CHARLES UNIVERSITY IN PRAGUE

Faculty of Science

DISSERTATION THESIS

2007 Jitka Lindová

Charles University in Prague, Faculty of Science
Department of Zoology

Gender differences in behavioral changes induced by latent toxoplasmosis

Dissertation thesis

Mgr. et Mgr. **Jitka Lindová**

Supervisor: Doc. RNDr. **Jaroslav Flegr**, CSc

Prague 2007

Prohlašuji, že jsem tuto práci, ani její podstatnou část nepředložila jinde k získání jiného nebo stejného akademického titulu.

I wish to thank Jaroslav Flegr in the first line. Only after I got to know him, I understood the right meaning of the word persistent. Being *persistent*, he made me become disciplined enough to function as a researcher. Where Jaroslav Flegr would perhaps not manage, I was backed by my "guru" Jan Havlíček who I also owe many thanks. From my other collaborators, great support came from Martina Novotná who always knew what to do without asking. Also many other colleagues have provided indispensable help. Credit belongs to Hana Hodková, Petra Kolbeková, Anna Skallová, Eva Jozífková, Martina Hrušková, Věra Pivoňková, Romana Vavřinová, Anna Kotrčová, Šárka Kaňková and others. I also thank Zdeněk Hodný for lightening long hours of blood taking and Martin Kolísko for making me think that I can be a researcher even without knowing how to fix my computer.

Many thanks belong to the "result-maker" Aleš Kuběna who challenged my statistical knowledge as well as my patients. I also thank Petr Kodym and his laboratory for diagnostics of toxoplasmosis.

Finally, I would like to thank my parents for being fans of my scientific aspirations and my husband for not hesitating to marry a scientist (and even a psychologist).

1. Introduction

The thesis is mainly focused on gender differences in relation to the influence of latent toxoplasmosis. In humans, toxoplasmosis was found to have gender-different effects on several aspects of personality, behavior, morphology and physiology. More specifically, it was found to have opposite effects on men's and women's personality traits warmth, conscientiousness and vigilance measured by Cattell's 16PF questionnaire (Flegr et al. 1996, 1999, 2000, Flegr and Havlíček 1999, Flegr and Hrdý 1994), behavior assessed by small experiments regarding the quality of relationships, self-control and clothes tidiness (**Lindová et al. 2006**), allocation of money in experimental games (**Lindová et al. submitted**), body height (**Flegr et al. 2005**), and testosterone level (**Flegr et al. submitted a**).

The effect of toxoplasmosis on the ratio between the second and the fourth digits (2D:4D) was significant for men, but not for women (**Flegr et al. 2005**). Additionally, infected men had higher perceived facial dominance and masculinity (**Hodková et al. 2007**). Corresponding data for women are not available at the moment.

In contrast, no gender differences were found for the psychobiological factor novelty seeking (lower score found both for women: Skallová et al. 2005 and men: Flegr et al. 2003, **Novotná et al. 2005**) as well as Cattell's factor O (guilt proneness; higher scores found both for men: Flegr et al. 1999, and women: Flegr and Havlíček 1999), although the shift in factor O was not confirmed by other studies (e.g., Flegr et al. 2000).

The mechanism of the gender different influence of latent toxoplasmosis is unknown. However, the results of the above mentioned studies yield at least three lines of indices.

1) Several studies point to the role of testosterone. Indirect evidence comprises increased dominance and masculinity in infected men (**Hodková et al. 2007**), decreased 2D:4D ratio of infected men and a trend in the same direction observed for women and greater body height of infected men (**Flegr et al. 2005**). Salivary testosterone levels were found to be lower in infected women than uninfected women, but a trend in the opposite direction was observed for men (**Flegr et al. submitted a**).
2) The fact that lower novelty seeking was also observed in subjects infected with a different neurotropic pathogen cytomegalovirus, which is spread by direct contact and not by predation, impugns the hypothesis saying that the changes represent a result of the manipulation activity of the parasite, and rather indicate that the observed changes are a byproduct of brain infections. The mechanism is supposed to go via dopamine which has been linked both to novelty seeking and inflammatory processes and was found to be increased in *Toxoplasma*-infected mice (Stibbs 1985).
3) The pattern of gender differences in induced changes, with women showing elevated pro-social behavior in contrast to men, indicates that experiencing stress and coping with stress could go together with the latent toxoplasmosis infection.

It exceeds the scope of this thesis to identify the mechanism of behavioral and other changes induced by latent toxoplasmosis. However, as attempts to find the mechanism have taken several disparate directions so far, the next step seems to be looking for interrelations among the factors presumptive to play a role.

Moreover, it is of great interest to be familiar with gender differences in the relevant aspects, i.e. personality, steroid hormones, immunological response to parasitosis, stress processes and stress coping, etc.

In the present thesis, I will commence with a review of gender differences in personality and explore if perhaps *Toxoplasma* intensifies these already present differences. After that, I will give a brief overview of endocrinological sex differences and the sex hormone-

personality associations. This will allow me to discuss the question of whether observed *Toxoplasma*-induced personality changes are likely to be caused by changes in hormone levels. Next, I will investigate the available evidence on the relationship between estrogens and inflammatory infections and try to find links to toxoplasmosis, dopamine and schizophrenia. Once again, I will try to explain *Toxoplasma*-induced personality changes, this time as the result of chronic inflammation regulated by estrogens. Finally, I will summarize recent evidence on gender differences in stress response and possible role of sex steroid and other hormones in stress processes. The discussion of a stress hypothesis of gender differences in *Toxoplasma*-induced personality changes will follow.

2. Personality

2. 1. Gender differences in personality

At the present, numerous cross-cultural studies and meta-analyses of gender differences in personality are available. The Five Factor Model of personality (FFM) seems to be relatively well cross-culturally valid and represents the far most used model of personality. Originally, it was discovered through analyses of English-language trait names (Tupes & Christal, 1961/1992). It is possible to measure an individual's standing on each of the five factors by asking them to rate themselves on a series of adjectives (Goldberg, 1992) or through the use of personality questionnaires, in which respondents indicate the extent to which they are accurately described by a series of statements about characteristic thoughts, feelings, and behaviors. A wide variety of measures of the FFM have now been developed (De Raad & Perugini, 2002), of which the most widely used is the Revised NEO Personality Inventory (NEO-PI-R; Costa & McCrae, 1992). The NEO-PI-R assesses 30 specific traits, six for each of the five factors, and has been shown to be a reliable and valid measure for the assessment of normal personality traits. Although the exact definitions of these five personality domains as well as number of personality domains present in specific cultures vary a little with the used method and studied culture, it mostly includes neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness.

Moderate sex differences were repeatedly found. A meta-analytic study by Shuquin and colleagues (1995) based on 76 studies from the years 1967 through 1992 done on American adults found significant and relatively strong gender differences in favor of women in agreeableness and neuroticism, and non-significant advantage of women over men in conscientiousness, and of men over women in openness to experience and extraversion. As to my knowledge, this study has never been published. One reason may have been that it is based only on the American culture.

More importantly, Costa and colleagues (2001) performed a secondary analysis of personality data collected with the NEO-PI-R in 26 cultures. They confirmed the women's precedence in neuroticism and agreeableness and further found women to score higher in warmth (a facet of extraversion) and openness to feelings (a facet of openness to experience). Men were found to score higher in assertiveness (another facet of extraversion) and openness to ideas (another facet of openness to experience). More specifically in the samples of adults, women from most cultures scored higher than men in anxiety, vulnerability, straightforwardness, and openness to aesthetics, whereas men scored higher in competence, assertiveness, excitement seeking, and openness to ideas. As the gender differences are universal, they may be biologically based. Surprisingly, the magnitudes of gender differences were more pronounced in European and American cultures than in more traditional societies and were altogether relatively small. Authors suggest a possible interpretation that gender differences in personality traits may not be as obvious in traditional societies because typical

masculine or feminine behavior is largely determined by social roles and thus is not attributed to differences in personality.

A completely different approach to personality is represented by Robert C. Cloninger and his colleagues who developed a psychobiological model of temperament and character. Originally, three temperament dimensions, novelty seeking, harm avoidance and reward dependence, were identified, which were thought to be related to genetically independent, but interactive, neurobiological systems, i.e. behavioral activation, behavioral inhibition and behavioral maintenance systems in the central nervous system, respectively. Variation in each of these dimensions has been associated with activity in a monoaminergic pathway: novelty seeking with low basal dopaminergic activity; harm avoidance with high serotonergic activity and reward dependence with low basal noradrenergic activity (Cloninger 1987). This model was later extended to four temperamental and three character traits. A meta-analysis of gender differences in four Cloninger's temperament dimensions novelty seeking, harm avoidance, reward dependence and persistence from 32 studies has been recently published by Miettunen and colleagues (2007). Women were found to score higher in reward dependence and harm avoidance. There were no differences in novelty seeking or in persistence. The sex difference in reward dependence was significantly smaller in Asian studies, the difference in harm avoidance was found in all studies involved.

Two most important older personality models built on factor analysis are the three factor model of Hans J. Eysenck and the 16 factor model of Raymond B. Cattell. A meta-analysis of gender differences in Eysenck's extraversion, neuroticism and psychoticism was performed by Lynn and Martin (1997) in 37 nations. Women of all comprised nations scored higher than men in neuroticism and men obtained higher mean scores than women in psychoticism in 34 countries and in extraversion in 30 countries.

According to my knowledge, a meta-analysis of gender differences in Cattell's 16 personality factor model has never been performed. Cattell and colleagues (1992) mention factors which are consistently and substantially sex-different among different cultures and subjects' ages: dominance (E), protension (L, vigilance, mistrust), and ego strength (C, emotional stability) show a male advantage and affectothymia (A, warmth), premsia (I, tender-mindedness), guilt proneness (O, apprehension), and ergic tension (Q4, tension) show a female advantage.

Other reviews and meta-analyses included studies using different methods of data collection and different personality models. For example, Maccoby and Jacklin (1974) identified in their review based on results of personality questionnaires and behavioral tests a number of temperament differences between men and women. According to them, men are more assertive (dominant), aggressive and less anxious than women. Later studies largely relied on the meta-analytic approach: Eagly and Steffen (1986) and Hyde (1984) found higher aggressiveness in men. Cohn (1991) found evidence for an ontogenetically earlier maturity in ego development in women. Hall (1984) found higher anxiety and a lower level of internal locus of control in women, but did not confirm any difference in assertiveness. (The theory of locus of control is based on differentiation between subjects who report having their life events under their control, i.e. internal locus of control, and subjects who are convinced that events in their life are out of their control, i.e. external locus of control; Sdorow 1990).

Finally, Feingold (1994) performed a meta-analysis of studies included earlier in the review of Maccoby and Jacklin (1974), repeated the meta-analysis of Hall (1984) with more recent studies and compared all three meta-analyses. He confirmed higher scores of assertiveness and lower anxiety in men. Higher assertiveness values in men were, however, predominantly apparent in self-rating scales, and higher anxiety in women was found in tests of general anxiety, but not social anxiety. The difference in locus of control was not consistent. Men had also higher scores of self-esteem, but the difference was very small.

Further, Feingold (1994) compiled norms of dozens psychological questionnaires. Scales of these questionnaires were categorized according to 30 "Big Five" facets from the NEO-PI. Nine of these traits most often measured by comprised questionnaires were meta-analytically processed. These traits were: anxiety (including also neuroticism, and the reversal of emotional stability), impulsiveness (including also self-control, caution), gregariousness (sociability, extraversion, affiliation), assertiveness (dominance, superiority), activity (liveliness, viability, persistence), ideas (cognitive factors relating to creative thinking, reflection, comprehension and self-perception), trust (tolerance, personal relations), tender-mindedness (sensitiveness, care, empathy) and order. Men scored higher in assertiveness and women scored higher in anxiety, gregariousness, trust and tender-mindedness. These differences were consistent for distinct age, national and educational groups and for different years of norm origins.

2.2. Gender differences in Toxoplasma*-induced personality changes*

Women infected by toxoplasmosis compared to uninfected women were repeatedly found to score higher in warmth and somewhat higher in conscientiousness and lower in viability/mistrust. Men in contrast were found to score lower in conscientiousness, higher in viability/mistrust and higher in guilt proneness when infected (Flegr et al. 1996, 1999, 2000, Flegr and Havlíček 1999, Flegr and Hrdý 1994). Both infected women and men were found to score lower in novelty seeking (Skallová et al. 2005, Flegr et al. 2003, **Novotná et al. 2005**). Infected men were also found to have lower values in behaviorally assessed warmth, self-control and showed less clothes tidiness than uninfected men. Infected women typically showed a trend in the opposite direction being significant in the variable self-control assessed by small experiments (infected women scored higher than uninfected women) (**Lindová et al. 2006**).

On the basis of the above reviewed results, we could speculate that toxoplasmosis amplifies already present gender differences. The evidence is, however, equivocal. Although personality traits are indeed generally shifted towards the gender typical pole, there are important gender different traits (as assertiveness/social boldness, emotional stability/neuroticism or tender-mindedness) that are not shifted by toxoplasmosis at all. In contrast, toxoplasmosis influences the non-gender-different trait novelty seeking.

To better comprehend the mechanism of gender different effects of latent toxoplasmosis on personality, it is therefore necessary to explore more specific biological processes possibly underpinning the gross differences in personality.

3. Sex hormones

3.1. Endocrinological gender differences

Sex specific hormones produced by gonads are androgens in men and estrogens and gestagens in women. Although they are typical for males or females, respectively, they are present and maintain important functions in both sexes.

Estrogens are produced by ovaries, placenta, adrenal cortex and testes. While the secretion is similar for men and for women in the menstrual phase of the cycle (about 0.1 mg/day), it grows higher for women around ovulation (0.7) and predominantly at pregnancy (8-15). Estrogens promote the development of female secondary sex characteristics, such as breasts, and are also involved in the thickening of the endometrium and other aspects of regulating the menstrual cycle (Silbernagl and Despopoulos 1988). In males, estrogen is important for the

reproductive tract function (Hess 2003). The most efficient gestagenal hormone is progesterone. It is produced by ovaries, placenta, and male and female adrenal cortex. The concentration of progesterone in women in the proliferation phase is again similar to the concentration in men (around 0.3 ng/ml), but it increases in the secretion phase (up to 15 ng/ml) and further in pregnancy (up to 100-200 ng/ml). It has a number of physiological effects, often regulatory, especially of the effects of estrogen. Estrogen often induces a multiplication of progesterone receptors. The principal target organ of progesterone is uterus. Progesterone converts the endometrium to its secretory stage to prepare the uterus for implantation and affects the vaginal epithelium and cervical mucus. Furthermore, it has an important role in pregnancy (Silbernagl and Despopoulos 1988).

The primary and most well-known androgen is testosterone. Testosterone is primarily secreted in the testes of males and the ovaries of females although small amounts are secreted also by adrenal glands. The level of secretion by testes in men varies around 7 mg/day and by ovaries and adrenal cortex in women around 0.3 mg/day. The concentrations in plasma are about 7 ng/ml and 0.5 ng/ml in men and women, respectively (but see Table 1 for salivary values and circadian fluctuations). Next to the principal influence of testosterone on male sex differentiation, spermatogenesis and growth and function of genitals, prostate and seminal vesicles, it also controls pubertal changes in both genders (e.g. the adult-type body odour, increased oiliness of skin and hair, acne, appearance of pubic and axillary hair, bone maturation) and the development of pubertal male secondary sexual characteristics (growth of facial, chest, and pubic hair, increase of muscle strength and mass, deepening of voice, growth of Adam's apple, jaw, brow, chin, nose etc.). In men, testosterone is further necessary for normal libido, erection and fertilization (Silbernagl and Despopoulos 1988).

Table 1. Examples of testosterone concentrations of men and women found by selected authors.

authors	day time	age (mean)	mean women *(SD)*	mean men *(SD)*
Dabbs and Mohammed 1992	evening	21-30 (25)	1.4 ng/dl *(0,7)*	7.4 ng/dl *(4,0)*
Dabbs 1990	10 a.m.	17-49 (23)	1.8 ng/dl	10.6 ng/dl
Mazur et al. 1997	1 – 10 p.m.	17-35 (20)	2.1 – 2.6 ng/dl *(0.9 – 1.1)*	9.5 – 10 ng/dl *(2.6 – 2.8)*

From Kunstmann (2005)

There are also other sex differences in hormonal production, e.g. hormones involved in the menstrual cycle or pregnancy, but their effects are less important and therefore they will not be reviewed here.

Instead, to be able to say if these sex differences in steroid hormones could be related to the observed toxoplasmosis-induced shifts in personality, I will review evidence on sex hormone-personality associations.

3.2. Testosterone

3.2.1. Testosterone and dominance/aggression in males

Research on the relationship of hormones and personality is mostly focused on testosterone and aggression and dominance in men. The association of testosterone with aggressiveness was found to be small but present by a few meta-analytic studies. Archer and colleagues (1998) meta-analyzed 18 studies and found a moderate correlation of r=0.20 between testosterone and aggression. Book and colleagues (2001) found a smaller association

of r=0.14 in a meta-analysis of 45 studies. Finally, Archer and colleagues (2005) criticized and reanalyzed the data of Book and colleagues and obtained an even smaller correlation of r=0.08. Slightly better results were obtained including only studies using young subjects and behavioral measures of aggression (and females: see below). Injection of testosterone induced a clear increase of aggressive behavior in only 2 out of 11 studies reviewed by Archer (2006). The author explains the lack of more positive findings with a high inconsistency in the studies, mainly in the aggression measures. Authors of other reviews on this topic conclude that administration of testosterone to people does usually not remarkably change their behavior (Mazur and Booth 1998, Zitzmann and Nieschlag 2001). Recently, there has been at least one additional study proving both the effect of testosterone on aggression and aggressive cues on testosterone levels: Klinesmith and her colleagues (2006) showed that testosterone levels increase in response to aggressive cues (interaction with a gun) and subjects who have been interacting with the gun showed more aggressive behavior (put more chili into a drink prepared for another person). Importantly, changes in testosterone partially mediated the effects of interacting with the gun on this aggressive behavior.

There is a more consistent association of testosterone with dominance (and related measures of leadership, toughness, personalized power, and aggressive dominance). Archer (2006) found the mean weighed r value of 13 relevant studies = 0.124 which after exclusion of two largest outliers improved to 0.27. There has been since then at least one additional study proving the association of basal testosterone with questionnaire dominance (Sellers et al. 2007) and another study which found testosterone level in a stressful situation to be positively correlated with peer-rated leadership (Kerschbaum et al. 2006). Moreover, a study by Josephs and colleagues (2006) has shown that individuals high in testosterone display behaviors intended to achieve high status and individuals low in testosterone similarly intend to maintain low status.

In contrast to the somewhat unconvincing evidence supporting the role of testosterone as the cause of dominance and aggressiveness (e.g. absence of behavioral change after administration of testosterone), there is strong evidence that testosterone responds to changes in status or, in the words of Archer (2006), to challenge of inter-male competition: it increases concentrations both before and after winning a competition and after a status evaluation, and falls after losing a competition and after status devaluation (Mazur and Booth 1998). A meta-analysis performed by Archer (2006) showed that testosterone slightly rises before sport or other competitions and further during the competitions, and it rises more in winners than in losers. The increase during the competition is particularly typical for sports, whereas the difference in rise between winners and losers is more pronounced for contrived competitions involving no activity.

In a review from 1998 Mazur and Booth conclude that high testosterone in adulthood (the same not being true for perinatal period and puberty where testosterone has primarily long-term organizational effects) encourages dominant behavior intended to achieve or maintain high status. This tendency is, according to their view, sometimes, but not necessarily, associated with aggression. In subordinated individuals, tendency to express dominance is often manifested as a greater frequency of breaking norms or laws. (Most behavioral studies of this phenomenon were done in prison where breaking laws was regarded as rebellious, antisocial or even criminal.) Moreover, they support a reciprocal model that implies feedback between dominance and testosterone, each reinforcing the other. Archer (2006) advocates in a more recent review the link with aggressiveness and suggests that testosterone is correlated with aggressive dominance, i.e. dominance based on direct (physically-based) contests. His argument is based on the challenge hypothesis that applied to humans who show high cooperativeness among men and male parental care says that testosterone will be relatively low in adult males, but rise during challenges relevant to reproduction. The rise of

testosterone in challenge situations as dominance disputes, mate guarding etc. will in turn facilitate aggression. Furthermore, the result of the cumulative effects of successful challenges should be that aggressive dominance will be positively correlated with testosterone levels.

A somewhat different interpretation of testosterone-aggression/dominance studies is given by Zitzmann and Nieschlag (2001). They point out different results of studies performed in prison (usually obtaining relatively strong correlations of testosterone with some form of aggression) and on normal population (low correlations with self-reported aggression), and hypothesize that people exhibit violent behavior in response to external (e.g. socioeconomic) factors also inducing testosterone secretion. In other words, environment is suggested to provoke both aggressive responses and changes in hormonal secretion patterns. Considering dominance and status, they similarly emphasize the role of previous experiences that elicit different activation pathways. This can be documented by a study of chess players where winners/winners-to-be had higher testosterone levels both after and before competition (Mazur et al. 1992).

These three leading theories by Archer, Mazur and Booth, and Zitzmann and Nieschlag, although seemingly contradictory, all illustrate that it is not merely the behavioral display (e.g., aggressive act) that is associated with increased testosterone, but rather the situation provoking such behavior. Key words describing such situation seem to be challenge, competition and status.

3.2.2. Testosterone and dominance/aggression in females

Literature on personality correlates of testosterone in women is more scant, but the results seem to show a similar (slightly inconsistent) link with dominance and aggression as in men. High-testosterone female prisoners were found to commit more unprovoked violence (Dabbs et al. 1988) and display more aggressively dominant behavior while in prison (Dabbs and Hargrove 1996). One study found a positive correlation between self-reported aggression and testosterone (von der Pahlen et al. 2002). Two studies found a correlation between testosterone and self-reported dominance in women (Grant and France 2001, Udry and Talbert 1988) and two other studies showed higher testosterone in women of higher occupational status (Purifoy and Koopmans 1979, Baucom et al. 1985). Cashdan (1995) found a positive relationship between testosterone and the speculative dominance display absence of smile among female roommates. Confusingly, testosterone correlated negatively with status of these women judged by peer assessments, but positively with the women's self assessment of their own status. A similar finding was obtained by Kerschbaum and colleagues (2006): women with higher stress-induced testosterone levels were regarded not as leaders, but as likeable individuals. Gladue (1991) found a positive correlation between scores in the Aggression Inventory and testosterone in men, but a negative one in women. A study by van Honk and colleagues (1999) found association between testosterone and attention to masked angry faces both in men and women. When testosterone was administered to young women, they showed heightened defence reflexes to angry faces. This behaviour was interpreted as facilitating dominant behaviour or decreasing fear by testosterone. Schultheiss and colleagues (2003) found that persons with high basal testosterone levels showed a tendency to view a situation as a way to assert power or dominance over others. Accordingly, Cashdan (2003) reported a tendency of low testosterone women “not to act on their competitive feelings”, i.e. not to perform any aggressive act (e.g. verbal dispute) when experiencing competitive feelings. The same was true for both sexes, although it was stronger for men. According to only one available study (Bateup et al. 2002) women are also responsive to competition. In this study, testosterone levels were elevated before match in female rugby players, and were

correlated with bonding, aggressiveness and focus. Interestingly, although post-game levels were also increased, they were unrelated to winning or losing.

The meta-analysis by Archer et al. (2005) found the association between testosterone and aggression to be stronger for women than for men (r=0.13 and 0.08, respectively). Similarly, after excluding the confusing study of Cashdan (1995), the remaining three studies on female subjects included in the meta-analysis of the testosterone-dominance association performed by Archer (2006) produced a mean weighted r value of 0.28, which is significantly higher than the one for the male samples (r=0.12).

3.2.3. Testosterone and other personality traits

There are only a few studies linking testosterone to other personality traits but dominance/aggressiveness. Sellers and colleagues (2007) found women, but not men, with high testosterone levels to score higher in conscientiousness. No other Big Five dimension in either women or men correlated significantly with testosterone. Olweus and colleagues (1980) correlated testosterone levels of male subjects with 29 different scales, most of them measuring aggressiveness, but also including measures of vigorousness, tempo (Thurstone temperament schedule), extraversion, psychoticism (both from EPQ), anxiety (from Multi-Component Anxiety Inventory and a situation-oriented questionnaire) and socialization (from CPI). None of these additional scales showed a significant correlation with testosterone. Harris and colleagues (1996) found testosterone to be not only positively related to aggressiveness, but also negatively to pro-social personality (altruism, empathy, nurturance). Lower peer-rated sympathy of subjects with higher testosterone levels was found in the study of Kerschbaum and colleagues (2006) for men, but the opposite was found for women. This same study found a significant positive correlation between testosterone and sensation seeking scales in women, but not in men. Aluja and Torrubia (2004) found testosterone levels in men to be positively related to sensation seeking. Gerra and colleagues (1999) studied endocrinological correlates of novelty seeking (from TCI) and sensation seeking on a Visual Analog Scale in males. They found a positive correlation of these personality scales with plasma norepinephrine, testosterone and prolactin levels and suggested that norepinephrine mediates the relationship of the other hormones (belonging to the downstream cascade of norepinephrine dependent hormones) with these personality traits. Several studies linked testosterone with negative affect. Dabbs and colleagues (2003), for example, showed that treatment with testosterone reduces positive affect of both women and men. Similarly, in the study using masked fearful faces mentioned above van Honk and colleagues (1999) found salivary testosterone to be significantly related to mood (i.e., anger and tension) in both sexes. On the other hand, in rodent models it was shown repeatedly that testosterone reduces anxiety (see review in Touflexis et al. 2006).

3.2.4. Could testosterone be responsible for observed personality changes in* Toxoplasma*-infected subjects?

Testosterone has been found to be significantly different in *Toxoplasma*-infected subjects compared to *Toxoplasma*-uninfected subjects (**Flegr et al. submitted a**). In the next part of the text, I will explore whether traits associated with testosterone correspond to changes in personality traits induced by *Toxoplasma*. The effect of *Toxoplasma* on testosterone is sex specific: infected women have lower testosterone levels than uninfected women, and infected men have higher testosterone levels than uninfected women (**Flegr et al. submitted a**). This finding is further supported by increased perceived dominance and masculinity, (**Hodková et al. 2007**), greater body height and lower 2D:4D ratio (**Flegr et al. 2005**) in infected compared

to uninfected men; all of these traits are supposed to be related to testosterone levels. We could therefore expect the occurrence of changes in the personality traits dominance/aggressiveness and related behavioural measures in *Toxoplasma*-infected subjects. A change in dominance has, however, never been observed in *Toxoplasma*-infected subjects, although Cattell's 16 PF questionnaire includes such a scale. On the other hand, dominance has not always shown clear correlation with testosterone in previous studies and this particular 16PF scale need not be suitable to detect testosterone-dependent dominance. Our preliminary results using an additional dominance self-report scale, however, also indicate the absence of a shift in dominance of infected subjects. Moreover, none of the personality traits shifted by toxoplasmosis seems to be related to dominance/aggressiveness.

Changes in the questionnaire traits warmth and vigilance/trust (Flegr et al. 1996, 1999, 2000) and the behaviourally assessed trait relationships (**Lindová et al. 2006**) induced by toxoplasmosis correspond to the finding of Harris and colleagues (1996) of the negative effect of testosterone on pro-social traits. In concord with Harris's et al. finding, *Toxoplasma*-infected women who show decreased levels of testosterone score higher in pro-social scales, whereas *Toxoplasma*-infected men who show elevated testosterone levels score lower in pro-social scales.

Although there are some indices about a possible association of novelty seeking (found lower in both infected women: Skallová et al. 2005, and men: Flegr et al. 2003, **Novotná et al. 2005**) with testosterone, this association is not well supported by evidence and seems to be mediated by other hormonal changes (see above). The observed changes of the questionnaire trait conscientiousness (Flegr et al. 1996, 1999, Flegr and Havlíček 1999), and the behaviourally assessed traits self-control and clothes tidiness (**Lindová et al. 2006**) contradict to the expectation based on the single finding of Sellers and colleagues (2007). Sellers and colleagues found increased conscientiousness in women with high levels of testosterone. Although *Toxoplasma*-infected women show *decreased* levels of testosterone, they score repeatedly higher in conscientiousness and related measures of self-control and clothes tidiness.

A result that could be viewed as partly in accord with the testosterone-based expectation is the finding of *Toxoplasma*-induced shifts in allocating money in experimental games Dictator Game and Trust Game. Infected men were found to allocate less money to opponents than uninfected men, while infected women were found to give less money in the Dictator Game, but behave more pro-socially, i.e. allocate more money in the Trust Game than uninfected women. Increased pro-sociality in women could be linked to lower testosterone levels (see Harris et al. 1996). Moreover, it has been shown that giving and helping in general is dependent on subject's mood (for a review, see **Lindová et al. submitted**). Hypothetically, reduced giving in infected men could have been caused by increased levels of testosterone inducing more negative affect.

In summary, although testosterone might be responsible for some observed gender different personality shifts, it seems obvious that one or more additional biological factors must be responsible for the personality- and behavioural shifts observed in *Toxoplasma*-infected subjects.

3.3. Female steroid hormones

3.3.1. Female steroid hormones and anxiety/depressiveness

Female steroid hormones are less frequently studied in relation to personality than testosterone which is most probably due to the fact that they highly fluctuate during the menstrual cycle and women's life span. However, they are considered to belong to important

biological causes of depressiveness and anxiety. There is evidence for both anxiolytic and anxiogenic effects of estrogens, depending e.g. on age and the stage of the reproductive cycle. In a review Arpels (1996) points out that women complaining of premenstrual symptom, postpartum blues, the perimenopausal transition and menopause all share the same symptoms (e.g. depression, sleep disturbance, irritability, anxiety etc.) and suggests that estrogen levels fallen bellow the minimum brain estrogen requirement are responsible for the symptoms in each of these cases. Similarly, Steiner and Dunn (1996) and Dunn and Steiner (2000) propose a biological susceptibility hypothesis linking mood disorders with the vulnerable neuroendocrine rhythmicity related to female reproduction.

In postmenopausal women, estrogen replacement therapy has been successfully used to improve mood, feelings of general well being, and increase activity levels (e.g., Nielsen et al. 2006). Also estrogen therapy of depressed, inpatient women significantly attenuated the depressive symptoms (Klaiber et al. 1979). On the other hand, female precedence in depression compared to men, starting in pubescence (for a review see Nolen-Hoeksema 1987), and decrease of self-reported depressive symptoms after menopause (Frieze et al. 1978) indicate a positive relationship between estrogen and anxiety/depressiveness. This is supported by the study reporting rapid increase of estrogen levels to be related to depressive affect and impulsiveness in pubertal girls (Warren and Brooks-Gunn 1989). Still other researchers did not observe any correlation between anxiety and depression and estrogen or progesterone (e.g., Hsiao et al. 2004, Schmidt et al. 1994).

Schmidt and colleagues (1998) studied response of women with and without premenstrual symptoms on ovarian suppression and following administration of estrogen and progesterone. Women with the premenstrual symptom had a significant decrease of symptoms after ovarian suppression and a recurrence of symptoms after administration of hormones. Women without premenstrual syndrome had no changes in mood in either situation. Authors conclude that the occurrence of symptoms in women with premenstrual syndrome represents an abnormal response to normal hormonal changes.

Equivocality also dominates the etiology of post-partum depressiveness. The study by Wieck and colleagues (1991) associated the onset of postpartum psychosis with a sharp fall of estrogen levels. On the other hand, rapid fall of progesterone after delivery correlated significantly with development of postpartum blues in the study by Harris and colleagues (1994), but this was not confirmed by Heinrich et al. (1994). Evidently, more research on this phenomenon is needed.

Slightly inconsistent evidence is provided also by animal studies. Anxiolytic effects of estradiol measured in the elevated plus maze were observed during rodent estrogen-high proestrus (but only under low light intensity, which is hypothesized by the authors to have anxiolytic effects itself; under high light intensity, this effect was rather reversed: Mora et al. 1996), or after exogenous hormone injections to ovariectomized female rats (Koss et al. 2004). However, the same study also identified an anxiogenic effect of estradiol injection on exploring a novel, same gender partner. A complex study indicating anxiogenic effects of estrogens was performed by Morgan and Pfaff (2001) on mice. Estradiol benzoate injected to ovariectomized mice caused decreased time spent in the centre and smaller overall activity in the open field test, decreased activity and less transitions in the light-dark transition test, entering less arms in the elevated plus maze, greater frequency of freezing in conditioned fear learning, and *greater* activity in the home cage running wheal. The authors concluded that estrogen treatment heightened fear responses in a range of fear and anxiety-provoking situations, but increased activity in the safer running wheal. Similarly, 17β-estradiol treatment decreased the locomotion frequency of rats in open field (Palermo-Neto and Dorce 1990) and estradiol injected to ovariectomized rats decreased open-arm exploration in the elevated plus maze under high light conditions, whereas progesterone had an opposite effect. Moreover,

retention of passive avoidance, another indicator of anxiety, was inhibited after both estradiol and progesterone injection (Mora and colleagues 1996).

Some authors explain the dichotomy of the estrogen effect by the existence of two distinct receptor systems mediating the actions of estrogen: estrogen receptor α and estrogen receptor β. Lund and colleagues (2005) performed behavioral tests with female and male rats treated with diarylpropionitrile - a selective agonist of the estrogen receptor β - or propyl-pyrazol-triol – a selective agonist of estrogen receptor α - or 17β-estradiol after gonadectomy. In the elevated plus maze, female rats treated with diarylpropionitrile had more open arm entries, more rears, less fecal boli, more head dips, and spent longer time on open arms and less time grooming than rats treated with propyl-pyrazol-triol, 17β-estradiol or controls. Similarly, injection of diarylpropionitrile reduced anxiety-related behaviour of females in the open field. Injection of propyl-pyrazol-triol tended to have opposite effects and estradiol-treated female rats showed intermediate behavior. Accordingly, male rats treated with diarylpropionitrile showed more open arm entries, more rears and head dips and spent longer time on open arms of the plus maze than controls. The importance of estrogen receptor β, predominantly in hippocampus, in the anxiolytic effect of estrogen was recently confirmed by numerous studies by Walf and Frye (e.g., 2007).

3.3.2. Female steroid hormones and aggression

Some studies were also looking at the relationship of estrogen with aggressiveness. Gladue (1991) took blood samples of men and women in early follicular phase. He found estradiol to be positively correlated to self-reported aggressiveness in men, but negatively in women. Cashdan (2003) did not find any correlation between aggressive tactic (expressing aggression physically or verbally versus not expressing competitive feelings at all) and estradiol levels in women in early follicular phase, but women with high estradiol levels reported more athletic competitions than women with low estradiol levels. On the other hand, in men estrogens were used to suppress violent sexual aggression (Field and Williams 1970) and they were repeatedly shown to attenuate dementia-related physical aggression in elderly men (e.g., Kyomen et al. 1999). Eriksson and colleagues (2003) found plasma estradiol to be negatively correlated with testosterone-related physical, violent aggression in a sample of former alcohol users and positively associated with psychological aggression and emotional negotiation in conflict situations in both alcoholics and controls.

In mice, estrogen receptor-β gene disruption has been shown to increase aggressive behavior of males (Nomura et al. 2006).

To conclude, more numerous and more detailed studies are needed to shed light on the association of estrogens with aggression.

3.3.3. Female steroid hormones and the "feminine" personality

Although a direct relationship of female steroid hormones with personality traits is a largely understudied phenomenon, we can expect female hormones (in addition to androgens), on the basis of the above mentioned indirect indices, to be responsible for a lot of gender differences in personality. Indirect evidence for the link between female steroid hormones and personality is also provided by the study **of Lindová et al. (in press)**. This study found women with more female-typical personality traits (i.e., lower emotional stability, lower social boldness and higher privateness) to have a higher second to fourth digit ratio (2D:4D) than women with a less feminine personality. Although the sexually dimorphic trait 2D:4D is usually considered a marker of prenatal testosterone rather than female steroids, findings of a positive correlation of 2D:4D with female steroid hormones (e.g., FSH, LH, progesterone,

less so estradiol) seem to be slightly more consistent than respective evidence of a negative correlation with testosterone (see Table 2 and 3). It is likely that both male and female hormones are important precursors of 2D:4D, with the estrogen/testosterone ratio affecting the establishment of the sexually dimorphic 2D:4D prenatally and secondly the female steroid hormones/androgens ratio influencing the later faster increase of 2D:4D in girls than boys in puberty (see **Lindová et al. in press**, McIntyre et al. 2005). Therefore, the pubertal rise of hormones in females could be the proximal cause of the development of some feminine personality traits. Among these, we can propose anxiety (or emotional stability) to be the most prominent one, since there is evidence of its relation to female steroids from the studies of female depressiveness and rodent anxious behavior, and it also appears among the prominent correlates with 2D:4D (see review in **Lindová et al. in press**).

Last but not least, estrogens and other female steroid hormones are critical for the onset of maternal behaviour (Rosenblatt 1994). I suggest that since e.g. sensitiveness, empathy or helping are important components of maternal behaviour, these "feminine" traits are also likely to be influenced by female hormones. No relevant work on this topic is, however, known to me.

Table 2. Correlations of testosterone levels and 2D:4D in most available studies

Men testosterone right 2D:4D	N	r	**Men testosterone left 2D:4D**	N	r
Manning et al. 1998	58	**- 0.29c**	Manning et al. 1998	58	**- 0.23c**
Neave et al. 2003	48	- 0.05	Neave et al. 2003	48	+ 0.03
Manning et al. 2004	94	- 0.08	Manning et al. 2004	94	+ 0.16
Benderlioglu a Nelson 2004	97	- 0.10	Benderlioglu a Nelson 2004	97	+ 0.08
Roney a Maestripieri 2004	39	+ 0.20			
Kempel et al. 2005	17	+ 0.03	Kempel et al. 2005	17	+ 0.11
Bang et al. 2005	360	- 0.03			
Bang et al. 2005	360	+0.03			
Falter et al. 2006	35	- 0.21			
Hönekopp et al. 2007	102	+ 0.04	Hönekopp et al. 2007	102	+ 0.10
Hönekopp et al. 2007	102	+ 0.08	Hönekopp et al. 2007	102	+ 0.11
Visnapuu and Jürimäe in press	*26*	*-0.10*	*both hands*		
Women testosterone right 2D:4D			**Women testosterone left 2D:4D**		
Benderlioglu a Nelson 2004	77	+ 0.03	Benderlioglu a Nelson 2004	77	+ 0.01
van Anders et al. 2005	75	- 0.10	van Anders et al. 2005	75	+ 0.04
Kallai et al. 2005	40	- 0.16	Kallai et al. 2005	40	- 0.02
Falter et al. 2006	34	- 0.20			
Kempel et al. 2005	23	- 0.22	Kempel et al. 2005	23	- 0.02
van Anders et al. 2005	18	**+ 0.56**	van Anders et al. 2005	18	+ 0.11
Hönekopp et al. 2007	64	+ 0.11	Hönekopp et al. 2007	64	+ 0.10

Table 3 Correlations of female hormone levels and 2D:4D in most available studies

Men FSH right	N	r	**Men FSH left**	N	r
Bang et al. 2005	360	+0.12			
Manning et al. 2004	43	**+0.39c**	Manning et al. 2004	43	**+0.33c**
Women FSH right			**Women FSH left**		
Hönekopp et al. 2007	64	+0.11	Hönekopp et al. 2007	64	-0.01
Men LH right			**Men LH left**		
Bang et al. 2005	360	+0.04			
Manning et al. 2004	43	**+0.50c**	Manning et al. 2004	43	**+0.59c**
Women LH right			**Women LH left**		
Hönekopp et al. 2007	64	+0.12	Hönekopp et al. 2007	64	-0.03
Manning et al. 1998	*58 men 40 women*	*+0.10*	*Manning et al. 1998*	*58 men 40 women*	*+0,07*
Men 17β-estradiol right			**Men 17β-estradiol left**		
Hönekopp et al. 2007	102	+0.04	Hönekopp et al. 2007	102	+0.12
Women 17β-estradiol right			**Women 17β-estradiol left**		
Hönekopp et al. 2007	64	-0.01	Hönekopp et al. 2007	64	+0.07
Visnapuu and Jürimäe in press	*29*	***-0.47***	*both hands*		
Manning et al. 1998	*58 men 40 women*	*+0.16*	*Manning et al. 1998*	*58 men 40 women*	*+0,08*
Women progesteron right			**Women progesteron left**		
Hönekopp et al. 2007	64	+0.20	Hönekopp et al. 2007	64	+0.16

From Hönekopp et al. 2007 (Table also includes unpublished data as cited by these authors, for full citations see Hönekopp et al. 2007) c denotes clinical samples

3.3.4. Could female steroid hormones be responsible for observed personality changes in Toxoplasma*-infected subjects?*

As mentioned above, changes observed in *Toxoplasma*-infected subjects do not match gender differences in personality very closely. Specifically, a shift in the consistently gender different trait emotional stability has never been observed. As emotionally stability is also the best candidate for a personality trait influenced by female hormones (see above), we can hardly expect *Toxoplasma* to affect personality through regulation of female steroid levels.

However, female hormones might still play a role in the establishment of gender differences of personality changes induced by toxoplasmosis, namely through their neuroprotective role, as will be discussed below.

4. Immunological mechanisms

4.1. Sex differences in the immunological response to Toxoplasma

In contrast to almost all studied protozoa where males are more susceptible to infection than females (Klein, 2004), the opposite is true for *Toxoplasma*. Mortality rates are higher in female than in male mice (Roberts et al. 1995, Kittas et al. 1984) and female mice develop more severe brain inflammation than male mice following infection (Henry and Beverly 1976). Several studies point to the role of female hormones: Susceptibility to *Toxoplasma*-infection was decreased after ovariectomy and increased after estrogen treatment in mice (Pung and Luster 1986, Kittas and Henry 1978, 1980). Pregnant mice infected with *Toxoplasma* were observed to have increased susceptibility to infection (Luft and Remington 1982), and more specifically reduced cytotoxic ability of peritoneal natural killer (NK) cells (Luft and Remington 1984) and decreased serum gamma interferon (IFN-γ) production (Shirahata et al. 1992). (Natural killers together with macrophages are thought to be the main factors responsible for early immune reaction of *Toxoplasma*. Following contact with the parasite, macrophages produce interleukin(IL)-12, which, together with IL-1β, IL-18, and tumor necrosis factor alpha (TNF-α), stimulates NK cells to produce IFN-γ. TNF-α and IFN-γ induce the expression of iNOS, which results in the production of nitric oxide with *Toxoplasma*-killing potential (Roberts et al. 2001).)

In humans, women show more numerous cases of *Toxoplasma*-associated lymphadenopathy than men, but only after 25 years of their age, whereas men show more lymphadenopathy in childhood age up to 15 years (Beverly et al. 1976). Women were also found to have a higher incidence of toxoplasmic encephalitis during AIDS by Phillips and colleagues (1994), but this was not confirmed by other studies (Grant et al. 1994, Jougla et al. 1996, Nissapatorn et al. 2004). Pregnant women who transmit *Toxoplasma* to fetus have low levels of circulating NK cells (Nigro et al. 1999).

Walker and colleagues (1997) argue that the sex difference in susceptibility to *Toxoplasma*-infection is caused by sex-hormone-mediated advanced innate immune response in males. In their study, male lymphocyte deficient (SCID) mice had lower mortality rates, lower number of brain cysts, less necrotic lesions, and more rapidly peaking circulating levels of cytokines, namely IL-12 and IFN-γ, than female SCID mice. Roberts and colleagues (1995) report sex differences in both the innate and adaptive immune responses. Male mice produced more TNF-α during the early stages of infection, and had an earlier peak of IFN-γ than females and females additionally inhibited activity of IFN-γ with the simultaneous production of interleukin-10. (IFN-γ together with IL-2 is produced by CD4+ Th1 cells, and causes expansion of CD8+ T lymphocytes which have cytotoxic effect on *Toxoplasma*; Roberts et al. 2001.)

4.2. Neuroprotective effect of estrogens

Estrogens are considered to have an important protective role in neurodegenerative illnesses like Alzheimer's disease and Parkinson's disease, ameliorate schizophrenic symptomatology, and are likely to be responsible for the later onset of schizophrenia in women (Lindamer et al. 1997). To mention a few direct observations of this effect: Estrogen levels were repeatedly found to be diminished in women with schizophrenia (e.g., Oades and Schepker 1994, Riecher-Rossler et al. 1994, 1998), and estrogen therapy leaded to clear improvement of dementia signs and symptoms in elderly subjects (Kyomen et al. 1999, 2002).

In a recent review Pozzi and colleagues (2006) explain the beneficial effects of estrogens by their neurotrophic and antiapoptotic functions and anti-inflammatory potential: Estradiol

increases neurone viability, differentiation, neurite outgrowth, and spine density and controls the ability of neurons to extend neurites and to form synaptic connections via dendritic spines (Maggi et al. 2004). Further, it protects neurons against cell apoptosis by regulating the genetic expression of anti- and proapoptotic proteins and later regulation of the activity of these proteins (see Pozzi et al. 2006).

The anti-inflammatory properties of estrogens have been proven on several levels of the immune response. Estrogen treatment of mice leaded to a reduction of in vivo natural killer (NK) cell activity (androgen treatment had no effect) (Seaman et al. 1978, Seaman and Gindhart 1979) and suppressed killing of tumours (Hanna and Schneider 1983, Baral et al. 1995, Ferguson and McDonald 1985, Hou and Zheng 1988, Nilsson and Carlstein 1994), although one study showed that this was true only for long-term administration, with initial treatment leading to enhancement of NK killing activity (Screpanti et al. 1987). Accordingly, patients with ovarian tumours, endometriosis, or mastopathy have elevated estrogen levels and low NK cell cytotoxicity (Roszkowski et al. 1993, 1997, Provinciali et al. 1995).

Macrophages are also regulated by estrogens, both in their effector functions (upregulation of phagocytosis, and production of reactive oxygen intermediates, downregulation of reactive nitrogen intermediates, Chao et al. 1994) and in their afferent functions: estradiol was found to downregulate the production of IL-1α, IL-6, and TNF-α after stimulation with lipopolysacharides (Deshpande et al. 1997), as well as the expression of TNF-α mRNA after phorbol ester stimulation (Shanker et al. 1994). However, other researchers reported unchanged TNF-α mRNA expression (Miller and Hunt 1998) or TNF-α production after administration of estrogen in vitro (Zuckerman et al. 1995). Moreover, increased serum TNF-α was found in estrogen treated mice with endotoxemia (Zuckerman et al. 1995), while in the same estrogen treated mice, IL-6 levels were reduced compared to controls. The inhibiting effect of 17β-estradiol in macrophages was reported to proceed via inhibition of cytoplasmic transport of a transcription factor for inflammatory genes (NF-κB) induced by inflammatory stimuli (Ghisletti et al. 2005).

In the brain, the activity of the immunocompetent macrophage-like cells microglia is of great importance. Microglia hyperactivation and their production of neurotoxins is associated with many types of brain injury (e.g. degenerative illnesses). Estrogen decreased the lipopolysacharid-induced production of nitrogen intermediates, TNF-α, neurotoxic prostaglandins and other inflammatory mediators by microglia (Baker et al. 2004, Vegeto et al. 2006).

Further, estrogen enhanced histamine and serotonin release from mast cells (Pang et al. 1995, Vliagoftis et al. 1992, Spanos et al. 1996), and increased degranulation (Silva et al. 1997) and adhesion to mucosal microvascular endothelial cells (Hamano et al. 1998) of human blood esinophils. Estrogen also repressed the adhesion of leukocytes (Santizo et al. 2000).

Finally estrogens, as well as testosterone, were repeatedly found to be able to directly affect the development, maturation and activation of T and B lymphocytes (DaSilva 1999, Seiki and Sakabe 1997). More specifically, estrogen and testosterone receptors are found both intracellularly and in the membrane of CD4+ and CD8+ T lymphocytes (Benten et al. 1998, 1999). During pregnancy, number of CD4+ and CD8+ T cells is reduced (Seiki and Sakabe 1997). Similarly, estrogen was found to deplete populations of these cells in the thymus (Rijhsinghani et al. 1996) and other tissues (Boll and Reimann 1996). Some cytokines as IL-2 and IFN-γ are downregulated, whereas others as IL-4, IL-5 and IL-10 are upregulated by estrogen (Salem et al. 2000, Ahmed et al. 1996, Wang et al. 1993). The association with IFN-γ is equivocal as other researchers observed increased IFN-γ mRNA transcription after estrogen stimulation (Fox et al. 1991) and increased IFN-γ production of antigen- and anti-CD3-stimulated CD4+ T cells after estrogen treatment (Correale et al. 1998, Gilmore et al.

1997). Estrogen treatment of animals with subsequently induced CNS inflammation downregulated the expression of chemokines and their receptors (Matsuda et al. 2001; Matejuk et al. 2001) and of apolipoprotein E (Horsburgh et al. 2002).

Other hormones, as progesterone or testosterone, have also been shown to modulate immunity (see e.g. Roberts et al. 2001). Their effects are however, not as strong and well documented as the ones of estrogens and will not be reviewed here.

4.3. Could estrogens be responsible for observed personality changes in Toxoplasma-*infected subjects?*

I propose that female hormones might play a role in the establishment of gender differences of personality changes induced by toxoplasmosis through their neuroprotective role. This argument is based on indices of the possibility that latent toxoplasmosis, although not manifesting itself by clear symptoms, causes inflammations in the brain tissue.

A first line of indirect evidence is presented by reports of increased dopamine levels (Stibbs 1985) and dopamine-related behavioral changes in infected rodents (as represented e.g. by results from our laboratory showing a) impaired learning and spatial memory and higher activity in running wheels which was interpreted by the authors as an impaired ability to recognize novel stimuli possibly caused by high dopamine concentration-induced lower sensitivity to dopaminergic activity in the striatum: Hodková et al. 2007; b) decreased locomotion in the open field in males and females, increased exploration in the holeboard test in females and a dopamine uptake inhibitor-induced suppression of holeboard-exploration in infected males: Skallová et al. 2006) and lower scores of dopamine-associated trait novelty seeking in infected men and women (Skallová et al. 2005, Flegr et al. 2003, **Novotná et al. 2005**). The association of novelty seeking with the background level of dopamine has been observed several times (e.g., Cloninger 1998, Hansenne et al. 2002). Changes in dopamine levels could result from chronic activation of the immune system during latent toxoplasmosis, as dopamine has been shown to be influenced by cytokines engaged in inflammation processes (Alonso et al. 1993; Petitto et al. 1997). (Altered cytokine expression was observed in animals chronically infected with toxoplasmosis (Arsenijevic et al. 1997, Schluter et al. 1997, see also Denkers and Gazzinelli 1998, Cai et al. 2000).)

A second line of indirect evidence comprises research linking toxoplasmosis with schizophrenia (for a review see Torrey and Yolken, 2003). Schizophrenic patients have been observed to experience inflammatory events, which correlate positively with severity of disease (Korschenhausen et al. 1996, Cazzullo et al. 1998, Muller and Ackenheil 1995, Maes et al. 1995, Wilke et al. 1996). They were also found to have an increased number of monocytes, activated microglia and higher levels of cytokines (Wilke et al. 1996, Bayer et al. 1999).

The forthcoming onset of first schizophrenia episode manifests itself with specific emotional and personality changes. The relationship of schizophrenia and personality was first recognized by Hoch (1910) who linked development of schizophrenia with detached personality type. This personality dimension named schizoidea or schizoid personality appears in typologies of Bleuler (1924), Kraepelin (1919) or Kretschmer (1934) and is identifiable even in the later personality model of Cattell (1965) under sizothymia-affectothymia. Meehl (1962) identified four symptoms indicating liability to schizophrenia (i.e., schizotypy): the thought disorder cognitive slippage, and three personality and emotional characteristics, namely interpersonal aversiveness, anhedonia, and ambivalence. Anhedonia is the inability to experience positive feelings, and ambivalence is a simultaneous experience of contradicting emotions towards one object, idea or person. Detachment from social

relationships and a restricted or inadequate expression of emotions in interpersonal settings have remained broadly recognized as the predominant features of the premorbid schizophrenia personality and are also the key diagnostic criteria for the schizoid personality disorder (ICD 10).

Observed *Toxoplasma*-induced personality changes in men seem to relatively well correspond to schizoid personality. Lower factor A (i.e., sizothymia) means detachment from social relationships and flatness and dryness of emotionality, and is suggested to distinguish between schizoid and cyclical types among psychiatric patients (Cattell et al. 1992). Lower scores in factor A were observed by Flegr and Hrdý (1994). Although the difference between infected an uninfected men in factor A was not significant in a later study by Flegr and colleagues (1999) (however, with the *Toxoplasma*-gender interaction on factor A being significant), men scored significantly lower in the behavioral composite measure Relationships, which was constituted so as to closely match the questionnaire factor A in the later study by **Lindová and colleagues (2006**).

Less direct, but still interesting links can be found between the schizoid personality and other Cattell's factors, namely factor G (conscientiousness, superego strength) and factor L (mistrust, protension). Cattell and colleagues (1992) describe that factor G is similar to factor C (emotional stability) in that it contributes to "self-controlled behavior and regard for others, as opposed to emotional and impulsive behavior" (p. 88). "The difference lies in the fact that G+ also operates in a 'drive to do one's best,' i.e., in persistence (which is not characteristic of the almost phlegmatic C+ behavior)" (p. 89). Regard for others, and adequate emotionality which helps to perceive goals can be seen as clear opposites of the schizoid profile. High factor L is especially indicative for paranoia rather then general schizophrenia (Cattell et al. 1992). Paranoid schizophrenia is, however, the predominant type of schizophrenia in most societies (ICD 10). Men infected with *Toxoplasma* scored lower in factor G (Flegr and Hrdý 1994, Flegr et al. 1996, 1999) and higher in factor L (Flegr and Hrdý 1994, Flegr et al.1999) than uninfected men. In the study by **Lindová and colleagues (2006**), infected men reached lower scores in the behavioral variable Self Control (designed to match factor G and the similar factor Q3) as well as in the rated tidiness of clothes than uninfected men. In summary, there are interesting similarities between the personality profile of men infected by *Toxoplasma* and the premorbid schizophrenia personality or the schizoid personality disorder.

Women do not show any similar changes. In contrast, they seem to be shifted in the opposite direction. An absence of changes similar to those observed in men could be explained by the neuroprotection of estrogens. We can hypothesize that estrogens inhibit minute inflammatory processes of the brain tissue induced by the latent toxoplasmosis infection which are in men the cause of both "schizoid" personality changes and greater prevalence of schizophrenia among *Toxoplasma*-infected subjects. Due to the neuroprotective effect of female hormones, we should also expect an absence or at least reduction of the schizophrenia-*Toxoplasma* link in women.

However, as far as I know no differences between men and women in the toxoplasmosis-schizophrenia association have been reported. It is problematic though, to deduce the absence of a phenomenon from the lack of its evidence. Therefore, I conclude that we need more studies on toxoplasmosis among psychiatric patients reporting data for men and women separately.

A second and perhaps more important objection to the above presented argument is that in fact, we do not observe an absence of personality changes in infected women, but rather an occurrence of shifts in the opposite direction. An increase in factor A (warmth), and G (conscientiousness) was found in the study by Flegr and colleagues (1999), and a correlation of the length of infection with the scores in factor G was reported by two studies by Flegr and colleagues (1996, 2000). Significantly higher scores in infected women compared to

uninfected women were also observed in one subscale of the behavioral composite variable Self Control in the study by **Lindová and colleagues (2006**). At the present, I do not see any way how to incorporate this in the "inflammatory hypothesis".

5. Response to stress

5.1. Animal studies

5.1.1. Sex differences in stress hormones, stress processes and the role of sex hormones

Since Walter Cannon's (1932) work, the typical response to stress is thought to be the fight-or-flight reaction. The main biological processes involved are activation of the sympathetic nervous system, release of catecholamines, norepinephrine and epinephrine, from adrenal medulla, and activation of the hypothalamic-pituitary-adrenocortical (HPA) axis with the resulting release of corticosteroids.

Sex differences are obvious mainly in the HPA axis. Female rodents have higher basal and stress-induced content of corticosterone in the adrenal cortex, higher secretion rate of this main rodent corticosteroid and higher plasma and serum levels and shorter half-life of corticosterone (e.g., Kitay 1961, Majchrzak and Malendowicz 1983, Ježová et al. 2002a). A greater size of female adrenal glands, most obvious in the cortex, has been known for a long time and it was reported e.g. by Hatai (1913). Several animal castration and replacement studies show that the growth of adrenal glands is inhibited by testosterone and elevated by estrogens (e.g., Hatai 1915, Carter 1956). Furthermore, female rodents have higher handling stress-induced plasma levels of the adrenocorticotropic hormone (ACTH) which is released from the pituitary gland and triggers the secretion of corticosteroids from the adrenal gland (Ježová et al. 2002a). Again, the level can be markedly reduced by ovariectomy and increased by orchiectomy, and retrieved by estrogen or testosterone replacement (e.g. Gemzell 1952, Handa et al. 1994). The mechanism of the estrogen effect on the HPA axis might proceed via the corticotropin-releasing hormone (CRH) produced by hypothalamus, which regulates the production of ACTH. The gene for CRH has been observed to contain estrogen-responsive elements in the promoter area, so that estrogens can directly stimulate the production of CRH (Vamvakopoulos and Chrousos 1994).

Sex differences were also found in other hormones involved in the stress reaction, besides sex hormones, the most important ones are probably the posterior pituitary neuropeptides oxytocin and vasopressin (Ježová et al. 1996). The role of oxytocin will be discussed below. As for catecholamines, in a recent study by Uji and colleagues (2007), cage-switch stressed male mice responded with elevated blood pressure and norepinephrine release while female mice had only slightly elevated blood pressure, but their norepinephrine level did not change.

5.2. Humans

5.2.1. Gender differences in stress hormones and processes

In humans, the sex difference in stress response is more complex and equivocal. Differences can by found right in the basal values of stress involved substances. Men were found to have a higher level of basal plasma ACTH (with the difference being caused by higher daily secretion) than women by Horrocks and colleagues (1990) and Roelfsema and colleagues (1993), while plasma cortisol levels did not differ between men and women in these two studies which they interpret as a greater sensitivity of the female adrenal cortex.

Other studies, however, found higher levels of basal cortisol in men than in women (e.g., serum: Schöneshöfer and Wagner 1977; plasma: Zumoff et al. 1974; saliva: Laudat et al. 1988, Kirschbaum et al. 1992). Still another study found lower level of basal plasma ACTH in young men than both young women and older subjects with identical basal secretion of cortisol in all groups being interpreted as an enhanced sensitivity of the male adrenal cortex (Born et al. 1995).

Gender differences do not seem to be caused by different sensitivity of the pituitary gland to releasing factors, although some indices have been reported. For example, Kirschbaum and colleagues (1992) observed no gender differences in saliva cortisol response after injection of synthetic human CRH, but female cortisol response seemed to be slightly prolonged. Born and colleagues (1995) did not find any difference in ACTH response to human CRH. Galluci and colleagues (1993) used ovine, instead of human CRH, and observed a larger increase of ACTH in women than in men. Cortisol concentrations were similar in men and women, although women's cortisol elevation was prolonged compared to men's, similarly as in the study by Kirschbaum and colleagues (1992) using human CRH.

5.2.2. Gender differences in stress response

Usually, men are found to show a stronger stress response, mainly to stressors of psychological or cognitive nature. A standardized tool used to measure psychosocial stress is the Trier Social Stress Test (TSST) consisting of free speech and mental arithmetic task performed in front of an audience. ACTH and cortisol responses were found to be greater in men than women after expose to TSST (Kirschbaum et la. 1992, 1999, Uhart et al. 2006). Different test were used by other authors, leading to similar results. For instance, in a study by Collins and Frankenhaeuser (1978), male engineering students submitted to a cognitive-conflict task were found to respond with elevated cortisol levels whereas no change in cortisol was observed in female engineering students. Male students also showed more elevated levels of epinephrine than female students in the same study. Similarly, men responded with more cortisol production (other hormones have not been tested) to a complex stress task consisting of an isometric hand exercise and a short memory test (Ježová et al. 2002b). But also short-term hypoglycemia caused more ACTH, epinephrine and growth hormone rise in men than in women (Radíková-Červeňáková et al. 2004).

Women seem to show higher responses rather in pharmacologically- or physiologically induced stress conditions: ACTH and cortisol responses have been found to be higher in women than men after expose to pharmacological stress by naloxon administration in the study by Uhart and colleagues (2006). Further, women have been found to be more responsive concerning total plasma cortisol elevation to pain (Petrie et al. 1999). Hyperthermia induced by recreational sauna therapy as well as short hypothermia leaded to a stress response with identical release of catecholamines in both genders, but women showed a greater increase of prolactin and ACTH levels than men. Women also responded with a greater heart rate speed up (Ježová et al. 1994, 1996). Other studies similarly report that while the increase of the heart rate is typical for women, men respond to stress rather with a rise of blood pressure (Allen et al. 1993, Collins and Frankenhaeuser 1978). However, emotional stress is also capable of inducing a high stress response in women. This was observed by Kiecolt-Glaser and colleagues (1998) on newlywed couples. On a day including marital conflict, greater ACTH and plasma cortisol level changes were found in women than men.

Gender differences in the stress response also seem to depend on age. While young male subjects showed higher increase of salivary cortisol than female subjects after a cognitive challenge, in older subjects (over 67 years of age), the pattern was reversed (Seeman et al. 2001). However, this study has been later criticized by other authors for methodological

weaknesses (see Kudielka and Kirschbaum 2005). In a recent meta-analysis, Otte and colleagues (2005) identified 45 studies on aging and cortisol response to psychological or pharmaceutical challenge. In older subjects, the response to challenge was larger, with the difference between young and old subjects being significantly stronger for women than for men.

5.2.3. Role of sex hormones in the stress response

Also in humans, sex hormones have been reported to influence the HPA processes. Firstly, the above mentioned meta-analysis by Otte and colleagues (2005) implies the role of estrogens or other female hormones, since an important difference between young, i.e. premenopausal, and old, i.e. postmenopausal, women was found. As we will see below, in contrast to the inhibiting effect of estrogen which we would expect on the basis of this age difference, rather opposite has been observed by other authors. Kirschbaum and colleagues (1996) manipulated the estrogen level in healthy young men. Those with experimentally induced higher estrogen levels (and consequently also slightly lower testosterone levels) had exaggerated increases of ACTH and cortisol after TSST compared to controls. There was even a slight difference in the stress-induced norepinephrine production in favour of men with elevated estrogen levels. This is also the opposite from what would have been expected on the basis of gender differences in psychological-stress response where men show more elevated values. Moreover, women's psychological-stress-induced cortisol levels were found to change over the menstrual cycle. Women in the estrogen-high luteal phase had higher response of salivary-free cortisol compared with women in the follicular phase. No difference was seen with respect to basal, stress-induced total plasma cortisol or stress-induced ACTH (Kirschbaum et al. 1999, Tersman et al. 1991). This can be seen as another evidence of the elevating effect of estrogen on the HPA axis. In contrast, Kudielka and colleagues (1999) did not observe any change in TSST-induced HPA axis response in postmenopausal women treated with estradiol; however, they found increased feedback sensitivity measured by simultaneous injecting of CRH and the glucocorticoid dexamethasone.

Another study by Rubinow and colleagues (2005) investigated the role of testosterone in the stress response and obtained rather confusing results as well. Men with suppressed testosterone levels (and consequently also slightly lower estrogen levels) by leuprolide acetate had moderately decreased ACTH, but clearly increased cortisol response to CRH stimulation. Baseline plasma values for ACTH and cortisol did not differ in the two conditions. Additionally, Kudielka and colleagues (1998) found increased ACTH, but not cortisol response to TSST in old women treated by dehydroepiandrosterone (DHEA) than in control women. Treatment of men with DHEA did not affect the HPA axis response.

In summary, these findings imply that, although the gender difference in human stress response seems to be rather reversed to that of rodents, estrogens identically have an elevating effect on corticosteroid secretion. The effect of testosterone is less clear and needs further research.

5.2.4. Evolutionary theories of gender differences in stress response

Shelley Taylor and her colleagues (2000) proposed an alternative evolutionary hypothesis to the traditional fight-or-flight response, applying predominantly for women. They argue that a fight response on the part of a woman may put herself and her offspring in jeopardy, and flight behavior may be compromised by pregnancy or care for young offspring. For women, it might be rather adaptive to affiliate to a social group which can provide protection for them and their offspring. Simultaneously, it should be adaptive for the women to help to create a

network of supporting associations. Therefore, women have evolved a "tend and befriend" stress response. This theory is in good accord with social science research which found women to seek more social support and vent emotions under stress, whereas men use more problem focused coping styles (Berns and Johnson 1989).

A similar theory by Stroud and colleagues (2000) suggests that men and women are distinctly sensitive to evolutionary relevant stressors, namely situations involving intellectual inferiority and performance failures for men and social rejection for women. Indeed, men but not women showed free cortisol increases in achievement situations whereas women but not men showed free cortisol responses to social rejection. This would explain greater responses to psychological stressors found also by previously mentioned authors, since they mostly used cognitive challenge simulation. Dickerson and Kemeny (2004) performed a meta-analysis of studies on cortisol response to psychological stress with the aim to identify and sort stressors which were successful at eliciting cortisol response in these studies. As they hypothesized, two main groups of stressors were characterized by uncontrollability and social-evaluative threat, respectively. Surprisingly, they did not find any gender differences in cortisol release between these two stress conditions. It might be caused by the fact that these two types of stressors identified by the authors did not correspond to achievement and social rejection situations, as defined by Stroud et al. (2000).

A recent theory by Kajantie and Phillips (2006) proposed the critical role of a different evolutionaty pressure, namely promoting optimal growth and development of the fetus by buffering the effects of excess maternal stress. In pregnancy, CRH produced by the placenta elevates cortisol production which, in turn, stimulates placental CRH release. This positive feedback loop seems to be a crutial mechanism for delivery timing regulation. Simultaneously, the fetus is protected from high cortisol levels by placental 11β-hydroxysteroid dehydrogenase-2 which converts cortisol to the inactive cortisone. According to the authors, as a consequence excess cortisol during pregnancy can lead to premature birth and unwelcome behavioral changes in newborns. This seems to be supported by some indirect evidence from humans and more direct evidence from animal studies, e.g. the finding of increased risk of preterm birth in stressful living conditions (Moutquin 2003) or hyperactivity and impaired negative feedback regulation in animal offspring of mothers submitted to prenatal stress (see review by Huizink et al. 2004). Via attenuating effects of estrogens on the HPA responsivenes mediated by arginine vasopressin this evolutionary pressure could be, as proposed by the authors, responsible for averall gender differences in the stress response. However, this theory does not seem to explain the previously mentioned reports of increased cortisol stress response in estrogen-high luteal phase of the menstrual cycle.

5.2.4. Testosterone and the stress response

Taylor and colleagues (2000) suggest that females are less likely to "fight" in response to stress, because aggression is associated with testosterone which they largely lack. The model implicitly proposes a causal relationship between stress and testosterone level. As we have seen above, testosterone is, however, not clearly bound to aggression (and neither is to stress, as I will show below). Most authors argue that higher levels of this androgen are linked to situations of dominance achievement or aggressive dominant behavior (Archer 2006, Mazur and Booth 1998). This would apply only to a proportion of stress situations, when the position of the individual in the hierarchy is threatened. In contrast, it would not apply to situations including threat from potential predators or dangerous natural conditions. Further, Taylor and colleagues propose that testosterone is of a minor or no importance in women's aggression. As I have shown above, available evidence seems to be rather contradictory. It might be that

women's hostility is not linked to sympathetic arousal as men's hostility, but studies to confirm this assumption need to be done.

In contrast to Taylor and colleagues, other authors rather propose a negative association of testosterone with stress based on the assumption that "reproduction is certainly one of the most expensive, optimistic things you can do with your body (especially if you are female), and it simply cannot be of high priority when you are sprinting for your life" (Sapolsky 1992, p. 294). Of course, one of the main ways of inhibiting reproduction is via suppressing the testosterone level.

The evidence on the role of testosterone in the stress response is large and somewhat equivocal. Most of it stems of course from studies on male samples. Two studies found a negative association between testosterone and stress measured as a psychological trait. Nilsson and colleagues (1995) measured free testosterone in over 400 males, all aged 51 years. The subjects also filled in a questionnaire listing psychosocial variables, and lifestyle and health questions. Those with low levels of free testosterone reported more negative psychosocial events and more psychological and health problems. Francis (2005) approximated psychological stress with measures of anxiety, hostility, and depression in males aged 30-55 years. Subjects high in these traits had lower serum testosterone levels, but did not differ in serum cortisol values.

Several studies confirmed a negative influence of long-term high physical training on testosterone. Lower testosterone level was observed in men submitted to endurance training and military training (Bernton et al. 1995, Hackney 2001, Opstad 1992). Similarly, sleep deprivation lead to lower testosterone (Opstad 1992, Cortés-Callegos et al. 1983). Anticipation of such an extreme effort is able to reduce the testosterone level just like the activity itself. This has been observed in individuals performing extreme outdoor sports as skydiving where skydiving volunteers had lower salivary, but not plasma testosterone level both before and after the jump (Chatterton et al. 1997) or in subjects performing long-distance survival marching (Gatti et al. 1992).

Short-term exercise, in contrast, seems to elevate the testosterone level. This was found e.g. considering serum levels in trained runners after strenuous treadmill running by Kraemer and colleagues (2003), and considering plasma levels in men exercising on a bicycle ergometer (Ježová-Repčeková et al. 1982), but also by a number of older studies (e.g., Métivier et al. 1980, Cumming et al. 1986, Mathur et al. 1986).

Testosterone was also observed to decreases after surgery-induced stress. Matsumoto and colleagues (1970) found lower plasma testosterone levels in male patients who underwent a surgery. Even watching a video showing tooth surgery had a negative effect on testosterone (Hellhammer et al. 1985).

Moreover, testosterone seems to fall after (and perhaps during) a cognitively demanding and potentially dangerous task. So Cullen and colleagues (1979) reported lower testosterone in subjects driving a heavy load truck and Leedy and Wilson (1985) observed decreased serum testosterone levels in pilots and crew of airforce fighter planes after flight, but not in pilots and other crew of cargo plains. Both of these studies, although showing clear changes in both testosterone and cortisol levels, failed to observe a correlation of the two. Surprisingly, Leedy and Wilson (1985) found elevated cortisol levels in non-pilots of both types of plains, but not in pilots of both types of plains.

The negative effect of stress on testosterone levels, however, depends on anticipations regarding the result of the stress situation. As discussed in chapter 3.2.1., anticipation of success or winning leads to a rather increased level of testosterone. In contrast, negative feelings, i.e. elevated anxiety, are correlated with an even greater decrease of testosterone under stress (Diamond et al. 1989).

Among other stressors, hypoglycemia acutely suppresses testosterone secretion. Insulin-induced hypoglycemia as well as the administration of hydrocortisone resulted in a rapid decrease in serum testosterone levels in the study by Cumming and colleagues (1983).

Finally, Girdler and colleagues (1997) observed increased testosterone in men during speech, Stroop, and math stress. Moreover, the amount of increase was correlated with the score in a hostility scale. Turning back to the beginning, this can be indeed seen as evidence for the hypothesis of Taylor and colleagues which propose that the typical male fight response to stress is mediated by the aggression-bound testosterone response.

In women, long-term stress seems to have a rather opposite effect on testosterone than in men. Fertmann (1991) found higher testosterone concentration in lactating mothers reporting a larger amount of psychosocial stress (which can, however, rather reflect a non-efficient coping style instead of a higher absolute stress load) and Demyttenaere and colleagues (1989) observed a positive correlation of testosterone response to watching emotionally stressful video with trait anxiety. Women pilots have been found to have elevated testosterone levels as compared to ground personnel (Dongyun and Yumin 1990). Cruess and colleagues (2001) observed decreasing levels of testosterone in breast cancer patients who were submitted to a stress-management intervention leading to more positive attributions regarding their illness indicating elevating effect of the illness on testosterone levels via anxiety or other negative feelings. Endurance running also leaded to elevated testosterone levels in women (De Crée et al. 1990).

5.2.6. Other hormones and gender differences in stress response: promising oxytocin

In addition to the absence of the "fight" response in women, supposedly caused by the absence of stress-induced testosterone release, Taylor and colleagues (2000) also point to an absence of the "flight" response. Evolutionary, their argument is based on the jeopardy of mother's flight tendency for her offspring which are unable to flee for several years after birth. Instead, the authors stress the importance of "tending" and "befriending" in women. The tendency to tend is thought to be derived from attachment/caregiving behaviors typical for the mother-child bond and the tendency to befriend from the natural desire to affiliate and seek support from conspecifics which is more typical for women.

Both the absence of the flight response and the presence of affiliating and caring needs under stress could be, as suggested by the authors, underpinned by the effects of oxytocin, a posterior pituitary hormone released in some types of stress and having rather parasympathetic, relaxing effects. Studies on the role of oxytocin in stress are, however, rare and based mostly on animals. Administration of oxytocin in different mammals was found to reduce anxiety and have mildly sedative effects in both sexes (e.g., Uvnäs-Moberg 1997). Moreover, oxytocin treatment enhanced social contact in rodents (Witt et al. 1990, Carter et al. 1995) and this held also for chronic administration (Witt et al. 1992). Animals are thought to prefer to spend time with animals in whose presence they have experienced high brain oxytocin activities in the past (Panksepp, 1998 as cited in Taylor et al. 2000). Oxytocin release in response to stress was found to be greater in female than in male rats by Williams et al. (1985). This study also reported that orchiectomy lead to enhanced release of oxytocin in stress, indicating an inhibitory effect of testosterone. Similarly, androgenization of young female rats reduced later stress-induced oxytocin release to levels similar as in males (Carter et al. 1988). In the study by Williams et al. (1985), ovariectomy had no effect. However, other authors provided some evidence for modulatory effects of estrogens (e.g., Nomura et al. 2002).

In humans, oxytocin was found to inhibit the release of glucocorticoids during sucking in women (Chiodera et al. 1991). Recently, oxytocin has been found to be strongly negatively related to depression severity and anxiety (Scantamburlo et al. 2007).

To sum up, there is some evidence justifying the role of oxytocin as a stress-induced factor responsible for specific sex differences in the stress response proposed by Taylor et al. (2000). This evidence is, however, rather scarce and there is need for further studies to be done on this topic.

5.3. Could gender differences induced by *Toxoplasma* be due to differences in stress response?

The first and principal premise for such a notion would be that *Toxoplasma* induces a stress response. We can speculate about the form of this potential stressor in the sense that it should be definitely mild, since it has not been detected yet, and chronical, as the parasite remains encysted in the hosts' tissues for the rest of their lives. To date, there are no direct data confirming or disputing this presumption. Virtually all we can look at are testosterone levels and psychological changes.

The pattern of changes in testosterone levels in infected subjects, with women showing a decreased concentration of salivary free testosterone and men showing rather an increased level, does not correspond to the pattern of changes in a chronical stress situation such as long-term intensive physical training, sleep deprivation, repeating negative psychosocial events or psychological and health problems, where a decreased testosterone concentration in men and the reversal in women has been found repeatedly (see above). Therefore, it does not seem likely that latent toxoplasmosis represents a stressor similar in effect to either one of these.

However, psychological changes point to the possibility that infected subjects might experience some stress. Both men and women have been found to score lower in novelty seeking when infected (Skallová et al. 2005, Flegr et al. 2003, **Novotná et al. 2005**). Novelty seeking might be decreased by chronical stress as chronically stressed rodents were found to explore less than controls in the open field (Conrad et al. 1999) and elevated plus maze (Wood et al. 2004). However, the influence of chronic stress of novelty seeking needs to be elucidated by more studies.

Most importantly, psychological and behavioral changes found in infected men and women fairly closely match gender different coping styles (in the terms of the social science research) or gender difference in evolutionary adaptive stress response (in the terms of evolutionary inspired research). Infected women were found to score higher in warmth (i.e. caring in evolutionary terms), conscientiousness or regardance for social norms (perhaps a good way to ensure the position in the social group and avoid rejection) and higher in trust (i.e. trustful relying on others) (Flegr et al. 1999). They also showed more conscientious, self-controlled behavior in behavioral experiments (**Lindová et al. 2006**). Moreover, *Toxoplasma*-positive women were found to repay more money from a gift/investment made by the playmate in the experimental Trust Game than uninfected women (**Lindová et al. submitted**). This was not caused by their general tendency of greater giving, since they were giving less money than uninfected women in the Dictator Game, where no reciprocity among players was possible.

Men in contrast were found to score lower in conscientiousness, higher in viability/mistrust and guilt proneness (Flegr et al. 1999) and had lower behaviorally assessed warmth and self-control, and less tidy clothes than uninfected men (**Lindová et al. 2006**). They also allocated less money in either condition (both reciprocal and non-reciprocal) in experimental games (**Lindová et al. submitted**). These changes indicate rather an increased

aversion from the social group than affiliation. It is fairly well supported by evidence that men's response to stress includes more antisocial coping styles and even substance abuse (Carver et al. 1989, Dunahoo et al. 1998, Monnier et al. 1998).

6. Conclusions

As I have preceded in chapter 1, additional research needs to be done before we will be able to identify the mechanism of gender differences in the influence of latent toxoplasmosis on human behavior. However, on the basis of the above presented review, we can demarcate areas in which research could lead to important findings.

As *Toxoplasma* has been shown to have gender different effects on the level of testosterone, it was hypothesized that this hormone could be responsible for observed psychological and behavioral gender differences. This is not very likely to be the case. Psychological changes associated with testosterone are very well documented and include e.g. increased aggression/dominance, although the relationship does not seem to be very strong. Such personality shifts have not been observed in our infected subjects. In contrast, other shifts appeared which cannot be derived from testosterone effect. Similarly, changes in estrogen levels do not seem to be directly responsible for the observed psychological shifts in infected men and women, since anxiety and related estrogen-associated traits are untouched. Perhaps, the fact that the pattern of *Toxoplasma*-induced personality changes in men and women does not reflect already present gender differences (in terms of exaggerating or alining them), also denotes that the mechanism does not lie in direct effect of changed sex hormone concentrations.

Estrogens could, however, still play a role in the gender difference in *Toxoplasma*-induced personality changes. Even on the level of primary immunological response to the parasite, men and women differ. Estrogens are thought to regulate this response. Additionally, estrogens are considered important substances involved in protection against neurodegenerative illnesses. Both estrogen effects on many components of the immune system and the association between estrogens and psychotic and neurodegenerative diagnosis are well supported by evidence. *Toxoplasma* cysts are localized in the brain and there are indices that they could be the cause for minor inflammations in the brain tissue. Thus women in the reproductive age with the naturally higher levels of estrogens could be better protected than men. As I have shown, this would explain the "schizoid"-like changes in men, but not the pattern of changes observed in women.

Most promising appears to be the stress hypothesis which implies that latent toxoplasmosis (perhaps via chronical inflammations in the brain tissue) induces long-term stress which men and women differently cope with. Evidence for gender differences in stress response stems from numerous endocrinological, etological, evolutionary and psychological studies. A promising line of research seems to be the identification of the "tend and befriend" stress response in females with the proposed principal role of oxytocin, as a counterpart of the traditional "fight or flight" response regulated by the sympathetical nervous system and the HPA axis. Although there is no experimental support for the possibility of latent toxoplasmosis representing a stressor, and our data on testosterone even speak against the notion, observed psychological changes fit very well to those found in men and women under stress.

In the future, it would be of great interest to investigate response of other hormones but testosterone to latent toxoplasmosis infection. Hot candidates should be corticosteroids or other hormones indicative of stress processes and oxytocin which is also released in stress and simultaneously is proposed to be responsible for women's "tend and befriend" coping behavior. Regarding the inflammatory hypothesis, estrogen data would also be helpful.

References

Agarwal, S. K., Marshall, G. D. 1998 Glucocorticoid-induced type 1/type 2 cytokine alterations in humans: a model for stress-related immune dysfunction. Journal of Interferon and Cytokine Research, 18, 1059-1068

Ahmed, S. A., Gogal, R. M., Walsh, J. E., Saunders, G. 1996 Estrogen induces defects in T cell functions of mice. The FASEB Journal, 10, 961

Alonso, R., Chaudieu, I., Diorio, J., Krishnamurthy, A., Quirion, R., Boksa, P. 1993 Interleukin-2 and -6 modulates evoked release of [3h]dopamine in rat cultured mesencephalic cells. Journal of Neurochemistry, 61, 1284-1290

Aluja, A., Torrubia, R. 2004 Hostility-Aggressiveness, Sensation Seeking, and Sex Hormones in Men: Re-Exploring Their Relationship. Neuropsychobiology, 50, 102-107

Archer, J. 2006 Testosterone and human aggression: an evaluation of the challenge hypothesis. Neuroscience and Biobehavioral Reviews, 30, 319-345.

Archer, J., Graham-Kevan, N., Davies, N. 2005 Testosterone and aggression: a re-analysis of Book, Starzyk and Quinsey's (2001) study. Aggression and violent behavior, 10, 241-261

Arpels, J. C. 1996 The female brain hypoestrogenic continuum from the premenstrual syndrome to menopause: A hypothesis and review of supporting data. Journal of Reproductive Medicine, 41, 633-639

Arsenijevic, D., Girardier, L., Seydoux, J., Chang, H. R., Dulloo, A. G. 1997 Altered energy balance and cytokine gene expression in a murine model of chronic infection with *Toxoplasma gondii*. American Journal of Physiology, 272, 908-917

Baker, A. E., Brautigam, V. M., Watters, J. J. 2004 Estrogen modulates microglial inflammatory mediator production via interactions with estrogen receptor beta. Endocrinology, 145, 5021–5032

Baral, E., Nagy, E., Berczi, I. 1995 Modulation of natural killer cell mediated cytotoxicity by tamoxiflen and estradiol. Cancer, 75, 591-599

Bateup, H. S., Booth, A., Shirtcliff, E. A., Granger, D. A. 2002 Testosterone, cortisol, and women's competition. Evolution and Human Behavior, 23, 181-192

Bayer, T. A., Buslei, R., Havas, L., Falkai, P. 1999 Evidence for activation of microglia in patients with psychiatric illnesses. Neuroscience Letters, 271, 126-128

Benten, W. P. M., Lieberherr, M., Giese, G., Wrehlke, C., Stamm, O., Sekeris, C. E., Mossmann, H., Wunderlich, F. 1999 Functional testosterone receptors in plasma membrane of T cells. The FASEB Journal, 13, 123-133

Benten, W. P. M., Lieberherr, M., Giese, G., Wunderlich, F. 1998 Estradiol binding to cell surface raises cytosolic free calcium in T cells. FEBS Letters, 422, 349-353

Berns, C., Johnson, M. E. 1989 Problem-solving appraisal and coping style: The influence of sex-role orientation and gender. Journal of Psychology, 123, 187-194

Bernton, E., Hoover, D., Galloway, R., Popp, K. 1995 Adaptation to chronic stress in military trainees. Adrenal androgens, testosterone, glucocorticoids, IGF-1, and immune function. Annuals of the New York Academy of Science, 774, 217-231

Beverly, J. K. A., Fleck, D. G., Kwantes, W., Ludlam, G. 1976 Age-sex distribution of toxoplasmic lymphadenopathy. Journal of Hygiene, 76, 215-228

Bleuler, E. 1924 Textbook of psychiatry. New York, Macmillan

Boll, G., Reimann, J. 1996 Oestrogen treatment depletes extrathymic T cells from intestinal lymphoid tissues. Scandinavian Journal of Immunology, 43, 345-350

Book, A. S., Starzyk, K. B., Quinsey, V. L. 2001 The relationship between testosterone and aggression: a meta-analysis, Aggression and violent behavior 6, 579-599

Cai, G., Radzanowski, T., Villegas, E. N., Kastelein, R., Hunter, C. A. 2000 Identification of STAT4-dependent and independent mechanisms of resistance to *Toxoplasma gondii*. The Journal of Immunology, 165, 2619-2627

Carter, C. S., DeVries, A. C., Getz, L. L. 1995 Physiological substrates of mammalian monogamy: The prairie vole model. Neuroscience and Biobehavioral Reviews, 19, 303-314

Carter, D. A., Saridaki, E., Lightman, S. L. 1988 Sexual differentiation of oxytocin stress responsiveness: effect of neonatal androgenization, castration and a luteinizing hormone-releasung hormone antagonist. Acta Endocrinologica, 117, 525-530

Carter, S. B., 1956 The influence of sex hormones on the weight of the adrenal gland in the rat. Journal of Endocrinology, 13, 150-160

Carver, C. S., Scheir, M. & Weintraub, J. K. 1989 Assessing coping strategies: A theoretically based approach. Journal of Personality and Social Psychology, 56, 267-283.

Cashdan, E. 1995 Hormones, sex, and status in women. Hormones and Behavior, 29, 354-366.

Cattell, R. B. 1965 The Scientific Analysis of Personality, The Chaucer Press, Bungay, Suffolk, Great Britain

Cattell, B. C., Eber, H. W., Tatsuoka, M. M. 1992 Handbook for the Sixteen Personality Factor Questionnaire (16 PF). Institute for Personality and Ability Testing, Inc., Champaign, Illinois

Cazzullo C.L.; Scarone S.; Grassi B.; Vismara C.; Trabattoni D.; Clerici M.; Clerici M. 1998 Cytokines production in chronic schizophrenia patients with or without paranoid behaviour Progress in Neuro-Psychopharmacology and Biological Psychiatry, 22, 947-957

Chao, T. C., Vanalten, P. J., Walter, R. J. 1994 Steroid sex-hormones and macrophage function – modulation of reactive oxygen intermediates and nitrite release. American Journal of Repruductive Immunology, 32, 43-52

Chatterton, R. T., Vogelsong, K. M., Lu, I-C., Hudgens, G. A. 1997 Hormonal responses to psychological stress in men preparing for skydiving. Journal of Clinical Endocrinology and Metabolism, 82, 2503-2509

Chiodera, P., Salvarani, C., Bacchi-Modena, A., Spailanzani, R., Cigarini, C., Alboni, A., Gardini, E., Coiro, V. 1991 Relationship between plasma profiles of oxytocin and adrenocorticotropic hormone during sucking or breast stimulation in women. Hormone Research, 35, 119-123

Cloninger, C. R. 1987 A systematic method for clinical description and classification of personality variants. Archives of General Psychiatry, 44, 573-588

Cloninger, C. R. 1998 The genetics and psychobiology of the seven-factor model of personality. In Biology of personality disorders (Eds.: Silk, K. R.) Washington, DC, American Psychiatric Press, Inc.; 63-92

Cloninger, R. C., Svrakic, D. M., Przybeck, T. R. 1993 A psychobiological model of temperament and character. Archives of General Psychiatry, 50, 975-990

Collins, A., Frankenhaeuser, M. 1978 Stress responses in male and female engineering students. Journal of Human Stress, 4, 43-48

Conrad CD, LeDoux JE, Magariños AM, McEwen BS. 1999 Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. Behavioral Neuroscence, 113:902–913.

Correale, J., Arias, M., Gilmore, W. 1998 Steroid hormone regulation of cytokine secretion of proteolipid protein-specific CD4(+) T cell clones isolated from multiple sclerosis patients and normal control subjects. Journal of Immunology, 161, 3365-3374

Cortés-Gallegos, V., Castaneda, G., Alsonso, R., Sojo, I., Carranco, A., Cervantes, C., Parra, A. 1983 Sleep deprivation reduces circulating androgens in healthy men. Archives in Andrology, 10, 33-37

Costa, P. T., Jr., McCrae, R. R. 1992 Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) professional manual. Odessa, FL: Psychological Assessment Resources.

Costa, P. T., Jr., Terracciano, A. McCrae, R. R. 2001 Gender differences in personality traits across cultures: Robust and surprising findings. Journal of Personality and Social Psychology, 81, 322-331.

Cruess, D. G., Antoni, M. H., McGregor, B. A., Kilbourn, K. M., Boyers, A. E., Alferi, S. M., Carver, C. S., Kumar, M. 2000 Cognitive-behavioral stress management reduces serum cortisol by enhancing benefit finding among women being treated for early-stage breast cancer. Psychosomatic Medicine, 62, 304-308

Cullen, J., Fuller, R., Dolphin, C. 1979 Endocrine stress responses of drivers in a "real-life" heavy goods vehicle driving task. Psychoneuroendocrinology, 4, 107-115

Cumming, D. C., Brunsting, L. A., Strich, G., Ries, A. L., Rebar, R. W. 1986 Reproductive hormone increases in response to acute exercise in men. Medical Science in Sports and Exercise, 18, 369-373

Cumming, D. C., Quingley, M. E., Yen, S. S. 1983 Acute suppression of circulating testosterone levels by cortisol in men. Journal of Clinical Endocrinology and Metabolism, 57, 671-673

Dabbs, J. M. 1990 Salivary testosterone measurements: reliability accross hours, days, and weeks. Physiology and behavior, 48, 83-88

Dabbs, J. M. Jr., Cate, K., Browner, A., Emery, C., Leander, P., Zachary, M. 2003 Testosterone treatment, affect, and appearance: Slight effects in normal subjects. Social Behavior and Personality, 31, 387-394

Dabbs, J. M. Jr., Hargrove, M. F. 1997 Age, testosterone, and behavior among females prison inmates. Psychosomatic medicine, 59, 477-480

Dabbs, J. M. Mohammed, S. 1992 Male and female salivary testosterone concentrations before and after sexual activity. Physiology and Behavior, 52, 195-197

Dabbs, J., Jr., Ruback, R., Frady, R., Hopper, C., Sgoutas, D. 1988 Saliva testosterone and criminal violence among women. Personality and Individual Differences, 9, 269-275

DaSilva, J. A. P. 1999 Sex hormones and glucocorticoids: interactions with the immune system. Annals of the New York Academy of Sciences, 876, 102-118

De Crée, C., Lewin, R., Ostyn, M. 1990 The monitoring of the menstrual status of female athletes by salivary steroid determination and ultrasonography. European Journal of Applied Physiology, 60, 472-477

De Raad, B., Perugini, M. (Eds.) 2002 Big Five assessment. Gottingen, Germany: Hogrefe and Huber Publishers.

Demyttenaere, K., Nijs, P., Evers-Kibooms, G., Koninckx, P. R. 1989 The effect of a specific emotional stressor on prolactin, cortisol, and testosterone concentrations in women varies with their trait anxiety. Fertility and Sterility, 52, 942-948

Denkers, E. Y., Gazzinelli, R. T. 1998 Regulation and function of T-cell-mediated immunity during *Toxoplasma gondii* infection. Clinical Microbiology Reviews, 11, 569-588

Deshpande, R., Khalili, H., Pergolizzi, R. G., Michael, S. D., Chang, M. D. Y. 1997 Estradiol down-regulates LPS-induced cytokine production and NPκB activation in murine macrophages. American Journal of Reproductive Immunology, 38, 46-54

Diamond, P., Brisson, G. R., Candas, B., Péronnet, F. 1989 Trait anxiety, submaximal physical exercise and blood androgens. European Journal of Applied Physiology, 58, 699-704

Dickerson, S. S., Kemeny, M. E. 2004 Acute Stressors and Cortisol Responses: A Theoretical Integration and Synthesis of Laboratory Research. Psychological Bulletin, 130, 355-391

Dongyun, S., Yumin, W. 1990 Flight influence on the plasma level of sex hormones of women pilots. Military Medicine 155, 262-264

Drigotas, S., Udry, J. 1993 Biosocial models of adolescent problem behavior: Extension to panel design. Social Biology, 40, 1-7

Dunahoo, C. L., Hobfoll, S. E., Monnier, J., Hulsizer, M. R., Johnson, R. 1998 There's more than rugged individualism in coping. Part 1: Even the lone ranger had tonto. Anxiety, stress, and coping, 11, 137-165

Dunn, E. J., Steiner, M. 2000 The functional neurochemistry of mood disorders in women. In: Steiner, M., Yonkers, K. A., Eriksson, E. (Eds.), Mood disorders in women. Martin Dunitz, London, pp. 71-82

Eriksson, C. J. P., von der Pahlen, B., Sarkola, T., Seppa, K. 2003 Oestradiol and human male alcohol-related aggression. Alcohol and alcoholism, 38, 589-596

Ferguson, M. M., McDonald, F. G. 1985 Oestrogen as an inhibitor of human NK cell cytolysis. FEBS Letters, 191, 145-148

Fertmann, R. 1991 Prolactin, sex hormones and stress during lactation. Homo, 42, 113-129

Field, L. H., Williams, M. 1970 The hormonal treatment of sexual offenders. Medical Science and Law 10, 27

Flegr, J., Havlíček, J. 1999 Changes in personality profile of young women with latent toxoplasmosis. Folia Parasitologica, 46, 22-28

Flegr, J., Hrdá, Š., Havlíček, J. 1999 Rozdíly v osobnostním profilu biologů nakažených a nenakažených *Toxoplasma gondii*. Remedia – Klinická mikrobiologie, 3, 268-273

Flegr, J., Hrdý, I. 1994 Influence of chronic toxoplasmosis on some human personality factors. Folia Parasitologica, 41, 122-126

Flegr, J., Kodym, P., Tolarová, V. 2000 Correlation of duration of latent *Toxoplasma gondii* infection with personality changes in women. Biological Psychology, 53, 57-68

Flegr, J., Preiss, M., Klose, J., Havlíček, J., Vitáková, M., Kodym, P. 2003 Decreased level of psychobiological factor novelty seeking and lower intelligence in men latently infected with the protozoan parasite *Toxoplasma gondii*: Dopamine, a missing link between schizophrenia and toxoplasmosis? Biological Psychology, 63, 253-268

Flegr, J., Zitková, Š., Kodym, P., Frynta, D. 1996 Induction of changes in human behaviour by the parasitic protosoan *Toxoplasma gondii*. Parasitology, 113, 49-54

Fox, H. S., Bond, B. L., Parslow, T. G. 1991 Estrogen regulates the IFN-gamma promoter . Journal of Immunology, 146, 4362-4367

Franchimont, D., Martens, H., Hagelstein, M.-T., Louis, E., Dewe, W., Chrousos, G. P., Belaiche, J., Geenen, V. 1999 Tumor Necrosis Factor α Decreases, and Interleukin-10 Increases, the Sensitivity of Human Monocytes to Dexamethasone: Potential Regulation of the Glucocorticoid Receptor The Journal of Clinical Endocrinology and Metabolism, 84, 2834-2839

Francis, K. T. 2005 The relationship between high and low trait psychological stress, serum testosterone, and serum cortisol. Cellular and Molecular Life Sciences, 37, 1296-1297

Frieze, I. H., Parsons, J. E., Johnson, P. B., Ruble, D. N. Zellman, G. L. 1978 Women and sex roles: a social perspective. New York: Norton.

Gallucci, W. T., Baum, A., Laue, L., Rabin, D. S., Chrousos, G. P., Gold, P. W., Kling, M. A. 1993 Sex differences in sensitivity of the hypothalamic-pituitary-adrenal axis. Health Psychology, 12, 420-425

Gatti, G., Meluzzi, A., Francesetti, G., Masera, R., Sartori, M. L., Maina, L., Carignola, R., Angeli, A. 1992 Psychoemotional, cognitive, chronoendocrine, and immune responses to a survival performance in an african desert. Evidence for divergent effects. Annals of the New York Academy of Sciences, 650, 251-256

Gemzell, C. A., 1952 Increase in the formation and secretion of ACTH in rats following administration of estradiol monobenzoate. Acta Endocrinologica, 11, 221-228

Gerra, G., Avanzini, P., Zaimovic, A., Sartori, R., Bocchi, C., Timpano, M., Zambelli, U., Delsignore, R., Gardini, F., Talarico, E., Brambilla, F. 1999 Neurotransmitters, neuroendocrine correlates of sensation-seeking temperament in normal humans. Neuropsychobiology, 39, 207-213

Ghisletti, S., Meda, C., Maggi, A., Vegeto, A. 2005 17β-estradiol inhibits inflammatory gene expression by controlling NF-κB intracellular localization. Molecular and cellular biology 25, 2957-2968

Gilmore, W., Weiner, L. P., Correale, J. 1997 Effect of estradiol on cytokine secretion by proteolipid protein-specific T cell clones isolated from multiple sclerosis patients and normal control subjects. Journal of Immunology, 158, 446-451

Girdler, S. S., Jammer, L. D., Shapiro, D. 1997 Hostility, testosterone, and vascular reactivity to stress: Effects of sex. International Journal of Behavioral Medicine, 4, 242-263

Gladue, B. 1991 Aggressive behavior characteristics, hormones, and sexual orientation in men and women. Aggressive Behavior, 17, 313-326.

Glaser, R., Rice, J., Sheridan, J., Fertel, R., Stout, J., Speicher, C., Pinsky, D., Kotur, M., Post, A., Beck, M. 1987 Stress-related immune suppression: health implications. Brain, Behavior, and Immunity, 1, 7-20

Goldberg, L. R. 1992 The development of markers for the Big-Five factor structure. Psychological Assessment, 4, 26-42.

Grant, I. H., Anastors, K., Ernst, J. 1994 Gender differences in AIDS-defining illnesses. Int Conf AIDS. 1991 Jun 16-21; 7: 346

Grant, J. V., France, J. T. 2001 Dominance and testosterone in women. Biological Psychology, 58, 41-47

Hackney, A. C., 2001 Endurance excercise training and reproductive endocrine dysfunction in men: alterations in the hypothalamic-pituitary-testicular axis. Current Pharmaceutical Design, 7, 261-273

Hamano, N., Terada, N., Maesako, K., Numata, T., Konno, A. 1998 Effect of stress hormones on eosinophilic inflammation in nasal mucosa. Allergy and Asthma Proceedings, 19, 263-269

Handa, R. J., Nunley, K. M., Lorens, S. A., Louie, J. P., McGivern, R. F., Bollnow, M. R. 1994 Androgen regulation of adrenocorticotropin and corticosterone secretion in the male rat following novelty and foot shock stressors. Physiology and Behavior, 55, 117-124

Hanna, N., Schneider, M. 1983 Enhancement of tumor metastasis and suppression of natural killer cell activity by β-estradiol treatment. Journal of Immunology, 130, 974-980

Hansenne, M., Pinto, E., Pitchot, W., Reggers, J., Scantamburlo, G., Moor, M., Ansseau, M. 2002 Further evidence on the relationship between dopamine and novelty seeking: a neuroendocrine study. Personality and Individual Differences, 33, 967-977

Harris, B., Lovett, L., Newcombe, R. G., Read, G. F., Walker, R., Riad-Fahmy, D. 1994 Maternity blues and major endocrine changes: Cardiff puerperal mood and hormone study II. British Medical Journal, 308, 949–953

Harris, J. A., Rushton, J. P., Hampson, E., Jackson, D. N. 1996 Salivary testosterone and self-report aggressive and pro-social personality characteristics in men and women. Aggressive Behavior, 22, 321-331

Hatai, S. 1913 On the weights of the abdominal and the thoracic viscera, the sex glands, ductless glands and the eyeballs of the albino rat (*Mus norvegicus albinus*) according to body weight. American Journal of Anatomy, 15, 87-119

Hatai, S. 1915 The growth of organs in the albino rat as affected by gonadectomy. Journal of Experimental Zoology, 18, 1-67

Heidrich, A., Schleyer, M., Spingler, H., Albert, P., Knoche, M., Fritze, J., Lanczik, M. 1994 Postpartum blues: relationship between not-protein bound steroid hormones in plasma and postpartum mood changes. Journal of affective disorders, 30, 93-98

Henry, L., Beverly, J. K. A. 1976 Age and sex differences in the response of lymph node post-capillary venules in mice infected with *Toxoplasma gondii*. Journal of Experimental Pathology, 57, 274-281

Hess, R. A. 2003 Estrogen in the adult male reproductive tract: A review. Reproductive Biology and Endocrinology, 1: 52.

Hoch, A. 1910 Constitutional factors in the dementia praecox group. Review of Neurology and Psychiatry, 8, 463-474

Hodková, H., Kodym, P., Flegr, J. 2007 Poorer results of mice with latent toxoplasmosis in learning tests: impaired learning processes or the novelty discrimination mechanism? Parasitology, Apr 20, 1-9 (Epub ahead of print)

Hönekopp, J., Bartholdt, L., Beier, L., Liebert, A. 2007 Second to fourth digit length ratio (2D:4D) and adult sex hormone levels: New data and a meta-analytic review Psychoneuroendocrinology, 32, 313-321

Horsburgh, K, Macrae, I. M., Carswell, H. 2002 Estrogen is neuroprotective via an apolipoprotein E-dependent mechanism in a mouse model of global ischemia. Journal of Cerebral Blood Flow and Metabolism, 22, 1189–1195

Hou, J., Zheng, W. F. 1988 Effect of sex hormones on NK and ADCC activity of mice. International Journal of Immunopharmacology, 10, 15-22

Hsiao, C. C., Liu, C. Y., Hsiao, M. C. 2004 No correlation of depression and anxiety to plasma estrogen and progesterone levels in patients with premenstrual dysphoric disorder. Psychiatry and Clinical Neurosciences, 58, 593–599

Huizink, A. C., Mulder, E. J. H., Buitelaar, J. K. 2004 Prenatal stress and risk for psychopathology: specific effects or induction of general susceptibility? Psychological Bulletin, 130, 115-142

The ICD-10 Classification of Mental and Behavioural Disorders. 1992 World Health Organization, Geneva

Ježová, D. Duncko, R., Lassanova, M., Kriška, M., Moncek, F., 2002b Reduction of rise in blood pressure and cortisol release during stress by ginkgo biloba extract (EGB 761) in healthy voluteers. Journal of Physiological Pharmacology, 53, 337-348

Ježová, D., Juránková, E., Mosnárová, A., Kriška, M., Škultétyová, I. 1996 Neuroendocrine response during stress with relation to gender diffferences. Acta Neurobiol Exp 56, 779-785

Ježová, D., Květňanský, R., Vigaš, M. 1994 Sex differences in endocrine response to hyperthermia in sauna. Acta physiologica Scandinavica, 150, 293-298

Ježová, D., Škultétyová, I., Makatsori, A., Moncek, F., Duncko, R., 2002a Hypothalamo-pituitary-adrenocortical axis function and hedonic behavior in adult male and female rats prenatally stressed by maternal food restriction. Stress, 5, 177-183

Ježová-Repčeková, D., Vigaš, M., Mikulaj, L., Jurčovičová, J., 1982 Plasma testosterone during bicycle ergometer exercise without and after L-dopa pretreatment. Endocrinologia Experimentalis, 16, 3-8

Josephs, R. A., Sellers, J. G., Newman, M. L., Mehta, P. H. 2006 The mismatch effect: when testosterone and status are at odds. Journal of Personality and Social Psychology 90, 999-1013

Jougla, E., Péquignot, F., Carbon, C., Pavillon, G., Eb, M., Bourdais, J.P., Bourdais, O., Hatton, F. 1996 AIDS-related conditions: Study of a representative sample of 1203 patients deceased in 1992 in France. International Journal of Epidemiology, 25, 190-197

Kajantie, E., Phillips, D. I. W. 2006 The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology, 31, 151-178

Kerschbaum, H. H., Ruemer, M., Weisshuhn, S., Klimesch, W. 2006 Gender-dependent differences in sensation seeking and social interaction are correlated with saliva testosterone titre in adolescents. Neuroendocrinology Letters, 27, 315-20

Kiecolt-Glaser, J. K., Glaser, R., Cacioppo, J. T., Malarkey, W. B. 1998 Marital stress: immunologic, neuroendocrine, and autonomic correlates. Annals of the New York Academy of Sciences, 840, 656-663

Kirschbaum, C., Kudielka, B. M., Gaab, J., Schommer, N. C., Hellhammer, D. H. 1999 Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. Psychosomatic Medicine, 61, 154-162

Kirschbaum, C., Wüst, S., Hellhammer, D. H. 1992 Consistent sex differences in cortisol responses to psychological stress. Psychosomatic Medicine, 54, 648-657

Kitay, J. I. 1961 Sex differences in adrenal cortical secretion in the rat. Endocrinology, 68, 818-824

Kittas, C., Henry, L. 1978 Effect of gonadectomy and oestrogen administration on the response of lymph-node post-sapillary venules to infection with *Toxoplasma gondii*. Journal of Pathology, 127, 129-136

Kittas, C., Henry, L. 1980 Effect of sex hormones on the response of mice to infection with *Toxoplasma gondii*. Brittish Journal of Experimental Pathology, 61, 590-600

Kittas, S., Kittas, C., PiaziBiza, P., Henry, L. 1984 A histological and immunohistochemical study of the changes induced in the brains of white mice by infection of *Toxoplasma gondii*. British Journal of Experimental Pathology, 65, 67-74

Klaiber, E. L., Broverman, D. M., Vogel, W., Kobayashi, Y. 1979 Estrogen therapy for severe persistent depressions in women. Archives of General Psychiatry, 36, 550-554

Klein, S. L. 2004 Hormonal and immunological mechanisms mediating sex differences in parasite infection. Parasite Immunology, 26, 247-264

Klinesmith, J., Kasser, T., McAndrew, F. T. 2006 Guns, testosterone, and aggression: an experimental test of a mediational hypothesis. Psychological Science 17, 568–571

Korschenhausen, D. A.. Hampel, H. J., Ackenheil, M., Penning, R., Muller, N. 1996 Fibrin degradation products in post mortem brain tissue of schizophrenics: a possible marker for underlying inflammatory processes: Schizophrenia Research, 19, 103-109

Koss, W. A., Gehlert, D. R., Shekhar, A. 2004 Different effects of subchronic doses of 17-β estradiol in two ethologically based models of anxiety utilizing female rats. Hormones and Behavior, 46, 158-164

Kraemer, R. R., Durand, R. J., Acevedo, E. O., Johnson, L. G., Synovitz, L. B., Kraemer, G. R., Gimpel, T., Castracane, V. D. 2003 Effects of high-intensity exercise on leptin and testosterone concentrations in well-trained males. Endocrine, 21, 261-265

Kraepelin, E. (1919) 1971 Dementia praecox and paraphrenia. Translated by Barclay, R. M., edited by Robertson, G. M., New York, Robert E. Krieger

Kretschmer, E. 1934 Textbook of Medical Psychology. Oxford, UK, Oxford University Press

Kudielka, B. M., Schmidt-Reinwald, A. K., Hellhammer, D. H., Kirschbaum, C. 1999 Psychological and endocrine responses to psychosocial stress and dexamethasone/corticotropin-releasing hormone in healthy postmenopausal women and young controls: the impact of age and a two-week estradiol treatment. Neuroendocrinology, 70, 422-430

Kunstmann, A. 2005 Differentielle Wirkung von Stress auf das Hypophysen-Gonaden-System unter geschlechteranthropologischen und kognitiven Aspekten. Doctor Thesis. Universität Hamburg

Kyomen, H. H., Hennen, J., Gottlieb, G. L., Wei, J. Y. 2002 Estrogen therapy and noncognitive psychiatric signs and symptoms in elderly patients with dementia. American Journal of Psychiatry 159, 1225-1227

Kyomen, H. H., Satlin, A., Hennen, J., Wei, J. Y. 1999 Estrogen therapy and aggressive behavior in elderly patients with moderate-to-severe dementia: results from a short-term, randomized, double-blind trial. American Journal of Geriatric Psychiatry, 7, 339-348

Laudat, M. H., Cerdas, S., Fournier, C., Guiban, D., Guilhaume, B., Luton, J. P. 1988 Salivary cortisol measurement: a practical approach to assess pituitary-adrenal function. Journal of Clinical Endocrinology and Metabolism, 66, 343-348

Leedy, M. G., Wilson, M. S. 1985 Testosterone and cortisol levels in crewmen of U.S. Air Force fighter and cargo planes Psychosomatic Medicine, 47, 4333-4338

Lindamer, L. A., Lohr, J. B., Harris, M. J., Jeste, D. V. 1997 Gender, estrogen, and schizophrenia. Psychopharmacological Bulletin, 33, 221-22

Luft, B. J., Remington, J. S. 1982 Effect of pregnancy on resistance to *Listeria monocytogenes* and *Toxoplasma gondii* infection in mice. Infection and Immunity, 38, 877-881

Luft, B. J., Remington, J. S. 1984 Effect of pregnancy on augmentation of natural killer cell activity by *Corynebacterium parvum* and *Toxoplasma gondii*. Journal of Immunology, 132, 2375-2380

Lund, T. D., Rovis, T., Chung, W. C. J., Handa, R. J. 2005 Novel actions of estrogen receptor-β on anxiety-related behaviors. Endocrinology, 146, 797-807

Lynn, R., Martin, T. 1997 Gender differences in extraversion, neuroticism, and psychoticism in 37 nations. Journal of Social Psychology, 137, 369-373

Maes, M., Bosmans, E., Calabrese, J., Smith, R., Meltzer, H. Y. 1995 Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. Journal of Psychiatric Research, 29, 141-152

Maggi, A., Ciana, P., Belcredito, S., Vegeto, E. 2004 Estrogens in the nervous system: mechanisms and nonreproductive functions. Annual Review of Physiology, 66, 291-313

Majchrzak, M., Malendowicz, L. K. 1983 Sex difference in adrenocortical structure and function. Cell and Tissue Research, 232, 457-469

Matejuk, A., Adlard, K., Zamora, A., Silverman, M., Vandenbark, A. A., Offner, H. 17β-estradiol inhibits cytokine, chemokine, and chemokine receptor mRNA expression in the central nervous system of female mice with experimental autoimmune encephalomyelitis. Journal of Neuroscience research, 65, 529-542

Mathur, D. N., Toriola, A. L., Dada, O. A. 1986 Serum cortisol and testosterone levels in conditioned male distance runners and non-athletes after maximal exercise. Journal of Sports Medicine and Physical Fitness, 26, 245-250

Matsuda, J., Vanier, M. T., Saito, Y., Suzuki, K., Suzuki, Ku. 2001 Dramatic phenotypic improvement during pregnancy in a genetic leukodystrophy: estrogen appears to be a critical factor. Human Molecular Genetics, 10, 23 2709-2715

Matsumoto, K., Takeyasu, K., Mizutani, S., Hamanaka, Y., Uozomi, T. 1970 Plasma testosterone levels following surgical stress in male patients. Acta Endocrinologica, 65, 11-17

Mazur, A., Booth, A. 1998 Testosterone and dominance in men. Behavioral and Brain Sciences 21, 353-63; discussion 363-97.

Mazur, A., Booth, A. Dabbs, J. M. Jr. 1992 Testosterone and chess competition. Social Psychology Quarterly, 55, 70-77.

Mazur, A. Susman, E. J., Edelbrock, S. 1997 Sex differences in testosterone response to a video game contest. Evolution and Human Behavior, 18, 317-326

McCrae, R. R., John, O. P. 1992 An introduction to the Five-Factor Model and its applications. Journal of Personality, 60, 175-215

McIntyre, M. H., Ellison, P. T., Lieberman, D. E., Demerath, E., Towne, B. 2005 The development of sex differences in digital formula from infancy in the Fels Longitudinal Study. Proceedings of the Royal Society of London, B, 272, 1473-1479

Meehl, P. E., 1962 Schizotaxia, schizotypy, schizophrenia. American psychology, 17, 827-838

Métivier, G., Gauthier, R., De la Chevrotière, J., Grymala, D. 1980 The effect of acute exercise on the serum levels of testosterone and luteinizing (LH) hormone in human male athletes. The Journal of Sports Medicine and Physical Fitness, 20, 235-238

Miettunen, J., Veijola, J., Lauronen, E., Kantojarvi, L., Joukamaa, M. 2007 Sex differences in Cloninger's temperament dimensions - a meta-analysis. Comprehensive Psychiatry, 48, 161-169

Miller, L., Hunt, J. S. 1998 Regulation of TNF-α production in activated mouse macrophages by progesterone. Journal of Immunology, 160, 5098-5104

Monnier, J., Stone, B. K., Hobfoll, S. E., Johnson, R. J. 1998 How antisocial and prosocial coping influence the support process among men and women in the U.S. Postal Service. Sex Roles, 39, 1-20

Mora, S., Dussaubat, N., Díaz-Véliz, G. 1996 Effects of the estrous cycle and ovarian hormones on behavioral indices of anxiety in female rats. Psychoneuroendocrinology, 21, 609-620

Morgan, M. A., Pfaff, D. W. 2001 Effects of estrogen on activity and fear-related behaviors in mice. Hormones and behavior, 40, 472-482

Moutquin, J. M. 2003 Socio-economic and psychosocial factors in the management and prevention of preterm labour. British Journal of Obstetrics and Gynaecology, 110, 56-60

Müller, N., Ackenheil, M. 1995 Immunoglobulin and albumin content of cerebrospinal fluid in schizophrenic patients: relationship to negative symptomatology. Schizophrenia Research 14, 223–228

Nielsen, T. F., Ravn, P., Pitkin, J., Christiansen, C. 2006 Pulsed estrogen therapy improves postmenopausal quality of life: A 2-year plcebo-controlled study. Maturitas, 53, 184-190

Nigro, G., Piazze, J., Paesano, R., Mango, T., Provvedi, S., Capuano, O., Pollastrini, L. 1999 Low levels of natural killer cells in pregnant women transmitting *Toxoplasma gondii*. Prenatal Diagnosis, 19, 401-404

Nilsson, N., Carlstein, H. 1994 Estrogen induces suppression of natural killer cell cytotoxicity and augmentation of polyclonal B cell activation. Cellular Immunology, 158, 131-139

Nilsson, P. M., Møller, L., Solstad, K. 1995 Adverse effects of psychosocial stress on gonadal function and insulin levels in middle-aged males. Journal of internal medicine, 237, 479-486

Nissapatorn, V., Lee, C., Quek, K. F., Leong, C. L., Mahmud, R., Abdullah, K. A. 2004 Toxoplasmosis in HIV/AIDS patients: A current situation. Japanese Journal of Infectious Disease, 57, 160-165

Nolen-Hoeksema, S. 1987 Sex differences in unipolar depression: evidence and theory. Psychological Bulletin, 101, 259-282

Nomura, M., Andersson, S., Korach, K. S., Gustafsson, J. A., Pfaff, D. W., Ogawa, S. 2006 Estrogen receptor-beta gene disruption potentiates estrogen-inducible aggression but not sexual behaviour in male mice. European Journal of Neuroscience, 23, 1860-1868

Nomura, M., McKenna, E., Korach, K. S., Pfaff, D.W., Ogawa, S. 2002 Estrogen receptor-β regulates transcript levels for oxytocin and arginine vasopressin in the hypothalamic paraventricular nucleus of male mice. Molecular Brain Research, 109, 84-94

Oades, R. D., Schepker, R. 1994 Serum gonadal steroid hormones in young schizophrenic patients. Psychoneuroendocrinology, 19, 373-385

Olweus, D., Mattsson, A., Schalling, D., Low, H. 1980 Testosterone, aggression, physical, and personality dimensions in normal adolescent males. Psychosomatic Medicine 42, 253

Olweus, D., Mattsson, A., Schalling, D., Low, H. 1988 Circulating testosterone levels and aggression in adolescent males: A causal analysis. Psychomosomatic Medicine 50, 261-272

Opstad, P. K. 1992 The hypothalamo-pituitary regulation of androgen secretion in young men after prolonged physical stress combined with energy and sleep deprivation. Acta Endocrinologica, 127, 231-236

Otte, C., Hart, S., Neylan, T. C., Marmar, C. R., Yaffe, K., Mohr, D. C. 2005 A meta-analysis of cortisol response to challenge in human aging: importance of gender. Psychoneuroendocrinology, 30, 80-91

Paleromo-Neto, J., Dorce, V. A. 1990 Influences of estrogen and/or progesterone on some dopamine related behavior in rats. Gen. Pharmacol. 21, 83-87

Pang, X., Cotreaubibbo, M. M., Sant, G. R., Theoharides, T. C. 1995 Bladder mast-cell expression of high-affinity estrogen-receptors in patients with intersticial cystitis. British Journal of Urology, 75, 154-161

Petitto, J. M., McCarthy, D. B., Rinker, C. M., Huang, Z. Getty, T. 1997 Modulation of behavioral and neurochemical measures of forebrain dopamine function in mice by species-specific interleukin-2. Journal of Neuroimmunology, 73, 183-190

Petrie, E. C., Wilkinson, C. W., Murray, S., Jensen, C., Peskind, E. R., Raskind, M. A. 1999 Effects of Alzheimer's disease and gender on the hypothalamic-pituitary-adrenal axis response to lumbal puncture stress. Psychoneuroendocrinology, 24, 385-395

Phillips, A. N., Antunes, F., Stergious, G., Ranki, A., Jensen, G. F., Bentwich, Z., Sacks, T., Pedersen, C., Lundgren, J. D., Johnson, A. M. 1994 A sex comparison of rates of new AIDS-defining disease and death in 2554 AIDS cases. AIDS 8, 831-835

Pope, H. G., Kouri, E. M., Hudson, J. I. 2000 Effects of suprapfysiologic doses of testosterone on mood and aggression in normal men: a randomized controlled trial. Archives of General Psychiatry, 57, 133-140

Provinciali, M., DiStefano, G., Muzzioli, M., Garzetti, G. G., Clavattini, A., Fabris, N. 1995 Relationship between 17-β-estradiol and prolactin in the regulation on natural killer cell activity during progression of endometriosis. Journal of Endocrinological Investigation, 18, 645-652

Pung, O. J., Luster, M. I. 1986 *Toxoplasma gondii*: decreased resistance to infection in mice due to estrogen. Experimental Parasitology, 61, 48-56

Purifoy, F. and L. Koopmans. 1979. Androstenedione, testosterone, and free testosterone concentration in women of various occupations. Social Biology 26: 179-188

Radíková-Červeňáková, Z., Penešová, A., Koska, J., Květňanský, R., Ježová, D., Hučková, M., Vigaš, M, Macho, L. 2004 Does orthostatic stress influence neuroendocrine response to subsequent hypoglycemia in humans? Annals of the New York Academy of Sciences, 1018, 576-581

Riecher-Rossler, A., Hafner, H., Stunbaum, M., Maurer, K., Schmidt, R. 1994 Can estradiol modulate schizophrenic symptomatology? Schizophrenia Bulletin 20, 203-214

Riecher-Rossler, A., Hafner, H., Dutsch-Strobel, A., Stunbaum, M. 1998 Gonadal function and its influence on psychopathology: a comparison of schizophrenic and non-schizophrenic female inpatients. Archives of Women's Mental Health, 1, 15-26

Rijhsinghani, A. G., Thompson, K., Bhatia, S. K., Waldschmidt, T. J. 1996 Estrogen blocks early T cell development in the thymus. American Journal of Reproductive Immunology, 36, 269-277

Roberts, C. W., Cruickshank, S. M., Alexander, J. 1995 Sex-Determined resistance to *Toxoplasma gondii* is associated with temporal differences in cytokine production. Infection and immunity, 63, 2549-2555

Roberts, C. W., Walker, W., Alexander, J. 2001 Sex-associated hormones and immunity to protozoan parasites. Clinical Microbiology Reviews, 14, 476-488

Roelfsema, F., van den Berg, G., Fröhlich, M., Veldhuis, J. D., van Eijk, A., Buurman, M. M., Etman, B. H. B. 1993 Sex-dependent alteration in cortisol response to endogenous adrenocorticotropin. Journal of Clinical Endocrinology and Metabolism, 77, 234-240

Rohleder, N., Schommer, N. C., Hellhammer, D. H., Engel, R., Kirschbaum, K. 2001 Sex differences in glucocorticoid sensitivity of proinflammaroty cytokine production after psychological stress. Psychosomatic Medicine, 63, 966-972

Rosenblatt, J.S. 1994 Psychobiology of maternal behavior: Contribution to the clinical understanding of maternal behavior among humans. Acta Paediatrica Supplement, 397, 3-8

Roszkowski, P. I., Hyc, A., Malejcyk, J. 1993 Natural killer cell activity in patients with ovarian tumors and uterine myomas. European Journal of Gynaecological Oncology, 14, S114-S117

Roszkowski, P. I., Hyc, A., Stopinska-Gluszak, U., Malejcyk, J. 1997 Natural killer cell activity and sex hormone levels in mastopathy. Gynecological Endocrinology, 11, 399-404

Rubinow, D. R., Roca, C. A., Schmidt, P. J., Danaceau, M. A., Putnam, K., Cizza, G., Chrousos, G., Nieman, L. 2005 Testosterone suppression of CRH-stimulated cortisol in men. Neuropsychopharmacology, 30, 1906-1912

Santizo, R. A., Anderson, S., Ye, S., Koenig, H. M., Pelligrino, D. A. 2000 Effects of estrogen on leukocyte adhesion after transient forebrain ischemia. Stroke, 31, 2231-2235

Salem, M. L., Matsuzaki, G., Kishihara, K., Madkour, G. A., Nomoto, K. 2000 beta-estradiol suppresses T cell-mediated delayed-type hypersensitivity through suppression of antigen-presenting cell function and Th1 induction. International Archives of Allergy and Immunology, 121, 161-169

Sapolsky, R. M. 1992 Neuroendocrinology of the stress-response. In: Becker, J. B., Breedlove, S. M., and Crews, D. (Eds.) Behavioral endocrinology, Cambridge, MA, The MIT Press.

Scantamburlo, G., Hansenne, M., Fuchs, S., Pitchot, W., Maréchal, P., Pequeux, C., Ansseau M., Legros, J. J. 2007 Plasma oxytocin levels and anxiety in patients with major depression. Psychoneuroendocrinology, 32, 407-410

Schlüter, D., Kaefer, N., Hof, H., Wiestler, O. D., Deckert-Schlüter, M. 1997 Expression pattern and cellular origin of cytokines in the normal and *Toxoplasma gondii*-infected murine brain. The American Journal of Pathology, 150, 1021-1035

Schmidt, P. J., Purdy, R. H., Moore, P. H., Paul, S. M. Jr., Rubinow, D. R. 1994 Circulating levels of anxiolytic steroids in the luteal phase in women with premenstrual syndrome and in control subjects. Journal of Clinical Endocrinology and Metabolism, 79, 1256-1260

Schultheiss, O. C., Dargel, A., Rhode, W. 2003 Implicit motives and gonadal steroid hormones: effects of menstrual cycle phase, oral contraceptive use, and relationship status. Hormones and Behavior, 43, 293-301

Screpanti, I., Santoni, A., Gulino, A., Herberman, R. B., Frati, L. 1987 Estrogen and antiestrogen modulation of the levels of mouse natural killer activity and large granular lymphocytes. Cellular Immunology, 106, 191-202

Seaman, W. E., Blackman, M. A., Gindhart, T. D., Roubinian, J. R., Loeb, J. M., Talal, N. 1978 beta-Estradiol reduces natural killer cells in mice. Journal of Immunology, 121, 2193-2198

Seaman, W. E., Gindhart, T. D. 1979 Effect of estrogen on natural killer cells. Arthritis and Reumatism, 22, 1234-1240

Seeman, T. E., Singer, B., Wilkinson, C. W., McEwen, B. 2001 Gender differences in age-related changes in HPA axis reactivity. Psychoneuroendocrinology, 26, 225-240

Seiki, K., Sakabe, K. 1997 Sex hormones and the thymus in relation to thymocyte proliferation and maturation. Archives of Histology and Cytology, 60, 29-38

Sellers, J. G., Mehl, M. R., Josephs, R. A. 2007 Hormones and personality: Testosterone as a marker of individual differences. Journal of Research in Personality, 41, 126-138

Shirahata, T., Muroya, N., Ohta, C., Goto, H., Nakane, A. 1992 Correlation between increased susceptibility to primary *Toxoplasma gondii* infection and depressed production of gamma interferon in pregnant mice. Microbiology and Immunology, 36, 81-91

Shuqin, G., Wang, X., Rocklin, T. 1995 Sex Differences in Personality: A Meta-Analysis Based on "Big Five" Factors. Paper presented at the Annual Meeting of the American Educational Research Association (San Francisco, CA, April 18-22, 1995)

Silbernagl, S., Despopoulos, A. 1988 Taschenatlas der Physiologie, Georg Thieme Verlag, Stuttgart

Silva, H., Tchernitchin, A. N., Tchernitchin, N. N. 1997 Low doses of estradiol-17 alpha degranulate blood eosinophil leucocytes and high doses alter homeostatic mechanisms. Medical Science Research, 25, 201-204

Skallová, A., Kodym, P., Frynta, D., Flegr, J. 2006 The role of dopamine in *Toxoplasma*-induced behavioural alterations in mice: an ethological and ethopharmacological study. Parasitology, 133, 525-535

Skallová, A., Novotná, M., Kolbeková, P., Gašová, Z., Veselý, V., Sechovská, M., Flegr, J. 2005 Decreased level of novelty seeking in blood donors infected with *Toxoplasma*. Neuroendocrinology Letters, 26, 480-486.

Spanos, C., El-Mansoury, M., Letourneau, R., Minogiannis, P., Greenwood, J., Siri, P., Sant, G. R., Theoharides, T. C. 1996 Carbachol-induced bladder mast cell activation: Augmentation by estradiol and implications for interstitial cystitis. Urology, 48, 809-816

Steiner, M., Dunn, E. J. 1996 The psychobiology of female-specific mood disorders. Infertility and Reproductive Medicine Clinics of North America, 7, 297-313

Stroud, L. R., Tanofsky-Kraff, M., Wilfley, D. E., Salovey, P. 2000 The Yale Interpersonal Stressor (YIPS): Affective, physiological, and behavioral response to a novel interpersonal rejection paradigm. Annals of Behavioral Medicine, 22, 1-11.

Taylor, S. E., Klein, L. C., Lewis, B. P., Gruenewald, T. L., Gurung, R. A. R., Updegraff, J. A. 2000 Biobehavioral responses to stress in females: tend-and-befried, not fight-or-flight. Psychological Review, 107, 411-429

Tersman, Z., Collins, A., Eneroth, P. 1991 Cardiovascular responses to psychological and physiological stressors during the menstrual cycle. Psychosomatica Medicine, 53, 185-197

Torrey, E. F., Yolken, R. H. *Toxoplasma gondii* and schizophrenia. Emerging Infectious Disease [serial online] Nov 2003 [13/7/2007]. Available from: URL: http://www.cdc.gov/ncidod/EID/vol9no11/03-0143.htm

Toufexis, D. J., Myers, K. M., Davis, M. 2006 The effect of gonadal hormones and gender on anxiety and emotional learning. Hormones and Behavior, 50, 539-549

Tupes, E. C., Christal, R. E. 1992 Recurrent personality factors based on trait ratings. Journal of Personality, 60, 225-251 (Original work published in 1961)

Udry, J. 1990 Biosocial models of adolescent problem behaviors. Social Biology 37, 1-10.

Uhart, M., Chong, R. Y., Oswald, L., Lin, P-I., Wand, G. S., 2006 Gender differences in hypothalamic-pituitary-adrenal (HPA) axis reactivity. Psychoneuroendocrinology, 31, 642-652

Uji, M., Yoshida, K., Shintani-Ishida, K., Morimoto, K. 2007 Sex difference in norepinephrine surge in response to psychological stress through nitric oxide in rats. Life Sciences, 80, 860-866

Uvnäs-Moberg, K. 1997 Oxytocin linked antistress effects – the relaxation and growth response. Acta Psychologica Scandinavica (Supplementum), 640, 38-42

Vamvakopoulos, N. C., Chrousos, G. P. 1994 Hormonal regulation of human corticotropin-releasing hormone gene expression: Implications for the stress response and immune/inflammatory reaction. Endocrinology Reviews, 15, 409-420

van Honk, J., Tuiten, A., Verbaten, R., van den Hout, M., Koppeschaar, H., Thijssen, J., de Haan, E. 1999 Correlations among salivary testosterone, mood, and selective attention to threat in humans. Hormones and Behavior, 36, 17-24

Vegeto, E., Belcredito, S., Ghisletti, S., Meda, C., Etteri, S., Maggi, A. 2006 The endogenous estrogen status regulates microglia reactivity in animal models of neuroinflammation. Endocrinology, 147, 2263-2272

Vliagoftis, H., Dimitriadou, V., Boucher, W., Rozniecki, J. J., Correia, I., Raam, S., Theoharides, T. C. 1992 Estradiol augments while tamoxifen inhibits rat mast cell secretion. International Archives of Allergy and Immunology, 98, 398-409

von der Pahlen, B., Lindman, R., Sarkola, T., Makisalo, H., Eriksson, C. J. P. 2002 An exploratory study on self-evaluated aggression and androgens in women. Aggressive Behavior, 28, 273-280

Walf, A. A., Frye, C. A. 2007 Administration of estrogen receptor beta-specific selective estrogen receptor modulators to the hippocampus decrease anxiety and depressive behavior of ovariectomized rats. Pharmacology, Biochemistry and Behavior, 86, 407-141

Walker, W., Roberts, C. W., Ferguson, D. J., Jebbari, H., Alexander, J. 1997 Innate immunity to *Toxoplasma gondii* is influenced by gender and is associated with differences in interleukin-12 and gamma interferon production. Infection and Immunity, 65, 1119-1121

Wang, Y., Campbell, H. D., Young, I. G. 1993 Sex-hormones and dexamethasone modulate interleukin-5 gene-expression in T-lymphocytes. The Journal of Steroid Biochemistry and Molecular Biology, 44, 203-210

Wieck, A., Kumar, R., Hirst, A. D., Marks, M. N., Campbell, I. C., Checkley, S. A. 1991 Increased sensitivity of dopamine receptors and recurrence of affective psychosis after childbirth. British Medical Journal 303, 613-616

Wilke, I., Arolt, V., Rothermundt, M., Weitzsch, C. H., Homberg, M., Kirchner, H. 1996 Investigations of cytokine production in whole blood cultures of paranoid and residual schizophrenic patients. European Archives of Psychiatry and Clinical Neuroscience, 246, 279-284

Williams, T. D. M., Carter, D. A., Lightman, S. L. 1985 Sexual dimorphism in the posterior pituitary response to stress in the rat. Endocrinology 116, 738-740

Witt, D. M., Carter, C. S., Walton, D. 1990 Central and peripheral effects of oxytocin administration in prairie voles (*Microtus ochrogaster*). Pharmacology, Biochemistry, and Behavior, 37, 63-69

Witt, D. M., Winslow, J. T., Insel, T. R. 1992 Enhanced social interactions in rats following chronic, centrally infused oxytocin. Pharmacology, Biochemistry, and Behavior, 43, 855-886

Wood, G. E., Young, L. T., Reagan, L. P., Chen, B., McEwen, B. S. 2004 Stress-induced structural remodeling in hippocampus: Prevention by lithium treatment. Proceedings of the National Academy of Sciences, USA, 101, 3973–3978.

Zuckerman, S. H., Bryanpoole, N., Evans, G. F., Short, L., Glasebrook, A. L. 1995 In-vivo modulation of murine serum tumor-necrosis-factor and interleukin-6 levels during endotoxemia by estrogen agonists and antagonists. Immunology, 86, 18-24

Zumoff, B., Fukushima, D. K., Weitzman, E. D., Kream, J., Hellman, L. 1974 The sex difference in plasma cortisol concentration in man. Journal of Clinical Endocrinology and Metabolism, 39, 805-808

Attached publications

I. Novotná, M., **Hanušová, J**., Klose, J., Preiss, M., Havlíček, J., Roubalová, K., Flegr, J. 2005 Probable neuroimmunological link between *Toxoplasma* and cytomegalovirus infections and personality changes in the human host. BMC Infectious Diseases, 5:54

II. Flegr, J., Hrušková, M., Hodný, Z., Novotná, M., **Hanušová, J.** 2005 Body height, body mass index, waist-hip ratio, fluctuating asymmetry and second to fourth digit ratio in subjects with latent toxoplasmosis. Parasitology, 130, 621-628

III. **Lindová, J.**, Novotná, M., Havlíček, J., Josífková, E., Skallová, A., Kolbeková, P., Hodný, Z., Kodym, P., Flegr, J. 2006 Gender differences in behavioural changes induced by latent toxoplasmosis. International Journal for Parasitology, 36, 1485-1492

IV. Hodková, H., Kolbeková, P., Skallová, A., **Lindová, J.**, Flegr, J. 2007 Higher perceived dominance in *Toxoplasma* infected men – a new evidence for role of increased level of testosterone in toxoplasmosis-associated changes in human behavior. Neuroendocrinology Letters, 28, 110-114

V. **Lindová, J.**, Hrušková, M., Pivoňková, V., Kuběna, A., Flegr, J. Digit ratio (2D:4D) and Cattell's personality traits. European Journal of Personality, accepted to press

VI. **Lindová, J.**, Kuběna, A., Hodková, H., Vavřinová, R., Novotná, M., Kotrčová, A., Jozífková, E., Havlíček, J., Kodym, P., Flegr, J. Money allocation in experimental games supports the stress hypothesis of gender differences in *Toxoplasma*-induced behavioural changes. Submitted to Proceeding of the Royal Society of London, Series B

VII. Flegr, J., **Lindová, J.**, Kodym, P. a) Sex-dependent toxoplasmosis-associated differences in testosterone concentration in humans. Submitted to Parasitology.

VIII. Flegr, J., **Lindová, J.**, Pivoňková, V., Havlíček, J. b) Toxoplasmosis-associated differences in testosterone concentration – an important confounding factor in second to fourth digit ratio studies. Submitted

I.

II.

III.

IV.

V.

VI.

VII.

VIII.