an article written by Bos and colleagues in 2012.[213]

### 3-4-1. Estrogen and Oxytocin: structure, synthesis and effects

#### *Structure*

Cholesterol is the parent compound from which all steroid hormones are derived.
The latter can be divided in five substance classes: the estrogens, the androgens, the progestogens, the glucocorticoids and the mineralocorticoids. They are synthesized in the gonads (estrogens, testosterone, progesterone) and the adrenal glands (cortisol, aldosteron). This procedure is controlled by the hypothalamic-pituitary-gonadal endocrine axis. Steroids can also cross the blood brain barrier. As for this this study, we will restrict ourselves to E and T.
On the other hand OT and AVP have very similar structures and both are composed of nine amino acids.

#### *Synthesis*

Three types of Estrogen exists: oestrone (E1), oestradiol (E2) and oestriol (E3). Their precursors are androstenedione or testosterone. E2 can be oxidized reversibly to E1 and both can be converted into E3. E2 has the strongest biological effect and is premenopausal the principle estrogen secreted by the ovaries. At menopause, ovarian production of estrogen ceases. In postmenopausal women E1 is aromatized by the aromatase in different tissues (e.g., skin, soft tissue, muscle and liver) and becomes the main unconjugated estrogen. In men, 80% of circulating E2 is provided by the peripheral conversion of androgens and only 20% are produced in the testes. E3 is made in the placenta and plays a major role in pregnancy, but it is of little importance in nonpregnant women and was not taken into further consideration in this paper.[226] Most E2 is bound to sex hormone-binding globulin (SHBG).

OT and AVP are produced in the hypothalamus (mainly in the supraoptic nuclei and paraventricular nuclei) and released into the circulation through the neurohypophyseal system. OT and AVP are the only known hormones released by the human posterior pituitary gland to act at a distance. In the brain, OT and AVP are synthesized primarily in magnocellular neurons of the hypothalamus, which project directly to the posterior

pituitary, where the hormones are released into the bloodstream.[227]

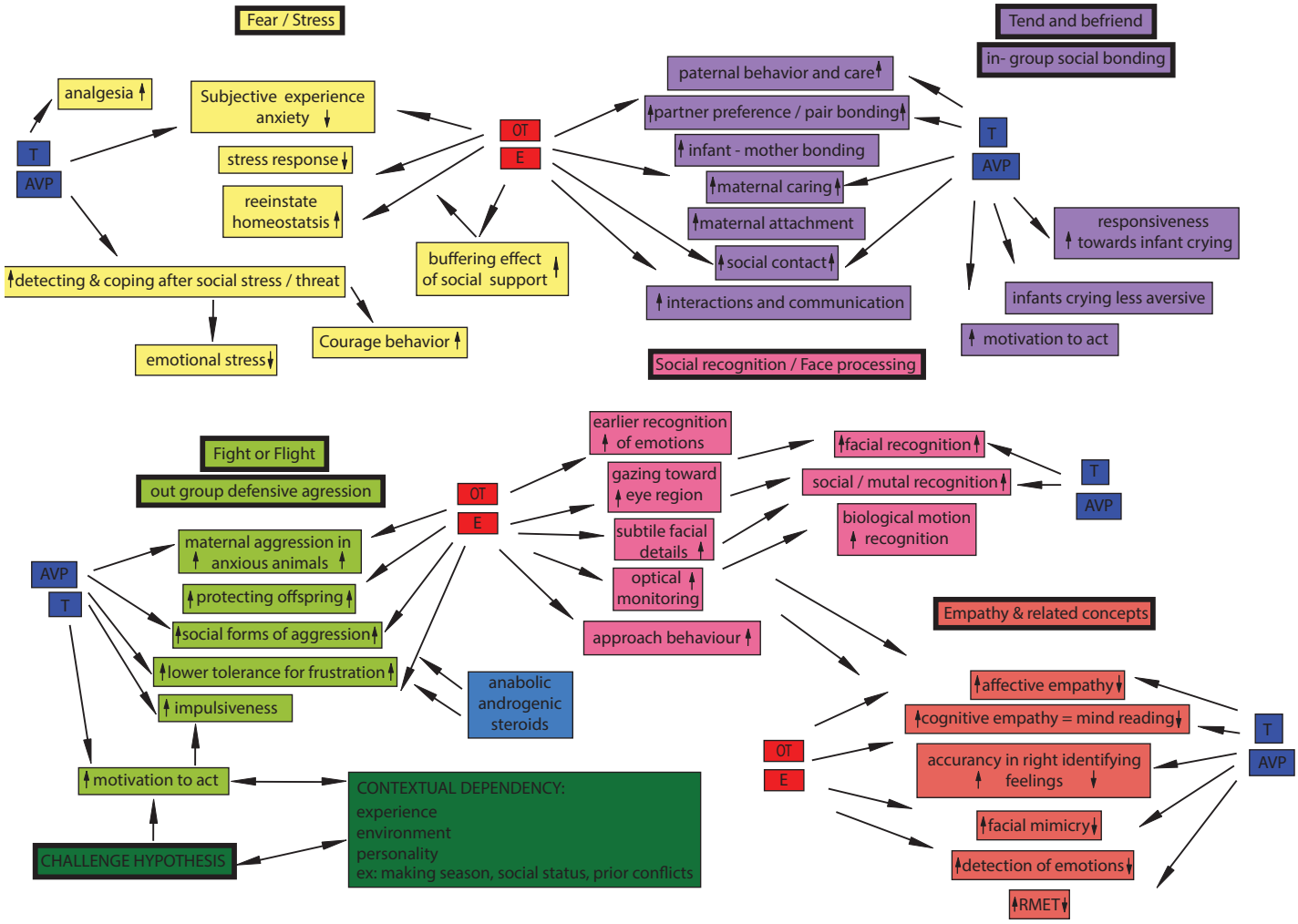
*General effects*

E can mediate their effect by slow and long lasting genomic or by rapid non-genomic mechanisms. Further it can be conversed in the brain from T by aromatase thus providing a source of fast and locally high concentrations of the steroid.[228] Receptors for E are nuclear transcription factors.

E controls various aspects in the female reproductive system before and after birth. E controls the gonadal development and stimulates the endometrial and uterine growth, maturation and differentiation. Apart from its implication in the sexual differentiation it also influences the cardiovascular system (dilation of the small blood vessels), it has effects on the coagulation system (specific up and down regulation of coagulation factors) bones (anti- osteoporotic), the liver,[229] anabolic and water retaining effects. Further, E plays a crucial role in sexual behavior and in the sexual differentiation of the brain.[230] This hormone brings forward the formation of synapses, anticipates neuronal cell death and modulates learning and memory.[231]

Peripherally released OT facilitates parturition and milk ejection during nursing.[227] AVP on the other hand regulates the water retention of the human body.[232] The effects of centrally released OT and AVP will be discussed later.

**Figure 4: Heuristic model of the effects of Estrogen, Testosterone, Oxytocin and Vasopressin on the human social behavior.**




Tend and befriend | in- group social bonding — For a detailed overview see:
a. In-group Social bonding and out-group aggression
f. In-group social bonding

Empathy & related concepts / Social recognition / Face processing — For a detailed overview see:
b. Social recognition, mind reading and empathy
g. Facial recognition, Social cognition and empathy

CHALLENGE HYPOTHESIS — For a detailed overview see:
h. Aggression

Fight or Flight | out group defensive agression — For a detailed overview see:
a. In-group Social bonding and out-group aggression
h. Aggression

Fear / Stress — For a detailed overview see:
e. Fear
i. Fear

OT Oxytocin | E Estrogen | T Testosterone | AVP Vasopressin | anabolic androgenic steroids

In this overview E and OT are not treated separately; to add by the way of explanation, in some brain areas the behavioral effects of OT are regulated by E and OT play a crucial role in mediating estrogen-dependent responses. E influences directly the expression and activation of OT producing neurons[233] and heightens the rate of transcription of the OT receptor. It is therefore difficult to consider E and OT separately.[234] The observation that E administration stimulates the release of OT, accentuates their similar effect.[235] One can offer the example of female sexual behavior and maternal behavior, which are both E and OT dependent.[236]

### *a. In-group Social bonding and out-group aggression*

One of the most ancient forms of bonding, the mother-infant bond is regulated by E, OT and also by AVP.[237] Other hormones and transmitters also contribute to this process, but we shall limit ourselves to the one mentioned above. Interestingly, it has been shown that these hormones are also involved in paternal behavior, partner preference,[238,239] partner bonding[240] and infant-mother bonding.[237] In literature it is proposed that maternal care and bonding are at the bottom of empathy.[241] Moreover OT, E and AVP also facilitate social contact and promote the formation of partner preferences.[242]
Recent studies described that OT blood levels are correlated with maternal caring behavior, attachment and bonding.[210-212] Further support for the role of endogenous OT in maternal behavior has been derived from studies showing that an OT antagonist or OT antisera blocked the onset of maternal behavior in rats that have just given birth.[243,244] Moreover OT administration leads to more positive interactions between fathers and their children[238] and also partners showed significantly increased positive interactions and communication.[240] E and OT increase in-group caring and social bonding.

Interestingly, OT could both favor a "tend and befriend" response, that promotes trust and cooperation for in-group members or a “fight or flight” defensive, but not offensive, aggressive response towards competing out-groups.[245,246]
This type of reaction is also mediated trough OT and E and can increase maternal aggression against conspecifics.[247] This might seem opposed to the general anti aggressive effects of E and OT, but it is connected to protection and care of the offspring. As a note aside it has also been shown that AVP leads to increased maternal aggression in anxious female rats.[248]

### *b. Social recognition, mind reading and empathy*

Interestingly, fMRI studies using the *Reading* the *Mind in the Eyes* Test (RMET) found the same neural activation for face processing, empathy and social recognition. Hence we consider these concepts together.[249,250] The areas, which are believed to be involved in hormonal modulation, are the superior temporal sulcus, the amygdala and the inferior frontal gyrus.[213]

It does not come as a surprise that the same hormones, which are associated with bonding are also implicated in social recognition, since recognition is a central key factor for attachment.[213] The ability to distinguish familiar conspecifics from strangers and to remember individuals is critical for successful group living. This process is called social recognition, and OT has been shown to be important for this memory ability.[251] Again the effect of the steroid hormones cannot be seen separately from the effects of the neuropeptides OT and AVP.[252] OT seems to be involved in enhancing the processing of social information, it specifically improves recognition memory for human faces and motions, but not for nonsocial stimuli.[227,253,254]

Unfortunately, the current state of facts revealed inconclusive data concerning the type of emotion, which are triggered or enhanced by OT administration. A study by Savaskan et al. showed that OT improves identity recognition memory for neutral and angry faces, independently of participant's gender.[255] Other more recent studies found that the encoding of positive social cues was facilitated through OT[256,257] and another study suggested that OT plays a specific role in fear recognition.[258] It remains unresolved, whether increased emotion recognition is selective or not.
It seems that OT facilitates facial recognition by enhancing gaze specifically toward the eye region of human faces.[259] This may be one mechanism by which OT increases social and emotion recognition. Further, it modulates emotion processing and promotes approach behavior by reducing the salience of threatening social stimuli.[260,261]

Observing the eye region and the facial expression is an integral part of the correct identification of feelings, perceptions and expressions and is ergo the bases for mind reading and empathy.[262] Data from a study by Domes et al. confirmed that OT enhanced the ability to infer the mental state of others by increasing the sensitivity for subtle facial details, especially in the eye region and therefore improves mind reading.[263] This might be the consequence of strengthened optical monitoring of faces.[213] Further, according to a recent study, people recognize earlier positive emotional expressions on faces,[257] while another study proved the same results exclusively for fearful expressions.[258] Also affective empathy seems to improve with OT application in men.[264] In patients with autism spectrum disorder, OT improved the mind reading capacities (cognitive empathy), measured with the RMET.[262,263]

Another Study by Bartz et al. demonstrates that OT has also a positive impact on people's affective empathy skills, especially for individuals with low social competences.[265] The subjects were more likely to detect accurately the feeling of the other person. In a comparable task, where subjects had to judge emotional pictures, participants judged the pictures more emotional after OT administration.[264]

### *c. Trust*

Previous studies demonstrated that OT administration led to enhanced interpersonal trust during economic games.[266] OT had such a strong influence that participants in a study by Baumgartner et al. continued trusting even after they learned that their trust had been breached several times.[267] This increase in trust, especially after betrayal may be referable to a decrease in activation of circuits involved in fear processing, such as

the amygdala.[267,268]

*d. Mood changes*

In women mood changes are associated with variations across the menstrual cycle: An increase in the pleasantness[269,270] and positive mood[215,216] was found when E levels were high, whereas negative affects and depression were associated in a greater extent to low E levels.[271]

*e. Fear*

Previous studies have also shown that E has anxiolytic effects in rodents.[272,273] Further, in challenging situations OT is released and reduces anxiety, attenuates the stress response[274] and reinstates homeostasis after threat.[246,275] OT seems to enhance the buffering effect of social support on stress responsiveness and subjective felt anxiety.[276] The reduced fear might be explained by the promotion of friendly behavior and the search for proximity with others.[213]

### 3-4-3. Testosterone and Vasopressin: structure, synthesis and effects

*Structure*

Androgens are steroid hormones with 19-carbon atoms. The best-known androgen is testosterone; others are dihydrotestosterone and androstenedione.

*Synthesis*

Androgens have a genomic effect that typically takes at least more than half an hour and a rapid or non-genomic pathway that acts within seconds to few minutes.[277,278]

*General effects*

In men T promotes the differentiation and maturation of the sexual organs and provides the appearance of secondary sex characteristics. Further, T has anabolic effects on the skeletal muscle, promotes erythropoiesis and bone maturation. In addition, it is associated with risk for metabolic syndrome and cardiovascular diseases. Research has shown that some of the effects of T are completely or partially mediated by aromatized estradiol.

## 3-4-4. Testosterone and Vasopressin: effects on human social behavior

Especially T, but also E has a strong influence on the expression of AVP in several limbic brain regions. Steroid hormones not only have an influence on the expression but also on the receptor distributions of social neuropeptides. Male behavior is stronger influenced by AVP and female behavior is more heavily influenced by OT.[279]
T and E and their related social neuropeptides, especially AVP (but also OT) are good candidates for being responsible for the regulation of social competitive behavior.[280,281] Given that AVP synthesis is dependent on androgens,[282] both are closely linked in the types of social behaviors they influence.

*f. In-group social bonding*

First, we saw that social bonding is related to E and OT, but there is evidence that also T increases care.[283,284] This effect is mediated by two potential mechanisms, first by the conversion of T to E (E2) by aromatase, whereupon E could increase the OT synthesis.[228,282,284] Second, by promoting the direct increase of AVP synthesis by T,[284] paving the way for AVP to exert its effects in maternal care.[285] In young women parental care was up regulated after T administration[286] and the neural responsiveness in men and women[238] towards infant crying was enhanced, reducing it's aversive effect and encouraging the motivation to act.[286,287]

*g. Facial recognition, Social cognition and empathy*

Knockout mice, in which the OT or AVP receptors are disabled, show large disturbances in social recognition.[288,289] OT is essential for the formation of social memory in the medial amygdale and AVP facilitates social recognition by acting on the lateral septum.[290] But this peptide can only accomplish its function in presence of sex-specific

hormones.[252] An impairment of recognition seems to occur if T or aromatase are lacking.[291] Few studies investigated the role of AVP in social recognition: it seems that AVP enhances the encoding of happy and angry facial expressions, by increasing the attention towards emotionally significant stimuli[292] and that positive and negative social cues become more memorable, what could lead to bonding or on the contrary to aggressive behavior.[213]

In regards to empathy, a negative correlation between free T and affective empathy (RMET) and cognitive empathy (empathy quotient) was found.[293] Moreover, facial mimicry, a component of empathy, is reduced in women after T administration.[294] A study by van Honk showed that the detection of emotions is prolonged after T administration as well as the identification of facial signals of anger.[295]
Based on these findings it is reasonable to believe that T reduces mind reading capacities.[213] Although it must be recognized that the specific role of T in empathy remains elusive.

Previous studies have found that free T is inversely correlated with social behaviors such as eye contact in infancy, peer relationships in preschoolers, and mentalistic interpretation of animate motion. In line with this findings is a study conducted by Harris et al., which has demonstrated that T correlates negatively with a pro-social personality.[296]

### *h. Aggression*

In the past a lot of studies found a positive correlation between T and aggression.[296] Olweus and colleagues demonstrated that higher T plasma levels are related to lower tolerance for frustration among adolescent boys.[297] They react more aggressively in situations where they were provoked compared to boys with lower T levels. A study by Dabbs et al. showed that T is related to criminal violence and aggressive dominance in prison among women and also men.[298] Moreover, the use of anabolic androgenic steroids has been shown to directly affect impulsiveness and indirect aggression.[299] Last but not least the anger intensity is reported to be more pronounced in men than in women.[300]

More recent findings demonstrated that aggression and competitive behavior are indeed connected to AVP and T but that they only increase social forms of aggression (aggression against an intruder, subordinate or competitive behavior).[301] For this reason the "challenge hypothesis" was proposed, hypothesizing that in social challenging situation, T can lead to aggressive response if this type of reaction would be beneficial, but might also lead to increased sociality, if a moderate response is required.[302,303] This aggressive behavior is triggered by rapid changes in neural sensitivity to steroid hormones[304] and local fluctuation of their level in the forebrain.[305]
AVP is acting in concert with T on the amygdala[306] and on the hypothalamus when T is up-regulating the AVP receptor density.[307] Further, AVP exerts its effect on the lateral septum, where AVP and T are both increasing aggressive behavior.

New data suggest that AVP can also decrease aggression when acting on the bed nucleus of the stria terminalis, showing that different locations can provoke more or less aggressive responses.[308]
In women, after T administration a neural circuitry is activated in response to angry faces.[309] This circuitry is called "the neural circuitry of dominance and reactive aggression" (amygadala, inferior frontal gyrus, hypothalamus and brainstem). In response to angry faces, T increases in women the heart rate, enabling a fast reaction like flight or fight.[310]

*i. Fear*

T may enhance analgesia and reduce anxiety, but its mechanisms are not well understood yet.[311-313] The reduction of fear by T should enable one to better handle challenging situations. In other words T and AVP promote the efficiency to detect and cope with threat and promote "courageous" behavior. Therefore T leads to reduce fear and increase motivation to act.[213]

*j. Risk taking*

T administration heightens the general motivation to act.[314] Furthermore, it leads to more risk taking during gambling and increases sensitivity for reward.[315,316] Further, Bos et al. showed that T decreases specifically trust in high-trusting humans.[317]

Taken together, the studies evaluating the effect of T and AVP demonstrate that they are less implicated in exertion of specific behavioral repertoires, but more in increasing the underlying motivational stance. This motivational attitude depends on the person's personality and on the environmental factors, which together may promote certain actions.[302,304,318]

## 3-5. Cross hormone treatment

Interestingly, the *World Professional Association for Transgender Health* (WPATH), whose mission it is to promote evidence based care, education and research did not mention in their 7th version of care standards[162] the psychological effects of hormone treatment. This fact underlines the tendency to only focus on the physical aspects of steroid treatment and to neglect the psychological dimension.
In our overview, it should be first empathized that endocrine treatment brings relief from the dichotomy between physical appearance and gender identity.[319] However, it is also noteworthy that not all psychological effects are likely attributable to the influence of the treatment. It is important to remember that each individual has his own attributions and stereotypes of what makes a man a man and a woman a woman. These beliefs surely influence the behavior and the coping strategies during transition. So not all displayed behavior might be the cause of cross hormone therapy. Though the best proof that hormones achieve success are reflected by the decrease in depression and suicide rates in treated compared to non-treated transgender patients.[197]

Although much is known about the physical effects of hormone treatment knowledge of the influence of endocrine treatment on the psychological functioning in transsexuals remains scant.

### 3-5-1 Cross Hormone treatment for transsexual women

Hormone treatment appears to have beneficial effects for the emotional condition of trans women, as incidence of depression decrease upon treatment.[320]
Consistent with these observations, after eight weeks of anti-androgen treatment, trans women experienced an increase in positive emotions, such as happiness and liveliness, energy, and relaxation and anger readiness.[321-323] They reported that they were more emotionally expressive.[321] It seems that E treatment is associated with a calming, almost antidepressive effect.[324] Moreover, the verbal fluency of trans woman and the affect communication (non-verbal emotional expressiveness) improved.[321,323] Conflicting these findings, Slabbekoorn et al. found neither a declining effect on spatial ability, nor an enhancing effect on verbal fluency in trans women if E was added to the anti-androgen treatment.[325]

Furthermore, feelings of fear and exhaustion decrease.[322] In addition, androgen deprivation decrease anger and aggression proneness, sexual arousability and spatial ability.[323]

It is not surprising that at the beginning of the cross hormone therapy trans women experience negative emotions more intensely than trans men,[321-323] which can be explained by the fact that the desired physical changes need more time or are less pronounced (reduced body hair, breast growth). On the other hand, the physical masculinization occurs much faster for trans men and therefore opposite sex appearance and satisfaction could be achieved sooner.[326]
The negative emotions of trans women range from feelings of powerlessness, tiredness,

depression, disappointment to sadness.[321] Interestingly, trans women reported more mood swings than trans men, showing a peak in the second month.[323]

### 1-5-2 Cross Hormone treatment for transsexual men

Transsexual men reported mood swings, increased aggression, sexual arousability and anger readiness.[323] We must be careful not to reproduce one of the most common myths about transsexual men, who take T: the anecdotal reports of "roid rage" by androgenic steroid users (mostly known from athletes or body builders). In sports medicine the „´roid rage“ is „an acute psychotic response–uncontrolled outbursts of anger, frustration or combativeness–of unknown pathogenesis seen in those who abuse anabolic steroids, usually in body builders“.[327] Several studies found no increased anger behavior in men, who received supraphysiologic doses of T.[328,329] Although an actual risk for clinically significant negative effects is small, a tendency towards aggressive behavior might be possible. Additionally, in a study that compared before and after hormone therapy, trans men reported more contentment, greater extroversion and less somatization after treatment.[330]

Moreover, it could be demonstrated that T treatment generally had a diminishing effect on the affect intensity (both for positive and negative emotions) in trans men. Further, they seemed to be less emotionally susceptible to life events, but more to situations with a provocative or sexual content.[321]

Concerning cognitive effects, researchers found an enhancing effect on spatial ability performance, approximately corresponding to cisgender male.[325]
A possible deteriorating effect on verbal fluency tasks[323] has been reported, but could not be confirmed.[323,325,331]

Overall, it appears that although T treatment may have some adverse psychological effects, improved psychological health is the prevailing outcome.

# B) STUDY PROTOCOL

Data used in this diploma thesis are part of the study „Effects of steroid hormones on human brain function, structure and connectivity: A longitudinal study using 7 Tesla Ultrahigh-field Magnetic Resonance Imaging“, funded by a grant awarded to Assoc. Prof. Priv.-Doz.Dr.Rupert Lanzenberger, MD by the FWF Austrian Science Fund P 23021. The Ethics Committee of the Medical University of Vienna, Austria approved this study and all involved procedure. (Ethics Committee No. 466/2010, http://www.univie.ac.at/ethik-kom/). This study was carried out according to the Declaration of Helsinki, the Austrian Arzneimittelgesetz and the EC-GCP guidelines.

## IV. Scheme of the study

As mentioned above, this Diploma Thesis is part of the study „Effects of steroid hormones on human brain function, structure and connectivity: A longitudinal study using 7 Tesla Ultrahigh-field Magnetic Resonance Imaging“. This study is a single blind, longitudinal mono-center study. In this thesis, two groups of subjects are reviewed: 44 transsexual subjects (23 FtM, 21 MtF) and 64 healthy controls (35 FC, 29 MC) matched for sex and age. All participants underwent the same procedures: First a screening visit, which was followed by the first MRI scan. For the transsexual subject this scan was performed prior to treatment. The second scan was performed at least four weeks after treatment onset and the last one at least four months after treatment onset. The subjects were discharged after a final physical examination. The three sessions consisted of a blood draw and the assessment of questionnaires. Because the original study was only half completed, when the data for this thesis were analyzed, only 19 of the 44 transsexual subjects had finished all 3 MRI scans and only 10 of the 64 healthy controls had completed all the visits. We expect around 10% dropouts and have estimated the number of participants required for statistical evaluation by sample size calculation (power ≥80%) with $\alpha$= 0.05 and $\beta$= 0.2, using an effect size d≥0.8. Dropouts will be accounted for through the inclusion of additional subjects.

# V. Study hypothesis

The principal assumption of this study is that endocrinological therapy has a psychological effect; or more precisely, several specific effects on our empathizing abilities.

We hypothesized that cross hormone therapy has an effect on the participant's empathy skills. Therefore, transsexual patients would have a different outcome before and after treatment and, due to the opposite hormone treatment, transsexual women would have results distinct from transsexual men (group specific time effect).
What must be considered, however, is that at baseline, groups differ in their innate empathy faculties: we expected to confirm previous studies demonstrating that women achieve greater scores than men. Also, besides the interindividual distinction, we expected to find intraindividual differences. High or low plasma steroid hormone levels should correlate with different empathy scales.

Given the controversial results of previous studies, the aim of the present study was to strengthen some specific E and T interactions with gender unique behaviors. Firstly we expected to demonstrate an anxiolytic effect of both hormones, E and T; Secondly, we expected T to increase social forms of anger and of anger contagion; Thirdly, we intended to show that T has a decreasing and E an increasing effect on the extent to which a person is emotionally aroused, and last but not least that T decreases the extent to which someone is willing to verbalize his emotions whereas E increases it.

# VI. Material and methods

## 6-1. Subjects

### 6-1-1. Healthy Control Subjects

*Inclusion and exclusion criteria*

The subjects were recruited from the community via advertisements posted in the University of Vienna and the Medical University of Vienna, Vienna, Austria and word-of-mouth recommendation. 35 caucasian female subjects (FC) aged 18—43 years (age 25.3 ± 5.9 years, mean ± SD) and 29 caucasian male subjects (MC) aged 19-50(age 27.9 ± 7.5 years, mean ± SD) took part of the study.

Volunteers had to fulfill several inclusion criteria. General physical health examinations

based on a general physical examination including neurological status, electrocardiogram and a laboratory screening. The participants were screened for history of any psychiatric or mental disorder by using the German version of the structured interview of DSM IV (SCID)[332] the Hamilton anxiety scale (HAMA) and the Hamilton depression rating scale (HAMD). Further, they had to have the competence and willingness to sign the informed consent. All subjects were paid for their participation. Volunteers with an overall healthy state and no relevant abnormalities were included. Exclusion criteria comprised severe diseases, abnormalities in the physical examination or in the routine laboratory screening, any implant or stainless steel graft, any chronic medication or hormonal treatment, including birth control pill, phytohormones within 2 months prior to the study, current substance abuse, pregnancy or failure to comply with the study protocol or to follow the instructions of the investigating team.

**Table 4: Study inclusion and exclusion criteria for healthy controls**

| **Inclusion criteria for healthy controls** | **Exclusion criteria for healthy controls** |
|---|---|
| Age 18 to 50 years | Chronic medication / hormonal contraception within 2 months prior to the study |
| Mental health | History of mental illness or present mental illness |
| Physical health | Severe diseases |
| Signed informed consent | Implant or stainless steel graft |
| | Drug abuse |
| | Pregnancy |
| | Failure to comply with the study protocol or to follow the instructions |
| | Claustrophobia |

6-1-2 Transsexual Subjects

*Inclusion and exclusion criteria*

Transsexuality is defined as incongruence between the biological sex and the experienced and self-declared gender identity (see II Transsexualism). Transsexuals urging sex reassignment were recruited in the General Hospital of Vienna to take part of the study. 23 female-to-male (FtM) aged 18-43 years (24.6 ± 6 years, mean ± SD) and 21 male-to-female (MtF) aged 18-45 years (32.1 ± 8.3 years, mean ± SD) took part of the study.
At baseline the transsexual subjects were free of hormone-treatment. No transsexual placebo group was included, because a latency of 4 months before the start of active

treatment was considered ethically questionable.
The inclusion criteria were a DSM-IV diagnosis of Gender Identity Disorder (DSM-IV: 302.85, 302.6; ICD-10: F64.9, F64.8) and general health based on a general physical examination including neurological status, electrocardiogram, a laboratory screening. Further, they had to have the competence and willingness to sign the informed consent. Exclusion criteria for transsexuals comprised severe neurological or internal diseases, abnormalities in the physical examination or in the routine laboratory screening, any implant or stainless steel graft, any treatment with psychotropic agents, such as SSRIs or hormonal treatment, including birth control pill, phytohormones within 2 months prior to the study, current substance abuse, pregnancy or failure to comply with the study protocol or to follow the instructions of the investigating team.

### 6-1-3. Pharmacological Interventions

In order to provide the sex reassignment for the transsexual subjects, the Department of Obstetrics and Gynecology, Division of Gynecologic Endocrinology and Reproductive Medicine, Medical University of Vienna is in charge of administrating the pharmacological intervention for the patients.

As a part of their sex reassignment, anti-androgens in combination with estrogens were administered to MtFs, while FtMs receive androgen therapy.
Cross hormone treatment is state of the art because untreated MtFs do not differ in sex hormone levels from other biological men[333] and FtMs do not differ in this respect from other biological women;[334] Through endocrinological treatment we have a successful and reliable form of therapy.
Sex hormonal therapy induces attenuated GnRH stimulation of LH and FSH, causing a reduction of serum sex hormone levels. Endocrinological treatment has a dual role: First the induction of feminization or virilization and second the suppression of the hypothalamic-pituitary-gonadal axis, leading to a reduction of endogenous estradiol or testosterone secretion.[335]

The FtM patients receive either 1000mg testosterone undecanoat every 12 weeks (Nebido® 250mg/ml, 4ml vial, intramuscular) or alternatively 50mg testosterone daily (Testogel® 50mg/5g bag per day, transdermal). If needed, patients may take 10-15mg/day lynestrenol (Orgametril® 5mg, oral) or in some cases 75µg/day desogestrel (Cerazette® 75µg, oral) for suppressing the menstruation.

**Table 5. Hormonal regimens in presurgical female-to-male transsexuals**

| Center | **Masculinizing hormone regimes** | **Optional** |
|---|---|---|
| *Department of Obstetrics and Gynecology, Division of Gynecologic Endocrinology and Reproductive medicine, Medical University of Vienna* | 1000mg testosterone undecanoat every 12 weeks (Nebido® 250mg/ml, 4ml vial, intramuscular)<br>**OR**<br>50mg testosterone daily (Testogel® 50mg/5g bag per day, transdermal) | 10-15mg/day lynestrenol (Orgametril® 5mg, oral)<br>**OR**<br>75µg/day desogestrel (Cerazette® 75µg, oral) |

Estrogen is the cornerstone for feminization of MTF transsexual people. They receive 50mg cyproterone acetate daily (Androcur® 50mg tablet, oral). Additionally, patients under 40 years of age will receive 100µg estradiol/day (Estradot ®, 1.56mg, 100µg/24hrs, transdermal therapeutic system (TTS) applied twice a week) or alternatively 25µg/day (Estramon®, 25µg/24hrs, transdermal). In case that the trans women are over 40 years of age they will primarily take 4mg/day estradiol hemihydrate (Estrofem® 2mg, oral). Alternatively, they may take estradiol hemihydrate 0,75-1,5mg/day (Estrogel-Gel®, 0,75-1,5mg/24hrs transdermal). In case of hair loss patients can receive 2,5mg alpha-5-reductase-inhibitor every second day (Finasterid Actavis/ Arcana / Aurobindo® 5mg, oral). Moreover, all patients may receive a GnRH-analogon, either triptorelin acetate 100µg daily (Decapeptyl 100µg in 1ml prefilled syringe, s.c.) or triptorelin acetate 4.12mg/month (Decapeptyl® 4.12mg/172mg powder for suspension for injection s.c. or i.m.) or 11.25mg/3 months leuprorelin acetate (Trenantone® 11,25g/130mg suspension for injection s.c) may be used if appropriate.

**Table 6: Hormonal regimens in presurgical male-to-female transsexuals**

| center | **Feminizing hormone regimes** | **Optional** |
|---|---|---|
| *Department of Obstetrics and Gynecology, Division of Gynecologic Endocrinology and Reproductive medicine, Medical University of Vienna* | 50mg cyproterone acetate daily (Androcur® 50mg tablet, oral)<br><br>**<40 yr old**<br>100µg estradiol/day (Estradot ®, 1.56mg, 100µg/24hrs,TTS applied twice a week)<br>**OR**<br>25µg/day (Estramon®, 25µg/24hrs, transdermal)<br><br>**>40 yr old**<br>4mg/day estradiol hemihydrate (Estrofem® 2mg, oral)<br>**OR**<br>estradiol hemihydrate 0,75-1,5mg/day (Estrogel-Gel®, 0,75-1,5mg/24hrs transdermal) | 2,5mg alpha-5-reductase-inhibitor every second day (Finasterid Actavis/ Arcana / Aurobindo® 5mg, oral)<br><br>triptorelin acetate 100µg daily (Decapeptyl 100µg in 1ml prefilled syringe, s.c.)<br>**OR**<br>triptorelin acetate 4.12mg/month (Decapeptyl® 4.12mg/172mg powder for suspension for injection s.c. or i.m.)<br>**OR**<br>11.25mg/3 months leuprorelin acetate (Trenantone® 11,25g/130mg suspension for injection s.c) |

After three months of hormone treatment, sex hormone levels of transsexuals are in the range of those of the opposite sex.[326]

## 6-2. Questionnaires

The psychological assessments were specifically selected for comprising the different aspects of empathy. For a detailed overview of the scales see: F) appendix scales

### 6-2-1. Emotional contagion scale“ (German version: ECS-D)

The Emotional Contagion Scale (ECS) was developed in 1997 by Doherty and was designed to be a short and reliable self-report scale used to measure individual differences in susceptibility to converge towards the emotions expressed by others.[336] This scale was validated on nearly 2000 volunteers and possesses a reliability of Cronbach $\alpha = 0.90$ and a retest-reliability of $\alpha \approx 0.84$.[336]
The ECS is a 15-item scale, which assesses the susceptibility to 'catch' the emotions of others. The ECS consists of five basic emotions represented each by 3 items: love, happiness, sadness, anger and fear. Each question can be answered with a 5-point Likert scales response format (Never, Rarely, Sometimes, Often and Always).
The term 'emotional contagion' refers to the tendency one has to 'catch' another person's emotions by mimicking and synchronizing with the other party and, consequently, to converge emotionally”. For an in-depth definition see: 1-3-1 *Coming to feel as another person feels*

**Table 7: Subscales of the ECS**

| Item | Example |
|---|---|
| **Happiness** | Example: When someone smiles warmly at me, I smile back and feel warm inside. |
| **Love** | Example: When I look into the eyes of the one I love, my mind is filled with thoughts of romance. |
| **Fear** | Example: Listening to the shrill screams of a terrified child in a dentist's waiting room makes me feel nervous. |
| **Anger** | Example: I clench my jaws and my shoulders get tight when I see the angry faces on the news. |
| **Sadness** | Example: I get filled with sorrow when people talk about the death of their loved ones. |

## 6-2-2. „Bermond-Vorst Alexithymia Questionnaire“ (BVAQ)

The Bermond-Vorst Alexithymia Questionnaire (BVAQ) was developed in 1991 by Harrie Vorst and Bob Bermond and was designed to measure the five dimensions of alexithymia.[337] This questionnaire was validated on nearly 1000 volunteers and possesses a reliability of Cronbach $\alpha = 0.79$ for the subscale and of $\alpha = 0.85$ for the total scales.[337]
The BVAQ consists of two versions (A and B) with 20 items each. Both parallel versions together constitute an enlarged questionnaire of 40 items. This self-report questionnaire comprises five subscales with 4 questions each (two indicative items and two contra-indicative items). The five response categories vary from 1 “definitely applies to me” to 5 “in no way applies to me”. High scores indicated high proneness to alexithymia.
The word “alexithymia” derives from Greek (*a* – lack, *lexis* – word, *thymos* – emotion) and means literally “no words for emotions”. Alexithymia refers to five parts: The reduction or incapacity to experience emotions (emotional life), the reduction or incapacity to verbalize emotions (describing feelings), the reduction or incapacity to fantasize emotions (fantasy), an absence of tendencies to think about one’s emotions (concrete and reality-based cognitive style) or the difficulty in identifying emotions (identifying feelings).[337]

**Table 8: Subscales of the BVAQ**

| Subscale | Definition and example |
|---|---|
| **Verbalising** | The extend to which someone can or is inclined to describe or communicate about his emotional reactions<br>Example: It is difficult to verbally express my feelings (negative) |
| **Fantasising** | The extend to which someone is inclined to fantasize, imagine, daydream<br>Example: Before I fall asleep, I make up all kinds of events, encounters and conversations (positive) |
| **Identifying** | The extend to which someone is able to define his arousal states<br>Example: When I am distressed, I know whether I am afraid or sad or angry. (positive) |
| **Emotionalising** | The extend to which someone is emotionally aroused by emotion inducing events<br>Example: When something totally unexpected happens, I remain calm and unmoved (negative) |
| **Analysing** | The extend to which someone is looking for explanations of one's own emotional reactions.<br>Example: I hardly ever go into my emotions (negative) |

Of these five subscales, three assess the cognitive alexithymia dimension (verbalizing, identifying, analyzing) and two assess the affective alexithymia dimension (fantasizing, emotionalizing). This two-factor structure has been validated in six languages and seven populations, the validity of BVAQ has been confirmed in several studies.[338]

*BVAQ and gender difference*

Alexithymia is almost twice (17%) as often in men as in women (10%). Multivariate analysis showed that alexithymia was associated with male gender.[337]

6-2-3„ Interpersonal Reactivity Index“ (German Version: Saarbrücker Persönnlichkeitsfragebogen)

The Interpersonal Reactivity Index (IRI) was developed in 1983 by Davis and was designed to be a multidimensional reliable self assessment test used to measure cognitive and affective aspects of empathy.[339] This scale was validated on nearly 500 volunteers and possesses a reliability of Cronbach α ranging from 0, 70 to 0.78 and a retest-reliability of α from 0.61 to 0.81.[339]
The questionnaire comprises 28 items, which can be divided in 4 subscales with 7 items each. The IRI consists of a 5-point response format (1) = does not describe me well to (5) = describes me very well.

**Table 9: Subscales of the IRI**

| Subscale | Definition and example |
|---|---|
| **Perspective-taking (PT)** | "Cognitive (thinking) empathy" "theory of mind"<br>PT measures the tendency to spontaneously take the psychological point of view of others.<br>Example: I believe that there are two sides to every question and try to look at them both. |
| **Fantasy (FS)** | "Imaginative empathy"<br>FS measures the tendency to get caught up in fictional stories and imagine oneself into the feelings and actions of fictitious characters in books, movies, and plays.<br>Example: I daydream and fantasize, with some regularity, about things that might happen to me. |
| **Empathic concern (EC)** | "Emotional empathy"<br>EC measures other-oriented feelings of sympathy, warmth and concern for others.<br>Example: When I see someone being taken advantage of, I feel kind of protective towards them. |
| **Personal distress (PD)** | "Self-oriented anxiety and discomfort"<br>PD measures the self-oriented feelings (anxiety, etc.) that gets in the way of helping others or when you experiencing others in distress.<br>Example: When I see someone who badly needs help in an emergency, I go to pieces. |

Three scale measure the affective empathy (Fantasy, Empathic concern, Personal distress) and one scale measures the cognitive empathy (Perspective taking).

*IRI and gender differences*

The author concluded that significant sex differences existed for each scale in his instrument with women always scoring higher.[339]

### 6-2-4. The advantages and disadvantages associated with questionnaires

Self-Report Indexes for measuring empathy have some obvious advantages:
First, such measures are easy to administer, can be completed in a short period of time and in a relatively cost effective way. Any person can carry them out without affecting its results and it can be analyzed thanks to the scaled response format more objectively than other forms of research.[340,341] However, the validity of reports are based on the premises, that the participants are aware of what they are feeling and are willing to report these feelings accurately. Another bias could affect the reliability of self-reports: self-presentation and social desirability adulterate the outcome.[342] Further, questionnaires can only contain a limited amount of information without space and freedom for explanations.[340]

## 6-3. Data analysis

Differences between groups and measurements were assessed by means of univariate ANOVA with repeated measurements using the group as fixed and time as repeated factors for both empathy questionnaires and the hormone levels as dependent variables. Similarly repeated measures ANOVA were performed for the test score of the questionnaires (IRI, ECS, BVAQ) dependent factor.
Correlation analysis was performed for the hormone levels and the self-report empathy questionnaires and assessed using Pearson product-moment correlation coefficient. Due to expected differences between sexes in the hormonal levels, correlations were run separately for the four groups (FC, MC, FtM, MtF).

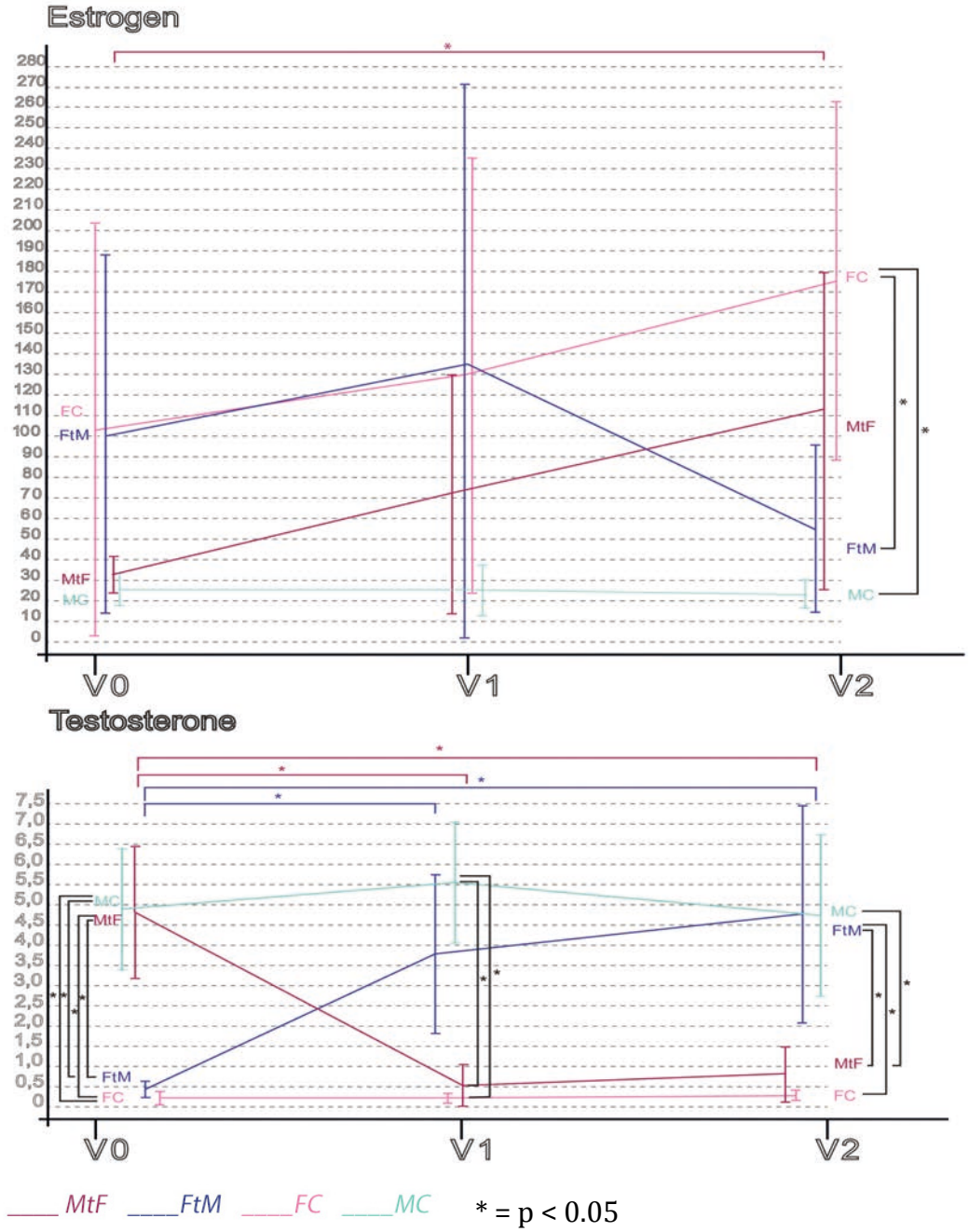
Data were analyzed using SPSS version 16.0 and values of $p < 0.05$ were considered significant. Analysis of variance and T-tests were applied when criteria for parametric testing were fulfilled (normal distribution was tested with the Kolmogorov–Smirnoff test); if violated, non-parametric tests (U-test) were applied. All *Post hoc.* analyses were corrected for multiple comparisons using the Bonferroni procedure.

# C. RESULTS

## 7-1. Hormone levels

As anticipated, groups differed between plasma levels of E [F (3,61)=8.16, p<0.001] and T [F (3,47)=28.33, p<0.001]. Further, hormonal treatment led to no significant change in plasma levels of E and T during time (p>0.05). Last, a significant interaction between the groups and time for E [F (6,73)=2.66, p=0.022] and T [F (6,37)=26.42, p<0.001] was observed.

**Figure 5: Group Difference over time for T and E**



**Abbreviations:** FC: female control; MC: male control; MtF: male-to-female; FtM= female-to-male; V0=first visit; V1=second visit; V2=third visit; plasma hormone levels are given in pg/ml.

*Differences between the groups for E and T*

Following the global repeated measures ANOVA, a *post hoc* one-way ANOVA was applied for the first visit and revealed a significant group difference for T ($F(3,104)=163$, $p<0.001$) and for E ($F(3,104)=7.49$, $p<0.001$), with MC and MtF having higher T levels and lower E levels compared to FC and FtM.
For the second visit, a significant group difference was assessed for T [$F(3,27)=22.63$, $p<0.001$], but not for E ($F(3,27)=2.10$, $p=0.123$). Thanks to cross hormone treatment, the T levels of MtF are becoming closer to T levels of FC and the T levels of FtM are becoming closer to the ones of MC. The third visit revealed a significant group difference for T [$F(3,25)=8.87$, $p<0.001$] and E [$F(3,25)=6.52$, $p=0.002$], with MC and FtM having higher T and lower E levels than FC and MtF.

*Differences over time*

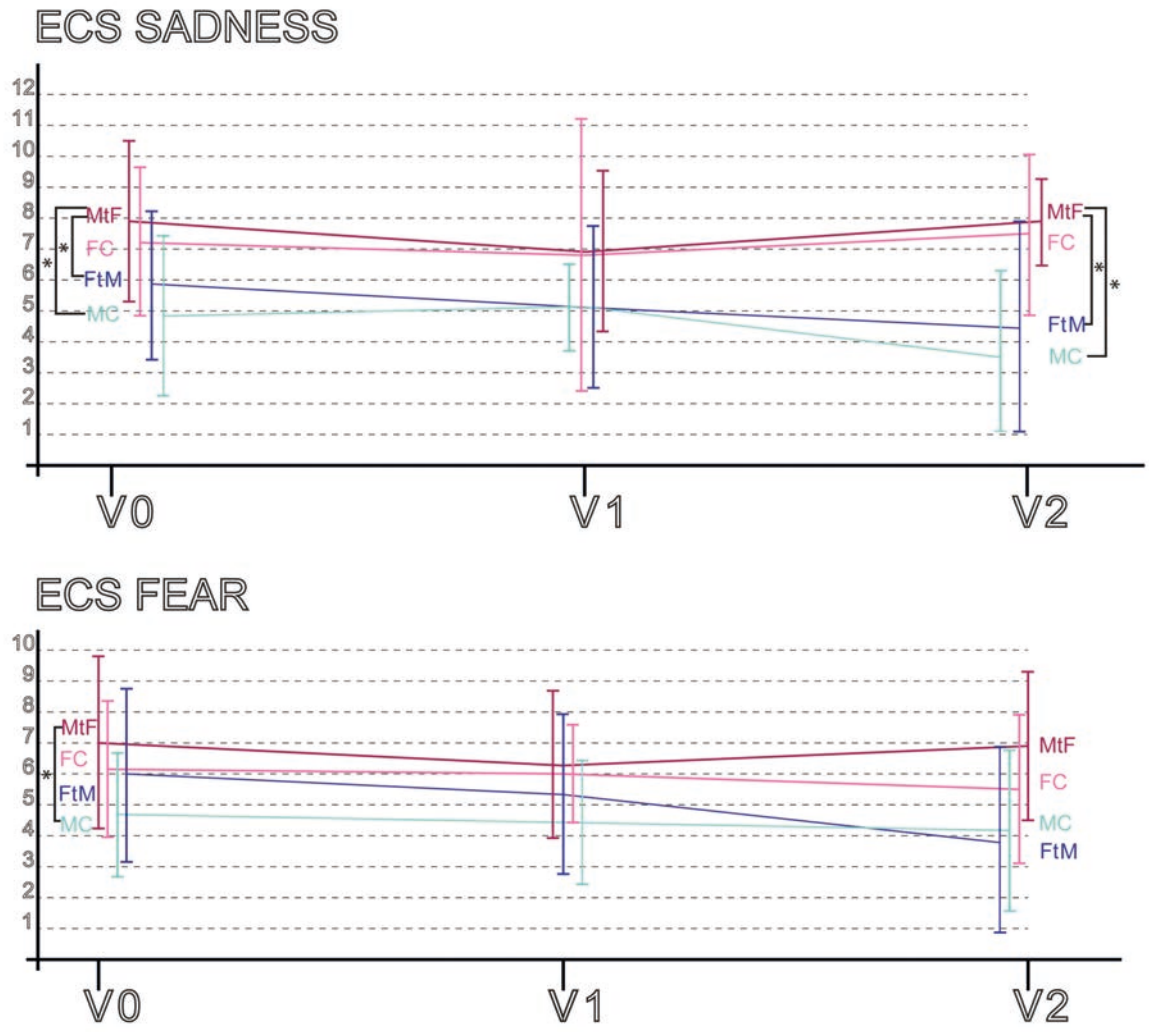
For the FtM subjects, no significant difference in the E hormone level was found over time [$F(2,38)=1.578$, $p=0.22$]. These results can be explained by the treatment: the subjects received T as a standard feature, therefore their E levels stayed steady. Accordingly, a *post hoc* T-test showed that the T levels augmented ($T=-4.8$, $p<0.001$) about 4.35 pg/ml ± 0.61 pg/ml between first and last visit, while the E level in the blood didn't change significantly ($T=-1.96$, $p>0.05$).
Due to hormonal treatment the E levels of the MtF subjects constantly increased during the four-month of our study ($T=3.34$, $p=0.001$). Between the first and the last inspection, E level increased by 82.07 pg/ml ± 18.35 pg/ml. T levels were higher at the beginning of the study and decreased about 4.06 pg/ml ± 0.57 pg/ml till the last visit ($T=-6.01$, $P>0.05$). These results confirmed the success of the treatment.
Analyses by T-test revealed that FC showed no significant difference ($T=1.44$, $p>0.05$) neither in their E levels over time nor in their T blood levels ($T=1.03$, $p>0.05$). The *post hoc* T-test of the MC showed no significant results for both E ($T=-0.644$, $p>0.05$) and T ($T=-2.94$, $p>0.05$). Both groups showed age-appropriated normal findings. (See *II hormones*)

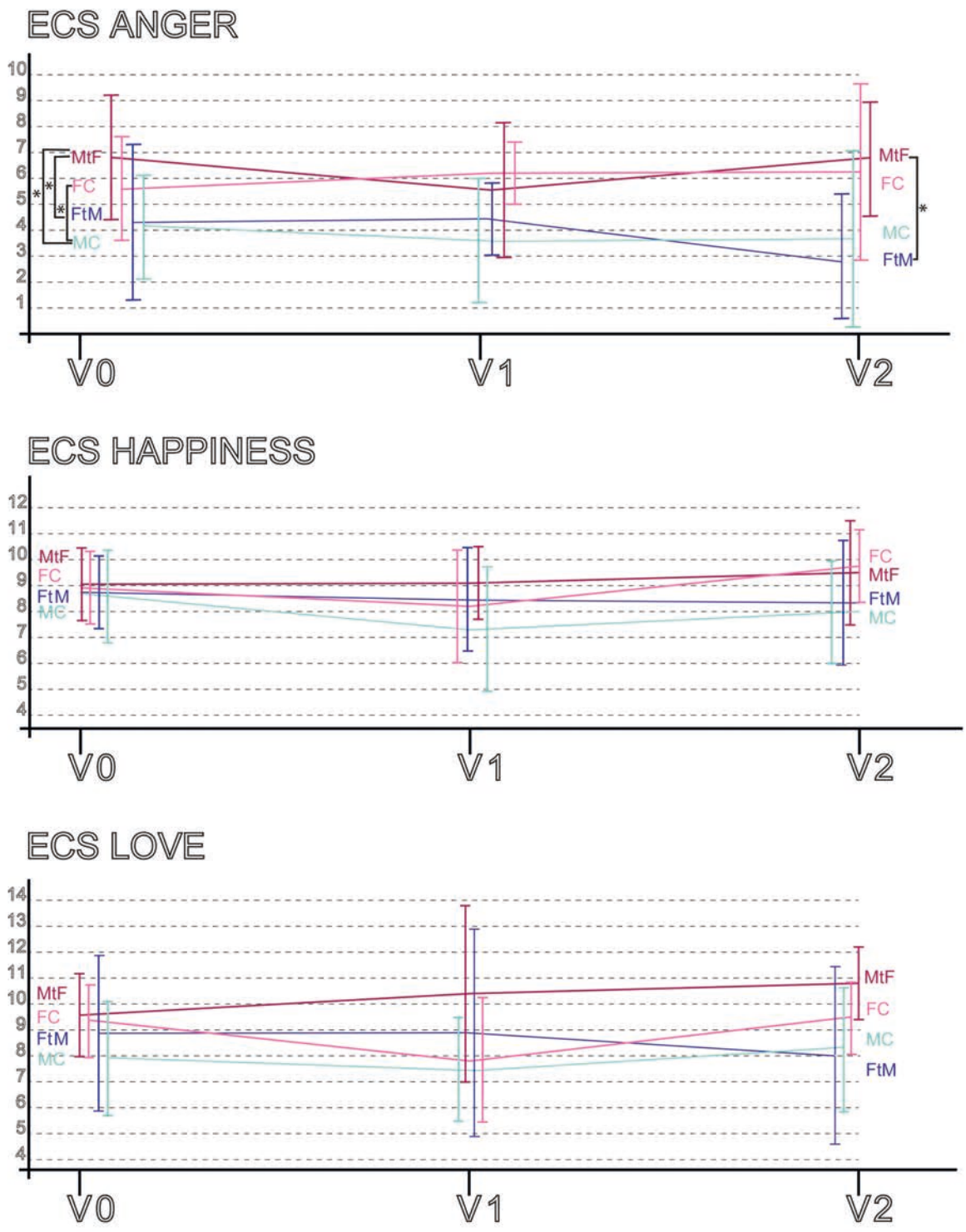
For an Overview of mean values and standard deviations for Testosterone and Estrogen plasma levels in FtM, MtF, FC and MC subjects see Appendix.

## 7-2. Emotion Contagion Scale

All subscales of the Emotion contagion scale, except for the happiness scale ($p>0.05$) showed a significant main effect of group. The values were [$F(3,63)=4.94$, $p=0.004$] for the love scale, [$F(3,63)=5.03$, $p=0.003$] for the fear scale, [$F(3,61)=9.51$, $p<0.001$] for the anger scale and [$F(3,66)=9.46$, $p<0.001$] for the sadness scale. No significant difference over time and no significant interaction between the groups and time were assessed ($p>0.05$).

**Figure 6: Group Difference over time for the subscales of the ECS**






**Abbreviations:** FC: female control; MC: male control; MtF: male-to-female; FtM= female-to-male; V0=first visit; V1=second visit; V2=third visit; ECS: Emotional contagion scale;

*Differences between the groups*

For the first visit, the *post hoc* one-way ANOVA revealed a significant group difference for the love scale [F (3,103)=3.089, p=0.03], the fear scale [F (3,103)=3.76, p=0.013], the anger scale [F (3,103)=6.64, p<0.001] and for the sadness scale [F (3,103)=7.95, p<0.001]. In all those scales MtF obtained the highest score, followed by FC, than FtM and lastly MC. A significantly differing score result was assessed between MC and MtF for the fear (p=0.01), anger (p=0.005) and sadness (p=0.047) scale and between the MtF and the FtM for the sadness scale. No significant difference was found for the happiness scale (p>0.05) although the same chronologic order was stated.
Interestingly, no significant group difference was found for the second visit; However, the one-way ANOVA of the last visit revealed a significant group difference only for two subscales of the ECS, with sadness being the scale with the biggest group difference [F (3,25)=5.35, p<0.001] followed by the anger scale [F (3,25)=4.13, p=0.016]. For FtM and MtF transsexuals the results for the anger scale were significantly different (p= 0.022). For the sadness scale the score of the MtF was significantly higher than the score of the FtM (p=0.04) and the MC (p=0.015).

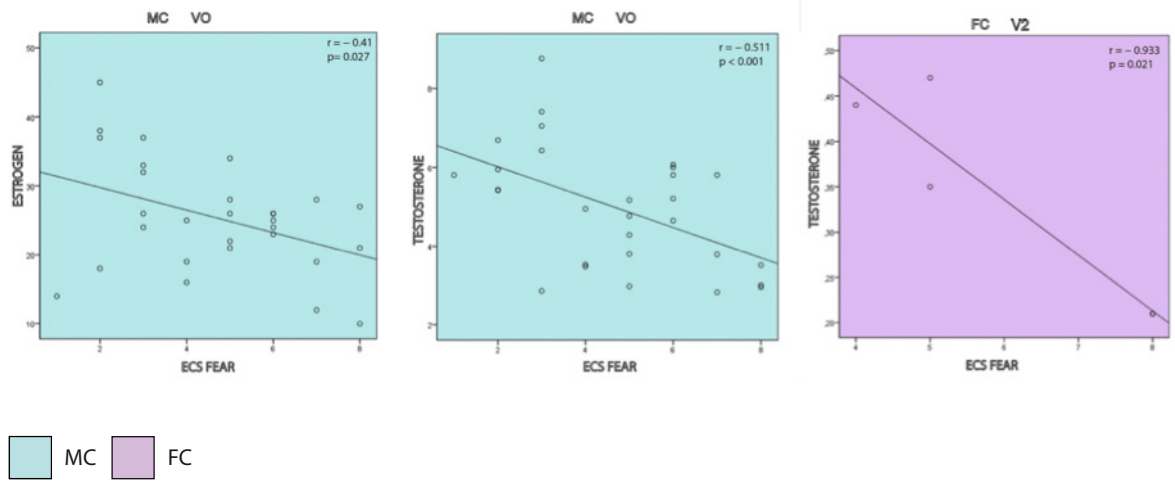
*Differences over time*

Although we found no significant time effect (p>0.05) for FtM subjects in the ECS, between the three visits, it is still interesting that the values of all the subscale were decreasing. Between the first and the last visit, specially for the fear scale FtM transsexuals achieved in average 2.22 ± 1.15 points less, for the Anger scale 1.53 ± 1.11 points less and in the sadness scale 1.42 ± 1.13 points less.
Either for MtF subjects no significant difference between the appointments was found (p>0.05). The happiness and the love scale augmented slightly between the first and the last visit (respectively about 0.45 ± 0.73 and 1.23 ± 0.68 points). The rest of the scales showed no variations between the first and the last visit (< 0.11 points difference).
Also for the FC and MC subjects no significant difference (p>0.05) was found for the ECS. The FC showed a variation under 0.85 points between the first and the last visit and the MC noted a difference under 0.69, except for the sadness scale, in which the average points decreased about 1.33 ± 0.98 points.

*Correlation ECS and Hormones*

For the first visit, correlation analyses in males between the ECS and hormone levels revealed significant negative associations between T and the fear scale (r=− 0.511, p<0.001) and between E and the fear scale (r =− 0.41, p=0.027).
For the second visit, a significant negative correlation was disclosed for FC between T and again the fear scale (r=− 0.933, p=0.021), but only 4 subjects were included, so the meaningfulness of these results is questionable.
All other scales showed no significant correlations with hormones.

**<u>Figure 7:</u> Significant hormone-subscale correlations**



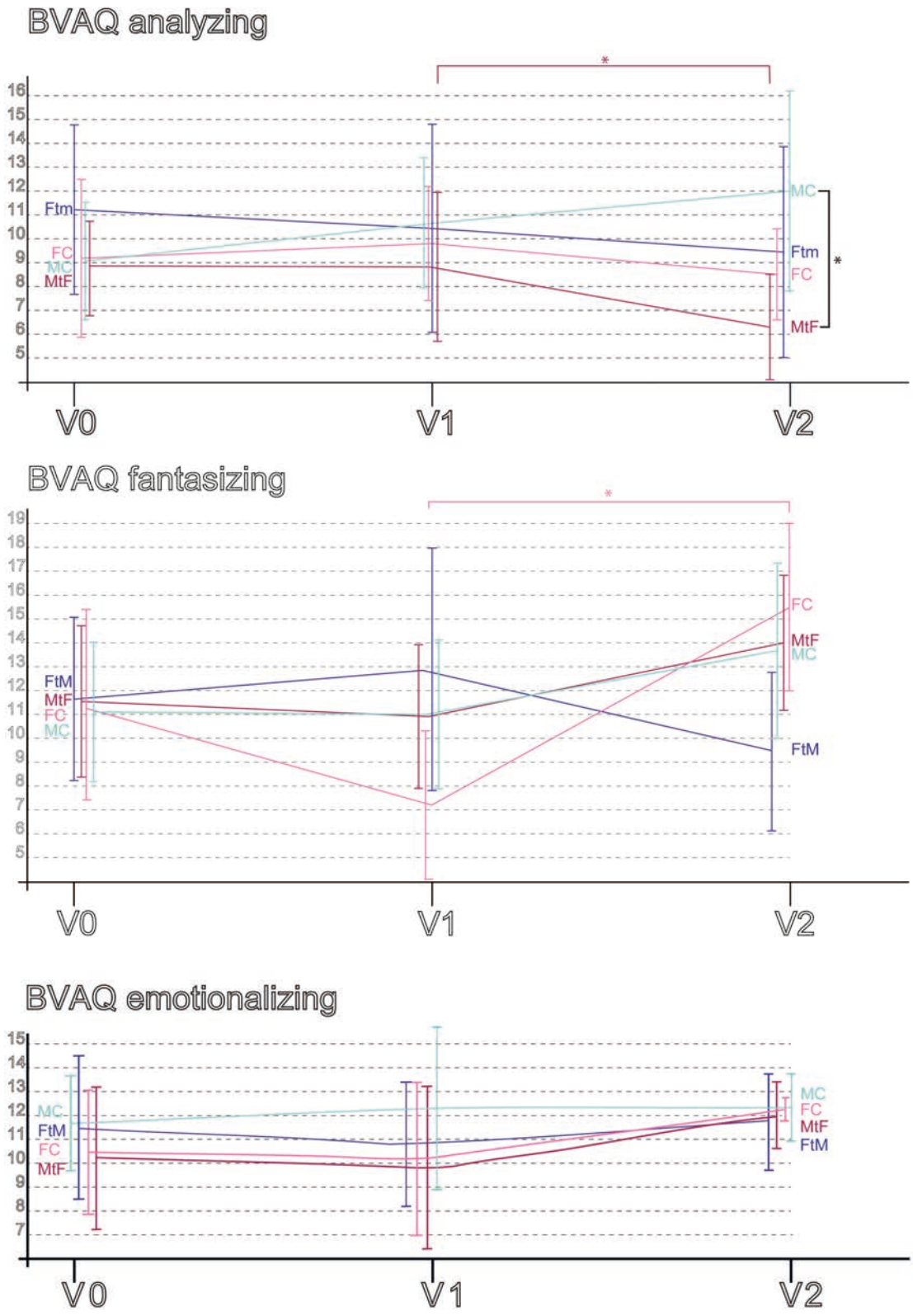

**Abbreviations:** FC: female control; MC: male control; V0=first visit; ECS: Emotional contagion scale; all plasma hormone levels are given in pg/ml.

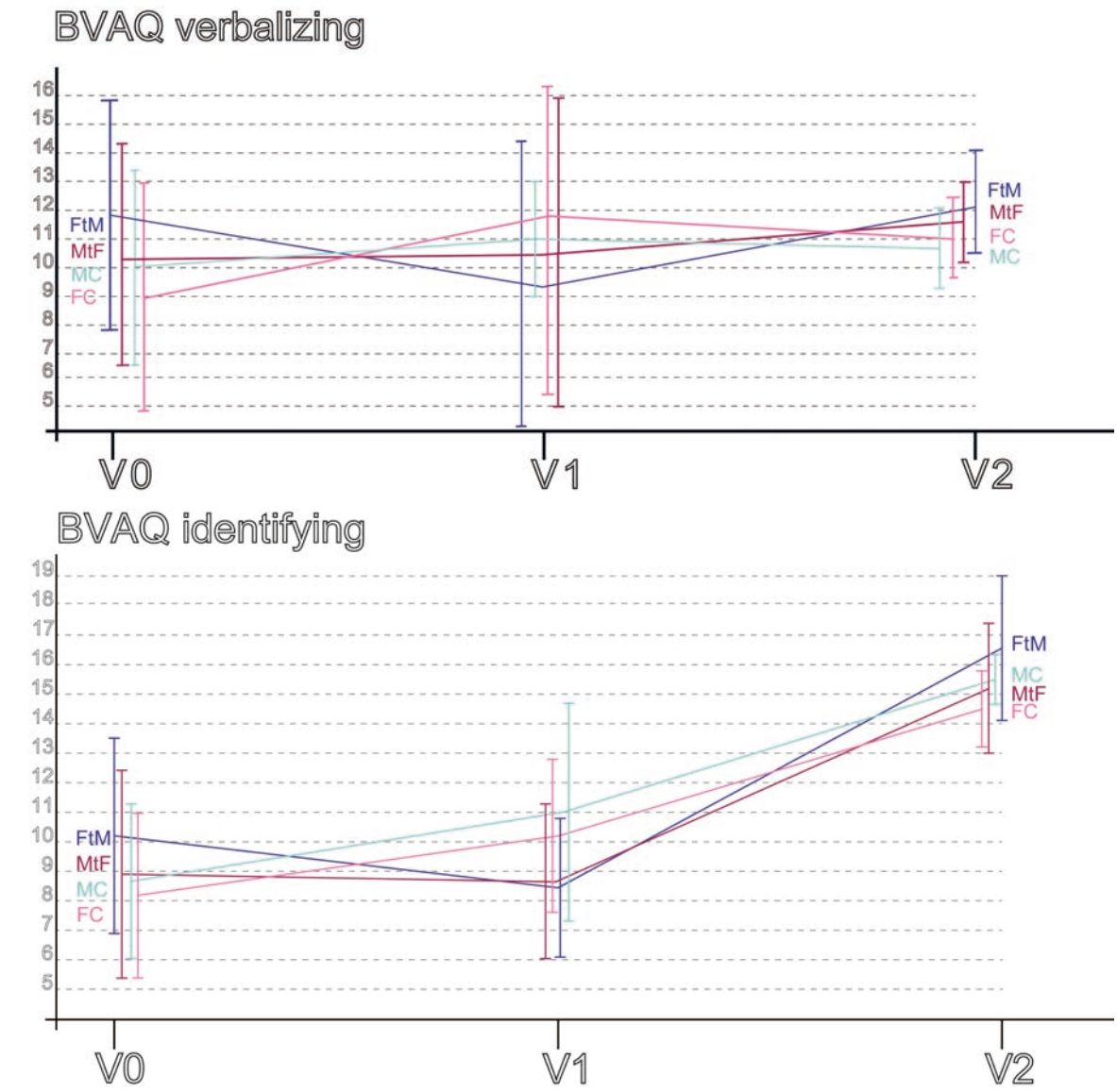
For an overview of mean values and standard deviations for the subscales of the emotional contagion scale in FtM, MtF, FC and MC subjects see Appendix.

## 7-3. Bermond-Vorst Alexithymia Questionnaire

No subscale of the BVAQ showed a significant main effect of groups ($p>0.05$), but they showed a significant main effect of time. The cognitive alexithymia score, which includes the verbalizing, the identifying and the analyzing scale, showed a significant difference over time [$F(2,65)=21.57$, $p<0.001$] and the affective alexithymia score, which comprehends the fantasizing and the emotionalizing sale, also demonstrated a significant difference over time [$F(2,67)=6.47$, $p<0.001$] and a significant interaction between the four groups and time [$F(6,67)=2.84$, $p=0.016$]. No other interaction between groups and time were found ($p>0.05$). For this scale it must be taken into account that high scores indicated high proneness to alexithymia and low scores indicated higher empathic skills.

**Figure 8: Group Difference over time for the subscales of the BVAQ**






**Abbreviations:** FC: female control; MC: male control; MtF: male-to-female; FtM= female-to-male; V0=first visit; V1=second visit; V2=third visit; BVAQ: Bermond-Vorst Alexithymia Questionnaire

*Differences between the groups*

A *post hoc* one-way ANOVA revealed for the first appointment a significant group difference for the analyzing subscale [F (3,103)=3.305, p=] and for the cognitive score [F (3,103)=4.44, p<0.001]. A significantly differing score result was assessed between FC and FtM for the cognitive score (p=0.004), where FTM achieved the highest point numbers. The second visit stated no significant group differences (p>0.05) and the third visit revealed a group difference for the fantasizing subscale [F (3,25)=4.7, p=0.01] the analyzing subscale [F (3,25)=3.56, p=0.028] the cognitive score [F (3,25)=3.41, p=0.03] and the affective score [F (3,25)=3.81, p=0.022].
Although the group differences are not pronounced enough to be significant for all

scales, a trend was detectable for the FtM subjects: For the first visit they were heading the list and scored the most points in total, except for the emotionalizing scale. In contrast, MtF subjects achieved the less points for the emotionalizing, the analyzing and the affective scale and FC for the verbalizing, the identifying and the cognitive scale. After four months of hormone treatment the order was altered.
Interestingly, concerning the last visit, it can be observed that the FtM achieved in the cognitive scale the same score than MC (38 points) and in two of its subscales (verbalizing and identifying) the highest scores. Further, they performed the weakest result in the affective score (21 points) and also in its two subscales (emotionalizing and fantasizing). On the other hand, MtF subjects obtained the smallest score in the cognitive scale (33 points).

*Differences over time*

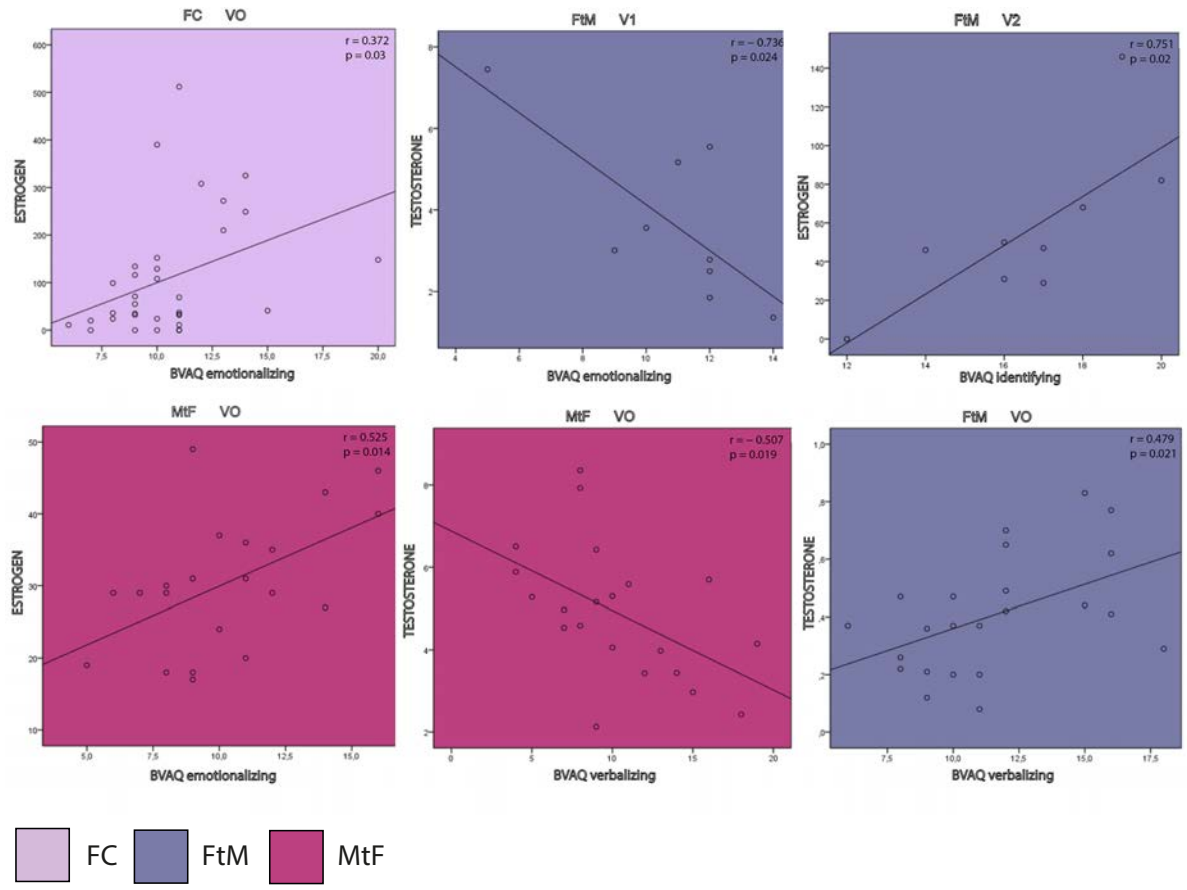
For the FtM subjects, the identifying scale [$F(2,38)=19.79$, $p<0.001$] as well as the cognitive score [$F(2,38)=3.4$, $p=0.044$] changed over time.
A post-hoc one-way ANOVA of the MtF subjects revealed that the identifying scale [$F(2,39)=16.87$, $p<0.001$], the affective score [$F(2,39)=3.97$, $p=0.027$] and the analyzing scale [$F(2,39)=4.36$, $p=0.02$] displayed a significant time difference. In the first two subscales, MtF had a higher score at the last visit compared to the first. Only in the analyzing scale they had a worse outcome, meaning that after four months of treatment they were looking increasingly for explanations for their behavior. The fantasizing scale just barely missed a significant outcome [$F(2,39)=3.05$, $p=0.059$]. The FC subjects had a significant outcome for the fantasizing scale [$F(2,40)=5.15$, $p=0.01$], for the identifying scale [$F(2,40)=10.55$, $p<0.001$] and the affective score [$F(2,40)=4.6$, $p=0.016$] through time. FC were less fantasizing and less identifying their emotions after the third visit compared to the first, as a result they scored higher in the affective alexithymia dimension. MC had a significant outcome for the identifying scale [$F(2,38)=17.27$, $p<0.001$] and the cognitive score [$F=(2,38)=6.83$, $p<0.001$] through time. They also achieved higher results over time.

*Correlation BVAQ and Hormones*

For the first visit, correlation analysis of hormone levels and the BVAQ revealed a significant positive relation between the E level and the emotionalizing scale for the MtF subjects ($r=0.525$, $p=0.014$) and a significant negative relation between T and the verbalizing scale ($r=-0.507$, $p=0.019$), first indicating a lower emotional arousal in MtF with higher E levels and second showing worse emotional verbalizing skills with lower T levels.
For FtM, significant positive correlations only emerged between T and the emotionalizing scale($r=0.479$, $p=0.021$) and T and the affective score ($r=0.422$, $p=0.045$).
Correlation analyses in FC between the BVAQ and hormone levels revealed significant positive associations between E level and the emotionalizing scale($r=0.372$, $p=0.03$) and significant negative associations between T and the fantasizing scale ($r=-0.383$, $p=0.025$).
For the second visit, significant negative correlations only emerged for the FtM between T and the emotionalizing score ($r=-0.736$, $p=0.024$).

The FC showed a significant positive correlation between E and the fantasy scale (r =0.898, p=0.038) and T and the cognitive score (r =0.902, p =0.036). Last but not least, correlation analyses in MC between BVAQ and hormone levels revealed significant negative associations between T and the affective score (r =– 0.818, p =0.047).
For the last visit correlation of the BVAQ and the hormones, results revealed no significant association, except for the FtM group, for whom a significant positive correlation emerged between E and the identifying scale (r=0.751,p =0.02). No other significant correlation between subscales of the BVAQ with E and T were assessed.

**Figure 9: Selected significant hormone-subscale correlations for the BVAQ**



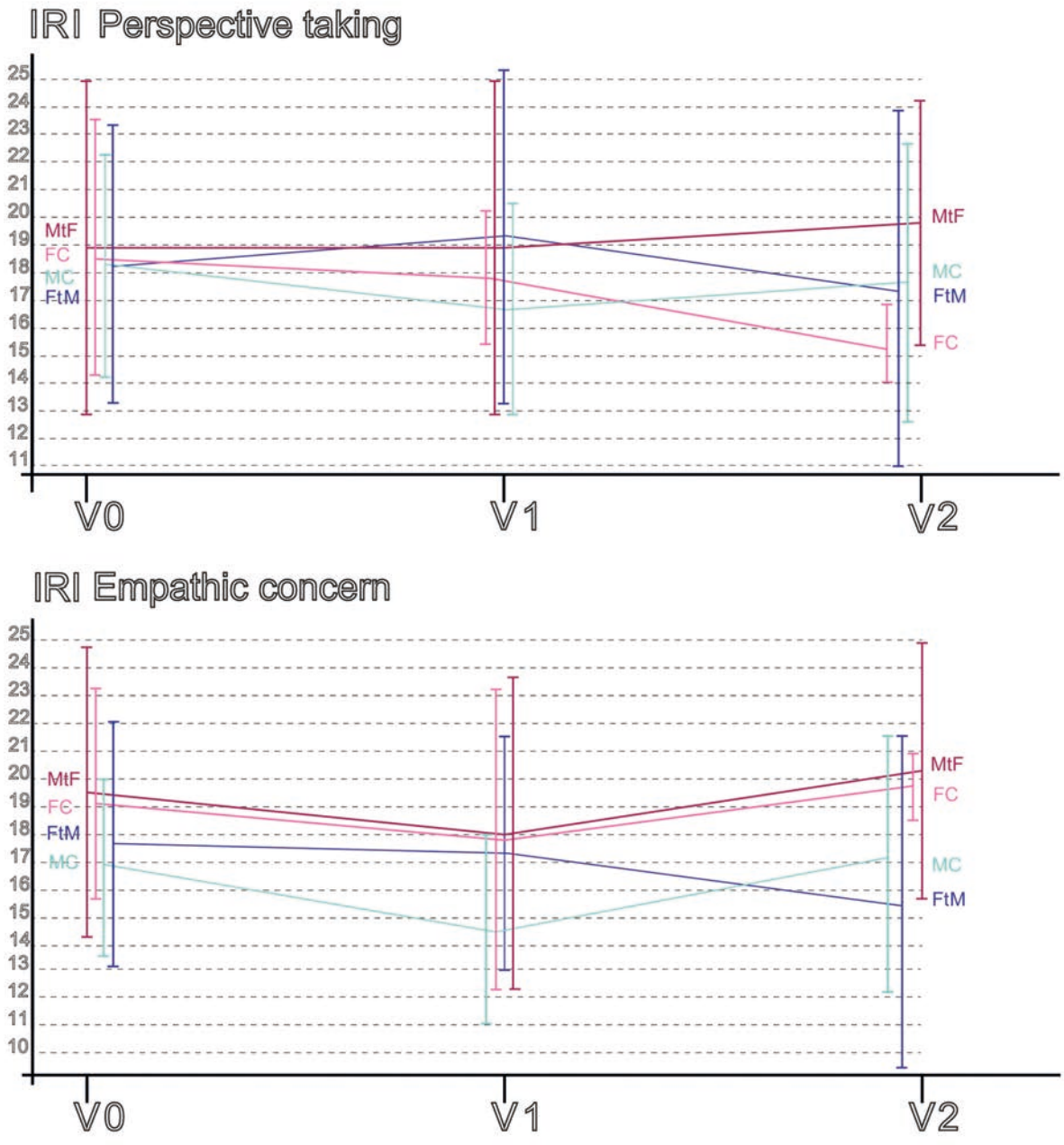

**Abbreviations:** FC: female control; MtF: male-to-female; V0=first visit; V1=second visit; V2=third visit; BVAQ: Bermond-Vorst Alexithymia Questionnaire; Estrogen plasma levels are given in pg/ml, testosterone plasma levels are given in ng/ml.

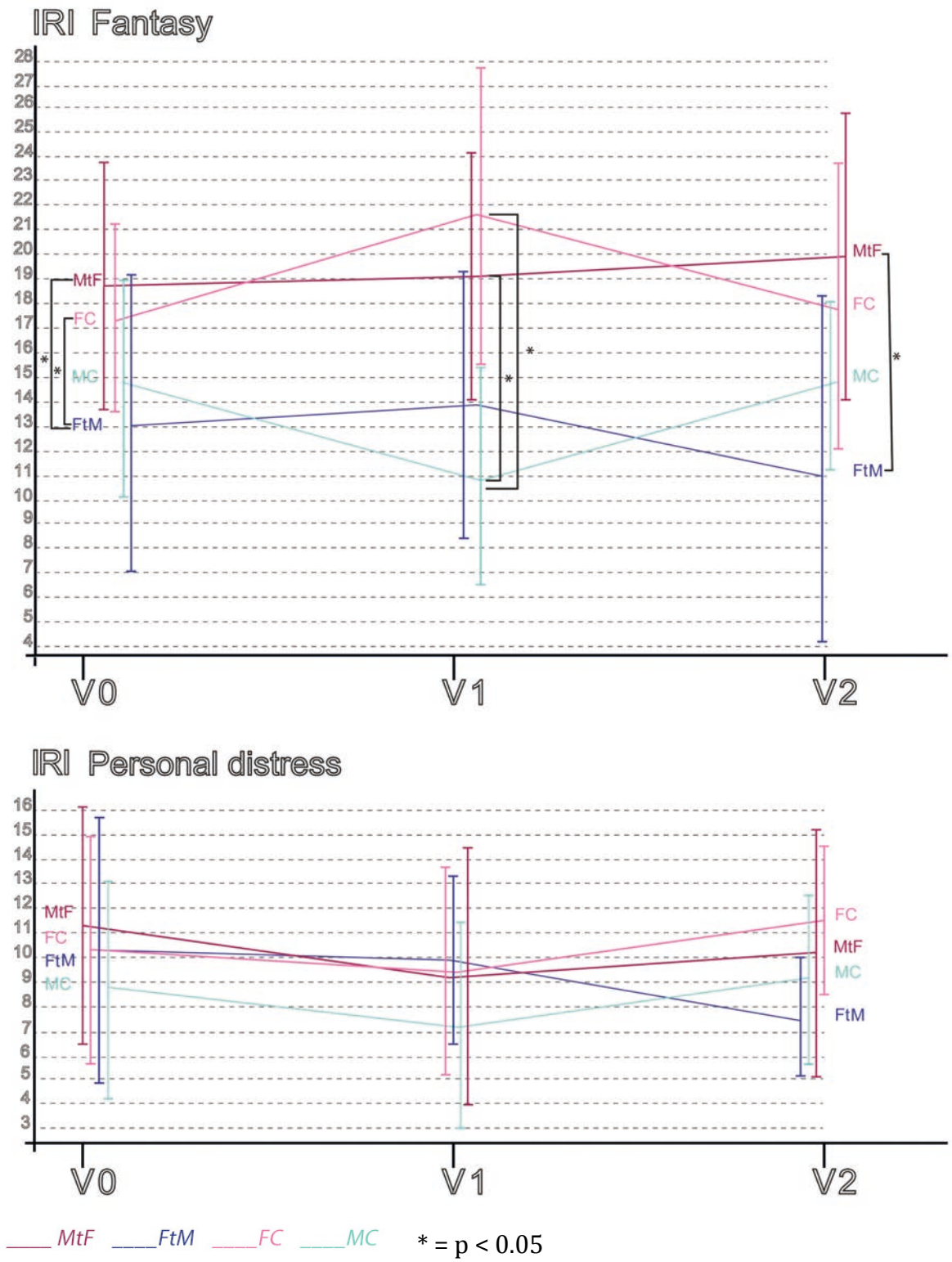
For an overview of mean values and standard deviations for the subscales of the Bermond-Vorst Alexithymia Questionnaire in FtM, MtF, FC, MC subjects see Appendix.

## 7-4. Interpersonal Reactivity Index

As predicted IRI total, a sum of all scales, showed a significant group difference [F (3,61)=5.28, p<0.001]. However, no difference over time was observed and no interactions between groups and time were found (p>0.05)

**Figure 10: Group Difference over time for the subscales of the IRI**






**Abbreviations:** FC: female control; MC: male control; MtF: male-to-female; FtM= female-to-male; V0=first visit; V1=second visit; V2=third visit; IRI: Interpersonal Reactivity Index

*Differences between the groups*

A post-hoc one-way ANOVA revealed for the first appointment a significant group difference for the F subscale [F (3,102)=5.664, p<0.01] and the IRI total score [F (3,103)=3.156 p=0.028]. FtM had significantly lower results in the F scale than MtF (p=0.003) and FC (p=0.019). For the remaining visits we detected a group difference in the F scale both for the second visit [F (3,27)=4.811, p<0.001] and the third visit [F (3,25)=3.424, p<0.033]. MC achieved in the F scale for the second visit, significantly lower scores than MtF (p=0.045) and FC (p=0.023) and for the last visit MtF scored significantly lower than FtM (p=0.027).

*Differences over time*

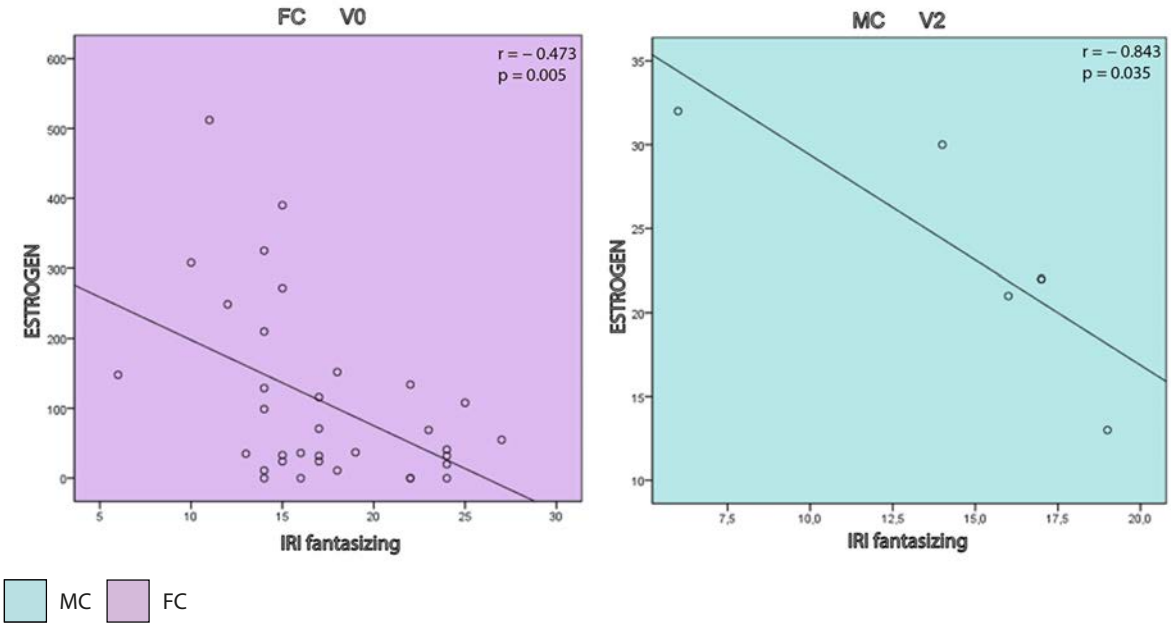
Although we found no significant time effect (p>0.05) for FtM subjects in the IRI, between the three visits, it is still interesting that the values of all the subscales are decreasing. Comparing the scores of the last visit to the scores of the first visit, we found that all scales are decreasing: the PT scale decreased about 0.894 ±2.289 points, the F scale about 2.045 ±2.628, the EC scale about 2.237 ±1.926, the PD scale about 2.874±1.856 and the IRI Total scale about 8.051 ±6.432 points.
For MtF no significant difference between the three appointments was found (p>0.05). But also for these subjects a trend is detectable. The mean score achieved in each scale, except the PD scale, augmented. Following results were recorded: comparing the last to the first visit the PT scale decreased about 0.895 ±1.979 points, the F scale about 1.186 ±2.086 points, EC scale about 0.776 ±1.993 points and IRI Total scale about 1.771 ±6.512 points.
For the FC and MC subjects no significant differences were found for the IRI (p>0.05). No consistent trends or tendencies were detected for these subjects.

*Correlation IRI and Hormones*

For the first visit, correlation analysis of hormone levels and the IRI revealed significant negative relations between the E level and the fantasy scale for the female subjects (r =− 0.473, p=0.005). For the last visit a significant negative correlation was found for male subjects between the fantasy scale and E (r =− 0.843, p=0.035) and for MtF subjects between The PT scale and T(r =− 0.646, p =0.044). No other significant correlations were observed.

For an overview of mean values and standard deviations for the subscales of the Interpersonal Reactivity Index in FtM, MtF, FC and MC subjects see Appendix.

**Figure 11: Selected significant hormone-subscale correlations for the IRI**




**Abbreviations:** FC: female control; MC: male control; V0=first visit; V2=third visit; IRI: Interpersonal Reactivity Index; Estrogen plasma levels are given in pg/ml.

# 7-5. Summary of the significant results

**Table 10: Significant differences between the groups**

| | V0 | V1 | V2 |
|---|---|---|---|
| E | | | FC/FTM<br>FC/MC |
| T | MC/FC<br>MC/FtM<br>MtF/FtM<br>MtF/FC | MC/FC<br>MC/MtF | MC/MtF<br>FtM/MtF<br>FtM/FC |
| ECS sadness | MtF/FtM<br>MtF/MC | | MtF/FtM<br>MtF/MC |
| ECS fear | MtF/MC | | |
| ECS anger | MtF/FtM<br>MtF/MC<br>FC/MC | | MtF/FtM |
| BVAQ analyzing | | | MtF/MC |
| IRI fantasy | MtF/FtM<br>FC/FtM | MtF/ MC<br>MC/FC | MtF/FtM |

**Table 11: Significant differences between over time**

| | | V0→ V1 | V1 → V2 | V0 → V2 |
|---|---|---|---|---|
| E | MtF | | | ↗ |
| T | FtM<br>MtF | ↗<br>↘ | | ↗<br>↘ |
| BVAQ analyzing | MtF | | ↘ | |
| BVAQ fantasizing | FC | | | ↗ |

**Table 12: Significant correlation between scales and hormones**

| | | V0 | V1 | V2 |
|---|---|---|---|---|
| MC | T / ECS fear | negative | | |
| | E / ECS fear | negative | | |
| | T/ BVAQ affective | | negative | |
| | E / IRI fantasy | | | negative |
| FC | T / ECS fear | negative | | |
| | E / BVAQ emotionalizing | positive | | |
| | T/ BVAQ fantasizing | negative | | |
| | E / BVAQ fantasy | | positive | |
| | E / BVAQ cognitive | negative | positive | |
| | E / IRI fantasy | negative | | |
| MtF | E / BVAQ emotionalizing | positive | | |
| | T /BVAQ verbalizing | negative | | |
| | T / IRI perspective taking | | | negative |
| FtM | T / BVAQ emotionalizing | positive | | |
| | T/ BVAQ affective | positive | | |
| | T / BVAQ emotionalizing | negative | | |
| | E/ BVAQ identifying | positive | | |

**Abbreviations:** FC: female control; MC: male control; V0=first visit; V1= second visit; V2=third visit; IRI: Interpersonal Reactivity Index; BVAQ: Bermond-Vorst Alexithymia Questionnaire; ECS: Emotional contagion scale; all plasma hormone levels are given in pg/ml; ↗= score higher; ↘=score lower; V0→ V1 = time between V0 and V1; V1 → V2 = time between V1 and V2; V0→ V2 = time between V0 and V2; negative = negative correlation; positive= positive correlation
All results in this graphic are significant with $p < 0.05$.

# D. Discussion

Some early studies have investigated the psychological effects of endocrinological therapy in transsexuals. Regarding empathy, research has so far not given it the attention it deserves; therefore, hardly any information can be found on how hormones might influence empathic abilities. Our current knowledge about empathy and hormones results from single hormone administration studies, which cannot compete with lifelong cross hormone therapy, as taken by transsexuals in regards to their explanatory power. This study indicates that hormones do have an effect on certain aspects of empathy; this is based on the fact that, we found (1) a treatment specific effect over time and (2) correlations between individual hormone plasma levels and specific facets of empathy.

As shown previously, cross hormone therapy achieved its goals in transsexual women by maintaining serum E levels within the normal range for healthy premenopausal ciswomen (<200 pg/ml) and suppressing T levels to those normally found in ciswoman (<0.55 ng/ml).[343] The medical management of transsexual man consisted of maintaining T levels in a range considered physiologically normal for men (3.2-100 ng/ml). Comparing the treatment with other studies, we conclude that the medical management undertaken in this study is state of the art.[162]

The discussion starts with a closer look at the ECS, a questionnaire that tries to quantify the ability to catch or internalize the emotions of others, what can be seen as a very basic mechanism of empathy. Using this tool, it was possible to show a different outcome for the four groups. The first visit takes stock of the data of all subjects before therapy: a significant difference was found between trans women, who achieved the highest scores, followed by ciswomen, then trans men and at last cismen. These results seem remarkable, especially because trans women scored higher than ciswomen, although this outcome may be interpreted using the symbolic self completion theory.[344] According to this theory, developed by Wicklund and Gollwizter, individuals long to define themselves with manifold labels. This sense of self, however, is occasionally threatened in that these persons tend to substantiate definitions of themselves. They will try to engage in behavior patterns that their community recognizes as aligned with their desired identity.[345] Trans women might embody some character traits that they will find especially suitable for ciswomen, which most probably will be congruent with what their community would deem to typify for the female gender role. As demonstrated, trans women become more likely to act empathic. That trans women obtained higher results than ciswomen is consistent with this theory. It seems that high emotional contagion ability are an important contributor to the sense of identity of transsexual women. Secondly, if we analyze the IRI, a questionnaire that assesses different components of empathy, similar results can be observed. Before treatment, a significant group difference and the same group order can be demonstrated. An explanatory model for this phenomenon could be the social desirability and self-completion, as discussed previously. Thirdly, we confirmed earlier findings, namely that ciswomen obtained better outcomes than cismen in all our questionnaires.[64-68] Further, it became apparent that in the IRI questionnaire a female gender identity (trans women and ciswoman) is predictive for a better empathy performance.
The overview of the IRI scale demonstrates impressively the effect of hormone therapy: While the scores of the control subjects stayed steady over time, trans men, who received T, had a worse performance over time and trans woman, who received E

and antiandrogen, a better one. Two different therapies provoked two opposite performances in transsexual patients.

Although the emotional contagion scale revealed no significant changes over time, it is worth mentioning that trans men achieved numerically lower scores in all the subscales after four months of T administration compared to the first visit. These findings are congruent with previous studies, which noted that T has a dampening effect on affect intensity in transsexual men and is making them less emotionally susceptible.[321] Diametrically opposite, trans women increased their love and happiness contagion. This observation is consistent with other studies, which noted that the intensity and expressiveness of emotions in trans women appeared to be positively influenced by anti-androgen and estrogen treatment.[321-323]

Interestingly, the second visit brought no significant result for the ANOVA for transsexuals. This fact might be interpreted as the result of a period of transition. The plasma hormone levels are not yet in a normal range, as the desired level is achieved only after three months.[326] The outcomes of a study by Kuiper is in support of the concept that the first weeks after the initiation of the hormone therapy can be seen as a time span of passage and transformation.[330] Kuiper found that occasionally, shortly after the onset of hormone therapy, trans women experienced increased feelings of affective lability and depression although long-term effects on the psychological condition are generally positive.[330] This phenomenon has been attributed to the influence of cross hormone treatment.[346] We hypothesize, that this rapid change of hormone levels in transsexuals at the beginning of the transition, may provoke unanticipated short-term psychological adjustments. After a period of stabilization the trans women emotionally adjust to E. Hormone therapy is usually a significant emotional moment in a transsexual person's life and it is conceivable that the symbolic self-completion does not come into effect at this period, since transsexuals are more introspective and self focused shortly after start of the treatment rather than later when they are familiarized with their new body feelings. Therefore, it appears justified to interpret these findings in the light of changing hormone plasma levels and of unanticipated psychological variations and adjustments.

In one subscale, the ECS evaluates an individual’s tendency to mimic the fear reaction of another person. Interestingly, in one out of three visits a low T level correlated with a high fear contagion scale for male and female controls. These results coincided with a study from Hermans et al., which showed that T generally decreases facial mimicry.[294] A second study by the same group provides direct evidence that a single dose of T reduces fear in female participants.[312] Critics may say that the fact that these outcomes were only assessed for men at the first visit and for women for the second visit shows that the correlation is coincidental. However, in support of Herman’s claims, other studies revealed similar results. Moreover, it is conceivable that rather than incidental the correlation might be susceptible to confounding variables (biases and confounders), though not always reproducible. Another point of interest is a study by van Honk et al., which found that T reduces unconscious fear, but not self-reported measures of anxiety. However, we found that high plasma level of T did reduce fear contagion assessed by the emotional contagion scale whereas low T levels increased fear contagion. Taken together, these results might underline a potential causal mechanism of T effects on empathy, especially on fear contagion. In cismen subjects, high E plasma level also correlated with low scores in fear contagion. These results highlight that elevated levels

of E prevent fear contagion and the hormone might assert its anxiolytic effect through this mechanism. The fact that there was no apparent anxiolytic effect of E and T was absent in transsexuals may be due to the design of this study (sample size, scales etc.), especially considering that a study by van Kemenade et al. showed that feelings of fear decreased in trans women.[322] On the other hand, it is conceivable that transsexuals have different, less hormone dependent, coping mechanisms for dealing with fear, therefore weaker correlations. This phenomenon would be an interesting focus for future studies.

Little is known about hormones and imagination. The fact that we found a group difference in the tendency to get caught up in fictional stories and imagine oneself into the feelings and actions of fictitious characters in both questionnaires, in the IRI as well as in the BVAQ, underlines that either both questionnaires assess the same phenomenon or that we have a very strong correlation for different aspects of fantasy with E and T. We found a negative correlation between E and the fantasy scale in the IRI for the first appointment for female participants. The same correlation occurred for female participants in the BVAQ for the second visit and for male controls in the IRI for the last visit. It thus seems that the lower the E plasma levels, the better woman and men can imagine fictitious scenarios or daydream. For the first visit, a negative correlation was found between T and the fantasy scale of the BVAQ for female controls, suggesting that a higher level of T predicts a high tendency to fantasize. Although imagination and fantasy are stereotypically associated with the female gender, a negative interaction with E was shown for both sexes. It thus seems that high E levels decrease the ability to imagine oneself in unreal situations. On the other hand, a high T seems predictive for the talent of fantasy, at least in women. The situation is less clear in transsexual participants. While we found that trans men are the most inclined to fantasize and imagine situation or daydream in the BVAQ after four months of treatment, they had the worse results in the IRI. These last findings from the BVAQ appear to be at odds with the results from the IRI. This last contradiction is maybe caused by the fact that both questionnaires do not exactly assess the same phenomenon. While the BVAQ captures the abstract imagination, the IRI gets into specifics examples (books and films), what might explain the different outcome for the two scales.

Affective empathy is primarily assessed through the BVAQ: this questionnaire quantifies the inability to identify and describe feelings (Alexithymia). The affective score offers a summary of the emotionalizing and the fantasizing scale. Interestingly, a group difference was found for the last visit, with cismen and trans woman scoring equally poor. Trans woman decreased in the affective score during their four months of E treatment. Both, in the emotionalizing and the fantasizing scale, showed a decrease, perhaps due to the influence of E and anti-androgen treatment. Surprisingly, males showed a negative correlation between T and the affective score for their second visit, indicating that if T plasma levels are high, males are more affective empathetic. This outcome might be caused by the increasing effect that T exercises on the fantasy scale, as shown previously in woman. In contrast, trans men, who had the physiological hormone status of a woman at their first visit, had high affective and high emotionalizing scores when their T levels were low. It does not come as a surprise that T reduces emotionality, since there are some earlier studies, which showed a similar correlation. Thus even more surprising, in trans men, after one month of T treatment, with T plasma levels slowly increasing, a significant negative correlation emerged

between T and the emotionalizing scale, suggesting that the more T trans men have, the better their emotional outcome. As a side note, during the three visits the outcome of trans men did not change. Even more surprising was the observation that a high E plasma level predicted a worse emotionalizing performance. This correlation was apparent in trans women and ciswomen at the first visit. These results contrast those from with other studies demonstrating that higher E levels increase someone's tendency to be emotionally aroused by emotion inducing events. These discrepancies may be due to weaknesses of our study.

Cognitive empathy is measured by the BVAQ and the IRI. In the first Questionnaire the cognitive scale is a summarization of three subscales: the verbalization, the identifying and the analyzing scale. As outlined under results, the cognitive scale did not only show group differences, but also a significantly lower empathic outcome over time for both, men and trans men. Because all four groups of participants exhibited a worse performance during the last exposition compared to the first, it seems possible that this effect is caused by habituation and multiple exposures to the test, rather than by hormone effects. It was surprising, that transsexual men had by far the poorest cognitive empathic skills prior to treatment. In all three subscales their outcomes were worst. If we take a closer look at the different subscales, we see that the same phenomenon is detectable in the identifying scale. It has been shown that all four groups achieved significantly more points, which means that the degree to which the subjects were able to define their arousal states became poorer. As discussed earlier this may be a consequence of multiple test exposures, rather than a collective declining of identifying abilities. Interestingly, in trans men four months after treatment, we found a positive correlation between E and the identifying scale. Hence, low E levels in trans women are associated with an overall increase in identifying abilities. Also this result should be interpreted with precaution because of the habituation effect discussed previously. Furthermore, the verbalization scale indicates the degree to which someone can or is inclined to describe or communicate about his emotional reactions. The following results are especially interesting as they bring new insights to the relation between T and the inclination to communicate about feelings. Literature tends to view T as a hormone, which does not promote communication, for example a study by Wolf et al. showed that T blocked the practice effect in verbal fluency in elderly men.[347] In our study, the contrary is the case. Trans woman with high T prior to hormone treatment had better verbalizing skills. In line with our results is a study by Cherrier et al., which demonstrated that short-term T administration enhances verbal memory in older men.[348] Another study revealed that healthy young men with decreased T levels demonstrate a significant decline in verbal memory.[349] Studies investigating the verbal fluency in transsexuals found inconclusive data, making reliable conclusions difficult.[321,323,325,331] To enable reliable statements, I would recommend that future studies should increasingly investigate the influence of T on human verbalization skills. The last subscale of the cognitive empathy scale is the analyzing scale. First and foremost, trans man seemed to have less need to define their arousal state, to communicate their emotional reactions or to look for explanations for them. Why trans men perform so poorly in analyzing their feelings may be explained by the symbolic self-completion theory. Following gender clichés, it does not befit men to analyze their emotional states or feelings. According to this theory, trans men prior to onset of treatment, have to act according to their self-attributed gender characteristics and gender-role behavior, witch overlaps with the general stereotypical image of men. Further support of this hypothesis is added by the fact that the analyzing willingness increased up to the last visit. For the last visit a striking group difference was shown:

trans woman improved significantly in their analyzing skills during the four months of treatment and achieved the best outcome. On the other hand, cismen scored the poorest. It may be that hormone treatment had a modifying effect on the extent to which trans women are looking for explanations of their emotional reactions. Transsexuals display an enhanced self-observation, as it was possible to observe through the work with them; taking hormones and seeing one's body and one's psychological functions changing seems to be a logical trigger factor for increasing self analyzing skills.

## 8.-1. Limitations of the present study

**Table 13: Sociodemographic information about Male-to-Female, Female-to-Male, female controls and male controls. The number of subjects for each visit is stated below. Mean values and standard deviations are presented.**

| GROUPS | AGE: mean ± S.D. | AGE: min.-max. | V0 | V1 | V2 |
|---|---|---|---|---|---|
| **FtM** | 24.6 ± 6.0 | 18-37 | 23 | 9.0 | 9.0 |
| **MtF** | 32.1 ± 8.4 | 19-47 | 21 | 11 | 10 |
| **FC** | 25.3 ± 5.9 | 18-43 | 35 | 5.0 | 4.0 |
| **MC** | 27.9 ± 7.5 | 19-50 | 29 | 7.0 | 6.0 |

**Abbreviations:** FtM: female-to-male; MtF: male-to-female; FC: female control; MC: male control; V0=first visit; V1=second visit; V2=third visit; min.: minimum; max.: maximum

To disentangle which effects are cause by hormone therapy and witch ones are due to social desirability in transsexuals, it would have been beneficial to add a desirability scale to this study (like the Marlowe–Crowne Social Desirability scale[350]) to control the possible effects of response bias. This is underscored by the fact that some studies have shown that social desirability is positively related to Davis's self-reported empathy scales (IRI).[351-353] Because showing empathy is generally considered as a desirable character trait,[354] the outcomes have been distorted in direction of a greater empathic concern and perspective-taking.

Further, the groups' size of the healthy controls may have a falsifying effect on the study outcome. For the first visit, data of 35 FC and 29 MC were collected, for the third visit the group size diminished to 4 FC and 6 MC (see table 6). This is due to the fact that the data collection is from an ongoing study. The power of this study would be greater with more participants; however we were able to show significant effects and correlations, despite the small sample size.

Further topics are the variables, which were uneven for the different groups. Primarily, an age difference was assessed between the four groups; the mean ages of trans females were greater than those of trans males (see table 6). Moreover participants have a different social and educational background, which was not assessed. Beside the personal distinctions the process of the data capture shows variable characteristics.

The data could be corrupted depending on seasonal influence, interpersonal influence of the study team etc. These variables, to name just a few, are partially unpredictable and uncontrollable but, for the purposes of completeness, should be mentioned.

The data acquisition started in 2011 and is ongoing. Because of compliance problems, technical limitations etc., it was not always possible to keep schedule. According to the timetable, the first visit is always before cross hormone treatment, the second, one month after treatment and the last, four months after treatment. Especially for the transsexual participants, temporary postponement might affect the accuracy of the hormone plasma level and consequently its effect on behavior. However, as shown earlier, the first time after hormone treatment is a period of transition; medical doctors try to find the right dosage and plasma hormone levels are fluctuating. Besides, not all patients received the same medication and even if they did, the same dose and the same ingredients do not have the same biological actions on each individual, therefore, this source of error is negligible. The rough division between short time effects (4-6 weeks) and long-term effects (16-19weeks) of endocrinologic therapy seemed more adequate than a rigid and unrealistic schedule.

In this study, we did not take into account additional physiological mediators and moderators of E´s and T´s influence on behavior. Studying only E and T, without having a closer look on other hormones and environmental factors, limits the significance of the outcome, as possible other underlying mechanisms and etiology are not considered. In earlier work, Archer and colleagues demonstrated that the effects of T on behavior can very easily be washed out when these modulatory and underlying factors are not accounted for.[355]

# E) Conclusions

This study provides evidence that cross-sex hormones affect gender specific behaviors. The study is also intended to clarify outdated prejudices, which are based on obsolete data or misbelieves, such as testosterone-induced "´roid rage". Eliminating prejudices, especially those concerning minority groups and identifying mechanisms underlying biological phenomena are also main goals of this study. I would like to endorse the vision of WPATH from a world wherein „transsexual, transgender, and gender nonconforming people benefit from access to evidence-based health care, social services, justice and equality."[162]
The investigation of effects of estrogen and testosterone on social behavior and social cognition in human studies may one day have direct implications of the treatment on the psychiatric disorders associated with social deficits such as autism spectrum disorders and schizophrenia.

In summary and consistent with earlier findings, our study shows that ciswomen obtain better outcomes than cismen in empathic questionnaires. We also found that female gender identity (trans women and ciswomen) is predictive for a better empathy performance in the IRI. In addition, the overview of the IRI scale clearly demonstrates the effect of hormone therapy: two different therapies provoked two opposite performances in transsexual patients. No intervention, in the control groups, resulted in steady outcomes. Similar results were obtained in some subscales of the ECS.

In line with my hypothesis and with recent literature, we found that before treatment of trans men, testosterone had a dampening effect on affect intensity and on emotional susceptibility. In contrast, trans women increased the intensity and expressiveness of emotions, especially of love and happiness contagion, which could be caused by anti-androgen and estrogen treatment. The next point to be considered is whether anxiolytic effects are related to steroid hormones or not. Our findings suggest that elevated levels of estrogen and testosterone prevent fear contagion and that perhaps through these mechanisms anxiolytic effects are exerted in humans.

Contradicting my hypothesis and results from other studies are the following findings: although we demonstrated that before hormone treatment testosterone had a dampening effect on affect intensity on trans men, after one month of testosterone treatment, when the testosterone plasma levels slowly increase, trans men showed a better emotional outcome if their testosterone level are high. This may be due to the rapid change of hormone levels in transsexuals at the beginning of the transition, which could provoke unanticipated short-term psychological adjustments. Second, literature suggests that estrogen increases the inclination to which someone is emotionally aroused by emotion inducing events. However, across this study it appeared that high estrogen plasma level might predict worse emotionalizing performance in female identity gendered individuals. Furthermore, contrary to our expectations the degree to which someone can or is inclined to describe or communicate about his emotional reactions is positively related to testosterone in trans woman.

Unexpectedly, we demonstrated an interesting association between hormones and fantasy. Although imagination is stereotypically associated with the female gender, a negative interaction with estrogen was shown for both sexes. It thus seems that high

estrogen levels decrease the ability to imagine oneself in unreal situations and on the other hand high testosterone is predictive for the talent of fantasy. Lastly, I found that trans women improved significantly in their analyzing skills during the four months of treatment. It may be that hormone treatment had a modifying effect on the extent to which trans women are looking for explanations of their emotional reactions.

At the end, I would like to empathize that it is important to be aware that each individual's own beliefs and stereotypes about what it means to be a men or a women, as well as their own pre-existing personality traits, may play into their behaviors and outcomes. Also social desirability and symbolic self-completion were not assessed in this study, but certainly do have a modeling effect on the outcomes. I have shown that it is reasonable to assume that steroid hormone levels have an effect on individuals, both physically and emotionally though not always the way we would expect them to act. Especially the findings of this study that are not in line with other studies would be interesting topics of new investigations.

*"Mir ist bis heute noch kein Problem – wie kompliziert auch immer – begegnet, dass sich nicht durch den richtigen Blickwinkel noch stärker verkomplizieren ließ." Paul Alderson (*1926)*

# F) APPENDIX: SCALES

## Emotional contagion scale (German version: ECS-D)

1. Wenn jemand, mit dem ich spreche, zu weinen beginnt, bekomme ich feuchte Augen.
2. Mit einer glücklichen Person zusammen zu sein gibt mir Mut, wenn ich mich traurig fühle.
3. Wenn mich jemand freundlich anlächelt, lächle ich zurück und empfinde wohlige Wärme.
4. Ich empfinde Trauer, wenn Menschen über den Tod von Nahestehenden sprechen.
5. Wenn ich die Gesichter zorniger Menschen im Fernsehen sehe, verspannen sich meine Schultern und mein Kiefer.
6. Wenn ich dem Menschen, den ich liebe, in die Augen sehe, sind meine Gedanken erfüllt von Romantik.
7. Es irritiert mich, wenn ich von wütenden Menschen umgeben bin.
8. Wenn ich ängstliche Gesichter von Opfern in den Nachrichten sehe, bin ich geneigt mir vorzustellen, wie sie sich fühlen.
9. Ich schmelze dahin, wenn derjenige, den ich liebe, mich fest umarmt.
10. Ich bin angespannt, wenn ich einem wütenden Streit zuhöre.
11. Wenn ich von glücklichen Leuten umgeben bin, erfüllt es mich mit glücklichen Gedanken.
12. In meinem Körper breitet sich ein Wohlgefühl aus, wenn mich derjenige, den ich liebe, berührt.
13. Ich spüre eine wachsende Anspannung, wenn ich von gestressten Menschen umgeben bin.
14. Ich weine bei traurigen Filmen.
15. Wenn ich im Warteraum in einer Zahnarztpraxis bin und schrille Schreie von einem verängstigten Kind höre, macht mich das nervös.

# Bermond-Vorst Alexithymia Questionnaire (BVAQ)

## Form A

1. Ich finde es schwierig, meine Gefühle in Worte zu fassen.
2. Bevor ich einschlafe denke ich mir oft allerlei Ereignisse, Begegnungen und Gespräche aus.
3. Wenn ich durcheinander bin, dann weiß ich ob ich ängstlich, traurig oder ärgerlich bin.
4. Wenn etwas absolut Unerwartetes passiert, bleibe ich ruhig und ungerührt.
5. Ich vertiefe mich kaum in meine Gefühle.
6. Ich erzähle anderen gerne über meine Gefühle.
7. Ich habe wenig Tagträume und Phantasien.
8. Wenn ich angespannt bin, bleibt mir unklar durch welches emotionale Gefühl das kommt.
9. Wenn ich sehe, dass jemand schrecklich weinen muss, bleibe ich ungerührt.
10. Emotionen muss man versuchen zu ergründen.
11. Sogar mit einem Freund oder einer Freundin finde ich es schwierig über meine Gefühle zu reden.
12. Ich benutze meine Phantasie oft.
13. Wenn Dinge mir zuviel werden, begreife ich meistens woran das liegt.
14. Wenn Freunde um mich herum fürchterlich streiten, werde ich emotional.
15. Wenn ich mich schlecht fühle, quäle ich mich nicht noch mehr dadurch, mich zu fragen, warum ich dieses Gefühl habe.
16. Wenn ich erzählen will, wie schlecht ich mich fühle, finde ich dafür leicht die richtigen Worte.
17. An Märchen und bizarren Erzählungen habe ich wenig.
18. Wenn ich mich wohl fühle, bleibt mir unklar, ob ich heiter, begeistert oder fröhlich bin.
19. Oft sprudeln Emotionen einfach so in mir nach oben.
20. Wenn ich mich nicht wohl in meiner Haut fühle, versuche ich herauszufinden, warum ich mich so fühle.

## Form B

1. Man sagt mir oft, dass ich mehr von meinen Gefühlen erzählen muss.
2. Ich phantasiere selten.
3. Ich weiß nicht was alles in mir vorgeht.
4. Auch wenn andere voller Enthusiasmus für etwas sind, bleibe ich unbewegt.
5. An Emotionen gibt es wenig zu begreifen.
6. Wenn ich durch etwas aus dem Gleichgewicht geraten bin, spreche ich mit anderen über meine Gefühle.
7. Ich erfinde gerne verrückte, phantasiereiche Geschichten.
8. Wenn ich fassungslos bin, dann weiß ich ob ich ängstlich oder niedergeschlagen oder traurig bin.
9. Unerwartete Ereignisse überspülen mich oft mit Emotionen.
10. Ich finde, dass man mit seinen Gefühlen verbunden bleiben muss.
11. Ich kann meine Gefühle in Worte fassen.
12. Phantasieren über irreale Sachen oder Ereignisse finde ich Zeitverschwendung.
13. Wenn ich mir selber im Weg stehe, bleibt mir unklar ob ich traurig, ängstlich oder unglücklich bin.
14. Enttäuschungen nehme ich emotionslos hin.
15. Ich finde es seltsam, dass andere soviel Interesse für ihr Emotionen haben.
16. Wenn ich mit Menschen spreche, dann eher über meine täglichen Beschäftigungen als über meine Gefühle.
17. Wenn ich wenig zu tun habe, bekomme ich Tagträume.
18. Wenn ich gute Laune habe, weiß ich, ob ich begeistert, fröhlich oder ausgelassen bin.
19. Wenn ich jemanden fürchterlich weinen sehe, fühle ich Traurigkeit in mir hochkommen.
20. Wenn ich gespannt bin, will ich genau wissen, wo das Gefühl herkommt.

## Interpersonal Reactivity Index (german Version: Saarbrücker Persönnlichkeitsfragebogen: IRI)

1. Ich habe öfters Tagträume und Fantasien über Dinge, die mir passieren könnten.
2. Ich empfinde oft warmherzige Gefühle für Leute, denen es weniger gut geht als mir.
3. Ich finde es manchmal schwierig, die Dinge vom Standpunkt eines anderen Menschen aus zu sehen.
4. Manchmal habe ich nicht viel Mitleid mit Leuten, die Probleme haben.
5. Die Gefühle einer Person in einem Roman kann ich mir oft sehr gut vorstellen.
6. In Notfallsituationen fühle ich mich ängstlich und unbehaglich.
7. Gewöhnlich bleibe ich sachlich, wenn ich einen Film oder ein Theaterstück sehe, und ich werde selten von der Handlung mitgerissen.
8. Ich versuche, bei einem Streit zuerst beide Seiten zu verstehen, bevor ich eine Entscheidung treffe.
9. Wenn ich sehe, dass jemand ausgenutzt wird, glaube ich, ihn schützen zu müssen.
10. Manchmal fühle ich mich hilflos, wenn ich inmitten einer sehr emotionsgeladenen Situation stecke.
11. Ich versuche manchmal, meine Freunde besser zu verstehen, indem ich mir vorstelle, wie die Dinge aus deren Sicht aussehen könnten.
12. Es kommt relativ selten vor, dass ich von einem Buch oder einem Film so richtig mitgerissen werde.
13. Wenn ich sehe, wie jemand verletzt wird, bleibe ich eher ruhig.
14. Gewöhnlich beunruhigt mich das Unglück anderer Leute nicht sehr.
15. Wenn ich überzeugt bin, dass ich Recht habe, verschwende ich nicht viel Zeit damit, die Argumente anderer Leute anzuhören.
16. Nach ich einen Film gesehen habe, fühle ich mich manchmal so, als ob ich eine der Personen aus diesem Film wäre.
17. Es macht mir Angst, in angespannten emotionalen Situationen zu sein.
18. Wenn ich sehe, dass jemand ungerecht behandelt wird, habe ich manchmal nicht sehr viel Mitleid mit ihm.
19. Ich kann normalerweise ziemlich kompetent mit Notsituationen umgehen.
20. Oft berühren mich Dinge sehr, die ich nur beobachte.
21. Ich glaube, jedes Problem hat zwei Seiten, und versuche daher, beide zu betrachten.
22. Ich würde mich selbst als eine ziemlich weichherzige Person beschreiben.
23. Wenn ich einen guten Film sehe, kann ich mich sehr leicht in die Hauptperson hinein versetzen.
24. Ich neige dazu, in Notsituationen die Kontrolle über mich zu verlieren.
25. Wenn ich böse auf jemanden bin, versuche ich normalerweise, mich für eine Weile in seine Situation zu versetzen.
26. Wenn ich eine interessante Geschichte oder ein gutes Buch lese, versuche ich mir vorzustellen, wie ich mich fühlen würde, wenn mir die Ereignisse in der Geschichte passieren würden.
27. Wenn ich jemanden sehen würde, der in einer Notsituation dringend Hilfe benötigt, würd ich bestimmt zusammenbrechen.
28. Bevor ich jemanden kritisiere, versuche ich mir vorzustellen, wie ich mich fühlen würde, wenn ich an seiner/ihrer Stelle wäre.

# G) APPENDIX: TABLES

**Table 14: Overview of mean values and standard deviations for Testosterone and Estrogen plasma levels in FtM, MtF, FC and MC subjects.**

| GROUPS | | ESTROGEN | | TESTOSTERONE | |
|---|---|---|---|---|---|
| | | Mean | S.D. | Mean | S.D. |
| FtM | V0 | 100.10 | 87.29 | 0.40 | 0.20 |
| FtM | V1 | 135.40 | 134.95 | 3.69 | 1.97 |
| FtM | V2 | 55.40 | 41.26 | 4.75 | 2.71 |
| MtF | V0 | 30.33 | 9.28 | 4.89 | 1.62 |
| MtF | V1 | 72.90 | 58.72 | 0.56 | 0,53 |
| MtF | V2 | 112.40 | 77.39 | 0.83 | 0.79 |
| FC | V0 | 102.97 | 100.53 | 0.31 | 0.16 |
| FC | V1 | 130.40 | 107.44 | 0.33 | 0.12 |
| FC | V2 | 175.25 | 86.94 | 0.37 | 0.11 |
| MC | V0 | 25.33 | 7.96 | 4.92 | 1.53 |
| MC | V1 | 26.85 | 12.37 | 5.53 | 1.51 |
| MC | V2 | 23.33 | 6.86 | 4.71 | 2.14 |

**Abbreviations:** FtM: female-to-male; MtF: male-to-female; FC: female control; MC: male control; V0=first visit; V1=second visit; V2=third visit; Estrogen plasma levels are given in pg/ml, testosterone plasma levels are given in ng/ml.

**Table 15: Overview of mean values and standard deviations for the subscales of the emotional contagion scale in FtM, MtF, FC and MC subjects**

| SUBJECTS | | EMOTIONAL CONTAGION SCALE | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | HAPPINESS | | LOVE | | FEAR | | ANGER | | SADNESS | |
| | | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. |
| FtM | V0 | 8.74 | 1.76 | 8.87 | 3.00 | 6.00 | 2.98 | 4.30 | 3.309 | 5.87 | 2.70 |
| FtM | V1 | 8.44 | 2.00 | 8.89 | 3.95 | 5.33 | 2.74 | 4.44 | 1.590 | 5.11 | 2.80 |
| FtM | V2 | 8.33 | 2.50 | 8.00 | 3.61 | 3.78 | 2.95 | 2.78 | 2.22 | 4.44 | 3.36 |
| MtF | V0 | 9.05 | 1.75 | 9.57 | 1.83 | 7.00 | 2.90 | 6.81 | 2.52 | 7.90 | 2.86 |
| MtF | V1 | 9.09 | 2.12 | 10.4 | 1.69 | 6.27 | 2.33 | 5.55 | 2.81 | 6.91 | 2.84 |
| MtF | V2 | 9.50 | 2.01 | 10.8 | 1.69 | 6.90 | 2.38 | 6.80 | 2.20 | 7.90 | 1.66 |
| FC | V0 | 8.91 | 1.56 | 9.38 | 1.56 | 6.15 | 2.20 | 5.85 | 2.00 | 7.21 | 2.24 |
| FC | V1 | 8.20 | 2.28 | 7.80 | 2.59 | 6.00 | 1.87 | 6.20 | 1.30 | 6.80 | 4.32 |
| FC | V2 | 9.75 | 1.71 | 9.50 | 1.73 | 5.50 | 2.65 | 6.25 | 3.77 | 7.50 | 2.52 |
| MC | V0 | 8.69 | 1.91 | 7.93 | 2.31 | 4.69 | 2.04 | 4.17 | 1.96 | 4.83 | 2.30 |
| MC | V1 | 7.29 | 2.29 | 7.43 | 2.15 | 4.43 | 1.99 | 3.57 | 2.37 | 5.14 | 1.34 |
| MC | V2 | 8.00 | 2.19 | 8.33 | 2.42 | 4.17 | 2.79 | 3.67 | 3.50 | 3.50 | 2.34 |

**Abbreviations:** FtM: female-to-male; MtF: male-to-female; FC: female control; MC: male control; V0=first visit; V1=second visit; V2=third visit

**Table 16: Overview of mean values and standard deviations for the subscales of the Bermond-Vorst Alexithymia Questionnaire in FtM, MtF, FC, MC subjects**

| SUBJECTS | | BVAQ | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Emotionalizing | | Verbalizing | | Fantasizing | | Identifying | | Analyzing | |
| | | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. |
| FtM | V0 | 11.48 | 3.17 | 11.83 | 4.06 | 11.65 | 3.42 | 10.2 | 3.31 | 11.22 | 3.55 |
| FtM | V1 | 10.78 | 2.59 | 9.33 | 5.02 | 12.89 | 5.08 | 8.44 | 2.35 | 10.44 | 4.36 |
| FtM | V2 | 11.78 | 2.17 | 12.11 | 1.96 | 9.44 | 3.32 | 16.56 | 2.45 | 9.44 | 4.42 |
| MtF | V0 | 10.24 | 3.00 | 10.29 | 4.27 | 11.57 | 3.17 | 8.90 | 3.52 | 8.86 | 1.98 |
| MtF | V1 | 9.82 | 3.49 | 10.45 | 5.65 | 10.91 | 3.01 | 8.64 | 2.62 | 8.82 | 3.12 |
| MtF | V2 | 12.00 | 1.63 | 11.60 | 0.70 | 14.00 | 2.83 | 15.20 | 2.20 | 6.30 | 2.21 |
| FC | V0 | 10.47 | 2.65 | 8.94 | 3.94 | 11.41 | 3.99 | 8.18 | 2.79 | 9.18 | 3.31 |
| FC | V1 | 10.20 | 3.42 | 11.80 | 5.80 | 7.20 | 3.11 | 10.20 | 2.59 | 9.80 | 2.39 |
| FC | V2 | 12.25 | 0.50 | 11.00 | 1.41 | 15.50 | 3.51 | 14.50 | 1.29 | 8.50 | 1.91 |
| MC | V0 | 11.66 | 2.14 | 10.03 | 3.76 | 11.10 | 2.92 | 8.66 | 2.62 | 9.07 | 2.46 |
| MC | V1 | 12.33 | 3.50 | 11.00 | 2.19 | 11.17 | 3.12 | 11.00 | 3.69 | 10.67 | 2.73 |
| MC | V2 | 12.33 | 1.21 | 10.67 | 1.51 | 13.67 | 3.67 | 15.50 | 0.84 | 12.00 | 4.19 |

| SUBJECTS | | BVAQ | | | |
|---|---|---|---|---|---|
| | | Cognitive | | Affective | |
| | | Mean | S.D | Mean | S.D |
| FtM | V0 | 33.30 | 7.29 | 23.13 | 5.10 |
| FtM | V1 | 28.22 | 11.20 | 23.67 | 5.96 |
| FtM | V2 | 38.11 | 5.95 | 21.22 | 3.80 |
| MtF | V0 | 28.05 | 6.91 | 21.81 | 4.79 |
| MtF | V1 | 27.91 | 9.07 | 20.73 | 4.94 |
| MtF | V2 | 33.10 | 2.28 | 26.00 | 3.62 |
| FC | V0 | 23.51 | 29.07 | 20.06 | 23.71 |
| FC | V1 | 25.69 | 37.91 | 11.15 | 23.65 |
| FC | V2 | 30.33 | 37.67 | 22.49 | 33.01 |
| MC | V0 | 27.76 | 6.87 | 22.76 | 4.08 |
| MC | V1 | 32.67 | 7.09 | 23.50 | 4.59 |
| MC | V2 | 38.17 | 3.54 | 26.00 | 4.73 |

**Abbreviations:** FtM: female-to-male; MtF: male-to-female; FC: female control; MC: male control; V0=first visit; V1=second visit; V2=third visit; BVAQ: Bermond-Vorst Alexithymia Questionnaire

**Table 17: Overview of mean values and standard deviations for the subscales of the Interpersonal Reactivity Index in FtM, MtF, FC and MC subjects.**

| SUBJECTS | | INTERPERSONAL REACTIVITY INDEX | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PT | | F | | EC | | PD | | Total | |
| | | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. | Mean | S.D. |
| FtM | V0 | 18.23 | 5.34 | 13.05 | 6.66 | 17.68 | 4.59 | 10.3 | 5.61 | 59.27 | 16.48 |
| FtM | V1 | 19.33 | 6.10 | 13.89 | 5.69 | 17.33 | 4.27 | 9.89 | 3.37 | 60.44 | 11.36 |
| FtM | V2 | 17.33 | 6.54 | 11.00 | 7.42 | 15.44 | 6.00 | 7.44 | 2.79 | 51.22 | 19.50 |
| MtF | V0 | 18.90 | 4.49 | 18.71 | 5.20 | 19.52 | 4.81 | 11.29 | 4.91 | 68.43 | 13.71 |
| MtF | V1 | 18.91 | 6.11 | 19.09 | 5.45 | 18.00 | 5.80 | 9.18 | 5.34 | 65.18 | 16.95 |
| MtF | V2 | 19.80 | 5.35 | 19.90 | 5.90 | 20.30 | 5.27 | 10.20 | 5.14 | 70.20 | 15.03 |
| FC | V0 | 18.50 | 4.56 | 17.29 | 4.90 | 19.12 | 3.96 | 10.32 | 4.89 | 65.24 | 12.02 |
| FC | V1 | 17.80 | 2.28 | 21.60 | 6.19 | 17.80 | 5.67 | 9.40 | 4.28 | 66.60 | 9.21 |
| FC | V2 | 15.25 | 1.29 | 17.75 | 5.91 | 19.75 | 1.26 | 11.50 | 3.11 | 64.25 | 6.70 |
| MC | V0 | 18.31 | 4.19 | 14.79 | 3.83 | 16.93 | 3.42 | 8.79 | 4.68 | 58.83 | 10.32 |
| MC | V1 | 16.67 | 3.98 | 10.83 | 5.42 | 14.50 | 3.78 | 7.17 | 4.21 | 49.17 | 14.69 |
| MC | V2 | 17.67 | 5.32 | 14.83 | 4.62 | 17.17 | 4.83 | 9.17 | 3.76 | 58.83 | 13.32 |

**Abbreviations:** FtM: female-to-male; MtF: male-to-female; FC: female control; MC: male control; V0=first visit; V1=second visit; V2=third visit; PT: perspective taking, F: Fantasy, EC: emotional contagion, PD: personal distress

# H) APPENDIX: ABREVIATIONS

**ACC:** anterior cingulate cortex
**AI:** anterior insula
**ANOVA:** analysis of variance
**AVP:** Vasopressin
**BVAQ:** Bermond-Vorst Alexithymia Questionnaire
**E:** Estrogen
**E1**: oestrone
**E2**: oestradiol
**E3**: oestriol
**EC:** Empathic concern
**ECS**: Emotional contagion scale
**FC:** Female control
**FS:** Fantasy
**FSH*:*** Follicle-stimulating hormone
**FtM:** female-to-male
**GnRH:** Gonadotropin-releasing hormone
**HAMA**: Hamilton anxiety scale
**HAMD**: Hamilton depression scale
**Hrs:** hours
**i.m.:** intramuscular
**IRI:** Interpersonal Reactivity Index
(German Version: Saarbrücker Persönnlichkeitsfragebogen)
**LH:** Luteinizing hormone
**max.:** maximum
**MC:** Male control
**mean:** mean values
**mg:** milligramm
**min:** minimum
**ml:** milliliter
**MPC:** medial prefrontal cortex
**MtF:**male-to-female
**OT:** Oxytocin
**PAM:** perception-action mechanism
**PD:** Personal distress
**pg/ml:** picogram/millilitre
**PT:** Perspective-taking
**RMET:** Reading the Mind in the Eyes Test
**SII:** secondary somatosensory cortex
**s.c.:** subcutan
**SCID**: German version of the structured interview of DSM IV
**S.D.:** standard deviations
**SHBG:** Sex hormone-binding globulin
**STS:** superior temporal sulcus
**T:** Testosterone
**TP:** temporal poles
**TPF:** temporo-parietal junction

**TTS:** transdermal therapeutic system
**V1:** Visit 1
**V2:** Visit 2
**V3:** Visit3
**WPATH:** World Professional Association for Transgender Health
**µg:** microgram

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