Psychobiological correlates of distress in pregnancy

by
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Declaration

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SUMMARY

Pregnancy is often accompanied by distressing psychological symptoms such as anxiety. These symptoms may result from changes in cognitive-affective processing, which in turn reflect hormonal changes during this time. However, findings on associations between psychological distress, cognitive-affective changes and hormones have been inconsistent. Furthermore, few studies have investigated the neural circuitry underlying distress and cognitive-affective processing in pregnancy. The prefrontal cortex (PFC) plays a specific role in regulating emotion. Determining the relationship between these changes in cognitive-affective processing and in prefrontal circuitry is important, given the high prevalence of depressive and anxiety disorders in pregnancy. The overall objective of this study was to investigate distressing psychological symptoms and their association with cognitive-affective processes and neurobiological changes over the course of pregnancy.

Pregnant women with low risk singleton pregnancies were recruited from Midwife Obstetric Units in the Western Cape. Non-pregnant healthy controls were also recruited from the same demographic area. Distress levels were assessed using the K-10, Spielberger State -Trait Inventory, and Perceived Stress Scale. Subjectively experienced cognitive ability was asked about. Objective cognitive ability was assessed using standardized neuropsychological tests. Selective attention to threat such as fear and anger was assessed using a Facial Stroop Task. Neural circuitry was assessed using Near-Infrared Spectroscopy while viewing dynamic emotional facial expressions of threat (Emotion Recognition Task). Glucocorticoid (cortisol) and gonadal hormonal levels (estrogen, progesterone, and testosterone) were also determined at each trimester of pregnancy. Associations between distressing psychological symptoms, cognitive-affective processes and neurobiology were assessed using standard statistical methods.

The main findings to emerge from this research were that,

1. pregnant women had significantly higher trait anxiety at trimester 2, compared to trimester 1 of pregnancy;
2. compared to non-pregnant women, pregnant women paid significantly more attention to fearful faces across trimesters, suggesting altered cognitive-affective processing in pregnancy compared to non-pregnancy;
3. pregnant women demonstrated significantly increased PFC activation in response to fearful and angry faces (all trimesters) that was particularly evident at trimester 2;
4. the PFC activation was, across trimesters, significantly correlated with distress and selective attention to threat; and
5. the PFC activation was, across trimesters, also significantly associated with increased glucocorticoid and gonadal hormone levels.

The main findings of this study are consistent with previous literature insofar as distress has previously been associated with altered cognitive-affective processing and prefrontal cortex activation, but extend it by showing that emotional regulation is altered in pregnancy compared to the non-pregnant state. These data provide an important insight into distressing psychological symptoms and their associations with cognitive-affective processes, and changes in neural circuitry and in hormone levels in pregnancy. These findings are also the first to show that structures involved in emotional processing (e.g. the PFC) also play a role in the regulation of affect in pregnancy. Future research should explore the causal mechanisms underlying altered emotional regulation in pregnancy, and include pregnant women that are clinically depressed or anxious as comparison subjects.

OPSOMMING

Swangerskap word dikwels geassosieër met stres-veroorsakende sielkundige simptome soos angstigheid. Hierdie simptome mag die gevolg wees van veranderinge in kognitief-affektiewe prosessering, wat op sy beurt mag dui op hormonale veranderinge. Bevindinge oor assosiasies tussen sielkundige stres, kognitief-affektiewe prosessering en hormone is tot dusver onbeslis. Voorts was min studies gerig op die neurologiese meganika onderliggend aan stres en kognitief-affektiewe prosessering tydens swangerskap. Die prefrontale korteks (PFK) het ’n spesifieke rol in die regulering van emosie. Die bepaling van spesifieke assosiasies tussen veranderinge in kognitief-affektiewe prosessering en in prefrontale regulering is belangrik, gegewe die hoë voorkoms van toestande soos depressie en angssteurings tydens swangerskap. Die doel met hierdie studie was ‘n ondersoek na assosiasies tussen stres-veroorsakende sielkundige simptome, kognitief-affektiewe prosesse en neurobiologie tydens swangerskap.

Swanger vroue met lae risiko enkel-swangerskappe is gewerf by klinieke in Wes-Kaapland. Gesonde nie-swanger vroue is uit dieselfde omgewing gewerf as kontroles. Angs-vlakke is geëvalueer met behulp van die *K-10*; die *Spielberger State-Trait Inventory* en die *Perceived Stress Scale*. Vrae is tydens ondersoeke gevra oor subjektief-ervaarde kognitiewe vermoë. Voorts is kognitiewe vermoë geëvalueer met behulp van gestandardiseerde neurosielkundige toetse. Hierbenewens is selektiewe aandag aan bedreigende gesigte wat vrees en woede toon, geëvalueer met behulp van ‘n *Facial Stroop Task*. Neurologiese funksie is geëvalueer met gebruik van Na-Infrarooi Spektroskopie terwyl dinamiese bedreigende emosionele gesigsuitdrukkings vertoon is (*Emotion Recognition Task)*. Gluko-kortikoïed (kortisol) en geslagshormoonvlakke (estrogeen, progesteroon, en testosteroon) is gemeet tydens elke trimester. Verwantskappe tussen stresvolle simptome, kognitief-affektiewe prosessering en neurobiologie is geëvalueer met standaard statistiese metodes.

Die hoofbevindinge het op die volgende gedui:

1. swanger vroue het betekenisvolle hoër *trait* angs-vlakke getoon in trimester 2, vergeleke met trimester 1;
2. vergeleke met nie-swanger vroue, het swanger vroue beduidend meer aandag geskenk aan angstige gesigsuitdrukkings tydens elke trimester wat mag dui op veranderde kognitief-affektiewe prosessering tydens swangerskap vergeleke met nie-swangerskap;
3. swanger vroue het beduidend hoër PFK aktivering getoon teenoor angstige en kwaai gesigte in alle trimesters, maar veral in trimester 2;
4. swanger vroue se PFK aktivering het, in alle trimesters, beduidend gekorreleer het met stres-vlakke en selektiewe aandag teenoor bedreigende stimuli; en
5. swanger vroue se PFK aktivering het, in alle trimesters, ook ‘n beduidende verwantskap getoon met verhoogde gluko-kortikoïed en geslagshormoonvlakke.

Die hoofbevindinge in hierdie studie stem ooreen met vorige literatuur wat aangedui het dat daar ‘n verband is tussen stres en veranderinge in kognitief-affektiewe prosessering en in prefrontale korteks aktivering, maar dui verder op veranderinge in emosionele regulering tydens swangerskap vergeleke met nie-swangerskap. Die data bied ‘n belangrike insig in stres-veroorsakende sielkundige simptome; hul verwantskap met kognitief-affektiewe prosesse; veranderinge in neurologiese netwerke; en veranderinge in hormoonvlakke tydens swangerskap. Sover bekend is dit ook die eerste keer bevind dat strukture wat betrokke is by emosionele prosessering (bv. die PFK), ook betrokke is in die regulering van emosie tydens swangerskap. Dit is belangrik dat toekomstige navorsing die onderliggende meganismes wat veranderinge in emosionele regulering teweeg bring, ondersoek. Verdere ondersoek om hierdie veranderinge in swanger depressie-lyers of diegene met angssteurings te vergelyk is ook van belang.

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CHAPTER 1

INTRODUCTION

Pregnancy has been associated with a range of distressing psychological symptoms. Although such symptoms may be influenced by various psychosocial factors (e.g. temperament and character, resilience, social support), they are thought to be a consequence of changes in cognitive-affective processes, which in turn result from hormonal and other physiological alterations during this time (Brett & Baxendale, 2001; Buckwalter et al., 1999; Casey et al., 1999; Janes et al., 1999). While these symptoms and associated processes are important for a number of reasons, they are particularly significant insofar as they may be related to the vulnerability of pregnant women to develop serious psychiatric disorders, including mood and anxiety disorders (Alder et al., 2007; Ross & McLean, 2006). A better understanding of the relationship between distressing psychological symptoms and associated changes in cognitive-affective processing might guide further research that may ultimately lead to improved treatment of such conditions.

There have been many advances in understanding psychological symptoms (Skouteris et al., 2009; Texeira et al., 2009; Heron et al., 2004) and cognitive-affective processes in pregnancy (Henry & Rendell, 2007; Brett & Baxendale, 2001). Furthermore, there have been important advances in understanding the neural circuitry involved in some of these symptoms (e.g. anxiety) and processes (e.g. attention to threat, emotional regulation) (Eysenck et al., 2007; Herrmann et al., 2003; Posamentier & Abdi, 2003). Nevertheless, many questions remain unanswered. In particular, there has been very few brain imaging studies of pregnant woman, so that the neural circuitry that mediates increased distressing psychological symptoms and altered cognitive-affective processing in pregnancy remains incompletely delineated. Similarly, work on the association of hormones with distressing psychological symptoms, altered cognitive-affective processing, and neural circuitry is inconsistent (De Groot et al., 2006; Van Honk & Schutter, 2006; Brett & Baxendale, 2001; Buckwalter et al., 2001, 1999).

This study aims to address this gap in the literature.

More specifically, the aims are:

1. To assess distress (e.g. anxiety) in this population, and its psychosocial correlates (e.g. temperament and character) over the course of pregnancy,
2. To assess the cognitive-affective processes associated with distress over the course of pregnancy,
3. To assess neural circuitry that is involved in distress and cognitive-affective processing, and
4. To assess hormonal changes, which are associated with distress, changes in cognitive-affective processes, and altered neural circuitry.

Chapter 2 reviews distressing psychological symptoms and altered cognitive-affective processes in pregnancy, as well as its neurobiology (outside of pregnancy). In Chapter 3, the methods of the study are described. Chapter 4 provides data on distressing psychological symptoms (including anxiety) in pregnancy and its psychosocial correlates (e.g. associations with temperament and character, resilience, and social support). Chapter 5 provides data on the cognitive-affective processes associated with distress in pregnancy. Chapter 6 provides data on the neural circuitry that is involved in distressing psychological symptoms and cognitive-affective processing. Chapter 7 provides data on hormonal changes, which are associated with distressing psychological symptoms, changes in cognitive-affective processes, and altered neural circuitry.

CHAPTER 2

LITERATURE OVERVIEW

2.1 Introduction

This chapter reviews distressing psychological symptoms and its psychosocial correlates (temperament and character, resilience, and social support). Altered cognitive-affective processes (in particular, of selective attention to threat) and their possible relationship to such psychological symptoms in pregnancy are also explored. Finally, given that most work on the neurobiological mechanisms and cognitive-affective process underlying distress has occurred in non-pregnant women, some of the relevant literature in this area is reviewed.

2.2 Distressing Psychological Symptoms in Pregnancy

2.2.1 Prevalence

A range of studies has explored the prevalence of distressing psychological symptoms in pregnancy. These include studies of depression and of anxiety. In this section, we briefly review this work, beginning with reports on scales such as the K-10, and then moving on to consider studies that have reviewed depressive symptoms, anxiety symptoms, and other symptoms.

There have been relatively few studies of scales of distress, such as the K-10, in pregnancy. The K-10 is a measure of distressing psychological symptoms, including depressive and anxiety symptoms (Kessler et al., 2003). The scale has been widely used in normal and clinical non-pregnant populations (Kessler et al., 2002; Furukawa et al., 2003), including to screen for postnatal depression (Baggaley et al., 2007). The first study to have used the K-10 in pregnancy (Spies et al., 2009) aimed to investigate the validity of the K-10 to predict depressive and anxiety disorders according to DSM-IV (Diagnostic and Statistical Manual of

Mental Disorders, 4th edition) criteria. That study used the same population of low-risk pregnant women as was used in the current investigation. Receiver-operating characteristic curve (ROC) analysis demonstrated satisfactory sensitivity and specificity of the K-10 in detecting depression (0.66) and posttraumatic stress disorder (0.69) in pregnancy.

Studies on the prevalence of depression have demonstrated that 25% to 35% of women experience depressive symptoms in pregnancy of whom approximately 10% meet diagnostic criteria for major depressive disorder (Steiner & Yonkers, 1998; O'Hara et al., 1991). The prevalence of depression in the general population is also twice as high in women as in men (Kessler, 2003; Llewellyn et al., 1997). This is suggested to be due to the neurobiological changes associated with the reproductive system in women (Parry & Newton, 2001) causing women to be particularly vulnerable to depression during the child-bearing years (Noble, 2005). A meta-analyses of studies of depression in pregnancy found a prevalence similar to the general female population at trimester 1 of 7.4%, and close to double rates of 12.8% at trimester 2 and 12% at trimester 3 (Bennett et al., 2004). Note however (as pointed out by these researchers) that the prevalence at trimester 1 could well be higher as participant numbers were low at this time point in studies. In contrast, prevalence rates were found to be lower when determined by structured interviews (e.g. the Structural Clinical Interview for DSM-IV or SCID (First, 2002)) compared to self-report. This may be due to subjective bias associated with self-report measures (Skouteris et al., 2009). A history of depression was a particularly significant risk factor for the development of depression in pregnancy.

Studies have also differentiated between prevalence rates of depression in pregnancy by development status, i.e. lower rates in developed countries (7%-15%) than in developing countries (19%-25%) (Bennett et al., 2004). The higher prevalence in developing countries is ascribed to adverse sociodemographic and psychosocial factors, respectively including poverty, and low socio-economic status; and a lack of social support, family conflict, and high exposure to stressful life events (Sawyer et al., 2009; Bennett et al., 2004). In this context, clinical settings often have poor resources (Noble, 2005) so that women only receive the

necessary medical care. These factors may predispose individuals to adverse social outcomes and a sense of limited personal control over their circumstances (Wheaton, 1996), which, in turn, create perceptions of distress that influence how they rate it (Rutter, 1985). Thus, women may be particularly vulnerable during pregnancy to develop depression especially when resources and clinical services are limited.

Recently the importance of anxiety has also been emphasized in pregnancy. Similar to depression the highest prevalence of anxiety has been found during the childbearing years (Ross & McLean, 2006). A systematic review of anxiety during pregnancy in African countries including South Africa found a prevalence of 14.8% (Sawyer et al., 2009). Rates of anxiety and depression (11.3%) in Africa during pregnancy were found comparable, or slightly higher than those in developed countries. A systematic review by Ross & McLean (2006) found prevalence rates as low as 0.2% for obsessive-compulsive disorder and up to 7.7% for posttraumatic stress disorder in pregnancy, while 5% to 15% of the general population may experience subclinical posttraumatic stress disorder symptoms (Kaplan & Sadock, 1998). Studies that aimed to assess changes in anxiety symptoms in pregnancy have generally found increased anxiety as pregnancy advanced (DiPietro et al., 2008; Da Costa et al., 1999; Cox & Reading, 1989; Keenan et al., 1998). The Spielberger State-Trait Anxiety Inventory (STAI; Spielberger, 1970), which assesses state and trait anxiety, was most commonly used to measure anxiety levels in pregnancy. State and trait anxiety refer to transitory perceived apprehension associated with certain stimuli, and relatively stable personality characteristic of anxiety proneness, respectively (Spielberger, 1970). However, few studies have looked at the course of anxiety across all trimesters of pregnancy. The studies that have done so, have yielded conflicting data on when anxiety levels are at their highest. For example, one study demonstrated decreasing anxiety from mid- to late pregnancy (e.g. Christensen et al., 1999), whereas another study demonstrated anxiety levels that were highest at trimester 1 (Esimai et al., 2008). Such inconsistencies require further investigation to determine the prevalence of anxiety symptoms by trimester.

Several other distressing psychological symptoms may occur in pregnancy. Otchet et al. (1999) has reported significantly higher distressing psychological symptoms including somatization, obsessive-compulsive disorder symptoms, and hostility in pregnant women compared to non-pregnant controls. The symptoms were assessed at trimester 3 using the Brief Symptom Inventory (Derogatis, 1993). Worries and concerns related to prenatal obstetric complications have also been demonstrated as assessed by the Pregnancy-specific Stress Questionnaire (PEQ) (Lobel et al., 2008; Da Costa et al., 1999). The scale focuses on pregnancy-related issues including concerns about medical care, physical symptoms, parenting, infant health, and bodily changes. Furthermore, the extent to which life is experienced as unpredictable, uncontrollable and demanding has been assessed in pregnancy using the Perceived Stress Scale (PSS-10; Cohen et al., 1983). Findings indicated that individual perceptions of distress were consistent over time (DiPietro et al., 2008). Thus, women may experience a variety of distressing psychological symptoms in pregnancy.

Psychosis and bipolar disorder have also been found to be prevalent in pregnancy (Steiner, 1998). In the general population there is a prevalence of 1% for bipolar disorder I in women and men (Kessler et al., 1994) and higher levels in women of 2% -3% for bipolar disorder II (Weisman et al., 1996). Women with a history of bipolar disorder may be at particular risk of recurrence during pregnancy (Viguera et al., 2002).

In this study the aim is to assess distressing psychological symptoms e.g. anxiety over the course of pregnancy in a South African population, representing a developing world. Distress scores will be compared to non-pregnant controls from the same demographic area.

2.2.2 Psychosocial Correlates

Distressing psychological symptoms in pregnancy may be influenced by both psychological and social factors. Relevant psychological factors that may be relevant include temperament

and character, and resilience. Facets of temperament and character that may influence how distress is rated include harm avoidance, self-directedness, and cooperativeness (see section 3.2.1.4 of Chapter 3 for information on all subscales of the Temperament and Character Inventory or TCI; Cloninger et al. (1993)). Harm avoidance (temperament) indicates the degree to which one is bold or careful to do things, and confident to interact with others. Self-directedness (character) indicates the degree to which one is mature and strong, responsible and reliable. For example, a person demonstrating high harm avoidance and low self-directedness will seek to avoid situations causing anxiety (Cloninger et al., 1993), and would arguably experience increased distress if avoidance of these challenging life situations, is not possible. Cooperativeness (character) indicates the degree to which one is socially tolerant, helpful and empathic. A person low in cooperativeness would possibly adhere less to the requests of others (Cloninger et al., 1993) when experiencing high distress.

Resilience, on the other hand, acts as a stress buffer by assisting in successful management of anxiety-provoking and stressful situations (Connor & Davidson, 2003). Resilience indicates hardiness or inner strength that enables quick recovery from illness or adversity and is assessed using scales such as the Connor-Davidson Resilience Scale (CD-RISC; Connor & Davidson, 2003). In contrast, lower resilience has been associated with proneness to negative affect (Campbell-Sills et al., 2006) and mental illness (Connor & Davidson, 2003). Thus, it is important to address the possible association between personality factors such as temperament and character and resiliency, and distressing psychological symptoms, as these may determine the outcome of emotional vulnerability (Federenko & Wadhwa, 2004).

Social factors that may be associated with distressing psychological symptoms in pregnancy include social support. Social support is assessed by scales such as the Multidimensional Scale of Perceived Social Support (MSPSS; Zimet et al., 1988). Adequate social support can act as a protective mechanism against the adverse effects of distress. Providing additional caring support to women at pregnancy clinics reduces distress (Edwards et al., 1994),

whereas a lack of proper social support from a partner or family members are likely to increase distress, and cause poor health outcomes (Kendall-Tackett, 2007). Lower social support has been associated with higher state anxiety in pregnant women at trimester 3 (Pagel et al., 1990). Social support may also interact with resilience to protect against the development of mental health problems (Campbell-Sills et al., 2006). Support from significant others, such as family members and friends, are therefore crucial to strengthen a woman's ability to handle any life circumstance successfully, including pregnancy.

2.2.3 Conclusion on Distressing Psychological Symptoms in Pregnancy

Studies have demonstrated that pregnancy is associated with increased distressing psychological symptoms e.g. anxiety, and that these symptoms are associated with psychosocial correlates including of the individual temperament and character, resilience and social support. However, few studies have documented distress symptoms and associated psychosocial correlates over the course of pregnancy, and even less studies have been conducted in a South African pregnant population. There are also inconsistencies in findings e.g. related to how women react to distress and their level of social support (Hamilton & Lobel, 2008). Furthermore, very little is known concerning the protective role of resilience against distressing psychological symptoms in normal adults (research has mostly focused on youth and traumatized adult patients) (Campbell-Sills et al., 2006) and particularly in pregnancy. The influence of resilience may be as strongly controlled genetically as vulnerability to distress (Rijsdijk et al., 2003). In this study, it is aimed to assess distress and its psychosocial correlates over the course of pregnancy in a South African population. The K-10 will be used to assess general distress, the STAI to assess anxiety, the PSS to assess perceived stress, the SCID to assess psychiatric diagnosis; and the TCI, CD-RISC and MSPSS to assess psychosocial correlates associated with distress (see section 3.2 of Chapter 3). Findings are reported in Chapter 4.

2.3 Altered Cognitive-Affective Processes in Pregnancy

What changes in cognitive-affective processing are associated with distressing psychological symptoms in pregnancy? Most work on cognitive-affective changes during pregnancy has focused on cognitive investigations of various neuropsychological domains (e.g. attention, executive function, memory). There has been less focus on affective processing in pregnancy, with limited studies on the emotional component of these domains (e.g. association of mood with attention and memory performance). Furthermore, there has been little work specifically aimed at the association of distressing psychological symptoms with cognitive-affective changes in pregnancy.

This section begins by reviewing the cognitive work on attention, executive function and memory during pregnancy. This section firstly comments on subjectively experienced cognitive impairment before going on to consider objectively tested cognitive ability.

2.3.1 Subjective Cognitive Impairment

Subjective cognitive impairment is well documented in pregnancy. One of the first studies to report on subjective cognitive impairment in pregnancy appeared in 1968. Kane et al. performed a psychiatric survey of pregnant women's subjective awareness of changes in their cognitive function. Women were assessed at 3-5 days postnatal and asked to reflect back on their experiences in pregnancy. Out of a sample of 137 women, 37% indicated effort to sustain attention, distractibility and memory impairment. In a study investigating subjective changes in thought and cognitive function during the last trimester of pregnancy (Condon and Ball, 1989), 50% of women reported significant impairment in a number of items, including focus, concentration, distractibility, memory, and word-finding ability.

Studies that are more recent have principally focused on subjective reports of memory function with most showing a strong indication of memory impairment (Crawley et al., 2003).

Furthermore, in the instances where self-ratings of attention were included, impairment was also demonstrated in this function (Crawley et al., 2003; Brindle et al., 1991; Parsons & Redman, 1991). Again, when women were asked to reflect on their cognitive function in pregnancy, an even greater number (64%) indicated impairment at 3-5 days postnatal (Parsons & Redman, 1991). In a second phase of this study, 82% of pregnant women specifically indicated impairment in concentration, absent-mindedness and short-term memory. Similarly, in other studies the majority of women also rated their memory as impaired in pregnancy (McDowall & Moriarty, 2000; Sharp et al. 1993; Casey et al., 1999; Janes et al., 1999). There is thus consistent self-reported impairment in attention and memory in pregnancy. However, in order to provide more insight into this impairment, objective cognitive measures are needed.

2.3.2 Objective Cognitive Impairment

Subjective reports can be biased by a variety of factors such as the mood of participants, fatigue and even by their assumptions regarding the expectations of the researcher. This has led to studies including objective measures to substantiate subjective findings. Generally, the aims were to characterize the impairment, and subsequently the relation of subjective to objective cognitive performance. Studies also aimed to determine the time point at which significant impairment occurred, when the impairment was at its worst, and whether a factor such as gravidity indicating the number of times that a woman has been pregnant, would impact on findings. Mainly, impaired selective attention to non-emotional visual stimuli, as well as deficits in general attention and concentration; verbal learning, word-finding ability, speed of cognitive processing, conceptual tracking, decision-making; and implicit, explicit and working memory were demonstrated (Henry and Rendell, 2007). This section reviews studies on attention, executive function and memory in pregnancy.

2.3.2.1 Impairment in Attention

From the limited number of studies that objectively assessed attention in pregnancy only a few found significant impairment, i.e. in this case two studies out of five (see next paragraph). Most tasks used tapped selective attention, and aspects of executive control, e.g. speed of cognitive processing (Kail & Salthouse, 1994) (see next section). Notably, assessment occurred predominantly during the third trimester of pregnancy.

Significant impairment in selective attention was demonstrated by the word Stroop task at trimester 3 of pregnancy (Buckwalter et al., 1999). Selective attention is utilized when a correct response requires the differentiation of target stimuli among distracting stimuli. The third phase of the word Stroop task (Stroop, 1935) creates interference between the inclination to read and colour-naming, forcing one to selectively attend to one stimulus (ink colour of word) while suppressing another (reading). Other studies also found worse performance on the word Stroop task throughout pregnancy compared to controls, but results failed to reach significance (De Groot et al., 2006; Crawley et al., 2003; De Groot et al., 2003a). Another study demonstrated impairment in selective attention across trimesters as assessed by the finger pre-cueing task (De Groot et al., 2003a).

2.3.2.2 Impairment in Executive Function

Few studies have assessed executive function in pregnancy. This may reflect methodological differences in the categorization of tasks according to the cognitive function assessed. For example, the Trail Making Test was suggested to assess either executive function (Buckwalter et al., 2001), attention (Stark, 2006) or working memory (Harris et al., 1996) in pregnancy. Thus, there is overlap in the cognitive functions assessed by tasks and task categorization may therefore require normative clarification.

Tasks used to assess executive function in pregnancy have included the word Stroop task (speed of information processing); Trail Making Tests (conceptual tracking); and the Concept Shifting Task (behavioural planning and shifting). Speed of cognitive processing was significantly impaired at trimester 3 as assessed by the Stroop task (Buckwalter et al., 1999), but not at trimester 1 (De Groot et al., 2003b). One study found significantly impaired performance on the Trail Making Test at trimester 3 (Buckwalter et al., 2001), but not other studies (Stark, 2006; Harris et al., 1996). No impairment was demonstrated using the Concept Shifting Task (De Groot et al., 2006).

2.3.2.3 Impairment in Memory

Memory problems have been documented in numerous studies of pregnant women. Studies of objective memory demonstrated impairment in different types of memory including, working memory, explicit memory and implicit memory. This subsection is preceded by a description of each memory type.

Working memory forms part of the executive system and operates as a short-term memory process that also taps attention. It actively shapes incoming cues in relation to relevant information from long-term memory stores (Gerrig and McKoon, 2001; Mazoyer et al., 2000). Implicit memory is a form of long-term memory that refers to the subconscious retrieval of experiences and cannot be consciously accessed (Davis, 2001). It is learned by priming or association (Keane et al., 1997). Priming involves the strengthening of links with specific stimuli, because of having encountered it before. Associations are learned, by pairing events with emotional responses, for example, pairing fear of darkness with having been assaulted in a dark corridor, resulting in avoidance of dark corridors. Explicit memory is a form of long-term memory, referring to learned information that can be accessed consciously (Vakil et al., 1997).

Working memory performance in pregnancy differed significantly compared to controls, as assessed by digit-span backwards (Janes et al., 1999). All trimesters were grouped together. Digit-span backwards involves, in addition to attention, the active holding and reversal of digit series in the mind for immediate recall, after verbal presentation. This impairment was replicated by another study at trimester 3 of pregnancy (Buckwalter et al., 1999), whereas other studies could not replicate this finding (Parsons et al., 2004; Shetty & Pathak, 2002; Casey et al., 1999). It should be noted that methodological issues such as controlling for gravidity, small sample size, and mode of output for example recall of digits by writing, could have influenced results. However, a recent meta-analyses of studies of cognitive impairment in pregnancy (Henry and Rendell, 2007), has demonstrated that findings on impaired executive ability (objective cognition) as measured by digit-span backward and self-reported memory (subjective cognition) correspond. This suggests that cognitive impairment is real in some cases. No impairment was found by studies investigating digit-span forwards (Stark et al., 2006; Parsons et al., 2004; Shetty & Pathak, 2002; Buckwalter et al., 1999; Casey et al., 1999). This form of the task is not as taxing as digit-span backwards as it only involves simple recall of digit series upon presentation.

Explicit memory impairment has also been demonstrated in pregnancy. Immediate and delayed verbal memory was found to be impaired at trimester 1 and 2 (De Groot et al., 2006; Sharp et al., 1993) and trimester 3 of pregnancy (De Groot et al., 2006; Buckwalter et al., 1999; Keenan et al., 1998; Sharp et al., 1993; Condon et al., 1991). Furthermore, animal naming was found to be impaired at trimester 1 (De Groot et al., 2003b), but not at trimester 3 (Parsons et al., 2004). Note that verbal memory performance, although significantly different in relation to controls, still fell within normal score ranges (De Groot et al., 2003b; Keenan et al., 1998). Other forms of verbal tasks including category naming were not found to be impaired, trimesters grouped together (McDowall & Moriarty, 2000; Casey et al., 1999).

In studies that did not demonstrate explicit memory impairment by verbal recall, pooling trimesters (Janes et al., 1999), grouping results by fetal sex (Vanston & Watson, 2005), and

using pregnancy-related words (Christensen et al., 1999) may have concealed differences. Christensen and colleagues (1999) e.g. demonstrated a significant improvement in verbal memory when words were pregnancy-related compared to unrelated words. A preoccupation with the pregnant state (Condon & Ball, 1989; Condon, 1987) may well explain such improved recall.

Implicit memory was found to be impaired across trimesters, in primi- and multigravidae as assessed by priming (Sharp et al., 1993). Another study demonstrated impairment in priming and word-stem completion, but only at trimester 2 and in primigravidae (Brindle et al., 1991). In contrast, similar studies (using the same task paradigm) did not demonstrate impairment at any trimester (Casey et al., 1999; Christensen et al., 1999; Janes et al., 1999; Keenan et al., 1998).

2.3.2.4 Conclusion on Cognitive Impairment in Pregnancy

Studies support the existence of a syndrome of impaired cognitive function in pregnancy that seems to involve subjectively experienced attention and memory impairment; and primarily verbal explicit and working memory as assessed by objective measures. A recent meta-analysis of memory impairment has suggested that impairment in these functions indicates worse executive cognitive control in pregnancy (Henry & Rendell, 2007). This is also underscored by De Groot et al. (2006, 2003a) who found impairment in selective attention and verbal explicit memory. Yet, findings remain contradictory and few studies have investigated attention in pregnancy so that findings on attention impairment remain speculative. Furthermore, data in the meta-analyses were collapsed across trimesters in order to explain memory impairment. Although this may have partly clarified our understanding of cognitive impairment in pregnancy, the impairment may vary by trimester. For instance, there is some indication that cognitive impairment mostly has its onset at trimester 2 (Brett & Baxendale, 2001) and is particularly prevalent at trimester 3 of pregnancy (Macbeth & Luine, 2010). Further research is needed to investigate the subtle and temporary

cognitive impairment that may occur in some pregnant women, particularly selective attention. The aim here was to investigate subjective and objective components of attention including selective attention, and memory over the course of pregnancy.

There has been much less work on the affective component of many of the neuropsychological domains. For example, few authors have commented on emotional memory in pregnancy. A major gap in the literature is the absence of work on emotional regulation in pregnancy. No authors for example, have used paradigms such as selective attention to threat to assess disturbances in emotional regulation in pregnancy.

Importantly, there is little information about how distressing psychological symptoms in pregnancy are associated with either cognitive or affective processes. Some data suggests that anxiety in pregnancy is associated with memory impairment (Macbeth & Luine, 2010; Buckwalter et al., 2001). However, studies have only explored the relationship between distressing psychological symptoms and emotional dysregulation (e.g. selective attention to threat) in non-pregnant women. Furthermore, few studies have explored selective attention over the course of pregnancy of which no studies included an emotional component. This investigation will therefore also include an emotional component, i.e. facial stimuli of threat, including expressions of fear and anger, in the assessment of selective attention over the course of pregnancy, and their association with distressing psychological symptoms.

2.4 Neurobiology of Distressing Psychological Symptoms

Although few studies have explored the neural circuitry of distressing psychological symptoms in pregnancy, there is a good deal that is known about the neurobiology of such symptoms. The neural circuitry of distressing psychological symptoms is briefly reviewed, before going on to consider the hormones involved in modulating this neural circuitry.

2.4.1 Neural Circuitry Underlying Depression and Anxiety

It is beyond the scope of this study to review in full the psychobiology of emotional symptoms. Instead, the focus will be on a number of recent systematic reviews on neural circuitry involved in mediating depressive and anxiety symptoms. Phillips et al. (2003a) have emphasized the importance of frontal-subcortical interactions in mediating depressive and anxiety symptoms in general. Specifically, two neural pathways have been suggested to be involved in firstly automatic processing related to recognition of the emotional significance of a stimulus and the resulting affective state and secondly conscious regulation of the affective states. These respectively are a ventral system that principally include the amygdala, ventral prefrontal cortex (PFC), striatum and anterior cingulate (AC), and insula; and a dorsal system that include the hippocampus, and dorsal PFC and AC. The involvement of both pathways ensures a holistic integration of biological and psychological cues related to emotionally salient stimuli, with the aim of producing appropriate behavioural responses for well-being.

Studies have demonstrated a principal involvement of the amygdala in automatic processing of anxiety or fear-related stimuli (Calder et al., 2001). The AC that has neural connections with the amygdala may have a specific role in response to sadness and depression (Phan et al., 2004). The insula also interacts with the amygdala to process somatic feelings induced by emotions e.g. disgust (Phillips et al., 1997). The amygdala is also generally activated by emotionally arousing stimuli (Calder et al., 2001). In turn, cortical areas in the dorsal pathway regulate amygdala and other subcortical activations to negative stimuli in order to direct attention and behavioural responses (Phan et al., 2004). For instance, there are modulatory interactions between the amygdala and hippocampus to place emotional stimuli in context, based on mental representations of previous experiences (Erickson et al., 2003) and further interactions of the two structures with the PFC (Richter-Levin & Akirav, 2003) to facilitate cognitive appraisal and management of stimuli.

A systematic review of studies have found associations between major depression and bipolar disorder and structural changes i.e. reduced size, and functional changes i.e. increased activity in the subcortical and cortical structures mediating emotion perception (Phillips et al., 2003b). In major depression for instance, reduced size of the AC, and increased activity in the AC and ventrolateral PFC were found. These changes are suggested to create limited emotional experience where emotion perception is biased towards negative emotions. A recent systematic review has also found neural changes and a heightened sensitivity to anxiety-provoking stimuli in anxiety disorders (Shin & Liberzon, 2010). Increased activity in the amygdala and insula has been demonstrated in social phobia, specific phobia and posttraumatic stress disorder, whereas decreased activity in the AC and ventromedial PFC has been associated with posttraumatic stress disorder. Although such neural changes are not expected in pregnancy, temporarily altered neural emotional regulation may occur that, in turn, is associated with increased distressing psychological symptoms (e.g. anxiety) during this time.

2.4.2 The HPA Axis

Again, it is beyond the scope of the review here, to discuss in detail the many molecules that may play a role in these neural circuits, in depression and anxiety. Nevertheless, it is important to emphasize the role of the hypothalamic-pituitary-adrenal (HPA) axis in mediating depressive and anxiety systems. Systematic reviews (De Mello et al., 2003; Tsigos & Chrousos, 2002), found that HPA axis activity is increased in response to depression and anxiety. The amygdala, limbic system and PFC respond to these symptoms (as reviewed above), which in turn regulates the HPA axis and associate neurobiological systems (e.g. the locus coeruleus-norepinephrine or LC-NE system that has extensive reciprocal neural connections in the central nervous system) to produce responses (De Mello et al., 2003). The HPA axis responds to depression and anxiety symptoms by the hypothalamus that controls the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary that, in turn, stimulates the secretion of glucocorticoid hormones from the adrenal cortex, i.e.

mainly cortisol (Tsigos & Chrousos, 2002). Major depression is associated with hyper-secretion of cortisol. This dysregulation by the HPA axis and associate increased cortisol may represent a mechanism by which structural changes occur in e.g. the amygdala and PFC, in major depression (Aan het Rot et al., 2009). In contrast, HPA dysregulation in anxiety disorders results in hypo-secretion of cortisol (Strohle & Holsboer, 2003; Boyer et al., 2000) that may also have specific deleterious effects on neural systems.

In pregnancy, a recent review has found that although cortisol increases, the response of the HPA axis to distress becomes blunted with similar ACTH levels than in the non-pregnant state (De Weerth & Buitelaar, 2005). For instance, anxiety throughout pregnancy has been associated with lower levels of ACTH (Carr et al., 1981). This may serve to protect the fetus against deleterious effects of high glucocorticoid levels (Brunton et al., 2008).

2.5 Neurobiology of Selective Attention to Threat

Once again, few studies have explored the neural circuitry of selective attention to threat in pregnancy. Nevertheless, a good deal is known about the neurobiology of this cognitive-affective process. In particular, much work has suggested that the PFC plays a key role in modulating subcortical areas in order to modulate symptoms such as anxiety, and in order to optimize emotional regulation (thus, this literature overlaps with that in the previous section). In this section we begin by discussing the definition of selective attention and methodology of assessing selective attention on a behavioural level, before going on to consider its neurobiology and assessment thereof on a neural level.

2.5.1 Selective Attention to Threat

Selective attention in everyday life is utilized when a correct response requires the differentiation of target stimuli among distracting stimuli; for example, selective attention is applied when one is cooking a meal while attending to one's children playing in the kitchen.

Where selective attention to emotions is concerned, responses may differ between people generally, and those suffering from anxiety and depression due to cognitive predisposition and previous experience.

Normal individuals demonstrate a natural tendency to recognize anxiety-provoking stimuli, for example threat faces, first compared to sad or conspiring faces (Ohman et al., 2001), after which they draw their attention rapidly away from the threat stimuli. Such cognitive predispositions are also seen in individuals with anxiety disorders (Ruiz-Caballero & Bermudez, 1997). However, their attention is held more persistently and longer by threat (MacLeod & Hagan, 1992) so that they have difficulty to withdraw their attention. In a study by Mogg et al. (2000), individuals with generalized anxiety disorder demonstrated a significant preference to attend to threat faces compared to neutral faces. This attention bias was not evident in controls or individuals with major depression. Individuals suffering from major depression also did not preferentially attend to sad faces, similar to previous studies that used negative stimuli (e.g. Ellenbogen et al., 2006). It is suggested that an attention bias to threat is a key feature of generalized anxiety disorder (Mathews et al., 1990), whereas major depression may rather be associated with subsequent memory processing, i.e. an extended reflection on depressive symptoms rather than early attentional focus (see below) (Moore et al., 2008; Williams et al., 1997). Thus, differing cognitive predispositions determine how threat is processed in normal and clinically anxious and depressed individuals.

How does this processing work, considering that e.g. anxiety is elicited by psychological distress? Under stress, selective attention to threat stimuli is intensified and increases anxiety levels (Ellenbogen et al., 2002), thus attention is more focussed to situations that elicit these emotions (Chajut & Algom, 2003). Psychological distress may also deplete cognitive resources (Wells & Matthews, 1994). Unrealistic anticipation of adversity due to high anxiety uses up attention resources, and consequently compromise the ability to focus on relevant situations (Moore et al., 2008). For instance, when threat stimuli are presented next to neutral stimuli, high anxiety interferes with cognitive control, causing difficulty to

disengage attention from threat (MacLeod & Mathews, 1991). Such cognitive appraisal styles that occur outside awareness may be a predictor of emotional vulnerability to stress in women (MacLeod & Hagan, 1992).

Studies have demonstrated further differences in selective attention to threat in normal individuals by anxiety proneness. Trait anxiety, i.e. an anxious temperament also influences selective attention to fearful facial expressions (Fox, 2002). Participants are trait-anxious when they generally experience more anxiety compared to other healthy individuals, but not on a level, that requires a clinical diagnosis of an anxiety disorder. Mogg et al. (2007) has for instance made a distinction between high- and low-trait anxious individuals by scores on the State-Trait Inventory (Spielberger, 1970) of ≥ 50 and ≤ 40 respectively. Trait anxiety also has enduring effects whereas state anxiety has a transitory mediating effect in reaction to threat stimuli (MacLeod & Hagan, 1992). However, normal high-trait anxious individuals, compared to clinically anxious patients, can consciously manipulate their fear reactions to reduce the effects of subconscious attention biases (MacLeod & Hagan, 1992). Yet, distress increases state anxiety levels and influences cognitive appraisal (Deary & Matthews, 1993), which maintain automatically increased interference in high-trait anxious individuals compared to low-trait individuals (MacLeod & Rutherford, 1992), and can override this conscious manipulation of fear reactions.

Another crucial factor determining selective attention to threat includes memory of events or previous experience. Enhanced explicit memory, i.e. conscious recall of threat stimuli is implicated in panic disorder and some support for enhanced implicit memory, i.e. automatic subconscious recall, for threat has also been observed for each anxiety disorder (Coles & Heimberg, 2002). Studies also provide support for a memory bias toward negative stimuli that may explain cognitive processing in depression. Emotional stimuli eliciting a negative response are better recalled than neutral stimuli in healthy women (Kuhlman et al., 2005; Buchanan & Lovallo, 2001), whereas depressed individuals excessively dwell on negative aspects of events (Moore et al., 2008). Normally, the experience of an event and emotions

felt at the time are laid down as associative implicit memories (Keane et al., 1997), which causes sensitization to emotionally laden experiences. When similar stimuli are re-encountered, automated processing is enhanced causing pronounced attention and explicit free recall of emotional stimuli (Arntz et al., 2005; Davis, 2001). Distress may particularly enhance emotional memory, while at the same time impairing recall of neutral stimuli (Payne et al., 2006). For example, having been assaulted by men in a parking garage driving in a black car, re-encountering a moving black car in a parking garage may provoke memories of the assault and anxiety with particular focus on who is in the car, causing difficulty to recall what you were about to do e.g. packing groceries into your car.

2.5.2 Methodology of Assessing Selective Attention to Threat

Selective attention has been measured with the word Stroop task in pregnancy (see section 2.2.2.1) (Buckwalter et al., 1999). However, as this original form of the Stroop task incorporates neutral words of colours, it has provided results of pure cognitive interference and no clues on how emotion influences selective attention processes. Investigators have used threat words in a Stroop paradigm, in normal and clinically anxious (e.g. generalized anxiety disorder) and depressed populations to investigate emotional responses to threat (Ellenbogen et al., 2006, 2002; MacLeod & Hagan, 1992; MacLeod & Rutherford, 1992; MacLeod & Mathews, 1991). A revised version of the Stroop task incorporating emotional facial stimuli has also proven to be useful in investigating the effect of emotion in selective attention processes (e.g. Mogg et al., 2007; Roelofs et al., 2007; Putman et al., 2004; Van Honk et al., 2000). The focus in this study will be on selective attention as it relates to anxiety symptoms, using threatening facial stimuli. This section firstly provide information on the Stroop task and then review studies that incorporated words and faces in the Stroop paradigm to investigate selective attention on a behavioural level.

Studies have incorporated words describing emotions in phases 2 and 3 of the Stroop paradigm to investigate cognitive-affective processing. The original version of the word

Stroop task (Stroop, 1935) that has demonstrated selective attention impairment in pregnancy, consist of three phases that require a response as quickly as possible. Phase 1 includes words of colours printed in black ink that requires one to read the words aloud. Phase 2 includes words of colours printed in the respective colours, where colour-naming is required; and the third phase creates interference between the inclination to read and colour-naming by presenting words of colours that is not printed in the corresponding colour, forcing one to selectively attend to one stimulus (ink colour) while suppressing another (reading). Similarly, phase 2 and 3 of the modified Stroop task, excluding phase 1, include emotion words in the place of colour words with the requirement of colour-naming, but the words are presented in unmasked and masked (with neutral non-specific figures) fashion respectively. This paradigm elicits unmasked processing that refers to cognitively controlled mechanisms within awareness, whereas masked processing refers to automatic subconscious processing, i.e. outside awareness (MacLeod & Hagan, 1992). The importance of eliciting both these processes is that emotion is not only consciously experienced and controlled, but also intrinsically managed by neurobiological factors. The paradigm has been applied in healthy non-pregnant women and clinically anxious and depressed populations.

Studies using masked threat or anxiety-provoking and neutral words, have demonstrated that anxiety is associated with longer reaction times, i.e. increased attention to stimuli, that causes interference in naming the colours of threat words in high trait-anxious participants (MacLeod & Hagan, 1992; MacLeod & Rutherford, 1992). In comparison, low-trait anxious participants demonstrated shorter reaction times, i.e. decreased attention in naming the colours of threat words. On the other hand, both high- and low trait anxious participants demonstrated decreased attention in response to unmasked threat words, which represents consciously-mediated processing strategies (MacLeod & Rutherford, 1992).

Happy faces have also been used together with threat faces to investigate selective attention. Roelofs et al. (2007) argued that the inclusion of happy faces would assess for an attentional bias for emotional stimuli per se. Since there were no attention biases found in

response to happy faces under normal and stressed conditions or by cortisol level in their investigation, the authors suggest that their findings (increased attention to threat (that was associated with higher cortisol)) was context relevant, i.e. specifically related to social threat. Although these studies using threat words provide an understanding on cognitive-affective processing, facial stimuli may be more efficient as it captures attention rapidly in comparison to words even before conscious awareness, and is socially more pertinent to guide behaviour (Vuilleumier, 2002). Especially in less literate samples, using faces may overcome difficulties that participants may have in comprehending the meaning of emotion words, whilst the same meaning is attached to facial expressions across cultures and groups (Russel, 1991). Facial expressions, including fearful and angry expressions have been shown to elicit attention biases similar to the effect of threat words (Mogg et al., 2007). For instance, high trait-anxious participants demonstrated increased attention to masked angry faces (Putman et al., 2004). Section 3.2.2.2 of Chapter 3 provides a description of a revised Facial Stroop Task (FST) that will be used here to assess the varying display of selective attention toward facial expressions of fear and anger, on a behavioural level, in pregnancy.

2.5.3 Neural Circuitry Underlying Selective Attention to Threat

Selective attention function is principally mediated by the PFC. The PFC exerts executive control by directing attention and affecting goal-directed behaviour (Mazoyer et al., 2000) and to regulate emotion (Davidson, 2002). Attentional avoidance of fear and anger e.g. may result from the PFC inhibiting amygdala activation (Ochsner & Gross, 2005). This section discusses the role of the PFC in cognitive-affective processing including selective attention to threat.

The PFC and associate FC areas demonstrate specific involvement in the processing of emotional facial expressions including fearful and angry faces. Studies using fMRI (functional Magnetic Resonance Imaging), Positron Emission Tomography (PET) and Electroencephalography (EEG) have demonstrated the common involvement of the inferior

frontal cortex (IFC) and orbitofrontal cortex (OFC), in addition to the amygdala in response to fearful and angry faces (Posamentier & Abdi, 2003; Calder et al., 2001; Blair & Cipolotti, 2000). The amygdala influences selective attention by modulating sensory processing of emotions especially fearful faces (Vuilleumier & Driver, 2007). Angry faces also activate the AC (Blair et al., 1999). In addition, differential effects are evident in the medial PFC (MPFC) (Smith et al., 2006a) depending on the facial expression involved (Herrmann et al., 2003).

The involvement of the FC in facial emotion processing is explained by differential functionality and connectivity of its areas. The IFC controls integration of stimulus information and semantic processing, whereas the OFC manages behavioural control (Posamentier & Abdi, 2003) together with the MPFC (Phan et al., 2004) and AC that is also indicated in attentional processes. The involvement of the OFC also represents the top-down influence of frontal areas in the fronto-parietal attentional pathways (Vuilleumier & Pourtois, 2007). Faces consistently activate the fusiform gyrus of the parietal lobe, also known as the fusiform face area, in face recognition (Posamentier & Abdi, 2003) in addition to the PFC and amygdala.

Lateralization effects may furthermore be evident in processing fearful and angry faces. Significant activation to fearful faces was demonstrated in the right MPFC using fMRI, in addition to the dorso-lateral PFC and dorsal AC (Williams et al., 2006). This activation effect to fearful faces, presented on a conscious level, was confirmed using repetitive Transcranial Magnetic Stimulation (rTMS) (Van Honk et al., 2002). The effect was also evident when comparing women to men, using Near-Infrared Spectroscopy (NIRS): women demonstrated significantly greater right (R) PFC activation to fearful faces compared to men (Marumo et al., 2009). Furthermore, dynamic facial expressions of anger notably involved right-distributed areas in the frontal cortex, and cerebellum, using PET (Kilts et al., 2003).

Left-sided PFC activation has also been demonstrated in response to fearful and angry faces. Phillips et al. (1997) has demonstrated left (L) IFC activation to anger, and L-dorsolateral FC and IFC activation to fear. Van Honk et al. (2002) have also demonstrated

dominant activation effects of the LPFC to angry faces. If a distinction is made in terms of positive approach-related behaviour and negative avoidance behaviour there seems to be differential PFC reactions, i.e. LPFC dominance in response to anger and RPFC dominance to fear. Then, the affective-valence hypothesis which posits that the LPFC is activated by positive emotions, whereas negative emotions predominantly activate the RPFC (Davidson, 1984), is not supported, but rather a motivational-direction model that eliminates the valence distinction from this hypothesis (Van Honk & Schutter, 2006). A study that demonstrated significant L-hemispheric activation compared to baseline using sad and happy faces, has also not found hemispheric differences by valence (Herrmann et al., 2003). PFC lateralization effects may thus depend on individual inclination in responding to anger and fear.

Noticeably, significant lateralization effects do not suggest that activation was exclusively limited to one side of the PFC and may depend on the stimulus type used. In the study by Williams et al. (2006) that demonstrated significant RPFC activation to fearful faces, activation started in the left dorsal MPFC and AC, after which it spread to the RPFC. Furthermore, NIRS studies that have used negative, positive and neutral emotional pictures or movie clips (Leon-Carrion et al., 2007; Yang et al., 2007; Herrmann et al., 2003) have not found PFC lateralization effects. Although dynamic facial expressions in another study using PET clearly involved right-distributed areas in the frontal cortex and cerebellum, i.e. judging the valence of static versus dynamic facial expressions of anger (and happiness), activation patterns overlapped by stimulus type (Kilts et al., 2003). Dynamic displays are created by using intermediary frames that rapidly change from a neutral to an emotional expression. Facial stimuli may thus be most effective compared to emotional pictures to investigate the nature of PFC activation in cognitive-affective processing (Herrmann et al., 2003), also due to its social relevance (Vuilleumier, 2002).

Considering base-level activation to faces, the LPFC is said to dominate in encoding and the RPFC in recognition to regulate emotional responses (Haxby et al., 1996). This makes sense

when taking into account that fearful faces may require longer scrutinizing to screen the environment for possible danger - RPFC (Ewbank et al., 2009), while angry faces may require a quick response to handle aggression - LPFC (Van Honk et al., 2005). However, if an angry face elicits fear reactions rather than dominance, as may be the case in traumatized individuals (Brown et al., 2008); the activation pattern may rather be reflected as RPFC dominance. Thus differences in PFC activation patterns may provide clues about cognitive predispositions that in turn, may elucidate the underlying neural mechanisms involved in emotional regulation.

In summary, numerous imaging modalities have been used to assess cognitive-affective processing such as attention to threat. Findings generally correspond in terms of PFC activation and the involvement of associated areas e.g. the amygdala, hippocampus and fusiform face area, but may not be as consistent when lateralization of PFC activation is considered. In addition, to our knowledge, the neural correlates of cognitive-affective processing have not been assessed in pregnancy. This may be because of uncertainty regarding the safety of brain imaging in pregnancy (De Wilde et al., 2005), so that only important diagnostic investigations are performed (Shellock & Crues, 2004). NIRS is a recent addition to imaging technology, which has characteristics that may prove it to be particularly safe compared to other imaging modalities for use in pregnancy.

2.5.4 Assessing Cognitive-Affective Processing in the Prefrontal Cortex Using Near-Infrared Spectroscopy

NIRS detects real-time upper cortical vascular responses to neural activation, by infrared spectrum light transmitted through diodes placed on the scalp. Activation reflects changes in haemodynamic responses, i.e. changes in oxy-haemoglobin (oxy-Hb) and deoxy-haemoglobin (deoxy-Hb) concentrations. Findings on changes in oxy-Hb are more confidently appraised whereas deoxy-Hb does not provide such consistent and robust activation patterns (Leon-Carrion et al., 2006; Plichta et al., 2006). The traits of NIRS include

non-invasive, real-time imaging; high temporal resolution; high sensitivity to haemo-dynamics; and feasibility of long term monitoring (Leon-Carrion et al., 2007). Although NIRS has lower spatially sensitivity than fMRI and PET and cannot detect activation in deep-lying subcortical structures (Yang et al., 2007), it also has several advantages, including the ability to measure PFC in moving participants, and no exposure to harmful radiation (Hoshi, 2007) (an important consideration in pregnancy). See section 3.2.3 of Chapter 3 for more details.

Studies have confirmed the validity of NIRS in relation to other modalities to study cognitive-affective processing (Leon-Carrion et al., 2006). NIRS is particularly useful for e.g. cognitive investigations due to its regional specificity, for instance its ability to demonstrate accurately, activation in the motor areas with finger tapping when the setup includes both motor and visual areas (Plichta et al., 2006). Thus, although NIRS cannot detect subcortical activation, it can detect cortical activation with high accuracy. Although relatively novel, the modality of NIRS has been used to assess pregnancy-related issues, including fetal health and development (see Rolfe (2000) for a review), placental oxygenation (e.g. Kawamura et al., 2007) and embryo viability (e.g. Nagy et al., 2008; Vergouw et al., 2008), but not cognitive function and affective processing in pregnancy.

Studies that have used NIRS have investigated PFC activation upon exposure to pleasant, unpleasant and neutral emotional pictures in men and non-pregnant women, and the relationship between the emotional intensity of pictures and activation (Leon-Carrion et al., 2007, 2006). In the study by Leon-Carrion et al. (2006), women demonstrated significantly enhanced PFC activation toward distressing pictures compared to men. The increased activation correlated positively with subjectively rated arousal levels upon exposure to emotional pictures. Another study investigating gender differences in PFC activation when viewing distressing pictures similarly demonstrated enhanced activation in women, but not men (Yang et al., 2007). However, using emotional pictures and emotional faces in a similar experiment, faces elicited significantly greater PFC activation compared to pictures, which confirms the social importance of faces (Herrmann et al., 2003). These findings support the

notion that women may be more emotionally vulnerable than men may and therefore more likely to develop mood problems, including the feasibility of using NIRS to investigate cognitive-affective processing using faces in pregnancy.

To investigate emotional regulation by the PFC, facial expressions displaying anger, fear, disgust and happiness (Ekman and Friesen, 1976) have been incorporated in an emotion recognition task (ERT) (Hermans et al., 2006b). Each emotional display of the ERT is computer-generated by having intermediary frames with increasing valence change rapidly from a neutral to an emotional expression (see section 3.2 of Chapter 3). The aim of this format is to create emotional displays in an experimental setting that can accurately elicit selective attention according to individual inclination, closely resembling real-life social encounters. The expectation is that clues will be provided on psychobiological correlates that subserve emotional behaviour. The causality of, for example, the relation between attention biases to fearful facial expressions and anxiety (Fox, 2002) is unknown (Salemink et al., 2007). These effects have also not been studied in pregnancy in this way, and a similar form of the ERT will therefore be used in this study.

2.5.5 Hormones Involved in Cognitive-Affective Processing

Glucocorticoid and gonadal hormones may mediate cognitive-affective processing in pregnancy. The glucocorticoid or stress hormone cortisol as well as the gonadal hormones estrogen, progesterone and testosterone represent hormonal factors that may play a part in this process. Since cortisol and gonadal hormones are suggested to be involved in emotional regulation (De Mello et al., 2003) and cognitive function (although inconsistently so) (Smith et al., 2006b) it is probable that these hormones also exert specific effects on the PFC in cognitive-affective processing in pregnancy. Cortisol is also elevated in response to increased distress in pregnancy (Obel et al., 2005), depression and anxiety (Kirschbaum & Hellhamer, 1994). Furthermore, evidence suggests that higher progesterone and testosterone may mediate mood, by their association with mood disturbance in pregnancy

(Buckwalter et al., 2001; 1999). This section reviews studies on cortisol and gonadal hormones as it relates to cognitive-affective processing.

The HPA axis seems to have an important role in emotional regulation. Cortisol may principally mediate emotional regulation in response to distress, under PFC control (Pruessner et al., 2010), by causing withdrawal of attention from negative stimuli (Ellenbogen et al., 2002) as an adaptive mechanism. Ellenbogen et al. (2006) has found a significant association between automatic processing of threat, i.e. decreased attention to masked threatening pictures (presented outside conscious awareness) and cortisol in individuals with anxiety disorders and controls, but not in major depression. Higher cortisol has also been associated with decreased attention to masked angry faces in normal individuals (Roelofs et al. 2007). In contrast, when stress was induced (Trier Social Stress Test) in the same study, the opposite effect was found; increased attention to anger was associated with lower cortisol. However, in pregnancy, the neurobiological mechanisms underlying attentional changes are unknown (De Groot et al., 2003a).

Although much research has been done to investigate the association between gonadal hormones and cognitive function in pregnancy, findings remain inconclusive (see Macbeth & Luine, 2010; Brett & Baxendale, 2001; Buckwalter et al., 1999 for reviews). It is for instance unclear whether estrogen and progesterone enhance or impair memory, whereas no associations have been found with attention. In addition, some studies have investigated the influence of gonadal hormones on emotional regulation, but only in non-pregnant populations. Progesterone may be associated with PFC regulation of fear in women (Conway et al., 2007). Van Honk et al. (2000, 1999) have investigated associations between testosterone and selective attention to threat. Increased selective attention to unmasked angry faces under stress-induced conditions (Trier Social Stress Test) was associated with higher testosterone (Van Honk et al., 2000). Administration of testosterone was also found to reverse normal patterns of increased attention to masked fearful faces; higher testosterone was associated with decreased attention to fear (Van Honk et al., 2005). Interestingly, a

recent fMRI study has demonstrated that such higher testosterone increases amygdala activation in response to angry faces (Hermans et al., 2004). However, these effects of testosterone may differ by gender when considering the PFC. Higher testosterone levels may not be associated with PFC activation, in response to angry faces in women (Stanton et al., 2009). This provides clues on how neurobiological mechanisms may regulate emotion.

2.6 Conclusion

Reviews on the prevalence of depression and anxiety, suggest that women have a significantly higher risk compared to men to develop depressive and anxiety disorders (Kessler, 2003; Llewellyn et al., 1997), particularly during the child-bearing years (Ross & McLean, 2006; Bennett et al., 2004). In pregnancy, such prevalence rates may double (Bennett et al., 2004), most likely due to the great physiological alterations including hormonal changes that accompany pregnancy (Skouteris et al., 2009). The body of a woman is never the same again after pregnancy. These distressing psychological symptoms, in turn, have clinical significance. Distress and anxiety in pregnancy often have adverse developmental and emotional outcomes on the mother and baby (Talge et al., 2007). It is also well known that psychiatric disorders cause significant disruption of daily functioning, and this may well be the case in some pregnant women; changes in mood due to pregnancy may increase the vulnerability of women to suffer emotionally and not being able to cope well during this time. Few studies have reported on distressing psychological symptoms in a South African pregnant population. Different populations may experience distress differently and this may be associated with specific psychosocial correlates (e.g. temperament and character, resilience, social support). More research is therefore justified into this area in our local population to facilitate refinements in etiologic theory and prediction of outcome.

What remains uncertain is how, in women who develop depression and anxiety during pregnancy, these symptoms is evident in cognitive-affective processing. Studies have suggested that executive attentional control and memory function are sub-optimal in

pregnancy (Henry & Rendell, 2007). If this is the case, then, the control centre of the brain - the prefrontal cortex, may not be able to manage distressing psychological symptoms as effectively as during the non-pregnant state. In turn, the brain has to adapt considerably to manage the psychobiological changes associated with pregnancy. The role of gonadal hormones in these processes is unclear.

The objectives of this study are to investigate, in our local population, the levels of distressing psychological symptoms of women that may be associated with the development of depressive and anxiety disorders; how such symptoms may manifest itself, for instance in cognitive-affective processing; and the neurobiological correlates of distress and cognitive-affective processing. Ultimately, understanding how these problems alter biopsychology in pregnancy and influence a woman's ability to regulate emotion, may assist in identifying emotionally vulnerable women and devise therapeutic interventions to optimize the health of women and the unborn baby.

The hypothesis here was that particular neural circuitry and changes in hormones operating in these pathways may lead to changes in cognitive-affective processing, and distressing psychological symptoms in pregnancy. It is plausible that increased anxiety in pregnancy is associated with particular psychosocial correlates such as higher harm avoidance, lower resilience, and lower social support. Increased anxiety may also be underpinned by increased attention to threat, which in turn is associated with greater PFC activation. Ultimately, such changes presumably reflect increased cortisol, estrogen, progesterone, and testosterone.

CHAPTER 3

METHODS

3.1 Participants

Pregnant women with low risk singleton pregnancies were randomly recruited from local Midwife Obstetric Units in the East Metro region of Cape Town (Tygerberg) by nursing staff and the candidate. These participants were enrolled as part of a study investigating stress development in pregnancy (referred to as the 'main study'). Since the clinic records suggested that women generally do not book appointments early in their pregnancy, i.e. during trimester 1, the cut-off gestational age for recruitment was set at 20 weeks. Participants thus entered the study at either trimester 1 or trimester 2 of their pregnancy.

All pregnant women who presented at the Bishop Lavis and Elsies River obstetric units for their first visit were randomly approached for participation. Interested women were individually seen in a private room to, discuss the study details, be screened for eligibility, and obtain informed consent. A study visit was then scheduled at the sonar division of Tygerberg hospital and tubes and instructions given to obtain saliva samples for cortisol measurement. The candidate or study nurse scheduled women, who were less than 12 weeks of gestation at recruitment, for a trimester 1 visit, i.e. at 13-14 weeks of gestation. Women who were between 12-20 weeks of gestation were scheduled for a trimester 2 visit, i.e. at 22-23 weeks of gestation. Although these participants had some missing data, we were cognizant of the need to ensure that sample size was similar to, or larger than, that in previously published literature (see Henry & Rendell, 2007). No formal power analysis was done at the start of the study, given that we had no preliminary data on the relevant measures. See Figure 1 in Addendum A (p 128) for recruitment details.

Inclusion criteria required participants to be 18 years of age or older; fluent in the Afrikaans and/or English language; in good health, i.e. not suffering from a serious medical condition;

without a history of significant adverse pregnancy-related conditions or terminations; and a single pregnancy and normal ultrasound scan at their first screening session. Based on their medical and obstetrics records, the participants thus had a low risk for complications in pregnancy.

Pregnant women were re-approached at Tygerberg hospital at either of the entry points into the main study, to also complete cognitive and affective tasks (after completion of questionnaires – see section 3.2 below for details) and an imaging session (within a week of a visit). Women were advised that completion of these additional measures would be required at each visit during pregnancy. However, women were not excluded if they could e.g. not complete the imaging session, thus women would complete the cognitive and affective tasks even if they could/did not want to attend the imaging session. The sample size for imaging was chosen based on previous work suggesting that these numbers provide sufficient statistical power (Hayasaka et al., 2007; Desmond & Glover, 2002).

Non-pregnant controls were also recruited from the Tygerberg region by the candidate for a once-off assessment session. Women were included if aged 18 years or older; fluent in the Afrikaans and/or English language; in good health; and not abusing any substances. The control group also included participants who have completed the 'main study' at 1-year postnatally. This ensured a time lapse of at least 3 months after exiting the study (i.e. when infant was one year old) to avoid carry-over effects in ratings of distress. In addition, some women in this subgroup of control participants completed the affective tasks in pregnancy, and would then do such tasks as controls after exiting the study. Thus, more than a year has passed since their initial assessments. Liao and Qu (2010) have found that practice effects are negligible when at least six months have passed between first and second assessment sessions using standardized cognitive tests. It was therefore our judgment that this would be an adequate period in between test dates to eliminate possible practice effects.

Informed, written consent was provided, although not all women agreed to the imaging. Consent was provided for the completion of self-report questionnaires, computer-based affective tasks and a brain imaging session. Pregnant women also provided consent at the recruitment visit for completion of a clinical interview; and to undergo an ultrasound scan to confirm a normal pregnancy and determine gestational age.

This study was approved by the Committee for Human Research at Stellenbosch University and was conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council Ethical Guidelines for Research.

3.2 Procedures

The study proceeded in 3 parts: (1) assessment of distressing psychological symptoms (e.g. anxiety) and its psychosocial correlates (e.g. temperament and character), (2) assessment of cognitive-affective processing, (3) brain imaging, and (4) assessment of hormonal levels. All pregnant participants participated in part (1) and (4), whereas only a subset agreed to also participate in parts (2) and (3). Controls selectively participated in parts (1) to (3).

Pregnant women were required to provide information on their demographics, and medical and obstetric history. Participants also completed self-report questionnaires, to assess general distress levels, trait and state anxiety, and perceived stress; temperament and character, and resilience; and perceived social support. Cognitive status of participants was assessed once-off by the candidate using a battery of neuropsychological tests at the first visit. Current psychiatric diagnoses were determined during a once-off diagnostic interview by a clinical psychologist using the Structural Clinical Interview for DSM-IV (First, 2002) at the first visit, which was either during trimester 1 or 2. In addition, at every visit, participants had to complete the Facial Stroop Task (FST) to assess their selective attention to specific

emotions, and an imaging session with Near-Infrared Spectroscopy (NIRS) to assess prefrontal cortex (PFC) activation while performing an emotion recognition task.

Assessments occurred longitudinally during trimester 1 (13-14 weeks), trimester 2 (22-23 weeks), and trimester 3 (32-33 weeks) of gestation (Table 1). These specific time points were determined on the basis of the literature, as key assessment periods in terms of fetal development. Participants completed questionnaires in either Afrikaans or English, while attending the sonar division at Tygerberg Hospital. To ensure reliability of results, participants had to follow standardized verbal instructions, which were explained by the candidate, psychologist and/or study nurse.

Table 1 Outlay of assessments by group

	Trimester 1	Trimester 2	Trimester 3	Controls
Detailed demographics	X			X
Update demographics		X	X	
Medical/Health	X			X
Update medical		X	X	
Structural Clinical Interview	X			
Kessler's K-10	X	X	X	X
Spielberger State-Trait Inventory	X	X	X	X
Perceived Stress Scale	X	X	X	X
Temperament and Character Inventory	X			
Connor-Davidson Resilience Scale		X		
Multidimensional Scale of Perceived Social Support	X			
Cognitive battery	X			X
Facial Stroop Task	X	X	X	X
Imaging	X	X	X	X
Hormones	X	X	X	

Before each visit, pregnant participants were required to provide saliva samples for the determination of cortisol levels. In addition, blood samples were collected to determine serum levels of gonadal hormones, i.e. estrogen, progesterone and testosterone.

Similar to pregnant participants, the controls provided information on demographics and general health during a once-off assessment session (Table 1). Neuropsychological tests and imaging procedures were also the same for controls and pregnant women. Controls only completed self-report questionnaires on general distress, perceived stress and state and trait anxiety. The imaging sessions occurred at the Cape Universities Brain Imaging Centre (CUBIC, Faculty of Health Sciences, Stellenbosch University) and lasted 2½ - 3 hours (detail to follow).

3.2.1 Distress

3.2.1.1 K-10

General distress of participants was assessed using the K-10, a 10-item self-rated measure of general distress (Kessler et al., 2003). Items are scored on a scale from 1 to 5 (1, none of the time; 2, a little of the time; 3, some of the time; 4, most of the time; 5, all of the time). A maximum score on the K-10 of 50 indicates severe distress, whereas a minimum score of 10 indicates no distress. Women scoring under 20 are likely to experience “normal” or situational appropriate rates of distress and are generally well, while those scoring 20 to 24 may be more likely to have a mild mental disorder. A score of 25 to 29 may suggest presence of a moderate mental disorder, while a score of 30 may suggest the presence of a severe mental disorder. The Structural Clinical Interview for DSM-IV (SCID-I Patient Version) (First, 2002) was used to identify the presence of any Axis I disorders (Ventura et al., 1998) in women scoring above 20 on the K-10. The K-10 has demonstrated good validity and reliability in assessing distress in the general population (Kessler et al., 2002).

3.2.1.2 Spielberger State-Trait Inventory

The Spielberger State-Trait Inventory (STAI Form Y), which is a 40-item, self-report questionnaire that contains two 20-item sub-scales, was used to assess state and trait

anxiety (Kennedy et al., 2001). Each item is scored on a scale from 1 to 4 (1, not at all; 2, somewhat; 3, moderately so; 4, very much so). Scores are reversed on the anxiety-absent items (state anxiety: items 1, 2, 5, 8, 10, 11, 15, 16, 19, 20; trait anxiety items: 1, 3, 6, 7, 10, 13, 14, 16, 19): i.e. 1=4, 2=3, 3=2, 4=1. *State anxiety* is the transitory or fluctuating condition of perceived tension associated with certain stimuli, i.e. current tension or apprehension, whereas, *trait anxiety* is defined as a relatively stable personality characteristic of anxiety proneness or disposition (Spielberger, 1970). Scores on each subscale can range from 20 to 80, with higher scores indicating higher levels of anxiety. The scale has demonstrated good validity and reliability in assessing anxiety in pregnancy (DiPietro et al., 2008).

3.2.1.3 Perceived Stress Scale

The extent to which life is experienced as unpredictable, uncontrollable and demanding was measured using the Perceived Stress Scale (PSS-10) (Cohen et al., 1983). Each of the 10 items is scored on a scale of 0-4 (0, never; 1, almost never; 2, sometimes; 3, fairly often; 4, very often). Scores are reversed on the four positive items (items 4, 5, 7, 8): i.e. 0=4, 1=3, 2=2, 3=1, and 4=0, and then summed across the 10 items to provide a total score. The scale has demonstrated good stability in measuring perceived stress over time in pregnancy (DiPietro et al., 2008).

3.2.2 Psychosocial Correlates

3.2.2.1 Temperament and Character Inventory

The self-report Temperament and Character Inventory (TCI) was also included in the test battery and is used to measure behaviours associated with seven personality dimensions, namely ‘novelty seeking’, ‘harm avoidance’, ‘reward dependence’ (temperament); and ‘self-directedness’, ‘cooperativeness’, and ‘self-transcendence’ (character) (Cloninger, 1993). Novelty seeking indicates the degree to which one is explorative, curious and enthusiastic

about new or different things. Harm avoidance indicates the degree to which one is bold or careful to do things, and confident to interact with others. Reward dependence indicates the degree to which one is attentive of the feelings of others and dependent on others. Self-directedness indicates the degree to which one is mature and strong, responsible and reliable. Cooperativeness indicates the degree to which one is socially tolerant, empathic, and principled. Self-transcendence indicates the degree to which one is wise, imaginative and self-forgetful, and in touch with the universe. Each of the two aspects of personality (temperament and character) interacts with one another to motivate adaptation to life experiences and influence susceptibility to mood disorders. The dimensions are measured by statements, which describe the attitudes, interests, opinions and other personal feelings of people. Each question is answered by selecting either 1 (true) or 0 (false); thus, higher scores on each of the subscales indicate increased endorsement of each of the personality traits. The TCI has demonstrated reliability and validity across cultures and versions (Brandstrom et al., 2003; Hansenne, 1999; Joyce et al., 1994).

3.2.2.2 Connor-Davidson Resilience Scale

The ability of participants to cope successfully with stressful events was assessed using the Connor-Davidson Resilience Scale (CD-RISC) (Connor & Davidson, 2003). This questionnaire was included based on the theory that resilience mediates individual appraisal of stress (Wells & Matthews, 1994). The questionnaire consists of 25 items, which are rated based on feelings during the past month, as 0-4 (0, not true at all; 1, rarely true; 2, sometimes true; 3, often true; 4, true nearly all of the time). The total score ranges from 0-100, with higher scores indicating greater resilience. The scale has demonstrated good validity and reliability in clinical samples and the general population (Connor & Davidson, 2003).

3.2.2.3 Multidimensional Scale of Perceived Social Support

Social support, which may influence cognitive performance and coping in reaction to stressful events (Wells & Matthews, 1994), was assessed using the Multidimensional Scale of Perceived Social Support (MSPSS). Adequate social support can act as a protective mechanism against stress and thereby lessen the impact of an attention bias to threat. The MSPSS is a measure of perceived social support from family, friends and significant others (Zimet et al., 1988) and consists of 12 items, which is scored on a scale from 1-7 (1, very strongly disagree; 2, strongly disagree; 3, mildly disagree; 4, neutral; 5, mildly agree; 6, strongly agree; 7, very strongly agree). The scale has proven reliability and validity to assess social support in a pregnant population (Zimet et al., 1990).

3.2.3 Cognitive-Affective Processing

3.2.3.1 Cognitive Battery

Pregnant women often rate their memory and attention as impaired (Brett & Baxendale, 2001; Buckwalter et al., 1999). Participants therefore had to subjectively rate their experience of their attention and memory ability at each visit, i.e. whether there were any recent changes from “normal” levels. In addition, to elucidate objective cognitive changes, a battery of neuropsychological tests were used. These tests were administered verbally by the candidate and included, standardized tests developed by Hodges (1994) and Strub & Black (1977), in the following order: i. word lists (assessing immediate short-term memory); ii. vigilance test (assessing attention); iii. animal naming (a verbal executive task); iv. digits forward and backward (assessing working memory), and v. delayed recall of words (assessing delayed short-term memory). These tests, except for digits backward has been adapted and standardized for use in a similar population as the one used in this study (see Roos et al., 2010).

Following is a description of each test:

i. Word lists: a word list including 10 simple words are presented three times in varying order, whereafter the participant must verbally recall as many words as possible after each trial.

ii. Vigilance test: a series of 60 random letters are read to the participant. The letter "A" appears randomly 18 times in the letter series. The participant is required to listen carefully and tap the desk whenever the letter "A" is heard.

iii. Animal naming: The participant is required to name as many different animals with four legs in one minute.

iv. Digits forward and backward: a series of simple numbers, starting with two numbers, is presented verbally and the patient has to repeat it. During the first phase of the test the digits are to be repeated as presented, i.e. forwards; and during the section phase backwards from what is presented.

v. Delayed recall of words: the participant is asked to recall the words, read three times, at the beginning of the test session.

3.2.3.2 Facial Stroop Task

The Facial Stroop Task (FST) was included to assess attention on a behavioural level. In particular, selective attention to threat, i.e. fearful and angry faces, and happy faces compared to neutral faces was assessed by a modified, computerised version of an established emotional Stroop task (Van Honk et al., 2005, 2002). One aim of this study was to investigate the association between cognitive-affective processing and distress. Anxiety can be viewed as a symptom of distress that is elicited by life-like pictures displaying emotional facial expressions of fear and anger. Pictures of happy facial expressions were used in the second phase of the task to separate the closely associated emotions of fear and anger. This would control for attentional biases to emotional stimuli per se (Roelofs et al., 2007). Neutral facial expressions were already incorporated in the task as comparative expressions to determine attention bias scores (see below).

The task was modified by the candidate, in collaboration with the Helmholtz Research Institute on Affective Neuroscience (Utrecht University, The Netherlands), in E-prime (Psychology Software Tools Inc., 2002). The task comprised of a set of ten different faces (five male, five female) from the standardized Ekman and Friesen's Pictures of Facial Affect (Ekman and Friesen, 1976) and mask-like stimuli created by the Utrecht group. Emotional and neutral faces were randomly displayed on a computer screen of a 60Hz computer; set up at eye-level at a distance of 60cm from the participant's face. Participants were required to name the colour in which the faces or masks appeared per emotion (red, green or blue), as quickly as possible during the first two of three sections of the task. The three task sections were the masked Stroop, the unmasked Stroop and an awareness check. The duration of the task was 35-40 minutes depending on the person's response speed whilst responses were recorded automatically by audio-equipment.

As demonstrated by previous studies, backward masking is an accurate method to investigate subconscious affective processing, with the target stimuli's invisibility being verified by an awareness check (MacLeod & Rutherford, 1992). Displaying stimuli targeted to subconscious awareness may be the most accurate way to assess cognitive-affective processing as it is not biased by the conscious management of, for example, anxiety symptoms (Roelofs et al., 2007).

Attention bias scores were determined by subtracting colour-naming latencies on neutral faces from colour-naming latencies for angry, happy or fearful faces. A positive attention bias score – indicating slower colour-naming reaction times to emotional faces compared to neutral faces, was interpreted as paying more attention to stimuli, whereas a negative attention bias score – indicating faster reaction times to emotional faces compared to neutral faces, was interpreted as paying less attention to stimuli (Roelofs et al., 2007; Van Honk et al. 2002).

There were three task sections per emotion; and the order that it appeared in was the following:

i. Masked Stroop

The purpose of the masked Stroop section of the FST is to assess response latencies to faces appearing outside conscious awareness. A fixation cross is displayed for 750 milliseconds (ms) followed by either an emotional or neutral face that is briefly presented for 2ms, and then a masking stimulus (Figure 1). The mask is displayed for 286ms after which a vocal response is required. The response is registered through a microphone connected to a response box unit (Psychology Software Tools Inc.). The task only continues to the next fixation cross and stimuli once a clear vocal response is registered. The process starts with 6 practice rounds and terminates after 60 actual rounds.

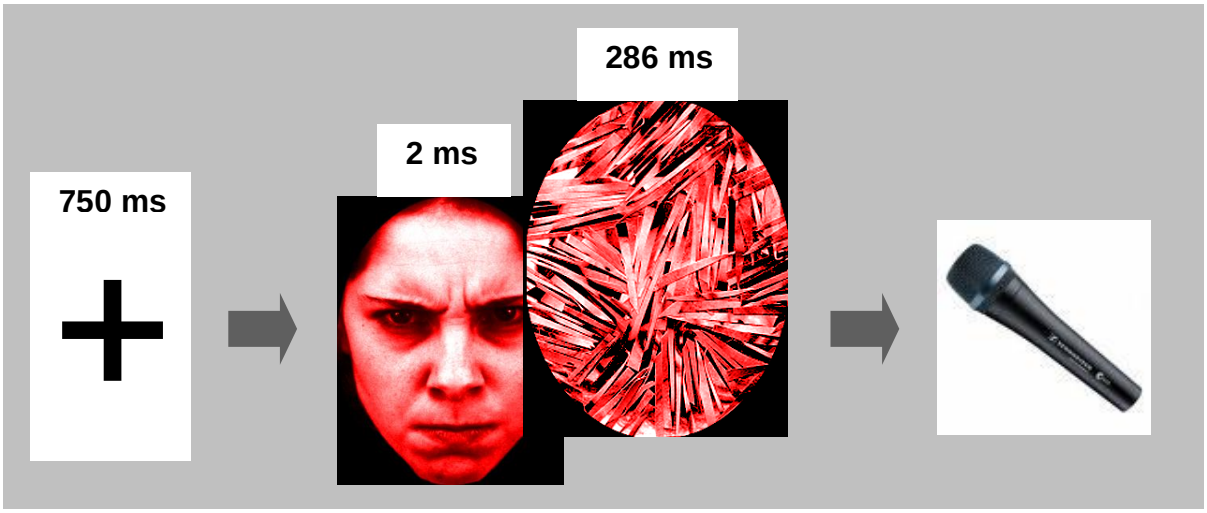

Figure 1 An emotional face is displayed briefly followed by an abstract image, whereafter a participant responds by naming the colour of the image

ii. Unmasked Stroop

The purpose of the unmasked Stroop section of the FST is to assess response latencies to faces within conscious awareness. The fixation cross is presented for 750ms after which a target stimulus is shown for 298ms. The task similarly includes a 6-face practice round and 60 rounds of the actual task, and continues to the next stimulus after vocal response registration.

iii. Awareness Check

The purpose of the awareness check section of the FST is to determine whether participants can distinguish between 40 emotional and neutral faces appearing outside conscious awareness, as is presented in the Masked Stroop section (i). A fixation cross is displayed for 750ms and then followed by a face that is briefly presented for 2ms, and followed by a mask (presented for 286ms). Ten emotional and 10 neutral faces are randomly displayed and the participant has to indicate whether it is an emotional face (by pressing "1") or a neutral face (by pressing "2" on the keyboard). A mean score of 20 is expected across trials, and indicates chance level identification of emotions, thus an inability to actually, see the face. If the score is much lower or higher than 20, the scores on the other two task sections may be invalid.

3.2.3.3 Emotion Recognition Task

Dynamic facial expressions of the emotions anger, disgust, fear and happiness (Hermans et al., 2006b; Ekman and Friesen, 1976) were used to investigate PFC activation patterns using Near-Infrared Spectroscopy (NIRS; see next section). The PFC, apart from the amygdala, is involved in the regulation of emotions, and is activated by emotional facial expressions. Determining the nature of PFC activation patterns in response to affective stimuli was deemed important as pregnancy may be accompanied by dramatic changes in mood and associated neurobiology. A computer presentation using E-prime 1.2 (Psychology Software Tools Inc.) and morphing software (WinMorph, version 3) was employed to generate 41 intermediary frames that change from a neutral to an emotional facial expression (see Figure 2). Four blocks, each comprising of seven repetitions of eight male and female faces per emotion, were sequentially displayed at 20 frames per second, each block running for approximately 22s, preceded by a fixation cross that appeared for 44s. Participants were required to press any key on a keyboard on appearance of the fixation cross, to sustain attention in viewing faces. Faces were displayed on a 60Hz computer screen, at a viewing distance of approximately 60cm from the participant's face.

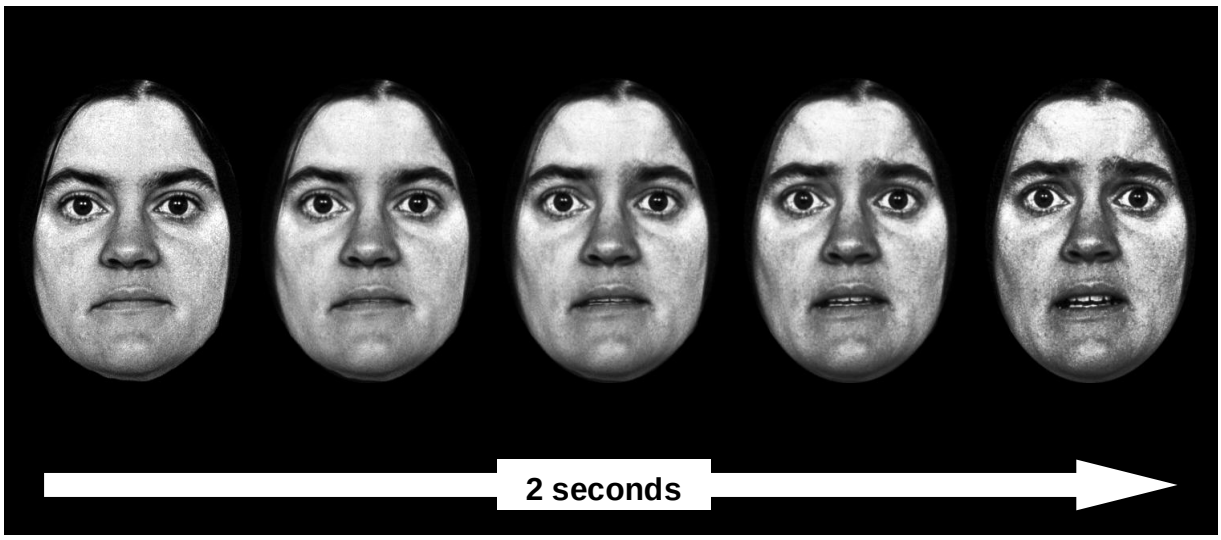

Figure 2 Fourty-one intermediate frames of an emotional face were displayed over 2s time

3.2.4 Neural Circuitry

Figure 3 Setup of diodes over the PFC

A DYNOT system (NIRx Medical Technologies, New York) was used to obtain NIRS data sets on PFC activation (e.g. Schmitz et al., 2000) during performance of the ERT. The system measures brain activity in response to stimuli by detecting real-time oxygenated (oxy) and de-oxygenated (de-oxy) blood flow patterns at a depth of 4cm from the head surface, by harmless infrared spectrum light transmitted through laser diodes placed on the scalp. Each diode simultaneously emits and detects the dual wavelength light for oxy- and de-oxy haemoglobin (Hb) (760nm and 830nm respectively). Although data was obtained on both wavelengths, only the oxy-Hb data was used in this instance, as de-oxy Hb may not provide as consistent and robust activation patterns (Leon-Carrion et al., 2006; Plichta et al., 2006).

The procedure was initiated by placing a lightweight adjustable helmet on the head of participants. To ensure standardized fitting of the helmet and effective covering of the PFC across participants, the Fp1 point of the 10-20 system was used as reference point (Jasper, 1958) (Figure 3). The Fp1 point, which is positioned 10% above the nasion bone, was determined by measuring the cross-diameter of the head between the nasion to inion bone.

The top end of the nose bone was located by touch on the nose of a participant and the cross-diameter of the head measured (cm) from this point to the edge of the skull at the back of the head. Of this measured distance, the 10% fraction was calculated and this distance re-measured from the nasion bone to locate the Fp1 point. The centre of the frame as well as the lower rim of the helmet was then positioned over the Fp1 point and 30 diodes were connected to the helmet. The Fp1 point was also used to determine the regions of interest including the RPFC, LPFC and MPFC. The RPFC and LPFC were determined to be right and left of the Fp1 point respectively, and the MPFC on the Fp1 point midline area. The diodes were held in place by ferrules fixed at a distance of 6mm from each other. An additional diode was connected to a phantom measuring head as a “one optical reference” channel. Diodes were fitted according to a Rectangle SD3X10 mesh model that covered the forehead i.e. PFC area from side to side (Yaling Pei, NIRx Medical Technologies: Brain FEM Models prepared for South Africa, 2005; see Bluestone et al. (2001) for a description of FEM mesh modelling). The participant was required to perform the emotion recognition task while remaining as still as possible. Data sets were acquired at a sampling rate of 1.8Hz and at a dynamic signal range of ~180 dB (1:10^9) on a host computer using Pacific Scientific OC950 motor control software (RAD motion), and software for instrument control and data acquisition (DYNOT, version 3.0).

NIRS is a relatively new imaging modality and has not been used to assess brain activation of pregnant women before. The modality is non-invasive, comfortable and does not use harmful radiation and is therefore particularly useful in pregnancy. Furthermore, the relationship between altered cognitive-affective processing, distress and emotional regulation in pregnancy is unclear. This study is the first to use NIRS in pregnancy and aims to elucidate, as has not been done before, how cognitive-affective processing is different in pregnancy.

3.2.5 Endocrinology

Biological changes in pregnancy including highly elevated gonadal hormone, i.e. estrogen, progesterone and testosterone, levels may be associated with particular changes in neural circuitry (Van Honk et al., 2000) and susceptibility to altered attention and increased distress (Buckwalter et al., 2001; Van Honk et al., 2000, 1999). As detailed in the background, glucocorticoids such as cortisol that is involved in stress responses and in maintaining bodily homeostasis also are elevated in pregnancy (Obel et al., 2005). The biological changes may therefore have significant effects on cognitive-affective processing in pregnancy. Thus, to gain a new understanding of how cognitive and affective changes affect well-being in pregnancy, it is important to consider both psychological and biological mechanisms that may be associated with these effects.

3.2.5.1 Cortisol

Saliva samples for cortisol measurement were collected by participants on four consecutive mornings, the fourth morning being the visit day. Independent saliva collection at home provides a convenient, non-invasive and reliable way to obtain saliva samples (Obel et al., 2005; Kirschbaum & Hellhammer, 1994). Participants were provided with comprehensive written guidelines on sampling and storage procedures of saliva samples collected using saliva collection sets (four 5 ml Eppendorf tubes and straws). Participants were instructed to collect samples between 08h00 and 09h00 prior to brushing their teeth, breakfast, taking liquids, smoking, chewing gum, or having put on lipstick or lotions with steroids, at least one hour before sampling. Samples were stored at 4°C (standard fridge) until the visit day, whereafter it was stored at -20°C until assaying was done by internal laboratories (MRC/Stellenbosch University Centre for Molecular and Cellular Biology, Tygerberg).

The in-vitro quantitative determination of free cortisol in human saliva was employed using lluminescence immunoassay methods (Cortisol Lluminescence Immunoassay, 2006). The

technique is based on the competition principle, i.e. sample antigen and enzyme antigen compete for antibody binding sites on wells covered with anti-cortisol antibodies. Morning cortisol values are expected to increase one- to twofold in comparison with the non-pregnant state, during the course of pregnancy (Kirschbaum & Hellhammer, 1994). Stress may further alter these values (Obel et al., 2005).

3.2.5.2 Gonadal Hormones

Bloods were collected by a study nurse at every visit and assayed by a private pathology laboratory (Metropolis Pathology Laboratories, Cape Town) for serum levels of estrogen (estradiol - E2), progesterone and free testosterone (AxSYM).

3.3 Data Analyses

The aims of this study were to investigate data gathered from pregnant women and controls to assess firstly levels of distressing psychological symptoms (e.g. anxiety), and its psychosocial correlates (e.g. temperament and character); secondly the relationship between cognitive-affective processing and distress; thirdly the neural circuitry that is involved in distress and cognitive-affective processing; and fourthly the relationship between hormonal levels operating in the neural circuitry, distress, and cognitive-affective processes, using standard statistical methods. Specifically, the aims were to assess levels of general distress, state and trait anxiety, and perceived stress in the local population and determine their association with temperament and character, resilience and social support; cognition (including attention and memory) and selective attention to threat stimuli, i.e. fear and anger, and their association with distress; PFC activation in response to threat stimuli and its association with selective attention to threat, and distress; and the associated corticoid and gonadal hormone levels.

In order to address these aims, one-way analyses of variance (ANOVA); mixed model repeated-measures ANOVA; correlational analysis; t-tests and regression analyses were used. These analyses were performed in consultation with the Department of Statistics (Faculty of Health Sciences, Tygerberg) using Statistica, version 8 (Statsoft Inc.). The tests were selected based on preliminary investigations of data, on whether tests met assumptions regarding normality, i.e. parametric vs non-parametric distributions of data by variable. Normal probability tests and tests of homogeneity of variances were used for this purpose. In the majority of cases, results of normal probability tests and tests of homogeneity of variances indicated that data of pregnant women (at all trimesters) and controls was normally distributed. In those instances where data distributions were found to be non-parametric, appropriate non-parametric tests were employed (e.g. Mann-Whitney U test).

One-way analysis of co-variance (ANCOVA) controlling for age and education was used to compare pregnant data per time point with control data in Chapter 4 (as age and education of the full sample, i.e. 110 pregnant women and 63 controls, were found to be statistically different between the groups). One-way ANOVA was also used to determine whether there were differences in data based on entry point into the study. Mixed model repeated-measures ANOVA, were used to investigate data over time (trimester 1-3). Mixed models are preferred to classic repeated-measures ANOVA in unbalanced designs, i.e. when sample sizes between groups vary over time. Multiple regression was used to determine the contribution of variables (e.g. anxiety) to explain the variance in specific data (e.g. harm-avoidance). Spearman correlational analyses were also used to investigate associations between variables.

Corrections to data were applied as applicable. For example, Fisher-correct was included as part of the Chi-square test to determine whether K-10 scores below or above 20, were associated with a clinical diagnosis (SCID). Other analyses such as mixed model repeated-measures ANOVA already controlled for varying sample sizes over time in pregnancy.

To investigate PFC activation to threat, Near Infrared Analysis, Visualization and Imaging software (NAVI, version 2.1; NIRx Medical Technologies); Statistical Parametric Mapping (SPM, version 5, 2005) and Magnetic Resonance Imaging software (MRIcro, version 1.4) were used.

The data analyses of each procedure and specific findings are described in detail in each chapter, according to the specific aims of the chapter.

CHAPTER 4

DISTRESS IN PREGNANCY

Abstract

Background: The aim of this chapter is to assess distress (e.g. anxiety), and its psychosocial correlates over the course of pregnancy. Although there is a wealth of literature on assessment of depression in pregnancy, there is less work on a general measure of distress and how it might change over time. A general measure of distress may be useful in detecting current psychiatric diagnosis. Furthermore, there is a paucity of work exploring the relationship of distressing psychological symptoms during pregnancy to psychosocial correlates including temperament and character, resilience, and social support.

Methods: Pregnant women (n=110) with low risk singleton pregnancies were recruited from Midwife Obstetric Units in the Tygerberg region of the Western Cape. Non-pregnant controls (n=63) were also recruited from the same demographic area. Assessments of distress occurred during trimester 1, 2 and 3, and once-off in controls. Distress levels were assessed using the K-10 (measuring general distress). In addition, the Spielberger State -Trait Inventory (STAI) (measuring state and trait anxiety) and Perceived Stress Scale (PSS) (measuring the degree to which life is experienced as difficult and challenging) were used. The Structural Clinical Interview (SCID) was used in pregnant women to identify the presence of any Axis I disorders in women scoring above 20 on the K-10. A receiver operating characteristic curve (ROC) analysis was performed in order to determine the ability of the K-10 to discriminate between women with and without depressive and anxiety disorders. Distress was quantified over time; and relationships between the measures and differences between pregnant women and controls; and associations with psychosocial correlates were determined using one-way ANOVA, mixed model repeated-measures ANOVA, and Spearman correlational analyses.

Results: Distress in pregnancy was relatively high throughout pregnancy compared with scores in previous publications. A non-significant increase in general distress was evident

from trimester 1 to 3 (μ_{T1} = 21.4; μ_{T2} = 22.3; μ_{T3} = 22.7). State anxiety increased significantly from trimester 1 to trimester 2 (p = 0.021), while scores remained high at trimester 3 (μ_{T1} = 38.0; μ_{T2} = 42.2; μ_{T3} = 40.1). Trait anxiety scores, measured either at trimester 1 or 2, were comparably high (μ_{T1} = 40.5; μ_{T2} = 45.7). Perceived stress remained consistent over time. Furthermore, general distress correlated significantly (p < 0.001) with state anxiety, trait anxiety and perceived stress. K-10 scores equal and above 20 corresponded significantly with having a current depressive and/or anxiety disorder across trimesters [Chi-square$_{T1}$ = 5.06, p = 0.025; Chi-square$_{T2}$ = 7.69, p = 0.006; Chi-square$_{T3}$ = 6.43, p = 0.011]. Using the K-10, 100% of current major depression cases could be identified at trimester 1, 86% at trimester 2, and 83% at trimester 3 of pregnancy. Distress was significantly associated with particular temperament and character traits, lower resilience (trait anxiety: r_{T1} = -0.33, p < 0.05; distress: r_{T2} = -0.66, r_{T3} = -0.38; p < 0. 001), and lower social support (distress: r_{T1} = -0.36, p < 0.05; r_{T2} = -0.59, p < 0.001).

Conclusion: These data suggest that it may be useful for clinicians to monitor distress over the course of pregnancy, as such measures are associated with Axis I psychiatric diagnoses. It is possible that interventions to increase resilience and social support would be useful in preventing distress and psychiatric diagnosis in pregnancy.

4.1 Background

The aim of this chapter is to assess distress (e.g. anxiety), and its psychosocial correlates over the course of pregnancy. As previously discussed in Chapter 2, pregnancy may be a time of increased vulnerability to distress (Dorn & Chrousos, 1997). The probability of developing pregnancy-related anxiety and mood problems is high (Alder et al., 2007; Ross & McLean, 2006; Noble, 2005; Nonacs & Cohen, 2002). As also noted, such distress may be associated with both psychological and social factors including particular temperament and character traits (e.g. harm avoidance), or decreased resilience and social support (Hamilton & Lobel, 2008; Campbell-Sills et al., 2006; Pagel et al., 1990).

Although there is a wealth of literature on assessment of depression in pregnancy, there is less work on a general measure of distress, and anxiety and how it might change over time. In both developed and developing countries, there is a need for more efficient and cost-effective screening methods to screen for depressive and anxiety disorders. This may be particularly relevant in resource-limited settings such as South Africa (SA). In this study, we chose to focus on the K-10, which has been developed for use in both community and clinical samples (Kessler et al., 2002; Furukawa et al., 2003).

Other scales that have been used to assess distressing psychological symptoms in pregnancy include the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger, 1970) and Perceived Stress Scale (PSS-10; Cohen et al., 1983). The STAI has commonly been used to assess state and trait anxiety in pregnancy (e.g. DiPietro et al., 2008; Grant et al., 2008; Christensen et al., 1999). The PSS provides an indication of how psychological distress is perceived over time in pregnancy. Yet, only a few studies have assessed anxiety over the course of pregnancy (e.g. Skouteris et al., 2009; Esimai et al., 2008; Da Costa et al., 1999). These scales may therefore be useful to assess different aspects of distress over the course of pregnancy.

As noted, further work is needed on relating distressing psychological symptoms to a range of psychosocial correlates such as temperament and character, resilience, and social support. For instance, avoidance of distressing situations may be associated with higher anxiety in pregnancy (Hamilton & Lobel, 2008). Resilience, on the other hand, may assist in successful management of anxiety-provoking and stressful situations (Connor & Davidson, 2003). Lower social support can be associated with increased distress (Kendell-Tacket, 2007).

This chapter aims to document the levels of distress e.g. anxiety in a SA pregnant population. There is a paucity of studies, which have investigated distress over the course of pregnancy, and particularly in our local pregnant women. Distress scales were also related to

one another and to diagnostic categories. In addition, the relationship between distress and temperament and character, resilience, and social support were investigated as these factors may influence how distress is rated.

4.2 Methods

4.2.1 Participants

Pregnant women with low risk singleton pregnancies were randomly recruited from local Midwife Obstetric Units in the Tygerberg region of the Western Cape by nursing staff and the candidate. Non-pregnant controls were also included from the same demographic area. See Chapter 3, section 3.1, for recruitment details.

4.2.2 Procedures

Pregnant women were required to provide information on sociodemographic factors such as income and employment, and complete various self-report measures on distressing psychological symptoms (K-10, STAI, PSS), psychosocial factors (TCI, CD-RISC, MSPSS) and a psychiatric interview (SCID). Trait anxiety was only measured once depending on when women entered the study. Controls also had to provide information on sociodemographic factors, but only completed self-reports on distress. See section 3.2 of Chapter 3 for an outlay and comprehensive description of procedures.

4.2.3 Statistical Analyses

Data was analysed in consultation with the Department of Statistics (Faculty of Health Sciences, Tygerberg) using Statistica, version 8 (Statsoft Inc.). Spearman correlational analyses were used to investigate interactions among separate distress scales, revealing significant correlations between the scales. A composite distress score was therefore also

ascertained (DiPietro et al., 2008). Both separate distress scales and composite distress scores were used in subsequent analyses.

In calculating a composite score from all distress scales, scale scores had to be standardized, since each scale had a different maximum score. Scale scores carried the same weight in contributing to the composite score. A standard score for each distress scale was calculated by subtracting the group mean score from the participant mean score and dividing it by the standard deviation of the specific scale. The validity of the standardised distress scores were investigated using the internal-consistency measure Cronbach's alpha.

Age, education and distress scores were compared between pregnant women and controls using one-way analyses of covariance (ANCOVA). To investigate variation in distress scores over time in pregnancy, mixed model repeated-measures ANOVA was used. Mixed models are preferred over classic repeated measures ANOVA in unbalanced designs, i.e. when sample sizes between groups vary over time.

A chi-square test was used to investigate whether K-10 scores were associated with the presence or absence of current depressive and/or anxiety disorders (SCID), by trimester. Fisher correction was applied in this analysis as only a small number of observations were expected to be positive, i.e. the number of pregnant women having a diagnosis. Women scoring 20 or above may have a psychiatric disorder while those scoring under 20 are likely to experience "normal" or situational appropriate rates of distress (Kessler et al., 2003). Furthermore, cut-off scores on the K-10 as suggested by Spies et al. (2009) were employed to predict a current major depression (≥ 21.5) by trimester.

Finally, significant associations between distress scores and psychosocial variables across groups were determined using Spearman correlational analyses. Regression analyses were used to determine to what extent these variables contributed to distress.

4.3 Results

4.3.1 Participants

Table 1 Demographic information of participants

	Pregnant women (n=110)			Controls (n=63)		
	n	Mean (SD)	Range	n	Mean (SD)	Range
Age (years)	-	25.2 (5.4)	18-41	-	29.0 (6.6)	18-43
Education (years)	-	10.9 (1.6)	5-15	-	9.6 (2.6)	4-13
Marital status						
Single	41	-	-	25	-	-
Married	39	-	-	21	-	-
Live with partner	18	-	-	8	-	-
Divorced	3	-	-	1	-	-
Separated	1	-	-	4	-	-
Widow	2	-	-	2	-	-
Employed*						
Yes	51	-	-	14	-	-
No	45	-	-	49	-	-
Annual household income (ZAR)*						
<10 000	32	-	-	14	-	-
10 000-20 000	11	-	-	7	-	-
20 000-40 000	15	-	-	4	-	-
40 000-60 000	9	-	-	4	-	-
60 000-100 000	8	-	-	3	-	-
>100 000	4	-	-	1	-	-

n, sample size; SD, standard deviation
*Not all subjects enclosed information on these factors; in some instances income was unknown.

A sample of 110 pregnant women and 63 non-pregnant controls was included in the study. Of the pregnant women, 107 were Coloured (of mixed race) and three were Caucasian, whereas of the controls, 55 were Coloured and eight were Black. One participant dropped out during the study. Marital status did not differ across the pregnant women and control group. Of the pregnant women, 37% were single and 35% married, whereas 40% of controls were single and 33% married. See Table 1 for demographic information.

4.3.2 Age and Education

The mean age of pregnant women and controls of 25 and 29 years respectively, differed significantly [$F(1, 171) = 17.625$, $p < 0.01$]. The mean level of education of pregnant women

and controls was the high school equivalent of grade 11 and grade 10 respectively and differed significantly [$F(1, 158) = 15.185$, $p < 0.01$]. All further comparative analyses in this chapter between pregnant women and controls were therefore controlled for age and education.

4.3.3 Distress

Although there were no significant differences in general distress over time as measured with the K-10 score (Table 2, Figure 1), women more often attained K-10 scores above 20 that differed significantly from mean scores below 20 ($p < 0.01$), over the course of pregnancy.

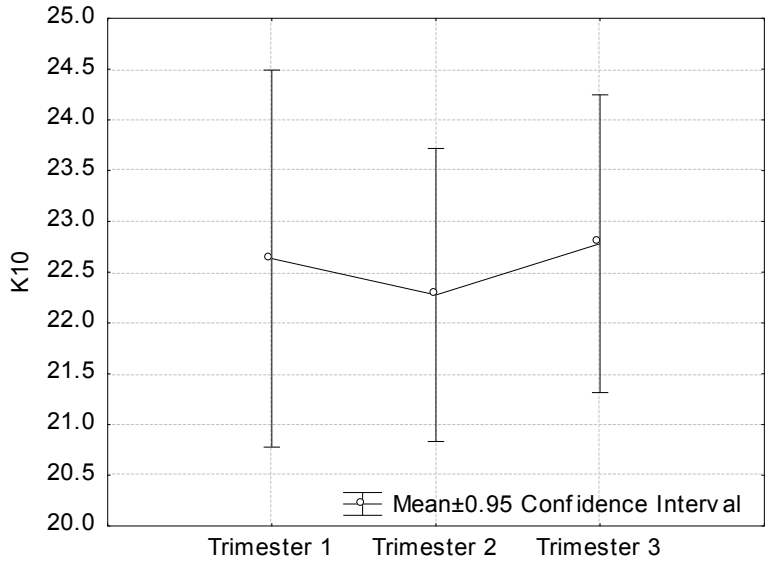

Figure 1 The distribution of K10 scores by trimester

During trimester 1, 55% (n = 27); trimester 2, 60% (n = 66); and trimester 3, 59% of women (n = 61) attained K-10 scores equal and above 20. K-10 scores equal and above 20 (μ_{T1} = 26.4; μ_{T2} = 27.1; μ_{T3} = 27.6), corresponded significantly with having a current depressive and/or anxiety disorder [Chi-square$_{T1}$ = 5.06, p = 0.025; Chi-square$_{T2}$ = 7.69, p = 0.006; Chi-square$_{T3}$ = 6.43, p = 0.011]. The cut-off score of $\geq$ 21.5 for major depression, as suggested by Spies et al. (2009) was applied. The sensitivity and specificity of this cut-off score to

predict major depression was, respectively, 1.00 and 0.37 at trimester 1; 0.86 and 0.47 at trimester 2; and 0.83 and 0.46 at trimester 3 of pregnancy.

STAI state anxiety scores changed significantly over time [F(2, 148) = 3.27, p = 0.041]. Specifically, scores increased significantly from trimester 1 to trimester 2 (p = 0.021), and were similar at trimester 2 and 3 (Table 2, Figure 2). Reported STAI trait anxiety scores were higher than state anxiety scores as measured once upon entering the study. Trait anxiety scores were significantly lower in participants who entered the study at trimester 1 than in those entering at trimester 2 [F(1, 98) = 5.54, p = 0.02] (Table 2, Figure 3). PSS scores remained consistent over time (Table 2, Figure 4).

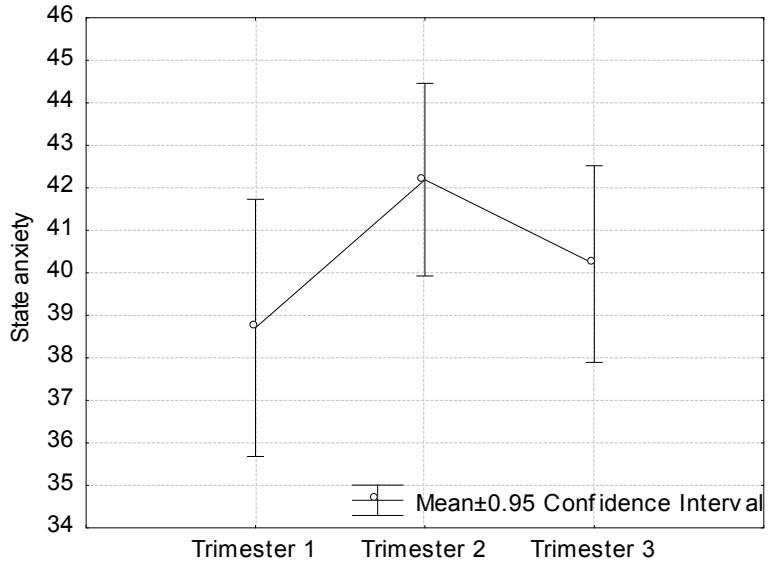

Figure 2 The distribution of state anxiety scores by trimester

Controls had significantly higher state anxiety [F(1, 107) = 5.869, p = 0.017] and trait anxiety scores [F(1, 106) = 5.993, p = 0.016] compared to women in trimester 1 of pregnancy (Table 2). There was a trend for higher state anxiety in controls compared to trimester 3 of pregnancy [F(1, 149) = 4.124, p=.044]. Controls also had significantly higher perceived stress scores compared to pregnant women (data from all trimesters included) [$F(1, 107)_{T1}$ = 10.007, p = 0.002; $F(1, 156)_{T2}$ = 6.012, p = 0.015; $F(1, 150)_{T3}$ = 11.266, p = 0.001] (Table 2).

Table 2 Distress scores of pregnant women and non-pregnant controls

	Trimester 1				Trimester 2				Trimester 3				Controls				T1-Ctrl	T2-Ctrl	T3-Ctrl
	n	Mean (SD)	CI		n	Mean (SD)	CI		n	Mean (SD)	CI		n	Mean (SD)	CI		p		
			5%	95%			5%	95%			5%	95%			5%	95%			
K10	49	21.4 (7.3)	19.3	23.5	110	22.3 (7.5)	20.9	23.7	104	22.7 (7.5)	21.2	24.2	63	26.7 (9.4)	24.3	29.1	0.050	0.068	0.063
<20	22	15.3 (2.5)	14.2	16.4	44	15.1 (2.4)	14.3	15.8	43	15.7 (2.2)	15.0	16.3	15	14.7 (2.7)	13.2	16.2	-	-	-
≥20	27	26.4 (6.0)	24.0	28.7	66	27.1 (5.6)	25.8	28.5	61	27.6 (5.8)	26.1	29.1	48	30.4 (7.3)	28.3	32.6	-	-	-
STAI-state	49	38.0 (10.3)	35.1	41.0	110	42.2 (21.6)	39.8	44.6	103	40.1 (11.5)	37.9	42.4	63	45.0 (11.4)	42.1	47.8	0.017*	0.837	0.044*
STAI-trait	48	40.5 (10.6)	37.4	43.6	53	45.7 (11.1)	42.6	48.8	-	-	-	-	63	46.5 (10.3)	44.0	49.1	0.016*	0.831	-
PSS	49	18.5 (6.3)	16.7	20.3	110	19.7 (6.1)	18.5	20.8	104	18.8 (6.0)	17.6	19.9	63	22.3 (4.8)	21.1	23.5	0.002**	0.015*	0.001**

n, sample size; SD, standard deviation; CI, confidence interval; T1, trimester 1; T2, trimester 2; T3, trimester 3; Ctrl, control; p, significance

*p<0.05

**p<0.01

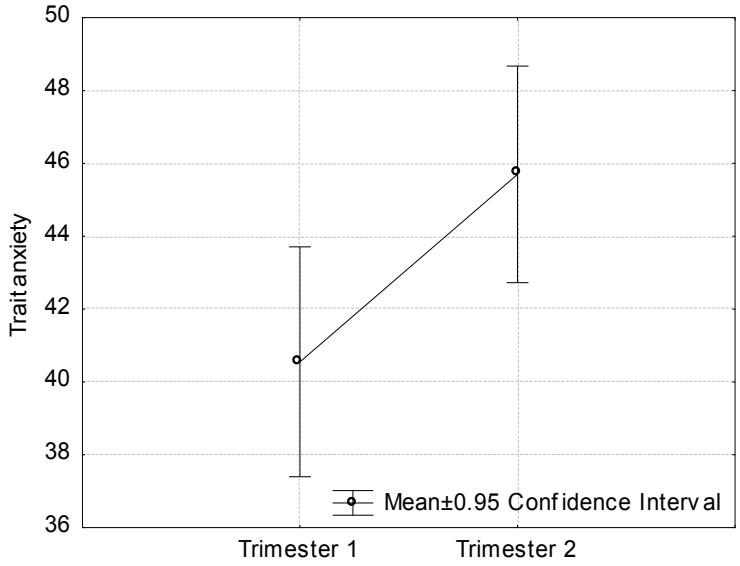

Figure 3 The distribution of trait anxiety scores by trimester

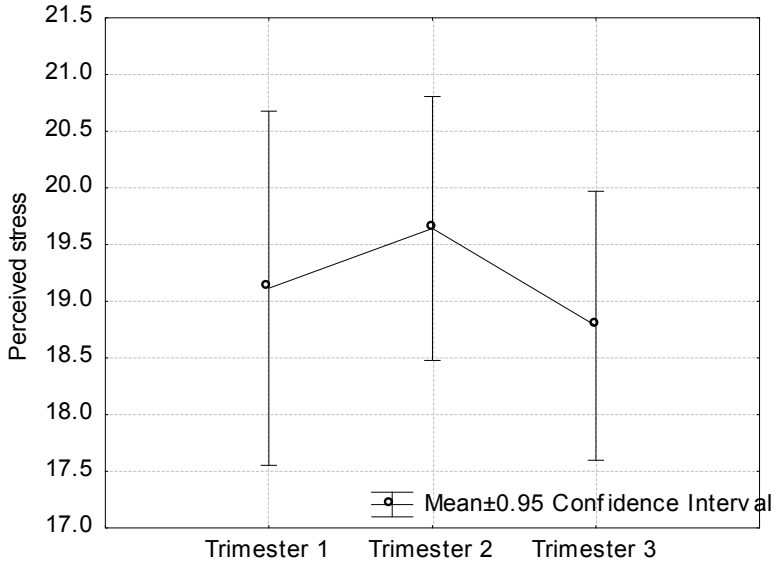

Figure 4 The distribution of perceived stress scores by trimester

4.3.4 Interactions among Distress Scales

Distress scales corresponded significantly with each other. K-10 scores correlated significantly with state anxiety scores over the course of pregnancy ($r_{T1} = 0.65$, $r_{T2} = 0.57$, $r_{T3} = 0.70$; $p < 0.001$), trait anxiety scores at trimester 1 and 2 ($r_{T1} = 0.66$, $r_{T2} = 0.70$; $p < 0.001$) and PSS scores over the course of pregnancy ($r_{T1} = 0.62$, $r_{T2} = 0.60$, $r_{T3} = 0.73$; $p < 0.001$).

Composite distress scores were highly reliable (Cronbach alpha's: T1 = 0.91, T2 = 0.89, T3 = 0.88) and demonstrated significant correlations with individual distress scales of 0.80 to 0.92 ($p < 0.001$). Both separate and composite distress scores were used in further analyses. State anxiety scores also correlated significantly with trait anxiety scores ($r_{T1} = 0.75$, $r_{T2} = 0.75$; $p < 0.001$), and PSS scores ($r_{T1} = 0.77$, $r_{T2} = 0.61$, $r_{T3} = 0.74$; $p < 0.001$).

4.3.5 Relationship between Distress Scores and Temperament and Character

The TCI that represents a stable measure of personality was completed once. TCI subscale scores correlated significantly with a number of distress scores over the course of pregnancy. See Table 3 for correlations between TCI subscales and distress. There was a significant positive correlation between harm avoidance and trait anxiety at trimester 2 ($r_{T2} = 0.63$, $p < 0.001$), and the composite distress score at trimester 2 ($r_{T2\_composite} = 0.60$, $p < 0.001$). There was also a significant negative correlation between self-directedness and trait anxiety at trimester 1 and 2 ($r_{T1} = -0.39$, $p < 0.05$; $r_{T2} = -0.63$; $p < 0.001$), and composite distress scores at trimester 2 and 3 ($r_{T2\_composite} = -0.53$; $r_{T3\_composite} = -0.52$, $p < 0.001$). In addition, there was a significant negative correlation between cooperativeness and trait anxiety at trimester 2 ($r = -0.53$, $p < 0.001$).

There was an association of trait anxiety at trimester 2 with scores on particular scales of temperament and character. The contribution of the TCI in explaining the variance in trait anxiety at trimester 2, when all TCI subscales were entered in multiple regression, was 57% [$R^2 = 0.57$; $F(6, 42) = 9.436$, $p < 0.001$]. Specifically there was a significant contribution of harm avoidance (beta = 0.46, $p = 0.002$) and self-directedness (beta = -0.37, $p = 0.03$) to the variance in trait anxiety. The level of contribution of novelty seeking (beta = -0.10), reward dependence (beta = -0.03), cooperativeness (-0.05) and self-transcendence (beta = 0.0) were not significant.

Table 3 Associations between distress and psychosocial correlates over the course of pregnancy

	Composite distress		
	Trimester 1	Trimester 2	Trimester 3
	r		
Temperament			
Novelty seeking	0.28	0.17	0.29*
Harm avoidance	0.24	0.60***	0.36**
Reward dependence	-0.06	-0.29*	-0.08
Character			
Self-directedness	-0.43*	-0.53***	-0.52***
Cooperativeness	-0.28	-0.44*	-0.30*
Self-transcendence	0.27	-0.04	0.20
Resilience	-0.25	-0.66***	-0.38***
Social support	-0.36*	-0.59***	-

r, correlation
*p < 0.05; **p < 0.001; ***p < 0.0001

4.3.6 Relationship between Temperament and Character and Resilience

There was a significant negative correlation between harm avoidance and resilience (r = -0.53, p < 0.001). There was also a significant positive correlation between self-directedness and resilience (r = 0.46, p < 0.001).

4.3.7 Relationship between Distress Scores and Resilience

Resilience correlated significantly with higher distress throughout the course of pregnancy. See Table 3 for correlations between resilience and distress. Although resilience was measured once, it is a stable personality measure that could be compared with distress over the course of pregnancy. Specifically, there was a significant negative correlation between resilience and trait anxiety (r_{T1} = -0.33, p < 0.05) at trimester 1, and all distress measures at trimester 2 and 3 ($r_{T2\_composite}$ = -0.66, $r_{T3\_composite}$ = -0.38; p < 0. 001). The contribution of resilience to explain the variance in trait anxiety at trimester 1 was 11% [R^2 = 0.11; F(1, 46) = 5.554, p < 0.001]. The contribution of resilience to explain the variance in distress was 53% at trimester 2 [R^2 = 0.53; F(1, 51) = 56.502, p < 0.001] and 13% at trimester 3 [R^2 = 0.13; F(1,

101) = 14.438, p < 0.001]. The correlation between resilience and trait anxiety at trimester 2 was particularly high (r_{T2} = -0.71, p < 0.001).

4.3.8 Relationship between Distress Scores and Perceived Levels of Social Support

Levels of perceived social support demonstrated a significant negative correlation with all measures of distress ($r_{T1\_composite}$ = -0.36, p < 0.05; $r_{T2\_composite}$ = -0.59, p < 0.001), except with the K-10 at trimester 1 (r = -0.25, ns). See Table 3 for correlations between social support and distress. The contribution of social support to explain the variance in distress at trimester 1 was 12% [R^2 = 0.12; F(1, 46) = 6.393, p = 0.018] and 34% at trimester 2 [R^2 = 0.34; F(1, 48) = 25.194, p < 0.001].

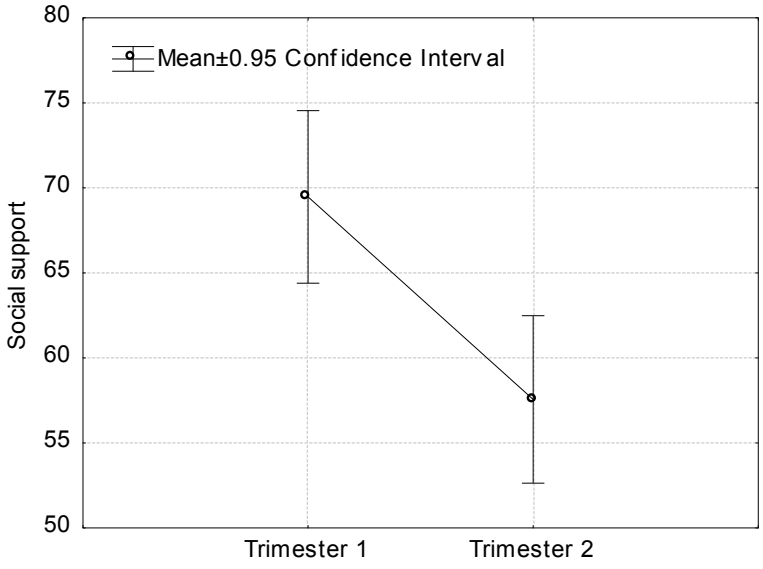

Figure 5 The distribution of perceived social support scores by trimester

Social support was either measured at trimester 1 or 2 depending on when a participant entered the study. However, when comparing participants who entered the study at trimester 2 compared to trimester 1 (Figure 5), social support scores were significantly lower in the former group [F(1, 99) = 11.174 , p < 0.01].

4.4 Discussion

The main findings included distress levels in our local pregnant population that were high in comparison with previous findings in pregnant samples. Furthermore, there were associations of features of temperament and character, lower resilience and lower social support with distress levels over the course of pregnancy.

The K-10 has not been used in other pregnant populations to assess general distress over the course of pregnancy, which made it difficult to compare results with existing literature. Mean K-10 levels were just above the conventional cut-off score of 20 for psychiatric disorders (Kessler et al., 2002) in 55% of cases in trimester 1, 60% of cases in trimester 2, and 59% of cases in trimester 3, indicating the likely presence of psychiatric disorders in two-thirds of this population. Indeed, K-10 scores above 20 were also associated with the presence of a current SCID diagnosis of a depressive and/or anxiety disorder, confirming the ability of the K-10 to separate DSM-IV cases from non-cases also in a pregnant population. However, two thirds of controls also scored above 20 on the K-10 (although K-10 scores may only be a reasonable indicator of psychopathology in this population (see next paragraph)). As it is unlikely that several low risk pregnant women had a psychiatric disorder, this cut-off level on the K-10 may have been too low in this SA population. A recent validity study that has determined specific K-10 cut-off scores by psychiatric disorder according to DSM-IV criteria in this population (Spies et al., 2009), has demonstrated specific cut-off scores for current depressive and anxiety disorders. The best cut-off score, according to a ROC analysis was, for major depression ≤ 21.5 (sensitivity, 0.73; specificity, 0.54); for posttraumatic stress disorder ≤ 28.5 (sensitivity, 0.5; specificity, 0.8); for social anxiety disorder ≤ 26.5 (sensitivity, 1; specificity, 0.75); and for panic disorder ≤ 38.5 (sensitivity, 0.5; specificity, 0.98). This suggests that a cut-off score of 20 on the K-10 to predict psychiatric disorders, was too low here, and it is therefore important to consider validated cut-off scores in assessing distress in both pregnant women and non-pregnant controls, since these

disorders may well be present in some pregnant women (Alder et al., 2007; Ross & McLean, 2006).

To investigate whether the cut-off score of 20 on the K-10 was in fact too low to predict certain psychiatric disorders in pregnancy, the cut-off score as determined by Spies et al. (2009) for current major depression of ≥ 21.5 (sensitivity, 0.73; specificity, 0.54), was employed by trimester. The sensitivity of this cut-off score was greater at each trimester (trimester 1, 1.00; trimester 2, 0.86; trimester, 0.83) compared to Spies et al. (2009). The specificity, however, was lower (trimester 1, 0.37; trimester 2, 0.47; trimester 3, 0.46) with a high rate of false positives. Thus, the K-10 is a reasonable indicator of the presence of major depression. However, more work is needed in larger samples of pregnant women to assess the value of the K-10 in predicting psychiatric disorders in this population.

K-10 levels were highly correlated, over the course of pregnancy, with the STAI (state and trait anxiety) and PSS (perceived stress) which have previously been used to assess levels of distress in pregnancy. K-10 scores were similar over the course of pregnancy, demonstrating a non-significant increase over the course of pregnancy. State anxiety was also highly correlated with trait anxiety and perceived stress at every assessment. In turn, the perceived stress score trend (similar over the course of pregnancy) was consistent with that of a previous study, although lower (DiPietro et al., 2008), suggesting retained accuracy in perceiving one's own distress levels (Lobel & Dunkel-Schetter, 1990). According to DiPietro et al. (2008), high inter-correlation of distress scales implies that the same underlying construct is measured. It is however likely that there is a strong relationship between general distress, anxiety and perceived stress due to these scales measuring different, but shared aspects of distress including depressive and anxiety symptoms.

State anxiety in our population was particularly high in comparison with studies that also used the STAI in pregnancy, i.e. above the conventional cut-off score of 40, which indicate anxiety on a clinical level (Spielberger et al., 1970) except at trimester 1 (previous studies

consistently reported scores below 40 in pregnancy). Again, this cut-off score may have been too low for this population. Scores also demonstrated a likely comorbid relationship with K-10 scores that were also above the recommended cut-off score for psychiatric disorders. The downward non-significant trend observed in state anxiety from trimester 2 to 3 corresponded with a previous study (Christensen et al., 1999), whereas other studies showed increases from trimester 2 to 3 (DiPietro et al., 2008; Da Costa et al., 1999). Increases in anxiety from trimesters 2 to 3 were also demonstrated using the anxiety subscale of the Profile of Mood States (DiPietro et al., 2008) and the Zung-anxiety scale, a self-report measure of emotional and physical symptoms (Keenan et al., 1998). None of these studies measured anxiety at trimester 1. It is likely that the great physiological changes including increased and fluctuating gonadal hormones were associated with the changes in anxiety levels.

Non-pregnant controls demonstrated significantly higher state and trait anxiety compared to pregnant women at trimester 1, and significantly higher perceived stress levels compared to pregnant women (data from all trimesters included). The control group had a notably higher unemployment rate (78%) than pregnant women (47%), and this may explain why these women experienced higher anxiety. This may also explain why controls perceived their distress as higher compared to pregnant women; considering that perceived stress is an indication of the degree to which life circumstances such as financial lack (likely due to unemployment) and associated poverty, are experienced as uncontrollable, demanding and difficult.

Trait anxiety in our population was also high at trimester 1 and 2, and above the cut-off score of 40, in comparison with previous studies (Skouteris et al., 2009; DiPietro et al., 2008). As these scores were attained upon entry into the study it is particularly noteworthy that women entering at trimester 2 had significantly higher levels than those that entered at trimester 1. It may be that women booking later have higher trait anxiety in comparison with women booking earlier, thus were influenced by individual inclination.

Furthermore, all distress scale levels were significantly associated with psychological correlates over the course of pregnancy, including particular subscales on the Temperament and Character Inventory. In particular, high trait anxiety (and the other distress levels) was significantly associated with higher harm avoidance, lower self-directedness and lower cooperativeness at trimester 2 of pregnancy. Women, who feel anxious, will seek to avoid anxiety-provoking situations (Hamilton & Lobel, 2008) that may include pregnancy-specific activities. Women experiencing high trait anxiety may therefore have displayed passivity in taking responsibility for their pregnancy, including less motivation to heed recommendations that dictate early attendance (i.e. trimester 1) of obstetric care units.

Pregnant women, who reported high trait anxiety at trimester 2 and displayed higher harm avoidance and lower self-directedness, also demonstrated significantly lower resilience. The association between resilience and changes particularly in trait anxiety was greatest at trimester 2. Resilience provides an indication of the ability to cope with stressful situations (Connor & Davidson, 2003) including homeostatic disturbances (Richardson, 2002) such as the psychobiological changes associated with pregnancy (Oates, 1989). Anxious women's likely passivity and less motivation may therefore have been due to a sense of insufficient inner strength and confidence to manage their pregnancy successfully. This finding is important as non-resilient pregnant women may find it particularly difficult to cope with pregnancy, partly explaining the increased vulnerability to experience distressing psychological symptoms during pregnancy.

Finally, lower social support was significantly associated with distress at trimester 1 and 2 when assessed. This is consistent with a previous study that demonstrated an association of inadequate social support with higher psychological distress (DeLongis et al., 1988). Similarly, participants in our study who indicated sufficient social support also experienced less distress, which suggests stress-buffering effects of social support in pregnancy (Collins et al., 1993). The effect of insufficient social support on distress is likely reflected by rumination, i.e. worrying or excessive focus on negative circumstances without taking action

to overcome it, and/or suppression of emotions as a self-protective mechanism (Moore et al., 2008). Both these strategies are associated with increased vulnerability to develop depressive and anxiety symptoms. Providing assistance in expanding the social networks of pregnant women, including stress reduction strategies for those who have low psychosocial resources, may counter the development of mental health problems and subsequent adverse maternal outcomes.

The work described in this chapter has a number of limitations. Firstly, the sample size was relatively small. However, it is comparable with that in other pregnancy studies of the relevant variables (Skouteris et al., 2009; DiPietro et al., 2008). There probably was an unintended element of sampling bias in that controls were more stressed and anxious than pregnant women were, although they were recruited from the same demographic area. The sample also consisted essentially of one ethnic group and findings therefore may not be generalisable to other populations. Secondly, having two entry points into the study may have introduced an element of bias that was for instance evident in particularly high trait anxiety in women entering at trimester 2. Thirdly, use of self-report screening scales may have introduced a number of biases. Low educational level caused some participants to have difficulty understanding self-report questionnaires. In such cases, particular effort was made to explain questions to participants and verify responses. Lastly, controls did not complete questionnaires on psychosocial variables, and the associations between distress and these variables in the control population could therefore not be reported.

This chapter adds to previous work by demonstrating high correspondence of the K-10 with previously used scales to assess distressing psychological symptoms over the course of pregnancy. General distress on the K-10 may be a useful indicator of current SCID diagnoses. The study also extends previous work by demonstrating high state and trait anxiety particularly at trimester 2 in a resource-poor clinical setting in a developing world. These results may reflect the adverse outcomes associated with continuing exposure of women of this SA community to poverty and associated violence and crime, and insufficient

resources. Although the K-10 appears to be a promising indicator of the presence of a psychiatric disorder, a cut-off score of 20 on the K-10 was too low to separate normally distressed from clinically distressed participants in this particular population. Larger studies are needed to delineate fully the sensitivity and specificity of K-10 cut-offs for predicting psychiatric disorders in this population. Psychosocial factors including temperament and character, resilience, and social support may influence how distress is perceived. Further work on the causal nature of the associations documented here is needed.

These findings may have important clinical implications for the care of pregnant women in developing countries such as SA. Specifically, the level of distress in this study population is cause for concern. Strategies to alleviate contributing factors to psychosocial distress should be devised to ensure the well-being of women and their unborn children. Clinicians should also incorporate strategies to identify individuals who may be at risk for the development of depressive and anxiety disorders. In the next chapter, cognitive-affective processing underlying distress is explored.

CHAPTER 5

COGNITIVE-AFFECTIVE PROCESSING IN PREGNANCY

Abstract

Background: The aim of this chapter is to assess the relationship between cognitive-affective processes and distress over the course of pregnancy. Findings concerning cognitive changes in pregnancy are inconsistent. There has been much less work on the affective component of cognition and how it influences distress. It might be hypothesized, for example, that selective attention to threat is increased during pregnancy, and leads to greater anxiety symptoms.

Methods: Pregnant women (n=53) with low risk singleton pregnancies from Midwife Obstetric Units in the Tygerberg region of the Western Cape were included in the study. These women constituted a subset of a larger sample of pregnant women (n=110) participating in a maternal stress study. Non-pregnant controls (n=10) were also included from the same demographic area. Subjectively experienced and objectively tested cognitive ability and selective attention to threat were compared in pregnant and non-pregnant women, and were correlated with distress at different time points during pregnancy. Subjectively experienced cognitive ability was asked about, and objective cognitive ability was assessed using standardized neuropsychological tests. Selective attention to masked and unmasked emotional stimuli, i.e. stimuli presented outside and within conscious awareness respectively, including angry, fearful and happy faces, were assessed over the course of pregnancy and in non-pregnant controls using a Facial Stroop Task. Distress levels were assessed using the K-10 (measuring general distress), Spielberger State -Trait Inventory (STAI) (measuring state and trait anxiety) and Perceived Stress Scale (PSS) (measuring the degree to which life is experienced as difficult and challenging).

Results: Although pregnant women reported subjective cognitive impairment in attention and memory particularly at trimester 2, this impairment was not significantly associated with their objective cognitive performance, nor did their objective function differ from that of controls.

There were few associations between subjectively experienced cognitive ability and distress, including a significant association between subjectively rated attention impairment (trimester 2) and higher perceived stress (PSS). Although pregnant women had increased selective attention to unmasked fearful faces compared to non-pregnant women at all time points in pregnancy, this was not significantly associated with distress.

Conclusion: Increased attention of pregnant women to fear stimuli suggests that particular neural circuits involved in emotional regulation are altered in pregnancy. However, such changes in cognitive-affective processing were not associated with cognition, suggesting that other relevant contributors to distress require exploration.

5.1 Background

The aim of this chapter is to assess the relationship between cognitive-affective processes and distress over the course of pregnancy. As noted in Chapter 2, studies have demonstrated deficits in subjectively and objectively rated attention and particularly memory in pregnancy. Up to 82% of pregnant women e.g. rate their memory as impaired (Crawley et al., 2003; Sharp et al., 1993), whereas some studies have found such impairment, using objective measures (Buckwalter et al., 1999). The few studies that assessed attention have specifically demonstrated altered selective attention to visual stimuli (De Groot et al., 2003a; Buckwalter et al., 1999) with evidence lacking regarding changes in attention over the course of pregnancy. Further research is needed to investigate in pregnant women the phenomenon of cognitive impairment, particularly attention.

There has been much less work on the affective component of cognition, including how it influences distressing psychological symptoms. The cognitive tasks that have been employed in studies of pregnancy have not addressed the impact of emotion on cognitive processes, using paradigms such as attention to emotional facial stimuli of threat. There is also little information about how distressing psychological symptoms in pregnancy are associated with either cognitive or affective processes. For instance, psychological stressors

intensify selective attention toward fear and anger stimuli and increases anxiety levels in non-pregnant populations (Ellenbogen et al., 2002). Adding an emotional component may be a way to investigate how cognitive function and distress (e.g. anxiety) impact on one another in pregnancy.

The aim of this chapter is to assess the relationship between cognitive-affective processes and distress over the course of pregnancy. Specifically, subjectively experienced and objectively rated cognitive ability; and selective attention to facial expressions of fear, anger and happiness presented outside (masked) and within conscious awareness (unmasked) are assessed, and the association of distress with such cognitive and affective processing is investigated. To our knowledge, this attention paradigm has not been used in pregnancy before.

5.2 Methods

5.2.1 Participants

Women were randomly recruited from an existing cohort of women taking part in a larger prospective study of maternal stress in pregnancy. Non-pregnant controls were also included from the same demographic area. See section 3.1 of Chapter 3 for recruitment details.

5.2.2 Procedures

Participants were required to provide information on sociodemographic factors including income and employment, and to complete a cognitive battery (subjectively experienced and objectively assessed attention and memory), a Facial Stroop Task (FST), and self-report measures of distress (K-10, STAI, PSS). See section 3.2 in Chapter 3 for a comprehensive description of procedures.

5.2.3 Statistical Analyses

The relationship between attention and memory, selective attention to threat, and distress measures, were investigated firstly using Spearman's correlational rank-order analyses and one-way analyses of variance (ANOVA). Secondly, to control for the effects that age and education may have on these associations, multiple regression was used. Selective attention to emotional facial expressions of fear, anger and happiness on the FST was investigated using one-way ANOVA (comparisons between pregnant women and controls) and a mixed model ANOVA to investigate the data over time in pregnancy (all trimesters).

Due to significant correlations among the separate distress scales, a composite distress score was also calculated and used in analyses in conjunction with the separate scale scores. See section 4.3.4 of Chapter 4 for a detailed discussion.

Data on attention and memory were categorised into relevant sub-domains as described by Henry and Rendell (2007) and Roos et al. (2010). These were attention (vigilance test), working memory (digit span forward and backward), immediate shortterm memory (word lists 1-3), delayed shortterm memory (word list 4), and explicit memory (animal naming).

5.3 Results

5.3.1 Participants

Table 1 Demographic information of participants

	Pregnant women (n=53)			Controls (n=10)		
	n	Mean (SD)	Range	n	Mean (SD)	Range
Age (years)	-	25.68 (5.67)	18-41	-	24.70 (5.74)	18-38
Education (years)	-	11.36 (1.38)	9-15	-	11.67 (0.82)	10-13
Employed						
Yes	24	-	-	5	-	-
No	26	-	-	5	-	-
Annual household income (ZAR)*						
<10 000	16	-	-	1	-	-
10 000-20 000	6	-	-	2	-	-
20 000-40 000	8	-	-	2	-	-
40 000-60 000	3	-	-	2	-	-
60 000-100 000	6	-	-	1	-	-
>100 000	2	-	-	1	-	-

n, sample size; SD, standard deviation

*Income of pregnant women was based on information of 41 subjects. Not all subjects enclosed this information; in some instances income was unknown.

A sample of 53 pregnant women (which is a subset of a larger sample of women (n=110) participating in a maternal stress study) and 10 controls were included in the study. Of the pregnant women, 46 were Coloured (of mixed race), three were Black and four were Caucasian, whereas nine controls were Coloured and one was Black. See Table 1 for additional demographic information. Distress scores of pregnant participants and controls are presented in Table 2. There were no significant differences between pregnant women and controls in age and education, in this sub-sample of women who completed distress, and cognitive and affective measures.

5.3.2 Cognitive Function

5.3.2.1 Subjective and Objective Cognitive Function

A number of pregnant participants rated their attention and memory to be impaired. Controls were not required to rate their attention and memory performance, but only completed objective cognitive tasks assessing these functions. Particularly during trimester 2, 41% and

Table 2 Distress scores of pregnant women and non-pregnant controls

	Trimester 1				Trimester 2				Trimester 3				Controls			
	n	Mean (SD)	CI		n	Mean (SD)	CI		n	Mean (SD)	CI		n	Mean (SD)	CI	
			5%	95%			5%	95%			5%	95%			5%	95%
K10	24	20.21(6.42)	17.5	22.9	53	23.06(8.09)	20.8	25.3	51	23.14(7.62)	21.0	25.3	10	20.30 (6.55)	15.6	25.0
STAI-state	24	38.29(10.44)	33.9	42.7	53	44.58(12.85)	41.0	48.1	51	41.63(10.86)	38.6	44.7	10	35.70 (10.34)	28.3	43.1
STAI-trait	23	39.87(10.42)	35.4	44.4	28	46.68(9.08)	43.2	50.2	-	-	-	-	10	37.30 (8.63)	31.1	43.5
PSS	24	18.83(6.55)	16.1	21.6	53	20.34(5.76)	18.8	21.9	51	19.08(5.15)	17.6	20.5	10	19.10 (3.28)	16.8	21.4

n, sample size; SD, standard deviation; CI, confidence interval

57% of participants rated their attention and memory as impaired, respectively. These ratings at trimester 2 were significantly positively correlated ($r = 0.36$, $p < 0.05$). Impairment vs no impairment ratings on attention and memory function, and corresponding mean distress scores are presented in Table 3. The subjective ratings of attention and memory impairment were not significantly associated with objectively rated cognitive test scores across trimesters.

There were no significant differences in objective cognitive performance between pregnant women and controls. Scores of the individual objective cognitive tests and sub-domains, including p-values of comparisons made between scores of pregnant women and controls, are presented in Table 1 of Addendum A (p 128).

Table 3 Distress scores of pregnant women by subjective cognitive impairment ratings

	Trimester 1				Trimester 2				Trimester 3			
	Impaired attention		Impaired memory		Impaired attention		Impaired memory		Impaired attention		Impaired memory	
	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no
	24%	76%	33%	67%	41%	59%	57%	43%	24%	76%	47%	53%
K10	21.3	19.1	18.6	20.1	25.6	22.6	24.9	22.3	25.5	23.0	25.1	22.3
STAI state	38.8	37.8	36.0	39.2	48.6	42.6	47.6	42.8	44.9	43.8	47.4	41.1
STAI trait	46.3	38.1	35.7	42.3	50.3	48.0	48.1	48.4	-	-	-	-

5.3.2.2 Relationship between Cognitive Function and Distress Measures

There were few significant associations between pregnant women's subjective ratings of impairment in attention and memory, and measures of distress throughout the course of pregnancy. Pregnant women, who subjectively rated their attention and memory as impaired, except for memory during trimester 1, also reported higher general distress throughout their pregnancy as measured by the K-10, and in most instances, higher state and trait anxiety (STAI) (Table 2), but this did not reach statistical significance. However, pregnant women who rated their attention as impaired at trimester 2, and had significantly lower educational levels, also perceived their distress as higher (PSS) [$R^2 = 0.33$; $F(3, 33) = 5.306$, $p < 0.01$].

There were few significant associations between objective cognitive performance of pregnant participants and measures of distress, including a positive correlation between working memory performance (digits-forward and backward) and state anxiety ($r = 0.57$, $p < 0.01$) and trait anxiety ($r = 0.42$, $p < 0.05$) at trimester 1 (Table 4). However, after controlling for age and education, these results were not significant. Performance of controls did not correlate significantly with distress or anxiety ratings.

5.3.3 Performance on the Facial Stroop Task

5.3.3.1 Awareness Check

Pregnant participants and non-pregnant controls attained scores of 18 to 21 on the awareness check. As a score of 20 indicates chance identification of emotional and neutral faces, the scores suggest that participants did not consciously perceive the faces (MacLeod and Hagan, 1992; Putman et al., 2004). Thus, it is unlikely that they were able to consciously use strategies to adjust attentional biases to specific emotions presented on the subconscious level.

5.3.3.2 Selective Attention to Threat

There was a significant main effect of group for selective attention to emotions [$F(6, 51) = 2.651$, $p = 0.028$]. The effect was accounted for by fear (Table 5, Figure 1), i.e. there were significant differences between pregnant women (over the course of pregnancy) and controls in attending to unmasked fearful faces [$F(6, 26)_{T1} = 6.70$, $p = 0.015$; $F(6, 26)_{T2} = 12.84$, $p = 0.001$; $F(6, 26)_{T3} = 12.08$, $p = 0.001$]. Pregnant women paid significantly more attention to fearful faces (slower reaction times) at each time point compared to controls. Pregnant women also paid more attention to fearful faces as pregnancy progressed, although this finding did not reach statistical significance. There were no significant differences between pregnant women and controls in response to masked fearful faces. Notably, pregnant women

Table 4 Associations between objective cognitive performance and distress in pregnant women and non-pregnant controls

	Trimester 1				Trimester 2				Controls			
	r				r				r			
Cognitive sub-domains	K-10	State anxiety	Trait anxiety	PSS	K-10	State anxiety	Trait anxiety	PSS	K-10	State anxiety	Trait anxiety	PSS
Attention (Vigilance Test)	-0.16	-0.29	-0.22	-0.17	-0.02	-0.19	-0.15	-0.19	-	-	-	-
Working memory (Digit Span Forward and Backward)	0.37	0.57**	0.42*	0.40	-0.16	-0.27	-0.04	-0.14	-0.04	0.47	0.20	0.09
Immediate shortterm memory (Word Lists 1-3)	0.33	-0.01	-0.01	0.05	-0.27	0.06	-0.09	-0.13	0.20	0.05	0.22	0.48
Delayed shortterm memory (Word List 4)	0.01	0.09	-0.03	0.00	0.35	0.11	0.12	0.11	-0.06	0.24	0.35	0.46
Explicit Memory (Animal Naming)	-0.18	0.06	-0.05	-0.10	-0.01	0.15	0.18	0.12	-0.10	-0.07	0.23	0.05

PSS, perceived stress scale; r, correlation; p, significance

*p < 0.05

**p < 0.01

displayed opposite response patterns to masked fearful faces compared to unmasked fearful faces, i.e. non-significantly less attention (faster reaction times) was paid to fear as pregnancy progressed.

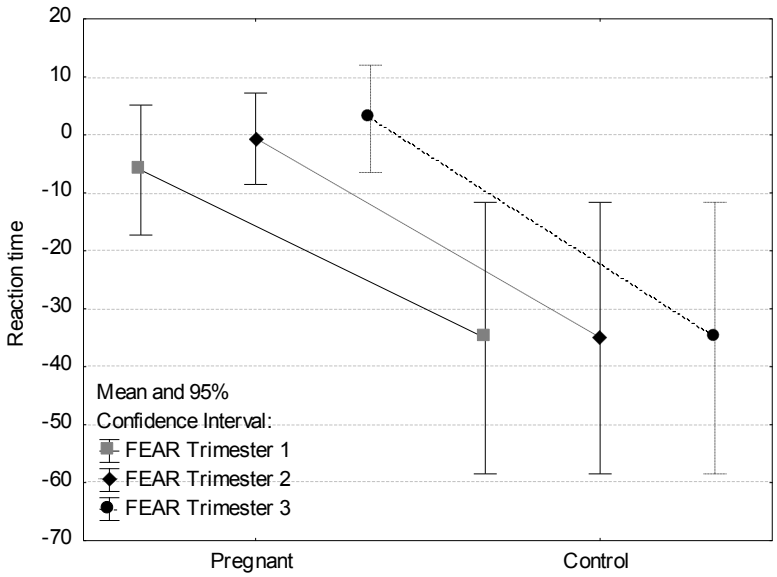

Figure 1 Selective attention to unmasked fearful facial expressions in pregnant women and non-pregnant controls

Reaction times in response to unmasked angry faces were similar for pregnant women and controls regardless of trimester. Controls demonstrated faster reaction times than pregnant women in response to angry faces did, but this difference was not statistically significant. Reaction times to masked angry faces were also similar between the groups, except at trimester 2 where pregnant women displayed non-significantly faster reaction times. Pregnant women and controls also demonstrated similar reaction times in response to masked and unmasked happy faces.

5.3.3.3 Relationship between Selective Attention to Threat and Distress Measures

There were no significant correlations between selective attention to threat and the K-10, STAI, and PSS measures at any time point.

Table 5 Selective attention to emotions on masked and unmasked level in pregnant women and non-pregnant controls

Reaction time (ms)	Trimester 1 (n=24)			Trimester 2 (n=50)			Trimester 3 (n=45)			Controls (n=10)		
	Mean (SD)	CI		Mean (SD)	CI		Mean (SD)	CI		Mean (SD)	CI	
		5%	95%		5%	95%		5%	95%		5%	95%
Angry masked	7.6 (24.0)	-2.8	17.9	-0.1 (28.5)	-8.3	8.1	2.4 (20.3)	-3.7	8.5	5.3 (15.3)	-5.6	16.2
Angry unmasked	9.4 (19.2)	1.1	17.7	10.6 (27.6)	2.7	18.4	7.1 (24.9)	-0.3	14.6	5.6 (23.2)	-11.0	22.2
Happy masked	0.5 (26.4)	-10.7	11.6	0.1 (32.7)	-9.2	9.4	-5.2 (26.1)	-13.1	2.6	-2.2 (18.8)	-15.6	11.2
Happy unmasked	-7.4 (31.1)	-20.4	5.8	9.0 (26.2)	1.2	16.4	5.2 (28.0)	-3.3	13.6	7.1 (40.8)	-22.1	36.2
Fear masked	6.7 (19.5)	-1.6	14.9	2.8 (23.9)	-4.0	9.5	-6.5 (33.6)	-16.6	3.6	14.6 (31.7)	-8.1	37.2
Fear unmasked	-6.1 (26.6)	-17.3	5.1	-0.7 (23.9)	-8.5	7.2	2.8 (30.8)	-6.5	12.0	-35.1 (32.7)	-58.5	-11.6

ms, milliseconds; n, sample size; SD, standard deviation; CI, confidence interval

Positive and negative reaction times respectively indicate increased and decreased attention to a facial expression.

There were significant correlations between selective attention to masked happy faces (presented outside conscious awareness) and the composite distress score at trimester 1 ($r = -0.46$, $p < 0.05$) and trimester 2 ($r = 0.38$, $p < 0.05$). Less attention was paid to happy faces at trimester 1, and more attention at trimester 2, when distress was high. Again, however, when controlled for age and education these findings were not significant.

5.3.3.4 Relationship between Selective Attention to Threat and Subjective and Objective Cognition

Selective attention to threat was not significantly associated with subjective and objective cognitive performance.

5.4 Discussion

The aim of this chapter was to assess the relationship between cognitive-affective processes and distress over the course of pregnancy. Pregnant women indicated subjective cognitive impairment in attention and memory. There were few associations between subjectively experienced cognition and distress, including a significant association between subjectively rated attention impairment (trimester 2) and higher perceived stress (PSS), in women with lower educational levels. Objective cognitive performance did not differ in pregnancy and controls, and were not associated with distress. Selective attention to unmasked fearful faces, i.e. faces presented within awareness, was significantly different between pregnant women and controls over the course of pregnancy.

Pregnant women demonstrated impaired subjective attention and memory predominantly at trimester 2 and 3 of pregnancy. The impairment was most prominent at trimester 2, particularly the memory impairment, as was also the case in previous studies (Crawley et al., 2003; Brindle et al., 1991). However, the impairment was not significantly associated with their objective cognitive performance, consistent with previous findings (Crawley et al., 2003;

McDowall & Moriarty, 2000; Janes et al., 1999). The attention and memory ratings at trimester 2 also corresponded significantly, which suggest co-morbidity of the two functions and consequent similarly altered perceptions of cognitive status. This confirms the general notion that some pregnant women perceive their cognitive function as impaired.

The reason why women perceive their cognitive function as impaired remains a matter of debate. In this study, pregnant women who rated their attention as impaired (trimester 2), also had significantly lower educational levels, and perceived their distress as higher (PSS). Work by DiPietro et al. (2008) that have demonstrated similar PSS scores in pregnant women than in this sample (see Table 2), has found a similar association between lower education and ratings of higher distress. It is well-known that educational level is associated with cognitive performance (Hodges, 1994; Strub & Black, 1977). Furthermore, women from low socio-economic status areas (as in our sample) generally have lower educational levels and more exposure to stressful life events (Brugha et al., 1985) that, in turn, is associated with higher self-reported distress e.g. anxiety in pregnant women (Kalil et al., 1993). This suggests that when life is experienced as uncontrollable and demanding (as measured by the PSS) probably due to life circumstances, this may influence how women view their cognitive ability.

It is also suggested that psychological factors such as individual variation may be associated with cognitive changes in pregnancy (De Groot et al., 2006). In a recent study that assessed temperament and character using the Temperament and Character Inventory (Celikel et al., 2009), patients suffering from depression demonstrated significantly lower harm avoidance and self-directedness in comparison with healthy controls. Further work needs to be done with this kind of approach in the current sample, although it can be noted that a significant association between lower harm avoidance and self-directedness, and increased distress did emerge here (see section 4.3.5 of Chapter 4).

Cognitive-affective processing of unmasked fearful faces was distinctly different between pregnant women and controls over the course of pregnancy. Pregnant women paid significantly and increasingly more attention to fearful faces from trimester 1 to 3 compared to controls. In contrast, controls drew their attention rapidly away from fearful faces. Decreased attention to fear indicates expected normal adaptive behaviour in the face of potential threat (Mogg et al., 2007) to manage negative emotion (Ellenbogen et al., 2006). However, when the opposite pattern is evident, i.e. increased attention to fear, significantly higher anxiety (Wilson & MacLeod, 2003; Fox et al., 2001) is a likely contributor that causes particular difficulty to draw attention away from threat stimuli (MacLeod & Mathews, 1991).

Increased attention in response to unmasked fear in pregnant women compared to healthy controls may suggest that particular neural circuits involved in emotional regulation are altered by pregnancy. The prefrontal cortex (PFC) plays a key role in modulating subcortical areas including the amygdala in order to optimize emotional regulation of threat by directing attention and behavioural responses, including the modulation of associated distressing psychological symptoms such as anxiety (Phan et al., 2004). For instance, attentional avoidance of fearful stimuli results from the PFC inhibiting amygdala activation (Ochsner & Gross, 2005). Pregnant women may however experience the opposite effect where the PFC is temporarily less effective in regulating attention to fear and anxiety due to greater neurobiological demands related to pregnancy.

Nevertheless, although higher distress was observed in this sample (see Table 2), it was not significantly associated with selective attention to unmasked fear. This is, consistent with previous studies in non-pregnant samples (MacLeod & Mathews, 1991; MacLeod & Hagan, 1992; MacLeod & Rutherford, 1992), and suggests that a range of other mechanisms – other tests of the same selective attention mechanism - may be relevant to explaining increased distress.

Pregnant women did not differ in their selective attention to masked fearful faces compared to non-pregnant controls. However, women did demonstrate the opposite effect in comparison with unmasked fearful faces, i.e. decreased attention to masked fear as expected. A study that has demonstrated opposite effects in masked versus unmasked processing of threat (Roelofs et al., 2007) suggests that this indicates processing that originates on an automatic level that is subsequently evident when conscious regulation follows. This may again be explained by how neural circuitry regulates emotion. For example, when threat is automatically detected by the senses, the faster ventral neural pathway of emotion processing automatically reacts to stimuli, to aid recognition of the emotional significance of a stimulus and production of an affective state in response (Phillips et al., 2003a; see section 2.3.1 of Chapter 2). This is followed by processing by the slower dorsal pathway to effect conscious processing of stimuli, to initiate decision-making and responses (Phillips et al., 2003a). However, fearful stimuli are predominantly processed by the PFC so that conscious processing may dominate. This may be because fearful stimuli requires longer scrutinizing e.g. in comparison with angry facial expressions to verify whether the stimuli is harmful and to decide on a response (Ewbank et al., 2009). Since pregnant women and controls demonstrated similar responses to masked fearful faces, this suggests that automatic neural regulation of threat is unchanged in pregnancy, whereas the conscious perception of threat (i.e. responses to unmasked fear) and regulation by the PFC may be altered in pregnancy.

In summary, this chapter has investigated the relationship between cognitive-affective processes and distress over the course of pregnancy. Perceptions of attention and memory ability indicated cognitive impairment in some pregnant women, which was in most instances not associated with distress. The cognitive tasks were not associated with distress. Furthermore, subjective and objective cognition were unrelated. Selective attention to unmasked fearful faces, on the other hand, was distinctly different in pregnant women compared to controls, indicating an enhanced sensitivity to threat during pregnancy. Nevertheless, this selective attention had only weak links to distress symptoms contrary to

what was hypothesized, i.e. significant associations between selective attention to threat and distress. It may be that the Facial Stroop Task did not have sufficient sensitivity to detect such associations.

Future studies should expand these findings in other pregnant populations and consider the inclusion of pregnant women that are clinically depressed or anxious as comparison subjects. In addition, the influence of early adversity including abuse and neglect warrants investigation as this may also influence selective attention to threat and distress levels. Further exploration of neural circuitry and associated biology including gonadal hormones underlying distress and cognitive-affective processing in pregnancy is necessary. See Chapter 6 and 7 for more details.

CHAPTER 6

NEURAL CORRELATES OF DISTRESS AND COGNITIVE-AFFECTIVE PROCESSING IN PREGNANCY

Abstract

Background: The aim of this chapter is to assess neural circuitry involved in distress and cognitive-affective processing over the course of pregnancy. In non-pregnant individuals, the prefrontal cortex (PFC), in addition to the amygdala, has been shown to be involved in the regulation of positive and negative emotions. Specifically, the left (L) PFC, right (R) PFC, and medial PFC (MPFC) are activated by attention to threat. Near-Infrared Spectroscopy (NIRS) is an imaging modality that detects real-time upper cortical changes in oxy-haemoglobin in response to neural activation by infrared spectrum light transmitted through diodes placed on the scalp. Its advantages include an absence of harmful radiation making it safe for use in pregnancy. NIRS was used first in the study to, determine the nature of cortical activation patterns in the PFC in response to stimuli perceived to be threatening (i.e. fearful and angry facial expressions) in pregnant women and non-pregnant controls, and second, determine the association between distress, selective attention to threat, and PFC activation.

Methods: Pregnant women (trimester 1, n=10; trimester 2, n=12; trimester 3, n=10) and non-pregnant controls (n=9) completed self-report questionnaires on distress and a Facial Stroop Task. Women subsequently underwent NIRS imaging with a DYNOT system (NIRx Medical Technologies) while viewing computer-based dynamic emotional facial expressions of fear and anger. Near Infrared Analysis, Visualization and Imaging; Statistical Parametric Mapping; MRIcro software; and Statistica were used to investigate oxy-haemoglobin data, and associations between distress, selective attention to threat, and PFC activation.

Results: There was significant activation of the PFC upon exposure to fearful and angry faces compared to a resting phase in both pregnant and control groups ($p < 0.001$). Within pregnancy, the activation was most pronounced at trimester 2, compared to the other

trimesters. In pregnant women only, distress and selective attention to fearful and angry faces, were significantly associated with PFC activation.

Conclusion: These findings here are the first to show that structures involved in emotional processing (e.g. the PFC) also play a role in the regulation of affect in pregnancy. The increased activation of the PFC during pregnancy in response to threat, and the association of such activation with distress at this time are new findings. It is possible that they point to alterations in underlying psychobiology, which in turn mediates emotional symptoms in pregnancy.

6.1 Background

The aim of this chapter is to assess neural circuitry involved in distress and cognitive-affective processing over the course of pregnancy. In Chapter 4 of this study distress (e.g. anxiety), and its psychosocial correlates (e.g. temperament and character) were assessed over the course of pregnancy; and in Chapter 5 cognitive-affective processes associated with distress were described. Indeed, it is well-known that increased distressing psychological symptoms and changes in cognition are common occurrences in pregnancy. The neural circuitry which underpins increased distress and cognitive-affective changes in pregnancy is however not clear. This chapter will focus on investigating this neural circuitry.

It is well-known from imaging studies of non-pregnant individuals that the prefrontal cortex (PFC), amygdala and hippocampus are intrinsically involved in cognitive-affective processing (Richardson et al., 2004; Erickson et al., 2003; Erk et al., 2003). In particular, much work has suggested that the PFC plays a key role in modulating subcortical areas in order to manage distressing psychological symptoms such as anxiety, and in order to optimize emotional regulation (Phillips et al., 2003a). High distress is associated with increased activation in the PFC, e.g. the right (R) PFC and medial (M) PFC (Morinaga et al., 2007; Ellenbogen et al., 2006) and impaired executive function (Dennis & Chen, 2007; Sarter et al., 2006; Bremner, 2004). The MPFC may for instance contribute to emotional regulation by its projections to the

amygdala and hippocampus, to terminate fear responses (Bremner, 2004). Selective attention function as assessed by the Stroop task is also principally mediated by the PFC. However, few studies have explored neural circuitry of distress and selective attention to threat in pregnancy.

Near-Infrared Spectroscopy (NIRS) provides a safe way to assess neural circuitry that is involved in distress and cognitive-affective processes in pregnancy. The aim of this investigation is to use NIRS first, to determine the nature of cortical activation patterns in the PFC, in response to facial emotional stimuli in pregnant women and non-pregnant controls; and second, to assess the association between distress, selective attention to threat, and PFC activation.

6.2 Methods

6.2.1 Participants

Pregnant women were randomly recruited from an existing cohort of women taking part in a larger prospective study of maternal stress in pregnancy. Non-pregnant controls, matched for age and education were also recruited from the same population group. See section 3.1 of Chapter 3 for recruitment details.

6.2.2 Procedures

As previously described, sociodemographic factors and measures of distress (K-10, STAI) were recorded, and a behavioural emotion task (FST) completed. Subsequently, during NIRS imaging with a DYNOT system, participants viewed dynamic emotional facial expressions (ERT). See section 3.2 in Chapter 3 for a comprehensive description of these procedures.

6.2.3 Image Processing and Analyses

Near Infrared Analysis, Visualization and Imaging (NAVI version 2.1; NIRx Medical Technologies, 2008), Statistical Parametric Mapping (SPM version 5, 2005) and MRIcro (version 1.4) software were used to investigate oxy-haemoglobin (oxy-Hb) data. Data was filtered using a band pass filter with low and high pass cut-off frequencies of 0.01 Hz and 0.1 Hz and normalized to "co-located/SD channel" using NAVI. Images were reconstructed and exported to 'Analyze' format, whereafter SPM was used to create contrast images to enable the application of 2nd/ group level ANOVAs and t-tests.

Firstly, main effects of PFC activation in response to fearful and angry facial expressions compared to a resting phase, and secondly differences in the activation of the PFC between pregnant women and controls, were investigated using ANOVAs and t-tests. General distress (K-10); and state and trait anxiety scores (STAI) were entered as covariates in separate one- and two-way factorial ANOVAs to determine the main effects of these factors on PFC activation. Reaction times (attentional responses to fearful and angry faces compared to neutral faces) were also entered as covariates in a separate model to determine whether individual selective attention contributed to the activation. The emotions were presented as *masked* (i.e. outside conscious awareness) and *unmasked* (available to conscious awareness) stimuli (see section 3.2.2.2 in Chapter 3 for a detailed description). Multiple comparisons were made with t-tests done at every voxel and p-values of < 0.05 were deemed significant. Multiple comparisons were error-corrected on cluster level using SPM.

To investigate lateralization effects, left and right clusters in a 5-7 mm radius surrounding the most significantly activated voxels were extracted at the individual level. The first level ß estimates were extracted for each cluster for fear and anger, respectively, compared to rest, and differences in group means (left vs right-sided estimates of pregnant women and controls, separately) were examined by means of t-tests using Statistica (version 8, Statsoft

Inc.). Using MRIcro, the statistical maps were overlaid on the anatomical MRI that was used as the basis for optical image reconstruction. Regions of interest included the RPFC, LPFC and MPFC.

Age, education and distress scores of pregnant women and controls were compared separately in Statistica using one-way ANOVA and two-tailed t-tests for independent groups.

6.3 Results

6.3.1 Participants

Table 1 Demographic information of participants

	Pregnant women (n=18)		Controls (n=9)	
	Mean (SD)	Range	Mean (SD)	Range
Age (years)	24.8 (5.6)	18-36	25.3 (5.7)	18-38
Education (years)	11.5 (1.2)	10-14	11.8 (0.8)	10-13

n, sample size; SD, standard deviation

Pregnant women (trimester 1, n=10; trimester 2, n=12; trimester 3, n=10) and non-pregnant controls (n=9) were included in the study. Of the pregnant women, all were Coloured (of mixed race), whereas 8 controls were Coloured and 1 was Black. Age and educational level did not differ significantly between the pregnant women and controls. See Table 1 for demographic information.

6.3.2 Distress and anxiety

On comparison of distress scores between pregnant women and controls, there were no significant differences in K-10, state and trait anxiety (STAI) scores at any time point. Within pregnancy, there was significantly higher state anxiety at trimester 2 compared to trimester 1 [$t = -2.41$, $p < 0.05$]. There were no significant differences in K-10 and trait anxiety (STAI) scores across trimesters.

6.3.3 PFC Activation to Threat

6.3.3.1 Fearful Faces

There was a significant main effect of activation in response to fearful faces across the PFC compared to rest ($p < 0.001$) in pregnant women (Figure 1) and controls. The finding showed that within pregnancy, the activation to fearful faces was significantly greater at trimester 2 compared to trimester 3 ($t = 1.69$, $p < 0.05$), but not trimester 1.

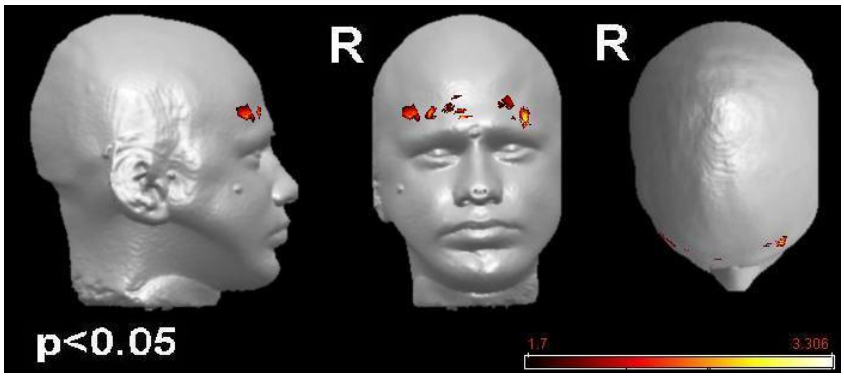

Figure 1 Increased activation in the PFC in response to fearful faces in pregnant women

On comparison of PFC activation in pregnant women at each trimester with controls, there were no significant differences in activation at any time point. However, there was a trend for greater PFC activation in the second trimester of pregnancy compared to controls ($p > 0.05$) in response to fearful faces.

6.3.3.2 Angry Faces

There was a significant main effect of activation to angry faces across the PFC compared to rest ($p < 0.001$) in pregnant women (Figure 2) and controls. The finding showed firstly that within pregnancy, the activation was significantly greater at trimester 2, and secondly on comparing findings at each trimester with those in non-pregnant controls; that activation was significantly less at trimester 1 than in controls.

Within pregnancy, the activation to angry faces was significantly greater at trimester 2 compared to trimester 1 ($t = 1.69$, $p < 0.05$), but not trimester 3.

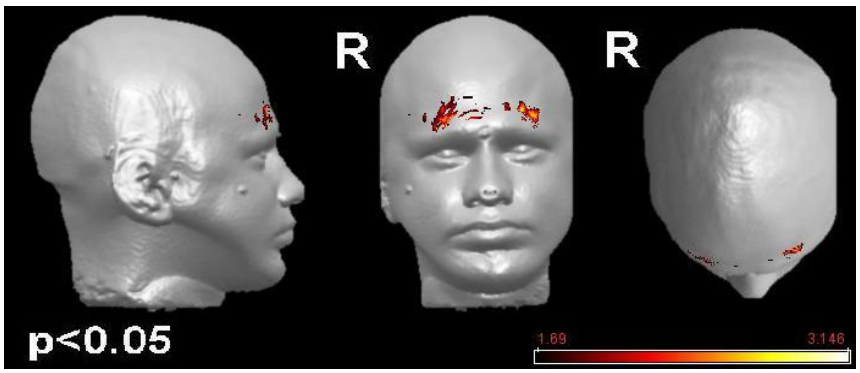

Figure 2 Increased activation in the PFC in response to angry faces in pregnant women

On comparison of PFC activation in pregnant women at each trimester with controls, there were significant differences at trimester 1 ($p < 0.001$) with significantly less activation in the LPFC at trimester 1 compared to controls (Figure 3). PFC activation was not significantly different at trimester 2 and 3 compared to controls.

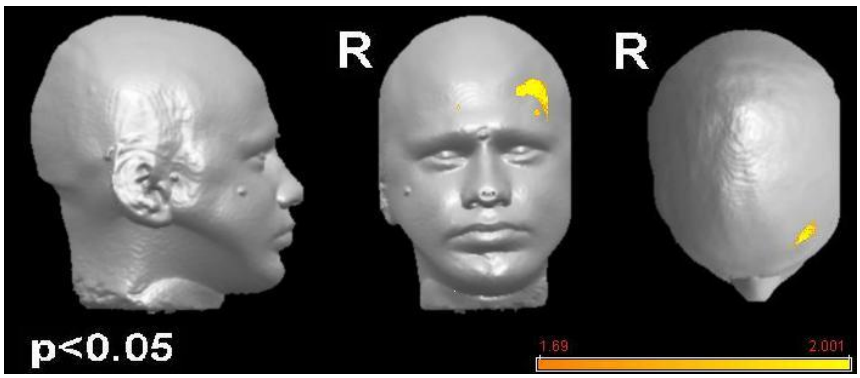

Figure 3 Decreased activation in the LPFC in response to angry faces in pregnant women at trimester 1 compared to non-pregnant controls

6.3.4 Lateralization Effects in the PFC

Overall, there were no significant lateralization effects for either the RPFC or LPFC in response to fearful and angry faces in pregnant women or controls.

6.3.5 Relationship between Distress and PFC Activation

General distress (K-10) was significantly associated with increased LPFC ($p < 0.001$) and decreased MPFC activation ($p < 0.001$) compared to rest, on the processing of fearful faces over the course of pregnancy, but not angry faces (as assessed by the ERT during NIRS imaging).

There was also a significant main effect of state anxiety ($p < 0.001$) and trait anxiety ($p < 0.001$) (STAI) over the course of pregnancy on the processing of fearful faces. State anxiety was significantly associated with increased activation (compared to rest) in the RPFC and LPFC to fearful faces. Trait anxiety was significantly associated with increased activation (compared to rest) in the dorsolateral LPFC, and decreased activation extending from the ventral parts of the LPFC into the MPFC and RPFC to fearful faces.

There was a significant main effect of trait anxiety ($p < 0.001$) (STAI), but not state anxiety or general distress (K-10), over the course of pregnancy on the processing of angry faces, compared to rest. Trait anxiety was significantly associated with greater activation in the LPFC to angry faces, compared to rest.

There were no significant associations between distress scores and PFC activation to threat when distress scores (K-10, STAI, PSS) of controls were included in the analyses.

6.3.6 Relationship between Selective Attention to Threat and PFC Activation

Reaction times, i.e. selective attention to masked fearful faces (as assessed by the FST), were significantly negatively associated with PFC processing of fearful faces over the course of pregnancy ($p < 0.001$) (ERT). When more attention was paid to fearful faces, activation was significantly decreased in the RPFC, LPFC and MPFC, compared to rest.

There was also a significant main effect of reaction times to masked angry faces, on PFC processing of angry faces over the course of pregnancy ($p < 0.001$). When more attention was paid to angry faces, activation was significantly increased in the LPFC, and significantly decreased in the RPFC, compared to rest.

There were no significant associations between reaction times in response to unmasked fearful and angry faces, and PFC activation in pregnant women. There were also no significant effects when selective attention data of controls were included in the analyses.

6.4 Discussion

The aim of this chapter was to assess neural circuitry involved in distress and cognitive-affective processing over the course of pregnancy. This chapter demonstrated significant activation across the PFC, in response to fearful and angry faces in both pregnant women and controls. On comparison of PFC activation in pregnant women at each trimester with controls, there was also a significant difference by group including less LPFC activation to angry faces at trimester 1. Only within pregnancy, general distress (K-10), state and trait anxiety (STAI); and selective attention to masked fearful and angry faces (i.e. faces presented outside conscious awareness), were significantly associated with PFC activation. These findings are indicative of altered prefrontal cortex function in pregnancy.

The involvement of the PFC in regulating emotion in pregnancy and controls using NIRS is consistent with data obtained from previous functional imaging studies in non-pregnant populations. This include work on activation of the RPFC (Marumo et al., 2009; Williams et al., 2006; Kilts et al., 2003; Van Honk et al., 2002), LPFC (Van Honk et al., 2002; Phillips et al., 1997), and the MPFC (Morinaga et al., 2007; Williams et al., 2006) in response to fearful and angry faces. Lateralization effects, i.e. dominance of the R- or LPFC in processing emotional stimuli, were not significant. Although a range of data, suggest lateralization of affective processing, the data here are consistent with previous NIRS studies (Leon-Carrion

et al., 2007; Yang et al., 2007; Herrmann et al., 2003). Notable is that findings on lateralization are generally inconsistent. Lateralization effects may differ depending on gender (e.g. Marumo et al., 2009) and task characteristics e.g. active recognition vs passive viewing requirements of faces or pictures; which may involve processing from either side of the PFC to differential degrees (Van Honk & Schutter, 2006; Herrmann et al., 2003; Kilts et al., 2003). This chapter is important in showing that findings on affective processing extend to pregnancy.

PFC activation in response to threat stimuli is associated with high distress, including anxiety, in non-pregnant populations (Ellenbogen et al., 2006). We found significant associations between PFC activation in response to fearful faces and general distress (K-10), state and trait anxiety (STAI) only in pregnant women at all trimesters. In addition, there was a significant association in pregnant women at all trimesters between PFC activation in response to angry faces and trait anxiety (STAI), but not in controls. The association between distress and PFC activation in response to threat suggests that the neural circuitry that is involved in cognitive-affective processing is also associated with distress in pregnancy. Certain changes in the PFC may be compensatory as an attempt to control distress symptoms; it may be that the PFC had to exert greater executive control to regulate emotion when distress was high in pregnancy.

LPFC activation in response to angry faces was significantly less in pregnant women at trimester 1, compared to controls. Within pregnancy, PFC activation to angry faces was significantly greater at trimester 2, compared to trimester 1 of pregnancy. Although it is not clear why activation in the LPFC was significantly decreased in pregnant women at this stage of pregnancy, it may be a reflection of the differences in the emotions experienced during the two trimesters. Arguably, strong positive emotions such as excitement, elation and expectancy, which may be associated with the initial stages of pregnancy, could have blunted sensitivity to threat at trimester 1 compared to trimester 2 of pregnancy. Alternatively, trimester 2 is a time of elevated responsivity to external threats, and this may be associated

with increased sub-cortical processing, with decreased activation of the LPFC in response to threat.

Furthermore, previous work suggests that the LPFC dominates in the encoding of emotions (Haxby et al., 1996), and the regulation of potentially aggressive interactions that may be signalled by angry faces (Van Honk et al., 2002). Conception is also followed by physiological changes including increased and fluctuating gonadal hormone levels (e.g. increasing progesterone levels; see Chapter 7 on the association between progesterone and PFC activation in response to angry faces). It may be that there was altered regulation of potentially threatening stimuli, which was associated with neurobiological changes at different stages of pregnancy. However, it is unlikely that protective mechanisms against potential threat were reduced at a critical stage of development, i.e. early pregnancy, and the finding may therefore be a false positive.

Increased attention to masked fearful and angry faces was also significantly associated with decreased PFC activation only in pregnancy. Decreased PFC activation is consistent with previous work (Bishop, 2009, 2008) indicating that in anxious individuals there is suboptimal PFC processing during attention tasks. PFC processing here of fearful and angry faces was significantly associated with distress and anxiety. There was also an association between increased PFC activation and increased selective attention to masked angry faces, which may reflect differentially altered responses to angry versus fearful facial expressions. Presumably, the PFC is less able to terminate threat responses under anxiety. The behavioural responses to threat may therefore be associated with emotional vulnerability to psychological distress (MacLeod & Hagan, 1992). Speculatively, psychobiological changes in pregnancy may lead to increased sensitivity to threat stimuli, with associated increases in distressing psychological symptoms and a reduced ability of the PFC to regulate disrupted emotions. This may explain why women have an increased vulnerability to develop depression and anxiety problems in pregnancy especially in women with a history of such problems.

Other factors including blood flow may also have altered PFC regulation of fear and anger in pregnancy. During pregnancy, there is a steady increase in blood volume until term (Ueland, 1976), that may have been associated with increased cerebral blood flow per se. Neural activation as assessed by NIRS reflects changes in the haemodynamic response, i.e. increased oxy-Hb is associated with increased neural activation. Thus, changes in the haemodynamic response due to pregnancy may also have contributed to the observed activation effects. Whether these responses to threat were different however in comparison with the haemodynamic response to neutral expressions remains to be investigated. As described in Chapter 3 (section 3.2.3.3), a morphing paradigm was used in the Emotion Recognition Task during imaging, where 41 intermediary frames were rapidly transformed from a neutral expression into an emotional expression in 2 seconds time. This paradigm probably did not leave validly analysable neutral segments. The paradigm would better be investigated by a different task format that incorporates separate blocks that also present neutral facial expressions, and/or happy expressions due to its non-specific neural activation (Posamentier & Abdi, 2003).

Finally, hormones most likely contributed to changes in neural circuitry. Previous studies have e.g. suggested that cortisol and testosterone (Van Honk et al., 2000), and neurotransmitters including serotonin (as suggested by Sugiura et al., 2000) play a role in emotional regulation (see Chapter 7 for more details on hormones).

This chapter had a number of limitations. The sample was small which may have reduced the power of the results. Habituation of responses to stimuli may also have occurred as a blocked design with repetitive viewing of the same emotional facial expressions was used. Yet, findings regarding habituation effects are inconsistent; the neural signal upon repetitive viewing of stimuli is not always reduced over time. Habituation effects may, for example, be lessened by having similar stimuli presented randomly between blocks (Posamentier & Abdi, 2003), as was the case here.

In conclusion, this chapter has found that during trimester 2 of pregnancy there is significantly increased activation of the PFC in response to threat compared both to other trimesters and to controls. Such activation was significantly associated with certain measures of distress (e.g. general distress, state and trait anxiety) and with cognitive-affective processing (e.g. selective attention to threat). These findings here are the first to show that structures involved in emotional processing (e.g. the PFC) also play a role in the regulation of affect in pregnancy. The increased activation of the PFC during pregnancy in response to threat, and the association of such activation with distress at this time are new findings. It is possible that they point to alterations in underlying psychobiology, which in turn mediates emotional symptoms in pregnancy.

Future studies should investigate the psychobiology of cognitive-emotion processing in clinically depressed and anxious pregnant samples. Such work should include rigorous assessments of the underlying circuitry (e.g. using larger samples), but also more detailed exploration of psychological factors such as harm avoidance (given that the degree to which one is bold or careful to do things, has been significantly negatively associated with cerebral blood flow in frontal, parietal and temporal cortices; structures that are involved in the regulation of anger (Posamentier & Abdi, 2003)).

CHAPTER 7

HORMONES INVOLVED IN DISTRESS, COGNITIVE-AFFECTIVE PROCESSING, AND NEURAL CIRCUITRY IN PREGNANCY

Abstract

Background: The aim of this chapter is to assess hormonal mechanisms associated with distress, cognitive-affective processes, and neural circuitry over the course of pregnancy. Although glucocorticoid hormonal (e.g. cortisol) and gonadal hormonal (e.g. estrogen, progesterone, testosterone) changes have been associated with both distress and related cognitive-affective processes (such as memory, and attention to threat), there is little work on these associations in pregnancy.

Methods: Pregnant women (n=49) with low risk singleton pregnancies from Midwife Obstetric Units in the Tygerberg region of the Western Cape were included in the study. Women completed self-report questionnaires to assess distress symptoms, underwent attention and memory testing, completed a Facial Stroop Task to assess attention to threat, and underwent Near-infrared Spectroscopy (NIRS) imaging while viewing computer-based dynamic emotional facial expressions of fear and anger to investigate relevant neural circuitry. Blood and saliva samples were collected to assess cortisol, progesterone, estrogen, and testosterone levels. Associations between these hormones and distress, ratings of attention and memory function, selective attention to threat, and prefrontal cortex (PFC) activation, were determined.

Results: There were occasional significant associations between estrogen and testosterone, and some measures of distress symptoms and the subjective experience of cognitive ability over the course of pregnancy. Cortisol was significantly associated with selective attention to unmasked fearful faces (presented within conscious awareness); and testosterone was significantly associated with selective attention to unmasked angry faces. Cortisol and testosterone were significantly associated with PFC activation in response to

fearful faces in all trimesters, whereas only progesterone was significantly associated with PFC activation in response to angry faces in all trimesters.

Conclusion: The lack of associations between hormones, distress and attention and memory, is perhaps not surprising given that peripheral (hormonal) measures do not directly reflect central processes. Given our previous finding in Chapter 5 that pregnant women have increased attention to fearful faces compared to controls, it can be speculated that different hormonal profiles in pregnancy and non-pregnancy (with cortisol lower in pregnancy) are associated with these differences. Associations between increased glucocorticoid and gonadal hormones, and PFC activation in response to threatening faces during pregnancy are consistent with those seen in non-pregnant women.

7.1 Background

The aim of this chapter is to assess hormonal associated with distress, cognitive-affective processes, and neural circuitry, over the course of pregnancy. Chapters 4 to 6 have investigated changes in distress and cognitive-affective processing over the course of pregnancy, and associated neural circuitry. In this chapter, associations between hormones operating in these neural pathways, and distress, cognitive-affective processing and neural circuitry will be investigated.

The release of glucocorticoid and gonadal hormones is controlled by the hypothalamic-pituitary-adrenal (HPA) axis and neural structures involved in the reproductive system (e.g. also the hypothalamus). Since cortisol and gonadal hormones are suggested to be involved in emotional regulation (De Mello et al., 2003) and cognitive function (although inconsistently so) (Macbeth & Luine, 2010; Smith et al., 2006b) it is possible that these hormones exert specific effects on the prefrontal cortex (PFC) in regulating emotion and cognition. These associations have not however been well-studied in pregnancy.

As mentioned previously (section 2.4 of Chapter 2) the HPA axis has an important role in cognitive-affective processing, in depression and anxiety. Simplistically, hyper-secretion of cortisol may be associated with depressive symptoms (Aan het Rot et al., 2009), whereas hypo-secretion of cortisol may be associated with anxiety symptoms (Strohle & Holsboer, 2003; Boyer et al., 2000). Hypo-secretion of cortisol suggests that the HPA axis response is blunted in distress. It may therefore also be important to consider that the HPA axis has been found to be blunted in pregnancy in response to distress, in comparison with the non-pregnant state (Brunton et al., 2008; De Weerth & Buitelaar, 2005).

The HPA axis also seems to have an important role in emotional regulation (e.g. selective attention to threat). Higher cortisol has been associated with withdrawal of attention from negative stimuli in individuals with anxiety disorders and normal controls (not in major depression) (Ellenbogen et al., 2006; 2002), but also increased selective attention to threat under stress-induced conditions in non-pregnant women (Van Honk et al., 2000). However, in pregnancy, the neurobiology of selective attention processes is unknown (De Groot et al., 2003a).

Although much research has been done to investigate the association between gonadal hormones and cognitive function including attention in pregnancy, findings remain inconclusive. A recent systematic review has found inconsistent associations between estrogen and progesterone, and subjective and objectively assessed cognition in pregnancy (Macbeth & Luine, 2010). Testosterone may have specific effects on selective attention processing under normal and stress-induced conditions. For instance, an association between higher testosterone and increased attention to angry facial expressions has been demonstrated in normal populations, and the opposite effect under stress-induced conditions (Van Honk et al. 2005, 1999). In pregnancy, these effects may present differently due to the great fluctuations in gonadal hormones in pregnancy.

The aim of this chapter is to assess changes in hormone levels that may be associated with distress, cognitive-affective processes, and neural circuitry, over the course of pregnancy. There has been little prior work on the association between hormones and neural circuitry involved in these phenomena (distress and cognitive-affective processing) in pregnancy.

7.2 Methods

7.2.1 Participants

Pregnant women were randomly recruited from an existing cohort of women taking part in a larger prospective study of maternal stress in pregnancy. See section 3.1 of Chapter 3 for recruitment details.

7.2.2 Procedures

Participants were required to provide information on sociodemographic factors including income and employment, and complete measures on cognition (subjectively experienced attention and memory) and distress (K-10, STAI, PSS), a behavioural emotion task (FST), and imaging session with Near-Infrared Spectroscopy (NIRS) while viewing dynamic emotional faces (ERT). Bloods and saliva samples were collected to determine levels of cortisol; estrogen, progesterone and testosterone at each trimester. Hormone levels of controls were not assessed and findings therefore only relate to pregnant women. See section 3.2 in Chapter 3 for a comprehensive description of procedures.

7.2.3 Statistical Analyses

The relationship of cortisol; estrogen, progesterone, and testosterone; with distress and selective attention to threat were investigated using Spearman's correlational analyses in Statistica. Interactions among the hormones were also investigated using Spearman

correlational analyses. The association between hormones and subjective cognitive impairment was investigated using one-way analyses of variance (ANOVA). Hormonal data were furthermore entered as covariates in one-way factorial ANOVAs to determine the main effects of these hormones on PFC activation using Statistical Parametric Mapping.

7.3 Results

7.3.1 Participants

Data of pregnant women at each trimester (trimester 1, n = 21; trimester 2, n = 49; trimester 3, n = 41) were included in the analyses. Only a subset of women completed the imaging session (trimester 1, n = 10; trimester 2, n = 12; trimester 3, n = 10). See Table 1 for levels of cortisol and gonadal hormones, over the course of pregnancy.

Table 1 Levels of cortisol and gonadal hormones over the course of pregnancy

	Trimester 1	Trimester 2	Trimester 3	Non-pregnant
	Mean (SD)	Mean (SD)	Mean (SD)	Range
Cortisol (µg/dL)	0.3 (0.1)	0.5 (0.3)	0.5 (0.2)	0.2 - 1.0*
Estrogen (pmol/L)	33829.6 (49981.2)	49107.4 (45165.1)	87093.0 (70532.0)	-
Progesterone (nmol/L)	124.3 (45.4)	182.3 (70.3)	368.0 (146.8)	-
Testosterone (pmol/L)	14.0 (19.1)	17.9 (31.8)	9.7 (13.1)	3.5 - 39.0**

SD, standard deviation; µg/dL, micrograms per deciliter; pmol/L, picomoles per liter; nmol/L, nanomoles per liter

*Cortisol saliva range 0-3 hours after awakening; Westermann et al., 2004. **AxSYM.

7.3.2 Relationship between Cortisol, Gonadal Hormones and Distress

There was a significant positive correlation between estrogen and perceived stress (PSS) at trimester 2 of pregnancy ($r = 0.34$, $p < 0.05$). There were no significant correlations between cortisol, progesterone, testosterone; and distress.

7.3.3 Relationship between Cortisol, Gonadal Hormones and Cognitive Function

Gonadal hormone levels, but not cortisol, were significantly associated with ratings of impaired subjective attention. Estrogen was significantly positively associated with self-reports of memory ability at trimester 3 [$F(1, 30) = 4.73$, $p = 0.038$]. In addition, there was a significant negative association between testosterone and self-reports of attention ability at trimester 1 [$F(1, 10) = 5.72$, $p = 0.038$]. There was also a similar non-significant relationship at trimester 3 between testosterone and attention [$F(1, 25) = 3.56$, $p = 0.071$].

7.3.4 Relationship between Cortisol, Gonadal Hormones and Selective Attention to Threat

There was a significant negative correlation between cortisol and unmasked fearful faces at trimester 3 ($r = -0.36$, $p < 0.05$) (Table 2, Figure 1). The lower the cortisol levels, the more attention was paid to fearful faces. Testosterone demonstrated a significant positive correlation with selective attention to unmasked angry faces at trimester 2 ($r = 0.30$, $p < 0.05$) (Table 2, Figure 2). The higher the testosterone levels, the more attention was paid to angry faces.

There were no significant correlations between estrogen, progesterone, and selective attention to emotions in pregnancy.

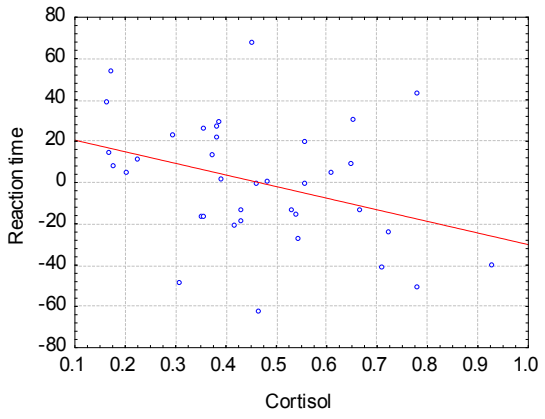

Figure 1 Relationship between cortisol levels and selective attention to unmasked fearful faces in pregnant women at trimester 3

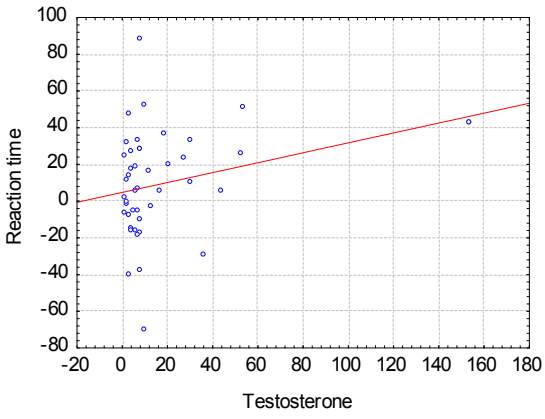

Figure 2 Relationship between testosterone levels and selective attention to unmasked angry faces in pregnant women at trimester 2

Table 2 Associations between hormones and selective attention to threat in pregnant women

	Trimester 1				Trimester 2				Trimester 3			
	r				r				r			
Selective attention to emotions (reaction time - ms)	Estrog	Prog	Test	Cort	Estrog	Prog	Test	Cort	Estrog	Prog	Test	Cort
Angry masked	-0.37	0.36	0.08	-0.13	0.03	-0.16	-0.16	-0.20	0.03	0.06	0.32	-0.03
Angry unmasked	0.18	0.01	-0.13	-0.23	-0.12	0.03	0.30*	-0.04	-0.05	-0.15	-0.33	-0.16
Happy masked	0.23	0.12	-0.08	-0.11	-0.15	0.02	0.12	0.04	-0.24	-0.15	0.08	-0.18
Happy unmasked	-0.07	-0.11	0.42	0.29	-0.15	0.09	0.07	0.02	-0.14	-0.01	-0.11	0.22
Fear masked	-0.09	-0.42	0.27	-0.30	-0.20	0.19	0.09	-0.05	0.13	0.00	0.15	0.07
Fear unmasked	-0.27	-0.17	-0.04	0.21	0.18	0.26	0.11	0.08	-0.13	-0.03	0.08	-0.36*

r, correlation; estrog, estrogen; prog, progesterone; test, testosterone; cort, cortisol; ms, milliseconds

*$p < 0.05$

**$p < 0.01$

7.3.5 Relationship between Cortisol, Gonadal Hormones and PFC Activation

There were significant effects of cortisol and testosterone on PFC activation in response to fearful faces, compared to rest. There were no significant differences between trimesters, when time was included as a factor. Cortisol was significantly associated with greater activation in the RPFC, in response to fearful faces ($p < 0.01$). Testosterone was significantly associated with greater activation in the RPFC and LPFC, in response to fearful faces ($p < 0.001$). There were no significant associations of estrogen and progesterone with PFC activation in response to fearful faces.

There was also a significant main effect of progesterone only ($p < 0.001$) on PFC activation, in response to angry faces in pregnancy, compared to rest. Although PFC activation was significant across trimesters, there were no significant differences between trimesters, when time was included as a factor. Progesterone was significantly associated with greater activation in the LPFC and MPFC, in response to angry faces.

7.4 Discussion

The aim of this chapter was to assess hormonal mechanisms associated with distress, cognitive-affective processes, and neural circuitry over the course of pregnancy. The main findings included an occasional correlation with distress, including a significant association between estrogen levels and perceived stress (PSS) at trimester 2 of pregnancy. There were also occasional correlations with cognition, including significant associations between estrogen (trimester 3) and testosterone (trimester 1) and the subjective experience of cognitive function. Similarly, there were only occasional correlations with attention to threat, including significant associations between cortisol and selective attention to unmasked fearful faces, i.e. faces presented within conscious awareness, at trimester 3; and of testosterone, with selective attention to unmasked anger at trimester 2. There were significant associations between PFC activation in response to threat and hormones. Cortisol

and testosterone were significantly associated with PFC processing of fearful faces, whereas progesterone was significantly associated with PFC processing of angry faces, in pregnancy.

Higher estrogen was significantly associated with higher perceived stress (PSS) in women at trimester 2 of pregnancy. In addition, although there were significant associations between K-10 and STAI scores representing feelings of depressive and anxiety symptoms, and PSS scores (see section 4.4.3 of Chapter 4), they were not associated with estrogen. The lack of consistent findings in pregnancy is in keeping with previous inconsistent findings regarding the association of hormones and distress symptoms in both non-pregnant and pregnant women.

Similarly, there were inconsistent findings regarding the association of hormones and attention and memory. Estrogen was significantly associated with positive reports of memory ability at trimester 3. The higher the estrogen levels, the more often women rated their memory as normal. Evidence is inconsistent regarding the association between estrogen and objective cognitive function in pregnancy (see Brett & Baxendale (2001) for a review) and in general (Alexander et al., 2007), with evidence lacking on the association between estrogen and subjective cognitive function. This finding therefore underscores the non-specific effects of estrogen also on subjective memory ability.

In turn, higher testosterone was significantly associated with reports of impaired subjective attention at trimester 1. Higher testosterone has been associated with depressive and anxiety symptoms in pregnancy (Buckwalter et al., 2001), but not cognition. Evidence on the association between testosterone and cognitive function in pregnancy is lacking and inconclusive (see Buckwalter et al., 1999 for a review). This finding may therefore have been a false positive.

Lower cortisol was significantly associated with increased attention to unmasked fearful faces at trimester 3 of pregnancy. This finding differs from that in non-pregnant women;

previous studies have demonstrated an association between higher cortisol and increased selective attention to threat, i.e. stimuli that elicits distressing psychological symptoms such as anxiety (Ellenbogen et al., 2006, 2002; Van Honk et al., 2000). Given our previous finding in Chapter 5 (section 5.4.2.3) that pregnant women have increased attention to fearful faces compared to controls, it can be speculated that different hormonal profiles in pregnancy and non-pregnancy (with cortisol lower in pregnancy) is associated with these differences.

There is evidence that suggests that the response of the HPA axis to distress is blunted in pregnancy in comparison with non-pregnancy (Brunton et al., 2008; De Weerth & Buitelaar, 2005), thus may result in lower secretion and/or inhibition of cortisol. Normally, there is an increase in cortisol levels throughout pregnancy (Heron et al., 2004) and further increases in response to distress (Obel et al., 2005; Kirschbaum & Hellhamer, 1994). In this pregnant sample, cortisol only increased up to trimester 2 of pregnancy (Table 1). Low levels of cortisol have been associated with generally slower attentional processes (Inaba & Ohira, 2003; Fontani et al., 2004). Lower cortisol levels may thus have been reflected as slower reaction times i.e. increased attention to fearful faces in pregnant women compared to non-pregnant controls.

Furthermore, higher testosterone was significantly associated with increased attention to unmasked angry faces at trimester 2 of pregnancy. A similar association has been demonstrated between higher testosterone and selective attention to angry faces in a non-pregnant population (Van Honk et al., 1999). These findings may therefore extend to pregnancy (see Table 2, Chapter 5 for comparative findings in this sample), suggesting a probable adaptive mechanism in response to potential threat.

The third set of findings is of particular interest; there was a relationship between multiple hormones and PFC activation in response to threatening faces across trimesters. PFC activation has been tentatively associated with increased levels of certain hormones (e.g.

cortisol) in healthy controls (De Mello et al., 2003). The current data are the first to show that similar associations may be found in pregnant women.

Cortisol levels were significantly associated with increased activation of the PFC in response to fearful faces in pregnancy. Previous work has indicated that the PFC plays an important role in regulating the HPA-axis response to distress, including stimuli that signal potential threat (Pruessner et al., 2010). Although there was no association between distress and cortisol, increased cortisol and increased PFC activation may play a causal role in distressing psychological symptoms.

Progesterone levels were significantly associated with increased activation of the PFC, in response to angry faces. Progesterone is suggested to have an important role in facilitating PFC executive function, particularly to perform tasks that require continual attention to stimuli (Solis-Ortiz & Corsi-Cabrera, 2008; Solis-Ortiz et al., 2004) as was the task requirement during NIRS imaging in this study. Progesterone has also been associated with emotional regulation in pregnancy (Buckwalter et al., 1999). This suggests that progesterone plays an important role in PFC-mediated emotional regulation during pregnancy. It is therefore possible that increased progesterone in pregnancy leads to increased PFC activation and increased attention to threatening stimuli.

Testosterone levels were significantly associated with increased activation of the PFC in response to fearful, but not angry faces. Consistent with recent evidence in non-pregnant populations (e.g. Hermans et al., 2006a; Van Honk et al., 2005) testosterone is suggested to have fear-reducing functions within PFC-amygdala neural regulatory systems; whereas testosterone may not have an association with PFC activation, specifically in women in response to angry faces (Stanton et al., 2009). Further research is needed to investigate the causal factors that might underlie the associations documented here.

This chapter had a number of limitations. The sample was small which may explain why no differences were found by trimester in hormonal control of neural circuitry involved in emotional regulation. Associations between glucocorticoid and gonadal hormones, and PFC activation may differ, depending on the specific PFC area that is involved, the tasks used to investigate emotional regulation (see Posamentier & Abdi (2003) for a review), and by gender (e.g. Marumo et al., 2009; Yang et al., 2007). Controls were also not assessed for hormone levels so that cross-comparisons by trimester could not be made with levels in the non-pregnant state.

In sum, distress was not significantly associated with glucocorticoid and gonadal hormone levels in pregnancy. There were significant differences in associations of the hormones and selective attention to threat between pregnant women and non-pregnant controls. Furthermore, our findings show that PFC activation is associated with hormonal changes in pregnancy. It is thus plausible that changes in neural circuitry during pregnancy reflect pregnancy-associated alterations in hormones affecting this circuitry, and that this, in turn, is associated with alterations in cognitive-affective processing.

Future studies should aim to elucidate exact functional and genetic mechanisms by which hormones exert an effect on distress and cognitive-affective processing, in normal and clinically depressed and anxious pregnant populations. This may assist in devising relevant treatment options for depressive and anxiety disorders in pregnancy.

CHAPTER 8

GENERAL DISCUSSION

A great deal of work has been done to investigate distress symptoms and cognitive processing in pregnancy (Alder et al., 2007; Henry & Rendell, 2007; Ross & McLean, 2006; Noble, 2005; Brett & Baxendale, 2001), and the association of pregnancy-related hormonal changes with such symptoms and processes (Macbeth & Luine, 2010; Smith et al., 2006b; De Mello et al., 2003). Yet, findings remain inconclusive. Furthermore, much less is known about the affective processes and associated neural circuitry that presumably mediate increased distressing psychological symptoms and altered cognitive-affective processing in pregnancy. Delineating the factors associated with such symptoms and processes is important, given that some women may be predisposed to develop mood and anxiety disorders when pregnant. The overall objective of this study was to investigate distressing psychological symptoms (e.g. anxiety) and the association of such symptoms with changes in relevant cognitive-affective processes and in neurobiology over the course of pregnancy.

Aim 1 was to assess distress (e.g. anxiety), and its psychosocial correlates (e.g. temperament, character, resilience, social support) over the course of pregnancy. In Chapter 4, it was demonstrated that distress levels, in particular state and trait anxiety levels reported by our local pregnant population, were high in comparison with previous findings in pregnant samples. Notably, scores on the K-10 reliably predicted the presence of current major depression at all trimesters of pregnancy. Furthermore, there were significant associations of distress levels with temperament and character, resilience and social support over the course of pregnancy. Higher trait anxiety was significantly associated with lower resilience, as well as higher harm avoidance, lower self-directedness, and lower social support. These findings support a theoretical model in which distressing psychological symptoms during pregnancy are influenced by a range of psychosocial factors, both psychological and social (Hamilton & Lobel, 2008; Campbell-Sills et al., 2006; Pagel et al., 1990).

Aim 2 was to assess the cognitive-affective processes associated with distress over the course of pregnancy. In Chapter 5, we reported that some pregnant women experienced impaired attention and memory, and that some of these impairments had significant associations with perceived stress. Scores on objective cognitive tasks, on the other hand, were not associated with distress. However, selective attention to masked fearful faces was distinctly greater in pregnant women compared to controls, suggesting an enhanced sensitivity to threat during pregnancy. Nevertheless, contrary to our hypothesis, this selective attention was only weakly associated with distress symptoms. These findings lend only partial support, then, to a theoretical model, which posits that distressing psychological symptoms in pregnancy are associated with altered cognitive-affective processes in general, and increased attention to threat in particular (Hahn-Holbrook et al., in press; Brett & Baxendale, 2001; Buckwalter et al., 1999).

Aim 3 was to assess the neural circuitry involved in distressing symptoms and altered cognitive-affective processing over the course of pregnancy. In Chapter 6, findings included significantly increased activation of the PFC in response to threat, i.e. fearful and angry facial expressions, in pregnant women across trimesters as well as in controls. Within pregnancy, this activation was significantly greater at trimester 2 in response to both fearful and angry faces, compared to other trimesters. Such activation was significantly associated with certain measures of distress (e.g. general distress, state and trait anxiety) and with altered cognitive-affective processing (e.g. increased selective attention to threat). Of note, in some instances, there were significant negative correlations between PFC activation and both distress and selective attention to threat. These findings are consistent with a theoretical model that distress and increased attention to threat are mediated by increased activation of subcortical structures, with decreased frontal control (Bishop, 2009, 2008).

Aim 4 was to assess the hormonal mechanisms associated with distress, cognitive-affective processes, and the neuronal circuitry. In chapter 7, we noted that increased estrogen and

testosterone might be associated with the subjective experience of impaired attention and memory over the course of pregnancy. Furthermore, there was a significant negative correlation between cortisol levels and selective attention to fearful faces. Finally, cortisol and testosterone were significantly associated with PFC activation in response to fearful faces (at all trimesters), while only progesterone was significantly associated with PFC activation in response to angry faces (again at all trimesters). These findings are consistent with a theoretical model which argued that pregnancy-associated hormonal changes lead to changes in neural circuitry, which in turn result in altered cognitive-affective processes (e.g. attention in general is impaired, but attention to threat is increased) (Hahn-Holbrook et al., in press; Henry & Rendell, 2007).

A range of theoretical and empirical work on the psychobiology of pregnancy and of distress (DiPietro et al., 2008; Alder et al., 2007; Ross & McLean, 2006; Noble, 2005; Nonacs & Cohen, 2002), might suggest that changes in pregnancy-related hormones influence neural circuitry during pregnancy, leading in turn to changes in cognitive-affective processing, and ultimately in distressing psychological symptoms. The study here was unable to directly address causal mechanisms. Nevertheless, the finding of altered PFC regulation of threat stimuli during pregnancy, perhaps particularly at trimester 2, is consistent with this hypothesized chain of events. Altered PFC regulation was, in turn, associated with altered levels of cortisol, testosterone and progesterone, again supporting the model put forwards here. It is possible that pregnancy-related hormonal changes lead to specific changes in the PFC, and in turn, to altered processing of fear-relevant stimuli. It is possible that decreased PFC function reflect increased attention to threat (Bishop, 2009, 2008) with suboptimal PFC processing. Alternatively, however, it is possible that certain changes in the PFC are compensatory, with increased PFC activation reflecting a compensatory attempt to control distressing symptoms. The experimental design used here is unable to distinguish between these theoretical alternatives, but lays the way for future work which can attempt to do so (e.g. by means of more detailed functional imaging tasks, given over time).

Pregnancy represents a biological transition that may be associated with physical and psychological vulnerability in some women, a vulnerability that is in turn, associated with altered responsiveness of the neurobiological system to stress (Grant et al., 2008; Dorn and Chrousos, 1997). Evolutionary perspectives suggest that increased anxiety during pregnancy may be adaptive, resulting in greater protection of mothers of themselves and their unborn children (Hahn-Holbrook et al., in press). The findings here add to previous findings on emotional regulation in non-pregnant populations (Solis-Ortiz & Corsi-Cabrera, 2008; Hermans et al., 2006b; Van Honk et al., 2005; Solis-Ortiz et al., 2004), by showing that reproductive hormones such as progesterone and testosterone may be involved in further "fine-tuning" of such emotional regulation, in order to optimize threat recognition in pregnancy. In general, then, the findings in this dissertation are consistent with evolutionary models which view threat recognition and responses as adaptive, particularly within the context of vulnerable times such as pregnancy (Hahn-Holbrook et al., in press; Neuberg et al., in press).

Not all of the empirical data here support the theoretical model put forward. Thus, there were no convincing associations between distress, selective attention to threat, and the investigated hormone levels. Indeed, as emphasized in the introduction of Chapter 2, although much work has been done to investigate distress and cognitive-affective processing in pregnancy, findings have been inconsistent. Methodological differences between studies may be a reason for such past inconsistency. Furthermore, some of these associations may be relatively weak, given the complexity of each of these systems (e.g. many factors influence distress, there are many hormones other than those measured here), and sample sizes both in previous work, and in the current study may be insufficiently high to be able to document such associations. The work here lays a foundation; perhaps, for rigorous power analyses of requires sample sizes to be undertaken in future work.

There are a number of limitations in this study. Only cortical activation can be assessed using NIRS, thus providing an incomplete view of neural structures that may be involved in

emotional regulation. This contributed to our inability to choose between alternative explanations of the role of neural structures (e.g. PFC as the area of primary impairment, or as an area of compensatory function). The sample of non-pregnant controls was relatively small, and they were only assessed on one occasion. As above, larger samples may be necessary in order to document relatively weak associations in a complex system.

Nevertheless, the findings from this study make an important contribution to the area of women's mental health, shedding some light on distress and its psychobiology in pregnancy. In particular, the dissertation provides new data on distressing psychological symptoms in pregnancy, and on the associations between such symptoms and altered cognitive-affective processes, changes in neural circuitry, and changes in hormone levels. The causal mechanisms underlying emotion regulation and distress in pregnancy nevertheless require much further exploration. Ultimately, a better understanding of psychological distress and its psychobiology in pregnancy may assist in the care of pregnant women and benefit maternal mental health.

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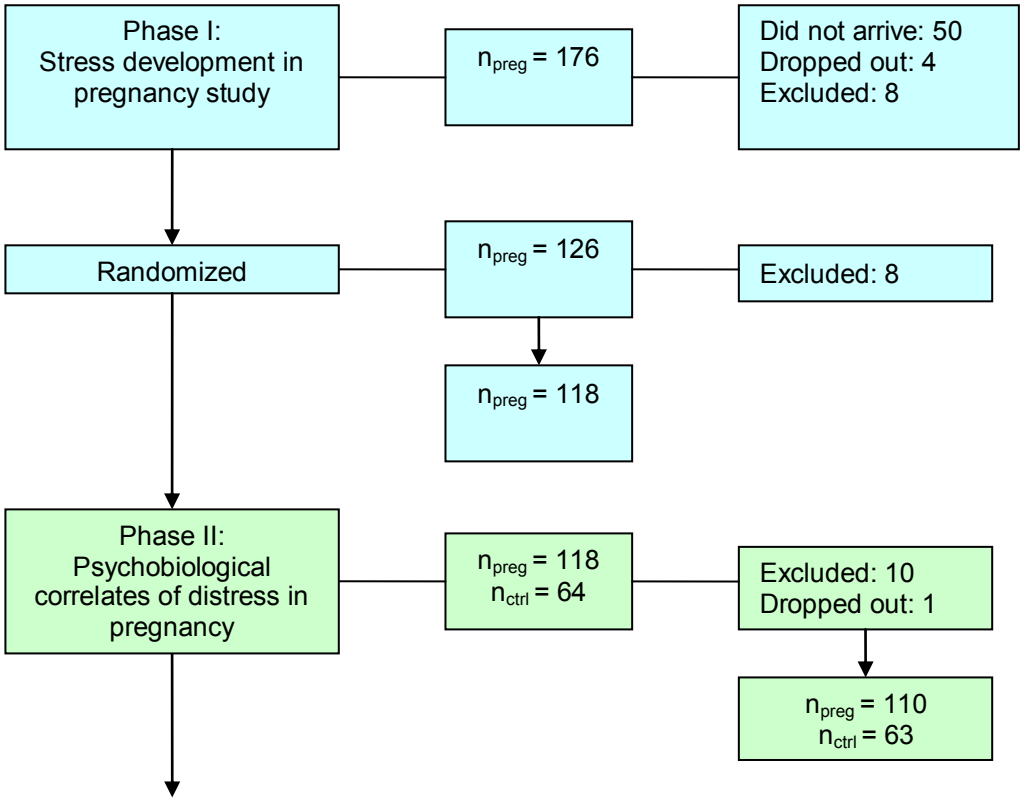
ADDENDUM A

SUPPLEMENTARY TABLES AND FIGURES

Figure 1 Number of participants recruited and assessed at each time point

Table 1 Objective cognitive performance of pregnant women and non-pregnant controls

Figure 1 Number of participants recruited and assessed at each time point



Sample size	T1	T2	T3	Ctrl
Distress	49	110	104	63
Cognitive and affective measures	24	53	51	10
Imaging	10	12	10	9
Hormones	21	49	41	-

During Phase I, women were excluded due to intra-uterine death, twin pregnancy, uterine systs, ectopic pregnancy, being too far pregnant (incorrect sonar estimation) and miscarriage. Women dropped out during Phase I due to work, family matters, having moved, and not wanting to continue with the study. During Phase II, women were excluded due to age (<18 years of age), current methamphetamine use and erroneous data. Women dropped out from Phase II due to not wanting to continue with the study. Although 110 pregnant women were recruited during Phase II, sample sizes were reduced in statistical analyses, due to incomplete data.
n, sample size; preg, pregnant; ctrl, control; T1, trimester 1; T2, trimester 2; T3, trimester 3.

Table 1 Objective cognitive performance of pregnant women and non-pregnant controls

	Trimester 1 (n=23) (1)			Trimester 2 (n=28) (2)			Controls (n=10) (3)				
	Mean (SD)	CI		Mean (SD)	CI		Mean (SD)	CI		p	
		5%	95%		5%	95%		5%	95%	(1)-(3)	(2)-(3)
Individual items											
Vigilance Test	18.0 (0.2)	17.9	18.0	17.9 (0.3)	17.8	18.0	18.0 (0.0)	-	-	-	-
Digit Span Forward	5.3 (1.1)	4.8	5.8	4.8 (0.9)	4.4	5.1	5.0 (1.1)	4.2	5.8	0.532	0.546
Digit Span Backward	3.4 (0.9	3.0	3.8	3.3 (1.0)	2.9	3.7	3.3 (0.7)	2.8	3.8	0.851	0.950
Word Lists Trial 1	6.2 (1.3)	5.6	6.8	5.5 (1.2)	5.1	6.0	6.4 (1.1)	5.6	7.2	0.791	0.053
Word Lists Trial 2	7.7 (1.0)	7.2	8.1	7.3 (1.2)	6.8	7.7	8.1 (1.1)	7.3	8.9	0.310	0.063
Word Lists Trial 3	8.2 (1.0)	7.8	8.6	8.2 (1.1)	7.8	8.6	8.5 (0.8)	7.9	9.1	0.520	0.462
Word Lists Trial 4	7.4 (1.3)	6.8	8.0	6.8 (1.1)	6.4	7.3	7.0 (1.4)	6.0	8.0	0.436	0.689
Animal Naming	17.2 (3.9)	15.5	18.9	16.5 (4.1)	14.9	18.1	16.0 (3.0)	13.9	18.1	0.500	0.730
Cognitive sub-domains											
Attention (Vigilance Test)	18.0 (0.2)	17.9	18.0	17.9 (0.3)	17.8	18.0	18.0 (0.0)	-	-	-	-
Working memory (Digit Span Forward and Backward)	8.7 (1.7)	7.9	9.4	8.1 (1.6)	7.5	8.7	8.3 (1.3)	7.3	9.3	0.560	0.740
Immediate shortterm memory (Word Lists 1-3)	7.4 (0.9)	7.0	7.8	7.0 (0.9)	6.6	7.4	7.7 (0.9)	7.0	8.3	0.400	0.060
Delayed shortterm memory (Word List 4)	7.4 (1.3)	6.8	8.0	6.8 (1.1)	6.4	7.3	7.0 (1.4)	6.0	8.0	0.436	0.689
Explicit Memory (Animal Naming)	17.2 (3.9)	15.5	18.9	16.5 (4.1)	14.9	18.1	16.0 (3.0)	13.9	18.1	0.500	0.730

n, sample size; SD, standard deviation; CI, confidence interval; p, significance

ADDENDUM B

LIST OF FREQUENTLY USED ABBREVIATIONS

• CD-RISC	Connor-Davidson Resilience Scale
• DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} edition)
• EEG	Electroencephalography
• ERT	Emotion Recognition Task
• fMRI	functional Magnetic Resonance Imaging
• FST	Facial Stroop Task
• HPA axis	Hypothalamic-Pituitary-Adrenal Axis
• K-10	Kessler's K-10
• MSPSS	Multidimensional Scale of Perceived Social Support
• NIRS	Near-Infrared Spectroscopy
• Oxy-Hb	Oxygenated Haemoglobin
• PET	Positron Emission Tomography
• PFC	Prefrontal Cortex
• PSS	Perceived Stress Scale
• SCID	Structural Clinical Interview for DSM-IV
• STAI	Spielberger State-Trait Anxiety Inventory
• TCI	Temperament and Character Inventory

PUBLICATIONS RELATED TO THIS STUDY

Spies, G.; Stein, D.J.; Roos, A.; Faure, S.C.; Mostert, J.; Seedat, S.; & Vythilingum, B. (2009). Validity of the Kessler 10 (K-10) in detecting DSM-IV defined mood and anxiety disorders among pregnant women. *Archives of Women's Mental Health 12*(2):69-74.