Chapter 9

Summary & General Discussion
Summary

This thesis aims to gain more insight into the role of biological and psychological factors in the pathogenesis of depression in general and in the peripartum in particular. Accordingly, the influence of the mono-amine system, HPA-axis functioning, female gonadal hormones and omega-3 / omega-6 fatty acids, in interaction with genetic factors and life events, were related to the onset and persistence of depressive symptoms in the peripartum. In an animal model the behavioral consequences of a rapid and a gradual parturition-like decline of estrogen and progesterone were investigated. In a series of clinical studies the various endocrine and monoamine systems were prospectively studied, the role of fatty acids was examined in a supplementation trial and the influence of several candidate genes was examined in participants of this trial, and in patients with a severely complicated pregnancy. All study designs were prospective, thus facilitating the assessment of the impact of these potential etiological factors.

The experiment performed with the pseudo-pregnancy model in rats, described in chapter 2, demonstrated that animals with a rapid, parturition-like decline of hormones had a temporarily increased startle response and increased anxiety-like behavior in the open field test. This was not found in the gradual decline and control groups, indicating that differences in adaptational capacity for large changes in levels of these hormones might underlie transient symptoms of anxiety and increased reactivity, as found in postpartum blues in humans. The HPA-axis response to stress was not found to be influenced by the rate of the hormonal decline, signifying that normalization of the HPA-axis and behavioral response to stressful stimuli are essentially independent, at least following a hormone withdrawal.

In the observational study, described in chapter 3, indices of serotonin and noradrenalin functioning were prospectively investigated in 26 pregnant women and related to postpartum blues. At the fifth day postpartum a decrease in serotonin metabolism was found, as indicated by a decrease in plasma tryptophan and a concomitant decrease in platelet serotonin content. This decrease was unrelated to postpartum blues. However, blues scores correlated positively with an index of the expression of the serotonin transporter (5-HTT), suggesting that the decrease in serotonin metabolism only induces blues in women with a high 5-HTT activity. Besides that, women with blues had higher plasma levels of the noradrenalin metabolite MHPG at six weeks postpartum, which we interpreted as indicative of higher stress sensitivity or decreased stress-coping. The
persistently high noradrenalin metabolism in women with blues at six weeks postpartum might be a causal factor or a consequence of later depression.

Chapter 4 describes a Randomized Clinical Trial (RCT) evaluating the effect of supplementation of omega-3 / omega-6 fatty acids (DHA or DHA + AA ; 220 mg) on postpartum blues and depressive symptoms and sleep quality at 36 weeks of pregnancy and 6 weeks postpartum. One-hundred-eleven healthy women with a relatively low intake of DHA, were supplied with DHA or DHA + AA. Women who used supplements did not differ from those using placebo in mean scores on depression and blues questionnaires or in indices of sleep quality. In addition, fatty acid status did not correlate with any of these measures.

In the women who participated in this trial we evaluated the effects of three candidate genes on the course of peripartum depressive symptoms. Included were genes involved in the metabolism of serotonin (5-HTT), noradrenalin and dopamine (MAOA & COMT). The results, described in chapter 5, show that women who carry the low activity variants of both COMT and MAOA have an increase in depressive symptoms at the end of pregnancy and 6 weeks postpartum. Symptoms returned to normal levels at 12 weeks postpartum. The same, but less pronounced, pattern was found in carriers of the high activity variant of 5-HTT. We hypothesized that due to the low activity of both MAOA and COMT, these women might have an altered capacity to neutralize the stress-evoked release of catecholamines, which might be experienced as high sympathetic tone associated anxious and depressive feelings. Women carrying the 5-HTT high activity variant might be more sensitive for the decreased serotonin metabolism of the peripartum.

In chapter 6, we investigated in the same group whether these candidate genes were also involved in subgroups of women with different courses of depressive symptoms. Subgroups were identified with latent class analyses. Three subgroups could be identified; a group of 70% of the women with low levels of depressive symptoms throughout the whole study period, a group of 20% of women with high levels of depressive symptoms during pregnancy, decreasing postpartum and a group of 10% of women developing depressive symptoms in the postpartum period. None of the subgroups was found to be related to the 3 candidate genes. These results emphasize that clinically identifiable subgroups do not necessarily share the same characteristics with subgroups based on genetic features.

The role of stressful life-events in the onset of affective disorders was investigated in chapter 7. In a prospective, exploratory study the incidence of depression and post traumatic stress disorder (PTSD) was compared between women with a pregnancy

Summary and General Discussion
complicated by HELLP, Pre-eclampsia (PE) or Pre-term Pre-labour Rupture of the membranes (PPROM) and women with uncomplicated pregnancies. Women with complicated pregnancies were found to have more post traumatic stress symptoms than controls, but the incidence of depression did not differ between complicated and uncomplicated pregnancies. Adding to that, the incidence of PTSD did not differ significantly between women suffering from HELLP/PE or PPROM, indicating that PTSD may rather be associated with pre-term birth than with the maternal condition. Fifty percent of the women with PTSD also had a depression. Risk factors for post traumatic stress symptoms and depressive symptoms were a self reported history of depression, depressive symptoms during hospitalization and infant death in the postpartum period. These risk factors together explained 39- 44% of the variation in post traumatic stress and depressive symptoms.

In chapter 8 we investigated whether the vulnerability for depressive and post traumatic stress symptoms following these complicated pregnancies could be explained by polymorphism in the 5-HTT gene. We found that the accumulated effects of 5-HTT l allele and a history of depression are associated with depressive symptoms in the postpartum period. Involvement of the 5-HTT l allele is probably related to the decreased serotonin metabolism in the peripartum. These results emphasize the complexity of the pathophysiological processes involved in the onset of depressive symptoms because of the contribution of multiple interacting risk factors.
Summary and General Discussion

General discussion

Putting the pieces together …

The studies described in this thesis all deal with depressive symptoms and are based on a variety of designs (animal model, observational studies, RCT) and a wide range of topics (female gonadal hormones, mono-amine metabolism, fatty acids, environmental and genetic aspects). Accordingly, many facets of depression were evaluated. When the findings are put together an image of depression emerges, showing a complex web of interactions, which might be unraveled by focusing on the course of the depressive symptoms.

Challenged systems & adaptational capacity

Involvement of any of the here discussed physiological systems in the onset of depressive symptoms became apparent only if 1) the system was challenged and 2) interindividual differences in functioning of the system were taken into account. This can be best exemplified by the findings regarding serotonergic functioning; the decrease in availability of tryptophan is related to blues symptoms, provided that the expression of the serotonin transporter is also taken into account (chapter 3). Additional evidence is found in chapters 5 & 8, indicating a role of the high activity variants of the serotonin transporter in peripartum depressive symptoms, only in periods characterized by a low tryptophan availability). A third example is found in chapter 5; the peripartum related events induced an increase in depressive symptoms in carriers of the low activity variants of both MAOA and COMT. This association is not found at 16 weeks of pregnancy and 12 weeks postpartum, indicating once more that 1) this system is found to be associated with depression only during the challenging periods; 2) and only in susceptible women, this susceptibility is associated with polymorphic variances in 2 different genes, which are both known to influence noradrenalin metabolism. The last illustration, the experiments with the animal model (chapter 2) showed that animals with a rapid, but not a gradual decline in hormonal levels exhibited most anxiety and reactivity, indicating that not the hormonal decline as such induces anxiety behavior, but that differences in the capacity to adapt to those changes (= time, or capacity to adapt GABA-A receptor expression) underlie the association between hormonal decline and these behavioral symptoms. Thus again, a challenge + interindividual differences in functioning of the system together lead to an increase in affective symptoms.
These observations fit the hypothesis postulated by Halbreich in 2005 (1) who stated that the vulnerability for pregnancy related affective disorders is constituted by hypersensitivity of an individual to changes in endocrine or other pregnancy related factors, due to altered adaptation mechanisms. The altered adaptation subsequently induces dysregulation of Central Nervous Systems (CNS) which finally evokes depressive symptoms. The second stage of Halbreichs’ model involves a phenotypic predisposition which is constituted by 1) interindividual differences in the systems involved in the vulnerability i.e. some women might be more sensitive to the serotonin related symptoms, while others may be more sensitive to the changes in GABA-ergic or noradrenergic metabolism; 2) interindividual differences in parts of the CNS, that are vulnerable for disturbances. The nature of the symptoms of the different phenotypes may depend on the vulnerable system involved. Evidence for this system specific symptom profile is found in chapter 8, which indicates that depressive symptoms, but not post traumatic stress symptoms are related to the l allele polymorphism of the 5-HTT gene.

In conclusion: functioning of the investigated endocrine and monoamine systems is not directly related to the development of depression, but an altered reaction to a challenge of these systems seems to be involved in the onset of depressive symptoms, instead. These data fit the hypothesis that altered adaptation mechanisms and consequent CNS dysregulation in vulnerable individuals might lead to depressive symptoms in reaction to the endocrine events of pregnancy.

**Interacting systems**

The relations between functioning of the diverse systems and the onset of depression are even more complex. Untill now the here investigated physiological systems have been considered as independent. However, all investigated systems are known to influence each other reciprocally. For example, challenges of the HPA-axis perturbs the serotonergic system and vice versa (2, 3). The same complex interactions have been described for the female gonadal hormones and the serotonergic system (4) and the female gonadal hormones and HPA-axis (5-7). An example of the complexity of the latter interaction is found in chapter 2 of this thesis, where we reported that animals treated with hormones had a diminished hypothalamic response to stress, but that the central and peripheral stress-response was not found to be different between hormone treated and control groups. A second example; omega-3 and omega-6 fatty acid status may influence serotonergic functioning by modulation of immune activity. An indication of the latter is found in data of the DHA/AA supplementation study described in this thesis. In a pilot experiment, using blood samples of week 36 of
pregnancy, DHA status was found to correlate with indices of IDO activity, indicating that DHA status may inhibit the pregnancy-related IDO-induced decrease in serotonergic activity by an inhibitory effect on IDO activity. However, before definite conclusions can be drawn, these relations have to be investigated in the whole study sample.

A final example, some of the studies also suggest an interaction between the serotonin and noradrenalin systems. The results of chapter 3 indicate involvement of serotonin metabolism in the onset of blues, which was subsequently found to be associated with an increased noradrenalin metabolism at six weeks postpartum. In chapter 5 gene polymorphisms involved in both the serotonergic system and noradrenalin metabolism were associated with depressive symptoms. The serotonin and noradrenalin systems are known to interact, both at the anatomical and the functional level, in such a complex way that is difficult to discuss in global terms (8). In general, functioning of both systems has been associated with depression, in which under-activation of the serotonin system and increased noradrenergic functioning are the most reported findings (8). The findings of chapters 3 and 5 indicate the same pattern of dysfunction.

Together, such complex interactions illustrate that the here reported relations between functioning of whichever system and the onset of affective symptoms should be interpreted with care, as the question remains whether dysfunction of a system directly causes affective symptoms, or do so in interaction with dysfunctioning in other related systems. Or as stated by Ressler and Nemeroff regarding the serotonin and noradrenalin interactions: ‘The underlying causes of these disorders, however, are less likely to be found within the NE and 5HT systems, per se. Rather their dysfunction is likely due to their role in modulating, and being modulated by, other neurobiologic systems that together mediate the symptoms of affective illness.’ (8). Halbreichs’ model also recognizes the role of these interacting circuitries, as shown in figure 1.

**Cumulative adversity**

The results of all studies indicate that a disturbance in one system may induce temporary emotional disturbances, however, a disturbance of a single system is not sufficient to induce depression; co-occurring disturbances in other physiological systems are needed to provoke longer lasting depressive symptoms.

Some examples: chapter 2, the rapid decline in hormones is related to a temporary (2 days) disturbance in reactivity, not to longer lasting depressive symptoms; chapter 3, platelets’ 5-HTT expression was related to blues, but not to depression at six weeks.
postpartum; chapter 4, the increase in peripartum depressive symptoms in carriers of MAOA, COMT low activity, or 5-HTT high activity variants was temporary as the symptoms were resolved at 12 weeks postpartum; chapter 8, in women with complicated pregnancies 5-HTT polymorphisms were not related to BDI scores.

However, when adversity in other systems, or other risk factors were taken into account the relations became more evident: chapter 3, 5-HTT expression was related to blues and blues to increased noradrenalin metabolism and depression; chapter 4, both MAOA and COMT low activity variants were related to depression, however, the effect was most apparent when both activity variants were combined; chapter 9, the 5-HTT high active variant was found to be related to depression, especially when the a history of depression was taken into account.

Probably, the accumulation of disturbances in several systems together results in depressive symptoms. The involvement of a cascade of physiological changes in the onset of affective symptoms is also suggested by the timing of the onset of blues, which is 3 – 5 days postpartum. In chapter 2, a rapid decrease in hormones was found to be related to blues-like symptoms at day 1 and 2 postpartum. In humans however, blues occur at day 3 postpartum, suggesting that beside the hormonal decrease other changes have to occur, which together induce the affective instability. It might be that the co-occurring decrease in tryptophan availability is required.

In conclusion: disturbances in single systems are not enough to provoke depression, probably a cascade of and/or parallel physiological changes, involving several systems, evoke longer lasting depressive symptoms.

**The course unravels the cause**

Most of the findings in this thesis became apparent only due to the use of longitudinal, repeated measure designs; because of that we were able to: register the temporality of the behavioral changes following a hormone drop (chapter 2); unravel the complex, sequential relationship between the serotonin and noradrenalin systems and blues (chapter 3); evaluate the influence of the gene polymorphisms on the course of depressive symptoms (chapter 4); and to identify three subgroups of women differing in the course of their depressive symptoms (chapter 5).

Apparently the course unravels the cause. This is also true for affective disorders in other periods in life as 1) affective disorders are more related to changes in and adaptation of functioning of diverse physiological systems, than to differences in basal functioning; 2) affective disorders are also strongly related to changes in social
functioning and life events; 3) affective disorders are not characterized by incident but by persisting depressive symptoms. Adding to that, the onset and persistence of affective symptoms might be influenced by different processes, as discussed in chapter 4. This can only be investigated if the course of depressive symptoms is taken into account. As a consequence, affective disorders should be studied in longitudinal studies in which symptoms, as well as modulating factors are investigated with a high frequency in a relatively small time frame.

... and consider them in a larger perspective

The changes in endocrine and neurotransmitter systems during pregnancy seem to play a role in the onset of affective symptoms in vulnerable women. But, to what extent do those changes contribute to the onset of affective disorders, and what does that teach us about the etiology of affective disorders? Only very recently (as mentioned in the general introduction of the thesis) the incidence of depression has been calculated reliably (9), showing that the 12 months prevalence of depression was slightly increased in the postpartum period compared to non-pregnant women (9.3% Standard Error 1.1%, versus 8.1%, SE 0.9). Information regarding the influence of pregnancy on the course of pre-existing depression is also available. About 50% of the women who were depressed during pregnancy were also depressed in the months preceding pregnancy (10) and 50% of the women who were depressed during pregnancy were so following pregnancy (11-13). All together, these data indicate that the influence of the peripartum related events on the incidence and course of depressive symptoms is small, as only 1% of the women develop a depression related to pregnancy, and the course of depression appears to be quite independent from pregnancy. Accordingly, the pregnancy related events are able to induce depressive symptoms only in a very small subgroup of pregnant women.

Why is only such a small subgroup of women ‘affected’ by pregnancy? The characteristics of this subgroup shed light on this question, as the risk factors for postpartum depression are a history of psychiatric illness, life events, and lack of social support (11). Apparently the changing physiology triggers depression only in women who were already vulnerable for depression, indicating that the vulnerability for depression is the prerequisite for the onset of peripartum affective disorders. Keeping this in mind, the difference between the incidence of postpartum blues and postpartum depression can be understood. Parturition induces blues symptoms in 30-50% of the women, proving that it can trigger affective symptoms in a substantial proportion of
women. However these symptoms persist only in a very small subgroup of women, showing that this trigger does not ‘cause’ depression. Other risk factors must have accumulated in these women, thereby causing a vulnerability that becomes manifest due to the physiological dysregulation accompanying parturition. Additional evidence for this idea is found in the meta-analysis regarding mono-amine depletion studies, showing that depletion of any mono-amine induces depressive symptoms only in individuals who recently remitted from depression, or in individuals with depressed family members (14).

Summarized, dysregulation of endocrine and neurotransmitter systems may trigger a depressive episode, but are not conditional, like the other risk factors, implicating that the role of dysfunctioning of these systems is moderating rather than causative.

The relatively small effect of pregnancy on affective functioning is both a fascinating and a common sense finding; fascinating because of the magnitude of the changes in functioning of the HPA-axis, and mono-amine metabolism, both of which are thought to be causally related to depression; common sense, because if pregnancy would induce depression this would alter the frequency and quality of the reproduction in human species, which is obviously not the case. What is the consequence of this observation regarding the hypothesized role of the HPA-axis and mono-amine system in psychiatry? I think we have to consider 3 issue’s concerning this question: 1) the presence of other conditional risk factors, as explained already; 2) mood stabilizing factors during pregnancy, and 3) reconsider the role of hypercortisolaemia and the serotonin system in the etiology of affective disorders.

*Mood stabilizing factors*

Most likely, pregnancy has some mood stabilizing effects. It is conceivable that the stable and high levels of progesterone and its metabolites (all GABA receptor agonists) and the high levels of estrogen (a neural growth factor) contribute to such mechanisms. Other endocrine factors, like oxytocin and prolactin might also add to this effect. Besides that, for most pregnant women pregnancy is a desirable condition, and the delivery and care for a young baby are among the most positive experiences in human life. The reverse side of this optimism, the death of a newborn, is therefore a very traumatic experience, as is also shown in this thesis. Adding to that, most pregnant women receive a lot of positive attention during and after pregnancy, and receive extra support both from professionals and their social network, all contributing to emotional
well-being. This is also shown by its reverse side i.e. unwanted pregnancies, single motherhood and lack of social support, all of which have been associated with peripartum depression.

However, the effect of these possible mood stabilizing effects should not be exaggerated, as most women who were depressed before pregnancy, are so during pregnancy, and new depressions do develop during pregnancy (11-13).

Reconsidering the HPA-axis and serotonin system in depression

Notwithstanding these compensating factors, the very existence of the decreased serotonin metabolism and the hypercortisolemia of pregnancy and the minor influence of these in the onset of depression, urge us not to overestimate the role of both systems in the onset of affective disorders. This conclusion regarding the serotonin system adds to cumulating evidence opposing the idea that low serotonin causes major depression:

Studies using Tryptophan depletion (TD) to investigate the role of the serotonin system on mood, fail to find a causal relation between low serotonin and depression (14). The moderate effect of TD on mood in patients with depression in remission and SSRI users can be explained by the SSRI-induced depletion of central serotonin stores, as was recently indicated by findings from our lab (3);

Studies in other naturally occurring low tryptophan conditions, like carcinoid disease and interferon treatment, also indicate that low tryptophan appears to be unrelated to depression, but to a much wider range of behavioral and affective symptoms like for example irritability and interpersonal sensitivity instead (3, 15, 16);

The influence of serotonergic medication on depressive symptoms is rather small, only 4% of the difference in depressive symptoms between medication and placebo groups can be attributed to medication (17).

Less explicit is the critique on the hypothesized role of HPA-axis dysfunctioning in the etiology of depression in literature, but evidence for only a limited role of the HPA-axis can be found. A selection of these findings:

The Cushing syndrome is an endocrine disease characterized by very high levels of cortisol. Adverse psychiatric reactions emerge in 13-62% of these patients (18, 19). The reported psychiatric symptoms are diverse i.e. mania, depression (mostly following mania) confusion, psychotic illness pathological anxiety (20), and cognitive dysfunctioning (21);
Adverse psychiatric reactions also come along with treatment with corticosteroids; on average 6% of the patients experience severe symptoms, and 28% mild to moderate symptoms (18, 19). Again, the symptoms are diverse and include agitation, anxiety, distractibility, fear, hypomania, insomnia, irritability, lethargy, labile mood, restlessness, tearfulness and depression;

The Dexamethasone suppression test and the Dex/CRH test have been promising diagnostic tests for depression for as long as 25 years (22, 23), but despite hundreds of studies, their diagnostic power is insufficient to justify their use in clinical practice (24);

Since the ‘80s a lot of effort has been put into the development of anti-depressive drugs targeting the HPA-axis. However, till now none of the tested substances has reached beyond the proof of concept stage (25).

These findings, all downplaying the role of these systems in depression, are not surprising when the complexity of the anatomy and physiology of both systems is considered. Within the serotonin system at least 14 distinct receptors have been identified, all of which are subject of genetic variation, thereby inducing even more differences in functionality and expression of these receptors (26); serotonergic neurons project to a variety of cortical and sub-cortical brain areas (27) and interact extensively with (nearly) all other neurotransmitter systems (28) thereby modulating a wide range of cortical, subcortical and limbic functions. The same level of complexity is found in functioning of the HPA-axis, which receives a rich, and biochemically differentiated, afferent supply that provides visceral, somatic and special sensory systems (29, 30). The HPA-axis response is regulated by several limbic structures. This regulation is intricate, both in anatomy and functionality, and the role of the various limbic structures is highly stimulus specific (31). Also the effects of glucocorticoids on physiological functioning is very complex, as glucocorticoids influence about 20% of the expressed human genome and their effects sparse almost no organ or tissue. Adding to that is the complexity of intracellular processing of the ‘glucocorticoid signal’ (32).

The complexity of both systems implies that the suggested causal relationships between functioning of these systems and the development of psychopathology, i.e. low serotonin causes depression or high cortisol causes depression, just cannot be that simple. The organization and functioning of these systems is of a much higher order, and likewise are the relationships between these systems and any behavioral, cognitive or affective outcome.
Dealing with complexity

The findings of the studies described in this thesis show a glimpse of the complexity of the pathophysiological processes involved in the onset of depression. Affective symptoms do not seem to be related directly to functioning of any physiological system. However, considering differences in adaptational capacity, interactions between systems, and the accumulation of adversity, both cross sectional (i.e. a cascade of disturbances) as well as longitudinal (a previous depression, childhood adversity) may be a better concept explaining the processes involved in depression.

This implies the need for a more complex view on causality in the etiology of depression. Factors involved in the etiology of depression do not directly cause depression, but increase the chance that a depression may occur, i.e. facilitate the onset of depressive symptoms. We therefore might need to reshape our thinking on the causality in the etiology of depression from strictly causal relations to stochastic processes (33).

Another implication of the findings in this thesis, is that the role of etiological factors for depression should be understood within the history of an individual, i.e. the chance that a disturbance in a certain system leads to depression depends on what has happened before. The recent findings in psychiatric genetics all point to such concepts, as relations between genotype and depressive symptoms are merely found when a combination of environmental effects are taken into account i.e. childhood adversity, the occurrence of several life events, the use of illicit drugs. Some molecular mechanisms which facilitate the modulation of gene function by environmental factors have been unraveled; the so called field of epigenetics. These mechanisms encompass covalent changes to DNA (notably DNA methylation), post-transcriptional modifications of histone N-terminal tails (by acetylation, methylation and others) as well as non-transcriptional gene-silencing mechanisms (by non-coding RNA, such as micro-RNA’s). These mechanisms can induce long lasting and heritable changes in protein availability and function, thus offering a mechanism by which environmental experiences can modify gene function in the absence of DNA sequence changes (34). Studies with animal models of depression so far found epigenetic changes (i.e. histone modification and chromatin remodeling) in the promoter region of the brain derived neurotrophic factor gene following social defeat, chronic electro convulsive seizures and imipramine treatment (35). Also animal models of stressful events early in life (maternal separation) are found to leave lasting epigenetic marks on the organism, mediated by increased and life-long persisting methylation of the glucocorticoid receptor (GR), which is found to be associated with GR expression later in life (36). A wide variety of environmental factors, like nutrition state, stress, inflammation etc. can induce epigenetic changes, some of which are
heritable, thereby influencing the development of the offspring. These processes might explain how behavior and the environmental conditions of the parents might influence the development of their children, thus explaining some of the transgenerational aspects of psychiatric disorders.

These findings advocate a developmental perspective for depression, as during life the ‘brain is shaped’, ‘memory is filled’ and behavioral responses or cognitive schema’s are formed all influencing the possibility that someone develops a depression. Such thinking might even urge us to reconsider depression as a single diagnostic entity for which a standard treatment is available. In addition, such a conceptualization might offer both scientists and clinicians the challenge to develop tools and designs for an evidence-based patient centered medical strategy.
Reference List


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AFTER THE DEPRESSION

On the edge of the newspaper he sketches skelets
tries to cry but that ancient feeling
evaporates in the loud headline of the sun - instead
he makes some coffee in the bitter realization
the world wants to know nothing of his dying

He crawls out of his watch into his clothes
shaves and sees in the mirror
someone rubbing his hands together
ready to strike, to intervene
in constellations and charts.

J. Bernlef