Hormonal Modulation of Social Cognition

and Functional Brain Organization

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Abstract
In the human brain, many cognitive processes are organized in an asymmetrical way. It is generally agreed that the principle of lateralized processing of cognitive tasks reflects an adaptive trend, because inefficient parallel processing can be precluded and processing speed and accuracy can be enhanced by the “division of labor” among the two hemispheres. In line with this assumption, there is unequivocal evidence for structural and anatomical correlates for most of identified lateralized functions in the brain. On the basis of these anatomical facts, theoretical models of neuronal mechanisms have been developed. One influential model for the ontogenetic formation of lateralized functions suggests that lateralization results from asymmetrical interactions between the two hemispheres of the brain. According to this, processing in the subdominant hemisphere is suppressed by neuronal signals originating in the task-dominant hemisphere. Importantly, functional cerebral asymmetries (FCAs) are not a stable principle, but show characteristic changes over time. Furthermore, FCA is neither unitary, but distinctive sex differences in both the magnitude and the variance of lateralized functions exist. Lateralization of functions is a fundamental principle in the organization of brain and behavior in all vertebrate species, but the proximate mechanisms of its development are not fully understood yet. The current thesis addresses two questions in this context: First, what are the mechanisms that drive dynamic changes in functional brain organization? Second, in the course of human evolution, which selective pressures have caused the development of the organizational patterns evident today? One group of neuronal messengers can potentially help answering both of these questions: gonadal sex hormones. Hormonal modulation of neurotransmitter receptors, such as gamma-aminobutyric acid (GABA)-ergic and glutamatergic receptors (that is, of neuronal excitation and inhibition), in the brain has been suggested as one probable answer to the first question. The second question has hitherto not been addressed with respect to hormonal effects. However, the assumption that natural (or
sexual) selection has favored the development of dynamic adaptations of functional brain organization driven by hormonal influence is legitimate: hormones have been documented to profoundly affect a range of behavior patterns in humans and non-human mammals. We know today that hormones also affect numerous aspects of cognition by modulating regions of the brain that mediate these functions. For many social cognitive functions, explanatory models based on evolutionism have been suggested. Now, the question just how these two hormone mediated processes are interconnected is at the core of the current thesis.
1. **General Introduction**
Whenever we encounter another (or even more than one other) person, our brain is flooded with social information. No matter if we discuss our salary expectations with our boss, wait at the checkout counter, or sit across an attractive stranger in the train compartment – we cannot help but register and interpret the gestures, facial emotional expressions, subtle changes in the pitch of the voice, and the meaning of words and paraverbal noises of our counterparts. In addition, a multitude of environmental information, such as time, place, norms and rules of the setting are assimilated, retrieved, and updated. All of this happens mostly outside of conscious awareness, and if we consciously notice a subtle twitch of the mouth, an eye-blink or catch a glimpse, this is an aversive experience, probably signaling danger and often causing rumination. Thus, in any given social context and within milliseconds, our brain perceives, processes, filters, and integrates enormous amounts of social and environmental stimuli. Without this multitude of parallel processes, we would not be able to understand what the other person is feeling, intending to do, expecting us to do and why the other wants us to react in a particular way. We would not be capable of understanding (and using) irony and sarcasm, of putting ourselves in somebody else’s position and feel with other persons, and we could not disguise our own expressions, lie or make up fake intentions. The severe consequences of impairments in any of these computational steps become apparent in psychiatric disorders, such as autism spectrum disorder, social phobia, schizophrenia, or depression, all of which are defined by impairments in social interactions. Studying such conditions has contributed to gain some insights about brain structures or neuronal networks, biochemical messengers, and environmental factors that are involved in the generation of certain emotional states, social motivations, or behavioral intentions. In addition, the study of disturbed social functioning has raised new questions that need to be considered, such as why the incidence of major depression or social phobia is about twice as high in women compared to men, whereas the sex ratio in autism and schizophrenia is cross-culturally estimated with 4:1 – 8:1
in favor of men (WHO, 2012). Men and women do not only differ with regard to the incidence of mental disorders and the expression of social behavior, but also in the performance of a range of other human-specific cognitive skills, such as verbal fluency, arithmetic thinking, face perception, or mental visualization of spatial configurations. Understanding the determinants of sex differences in diverse cognitive domains is not only important for the sake of the social-psychological implications that may (or may not) be drawn from findings, but to enable a better understanding of the particular cognitive processes in the first place. However, the brain-physiological expenditure and the complexity of neuronal activity that is required to produce adequate social behavior is barely conceivable, and our understanding of the underlying neuronal processes is still very limited today. In order to deepen our understanding of the mechanisms underlying social cognitive functioning, it will be necessary to first determine and investigate clearly delimitable sub-processes that are involved in generating diverse cognitive outcomes. One such detailed sub-process is the alteration of neuronal communication by a group of biochemical messengers; the gonadal sex hormones. Hormonal influences on social behavior were originally studied in animal models, where basic insights in hormonal influences on a variety of cognitive processes and social behaviors were obtained. However, the way that peripheral hormones such as steroid sex hormones exactly operate in the central nervous system (CNS), once they have passed the blood-brain barrier, is still poorly understood. Also, the fact that genetic and environmental factors influence behavior via hormonal regulation is often not considered thoroughly. First reports about hormonal effects on human behavior, for instance on aggression, sex drive, or food intake, have evoked the impression that humans were at the mercy of their hormonal states. Even though the organizational effects of several hormones can have massive implications, the direct functional impact of circulating hormones on behavioral outcomes has often been over-estimated. Especially in the popular science media, the picture of hormone-driven, absolute, and predetermined sex differences, for instance in spatial and verbal ability, was
transported starting in the 1990’s (e.g., “Why men don’t listen and women can’t read maps” by Allan and Barbara Pease, 1998). Consequentially, the need to scientifically approach the issue and to quantitatively estimate the magnitude of cognitive sex differences increased.

This thesis deals with the potential impact of sex hormones on cognitive processing. The objective is to contribute to a better understanding of hormonal effects on the functional brain organization. By providing new empirical input, the potential role of hormonal neuromodulation in the evolution of social cognition shall be examined. The introduction presents an overview about the current knowledge of functional brain organization, with a special emphasis on hemispheric asymmetries (Chapter 1.1). Gonadal sex hormones and their mode of action are presented in Chapter 1.2. Chapter 1.3 reviews more than two decades of research into sex differences and hormonal effects on lateralized brain functions and its remarkably conflicting results. The last part of the introduction deals with evolutionary accounts on human social and sexual behavior, as well as the role that hormones play in the regulation of social behavior (Chapter 1.4). The puzzling empirical inconsistencies in hormone/FCA associations were taken up in a large-scale study considering many aspects of the debate, and the results are presented in Chapter 2. The question why sex differences in lateralized functions evolved in the first place is addressed in Chapters 3 and 4. Evolutionary theories suggest that every feature of human behavior and brain functioning that is evident today can be interpreted as a result of natural and/or sexual selection, as having increased the fitness or survivorship for human ancestors from about two million years ago. According to this evolutionary perspective, short-termed and physiologically complex changes in functional brain organization across the menstrual cycle would not have evolved without an “adaptive purpose”, that is, without fulfilling some sort of fitness-increasing function. The idea that hormone-mediated functional brain plasticity serves the purpose of flexible social cognitive adaptations was investigated in two aspects of social cognition: the optimization of the ability to judge a conspecific’s
trustworthiness, and the adaptation of social motives. Consequently, one study dealt with an explicit behavioral measure of interpersonal trust as assessed in a modified game theoretical approach (Chapter 3). Another study examined menstrual cycle effects on self-regulation and implicit affiliation and power motivation (Chapter 4).

Taken together, this thesis set out to investigate the assumption that fluctuating sex hormones in women have not only evolved to physiologically regulate reproductive processes, but constitute a means to dynamically mediate social-cognitive adaptations to fluctuating reproductive states.

1.1 **Functional Brain organization**

The average adult human brain consists of 80 – 120 billion neurons which are connected via estimated 176,000 km (in men) or 149,000 km (in women) of myelinated axons (Marner et al, 2003). Compared to other primate brains, the human brain is much larger than would be expected from body size. The discontinuity from hominid ancestors mainly concerns the expansion of the cerebral cortex, especially the frontal cortex, which is associated with abstract executive cognitive functions such as logical reasoning, problem solving, or self-control. Generally, the cerebral cortex is organized in a crossed topographical manner, that is, the right side of the body is represented in the left hemisphere and vice versa.

1.1.1 **Lateralization of functions**

To a large extent, one hemisphere’s structural and functional organization is mirrored in the other one. However, modern neuroimaging techniques revealed several distinct anatomical and functional left-right-differences. Among the most often cited structural asymmetries is the left-ward asymmetry of the planum temporale, an area located posterior to the primary auditory cortex on the superior temporal gyrus. This language-associated area is typically larger in the left compared to the right hemisphere, therewith reflecting the functional dominance of the left
hemisphere in language-related processing. However, this clear-cut correlation between structural and functional differences between the hemispheres is exceptional (Dos Santos Sequeira et al., 2006). The discovery of qualitative functional differences between the left and the right cerebral hemisphere revolutionized the understanding of higher mental functioning in the human brain. The scholarly recognition of lateralized brain functions dates back to Paul Broca’s observations from lesion studies in the 1860s. The French neurologist had stated for the first time that language impairments resulted mainly from lesions to the left frontal hemisphere, a region that is now referred to as “Broca’s area”, and that has no functional equivalent in the right frontal lobe. Already in 1869, Broca declared functional asymmetry as “one of the principle traits of the human brain” (Broca, 1869). Triggered by this seminal idea, a new line of research started to explore the human brain for homologous areas in the right and left hemisphere that subserved qualitatively different functions (Hugdahl, 2000).

While the left hemisphere and the language system remained the sole focus of research in the early years, scholars gradually began to also explore lateralized sensory, cognitive, emotional, and motor functions in both the left and the right hemisphere (Harrington, 1995). Today, the fact that many higher cognitive functions exhibit relative hemispheric performance differences in terms of response speed and accuracy is well established and largely agreed upon (Kimura, 2002). While the left hemisphere, for instance, dominates in processing language-related stimuli and functions, such as abstract words, phonology, letters, and verbal memory, the right hemisphere is specialized for processing of spatial information, such as geometric patterns or spatial orientation, as well as rhythms, facial stimuli, and (negative) emotions (e.g. Geschwind & Galaburda, 1987; Hugdahl, 2000; Corballis, 2003; Vogel et al., 2003). It is important to point out that dominating a task does not imply that one hemisphere carries out this task exclusively, while neuronal networks in the other hemispheres are incapable of processing the same kind of information. Neuroimaging data have accumulated recently, indicating that in any given task, both hemispheres
are profoundly involved in task processing (McGilchrist, 2010). Nevertheless, the principle of hemispheric asymmetry is evident in the generation of a wide range of human-specific traits, such as language, emotions, fine motor manipulations, or mental visualization, and it has therefore been considered to be uniquely human (Luria, 1973; Crow, 1997; Gazzaniga, 2000). However, cerebral asymmetry seems to be a rather widespread phenomenon in the animal kingdom, having been observed in many invertebrate and vertebrate species (Rogers & Andrews, 2002; Ocklenburg & Güntürkün, 2012). This evidence challenges the view of human uniqueness, and FCA is acknowledged as a fundamental, cross-species principle of brain organization today.

1.1.2 What is the advantage of lateralized brain functions?
Evolutionary theories suggest that every feature of brain functioning that is evident today has to be interpreted as constituting an adaptive advantage. One of the most influential accounts for the evolutionary trend towards a division of labor between the two cerebral hemispheres proposes that FCA serves to enhance efficient parallel processing, while at the same time reducing inefficient redundant processes, allowing for a more efficient use of the limited cortical capacity (Cook, 1986; Ringo et al., 1994; Hugdahl, 2000; Vallortigara, 2006). A potential disadvantage of lateralized brain functions has been put forward by clinicians who observed more severe impairments after unilateral brain damage in highly lateralized functions, such as impairments of speech productions after left-hemispheric stroke (Boles, 2005). It has been suggested that the degree of lateralization could predict outcome after brain damage (the less lateralized a given function is, the greater and faster is the recovery of deficits in this function). However, there is little support for this assumption in clinical reality, and natural selection is unlikely to be sensitive for such disadvantages. In fact, the human brain became more and more divided in the course of evolution. It is assumed that the environmental context in which human performance asymmetries have developed (an estimated 2-3 million years ago) has put
demands on both language skills and orientation in a three-dimensional space. Thus, selection pressures may have shaped the formation of FCA in exactly these cognitive domains. In addition to theories about the ultimate origin of hemispheric asymmetries, it is important to understand the proximate mechanisms generating FCAs in the human brain.

1.1.3 Inhibitory theory of lateralization

Provided that there are specialized brain areas for certain cognitive functions, the actual neuronal implementation needs to be addressed. How comes that one hemisphere processes a given compound of incoming stimuli, and what happens in the other hemisphere at the same time? One theoretical account for the generation and maintenance of FCA is the inhibitory theory of cerebral lateralization, which is based on two major principles of neuronal communication in the CNS: excitation and inhibition. Both forms of neuronal communication are modulated by biochemical messengers; the neurotransmitters. Neurotransmitter molecules released from one cell induce either the excitation or the inhibition of connected neighbor cells. The primary exciting neurotransmitter is glutamate, and the primary inhibiting neurotransmitter is GABA. The interaction of these messengers is thought to be critically involved in rapid and coordinated communication between the two hemispheres, and thus for efficient processing. According to the inhibitory framework, FCAs emerge from a stimulus-specific activation of one hemisphere that inhibits activity within the contralateral hemisphere during task processing (Cook, 1984; Hellige, 1993; Chiarello and Maxfield, 1996). A prominent brain structure which can account for such fast information transmission is the corpus callosum (CC), the largest commissure in the mammalian brain consisting of up to 800 million myelinated axon fibers (Aboitiz et al., 1992; figure 1). In connecting homologous areas, most of the callosal fibers arise from excitatory and glutamatergic pyramidal neurons in one hemisphere and terminate on pyramidal neurons in the opposite cerebral cortex (Conti & Manzoni, 1994). These pyramidal neurons then activate GABAergic interneurons, from
which widespread inhibitory signals in the contralateral hemisphere are induced. Thus, cortico-cortical interactions via the CC seem to be characterized by short excitatory postsynaptic potentials and prolonged inhibitory postsynaptic potentials, instead of being purely excitatory or inhibitory (Kawaguchi, 1992). The main function of the CC can be summarized as keeping functions apart and to inhibit information transmission. In the course of evolution, the ratio of the CC to the volume of the hemispheres became smaller, and symmetrical topographic connections have in parts turned into area-specific asymmetric connections (for a review, see Marzi et al., 1991; Bitan et al. 2010). For example, Barrick et al. (2007) reported a rightward-asymmetric pathway connecting the posterior temporal lobe to the superior parietal lobe, possibly reflecting the rightward functional lateralization of auditory spatial attention and working memory. Furthermore, there is evidence for a leftward-asymmetric pathway connecting the parietal and frontal lobes to the temporal lobe (ibid), which may be related to leftward lateralization of language functions. In considering these phenomena, Güntürkün and Hausmann (2003) proposed a theoretical framework explaining the establishment of FCA. The concept of dual coding of FCA encompasses stable structural asymmetries on the one hand, and dynamically changing commissural asymmetries on the other hand. Once they have established during ontogenesis, structural asymmetries remain relatively stable over time. On the contrary, the functional level can be modulated by diverse messengers and environmental events. One group of biochemical messengers that is known to alter neurotransmitter activity is the group of steroid hormones. Because sex hormones as a subgroup of steroid hormones are assumed to play a role in neurotransmission, gonadal sex hormones and their already known neuromodulatory properties will be described in more detail in the following.
1.2 Gonadal sex hormones and their neuromodulatory properties

Steroid hormones belong to the lipid group of elements, which means that they are easily lipid, but hardly water soluble, and that they can act directly on target cells (Heffner & Schust, 2010). All steroid hormones are structurally very similar because all have a common biochemical progenitor: cholesterol. Five main groups of steroid hormones are distinguished according to the receptors they interact with: mineralocorticoids (primary exemplar: aldosterone), glucocorticoids (primary exemplar: the “stress hormone” cortisol), as well as three groups of gonadal sex hormones; androgens (primary exemplar: testosterone), estrogens (primary exemplar: estradiol), and progestagens (primary exemplar: progesterone). Their structural similarity makes it difficult to determine the particular effect of a single sex hormone. For instance, progestagens can be metabolized into androgens, which in turn can be converted into estrogens (Frick, 2012). Thus, total hormone concentrations can be more dependent on enzyme activity than on hormone producing gland activity. In general, sex hormone balance is understood to be regulated via the hypothalamic-pituitary-gonadal (HPG)-axis, which is organized in a hierarchical fashion. It begins in the ventral diencephalon with gonadotropine-releasing hormones, produced and released from hypothalamic cells, which control the synthesis

Figure 1: Coronal (A) and midsagittal (B) magnetic resonance images (T1-weighted) of the corpus callosum. Source: Westerhausen & Hugdahl, 2008.
and release of gonadotropines (luteinizing hormone (LH) and follicle stimulating hormone (FSH)) in the anterior pituitary gland. In a complex interaction, the gonadotropins control the production of gonadal steroid hormones, e.g. testosterone in the testis of men, or estradiol in the ovaries of women. Because of their lipophilic character, steroid hormones require transportation proteins to travel through the blood stream. It is not fully understood whether so-called binding globulins function to simply carry steroid hormones to their target tissues, or whether they function to prevent excessive steroid action on the target tissues (Romero, 2002). It is clear, however, that all bioactive hormone effects are restricted to the free-circulating, unbound proportion of the particular hormone. This is important because, for example, only 1 - 2% of circulating testosterone and estradiol are unbound and capable of entering cells (Heffner & Schust, 2010). It is important to note that neither the total serum levels, nor the number and density of sex hormone receptors alone can predict any hormonal effect in humans. Instead, there are complex fluctuation patterns, interactions, and feedback loops that have to be considered. In addition, there seems to be interindividual variability in the sensitivity, or responsiveness, to sex hormone effects, as well as intraindividual variability in tissue and cell specificity of gonadal steroid effects (Schmidt et al., 1998; Rubinow & Schmidt, 2002). The large variability is reflected in an important principle of hormone action: It is threshold-dependent. A good way to demonstrate these principles of hormone action is to take a closer look at the hormonal regulation of the menstrual cycle.

1.2.1 Hormonal regulation of the menstrual cycle
Typically, the menstrual cycle is divided in four distinct phases (Hatcher & Namnourn, 2004, figure 2). Counting starts on the first day of menstrual bleedings. The menstrual phase has an average length of 3-5 days. During this phase, progesterone and estradiol concentrations are very low, and also the negative feedback to the pituitary gland is low. Therefore, LH is synthesized, but stored in the brain, and not yet released. The consecutive
phase is called follicular phase, because through the release of FSH from the pituitary gland, follicle growth in the ovaries is activated. Simultaneously, a massive production of estradiol is stimulated in the ovaries. In the late follicular phase, estradiol reaches a threshold for a negative feedback to the pituitary, which reduces FSH release. This withdrawal causes the less mature follicles in the ovaries to die off. Normally, only one mature follicle, called “Graafian follicle”, continues to grow further. Crossing the threshold for a positive feedback, the surge of estradiol causes the sudden release of stored LH from the pituitary gland. This characteristic, sharp LH peak marks the beginning of the ovulatory phase, because it causes the rupture of the follicle, and, thus, ovulation, approximately 12 - 24 hours later (typically on cycle day 14 or 15). In the fallopian tube, the Graafian follicle is transformed into the corpus luteum, which immediately begins to produce large amounts of progesterone. The corpus luteum also produces estradiol, but the concentrations do not reach the threshold for a positive feedback again. This event is seen as the marker for the last phase of the menstrual cycle, the luteal phase, in which high levels of estradiol and progesterone together act on the uterus mucosa to prepare it for potential nidation of a fertilized ovule (approximately cycle days 20-25). Thereby, estradiol is known to cause an increase in both number and size of mucosa cells, whereas progesterone acts on uterine gland activity and the formation of uterine muscles. If conception does not occur, the corpus luteum atrophies, and estradiol and progesterone levels rapidly decline. Without the hormonal support, the extensive vaginal mucosa can no longer be supported; cells die off and get rejected, which leads to menstruation and hence the beginning of the next menstrual cycle.
Figure 2: Schematic diagram of cyclic fluctuations in ovarian hormones and gonadotropins across the menstrual cycle.

It is important to note that the described threshold-related feedback activation does not correspond to fixed hormone levels. Instead, the range of concentrations that are considered as above or below threshold is large, and the threshold can intraindividually vary from cycle to cycle (Hatcher & Namnoum, 2004). Hormone actions in the CNS are often not accurately considered with respect to threshold-dependency.

1.2.2 Central nervous effects of progestagens and estrogens
Due to their lipophilic character, sex steroids are capable of easily passing the blood-brain barrier. The small percentage of unbound sex hormones is sufficient to exert powerful neuromodulatory effects in the CNS, including the regulation of neuronal development and plasticity, neuronal excitability, and neurotransmitter synthesis, release, and transport (McEwen & Alves, 1999; Finocchi & Ferrari, 2011). To mention just one recent example, gray matter volumes in brain regions with a sexual dimorphism favoring women (the right fusiform/parahippocampal gyrus) has been shown to be significantly increased by high levels of female sex hormones (Pletzer et al., 2010). Whether or not a brain region and, thus, brain functions associated with the particular area are sensitive to modulations from biochemical
stimulation is commonly deduced by the presence or absence, as well as by the density of specialized receptor cells in that region. Estradiol and progesterone have specific receptors in the CNS, and the distribution of these receptors accumulates in brain areas that also display anatomic sex differences, such as the amygdala, nuclei of the preoptic area, and in the bed nucleus of stria terminalis (e.g., Sherwin, 2003; Güntürkün and Hausmann, 2007). Both estradiol and progesterone are known to be critically involved in the regulation of the balance of neuroexcitatory and neuroinhibitory activities, but in seemingly opposite directions. Progesterone, or rather its metabolites pregnanolone and allopregnanolone, modulate the GABA\(_A\) receptor complex in a way that it’s binding to the receptor causes enhanced GABA-ergic transmission (Majewska et al, 1986). Progesterone molecules interact at a site close to or identical with that for barbiturates, so that its general effect can be characterized as anxiolytic and sedative (Majewska et al., 1986; Andréen et al., 2009). Furthermore, progesterone suppresses the glutamate-induced excitatory responses of neurons by an estimated 87 % (Smith et al. 1987). While progesterone thus has a generally inhibiting effect on the CNS, estrogens are known to enhance neuronal excitability by augmenting glutamate receptor activity. Estrogens furthermore influence synaptic functional plasticity and learning behaviors (Wooley, 2007) by rapidly increasing the number of dendritic spines (Srivastava et al., 2010).

Another interesting interaction is that between estrogen levels and the striatal dopaminergic system. The reactivity of the reward system (orbitofrontal cortex, amygdala), as measured by means of functional magnetic resonance imaging, was found to be increased during the mid-follicular phase, during which estrogen is unopposed by progesterone (Dreher et al., 2007). Accordingly, Colzato et al. (2010) found the inhibition of a prepotent response in a stop-signal paradigm to be less efficient in the follicular phase, compared to menses and mid-luteal phase of the menstrual cycle. These authors proposed a weakening of inhibitory pathways through the over-supply of striatal dopamine in the follicular phase, leading to enhanced competition between responses. The available neuroimaging data point to
the direction that estrogens are mostly active within the prefrontal cortex (PFC), influencing functions dependent on this brain area. For instance, estradiol is associated with enhanced verbal memory and working memory in healthy cycling women (Maki et al., 2002; Wolf & Kirschbaum, 2002), and seems to be involved in social learning (Soares et al., 2010).

Despite the increasing knowledge of the distinct actions of progestagens and estrogens in the CNS, the combined effect and interactions are poorly understood. The addition of progestagens seems to interfere with the pure estrogen effects. For example, whereas estrogens generally have an enhancing effect on performance in cognitive tasks in which women typically excel (Rosenberg & Park, 2002), progestagens have been assumed to have an independent negative effect on cognition or to attenuate the beneficial estrogen effect (Sherwin, 2012). However, evidence exists that states the opposite. For example, the performance in the Wisconsin card sorting task and visual memory (both PFC-mediated tasks) has been reported to be superior in the luteal phase than during the preovulatory phase, as well as during menses (Berman et al., 1997). Also, the administration of synthetic progestagens in hormone replacement therapy showed beneficial effects on PFC-mediated tasks (enhanced cognition-related neural activity, ibid.).

Although progesterone and estradiol seem to have partly opposite neuromodulatory effects on GABA and glutamate receptors, the interaction of both hormones are suggested to have inhibiting effects on the cortico-cortical neurotransmission that is comparable to the isolated progesterone effect. This conclusion was drawn from the correlative observation that both in the preovulatory phase and in the mid-luteal phase, the transcallosal inhibition was reduced to an almost identical degree (Hausmann et al., 2006). It has been suggested that both steroids modulate the involved neuronal processes, just at different sites, or that possibly both steroids are only indirectly involved in these processes, e.g. in a metabolic chain (ibid.). It is therefore essential to design experiments in a way that allows for the
analysis of estradiol effects alone, as compared to analyses of combined estradiol/progesterone effects.

1.3 Sex differences and hormone effects on functional cerebral asymmetries

Men and women have repeatedly been reported to differ in performance on cognitive tasks that deal with spatial or verbal processing. The first empirical findings of general sex differences in cognitive functions were reported in the 1960 years (summary of early investigations by Garai and Scheinfeld, 1968). For the most, sex differences had been neglected before for mainly two reasons: On the one hand, the female image as the less intelligent sex in the late 19th, early 20th century led scholars to assume that women would be generally outperformed by men, without checking on this hypothesis. On the other hand, for practical reasons, early 20th century investigations in human brain asymmetry had focused on populations of brain-lesioned war veterans and epilepsy patients, both of which were mostly men. The notion that the same cognitive functions that display the largest degree of lateralization also show consistent sex differences induced a multitude of studies investigating the dimension on which both left- and right-hemispheric and male-female performance differs. Cross-culturally, the majority of data demonstrate that women outperform men in verbal tasks, such as speech fluency, speed of articulation, and grammar. This sex difference is already evident in language acquisition: in general, girls tend to begin to speak earlier than boys (Gazzaniga et al, 1998), and at the age of five years, girls tend to have a larger vocabulary than boys (Huttenlocher et al. 1991). Other cognitive domains in which women typically excel are perceptual speed, manual accuracy, and mental arithmetic (Nelson, 2000). Men, on average, outperform women in spatial cognitive tasks, such as labyrinth experiments, combining picture cues, map reading, and mentally rotating objects and figures. Furthermore, men tend to be faster and more accurate in tasks that involve mechanical skills, such as throwing and
catching objects, and arithmetic thinking (Kimura, 2002). The idea that the pattern of sex differences in verbal and spatial skills is related to sex differences in laterality gained increasing attention after the publication of a review on this question by Levy (1971). A wealth of studies has highlighted sex differences in hemispheric asymmetry since then, and several reviews and meta-analyses are available today. Although not all studies found interactions between FACs and sex (Fairweather, 1982; Hahn, 1987; Sommer et al., 2004), those who reported sex differences agreed in the pattern of lateralization: men tend to display a more asymmetrical brain organization, while the functional organization tends to be more symmetrical in women (Harris, 1978; Hyde & Linn, 1988; Hiscock et al., 1995; Voyer, 1996; Wisniewski, 1998; McEwen et al., 1998). For example, functional brain imaging studies revealed that verbal and visuo-spatial tasks are localized in opposite cerebral hemispheres in men, while there is a large overlap of these functions between the left and the right hemisphere in women (Kansaku et al., 2000). Also, deficits after unilateral brain damage are more pronounced in men compared to women (Inglis & Lawson, 1981). For example, the incidence of aphasia as a consequence of left-hemispheric lesions is approximately three times higher in men than in women (McGlone, 1980).

However, the impact of findings like this tends to be overrated, because the reported effect sizes for both left/right and male/female differences were typically rather small and the variability was large. As Voyer (1996) put it: there are presumably more studies that do not find sex differences in lateralized cognitive functions than studies that do find sex differences (but the first ones being subject to publication biases for positive results). Similarly, the variability of performance is supposed to be larger within one sex than between the sexes (Hausmann, 2005). Furthermore, the investigation of hemispheric asymmetries is complicated by both inter- and intraindividual variation in magnitude and direction of FCAs. The notion of this large variability led to the question to what extent sex differences in lateralization patterns are modulated by sex hormones. In addition to animal
studies, this issue has been addressed mainly by means of two distinct approaches: On the one hand by means of pharmacological studies, comparing the performance of individuals with natural hormone states to those who are under the effect of exogenously-fed pharmacological hormones. And on the other hand, the influence of naturally occurring hormone fluctuations, mostly in young women across the menstrual cycle, on cognitive functioning has been investigated.

This latter approach was assumed to be of special relevance, because on the one hand, the basic differences in hormone concentrations between men and women could potentially account for basic sex differences in brain organization. On the other hand, there are strong fluctuations in hormone concentrations in women, but not so much in men. These fluctuations could potentially account for the female data being on average more symmetric and more variant (since women participating in lateralization experiments are very likely to be tested at different phases of their menstrual cycle, hence, at significantly different hormonal states).

In the course of a change from a static to a more dynamic view of FCA, first attempts to detect asymmetry shifts mediated by the menstrual cycle were carried out in the late 1980’s. Until today, a wealth of studies on this topic has been conducted, and many have reported cycle-phase dependent fluctuations of FCAs (Heister et al., 1989; Hampson, 1990; Bibawi et al., 1995; Hausmann & Güntürkün, 2000; Hausmann et al., 2002, Weis & Hausmann, 2010). However, diverse studies on menstrual cycle effects on FCAs yielded a very heterogeneous and partly controversial picture of the lateralized events during menstrual cycle. In addition to the direction of hormone/FCA associations, the role of the involved hormones has been discussed controversially. In particular, there is a still ongoing debate about the relative impact of progesterone and estradiol.
1.3.1 Why have sex differences in functional cerebral asymmetries evolved?
Provided that having a lateralized brain is adaptive in an evolutionary sense, the notion of hormone-modulated shifts in cognitive abilities, such as mental visualization or rotation, is puzzling for evolutionary theorists. Principally, a mechanism that impairs an evolved trait contradicts the postulated advantage of this trait. The general evolutionary account for the development of cognitive sex differences is based on the theory of home base strategy (Lovejoy, 1981). It is assumed that the ecological conditions during the late Miocene (approximately 2 million years ago) have favored a generalist feeding strategy, that is, climatic trends such as cooling, aridity, and increased seasonality would have imposed a need for larger feeding ranges. However, for pregnant or lactating females, travelling to foraging sites implies an increased risk of accidents, exposure to predators, and limited parenting behavior. The home base strategy postulates an evolutionary stable strategy for males collecting available food items and returning them to their mates and offspring, because this would directly increase their reproductive rate by correspondingly improving the protein and calorie supply of the female who could then accommodate greater gestational and lactation loads and intensify parenting. The male superiority in visual-spatial cognitive processing (which might be associated with high levels of testosterone) is therefore seen to result from this provisioning strategy (Placvan & van Schaik, 1997). The progesterone/estradiol-related reduction in spatial performance in women is explained by the benefit of limited mobility on survivorship (Sherry and Hampson, 1997). However, this explanation has also been challenged; in particular, it has been questioned that the benefit of a reduced mobility radius would outweigh the benefit of important spatial functions (Hromatko et al., 2008). Contrasting this suggestive disadvantage of hormone-mediated impairment in FCA, there is evidence for a range of adaptive effects of hormone-modulation on social cognitive functions. In order to better understand the context in which these adaptive (in terms of sexual selection) hormone
effects are postulated, a short introduction to the evolutionary conception of human reproduction is provided in the next paragraph.

1.4. An evolutionary perspective on human sexual behavior

Humans are, in many respects, unusual mammals. With regard to reproduction, the most striking discontinuities from other primates include the increased parental investment in fewer offspring, prolonged life-span especially in females beyond the reproductive life span, and the extensive regression of visible signs of ovulation. Unlike in most mammals, it is not the physical ability, but the psychological motivation for sexual intercourse that is under hormonal control in humans (Bancroft, 1981). Whether or not sexual activity is still coupled with fertility is a matter of debate; while some scientists did not find any hormone-related pattern across the menstrual cycle (Bancroft, 1981, Guillermo et al., 2010), others reported clear-cut peaks of female-initiated sexual activity in the late follicular phase (Bullivant et al., 2004, Pillsworth et al., 2004). However, the extent to which estradiol, testosterone, or progesterone is involved in the modulation of female sexual interest and activity is poorly understood. It has been proposed that with the advent of sexual intercourse outside of reproductive contexts (such as in the luteal phase of the menstrual cycle or during pregnancy), a stronger impact of social context on sexual behavior emerged. For instance, the frequency of sexual intercourse might be more dependent on female initiation, and the strong hormonal impact on sexual motivation might have become replaced by the potential social consequences of engaging in sex in group settings (Wallen, 2001). Furthermore, with “concealed ovulation”, reproductive success requires constant proximity of the male and constant copulatory vigilance in both sexes. This increased sexual vigilance is thought to be reflected in evolved anatomic features, such as body and facial hair and the conspicuous penis in men, as well as the prominent and permanently enlarged mammae in women. Extended sexual intercourse is furthermore assumed to be involved in the formation
and maintenance of pair bonds because it increases pair-bond adhesion and serve as a social display asserting that bond (Lovejoy, 1981).

Given the disequilibrium in male and female investment in procreation (women bear the costs of energy-consuming and potentially life-threatening pregnancy, delivery, and offspring’s nutritive dependency in the first years of life, while men’s investment basically incorporates one ejaculation), the theory of sexual selection postulates that women’s mating strategies have adaptively evolved to minimize the risk of costly errors. A large body of literature supports the notion that the ways in which women and men identify, attract, and retain optimal mates differ dramatically (Chapter 1.4.3). From the male’s perspective, the optimal strategy involves attention to a mate’s reproductive potential (mainly, indicators of youth and health) and to male competitors. Apart from that, for the sake of maximal gene propagation, men would have to mate with as many partners as possible. On the contrary, the optimal female mating strategy involves attention to a mate’s social status and together with that, his willingness and ability to provide resources and protection to the woman and her offspring. In addition to this preference for good providers, women seem to also have evolved a preference for indicators of “good genes”, such as facial masculinity and bilateral symmetry (Penton-Voak et al., 1999; Johnston et al., 2001). In order to achieve maximum gene propagation, women would have to (implicitly) focus on “quality” in mate choice, but might have to make trade-offs because men with good gene indicators are likely to pursue multi-partner strategies instead of single-partner resource investment (Gangestad & Simpson, 2000; Sefcek et al., 2006). Thus, both the described male and female “strategies” serve the ultimate goal of fitness maximization, but need to be translated into proximate mechanisms. Enhanced higher cognitive functioning, such as memory, logical reasoning, as well as social cognitive functioning, such as social alertness, interest in opposite-sex individuals and desire for sexual intercourse, are likely to be involved in the proximate transfer of the ultimate goal to adaptively reproduce. However, given the complexity of
human social group living, proximate psychological mechanisms would have to be highly flexible. For example, environmental factors, such as stress, have been shown to affect mating preferences in men (Lass-Hennemann et al., 2010), and culturally determined age, place, and time conventions have presumably become a more decisive factor to predict both mate choice and the occurrence of sexual intercourse in humans. For instance, Palmer et al. (1982) found in a sample of almost 2000 American couples that sexual intercourse peaked on weekends, especially on Sunday mornings, and not necessarily in times of highest likelihood of conception. However, although social context is likely to have influenced human sexual behavior already in ancient times, biological and physiological factors are likely to play an important role, still. Selective pressures to develop flexible mating strategies were presumably more pronounced on women, compared to men. This is because, while the male strategy would be equally adaptive across the reproductive life span, female’s chance to arrive at a maximum reproductive value was restricted to only a few years between menarche and menopause, states of being neither pregnant nor lactating, and then to only a small window within the menstrual cycle. One has to bear in mind that ovulation was presumably a rather infrequent event at the time of *Homo sapiens*’ inception. It is assumed that women that lived 100,000 – 50,000 years ago have spent much of their reproductive life in biological states characterized by high levels of progestagens and estrogens, as well as the polypeptide prolactin (that is, pregnant or lactating); states that suppress ovulation (Symons, 1995). Therefore, in the majority of time, the optimal mate choice would it have been to focus on men who provide support and protection. Only in relatively rare episodes of hormonal states in which ovulation could occur, the choice of the best gene-providing mate would have been essential. Indeed, women have been shown to be particularly choosy when they are fertile (Gangestad & Thornhill, 2008). Furthermore, given the restricted opportunities for conception, selection pressures are likely to have acted on unmated, fertile women: They would have had to compete against potential female rivals for copulating with the best
available mate, and especially so if there was a shortage of available “good” mates. Across species, physical forms of intrasexual aggression are assumed to be widely reduced in females, probably because of their higher parental investment and the consequently greater reproductive cost of injury or death (Campbell, 2004). The proximate mechanism to ensure restriction from aggressive competition is thought to be mediated by fear and behavioral inhibition, which is stronger expressed in women compared to men (Arrindell et al., 1993). It was proposed that women’s forms of intrasex competition evolved in ways that maintain physical inviolacy. While men compete with overt, sometimes lethal aggression, women are assumed to compete in attractiveness, defaming rivals by debasing their sexual attractiveness or exclusiveness, and thereby reducing the victim’s social support and reputation (Bjorkqvist et al., 1992). In accordance with this assumption, it was suggested that women’s sensitivity to other women’s attractiveness may be an adaption to detect potential female rivals (Jasienska et al., 2005). This is likely to have been a major factor, given that the number of available mates is estimated to have been limited in the Pleistocene, where groups of approximately 170 - 400 individuals of both sexes, only half of them at reproductive ages, are thought to have lived together (Wobst, 1974).

Taken together, in evolutionary terms, a women’s mate-choice is optimal if it flexibly adapts to both the current hormonal status and complex social and environmental factors. Sex hormones are proposed to act as vehicles to realize such proximate, flexible adaptations.

1.4.1 Hormone effects on general social cognitive functions
The fact that certain kinds of social behaviors are influenced by hormones, via modulation of neuronal pathways of social behavior, is well established today. However, it is important to say that hormones do not directly cause behavior. Instead, acting within minutes (not seconds), hormones can modulate the expression of behaviors (Soares et al., 2010). Among the most well-known examples of this is the effect of testosterone on aggression and
dominance behavior in many species (Wingfield et al., 2006), or the promoting effect of oxytocin and progesterone on affiliative behavior, such as social bonding and parental care (Donaldson & Young, 2008; Harmon-Jones & von Honk, 2012; Feldman, 2012). The evidence about hormone effects on human social behavior is less clear-cut. Even if behavioral traits are observed that can be interpreted as behavioral adaptations to hormonal states, such as reports about increased self-perceived attractiveness, sexual fantasies and desire, or a more provocative dress style, or even higher amounts of tip earned by female lap dancers at times of highest fertility (reviewed in Alvergne & Lummaa, 2010), the actual impact of hormones remains somewhat obscure. There is a general agreement on the sedative, anesthetic, and anti-epileptic effects of progesterone in humans (Sunstrom-Poromaa et al., 2003). Furthermore, not the total progesterone concentration, but rather the sudden withdrawal (e.g., pre-menstrually or postpartum) of progesterone is associated with strong effects on mood and irritability. Progesterone-modulated influence on mood is assumed to act, for instance, via a selective increase in neural responsiveness in the amygdala to angry and fearful faces (van Wingen et al., 2008). Given the high density of progesterone receptors in the amygdala, this hormone could potentially also play a role in person perception and, for instance, the ability to judge the trustworthiness of others which has been shown to depend to a large extent on amygdala activity (Adolphs, 2003). Another account on the mode of progesterone action on mood proposes that progestins may influence mood negatively by enhancing GABA-inhibitory action and by lowering neuronal excitability (Genazzani, 2002; see also section 1.2.2). High levels of progesterone have furthermore been found to be related to increased sensitivity to facial cues carrying sources of threat or contagion (Conway et al., 2007), and accordingly with a biased behavioral tendency towards avoidance as opposed to approach (Derntl et al., 2008). Such effects have been discussed as reflecting an adaptation to increased costs of social and physical threat or danger in pregnant women. Similarly, Fleischman and Fessler (2011) postulated that high levels of progesterone trigger the down-
regulation of inflammatory immune responses, which could serve to facilitate implantation and development of the half-foreign blastocyst. These authors found women with increased progesterone levels to be more attentive to hygiene issues and more sensitive to cues of sickness; a possible behavioral adaptation to the increased vulnerability to infection that comes along with this hormonal state.

In recent years, findings about effects of the neuropeptide oxytocin on social cognitive functioning have gained increasing attention in the literature (Frick, 2012). For example, a single intranasal administration of oxytocin in male research participants has been shown to cause massive increases in interpersonal trusting behavior, even if trusting behavior had been abused before (Kosfeld et al., 2005; Baumgartner et al., 2008). Because those effects were clearly dependent on social contexts, it has been assumed that oxytocin has beneficial effects on human trusting behavior. A growing number of studies are now available using game theoretical approaches to test hormonal effects on human social cognitive functioning, but game theoretical investigations of gonadal sex hormones on these social cognitive functions are, to the best of my knowledge, as yet unannounced.

1.4.2 Hormone influences on social motivation and decision making
The key idea that female sexual psychology has evolved in mostly automatic, categorical programs fits with the general characteristic of evolved phenomena: given the limited cognitive processing capacity, they have to be simple, generic, and apply to a multitude of potential situations in complex social environments. It is somewhat surprising that the literature about hormone effects on the generation of people’s social-cognitive processes and products still is so limited, given the fact that hormones are known to effect information processing and response generation (Erlanger et al., 1999). Evolved psychological mechanisms may be modulated by hormonal factors in such a way that the perception of biologically relevant targets in the environment becomes accelerated and the retrieval of categorical information about the target is facilitated, so that the perceiver
can access applicable information as rapidly and efficiently as possible (Macrae et al., 2002). In accordance with this assumption, these authors found facilitated activation and access to category-related knowledge about men during the cycle phase of highest conception risk. Recent attempts in neuroimaging and electrophysiological studies further support the link between the menstrual cycle and processing speed for reproductive-relevant stimuli. For instance, Fernández et al. (2003) found localized changes in brain plasticity and brain activity related to the menstrual cycle, and Krug et al. (2000) reported a larger peak in the late-positive component of the event related potential for sexual stimuli than for similar, but non-sexual stimuli in the most fertile period of the menstrual cycle.

The idea that situational cues become more salient as a function of biological states and/or psychological needs is also taken up in motivational psychology. Many motivational theories are oriented on Maslow’s seminal work about human basic needs (Maslow, 1943). According to this framework, human motivation is hierarchically organized, from basal physiological needs (such as breathing, food, sleep), over safety and belonging, up to self-esteem and self-actualization. Several classes of motives have been described in motivational psychology, but the three basic motives encompass power, achievement, and affiliation motives. These are thought to have been shaped by evolutionary pressures and to have become embedded in human congenital repertoire, but are also modified by individual experience and learning history. Implicit motives are assumed to orient attention (according to the prevailing need), to select intentions, implement concrete actions, and energize goal-directed behavior (McClelland, 1987). Referring to latent behavioral predispositions, most of human motivation is assumed to act outside of conscious awareness, but to be closely related to emotional states. A motive can be spontaneously triggered by environmental cues and internal states, but the striving for need satisfaction can easily be inhibited in humans (Kuhl, 2001). For example, all humans are born with the basic need to take in food, which is modulated by complex biochemical interactions such as increases in ghrelin.
concentrations and decreases in glucose and insulin concentrations. The “hunger motive” enhances behavioral tendencies to seek out for environmental cues signaling the availability of food, but the enactment of this motive varies interindividually. This process would be termed “hunger motivation”. Similarly, it can be assumed that complex hormone interactions act as internal stimuli, which implicitly influence attention control and behavioral predispositions. A few examples of such hormone effects on assessable behavioral alterations are described below.

1.4.3 Subtle hormone effects on female mate preferences
A body of literature is available on the relationship between hormone fluctuations (mostly across the menstrual cycle) and variation in female mate preferences. This includes the preference for masculine faces (Jones et al., 2008), for symmetry in faces (Gangestad & Thornhill, 1998; Little et al., 2007), for odor that is linked to major histocompatibility complex (MHC) -similar or -dissimilar men (reviewed in Havlicek & Roberts, 2009), for creative men (Haselton & Miller, 2006), or for unmated men (Bressan & Stranieri, 2008). Also, variation in sexual desire (Hill, 1988; Van Goozen et al., 1997; Pillsworth et al., 2004), or female-initiated sexual activity (Adams et al., 1978; Bancroft, 1981; Harvey, 1987; Bullivant et al., 2004) has been documented. However, the results were often inconsistent, with contradictions about the particular cycle phase in which changes in the various measures occur, methods of cycle phase assessment, and the consideration of sample characteristics, such as age, history of hormonal medication, wish for children or motivation to avoid pregnancy, history of pregnancies, educational level, or relationship status of the investigated women. Also, not all researchers distinguished between potential short-term and long-term partners when asking their participants to evaluate stimuli. However, there is evidence that exactly this distinction does account for a large portion of the variance (Gangestad & Thornhill, 2008). Furthermore, the majority of studies did not measure outcomes in control groups, such as same-aged women with stable hormone concentrations due to the use of
hormonal contraceptives. Those few exceptions that did involve control groups report that the effects of menstrual cycle on perceptions were not evident in women who were using hormonal contraceptives (e.g., Penton-Voak et al., 1999), a notion that underpins the original hormone effect. Another shortcoming in many studies is the strong emphasis on self-report in forms of questionnaires or interviews, and the concentration on measures that are obviously and directly associated with sexual behaviors and preferences. This can be problematic for two reasons: Firstly, such study designs are prone to socially acceptable response behavior. Secondly, the relevant proximate psychological mechanisms may be of rather indirect, implicit nature; subtly embedded in social cognitive heuristics.

1.4.4 Physiological and Psychological effects of hormonal contraceptives

Oral contraceptives are used by millions of women worldwide, notwithstanding the poorly understood effects on cognitive functioning, mood, and female sexuality. The contraceptive effect itself is known to be two-fold: On the one hand, the high levels of synthesized progestagens and estrogens interfere with the above described HPG-axis action, in that the release of gonadotropines from the pituitary gland and, thus, ovulation is suppressed. On the other hand, effects on uterus mucosa facilitating conception and implantation of fertilized ovule are disturbed, too. As a side-effect, which unintentionally acts in a contraceptive manner, decreases in sexual desire and vaginal lubrication are commonly reported, but it is not entirely clear if this effect is due to the entailed suppression of testosterone in oral-contraceptive using women (e.g., Dennerstein et al., 1980, Alvergne & Lummaa, 2010, Coenen et al. 1996). Furthermore, in women using oral contraceptives, the preference for “good gene indicators” seems to be altered into a continuous preference for “good material investment indicators” (reviewed in Alvergne & Lummaa, 2010).
1.5 **Hypothesis**
Based on the described considerations, the current thesis aimed at testing the following predictions:

*Hypothesis 1:* High levels of the ovarian hormones progesterone and estradiol are associated with reduced interhemispheric inhibition. The reduced inhibition is reflected in less pronounced FCA in both left- and right-hemispheric dominant tasks, in prolonged interhemispheric transfer time, and in increased interhemispheric integration in phases of the menstrual cycle when these hormones occur in highest concentrations, as compared to the low-hormone menstrual phase (Chapter 2).

*Hypothesis 2:* There is a common hormonal mechanism for menstrual cycle phase-related shifts in functional brain organization and shifts in social cognitive functions that are implicitly related to female sexual motivation. The inhibitory processes at times of high ovarian hormones are associated with more positive evaluations of trustworthiness and willingness to cooperate with attractive players in a trust game (Chapter 3), as well as increased implicit affiliation motivation and reduced inhibitory levels of motive enactment (Chapter 4).
Chapter 2:

Sex hormonal influences on functional brain organization revisited: disentangling the effects on interhemispheric inhibition and integration

Abstract | Neurotransmission within and between the cerebral hemispheres builds the basis for a fundamental organizational principle in mammalian brains: functional cerebral asymmetries (FCAs). Numerous studies have investigated hormonal influences on FCA, however the empirical picture remains to be remarkably conflicting. The current study used an extensive experimental design in order to coherently address the following major matters of debate: 1. Do hormones exert influence on only one or on both hemispheres? 2. Are activating or inhibiting hormone effects decisive? 3. Do sex hormones effect inter-hemispheric inhibition and interhemispheric integration differently? 4. Are FCAs affected by absolute or relative changes in hormone concentrations? 5. What is the particular contribution of the involved sex hormones? In normally cycling women, a reduced degree of lateralization, slowed interhemispheric transfer time, and enhanced inter-hemispheric integration in the mid-luteal phase, compared to the menstrual and preovulatory phase, was observed. Despite the small effect sizes, these results are generally in accordance with the framework of sex hormone-modulated interhemispheric decoupling.

2.1 Chapter Introduction

Following first attempts to detect asymmetry shifts mediated by the menstrual cycle in the late 1980’s, a wealth of studies on this topic has been conducted, and many have reported cycle-phase dependent fluctuations of FCAs (e.g., Heister et al., 1989; Hampson, 1990; Bibawi et al., 1995; Hausmann & Güntürkün, 2000; Hausmann et al., 2002). However, the reported effects varied significantly in terms of task and modality-specificity, target site in the brain, and the particular contribution of the
involved gonadal sex hormones. In fact, for almost every reported effect, contradictory evidence exists. For instance, whereas some researchers proposed a selective effect of estradiol on left-hemispheric performance (Hampron, 1990; Bibawi et al., 1995), others reported an enhancing effect of estradiol on right-hemispheric performance (e.g. facilitated face processing at the time of preovulatory estradiol surge, compared to premenstrual phases in Heister et al., 1989), or associations between estradiol and enhanced right-hemispheric performance in verbal processing (Sanders & Wenmoth, 1998; Bayer & Erdmann, 2008). In contrast to these single-hemisphere accounts, some authors have suggested that both hemispheres are task-independently activated by the high-hormone concentrations in the luteal phase of the menstrual cycle (Broverman et al., 1968; McCourt et al., 1997). Fewer studies have been published reporting no performance differences across the menstrual cycle (Gordon & Lee, 1993; Epting & Overman, 1998).

Another theory postulated that high levels of sex hormones neither exert influence on one hemisphere alone, nor on both hemispheres simultaneously. Instead, Güntürkün & Hausmann (2000) suggested that hormones affect interactions between the hemispheres. Based on findings of reduced FCA at the high-hormone luteal phase in naturally cycling women in both left-hemispheric and right-hemispheric dominant tasks, as well as strong positive associations between progesterone and left-hemispheric performance in a right-hemispheric dominant figure recognition task, the authors provided a theoretical model of the neuronal mechanisms underlying the modulating effect of ovarian hormones on FCA. This model is based on the inhibitory theory of cerebral lateralization (Chapter 1.1) and assumes that interhemispheric inhibition plays a central role in the regulation of a coordinated output from parallel processes in the two hemispheres. The described neuromodulatory properties of progesterone (Chapter 1.4) can be assumed to cause a qualitative reduction of cortico-cortical transmission by suppressing the excitatory responses of cortical pyramidal neurons to glutamate, as well as by enhancing the inhibitory
responses of cortical interneurons to GABA. The combined effect would result in reduced interhemispheric inhibition. When the hemispheres are functionally “decoupled”, the suppression of the subdominant hemisphere would no longer be effective, performance of this hemisphere could increase, and, therefore, the degree of left-right differences would be temporally reduced (figure 3).

The model of progesterone-mediated interhemispheric decoupling received both supportive data and data that questioned the assumptions of the model in the literature. An early point of criticism concerned the fact that the model addresses interhemispheric communication without directly measuring it (Compton et al, 2004). According to the inhibitory framework, inhibitory coupling is required for the dominant hemisphere to achieve meta-control about the output during task performance. Furthermore, information presented to the subdominant hemisphere has to be transferred to the dominant hemisphere for processing. The delayed response that is typically observed when stimuli are presented to the subdominant, compared to the dominant hemisphere, is assumed to reflect this transfer time. Because of the reduced cortico-cortical transmission in high-hormone phases, the decoupling hypothesis would predict a less efficient callosal transfer and hence longer interhemispheric transfer time (IHTT) at this time.

A more elaborate way of addressing hormonal effects on interhemispheric communication is the investigation of cognitive demanding tasks in which the solution requires the integration of information from both hemispheres across the menstrual cycle. There is evidence that in relatively simple conditions, that require only few computational steps to reach a decision, participant’s reactions are faster in within- than in bi-hemispheric trials (Banich & Belger, 1990). However, this pattern inverts in computationally more complex conditions, when processing of task components is divided between the hemispheres and integrated at later computational steps. An extensive body of literature is available showing that the degree to which interhemispheric cooperation improves performance changes with the complexity of the task being performed across different modalities (Belger
& Banich, 1992; Weismann & Banich, 2000; Passarotti et al., 2002; Yoshizaki et al., 2007). In visual half-field stimulation tasks, this phenomenon is referred to as across-field advantage (AFA). Based on the decoupling hypothesis, one could expect that the progesterone-modulated decrease in interhemispheric communication is reflected in a reduced AFA at the high-progesterone mid-luteal phase. Accordingly, a negative correlation between progesterone levels and AFA could be expected (Compton et al., 2004). However, interhemispheric interaction is a multifaceted phenomenon that might be differentially involved in interhemispheric integration (as required in the Banich-Belger task), and interhemispheric inhibition (as required in tasks measuring perceptual asymmetries). Therefore, other scholars arrived at the conclusion that high levels of progesterone could just as well lead to a stronger integration between the hemispheres due to the reduced interhemispheric inhibition, and predicted even stronger AFA in the high-hormone mid-luteal phase, compared to low-hormone menses (Bayer et al., 2008).

![Figure 3: Schematic illustration of the hypothesis of progesterone-modulated interhemispheric inhibition. High levels of progesterone are postulated to reduce corticocortical transmission during the midluteal phase. Source: adapted from Weis & Hausmann 2010.](image-url)
2.2 Experimental Design

In an attempt to shed light on these conflicting predictions and suggested modes of hormone action on functional brain organization, the present study was designed in a way that considered most of the issues of debate: healthy young women with regular menstrual cycles were tested three times in the course of one or two consecutive cycles. Their performance in a range of cognitive tasks at times of lowest (menses, cycle days 2-5) and highest (mid-luteal phase, cycle days 19-22) concentrations of progesterone and estradiol was compared. In order to be able to separate the effect of high estradiol concentrations from the combined effect of estradiol and progesterone, women were tested additionally in their preovulatory phase at mid-cycle (cycle days 11-15), a phase that is characterized by low progesterone levels, but a strong estradiol surge. Because of the known dramatic inter- and intraindividual variation in hormone fluctuations across the menstrual cycle, emphasis was placed on exact hormone determination. Every participant was tested at the same time of day in order to control for circadian variation in hormone release, and blood samples were taken after every testing session. In addition to progesterone and estradiol, the gonadotropines LH and FSH were also analyzed, so that a more accurate validation of cycle phases, particularly the preovulatory phase, was made possible. To control whether participants in the group of naturally cycling women were actually free of any hormonal medication, the concentration of sex hormone binding globulin (SHBG) was analyzed, too. SHBG concentrations > 120 nanomol per liter typically indicate hormonal contraceptive action. Thus, women with concentrations above this threshold were excluded from analysis. In order to rule out the possible explanation that hormones target on only one hemisphere, women conducted both a language-related left-hemispheric dominant task and a spatial cognitive right-hemispheric dominant task at all three testing sessions. To also account for specific impacts on different sensual modalities, one test that was based on visual stimulation (tachistoscopic half-field stimulation) and one test based on auditory input (dichotic listening) was used. Furthermore,
IHTT was measured behaviorally in a simple reaction time task during all three testing sessions. In order to discriminate between hormonal effects on interhemispheric inhibition (perceptual asymmetry tasks, IHTT) and interhemispheric integration, the AFA in a cognitively more demanding task (the complex condition of the Banich-Belger task) was tested at three cycle phases. Because the independent variable in this study was the cycle-phase dependent hormone level, it was necessary to compare the performance of naturally cycling women with women that do not experience hormonal fluctuations. In the past, many studies have chosen post-menopausal women as a control group because these women no longer experience regular hormone fluctuations. However, there is a large inter-individual variability in hormone concentrations in menopausal women. Furthermore, these women are inherently much older than naturally cycling women. Because the effects of aging on cognitive performance are a matter of debate as such (Beste et al., 2006), the comparison of naturally cycling women’s performance with same-aged women who persistently use a combined estrogen/gestagene prescription drug as a means of hormonal contraception (Nuva®Ring) was preferred in the present study. This vaginal ring delivers on average 0.12 mg etonogestrel and 0.015 mg ethinyl estradiol per day over a three-week period of use (Roumen et al., 2001). The endogenous hormone production of women using this ring is very low and stable, which is why this homogenous control group was chosen instead of a group of menopausal women or a group of women using different kinds of anti-baby pills. To control for general sex differences, 30 men of the same age were also tested. The order of testing was counter-balanced across naturally cycling women’s cycle phases. Participants in the control groups were tested at approximately 10 day intervals. A stable pattern of hemispheric asymmetries, IHTT, and interhemispheric integration in a cognitively demanding task was expected in women with stable hormone levels, and in men. In accordance with the hypothesis of sex hormone-mediated interhemispheric decoupling, the following modulations of interhemispheric communication were predicted in naturally cycling women: First, FCA in
both right- and left-hemispheric dominant tasks was expected to be reduced in the mid-luteal and preovulatory phase, compared to menses. Second, the IHTT was expected to be slower in the high-estradiol mid-cycle phase and in the high-estradiol and high-progesterone mid-luteal phase, compared to the menstrual phase. Third, AFA in the complex condition of the Banich-Belger task was expected to be more pronounced in high- compared to low-hormone phases. Fourth, these cycle-phase related modulations should be reflected in associations between the particular hormone levels and the effects of interest, respectively.

2.3 Right-ward perceptual asymmetry

For testing changes in hemispheric asymmetry with respect to spatial processing, a figure recognition task was conducted in the divided visual field paradigm (for a detailed description, see Güntürkün & Hausmann, 2000). In this task, participants have to decide whether a laterally presented geometrical figure matches with a centrally presented trigger figure or not. Typically, responses are faster and more accurate when the test figures are tachistoscopically presented in the left visual field, that is, when they are processed in the right hemisphere, compared to when figures are presented in the right visual field and processed in the left hemisphere.

33 naturally cycling women were initially invited to three testing sessions. Post-hoc validations of cycle phases revealed that five women were tested in their early luteal phase, instead of the preovulatory phase (progesterone values >2 ng/ml, estradiol <20 pg/ml). All other values (see table 1) were in the normal range (Stricker et al., 2006). The data of the remaining 28 women were analysed using repeated measures ANOVA with the within-subjects factors cycle phase (menstrual, preovulatory, mid-luteal) and visual field (left, right). These calculations were conducted for both median reaction times and percent of correct responses. The results showed that in both speed of response and accuracy, the strongest right-ward asymmetry occurred in the high-estradiol mid-cycle phase. In the low-hormone menstrual phase, there was a non-significant left-hemispheric advantage in
both response speed and accuracy. In the preovulatory phase, the typical right-ward asymmetry was found, and the left/right differences were smallest in the mid-luteal phase (figure 4). However, the cycle phase by visual field interaction in both percent correct responses, $F(2, 27) = 2.6, p = .089$, est. $\eta^2 = .08$, and median reaction times, $F(2, 27) = 2.89, p=.070, \eta^2 = .157$, missed statistical significance. In the group of 28 women using hormonal contraceptives, the overall left/right differences were clearly more pronounced than in the naturally cycling women (e.g., in accuracy data, there was a highly significant main effect of visual field, $F(1, 27) = 14.45, p < .01$, est. $\eta^2 = .35$; with 90.2 % correct responses when stimuli were presented in the left visual field, and 87.8 % correct responses when stimuli were presented to the right visual field). For women using hormonal contraceptives, the test session by visual field interaction was not significant, $F(2, 54) = .61, p = .56$, est. $\eta^2 = .02$. Men tended to be even more lateralized (correct responses left visual field: 88.87 % versus correct responses right visual field: 86.2 %; main effect of visual field for median reaction times, $F(2, 27) = 16.24, p < .001$, est. $\eta^2 = .38$.

![Figure 4](image_url)

**Figure 4**: Figure recognition task. Distribution of naturally cycling women’s correct responses when stimuli were presented in the left visual field (gray bars) compared to stimuli presented in the right visual field (black bars). Cycle phases correspond to 1= menses, 2= preovulatory phase, 3= mid-luteal phase.

In order to investigate potential associations between hormone concentrations and left/right differences, laterality quotients (LQ) for
accuracy and reaction time data were calculated by subtracting right visual field responses from left visual field responses. No significant associations between hormone levels and LQs were evident in the mid-cycle and mid-luteal phase. However, during menses, there was a moderate correlation between the reaction time-LQ and progesterone, $r = .55, p < .01$.

Table 1: Mean Concentrations of progesterone, estradiol, testosterone, FSH, and LH at three distinct points in the menstrual cycle of naturally cycling women, as well as hormone concentrations in two control groups (women using a hormonal contraceptive, men).

<table>
<thead>
<tr>
<th>Group</th>
<th>Cycle Phase</th>
<th>Progesterone (ng/ml)</th>
<th>Estradiol (pg/ml)</th>
<th>Testosterone (ng/dl)</th>
<th>FSH (U/l)</th>
<th>LH (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naturally cycling women (N=28)</td>
<td>Menstrual</td>
<td>0.29 0.13</td>
<td>37.9 18.23</td>
<td>33.7 14.5</td>
<td>6.58 2.16</td>
<td>5.82 3.09</td>
</tr>
<tr>
<td></td>
<td>Mid-Cycle</td>
<td>0.48 0.7</td>
<td>105.61 57.23</td>
<td>37.56 15.21</td>
<td>5.89 1.63</td>
<td>9.55 4.11</td>
</tr>
<tr>
<td></td>
<td>Luteal</td>
<td>7.43 3.68</td>
<td>98.53 47.01</td>
<td>33.99 15.46</td>
<td>3.97 1.44</td>
<td>4.71 3.85</td>
</tr>
<tr>
<td>Contraceptive women (N=28)</td>
<td>T1</td>
<td>0.25 0.09</td>
<td>29.84 12.13</td>
<td>31.22 14.47</td>
<td>4.62 2.77</td>
<td>4.46 3.75</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>0.23 0.07</td>
<td>24.2 8.71</td>
<td>26.13 12.21</td>
<td>2.19 1.82</td>
<td>1.51 1.98</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>0.88 3.59</td>
<td>23.25 6.21</td>
<td>25.92 11.66</td>
<td>2.05 2.28</td>
<td>1.45 2.36</td>
</tr>
<tr>
<td>Men (N=28)</td>
<td>T1</td>
<td>0.32 0.15</td>
<td>27.2 9.37</td>
<td>412.2 109.52</td>
<td>- -</td>
<td>5.17 2.28</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>0.33 0.12</td>
<td>24.16 7.25</td>
<td>400.51 127.63</td>
<td>- -</td>
<td>4.47 1.48</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>0.32 0.14</td>
<td>25.04 9.02</td>
<td>411.23 118.08</td>
<td>- -</td>
<td>4.97 1.82</td>
</tr>
</tbody>
</table>

2.4 Left-ward perceptual asymmetry
For testing cycle phase effects in naturally cycling women within the auditory modality, all participants were simultaneously presented with two different consonant-vowel stimuli, one to each ear. This well established dichotic listening paradigm normally produces a strong right ear advantage (REA), that is, in a forced decision participants report the syllable that was presented to the right ear much more often than the syllable that was presented to the left ear. The REA is seen to reflect the limited capacity of the brain to handle two things at the same time, and probably results from the stronger contra- than ipsilateral auditory projections from the cochlear nucleus in the ear to the primary auditory cortex in the temporal lobe, and the left hemisphere dominance in processing language-related stimuli (Kimura, 1967). For that reason, a stronger REA indicates a larger degree of lateralization in perceptual asymmetry. However, according to findings in
commissurotomized patients, in whom the left ear channel is nearly completely extinguished (Milner et al. 1968) one would expect a REA-increase in phases of hormone-related reduced callosal transfer. Thus, although the hypothesis of progesterone-mediated interhemispheric decoupling generally predicts reduced lateralization in high-hormone phases, with respect to dichotic listening, it would predict larger LQs in the mid-luteal phase. However, in our sample of 28 naturally cycling women, the REA as defined in percent of correct responses turned out to be unaffected by cycle phase (figure 5); the cycle phase by ear interaction was not significant, $F(2, 54) = 1.01, p = .35$. In the control group of contraceptive using women, the REA was stronger expressed than in naturally cycling women (main effect of ear, $F(1, 27) = 16.24, p < .001$) and vertically identical across the three test sessions (test session by ear interaction, $F(2, 54) = .02, p > .05$). The pattern for the male control group was comparable to that of hormonal contraceptive using women: Men expressed a strong (main effect of ear, $F(1, 27) = 57.69, p < .001$) and stable (session by ear interaction, $F(2, 54) = .34, p > .05$) REA across all three testing sessions. However, these group- and sex-differences in REAs were small, as indicated by the non-significant ear by group interaction, $F(2, 137) = .92, p > .05$.

![Figure 5: Dichotic listening: Percent of correct responses in right ear (light gray bars) and left ear (dark gray bars) input in naturally cycling women at menses (left), preovulatory phase (middle), and mid-luteal phase (right).](image-url)
In order to investigate potential associations between hormone concentrations and left/right differences, LQs for accuracy and reaction time data were calculated by subtracting left ear responses from right ear responses. No significant associations between hormone levels and LQs were evident in the mid-cycle and mid-luteal phase. Interestingly, during menses, there were moderate correlations between the accuracy-LQ and progesterone, \( r = .39, p < .05 \). Estradiol levels during menses were positively correlated with reaction time-LQ, \( r = .47, p < .05 \). Linear regression analysis resulted in a significant model for reaction time-LQ at menses, \( F(6, 15) = 3.12, p < .05 \), with estradiol \( (B = 16.73, \beta = .6, p < .05) \) and LH levels \( (B = -97.24, \beta = -0.59, p < .05) \) as significant predictors.

### 2.5 Interhemispheric Transfer Time

The simplest way of measuring the efficiency of interhemispheric communication is to measure IHTT. A classical means for estimating the IHTT is a reaction time task which is based on the crossing in both visual and motor projections developed by Poffenberger (1912). Participants are subliminally presented with visual stimuli (in the present study, white dots against a black background were used) either in the left or in the right visual field. Their simple task is it to respond as fast as possible and as soon as possible when they have perceived a stimulus, by pressing a key with either the left or the right hand. This way, an uncrossed condition, in which both the processing of a visual stimulus and the control of the responding hand occur in the same hemisphere (no transfer required) can be compared to a crossed condition, in which the visual stimulus is presented contralaterally to the responding hand control (transfer required, typically longer latencies). The crossed-uncrossed difference (CUD) is supposed to reflect IHTT: the smaller the CUD, the more efficient the transfer. According to the decoupling hypothesis, larger CUDs would be expected in high-hormone, compared to low-hormone phases.

Due to technical error or schedule difficulties, only 24 naturally cycling women completed the Poffenberger task three times during their menstrual
cycle. In accordance with the decoupling hypothesis, the absolute reaction times showed that the CUD was larger both in the luteal phase (mean = 3.99 ms, S.D. = 7.97) and in the preovulatory phase (mean = 4.36 ms, S.D. = 9.69), compared to the menstrual phase (mean = -0.0354 ms). However, these differences were not statistically significant, F (2, 46) = 2.35, p > .05, and cycle phase explained only approximately 1% of the variance, est. $\eta^2 = .09$. Naturally cycling women’s CUDs were compared to mean reaction times in a group of 28 women who used hormonal contraceptives (mean CUD: 1.49 ms) and to reaction times in a group of 28 young men (mean CUD: 3.35 ms). The groups differed significantly in CUDs (main effect of group, F (4, 185) = 2.8, p < .05).

### 2.6 Interhemispheric Integration

Banich & Belger (1990) developed a lateralized letter matching task that allows for a 4-field matrix analysis: bi- and within-hemispheric processing in a simple (physical identity) and a complex (semantic identity) condition. Participants are presented with a triangle-shaped array of letters and are to decide whether the bottom letter is identical to either of the two top letters. The critical item either appears in the same visual field (within-field trial) or in the opposite visual filed (across-field trial). Thus, when both matching items are presented to the same visual field, one hemisphere alone can correctly identify that a match has occurred, but when the matching items are divided across the visual fields, communication between the two hemispheres is required before a match between the two items can be detected. As stated above, the typical pattern of results in this task is a better performance of within-field trials in the physical identity task, but a better performance of across-field trials in the semantic identity task. Compton et al. (2004) used the Banich-Belger task to check on the hypothesis that the AFA in the complex condition was only evident in the menstrual phase, but not in the high-hormone luteal phase of the menstrual cycle. As a matter of fact, these authors found that the AFA was not influenced by cycle phase, neither in a within-subject, nor in a between-subject design. The association
between progesterone and reaction times was found to be marginally positive, \( r = .26 \), a finding that contradicts the predictions derived from the decoupling model. In a second attempt to demonstrate cycle phase effects on the AFA, Bayer et al. (2008) adopted the Banich-Belger task and found the AFA to be affected by cyclic hormone fluctuation, but the results pointed into the opposite direction: During the high-hormone luteal phase, naturally cycling women displayed an AFA that was comparable to post-menopausal women and men. However, during menses, no advantage of interhemispheric integration was observed. Neither study revealed a direct relation between progesterone and interhemispheric integration.

Another pattern of results was found in the present study when the Banich-Belger task was conducted at three different time points during the menstrual cycle with 24 naturally cycling women. Similar to previous findings, a strong AFA was observed only in the more demanding semantic identity task (main effect of trial type, \( F(1, 77) = 118.27, p < .001, \text{est. } \eta^2 = .61 \)). The cycle phase by trial type interaction approached significance, \( F(2, 152) = 2.67, p = .073, \text{est. } \eta^2 = .03 \), and the trend of the data pointed into the direction predicted by Bayer et al. (2008): The AFA was larger in the mid-luteal phase (mean AFA: 40.34 ms) than both in the preovulatory phase (mean AFA: 29.24 ms) and in the menstrual phase (mean AFA: 33.42 ms). However, the overall effect of cycle phase was not statistically significant.

In the female control group, the row data pointed into the opposite direction. The mean reaction time-AFA was almost identical in the first two sessions (mean = 21.39 ms approx. four days after inserting a new vaginal ring and mean =19.81 ms after approx. 12 days), but decreased at the third testing session (mean = 8.31 ms after approx. 20 days). However, also this variation was not statistically significant (main effect of cycle phase, \( F(2, 54) = 1.57, p > .05 \)). In the male control group, the overall reaction time-AFA had a mean value of 15.27 ms and did not vary significantly across the three testing sessions (main effect of test session, \( F(2, 54) = .46, p > .05 \)).

Regression analyses of the naturally cycling women data only resulted in two significant models for the reaction time-AFA; one in the menstrual
phase, $F(5, 23) = 4.34, p < .01$, and one in the preovulatory phase; $F(5, 23) = 4.73, p < .01$. Surprisingly, in the low-hormone menstrual phase, progesterone ($r = .36$) and FSH ($r = .44$, all $ps < .05$) were positively associated with the AFA. During the preovulatory phase, there was a strong positive correlation between testosterone levels and reaction time-AFA ($r = .57, p < .01$) in naturally cycling women. No regression model reached statistical significance in the luteal phase, but the AFA in accuracy data was positively correlated with progesterone levels ($r = .56, p < .05$).

2.7 Chapter Discussion

Based on the available literature on effects of fluctuating sex hormones on hemispheric asymmetry and interhemispheric communication, a conflicting picture ensues. Overall, data records indicate a relatively small impact of sex hormones on the functional brain organization, given the generally small effect sizes (Hyde, 2005). Also in the present study, the observed pattern of results was ambiguous and effects were evident, but small, albeit the extensive investigation with comparably large sample sizes and precise measurement of both behavioral data and hormone concentrations. If at all, the pattern of results fits best with the framework of sex hormone-modulated interhemispheric decoupling. In accordance with the assumptions of this model, the lowest degree of lateralization (figure recognition task), slowest IHTT (Poffenberger task), and greatest advantage of interhemispheric integration (Banich-Belger task) was observed in the mid-luteal phase. In all four investigated domains, the variance in behavioral data was largest in the group of naturally women, and smallest in the male control group. Although the statistical power in the present study was not sufficient to arrive at empirically sound conclusions, the trend of the raw data points into a direction predicted by the decoupling framework. Therefore, it is still of relevance to discuss the main points of conflict in light of our results in more detail.

*Target site of hormone effects in the brain:* The results suggest a hormone-modulated reduction of FCA in a right-hemispheric dominant task (figure
recognition), but they are unsuggestive of a modulating effect in a left-hemispheric dominant task (speech sound processing in the dichotic listening task). However, because these two domains were purposely not measured in the same modality, one cannot rule out that for instance a visually presented lexical decision task would have resulted in reduced FCA also in typically left-hemispheric dominant task. The inherent problem of such comparisons is that spatial cognition and language processing cannot equally well and reliably be measured in any behavioral paradigm.

Numerous reports about cycle-phase related changes in asymmetrical performance (Hampson, 1990; Sanders & Wenmoth, 1998; Weekes & Zaidel, 1996; Wadnerkar et al., 2008), as well as brain activations (Dietrich et al., 2001) during language-related processing indicate that left-hemispheric dominant functions are similarly modulated by gonadal sex hormones than right-hemispheric functions. Based on this assumption and given the trend in the present data towards reduced interhemispheric communication at the mid-luteal phase, it can be concluded that high hormone concentrations do not lead to the selective activation or inhibition of only one hemisphere. Instead, the hormonal effect seems to target the interhemsipheric communication, as proposed by the model of progesterone mediated interhemsipheric decoupling.

Do sex hormones affect the efficiency of interhemsipheric transfer? The finding that the IHTT was not affected by hormone fluctuations is in accordance with earlier studies which did not find variance in IHTT across the menstrual cycle (Bayer et al., 2008) or as a consequence of hormone replacement therapy (Bayer & Hausmann, 2009), either. However, these results do not necessarily contradict the assumptions of the decoupling hypothesis, but may rather indicate that the IHTT as an expression of CUD based on behavioral response times in the range of milliseconds is too inert to detect sex and sex-hormonal effects on callosal neurotransmission. On the neuronal level, IHTT as measured by electro-encephalogram (EEG) has been shown to differ between men and women in that men displayed more asymmetrical and longer IHTT than women (Moes et al., 2007).
Furthermore, EEG-derived IHTT as defined by means of left/right differences in the N170, a component of the event-related potential that reflects the processing of faces, has been reported to be longer during the luteal phase than during menses (Hausmann, et al., 2009, cited from Güntükün & Hausmann, 2007). Similarly, cycle phase effects on transcallosal inhibition have been demonstrated by means of transcranial magnetic stimulation (Hausmann et al., 2006). These authors measured voluntary muscle tone activity after motor cortex stimulation, and found that the silent period and thus the interhemispheric transfer was affected by the menstrual cycle. In naturally cycling women, the silent period was shorter in high-hormone phases than in the low-hormone phase. This finding is in accordance with the framework of progesterone mediated interhemispheric decoupling, and it furthermore implies that cyclic variation in transcallosal inhibition is also evident in the motor system.

*What is the particular contribution of progesterone and estradiol, respectively?* The most important causation of the empirical chaos is presumably the generally complex mode of action of steroid sex hormones. This is because all steroids share a common biochemical progenitor, cholesterol, and thus possess diverse structural similarities. The metabolic chain (e.g., Progesterone is metabolized into androgens, which are again converted into estrogens), is rarely considered by asymmetry researchers. However, it can be essential to distinguish between effects that result from a particular hormone, binding directly to its receptor, and effects of the downstream actions of metabolites. Even though the design of the current study with three distinctive phases of the menstrual cycle allowed for the analysis of relative contributions of estradiol alone versus a combined effect of estradiol and progesterone, no strong and resistant hormone/FCA associations were observed. The fact that significant correlations evinced mainly in the low-hormone menstrual phase is somewhat surprising, but may stem from the larger variance in behavioral data at this period in naturally cycling women.
In conclusion, given the large number of studies reporting sex differences and hormone effects on FCA, sex hormones can be considered as important agents of intra- and inter-individual variation in hemispheric asymmetries. Albeit the effect on the behavioral level is relatively small, modifications in brain plasticity induced by high levels of sex-hormones occurring within days are theoretically meaningful. The effects, ranging from interhemispheric inhibition to interhemispheric transfer time and integration of information from both hemispheres, seem to be task-specific, and are foremost evident in cortical interactions that also exert sex differences. Whether these effects are side-effects of the peripheral reproduction-related processes, or serve a unique phylogentic purpose, cannot be fully answered at present.
Chapter 3: 
Variability in ratings of trustworthiness across the menstrual cycle

Abstract | Interpersonal trust is a pre-requisite for many aspects of specific human behavioral traits such as social bonding and cooperation. From an evolutionary perspective, a selective modulation of social cognitive functions in young women across the menstrual cycle could be highly adaptive. Because adaptations of trusting behavior would be essential during the fertile phase at mid-cycle, it is conceivable that trust modulation is driven by those sex hormones that also regulate the reproductive cycle. The present study investigates how trusting behavior varies in naturally cycling women, as a function of sex and attractiveness of players in a trust game at three distinct phases of the menstrual cycle. Women indeed acted more cautiously in an investment game at the fertile preovulatory phase, compared to the low-hormone menstrual, and the high-hormone mid-luteal phase. Reduced willingness to trust in strangers was particularly expressed towards male players. Detailed hormone analyses revealed a two-fold effect in the preovulatory period: (1) rising levels of the gonadotropine FSH correlated with a decrease of investment in unattractive female players, and (2) the increase of estradiol was associated with a general increase in interpersonal trust. However, no particular contribution of a single hormone level could be identified for the generally reduced willingness to trust in strangers. Thus, the results emphasize the impact of the menstrual cycle on interpersonal trust, albeit the exact mode of hormonal action needs to be further investigated.

3.1 Chapter Introduction
Cooperation among genetically unrelated individuals of the same species is associated with the risk of exploitation or defection (Trivers, 1971). Modern adaptationist theories predict that, in humans, social cognitive functions are
sensitive to and calibrated by relevant environmental inputs (Delton et al., 2010). According to the social neuroscience view, these flexible adaptations are mediated by activating effects of steroid hormones. Sex hormone receptors are widespread in the central nervous system (Stumpf & Sar, 1976), and steroids have powerful neuromodulatory properties (Sherwin, 2003) and modulating effects on perceptive, motivational, and cognitive processes (Frye, 2009). These processes, in turn, influence the expression of a wide range of social behaviors and, thus, enable individuals to rapidly evaluate situational costs and benefits (Soares et al., 2010). Nevertheless, reducing social behavior to biological frameworks has been challenged (Wallen, 2001; Eisenegger et al., 2009; Dias, 2009; Storey et al., 2011). Specifically, the extrapolation of findings from animal research to humans is questioned, because cultural and social influences may have superseded genetically programmed behavioral responses in humans (Campbell, 2010). Thus, the question to what extent neurobiological stimuli affect social cognitive processes and trigger the expression of social behavior is a focus of interest. In this context, a set of studies tested whether natural sex hormone fluctuations occurring in the course of the menstrual cycle have measurable effects on diverse social cognitive measures. For instance, both the gonadotropine LH and the ovarian hormone estradiol regulate the reproductive cycle (Rossmanith et al., 1994) and they may drive female sexual desire (Bullivant et al., 2004). Increasing levels of LH cause increased releases of estradiol in the late follicular phase, and lead to ovulation at mid-cycle. During this period, women have been reported to show a greater preference for signals of genetic quality such as symmetrical faces (Little et al., 2007), signs of “maleness” (Macrae et al., 2002), or apparent health (Jones et al., 2008), than at other stages of the menstrual cycle. Furthermore, women reduce risky behavior at mid-cycle (Bröder & Hohmann, 2003, but see Zethraeus et al. 2009). Bos et al. (2010) found that women with high interpersonal trust levels significantly decrease their trust for unfamiliar faces after the administration of 5 mg testosterone. This androgen also fluctuates in naturally cycling women and peaks in the late
folllicular phase (Sinha-Hikim et al., 1998). Therefore, Johnson and Breedlove (2010) postulated an evolutionary advantage for a testosterone-modulated preovulatory decline in ratings of trustworthiness for women at risk of being overly trustful when evaluating strangers. However, this assumption has not been tested in naturally cycling women across the menstrual cycle.

Indeed, the ability to correctly judge other people’s trustworthiness is an important prerequisite for successful cooperation across all human societies. From an evolutionary perspective, this ability becomes most essential for women when the consequences of misjudging a mate’s willingness to cooperate are most devastating, that is, when selecting a mate and engaging in sexual intercourse during the 3-5 most receptive days of the menstrual cycle. The administration of exogenous hormones, such as the neuropeptide oxytocin, powerfully modulates human interpersonal trusting behavior (Kosfeld et al., 2005). The administration of testosterone has been reported to increase fairness and, thus, the efficiency of social interactions in women (Eisenegger et al., 2010).

The current study aimed at investigating the effects of naturally occurring sex hormone fluctuations on judgments of trustworthiness. A game theory approach was chosen in order to model participants’ interpersonal trusting behavior on an individual basis. Even though financial decisions surely differ from decisions related to sexual behavior, it is unlikely that two distinct cognitive mechanisms have evolved for the processing of risk with respect to sexual versus financial exploitation. It was hypothesized that the demanding task of estimating other individuals’ willingness to cooperate, e.g., their trustworthiness, is affected by the differential reproductive risks in the course of the menstrual cycle. Because social exploitation is costly, evolutionary pressures may have forced an adjustment of interpersonal trusting behavior in women when the risk of fertile insemination by unfavorable mates is highest. More precisely, it could be adaptive if women were more cautious about being trustful at this time, compared to lower risk phases such as during menses. This study further set out to examine the
extent to which fertile women adapt their trusting behavior according to their interaction partners, as a function of hormone state or cycle phase. It was hypothesized that women are less willing to cooperate with other attractive female players, who may represent potential female rivals, during the high estradiol late follicular phase, compared to the low estradiol menstrual phase and to the pregnancy-resembling hormonal state in the mid-luteal phase. At the same time, trust in other attractive male players should increase at the fertile ovulatory phase of the cycle.

3.2 Methods

3.2.1 Participants and design
Participants were recruited via advertisements on campus of Ruhr-University Bochum, Germany, and were invited to attend three testing sessions. A monetary exchange experiment was conducted with three groups, using an intra-subject design. The first group consisted of 33 naturally cycling women who reported that they had not experienced any kind of hormonal intervention for at least 6 months prior to testing and had regular cycles ranging from 26 to 30 days. The second group consisted of 33 women who reported using a vaginal ring (Nuva®Ring) as a hormonal contraceptive for at least 6 months prior to testing. Because significant hormonal fluctuations were not expected in this group, these participants served as the control group for the naturally cycling women. Additionally, 30 young men were tested to control for general sex differences in ratings of trustworthiness.

For every naturally cycling woman, three test sessions that depended on when the menstrual cycle began were arranged according to reference values for progesterone and estradiol provided by Stricker et al (2006). One test session took place during the menstrual phase (days 2-5), when the concentration of sex hormones is lowest. Another session was arranged between days 11-15 of the cycle, during the preovulatory LH-peak and the highest concentrations of estradiol and testosterone, and corrected for
individual cycle length. Yet another session was scheduled for the mid-luteal phase (days 19-23) in order to have the women tested at their highest progesterone concentrations and the second surge of estradiol. Cycle phases and testing order were counter balanced across all participants. Test sessions were organized in a similar way for the women using hormonal contraceptives, taking the day of applying a new vaginal ring as day 1. They were then scheduled for a test session between ring cycle days 2 and 5, followed by a session between ring cycle day 11-15 and one shortly before or directly after removing the ring between ring cycle days 19 and 23. For the male participants, test sessions were arranged with 8-10 days intervals. Individual test sessions were allocated randomly to the menstrual cycle phase sessions of the naturally cycling women, to control for test order effects. The time of day was held constant (either 9 a.m. or 1 p.m.) across all test sessions for each participant, to control for circadian variability in hormone release.

Anonymity was guaranteed at all times. The study protocol was approved by the ethics committee of the Ruhr-University Bochum, and all participants gave written, informed consent before participation. They were reimbursed for participation with a fixed charge and could earn some extra money, depending on their performance in the trust game.

### 3.2.2 Trust Game

Trust games have repeatedly been employed to measure interpersonal trust (e.g., Chang et al., 2010; Hillebrandt et al., 2011; Unoka et al., 2009) and to examine hormonal effects on trusting behaviour (Mikolajczak et al., 2010; Zak et al., 2005). A modified version of the trust game described in Kosfeld et al. (2005) was used. In contrast to previous studies, natural hormone states were used in the current experiment, instead of administering hormones. Covering the individually distinct cycle phases requires testing participants separately, not with up to 12 persons in a room, as it is typically the case. In the version of the trust game used here, participants always assumed the position of the investor, and a black-and-white photo of a
fictive trustee was presented on a computer screen, against a black background. The participants were told that the trustees were students from a South German university who had played the same game and whose responses had been recorded. Since they would receive the original answer of every trustee, the participants had to judge the trustworthiness of the other player by sending 0, 4, 8, or 12 money units (MU) of their initial endowment. Thus, if their judgement was faulty and they entrusted too much to a deceiving player, their overall payoff would decrease.

Pictures of the fictive trustees’ faces (provided by an internal database of the Institute for Cognitive Neuroscience at Ruhr-University Bochum, Germany) had previously been judged for attractiveness on a seven-point Likert-scale by 30 female volunteers. Using the MathWorksTM software Matlab® (version 7.8.0) and the Biopsychology Toolbox (Rose et al., 2008), three parallel versions of the Trust Game were then constructed with five attractive and five unattractive male trustees, and five attractive and five unattractive female trustees, respectively. The games were programmed to present the 20 pictures in random order. The trustees’ back transfers were held at a constant level of 40 – 60 % of their payoff, so that all trustees were equally cooperative. If a participant invested, for instance, 8 MU in a given trustee, this amount was tripled and added to the other player’s 12 MU initial endowment ((8x3) + 12 = 36). In this example, the computer randomly chose an amount between 14.4 and 21.6 MU and sent it back to the investor.

The actual experiment was preceded by six training trials, to reinforce the participant’s impression of participating in a quasi-social interaction. This was achieved by presenting six faces from the middle of the attractiveness scale (three males and three females). A random event generator chose two of these six players to betray the participant’s trust by not sending any MU back. The experimenter commented this and reinforced the participants to look for signs of trustworthiness before taking a decision. In the experimental game, the participants were alone in the experimental room, in order to control for bystander effects (Earley, 2010). They played 20 trials
with one second inter-trial intervals. The total payoff was presented on the screen only after the last trial, and the participants immediately received their payoff in Euros, rounded to increments of ten cents. Thus, if a participant had earned, for instance, 378 MU, she received 3.80 Euros (approx. USD 4.20). None of the participants expressed disbelief in the cover story, or showed discomfort at being deceived (for an evaluation of the use of deception in psychological research, see Christensen, 1988). Participants’ decisions were registered separately for every trustee. The total investment, as well as the investment in male versus female, attractive versus unattractive players, could thus be analyzed.

3.2.3 Hormone Assays
Immediately after completing a test session, participants were accompanied to a medical practice on campus, where blood samples were taken and processed. Estradiol, progesterone, testosterone, LH, and FSH were determined by a solid-phase, competitive chemiluminescent enzyme immunoassay (Siemens Diagnostic GmbH, Munich, Germany). The intra- and interassay coefficients of variation for a low point of the standard curve were 3.1 - 7.9 % and 4.1 - 7.8 %, respectively. These hormone analyses served to confirm naturally cycling women’s self-reported cycle phases. For the preovulatory phase, inclusion criteria were progesterone levels < 2.0 ng/ml, estradiol levels > 34 pg/ml, LH levels > 5 IU/L, and FSH levels > 4 IU/L. For the mid-luteal phase, inclusion criteria were progesterone > 2 ng/ml, and estradiol levels > 30 pg/ml. In addition, by means of SHBG determination, the use of hormonal contraceptives could be detected (as defined by SHBG levels > 120 nmol/L). On the other hand, in the hormonal contraceptive control group, SHBG levels > 120 nmol/L was considered as group inclusion criterion.

3.2.4 Data Analyses
There is evidence that the total hormone concentration does not account best for the bioactive effects of gonadal hormones (Maguire and Mody, 2009),
but rather that significant changes in hormone levels cause physiological, psychological or behavioral effects. Therefore, for all test sessions, the changes in hormone levels and behavioral measures were calculated and expressed in delta values (Δ).

All statistical analyses were calculated using PASW Statistics 18.0. To test the influence of cycle phase (or test session in men) on the investment in attractive and unattractive, male and female players, a repeated measures analysis of variances (ANOVA) was carried out with the within-subject factors ‘cycle phase’ (menses, preovulatory, mid-luteal), and ‘player’ (amount of MU invested in attractive/unattractive, male/female other players), and the between-subject factor ‘group’.

3.3 Results

3.3.1 Hormone analyses

Valid measurement thresholds of the hormone assays were at 0.2 ng/ml for progesterone, 20 pg/ml for estradiol, 20 ng/dl for testosterone, and 0.1 U/l for LH and FSH. For cases of hormone concentrations below these thresholds, all values were placed at the threshold value minus 0.1.

In the group of naturally cycling women, nine out of 33 women did not meet the hormonal inclusion criteria (in seven women, the preovulatory phase was missed, and in two women, progesterone levels were too low for the mid-luteal phase). Another eight women did not complete all three testing sessions, due to schedule difficulties or technical error. 4 more women in this group had to be excluded from analysis because they had answered invariantly in the trust game in at least one of the test sessions. The remaining 12 women with three complete and valid sets of data in this group had a mean age of 23.92 years (S.D. = 2.4), and a mean average cycle length of 28.92 days (S.D. = .99).

From 33 tested contraceptive using women, four had to be excluded from analysis due to mismatch with the hormone inclusion criteria. Another five did not complete all three testing sessions due to schedule difficulties or
technical error. Three more had to be excluded because of invariant responses in the trust game. The remaining 21 women had a mean age of 23.29 years (S.D. = 2.41).

All of the 30 men completed three sessions and had hormone data in the male normal range. However, the rate of participants answering invariantly in the trust game was higher in the male control group, which is why nine participants had to be excluded from analyses. The remaining 21 men had a mean age of 24.95 years (S.D. = 4.44).

All hormone levels in the group of naturally cycling women were in the normal range for the corresponding cycle phase (see table 2). A repeated measures 3 (cycle phases) x 5 (serum values of progesterone, estradiol, testosterone, LH, and FSH) ANOVA confirmed a significant cycle phase by hormone interaction, $F(8, 88) = 14.8, p < .001$. Expectedly, this interaction was not significant in men, $F(6, 114) = .94, p > .05$, and in women using hormonal contraceptives, $F(8, 136) = 1.04, p > .05$.

### Table 2: Hormone concentrations for naturally cycling women in the menstrual phase, the peri-ovulatory phase, and the mid-luteal phase, compared to hormone concentrations of women using hormonal contraceptives and men.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cycle Phase</th>
<th>Progesterone (ng/ml)</th>
<th>Estradiol (pg/ml)</th>
<th>Testosterone (ng/dl)</th>
<th>FSH (U/l)</th>
<th>LH (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naturally cycling women</td>
<td>Menstrual</td>
<td>0.29 ± 0.11</td>
<td>30.92 ± 12.85</td>
<td>32.31 ± 13.26</td>
<td>6.91 ± 2.26</td>
<td>5.62 ± 2.11</td>
</tr>
<tr>
<td></td>
<td>Ovulation</td>
<td>0.67 ± 0.99</td>
<td>89.66 ± 34.46</td>
<td>46.22 ± 17.72</td>
<td>6.10 ± 1.44</td>
<td>9.49 ± 3.15</td>
</tr>
<tr>
<td></td>
<td>Mid-Luteal</td>
<td>6.61 ± 2.50</td>
<td>94.26 ± 34.56</td>
<td>33.59 ± 11.16</td>
<td>3.42 ± 1.19</td>
<td>6.79 ± 5.80</td>
</tr>
<tr>
<td>Contraceptive women</td>
<td>T1</td>
<td>0.27 ± 0.11</td>
<td>27.46 ± 10.54</td>
<td>29.52 ± 13.92</td>
<td>4.11 ± 2.11</td>
<td>4.16 ± 3.71</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>0.24 ± 0.08</td>
<td>23.43 ± 6.28</td>
<td>26.46 ± 11.21</td>
<td>1.94 ± 1.96</td>
<td>1.65 ± 2.29</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>0.24 ± 0.11</td>
<td>22.93 ± 4.81</td>
<td>27.17 ± 13.31</td>
<td>2.07 ± 2.53</td>
<td>1.66 ± 2.74</td>
</tr>
<tr>
<td>Men</td>
<td>T1</td>
<td>0.34 ± 0.16</td>
<td>28.06 ± 9.85</td>
<td>432.20 ± 126.81</td>
<td>-</td>
<td>5.61 ± 2.30</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>0.34 ± 0.14</td>
<td>24.43 ± 8.33</td>
<td>430.25 ± 121.92</td>
<td>-</td>
<td>4.37 ± 1.58</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>0.04 ± 0.16</td>
<td>25.26 ± 9.96</td>
<td>439.00 ± 124.44</td>
<td>-</td>
<td>4.91 ± 1.87</td>
</tr>
</tbody>
</table>
3.3.2 Trust Game

Only in the group of naturally cycling women, the overall investment varied significantly across the three test sessions. In this group, 24.2% of the variance in overall investment was explained by the factor cycle phase, $F(2, 22) = 3.52, p < .05$. Irrespective of the particular other player, the investment was largest in the mid-luteal phase. The investment in the menstrual phase was similar to the mid-luteal phase, but in the preovulatory phase, overall investment was significantly reduced (figure 6). The variation in overall investment across the three test sessions was neither significant in hormonal contraceptive using women (main effect of test session, $F(2, 40) = .76, p > .05$), nor in men (main effect of test session, $F(2, 40) = .29, p > .05$).

![Figure 6: Overall investment across three test sessions. While the overall investment was stable over three test sessions in women using hormonal contraceptives (white bars) and men (gray bars), it was significantly reduced at the preovulatory phase in naturally cycling women (black bars). Error bars indicate standard error.](image)

Analyzing the investment separately for the four types of other players revealed that the factor “player” significantly affected naturally cycling women’s investment (main effect of player, $F(3, 33) = 8.46, p < .01$); the amount of MU invested in female other players was higher than the investment in male other players. Although the absolute reduction of
investment at the preovulatory phase was more pronounced in investment in male other players than in female other players (figure 7), the cycle phase by player type interaction was statistically not significant, F (6, 66) = .99, p > .05). The factor “player” was also significant in hormonal contraceptive using women, F (3, 60) = 37.25, p < .001, and in men, F (3, 60) = 16.26, p < .001, but the cycle phase by player interaction was not significant in these groups (hormonal contraceptive using women, F (2, 40) = .76, p > .05; men, F (2, 40) = .03, p > .05).

Figure 7: Distribution of naturally cycling women’s investment to four types of other players. The largest amount of MU was invested in attractive female players in all cycle phases. The investment in unattractive male players was particularly reduced in the preovulatory phase. Error bars indicate standard error.

To test if hormonal changes and alterations in trusting behavior were correlated in naturally cycling women, bivariate correlation analyses were computed. There was a significant relationship between progesterone (r = .58) and estradiol (r = .59) and the amount of MU invested in attractive female other players in the menstrual phase. Furthermore, the estradiol level was correlated with the overall investment in the preovulatory phase (r = .59). In the luteal phase, reaction times for the investment decision towards attractive male players were correlated with progesterone (r = .67) and with estradiol (r = .61), indicating prolonged reaction times towards this type of
other player in the high-hormone phase. The analysis of $\Delta$-values also revealed evidence for significant associations between hormone fluctuations and changes in the behavioral data, however, these effects partly pointed into the opposite direction: the increase of FSH from menses to the preovulatory phase was correlated with the reduction of investment in unattractive female other players ($r = .6$). The increase of estradiol from menses to the mid-luteal phase was associated with the reduction of investment in unattractive male other players ($r = -.68$). On the other hand, the increase of progesterone from menses to the mid-luteal phase was associated with the increase of investment in unattractive female players ($r = .73$, $p < =0.01$, all other $ps < .05$). No significant associations of hormone/behavior changes were observed in the $\Delta$-values between the preovulatory and the mid-luteal phase. Similarly, there was no evidence for a relationship between hormone levels and behavioral output in the investment game either in the group of women using Nuva®Rings, or in the group of men.

3.4 Chapter Discussion

This study tested the hypothesis that young women dynamically adapt their interpersonal trusting behavior according to their fertility status. In line with this hypothesis, we found that these women significantly reduced their investment, or acted less trustfully, in the most fertile phase of their menstrual cycle, compared to the low-hormone menstrual and to the high-hormone mid-luteal phase. The reduction of investment was mainly expressed towards male players. Detailed hormone analyses did not allow for a clear-cut identification of the particular sex hormone that triggered this reduction, because neither the total concentration nor the relative change in hormone concentrations was significantly correlated with reduced investment. On the contrary, progesterone and estradiol were positively correlated with the amount of MU invested, particularly when the investment was directed to other female players, and even more so to
attractive female players. A comparison of naturally cycling women with women using a hormonal contraceptive and with men demonstrated significant group differences. The variation in behavioral output varied significantly only in individuals with physiological hormone fluctuations. This confirms the impact of menstrual cycle phase on social cognitive measures and is in accordance with earlier work documenting reduced risk taking behavior in real life at mid-cycle (Bröder and Hohmann, 2003; Chavanne and Gallup, 1998). It also supports the assumption of Bos et al. (2010), that fertile women’s readiness to trust strangers is least pronounced at the phase of highest testosterone levels during the menstrual cycle, albeit testosterone levels were not associated with reduced trusting behavior in the presented data.

In contrast to pharmacological studies, recent investigations of natural hormone fluctuations across the menstrual cycle have often failed to demonstrate a significant hormone/behavior relationship (Bowen et al., 2011; Farrelly, 2011; Hagemann et al., 2011). In the current study, however, evidence for a relationship between rising hormone levels and changes in judgments of trustworthiness was observed. At the time of highest likelihood for conception, monetary decisions were more conservative than at times of lowest or highest hormone concentrations. In accordance with our hypothesis, this reduced readiness to trust in strangers was particularly expressed towards other male players.

However, the preovulatory phase was not uniformly associated with an overall reduction of trust levels, as measured in overall investment. Instead, in naturally cycling women, the peak of estradiol correlated positively with the amount of MU invested. It is conceivable that estradiol increases both sexual behavior and interpersonal trust (Bullivant et al., 2004; Kosfeld et al., 2005) and therefore investment at mid-cycle. Interestingly, in the control group of women with high pharmacological doses of estrogens and progestagens, there was no evidence for enhanced trusting behavior. More research is needed to shed light on the differential effects of endogenous and
exogenous hormone effects on the CNS and to understand how these effects are translated into actual social behavior.

Taken together, the preovulatory period seems to be associated with two changes of behavior that are driven by diverse hormonal mechanisms: Whereas the increase of FSH levels correlates with reduction of trusting behavior towards unattractive female strangers, the estradiol surge seems to generally facilitate interpersonal trust. Because the preovulatory phase was characterized by a generally reduced willingness to trust in strangers, one can assume that neither of the investigated hormones triggers this effect alone. Instead, a combined effect of the measured hormones, metabolites of these hormones not determined in the present investigation, or other menstrual cycle-related parameters might account for the change in judgments of trustworthiness.

From an evolutionary perspective, hormone-mediated processes that result in generally more liberal or more conservative judgments would not be adaptive. Principally, reproductive success requires both the readiness to approach and cooperate with non-kin individuals, and an increased sensitivity to potential social exploitation. However, for both aspects of social judgment, a magnitude of contextual information needs to be considered and integrated in order to come to the most beneficial and least costly decision. It is therefore conceivable that varied hormonal states in the course of the menstrual cycle lead to varied internal behavioral predispositions, though the actual behavioral output is more strongly influenced by external factors. This mode of hormonal action on social behavior would also be in accordance with previous reports of a strong impact of context conditions on hormone-related social decisions. For instance, the increasing effect of the peptide hormone oxytocin on interpersonal trust was only found in social interactions, but was absent in explicitly stated person-computer-interactions (Kosfeld et al. 2005).

The facilitating effect of estradiol on trust towards other women might be linked to a crucial aspect in human social cognitive evolution called “cooperative breeding” (Burkart et al., 2009). It would be of interest to test
this assumption by investigating women’s trusting behavior towards other women during other high-hormone level phases, such as the mid-luteal phase or during pregnancy.

In summary, the results support an interaction between menstrual cycle phase and stimulus-specific effects that leads to a modulation of interpersonal trusting behavior. Although social context and past experience are likely to affect interpersonal judgments to a large extent, the role of fluctuating hormone concentrations on social cognitive functioning should not be underestimated.
Chapter 4:
Sex hormones modulate the type of implicit motive enactment

Abstract] Sex hormones have been reported to dynamically modulate the expression of implicit motives, a concept that has previously been thought to be relatively stable over time. This study investigates to what extent the need for affiliation, power, and achievement, as well as the form of enactment of these needs, as measured with the Operant Motive Test (OMT), are affected by cycle-phase dependent sex hormone fluctuations. In addition to measuring the strength of motive expression, the OMT also captures different forms of motive enactment and, thus, intuitive behavior control. In an intra-subject design with repeated measures, no evidence for cycle-phase related variation in overall motive scores was found. However, when different forms of motive-enactment were considered, an effect of menstrual cycle was observed. The incentive-based inhibition of the power motive was significantly reduced at the time of ovulation, compared to the menstrual and to the mid-luteal phase, in naturally cycling women. In women with relatively stable hormone concentrations (due to using hormonal contraceptives), no significant changes in the form of motive enactment were evident. The results indicate a specific hormone effect on behavioral inhibition. Furthermore, the study provides evidence for a relationship between hormonal states and motive-related cognitive processes, including social motivation.

4.1 Chapter Introduction

To a large extent, human behavior is selected and accomplished outside of conscious awareness. Building on the pioneering work of Atkinson (1964), motivational psychology claims that the behavioral output is mainly influenced by two distinct entities: One comprises momentary situational cues, including both internal states like hunger or fatigue, and social contexts. The other encompasses enduring personal preferences for
affectively charged incentives. The latter are considered as the basis of implicit motives, a network of experiential knowledge acquired during early, partly preverbal childhood (McClelland, 1987). From the 1940’s onwards, researchers have investigated implicit motive systems and developed diverse approaches to empirically measure inter-individual differences in motive characteristics (Murray, 1942; Smith et al., 1992; Schmalt, 1999). The prevailing measurement techniques are based upon content analysis of written reports in response to motive-arousing picture cues. These are based on the rationale that when a need is activated, a particular configuration of the mental apparatus is aroused that supports need-specific cognition and behavior (Kazén & Kuhl, 2005). High levels of motive-related contents recorded under neutral conditions, that is, in the absence of experimentally induced motivational arousal, are considered as chronically aroused needs (McClelland et al., 1953). According to this view, there are large inter-individual differences in the extent to which people associate positive feelings with the striving and realization of three basic motives: The affiliation motive (e.g., the need for secure and harmonious relationships with others), the power motive (e.g., the need to have impact on others), and the achievement motive (e.g., the need to accomplish and to be good at what one is doing) (for an overview, see Schultheiss & Brunstein, 2010).

The emphasis on the rewarding nature of goal attainment, and on the role of positive and negative affective states in behavior control, suggests a significant neurobiological involvement in motivational processes. In particular, sex hormonal effects on behavior control are well established and can best be demonstrated whenever significant changes in sex hormone concentrations occur (e.g., during puberty, pregnancy, post-partum, during menopause). Rapid de- or increases in sex hormone levels, even the comparably small hormone fluctuations in the course of the menstrual cycle, have repeatedly been shown to affect mood (Rubinow et al., 1988; Metcalf et al, 1989; Klaiber et al., 1996). Although the interindividual variability in the degree to which women experience affective changes across the
menstrual cycle seems to be large, the pharmacological effects of reproductive hormones are well established. While high doses of progesterone are generally associated with beneficial effects on mood, such as sedation and anxiolysis (Andréen et al., 2009), additional high doses of estradiol (that is, a progestagen-estrogen combination) commonly lead to increased tension, irritability, and depressed mood (Freeman, 2002; Björn et al., 2003). However, these effects seem to depend on the dose of pharmacological hormones, as well as on individual differences in response to these steroids (Kiesner, 2011). Further evidence exists about hormonal influence on other motivation-modulated processes, like executive functions (Berman et al., 1997), memory functions, in particular with regards to social cues (Phillips & Sherwin, 1992; Wolf et al., 1999; Maki et al., 2002; Walf et al., 2006; Kinsley & Lambert, 2008), and the general neural reactivity to emotional stimuli, regardless of the valence of the stimuli (Protopopescu et al., 2005). Inter alia, the finding of characteristic sex differences in the expression of the three basic motives, with women displaying on average stronger affiliation motives than men, and men displaying on average stronger power motives than women (Schultheiss & Brunstein, 2001; Pang & Schultheiss, 2005) has fostered the notion that sex hormones play a role in the formation and enactment of implicit motives. Consequently, effects of sex hormones on the strength of implicit motives have been investigated. Schultheiss et al. (2003) reported elevated levels of affiliation motivation, and decreased levels of power motivation in women at the time of ovulation. Across three different cycle-phases, the authors found positive correlations between the power motive and testosterone levels in men, and estradiol in women, accordingly. Estradiol has also been linked with attachment and caregiving behavior in both women (Fleming et al., 1997) and men (Berg & Wynne-Edwards, 2001), and estradiol is positively associated with intimacy motivation (Edelstein et al., 2010). Furthermore, Schultheiss et al. (2004) provided evidence that there is a bi-directional relation between hormone levels and motive scores: when the affiliation motive was experimentally aroused, increases in progesterone levels were observed.
Studies depicting motive-hormone associations have hitherto relied on classical content coding measurement techniques, such as the Picture Story Exercise (PSE). However, these instruments neither assess the affective content, nor the degree to which pre-conceptual motives are connected with self-regulatory functions (e.g., self-determined versus more incentive-focused forms of motivation). A more recent method that considers functional properties of positive and negative affect is the OMT developed by Kuhl and Scheffer (1999). This approach claims to extend the classical thematic apperception test (TAT) developed by Murray (1942) to include self-regulatory mechanisms in motive enactment. It is based on the Personality Systems Interaction (PSI) theory, according to which positive and negative affect play an important role in activating and inhibiting motivational states and the degree of self-regulated versus incentive-based motive enactment (for a more detailed introduction, see Kuhl and Kazén, 2006; Baumann et al., 2010). With respect to the consideration of approach and avoidance, as well as associated concepts of reward and punishment, PSI theory resembles other, more general models of neurobiology/motivation interactions (e.g., Gray, 1982; Depue and Collins, 1999). PSI-theory is based on the assumption that behavioral inhibition is more influential than behavioral activation in situational adaptations of behavior control. Two main forms of behavior control are distinguished in this model: one in which the individual mainly acts upon internal states and implicit needs, with a high degree of self-regulation, and one in which behavior is guided by external stimuli or incentives, with low degrees of self-regulation. Behavioral inhibition is postulated to be more strongly involved in the latter type of behavior control, because internal states and implicit needs are assumed to be down-regulated there. The OMT was designed to assess the degree of behavioral inhibition in the striving for motive attainment. Therefore, this coding system includes five levels of enactment for each of the three basic motives. These levels differ in associated affective states (predominant positive or negative affect), and in degree of self-regulation (intrinsic, self-regulated forms of enactment or
extrinsic, incentive-based forms of enactment). Through the introduction of the five levels of motive enactment, implicit motives are assessed with respect to individual differences in cognitive/affective interactions (table 3). Although the notion of hormone/mood/behavior interactions is generally accepted and considered as a promising route of investigation, research linking human natural hormone levels to motivational processes is still relatively rare. This may be due to the complexity of hormonal actions that requires a careful consideration of participant recruiting (e.g. with respect to sex, age, history of pregnancies or hormone therapy) and experimental set-up (e.g. small variation of the environmental and biological conditions may alter the hormonal impact on the behavior in question). Furthermore, it must be determined whether the effect is due to a single hormone, or rather reflects the result of a metabolic process, or a combined effect of several hormones acting together.

The present study set out to explore for the first time the relationship between sex hormones that fluctuate across the menstrual cycle in young women (progesterone, estradiol, testosterone, LH and FSH) and the different basic motive’s forms of enactment as measured with the OMT. On the basis of previous findings, a positive association between progesterone and estradiol levels and the overall affiliation motive, and a negative association between these hormones and power motive scores were predicted. Accordingly, affiliation motivation was expected to be stronger expressed and power motivation was expected to less strongly expressed in high-hormone phases of the menstrual cycle (preovulatory phase at mid-cycle, mid-luteal phase) than in a low-hormone phase (menstrual phase). By contrast, no fluctuations in motive scores were expected to be found in women with stable hormone levels due to hormonal contraceptive use. Furthermore, also the achievement motive was included in the analysis to explore potential associations between hormone fluctuations and different levels of achievement enactment levels. Because high levels of progesterone and estradiol have been associated with increased behavioral inhibition, we expected OMT-levels 2, 4, and 5 (which are assumed to reflect the more
incentive-based forms of motive enactment with high degrees of behavioral inhibition) to be stronger expressed during high-hormone phases of the menstrual cycle. Likewise, the inhibiting effect of progesterone and estradiol was expected to be related to decreased expression of OMT-levels 1 and 3 scorings (which are supposed to reflect the more self-regulated forms of motive enactment with low degrees of behavioral inhibition).

Table 3: Coding system of the OMT

<table>
<thead>
<tr>
<th>Form of enactment</th>
<th>Motive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 2: PA (incentive-based)</td>
<td>Affiliation: Sociability</td>
</tr>
<tr>
<td>Level 3: NA (self-regulated)</td>
<td>Affiliation: Coping with rejection</td>
</tr>
<tr>
<td>Level 4: NA (incentive-based)</td>
<td>Affiliation: Avoiding insecurity</td>
</tr>
<tr>
<td>Level 5: low PA and high NA (passive fear, rumination)</td>
<td>Affiliation: Dependence</td>
</tr>
</tbody>
</table>

PA = positive affect; NA = negative affect. Table adapted from Baumann et al., 2010.

4.2 Methods

4.2.1 Participants and design

The experimental group consisted of 33 women who reported to have regular menstrual cycles ranging from 26 to 30 days, and that they had not experienced any kind of hormonal intervention for at least six month prior to testing. The control group consisted of 33 women who reported that they had used a vaginal ring (Nuva®Ring) as a hormonal contraceptive for at least six months prior to testing. This prescription drug delivers on average 0.12 mg etonogestrel and 0.015 mg ethinyl estradiol per day over a three-week period of use (Roumen et al, 2001). All participants had a German university-entrance diploma, and verbal intelligence quotients above 80 as measured with the Mehrfach Wortwahl Test, a standard German intelligence
test (Lehrl, 2005). In addition to this, all subjects were neurologically and psychologically healthy, as indicated by t-values < 60 in the positive symptom distress index from the Symptom Check List-90-Revised.

Each woman was invited to three testing sessions. These were scheduled in such a way that one session took place during naturally cycling women’s menses (cycle days 2-5) when all sex hormones were expected to have low concentrations. Another session was scheduled to capture the preovulatory estradiol surge, and eventually the characteristic LH-peak (cycle days 11-15, corrected for individual cycle-length). A third session took place in the mid-luteal phase between cycle days 19-23 (also corrected for individual cycle-length), when progesterone levels were expected to be highest and estradiol levels were expected to have a second peak. The definition of these three cycle phases was based on reference values for the involved sex hormones reported by Stricker et al. (2006), and allowed for the evaluation of estradiol effects (preovulatory) separated from the combined estradiol/progesterone effect (mid-luteally). Testing dates were calculated in a similar way for participants in the control group, but with the day of applying a new vaginal ring as day 1 of the (ring-) cycle. Cycle phases and testing order were counter balanced across all participants. Time of day was held constant (either 9 a.m. or 1 p.m., respectively) across all test sessions for each participant to minimize the effects of circadian variability in hormone releases.

Anonymity was guaranteed at all times. The study protocol was approved by the ethics committee of the Ruhr-University Bochum, and all subjects gave written, informed consent before participation. They were reimbursed for participation after every test session.

4.2.2 The Operant Multi-Motive Test
Implicit motives were assessed with the seven-picture short version of the OMT. Similar to other implicit motive coding systems, the OMT measures the extent to which the three basic motives affiliation, power, and achievement are expressed in participant’s spontaneous associations to
ambiguous pictures that depict social and non-social episodes (figure 8). The main difference between the OMT and standard methods like the TAT (Murray, 1942), and the PSE (Smith et al., 1992) exist in the response format. While participants are required to write full short stories in the TAT and PSE, they are instructed to think of a short story and to select one person in each picture as the protagonist, but to write down only keynotes to the following questions: What is important for the person in this situation and what is the person doing? How does the person feel? Why does the person feel this way? How does the story end? in the OMT. In addition, while in the PSE only one motive is assessed in one picture, the three basic motives can be assessed simultaneously in every picture of the OMT. The most important aspect that differentiates the OMT from earlier methods is the consideration of different forms of “enactment” for the basic motives. Combined, there are five levels for every motive: internally, self-regulated positive affect (level 1), externally, incentive-based positive affect (level 2), self-regulated coping with negative affect (level 3), coping with negative affect by instrumental action, “actionism” (level 4), passive coping with negative affect, “rumination” (level 5).

In summary, the OMT-coding system provides information on both the motivational topic (i.e., “what” a person is striving for; affiliation, power, or achievement), and the form of need satisfaction, (“how” a person is striving to meet his or her needs; levels 1-5), leading to one out of 15 cells (3 motive contents x 5 levels) per picture (table 3). All OMTs were analyzed by a well-trained and certified scorer who had reached sufficient reliability across several studies. Moreover, the scorer was naive to the purpose of the study, as well as to sex and hormonal state of the participants. This procedure was chosen to reduce distortions caused by experimenter effects, and the scorer was paid for her expenses. The same seven ambiguous line drawings were used in the same order in every testing session. Participants were instructed to write down their first association and spontaneous answers to the four questions (see above), no matter if they had thought about the same story at the last session(s) or came up with a new story.
Because subjects never repeated the exact wording when thinking about the same story, this procedure was considered sufficient in detecting cycle phase dependent variation in the motive expression. Empirical testing of the OMT’s suitability in scientific studies documents a sufficient internal consistency of $\alpha=0.74$. The retest stability was reported with $r = .72$ (Kuhl et al., 2003, Scheffer, 2005).

Figure 8: Sample pictures from the OMT, chosen to arouse implicit power motivation (left side), affiliation motivation (middle plane), and achievement motivation (right side). Reprint with permission from Julius Kuhl.

4.2.3 Hormone Assays

Testing women during distinct phases of their menstrual cycle requires a confirmation of the self-reported cycle phases by means of exact hormone determination. Earlier work on the relation between implicit motives and gonadal steroid hormones (e.g., Schultheiss et al., 2003) used non-invasive saliva samples to analyze hormone levels. However, those authors pointed out some limitations of saliva-based hormone determination, such as the rapid fluctuations of steroid hormone concentrations in salvia, or the impossibility to partition hormone levels into endogenous and exogenous portions in women using hormonal contraceptives. Therefore, hormone data were recorded by means of less distraction-prone blood serum analysis, which allow for more accurate, total hormone level determination. Following every individual test session, 5 - 7 ml venous blood was taken from every participant in a medical praxis on campus. The processing of the samples took place in the associated endocrinological laboratory. After the
cellular parts of each sample had been centrifuged, blood serum was analyzed. Estradiol, progesterone, testosterone, LH and FSH was determined by a solid-phase, competitive chemiluminescent enzyme immunoassay (Siemens Diagnostic GmbH, Munich, Germany). This assay features intra- and interassay coefficients of variation for a low point of the standard curve of 3.1 - 7.9 % and 4.1 - 7.8 %, respectively. The cycle phases of interest were defined according to the following hormonal inclusion criteria: In the preovulatory phase, progesterone levels < 2.0 ng/ml, estradiol levels > 34 pg/ml, LH levels >5 IU/L, and FSH levels >4 IU/L were included. In the mid-luteal phase, progesterone levels > 2 ng/ml, and estradiol levels > 30 pg/ml were included. To check whether the naturally cycling women were actually free of hormonal medication, SHBG was analyzed and only participants with SHBG levels > 120 nmol/L were included. On the other hand, in the hormonal contraceptive control group, SHBG levels > 120 nmol/L was considered as group inclusion criterion.

4.2.4 Statistical procedures
All statistical analyses were conducted with PASW Statistics 18.0. To test the influence of cycle phase (or test session in women using hormonal contraceptives) on the overall motive expression, a repeated measures analysis of variances (ANOVA) was carried out with the within-subject factors ‘cycle phase’ (menses, preovulatory phase, and mid-luteal phase), ‘motive’ (affiliation, power, achievement), and ‘OMT-level’ (1-5). The association between hormone concentrations and motive expressions was tested using Pearson’s bivariate correlation analyses.

4.3 Results
4.3.1 Hormone analyses
In the group of naturally cycling women, 12 out of 33 women did not meet the hormonal inclusion criteria (seven women were already in their early luteal phase when expected to be in the preovulatory phase, and five women showed unusually low progesterone levels in the mid-luteal phase). Another
five women did not complete all three testing sessions due to schedule difficulties. Thus, the final sample of naturally cycling women consisted of 16 participants, with a mean age of 24.13 years (S.D. = 2.63), and a mean average cycle length of 28.94 days (S.D. = .99).

From 33 tested contraceptive using women, five did not complete all three testing sessions due to schedule difficulties. Two more had to be excluded from analysis due to mismatch with the hormone inclusion criteria. The remaining 26 women had a mean age of 23.65 years (S.D. = 2.94).

Valid measurement thresholds of the hormone assays were at 0.2 ng/ml for progesterone, 20 pg/ml for estradiol, 20 ng/dl for testosterone, and 0.1 U/l for LH and FSH. For all cases of hormone levels below these thresholds, values were placed at the threshold value minus 0.1. This commonly accepted procedure reduces variance in minimal values. Table 4 depicts mean values and standard deviations for all hormone levels in naturally cycling women and women using the NuvaRing. All hormone levels were in the normal range for the according cycle phase (Stricker et al., 2006). A 3 (cycle phases) x 5 (serum values of progesterone, estradiol, testosterone, LH, and FSH) repeated measures ANOVA with group as between subject factor yielded a significant cycle phase by hormone by group interaction, F (8, 256) = 19.17, p < .01, est. η² = .38. As expected, there was no significant variance of hormone concentrations across the three testing sessions in women using hormonal contraceptives (main effect of cycle phase, F (8, 176) = 2.55, p < .05).

Table 4: Deskriptive statistics of hormone concentrations

<table>
<thead>
<tr>
<th>Group</th>
<th>Cycle Phase</th>
<th>Progesterone (ng/ml)</th>
<th>Estradiol (pg/ml)</th>
<th>Testosterone (ng/dl)</th>
<th>FSH (U/l)</th>
<th>LH (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
</tr>
<tr>
<td>Naturally cycling</td>
<td>Menstrual</td>
<td>0.28 0.09</td>
<td>31.76 13.78</td>
<td>29.3 12.12</td>
<td>6.81 2.13</td>
<td>4.98 2.09</td>
</tr>
<tr>
<td>women (N=16)</td>
<td>Mid-Cycle</td>
<td>0.57 0.83</td>
<td>108.01 58.99</td>
<td>40.89 18.38</td>
<td>5.89 1.49</td>
<td>9.11 3.51</td>
</tr>
<tr>
<td></td>
<td>Luteal</td>
<td>7.2 2.29</td>
<td>99.67 34.27</td>
<td>32.23 11.3</td>
<td>3.31 1.05</td>
<td>5.38 5.24</td>
</tr>
<tr>
<td>Contraceptive women</td>
<td>Session 1</td>
<td>0.23 0.07</td>
<td>26.22 7.9</td>
<td>29.24 13.66</td>
<td>4.62 4.07</td>
<td>4.25 3.83</td>
</tr>
<tr>
<td>(N=26)</td>
<td>Session 2</td>
<td>0.21 0.09</td>
<td>21.88 5.78</td>
<td>24.89 10.92</td>
<td>6.72 13.43</td>
<td>1.38 2.21</td>
</tr>
<tr>
<td></td>
<td>Session 3</td>
<td>0.23 0.1</td>
<td>21.65 2.72</td>
<td>24.94 9.5</td>
<td>1.64 2.1</td>
<td>3.63 7.69</td>
</tr>
</tbody>
</table>
4.3.2 Covariates and between-subject factors
Neither in the ANOVAs, nor in the correlation analysis, entering relationship status as a between-subject factor and/or order of test session as a covariate contributed significantly to the explained variance. Neither in the group of naturally cycling women, nor in the control group of women using hormonal contraceptives, partnered women differed significantly from single women. Furthermore, there was no evidence for carry-over effects in neither group. Therefore, these factors were not further considered.

4.3.3 Effects of cycle phase on motive scores and OMT-levels
Overall, naturally cycling women scored highest in power motivation and lowest in achievement motivation, and the differences were statistically significant (main effect of overall motive score, F (2, 30) = 15.07, p < .01, est. $\eta^2 = .5$). The motive scores, accumulated across the five OMT-levels, pointed into the expected direction, that is, increased affiliation motivation and reduced power motivation at the preovulatory phase (figure 9). However, the differences were only marginal and not statistically significant (affiliation motive: F (2, 30) = .58, p > .05; achievement motive: F (2, 30) = .19, p > .05; power motive: F (2, 30) = .62, p > .05). Similarly, the analysis of the five OMT-levels, accumulated across the three basic motives, revealed that the number of level scores did not vary significantly across the three cycle phases (cycle phase by level interaction F (8, 20) = 1.46, p > .05, est. $\eta^2 = .09$; figure 3). It was only when the interaction between basic motives and the OMT-level was considered that a significant cycle effect was observed: In the preovulatory phase, level 4 power motivation (inhibited power dominance) was significantly reduced (mean score = 0.75), compared to menses (mean score = 1.38) and mid-luteal phase (mean score = 1.5), F (4, 60) = 4.8, p < .05, est. $\eta^2 = .24$. 


Figure 9: Distribution of motive scores in naturally cycling women at three distinct cycle phases. Significant variation was not observed in any motive.

The comparison of overall motive scores (with accumulated levels) between naturally cycling women and women using hormonal contraceptives revealed no significant motive by group interaction, F(2, 66) = 1.31, p > .05, η² = .04. Just like naturally cycling women, women in the control group scored highest in power motivation and lowest in achievement motivation. Again, significant interactions were only observed when the five OMT-levels were considered. The cycle phase by motive by level by groups interaction was significant, F(16, 528) = 2.16, p < .05, est. η² = .06). The level by group interaction approached significance, F(4, 132) = 2.23, p = .069, est. η² = .06). Post-hoc tests revealed that there was neither a significant test session by overall motive score interaction in women using hormonal contraceptives (main effect of session, F(4, 100) = .8, p > .05, est. η² = .03), nor a significant test session by overall OMT-level score interaction (main effect of session, F(4, 184) = .51, p > .05, est. η² = .02) in this group. Level 4 scores tended to be higher and remained stable throughout the three testing sessions in women using hormonal contraceptives, compared to naturally cycling women (mean score at session 1 = 1.26, at session 2 and session 3 = 1.37; figure 10).
Figure 10: Distribution of motive enactment levels in naturally cycling women (left side) and women using hormonal contraceptives (right side). Level 1 reflects self-regulated positive affect, level 2 incentive-based positive affect, level 3 self-regulated coping with negative affect, level 4 incentive-based active coping with negative affect, and level 5 passive fear of motive frustration.

4.3.4 Motive-hormone associations

To test if naturally cycling women’s hormone fluctuations were linked with motive or motive enactment scores, bivariate correlation analyses were calculated. There was evidence for a significant relationship between progesterone levels and the number of OMT-level 2 and level 3 scores: during the preovulatory phase, progesterone was significantly correlated with overall-level 2 (incentive orientation), $r = -.61$, with overall-level 3 (self-regulated coping), $r = .56$, and particularly with level 3 power motivation (coping with power-related thread), $r = .59$ (all $p s < .05$). In the mid-luteal phase, progesterone was significantly correlated with the achievement motive, in particular with level 3 achievement (self-regulated coping with failure), $r = -.65$, and with level 5 achievement (passive fear of failure), $r = -.52$. Level 5 achievement motivation was also correlated with estradiol, $r = -.52$, and with LH, $r = .72$ (all $p s < .01$) in the mid-luteal phase. Furthermore, a significant relationship between level 2 affiliation motive scores and LH concentrations during the mid-luteal phase was found, $r = .56$, $p > .05$. 
4.4 Chapter Discussion

This study explored whether cycle phase associated changes in the expression of implicit motives can be demonstrated using a novel measurement approach, the OMT. Indeed, type of motive enactment as the key feature of the test applied here turned out to be modulated by cycle phase. In the preovulatory phase, inhibited power dominance (OMT-level 4) was significantly less expressed compared to the menstrual and to the mid-luteal phase in naturally cycling women. Similarly, bivariate correlation analysis displayed significant relationships between hormone concentrations and OMT-enactment levels, rather than with the three basic motive values per se. Contrasting findings derived with the PSE (Schultheiss et al., 2003), the implicit need for affiliation, power, and achievement was not subject to cycle phase effects in the current study. There are several other aspects of divergence between the present study and earlier findings, which are discussed separately below.

While sex hormone fluctuations across the menstrual cycle were not associated with changes in the motive scores, cycle-phase associated changes in motive enactment were evident in naturally cycling women. This finding corroborates the conceptual distinction of motive themes and forms of motive enactment that constitutes the OMT. The construction of five levels of motive enactment reflects cognitive and emotional processes that are likely to be sensitive to sex- and cycle phase dependent variation. Higher scores of those levels of motive enactment that reflect higher degrees of behavioral inhibition (OMT levels 2, 4, and 5) were expected in the high-hormone phases, compared to low-hormone phase. In fact, those forms of motive enactment were generally stronger expressed than less inhibited, self-regulated forms of motive enactment (OMT-levels 1 and 3). Instead of a stronger expression of incentive-based forms of motive enactment, there was evidence for a partly inverted pattern during the high-estradiol mid-cycle phase, that is, a decrease in inhibited power dominance (OMT level 4). Thus, the OMT-result pointed towards a selective reduction in fear of
loosing power at the time of highest likelihood of conception. In accordance with this result, no such variation in level 4 scorings was evident in the control group of women with exogenously suppressed and stable hormone concentrations. Albeit no direct link between estradiol concentration and number of level 4 scorings was observed, women in the control group (who used the NuvaRing and displayed significantly reduced endogenous estradiol levels) displayed higher level 4 scores throughout the three testing sessions. Therefore, it can be assumed that high levels of estradiol are associated with a reduced fear of motive frustration. The theoretical construction of OMT levels intends to reflect mechanisms underlying actual behavior control. From a neuropsychological point of view, both excitatory (approach) and inhibitory (avoidance) processes are involved in behavior control. According to Bancroft and Graham (2011), individuals differ in their propensity for one of these processes, and it is suggestive that there is also intra-individual, potentially hormone-driven variability in approaching or avoiding behavior tendencies. It can be proposed that the generally activating effects of estradiol may reflect an interaction of exciting and inhibiting processes that finally lead to reduced inhibition. Thus, the estradiol peak in the preovulatory phase would act as a brake release in behavior control at the time of highest likelihood of conception. From an evolutionary point of view, it is conceivable that the hormonal actions regulating the biological reproductive process simultaneously affect psychological processes that facilitate conception. The reduced fear of motive frustration may thus reflect such an evolutionary adaptation. However, because the gonadotropines FSH and LH reach their highest concentrations in concert with the estradiol peak at the preovulatory phase, caution is warranted in inferring causal relationships. It remains an open question to what extent these hormones affect the reduced fear of motive frustration and how these hormones might interact to produce this effect. In contrast to existing evidence, the relationship between progesterone/estradiol and affiliation motivation/attachment behavior, as well as higher affiliation than power motivation in women, is not reflected
in the current results. One possible explanation for the lack of a strong association between motive themes and hormone concentrations is the conceptual difference in motive assessment methods. Although both the previously used PSE and the newly applied OMT have been subject to thorough methodological validation and proved to excel sufficient internal consistency and reliability, they may not measure exactly the same constructs. The PSE was developed in order to capture motives as basal needs, whereas the focus of the OMT lies on the enactment of needs. In addition, due to the methodological differences in motive coding, it can be assumed that the PSE is more sensitive to intra-individual variation (because intra-individual variation can be estimated across all pictures), whereas the OMT is likely to be more sensitive to inter-individual variation (only one motive per picture). It would be feasible to conduct a study using both instruments and comparing the motive scores in order to rule out this potential confound. Besides the motive measurement technique, the current study differs from other available evidence in two more methodological issues: First, while previous work used three parallel sets of motive arousing pictures, the OMT coding procedure allowed for using the same seven pictures at every testing session. The impact of this methodological difference could be controlled for by replacing the within-subject design (which implies repeated-measures designs) by a between-subject design. However, given the large interindividual difference in both the scope of hormone fluctuations and motivational schemes, a within-subject design should be preferred in order to control for pre-existing differences. Second, while blood serum hormone values were used in the current study, the more confounding-prone saliva-based hormone analysis was used previously. The advantage of saliva-sampling lies in the non-invasive, more readily available sampling method, which might also facilitate the recruitment of larger samples. In addition, saliva-derived hormone values reflect only the unbound and bioavailable portions of the circulating steroids. However, saliva-derived values are sensitive to distortion from food aliment or mouth micro-injury residues, as well as hormone/hormone-binding protein
interactions. Therefore, total hormone levels derived from blood serum analysis can be considered as the more accurate measure, albeit it requires more organizational effort.

In summary, the results of this study further support the assumption that gonadal sex hormones act as internal stimuli on the formation of social motivation. Similar to fluctuations in glucose levels acting as internal stimulus on behavior systems related to hunger and food intake, sex hormones seem to have a modulating effect on the intuitive control of a range of social behaviors, such as attachment, affiliation, cooperation, or competition. Although implicit motives are defined as enduring personal preferences for affectively charged incentives, what is measured in content analytic procedures seems to depend on both external arousal and internal, physiological incitement. Because both internal and external motive inducement are variable, it is conceivable that a change or manipulation of triggers leads to a change in the motive outcome. The OMT has been shown to be a suitable methodological amplification in the study of the psychoendocrinological background of motivation. Especially because of its consideration of different emotional states and different forms of motive enactment, the OMT is a promising instrument for future research attempts to disentangle the complex inter-relation of hormonal states and motive-driven behavior.
Chapter 5: General Discussion

5.1 Summary of the main findings

5.1.1 Hormone effects on the functional brain organization

This thesis had two main objectives: Firstly, to contribute to a better understanding of hormonal influences on the functional brain organization. Secondly, to identify potential adaptive functions of this modulation. To this end, an extensive research of the existing literature was conducted in order to outline the essential points of contradiction in the field of sex- and hormone-related brain processes. The results of this preparatory work were integrated in a comprehensive study, designed to soundly examine hormonal influences on different aspects of functional brain organization. In order to maximize the degree of clarification, a combined broad and in-depth approach was chosen.

Although this large-scaled study did not provide definite answered to all open questions, the recorded data support the view that activating hormone effects modulate neurotransmission in the human brain. In simple behavioral paradigms, individuals in two control groups with stable hormone concentrations produced the expected effects, including a rightward asymmetry in a figural comparison task, a left-ward asymmetry in a dichotic listening task, prolonged reaction times in tasks requiring interhemispheric transfer, and an advantage of interhemispheric integration in a computationally complex task. Women with fluctuating hormone concentrations, on the contrary, clearly differed from these normal patterns. Thus, because the tests proved to be suitable to produce hemispheric asymmetries, and the three experimental groups were composed with respect to comparable demographic features, any particular variation in the naturally cycling women’s data can be related to their differing hormone levels with some confidence. During highest progesterone concentrations (and simultaneously high estradiol concentrations), the degree of FCA was reduced, the interhemispheric transfer tended to be less efficient, and the
interhemispheric integration tended to be more advantageous in naturally cycling women. In comparison, at the time of highest estradiol (and low progesterone) concentrations, perceptual asymmetry was most pronounced and interhemispheric integration was less advantageous in the complex condition of the Banich-Belger task. In addition to the fact some of these effects missed statistical validation; two findings interfered with this overall pattern of results. One is the finding that the IHTT was prolonged during the high-progesterone/low FCA cycle phase, as well as during the high-estradiol/high FCA cycle phase. The other one is the absence of direct links between hormone concentrations and behavioral measures (except of the increased AFA in the mid-luteal phase, when progesterone was positively correlated with the AFA). Interestingly, there was evidence for a moderate correlation between progesterone and estradiol concentrations and the laterality quotient in the figural comparison task during menses, indicating a positive effect of these hormones on performance in the task-specifically subdominant hemisphere. Together, although neuronal activity was not directly measured, it can be concluded that hormone fluctuations across the menstrual cycle were associated with a varied nature of functional brain organization. From the available theoretical accounts for the generation and maintenance of FCA, these results fit best with the model of sex hormone-mediated interhemispheric decoupling. Given the known neuromodulatory properties of progesterone and estradiol, their regular cyclic increases and decreases can be assumed to be accompanied by alterations in neurotransmission. More specifically, inhibitory processes that normally dominate the interhemispheric transfer of neural information are assumed to be extenuated by the increased presence of progestagen molecules in the brain. Although the impact of these neuronal alterations for everyday life cognitive performance can be expected to of minor relevance, they demonstrate a theoretically meaningful aspect of brain plasticity that deserves further consideration. Even if this cyclic variation in neurophysiological brain organization is small, it means a transient attenuation of the efficacy of interhemispheric transfer processes.
5.1.2 Hormone effects on social cognition

The results of the studies described in Chapter 3 and 4 are in accordance with the view that such seemingly detrimental effects represent beneficial adaptations in the social cognitive domain. It was predicted that adaptations to varied hormonal states can be demonstrated in varied social cognitive processes. Also this second objection of the current thesis was addressed comprehensively, using two different approaches. They were designed with consideration to the presumption that selective pressures shape generic, categorical cognitive programs that can be activated by internal (including hormonal) states, as well as by situational social stimuli. Therefore, none of the applied tests relied on direct measures of explicit cognitive content or self-reported mental states. Instead, one study relied on implicit social motives, analyzed by means of content coding (Chapter 4), and another study assessed readiness for interpersonal cooperation and disposition for judgments of trustworthiness by means of a game theoretical paradigm (Chapter 3). Both approaches had the advantage of sufficiently concealing the objective of the research, which was important because the participants were inherently aware of the fact that menstrual cycle effects were investigated. Therefore, attempts should be made to diminish influences of personal believes about menstrual cycle effects, or socially-accepted response patterns. However, this benefit of avoiding such confounds came with the cost of a certain degree of noise in the data, because both experimental designs relied on constructions of cognitive processes. The rest of probability that the tests actually assess something different from the cognitive constructs they were designed to assess cannot be completely ruled out, even though both tests were known to exert sufficient internal consistency and both had been repeatedly applied in social cognitive and neuroscientific research before. The dual strategy of using both an implicit motive measure and an explicit behavioral measure (that is, amount of MU invested in the trust game) was chosen to minimize this noise and to mutually support findings.

The results of the second part of the present thesis confirm this dual strategy. Combined, the results of the two studies give rise to interesting
implications regarding modulations of social cognitive processes by fluctuating gonadal sex hormones. The main finding of the trust game experiment (Chapter 3) was the significantly reduced overall investment of naturally cycling women at the time of highest fertility. This can be interpreted as a disposition for more conservative judgments of trustworthiness, or a reduced preparedness to cooperate with strangers, or also reduced risk-taking behavior in parallel with this particular hormonal constitution. The assumption that hormones only channel social decision making as a function of social stimuli configuration was supported by the main effect of other player on the investment behavior: all participants varied their investment according to sex and attractiveness of the other player, indicating that attractive women were acknowledged as being most trustworthy. This readiness to trust in women was associated with progesterone and estradiol levels; participants with higher levels of these gonadal hormones also invested more MU in attractive female players at menses. Also in the preovulatory phase, high levels of estradiol were associated with high overall amounts of MU invested, although the average investment was reduced at this time. Furthermore, the progesterone increase from menses to mid-luteal phase was positively correlated with the increased investment in unattractive female players. On the contrary, unattractive men seemed to be acknowledged as being least trustworthy, and the trustworthiness of unattractive men was particularly disregarded in the preovulatory phase. However, direct links between increased hormone levels in this cycle phase and the decreased investment in unattractive male players were not observed. Instead, parameters of estradiol and investment in unattractive male player correlated negatively between menses and mid-luteal phase. Also the negative correlation between FSH levels and investment in unattractive female players indicates a connection between increased hormone concentrations and decreased trusting behavior.

The trust game study indicates increased behavioral inhibition at the time of highest fertility, albeit the prevailing hormone action (estradiol surge) was associated with decreased behavioral inhibition. The main finding of the
third study (Chapter 4) adds to the theory of activating estradiol effects, as opposed to inhibiting effects of the combined progesterone/estradiol surge. Here, the reduced number of OMT-level 4 scorings in the power motive during the high-estradiol mid-cycle testing can be seen as reflecting decreased behavioral inhibition. During the high-progesterone/high-estradiol mid-luteal phase, there was no such indication of reduced inhibition. Together, the variation in explicit investment behavior and in implicit motive enactment is indicative of menstrual cycle phase-related alterations in social cognitive processes.

5.2 Theoretical integration and outlook

The work presented in this thesis combined specialized knowledge and technical approaches from diverse scientific disciplines, including biopsychology, cognitive psychology, motivational psychology, social and personality psychology, social endocrinology, evolutionary biology, and evolutionary psychology. The result signifies the advantage of accumulating synergies in order to fully account for complex phenomena such as the subject matter of this thesis. However, the multi-disciplinary approach also implied some aspects that complicate a comprehensive interpretation of the partial results. Some of the complicating and limiting factors are discussed below.

5.2.1 Implications of hormone-mediated alterations in FCAs

The first prediction stated in the general introduction concerned the assumptions of the model of hormone-mediated interhemispheric decoupling. Consistent with predictions, FCA in a spatial cognitive task was least pronounced when concentrations of progesterone and estradiol where highest. This result is also consistent with earlier findings derived from behavioral data (Heister et al., 1989; Bibawi et al., 1995; Weekes & Zaidel, 1996; Sanders & Wenmoth, 1998; Hausmann & Güntürkün, 2000; Hausmann et al., 2002; Sherwin, 2003), as well as neuroimaging data (Weis
et al., 2011). However, the predicted hormonal impact of reduced inhibitory processes was not as clearly demonstrated in the other investigated tasks. Notwithstanding, evidence for the existence of hormone effects on all of the investigated tasks is available. The REA has been reported to be reduced in the mid-luteal phase (Mead & Hampson, 1996), the IHTT has been observed to be prolonged (Hausmann et al., 2011), and also the AFA in the Banich-Belger-task has been argued to be affected by cycle phase (Bayer et al., 2008). Based on these previous reports and the fact that the current dataset did not appear to reflect a random distribution, but pointed into the predicted direction, it can be concluded that in young naturally cycling women, changes within the physiological range of ovarian sex hormone levels during a normal menstrual cycle influence brain plasticity, and hence the performance on cognitive tests. However, the practical implications of the impaired interhemispheric inhibition are presumably very limited. The cognitive skills under investigation apparently differ substantially from cognitive skills required in everyday life activities, which rarely require a particular cognitive function as isolated as in psychological experiments. Furthermore, recent investigations of the relationship between the degree of lateralization and performance in a given cognitive domain pointed out that this relationship is best described by an inverted U-shaped curve, instead of by a linear function (Hirnstein et al., 2010). Therefore, it can be argued that variation in FCA observed in naturally cycling women simply reflects noise around an optimum, and is not of significant relevance for everyday life functioning.

5.2.2 Trade-off between accurate cycle-phase determination and sample size

Every study that deals with menstrual cycle effects has to consider cost-benefit ratios before starting data recording. Repeated measures designs have the benefit of ruling out pre-existing differences in sample characteristics, but they come along with the cost potential carry-over effects and of reduced statistical power, compared to between-subject
designs. In the case of the present work, the objective was to study physiological hormone fluctuations as they occur in naturally cycling women. The problem was that the interindividual variation in hormone profiles was known to be tremendous (Kiesner, 2011; Frick, 2012). This fact turned out to be confirmed in the present samples, where, for instance, one participant’s lowest progesterone value was another participant’s highest. Moreover, there is also evidence for large intraindividual variation in hormone profiles from one cycle to the next (Hatcher & Namnoum, 2004). For example, in a three month survey, only 62 % of women at the same age as the of naturally cycling women tested here ovulated in every cycle (Metcalf & Mackenzie, 1980). Therefore, the exact individual definition of the three cycle phases of interest was essential. Defining cycle phases on the basis of estimations from self-reported menstrual bleeding onset are regarded as very imprecise (Pillsworth et al., 2004). When hormones are controlled for, drop-out rates of 20 – 30 % due to misclassifications of cycle phases have been reported (Hampson, 1990; Hausmann, 2005; Bibawi, 1995). Therefore, defining cycle phases by taking physiological measures, such as blood or saliva samples, is mandatory. But then again, taking physiological measures automatically increases demands on research participants, because they need to visit the lab more often, need to restrain from eating and drinking (in saliva sampling), or have to agree to venous puncture (in blood sampling). Furthermore, analyzing actual hormone concentrations is time, energy, and money consuming. Taking physiological measures, thus, increases study costs and decreases the number of participants that can be investigated. In this work, sample sizes required for demonstrating moderate effect sizes were calculated using G*power (University of Düsseldorf, Germany). The samples that were finally recruited and tested were at the minimum size in which moderate effects could be detected, according to the G*power analysis, but at the maximum size that could be realized with regard to the available financial and personnel capacities. However, a drop-out rate of 15 % due to misclassified cycle phases was not anticipated, and drop-out rates of 27 – 63 % in the
separate tests were even less expected. Compared to other menstrual cycle studies in the literature, however, the samples still were comparably large (Voyer, 1996). Nevertheless, analyses would presumably have yielded statistically stronger results if the under-powering problem could have been circumvented.

5.2.3 Interpreting hormone data
Another way of dealing with the problem of large interindividual hormone variation in menstrual cycle studies would be to continuously analyze intraindividual difference values instead of absolute hormone and behavioral data. It may be that the degree of hormone change is of higher explanatory value, compared to the interpretation of a single hormone value. After all, it is mainly the surge or withdrawal of a single hormone concentration that is known to cause bioactive effects. Likewise, it is the prevention of hormone fluctuations that suppresses typical hormone action (e.g., the mode of action in hormonal contraceptives). Similar to the required crossing of hormonal thresholds for the described physiological hormone effects in the reproductive cycle, I suggest that there may also be a hormone threshold under which no assessable neuromodulatory effects occur. This threshold might differ interindividually, just like it is the case in the physiological hormone effects. If this were the case, it would be conceivable that this threshold was not exceeded in some participants at the time of testing. Thus, even if the predicted neuromodulatory hormone effect truly exists, it might have been concealed by this grouped analysis. Furthermore, the suggested threshold may differ in the six tasks used in the present work. This could explain why some test outcomes turned out to be effected by varying hormone levels (e.g., a lower hormone threshold for the figure comparison task), while others did not (e.g., a higher hormone threshold for processes in the auditory modality than in the visual modality in the dichotic listening task or for interhemispheric integration in the Banich-Belger task). In this context, the properties of the task-specifically involved neuronal structure may play a role. The hypothesis of
interhemispheric decoupling focuses on the neurophysiological properties of CC fibers, but with the assumption put forward by Corballis (2002), different parts of the CC were involved in the different tasks applied here (but see Cherbuin et al., 2012). The IHTT decreases linearly with increasing degree of myelinization and diameter of neurons (Aboitiz et al., 2003). The parts of the CC connecting brain areas that require fast neurotransmission (such as motor, somatosensoric, and visual areas) consist of thicker neurons than parts of the CC connecting (pre)frontal brain areas that are involved in complex cognitive processes (Aboitiz et al., 1992). Based on this assumption, it is conceivable that hormones have differential effects on these tasks, e.g. because a hormonal threshold is lower for thinner callosal fibers than for thicker fibers. This may explain why a modulation was observed in the visual half field paradigm, but not in the auditory dichotic listening paradigm. In order to investigate this new hypothesis of threshold-dependent hormone-mediated interhemispheric decoupling (figure 11), callosal fibers would have to be examined more thoroughly. The distribution of number and cell types of progesterone and estradiol receptors should be quantified (e.g., by means of radioligand binding assays) in order to draw conclusions about differential biochemical properties across different parts of the CC. Moreover, such an analysis would also give more appropriate consideration to the general complexity of steroid’s neurophysiological properties. Predictions about hormone effects in the CNS can hardly be drawn without detailed information about the type of receptor the hormone is binding to, a fact that has largely been neglected in previous theory formation. All of these suggestions call on a closer collaboration of related disciplines in cognitive neuroscience. The problem of too small sample sizes might as well be solved by a more intensive use of the potential that lies in building synergies.
**Figure 11:** Illustration of the hypothesis of threshold-dependent hormone-mediated interhemispheric decoupling. The threshold marks the estradiol concentration required to cause a detectable neuromodulatory effect. In this example, three fictive participants’ estradiol profiles demonstrate that participant A crossed the threshold at both testing sessions, whereas participant B crossed the threshold only once at test session 1, and participant C did not cross the threshold at all.

### 5.2.4 Neuronal inhibition in relation to behavioral inhibition

Provided that hormonal changes actually modify inhibitory processes in the brain, the question to what extent behavioral inhibition is related to such a modulation still remains. One promising way of approaching this question would be to translate the inhibitory framework for regulating FCA to a new framework for the adaptation of social cognition and, hence, social behavior. Similar to the stimulus-specific activation of one hemisphere that inhibits activity within the contralateral hemisphere during task processing, there may be a stimulus-specific inhibition of neural circuits that is crucial for appropriate social motivation and emotion regulation. The importance of behavioral inhibition has gained increasing attention in the literature, for example as a means to restrict from potential social threat (van Wingen et al., 2008) or to restrict from aggressive competition in women (Arrindell et al., 1993), and to reduce the risk of infection with contagious disease (Fleischman & Fessler, 2011). Neuroimaging studies have recently started to investigate hormonal modulation of brain areas that are thought to be
involved in social cognition and behavior control, such as the amygdala and the medial prefrontal and the orbitofrontal cortex (Adolphs, 2003; Caldú & Dreher, 2007; Dias, 2009; Frye, 2009; Blumstein et al., 2010). There is evidence that the neuronal coupling of amygdala and prefrontal areas, which is thought to be essential in the regulation of behavioral inhibition, is affected by progesterone and estradiol. Van Wingen and collaborators (2011) found an enhancing effect of progesterone on amygdala reactivity and its connectivity with the medial prefrontal cortex, whereas estradiol was found to be associated with decreased activity in these neuronal structures. Such opposing effects were proposed to play a role in behavioral inhibition (ibid.). However, there is a still ongoing debate about the stimulus-specificity of behavioral inhibition (Protopopescu et al., 2005). Based on these recent findings, it can be concluded that there are stable neuronal structures involved in the generation of social motivation, but that these structures are dynamically modulated by hormone fluctuations. The modulation of trust game reaction times in the mid-luteal phase presented in this work is in accordance with this idea. Here, the correlation between high progesterone levels and reaction times in trials with attractive other players is indicative of a stimulus-specific response inhibition in naturally cycling women. Estradiol, on the contrary, seems to be associated with a weakening of the inhibitory pathways (Colzato et al., 2010). The reduced motive inhibition at the time of highest estradiol levels is in accordance with this notion. However, this effect was only evident in the power motive, but not in the affiliation or in the achievement motive. A stimulus-specific modulation of behavioral inhibition was also indicated in a Stroop-interference paradigm, a test that measures frontal lobe mediated inhibitory control (Kazén & Kuhl, 2005). These authors reported that a negative mood priming was associated with increased inhibition. Likewise, performance in the Stroop test was also found to be superior in women with elevated endogenous estradiol levels (Wolf & Kirschbaum, 2002). Thus, predisposed and stable social motives and dynamic biological triggers are likely to interact in the regulation of any kind of behavioral output in social contexts.
Behavioral inhibition, and principally every kind of social behavior, can be triggered by many different stimuli, motives, or psychological mechanisms. Furthermore, the change of a single hormone level has presumably many different effects on a range of social cognitive parameters. Presumably, there is a large interindividual and also intraindividual variation in the motivational relevance of environmental stimuli; a fact that is hardly controllable in experimental set-ups. Deducing practical implications is limited by the trade-off between experimental separation of single functions and control of confounding factors on the one hand, and the claim to illustrate complex everyday life processes on the other hand. This also bears the risk of arriving at oversimplified and imprecise predictions. For example, claims about interpersonal trust and cooperation derived from game theoretical experiments may disregard complex real-life social relationships, which may contribute to the large behavioral variance (Soares, 2010). Hormone-mediated effects on the tendency to seek out for socially motivated behavior presumably only add on to, or interact with other underlying mechanisms. Gender stereotypes have been proposed to be one such mechanism, because it could be demonstrated that the activation or deactivation of gender stereotypes (e.g., women are more empathetic than men, or men have superior spatial cognitive abilities than women) have a significant impact on cognitive sex differences (Massa et al., 2005). Furthermore, self-assessment as a socio-psychological factor has been shown to be a better predictor of sex differences in spatial cognition in real-life situations than biological factors (Wolf et al., 2010). In conclusion, there seems to be no simple answer to question to what extent such proximate adaptations of social cognition and behavior control have been shaped by subliminal consequences at the distal level. Social, cultural, as well as hormonal contexts have to be considered and optimally disentangled in order to draw conclusions about the particular contributions to the assessable behavior. At present, the precise nature of neither ultimate nor proximate causes of hormone-mediated social cognitive and behavioral variation can be clearly determined.
5.3 Conclusion

This thesis was based on the supposition that distinct hormone-regulated reproductive states, such as menstruating followed by seeking (and potentially competing) for an optimal genitor versus being pregnant or nursing an infant, put different demands on concomitant social cognitive processes. In the latter state, a social cognitive mode supporting the capability to form and maintain protecting and providing social bonds has been argued to be most advantageous. On the contrary, the readiness to assert social risks and to stand up against potential rivals for the best mate is likely to be most advantageous in the (evolutionary) rare events of the first mentioned hormonal state. Because either social cognitive mode would be seriously disadvantageous in the respective other hormonal state, the capability of flexibly and appropriately switching between these social cognitive modes may have been adaptive. It was further proposed that the most obvious vehicle for solving this adaptive problem would be a coupling of hormonal processes that physiologically regulate reproduction with social cognitive processes that support the respective “intent” on the neurophysiological level. The results of this work are largely consistent with available evidence from human studies and give rise to the conclusion that in naturally cycling women, the functional brain organization is modulated by fluctuations in gonadal sex hormones. Albeit to a minor extent, such modulations have influences on the performance in cognitive tasks. Two implications follow from this notion: Firstly, short-termed and physiologically complex changes in brain plasticity appear to enable flexible alterations in motive enactment and behavioral inhibition. Secondly, inter-sex differences in cognitive strategies, as well as intra-sex (in women) variation in the same cognitive processes both seem to be under hormonal influence. Hormonal modulations should be seen as one (among many other) vehicles for the regulation of activating and inhibiting brain processes, but such hormone actions are supposedly threshold-dependent. Once individually variable hormone thresholds are crossed, female sex
hormone fluctuations seem to alter the costs of reduced efficiency of interhemispheric transfer to the benefit of optimized mate choice. This hypothesis of threshold-dependent hormone-mediated alteration of cognitive processes allows for the generation of testable predictions for future research attempts to further deepen our understanding of how mental events are implemented in human biology.
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AFA</td>
<td>across-field advantage</td>
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<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<tr>
<td>CAH</td>
<td>congenital adrenal hyperplasia</td>
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<tr>
<td>CC</td>
<td>corpus callosum</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CUD</td>
<td>crossed-uncrossed difference</td>
</tr>
<tr>
<td>EEG</td>
<td>electro-encephalogram</td>
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<tr>
<td>FCA</td>
<td>functional cerebral asymmetry</td>
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<td>FSH</td>
<td>follicle stimulating hormone</td>
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<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
</tr>
<tr>
<td>HPG</td>
<td>hypothalamic-pituitary-gonadal</td>
</tr>
<tr>
<td>IHTT</td>
<td>interhemispheric transfer time</td>
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<tr>
<td>LH</td>
<td>luteinizing hormone</td>
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<tr>
<td>LQ</td>
<td>laterality quotient</td>
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<tr>
<td>MU</td>
<td>money unit</td>
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<tr>
<td>OMT</td>
<td>operant motive test</td>
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<tr>
<td>PFC</td>
<td>prefrontal cortex</td>
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<td>PSE</td>
<td>Picture Story Exercise</td>
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<tr>
<td>PSI</td>
<td>Personality Systems Interactions</td>
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<tr>
<td>REA</td>
<td>right ear advantage</td>
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<tr>
<td>TAT</td>
<td>thematic apperception test</td>
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<tr>
<td>TOM</td>
<td>theory of mind</td>
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<tr>
<td>SHBG</td>
<td>sex hormone binding globulin</td>
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Appendix A: Curriculum Vitae

Name: Anna Ball, née Sievering
Date of Birth: 16. 08. 1984
Nationality: German

Academic Qualifications

2009 M.Sc. Psychology, Faculty of Psychology, University of Bochum, Germany
Thesis: “Comparing two modes of action in the A-not-B paradigm” supervised by Prof. Dr. A. Schölmerich and Prof. Dr. Claes von Hofsten

2007 B.Sc. Psychology, Faculty of Psychology, University of Bochum, Germany
Thesis: “Predicting cardiovascular activity by semantic descriptions of childhood experiences in the adult attachment interview”. Supervised by Prof. Dr. A. Schölmerich and Dipl. Psych. J. Heete.

Education

Since 04/2010: Member of the Ruhr-University Research School, structured interdisciplinary graduation programme, including research related training and generic skills courses

Since 09/2009: Research assistant and PhD- student at the Dept. Biopsychology and Dept. Cognitive Psychology, Faculty of Psychology, Ruhr-University Bochum, Germany

Since 03/2009: Behaviour Therapy at the DGVT Münster, Germany

08/2007-05/2008: Study abroad at Uppsala University, Uppsala, Sweden
Work Experience

08/2010 – 07/2011 Part-time psychologist trainee at the St. Antonius Hospital in Bottrop-Kirchhellen, Germany: Clinical diagnostics and psychotherapy in a general psychiatric ward, supervised by Dipl.-Psych. B. Lewe.

08/2008 – 07/2009 Student assistant at the neuropsychological therapy section of Fachkliniken Rhein-Ruhr in Essen-Kettwig, Germany: Treatment of stroke patients and other brain injured patients, supervised by Dipl. Psych. S. Steidle.

10/2007 – 05/2008: Internship at Uppsala University’s Babylab: Planning and executing an eye-tracker study on infant cognition, supervised by Prof. C. von Hofsten, Uppsala, Sweden


Administrative Work

05/2010 – 12/2010: Co-ordinator of an international PhD exchange program sponsored by the German Academic Exchange Service (DAAD)

06/2008 – 02/2009: Student member of the search committee for the Mercator Research Group “Structure of Memory” at Ruhr-University, Bochum, Germany

11/2006 – 05/2007: Member of the organizational committee of the 12th psychology student’s congress “Future Networks”, funded by the professional organization of German psychologists (BDP), in Bochum, Germany

Research Instruments

- Eye Tracking
- Visual Half-field stimulation
- Dichotic Listening Paradigms
- Operant Motive Test
- Game Theory Paradigms
Publications: Peer-reviewed journal articles


Publications: Manuscripts in preparation


Publications: Abstracts of Conference Contributions

Invited presentations

- “Neurobiological basis of body perception and disorders of body perception” at the annual convention of the society for psychological pain therapy and research (DGSPF) in Essen, Germany, June 2010.

- “The effect of steroid hormones on Social Cognition. PhD project outline” during a lab visit of the university of Padova in the course of the DAAD PhDNet program, December 2010

- “Social Cognition across the menstrual cycle” at the research colloquium of the department of cognitive psychology, Ruhr-University Bochum (Host: Prof. Oliver Wolf), April 2011

- “Sex hormones as modulators of social cognition” at the research colloquium of the department of behavioural biology, Vienna University (Host: Prof. Eva Milessi), Mai 2011

Teaching Experience

- Stand-in lecture on sex differences in cerebral asymmetries within the lecture “Left Brain Right Brain” (Winter term 2011)

- Lecture on human evolution (Summer term 2011)

- Seminar: “Interactions in the brain – from hormones to awareness” (Summer term 2011)

- Seminar: “The bridges of the brain: Priority to the left on the callosal highway?” (Winter term 2010)

- Seminar and stand-in lecture on “Evolution and Emotion” (Summer term 2010)

- Seminar on Developmental Psychology (Summer term 2009)

- Assistant supervisor of ”The Painting and Crafts Workshop of the human brain” (Summer term 2007)

Student Supervision


- Patricia Sophie Schneider, Bachelor thesis “Progesterone and Estradiol as modulators of interhemispheric transfer” (2011)


- Several student internships (Psychology and Biology students)
Honors and awards:

- The Rotary Foundation Ambassadorial Scholarship for the academic year 2007/2008
- Poster Price at the 1st International Conference on Motivation, Self-Regulation and Gender in Gdansk, June 2010, Poland
- Poster Price at the 1st Research Day, November 2011, Ruhr-University Research School, Bochum, Germany
Appendix B: Declaration (Erklärung)

Ich versichere, dass ich die von mir vorgelegte Dissertation selbstständig und ohne unzulässige Hilfe angefertigt habe, die benutzten Quellen und Hilfsmittel vollständig angegeben habe, dass sie noch nicht veröffentlicht worden ist, sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde. Die Bestimmungen der geltenden Promotionsordnung sind mir bekannt.

Bochum, April 2012

Anna Ball