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Research report

# Altered prefrontal cortical function during processing of fear-relevant stimuli in pregnancy

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ABSTRACT

In non-pregnant individuals, the prefrontal cortex (PFC) is involved in the regulation of emotion, and appears to play a role in anxiety. Near-infrared spectroscopy (NIRS) detects cortical neural activation without harmful radiation making it safe for use in pregnancy. The aims of this study were to assess neural circuitry involved in processing fear-relevant stimuli during pregnancy using NIRS, and to determine associations between activation of this circuitry, distress and anxiety symptoms, attention to threat, cortisol, estrogen, progesterone and testosterone levels. There was significant activation of the PFC in response to fearful faces compared to rest in both pregnant and control groups. Within pregnancy, the activation was most pronounced at trimester 2, compared to the other trimesters. In pregnant women only (all trimesters), PFC activation was significantly associated with increased distress and anxiety, but with decreased selective attention to masked fear. PFC activation was also significantly associated with increased levels of cortisol and testosterone in pregnancy. PFC function appears to be altered during processing of fear-relevant stimuli in pregnancy. Changes in hormone levels may lead to changes in PFC function, and in turn to changes in cognitive-affective processing and anxiety. Further work is needed, however, to explore precisely how PFC function is altered in pregnancy; it is possible that certain changes reflect altered processing of threat stimuli, while others reflect attempts to compensate for distressing and anxious symptoms that emerge during pregnancy.

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## 1. Introduction

Pregnancy has been associated with emotional dysregulation [8,33] and with increases in a range of distressing psychological symptoms such as anxiety [22,50,54] and depression [40,53]. Indeed, the highest prevalence of anxiety disorders is found in women during their childbearing years [47], with a prevalence rate of 14.8% [48].

In non-pregnant women, there have been important advances in understanding the neural circuitry involved in symptoms such as anxiety, and in relevant underlying processes such as perception of fear-relevant stimuli and attention to threat [18,23,43]. The prefrontal cortex (PFC) appears to play a particularly important role in emotional regulation, via its control of a range of limbic and subcortical structures including the amygdala and hippocampus [16,17,45]. Furthermore, since glucocorticoids (e.g. cortisol) and gonadal hormones (e.g. estrogen, progesterone and testosterone) are thought to be involved in emotional regulation [11], it is possible that these hormones exert specific effects on the PFC in regulating emotion and cognition in pregnancy. It may therefore be hypothesized that pregnancy is characterized by altered PFC function.

To date there have been few functional neuroimaging studies during pregnancy. Such work is important insofar as it is relevant to understanding the vulnerability of pregnant women to develop anxiety and mood disorders [1,47]. Appropriate concerns about the safety of brain imaging during pregnancy [12] have hampered such work from proceeding.

Near-infrared spectroscopy (NIRS) provides a safe way to assess neural circuitry in pregnancy. NIRS detects real-time upper cortical vascular responses to neural activation by infrared spectrum light transmitted through diodes placed on the scalp. NIRS does not involve harmful radiation [24] and is non-invasive, has high temporal resolution and high sensitivity to haemo-dynamics, and allows long term monitoring [32]. Although NIRS has lower spatial sensitivity than functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) and cannot detect activation in deep-lying subcortical structures [61], it therefore has several advantages, particularly during pregnancy.

The aims of this study are to (1) assess neural circuitry involved in processing fear-relevant stimuli in pregnancy, specifically PFC activation, to (2) determine associations between activation of this

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circuitry, distress and anxiety symptoms, and attention to threat, and (3) determine associations of PFC activation with cortisol and gonadal hormone levels, during the course of pregnancy.

## 2. Methods

### 2.1. Participants

Pregnant women were randomly recruited from Midwife Obstetric Units in the East Metro region of the Western Cape (South Africa) by nursing staff and the first author. Pregnant participants (trimester 1, $n = 10$; trimester 2, $n = 12$; trimester 3, $n = 10$) were 18 years of age or older (mean (SD) age, 24.8 (5.6) years; mean (SD) education, 11.5 (1.2) years). Participants were also fluent in Afrikaans and/or English; in good health, i.e. not suffering from a serious medical condition; without a history of significant adverse pregnancy-related conditions or terminations; and had 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.

Non-pregnant controls ($n = 9$), matched to the pregnant group for age and level of education (mean (SD) age, 25.3 (5.7); mean (SD) education, 11.8 (0.8) years) were also recruited from the same population. Control participants were 18 years or older; fluent in Afrikaans and/or English; in good health; and not abusing any substances.

Informed, written consent was provided for brain imaging as well as the completion of self-report questionnaires and a computer-based affective task. Pregnant women also provided consent at the recruitment visit to undergo an ultrasound scan to confirm a normal pregnancy and to determine gestational age. This study was approved by the Committee for Human Research at Stellenbosch University and was conducted at Tygerberg Hospital and the Cape Universities Brain Imaging Centre 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.

### 2.2. Procedures

Pregnant participants provided information on demographic variables, and medical and obstetric history. Assessments occurred longitudinally during trimester 1 (13–14 weeks), trimester 2 (22–23 weeks), and trimester 3 (32–33 weeks) of gestation. At each visit firstly, participants completed self-report questionnaires to assess general distress levels (K-10), and state and trait anxiety (Spielberger State-Trait Inventory), as well as the facial Stroop task to assess their selective attention to threat on a behavioural level. Subsequently, at each visit, participants completed an imaging session with NIRS to assess PFC activation in response to facial expressions of fear (Emotion Recognition Task). Bloods and saliva samples were collected to determine levels of cortisol, estrogen, progesterone and testosterone at each trimester.

Controls provided information on demographic and general health variables during a once-off assessment session. Neuropsychological assessments and imaging procedures were the same for controls and pregnant women and lasted 2.5–3 h.

#### 2.2.1. Neural circuitry

A DYNOT system (NIRx Medical Technologies, New York) was used to obtain NIRS measurements from the PFC (e.g. Schmitz et al. [49]) during performance of the Emotion Recognition Task (see Section 2.2.2.). The system measures brain activity in response to stimuli by detecting real-time changes in oxygenated (oxy) and de-oxygenated (de-oxy) haemoglobin at a maximum depth of 3 cm from the head surface. Laser diodes placed on the scalp simultaneously emit near infrared light at wavelengths of 760 nm and 830 nm. Changes in the concentrations of oxyhaemoglobin and de-oxyhaemoglobin are calculated from the light attenuation at these wavelengths measured by detectors at each diode location. Only the oxyhaemoglobin data was used in this instance as de-oxyhaemoglobin measurements have lower signal to noise ratio and may not provide as consistent and robust activation patterns [31,42].

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 [25]. The position of the Fp1 point is 10% of the nasion to inion distance above the nasion bone. The lower rim of the helmet-centre was then positioned on this point and 30 diodes were connected to the helmet. The diodes were held in place by ferrules fixed at a distance of 6 mm. Diodes were fitted in a 3 by 10 grid pattern across the forehead (PFC area) to enable image reconstruction on a finite element model (FEM) mesh using NAVI software (NIRx Medical Technologies; see Bluestone et al. [6] 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 1.8 Hz 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).

#### 2.2.2. Emotion Recognition Task

Dynamic facial expressions of the emotions anger, disgust, fear and happiness [15,21] were used in the Emotion Recognition Task to investigate PFC activation patterns using NIRS. For the purpose of this study, only PFC activation in response to fearful faces was extracted. 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. 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 22 s, preceded by a fixation cross that appeared for 44 s. Participants were required to press any key on a keyboard on appearance of the fixation cross, to sustain attention in viewing faces.

#### 2.2.3. Distress and anxiety

*2.2.3.1. K-10.* General distress of participants was assessed using the K-10, a 10-item self-rated measure [28]. 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), with higher scores indicating more severe distress. The K-10 has demonstrated good validity and reliability in assessing distress in the general population [27] and in pregnancy [52].

*2.2.3.2. Spielberger State-Trait Inventory.* State and trait anxiety was assessed using the Spielberger State-Trait Inventory (STAI) by means of two 20-item self-report sub-scales [26]. 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 [51]. 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 on some items are reversed. Scores can range from 20 to 80 with higher scores indicating higher levels of anxiety. The STAI has been found to have adequate validity and reliability in assessing anxiety in pregnancy [13].

#### 2.2.4. Facial Stroop Task

The facial Stroop task was included to assess selective attention to threat, i.e. fearful faces, compared to neutral faces using a modified, computerised version of an established emotional Stroop task [56,58] (Helmholtz Institute, Utrecht). Neutral facial expressions were used in the task as comparative expressions to determine attention bias scores, i.e. reaction times in response to threat stimuli.

The task was presented in E-prime (Psychology Software Tools Inc., 2002) and was comprised of five different male and female faces from the standardized Ekman and Friesen's Pictures of Facial Affect [15] and mask-like stimuli created by the Utrecht group [56,58]. Emotional and neutral faces were randomly displayed on a computer screen of a 60 Hz computer, which was set up at eye-level at a distance of 60 cm from the participant's face. Participants were required to name the colour in which the faces or masks appeared (red, green or blue), as quickly as possible during the first two of three sections of the task; while responses were recorded automatically through a microphone connected to a response box unit (Psychology Software Tools Inc.). The duration of the task was 35–40 min depending on the response speed of the participant.

The three task sections were the masked Stroop, the unmasked Stroop and an awareness check. In the *masked* Stroop, reaction times to faces appearing outside conscious awareness were assessed. A fixation cross was displayed for 750 ms followed by either an emotional or neutral face that was briefly presented for 2 ms, which in turn was followed by a masking stimulus. The mask was displayed for 286 ms after which a vocal response was required.

In the *unmasked* Stroop, response times (ms) to faces appearing within conscious awareness, was assessed. Here, the fixation cross was presented for 750 ms after which a target stimulus was shown for 298 ms. Both task sections started with 6 practice rounds and terminated after 60 actual rounds.

The *awareness check* was included to verify the invisibility of target stimuli [34]. Backward masking may be the most accurate method to investigate subconscious cognitive-affective processing as it is not biased by the conscious management of, for example, anxiety symptoms [46]. Participants had to distinguish between 40 emotional and neutral faces appearing outside conscious awareness, which are also presented in the *masked* Stroop section. A fixation cross was displayed for 750 ms and then followed by a face that was briefly presented for 2 ms, and followed by a mask (presented for 286 ms). Ten emotional and 10 neutral faces were randomly displayed; whereafter the participant had to indicate whether it was 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.

Attention bias scores were determined by subtracting colour-naming times on neutral faces from colour-naming times for 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 [46,58].

#### 2.2.5. Endocrinology

*2.2.5.1. Cortisol.* Saliva samples for cortisol measurement were collected by pregnant participants on four consecutive mornings, the fourth morning being the visit day. Independent saliva collection at home provides a convenient, non-invasive and

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