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The embarrassed brain : towards a neurobiology of generalized social anxiety disorder

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Citation

Veen, J. F. van. (2010, October 28). *The embarrassed brain : towards a neurobiology of generalized social anxiety disorder*. Retrieved from <https://hdl.handle.net/1887/16086>

Version: Corrected Publisher's Version

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Introduction

Introduction

Since the 1980s, social anxiety disorder (SAD) was recognized as a diagnostic entity (American Psychiatric Association, 1980). As described in DSM-IV-TR, social anxiety disorder is characterized by a persistent fear of one or more social or performance situations in which the person is exposed to people or to possible scrutiny by others. Examples of such situations are meetings, parties, speaking in front of an audience, or making a phone call in public. The feared situations are avoided or are endured with intense anxiety and distress (American Psychiatric Association, 2000). Experiencing anticipatory anxiety and shame afterwards are characteristic of SAD. Somatic symptoms of anxiety that occur in social situations are palpitations, blushing, trembling and sweating. Two subtypes of SAD can be distinguished: the specific (sSAD) and the generalized type (gSAD) (American Psychiatric Association, 2000), the latter being the most disabling, most severe and complete subtype, showing all aspects of social anxiety. In this thesis, we chose to investigate gSAD, anticipating to find most pronounced neurobiological dysfunctions.

SAD is among the most prevalent mental disorders, however, most epidemiological studies did not make a distinction between subtypes. Reason for this is that at first there was no evidence for a possible distinction, and DSM-III defined social phobia primarily as performance anxiety. In DSM-III-R (1987) the generalized subtype was introduced, in which the phobic situation included most social situations, but no additional criteria were provided. In 1995, Manuzza et al. showed that generalized and non-generalized social phobia were valid subtypes, and that on a biological level familial social phobia was more common among patients with generalized social phobia (Mannuzza et al., 1995).

In European community studies, lifetime prevalence rates of 3.9 to 13.7% according to DSM-IV criteria were found and more women were affected than men (Fehm et al., 2005). The National Comorbidity Survey Replication in the United States reported life time prevalence rates of 12.1% (Ruscio et al., 2008). An epidemiological survey in Ontario, Canada, did discriminate between the specific (sSAD) and the generalized subtype (gSAD) and reported life time prevalence rates of 7.0% for sSAD and 5.9% for gSAD (Stein and Kean, 2000). The prevalence estimates of gSAD were higher in women than in men, but no exact data were reported on this (Stein and Kean, 2000). Symptoms of gSAD might also be more severe in women than in men. The onset of gSAD is often at puberty or before (Keller, 2003; Wittchen and Fehm, 2003; Stein and Kean, 2000).

gSAD is still generally underrecognized even among psychiatrists and the effects of gSAD are still underestimated. The National Comorbidity Survey showed that gSAD is associated with impairment of social functioning, family-life and close relationships (Lampe et al., 2003; Patel et al., 2002; Stein and Kean, 2000; Wittchen et al., 1999). In addition, patients with gSAD are less likely to be in a relationship or marriage (Dingemans et al., 2001). gSAD was also associated with early leave of school (Stein and Kean, 2000), lower level of education (Katzelnick and Greist, 2001; Wittchen et al., 1999), a higher risk of being unemployed (Patel et al., 2002; Lampe et al., 2003), and engagement in jobs below the level of qualification (Katzelnick and Greist, 2001). Furthermore, shame leads to patients delay in receiving treatment (Dingemans et al., 2001). gSAD patients

without comorbid disorders but with the worst fears were least likely to receive treatment (Ruscio et al., 2008).

Although gSAD is a disabling disease, only half of the patients receive treatment (Ruscio et al., 2008). Treatments of choice for gSAD are serotonin reuptake inhibitors (SSRIs), serotonin-noradrenalin reuptake inhibitors (SNRIs) and cognitive behavioural therapy (CBT) (Bandelow et al., 2007; Ipser et al., 2008). Monoamine oxidase inhibitors (MAOIs) and benzodiazepines are also effective, but are regarded to be second-line agents: MAOIs, because treatment requires dietary and medication restrictions, and benzodiazepines, because of cognitive adverse events, addiction and the requirement of slow withdrawal (Ipser et al., 2008).

Neurobiological background

The underpinnings of the neurobiology of gSAD are not clear yet. Research in other affective disorders showed that several hormonal and neurotransmitter systems such as the serotonergic and dopaminergic neurotransmitter systems, are involved in the neurobiology of these disorders, as well as the stress system and female gonadal hormones, as will be described in short in the following section.

The efficacy of SSRIs suggests that the neurotransmitter serotonin, regulating among other things mood and anxiety, might be involved in major depressive disorder, posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD) and panic disorder (PD) (Hoffman and Mathew, 2008; Vaswani et al., 2003). Dopamine, central in reward and motivation, might be involved in the neurobiology of PTSD, as was shown in a study in which increased excretion of dopamine and its metabolite were found in the urine of PTSD patients (Heim and Nemeroff, 2009). In addition, dysregulation of the stress system, the hypothalamic-pituitary-adrenal-axis (HPA-axis) and autonomic nervous system (ANS), in affective disorders was reported. Cortisol, the major final product of the HPA-axis in humans, modulates at several levels the function of many neurotransmitters, including serotonin and dopamine. Hyperfunctioning of the HPA-axis was found in major depression, whereas in PTSD predominantly hypofunctioning was found with increased sensitivity of the HPA-axis to negative glucocorticoid feedback (Swaab et al., 2005; Brown et al., 2009; Heim and Nemeroff, 2009). Furthermore, in panic disorder, HPA-axis hyperactivity in response to contextual cues was reported (Abelson et al., 2007). Other studies found that baseline HPA-axis functioning in panic disorder was the same as in healthy controls (Strohle and Holsboer, 2003). Hyperfunctioning of the HPA-axis was also reported in generalized anxiety disorder (GAD) (Mantella et al., 2008). Hyperactivity of the other branch of the stress system, the autonomic/sympathetic nervous system, was described in major depression, PTSD, and might be the case in PD (Brown et al., 2009; Heim and Nemeroff, 2009; Grassi and Kiowski, 2002). Studies on female gonadal hormones reported that they affect the course and severity of several symptoms of anxiety. Premenstrual increase of anxiety symptoms was reported in healthy women, and exacerbation of psychiatric symptoms in women with depressive disorder and in women with anxiety disorders, such as GAD and PD (Rofe et al., 1993; Hsiao et al., 2004; Brambilla et al., 2003).

Aim of the thesis

Knowledge of the neurobiology of gSAD is essential for the development of new treatments. Since many systems seem to be involved in the neurobiology of affective disorders, we aimed in this thesis to make an exploration of the serotonergic and dopaminergic systems, the two branches of the stress system, namely the HPA-axis and the noradrenergic system/ANS, and we did a first step in studying the influence of reproductive hormones in gSAD.

Introduction of the neurotransmitter and hormonal systems that were studied in this thesis

Serotonin (5-hydroxytryptamine = 5-HT) is a metabolite of the amino acid tryptophan. Following transport of tryptophan into the serotonin neuron, tryptophan is converted into 5-hydroxytryptophan (5HTP) by the enzyme tryptophan hydroxylase, which is the rate limiting step in the synthesis. 5HTP is then quickly converted into serotonin by the enzyme aromatic amino acid decarboxylase. After release into the synapse, the serotonin transporter regulates the availability of serotonin in the synapse by a reuptake mechanism. Serotonin is a regulatory neurotransmitter and is among other functions involved in the regulation of stress, mood, sleep, appetite, impulse control, and reproduction.

Dopamine is a catecholamine synthesized from the precursor tyrosine. The activities of tyrosine hydroxylase, the rate limiting step, and dihydroxyphenylalanine decarboxylase lead to production of dopamine. Dopamine can be metabolized by catechol-O-methyltransferase (COMT) or monoamine oxydase (MAO), the same enzymes involved in the metabolism of norepinephrine and epinephrine. Dopamine is thought to be involved in motivation, reward, reinforcement and motor functions and plays a poorly understood role in some sympathetic ganglia of the ANS.

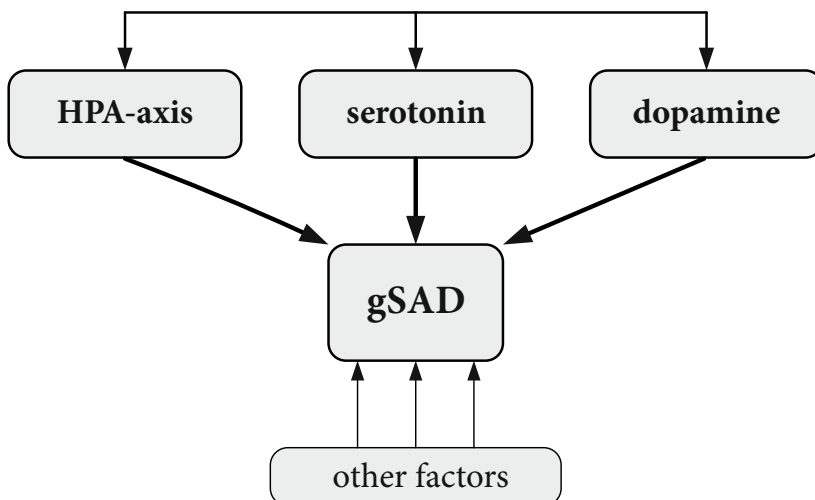
Central in stress response is regulation of the hypothalamic-pituitary-adrenal axis (HPA-axis) and the ANS. Stress initiates the release of corticotrophin releasing hormone (CRH), which potentiates the stress response by organizing the ANS response and the HPA-axis response. Thus both branches of the stress system are activated in times of stress, and therefore are likely to be hyperactive in anxiety disorders.

HPA-axis activity is regulated by CRH and arginine-vasopressine (AVP), which are released in the paraventricular nucleus of the hypothalamus. They coordinate the release of adrenocorticotrope hormone (ACTH) by the pituitary. ACTH induces the secretion and release of cortisol in a pulsatile manner from the adrenal glands. Cortisol modulates at the periphery energy mobilization, the immune system, bone and muscle growth, epithelial cell growth, erythroid cell production and the cardiovascular system. In the brain cortisol influences the limbic system by binding to two receptors, the high affinity mineralocorticoid receptor (MR) and the low affinity glucocorticoid receptor (GR). The GR plays an important role in the negative feedback of the system. HPA-axis activity is determined by two factors: stress and the normal circadian rhythm (Lanfumey et al., 2008). Recent studies in healthy humans indicated that HPA-axis function in stress and in non-stressed conditions is highly complex controlled both by limbic structures, including the amygdala and the hippocampus

(Buchanan et al., 2004; Kern et al., 2008) and the prefrontal cortex (Kern et al., 2008).

The somatic symptoms of gSAD like palpitations, blushing, trembling and sweating are under autonomic control. Noradrenaline is synthesized from the precursor tyrosine. In the periphery, the most prominent neurons that synthesize noradrenaline are the sympathetic ganglion cells of the Autonomic Nervous System (ANS). In the brain, noradrenaline is produced in the locus coeruleus, a brainstem nucleus that projects to forebrain targets, influencing sleep and wakefulness, attention, and feeding behaviour. The reciprocal interaction between the locus coeruleus and the paraventricular nucleus provides a link between both systems. One of the important receptors is the α_2 -adrenergic autoreceptor, modulating presynaptically the release of several other neurotransmitters. The ANS is influenced by many brain structures, mostly via the hypothalamus. The hypothalamus integrates all the information into a coherent pattern of autonomic response. The hypothalamus regulates the ANS in two ways. It projects to neurons in the brain stem and spinal cord for the control of temperature, heart rate, blood pressure and respiration.

The gonadal hormones estrogen and progesterone regulate female hormonal phases and are also considered neuroactive steroids, because of their capacity to modify neural activities (Le Melledo et al., 2001; Dubrovsky, 2005). Estrogens influence the serotonergic system through the estrogen receptor $ER\beta$ by promoting serotonergic transmission (Osterlund et al., 2005). Progesterone interacts with several neurotransmitter systems, neuropeptides and the HPA-axis. It influences anxiety probably by its effects on the gamma-aminobutyric acid (GABA)_A-receptor. The GABA_A-receptor modulates the output of for example the dopaminergic, adrenergic, and serotonergic systems (Le Melledo and Baker, 2004). Furthermore, sex steroids play a role in lifelong structural plasticity of several brain regions, including areas involved in stress response, such as the amygdala and hippocampus (McEwen and Magarinos, 2001).



Outline of the thesis

In **chapter 2** we describe a serotonergic challenge with rapid intravenous meta-chlorophenylpiperazine (m-CPP) in seven patients with panic disorder, seven patients with gSAD and seven healthy controls in order to confirm the involvement of serotonin in gSAD and to evaluate the possibility of a shared neurobiology of gSAD and panic disorder. For this study we used meta-chlorophenylpiperazine (m-CPP), which is a (partial) 5-HT_{2C} receptor agonist that also possesses moderate to low affinity for other 5-HT receptors, as well as for (α_2) adrenergic and dopamine receptors. Rapid intravenous administration of 0.1 mg/kg m-CPP is highly sensitive and selective in the provocation of panic attacks in patients with panic disorder as compared to healthy controls (Van Der Wee et al., 2004). It was our aim to confirm that serotonin is involved in the neurobiology of gSAD and that gSAD and panic disorder are neurobiologically distinct disorders.

In **chapter 3** we studied the involvement of the serotonergic and dopaminergic system in gSAD by means of a single photon emission computed tomography (SPECT) neuroimaging study with ¹²³I- β -(4-iodophenyl)-tropane (¹²³I- β -CIT), which binds to the serotonin and dopamine transporters, in twelve gSAD patients and twelve healthy controls. We used ¹²³I- β -CIT SPECT to visualize both the dopamine and the serotonin transporter in the human brain after a single administration of the ligand. Binding of ¹²³I- β -CIT in the striatal region has been shown to reflect mainly binding to the dopamine transporter, binding in the thalamus, midbrain and pons to reflect predominantly binding to the serotonin transporter (Pirker et al., 1995; De Win et al., 2005). The first SPECT scan was made four hours after the infusion of ¹²³I- β -CIT to visualize serotonin transporter binding, and another SPECT scan was made twenty-four hours after infusion to visualize dopamine transporter binding. It was our aim to find differences in the dopamine and serotonin transporter binding in gSAD.

Chapter 4 describes an open-label pilot study in which we investigated the efficacy of mirtazapine, an antidepressant blocking the α_2 -adrenergic autoreceptors and therefore stimulating noradrenergic and serotonergic pathways in gSAD. In this study fourteen gSAD patients were treated for twelve weeks with mirtazapine 30 mg. The primary outcome measure was the change in score on the Liebowitz Social Anxiety Scale (Liebowitz, 1987). We expected to find that mirtazapine might be an effective treatment in gSAD.

In **chapter 5** we studied the involvement of the stress system in gSAD in basal (non-challenging) conditions. We investigated the two branches of the stress system, the HPA-axis and the ANS, in concert in 43 gSAD patients and 43 controls in basal (non-challenging) conditions, and after a low dose of dexamethasone to investigate the feedback sensitivity. We used the non-invasive markers salivary cortisol for the HPA-axis and salivary alpha-amylase (sAA) for the ANS. sAA is a relatively new marker for the ANS. sAA is produced by the salivary glands, primarily by acinar cells. Acinar cells are innervated by both the sympathetic and parasympathetic nervous system. The results of studies in animals and humans indicate that the ANS plays a powerful role in the secretion of sAA, with contributions of both the alpha-adrenergic and beta-adrenergic mechanisms. Therefore sAA might be regarded as a marker of autonomic activation (For a review

see Nater and Rohleder, 2009). We aimed to find differences in the activation of the two branches of the stress system in basal non-stressed conditions in gSAD.

The interplay between the serotonergic system and the two branches of the stress system in gSAD was studied as described in **chapter 6**. Therefore the cortisol and sAA responses to a tryptophan depletion challenge versus a control condition combined with a public speaking challenge, were measured in two groups of nine gSAD patients. Acute tryptophan depletion is a procedure that temporarily decreases serotonergic neurotransmission (Hood et al., 2005). Drinking a large neutral amino-acid (LNAA) mixture without tryptophan (TRP) leads to a decreased plasma TRP/LNAA ratio. Since TRP and large neutral amino acids (LNAAs) compete for transport through the blood-brain-barrier, less TRP will be available in the brain, decreasing the synthesis of serotonin. This in turn diminishes the effects of SSRIs (Hood et al., 2005). It was our aim to find differences in the activation of the autonomic nervous system and the HPA-axis following stress after manipulation of the serotonergic system in gSAD.

In **chapter 7** we describe a retrospective inventory of the course of gSAD symptoms during the female hormonal cycle to investigate whether female gonadal hormones are likely to be involved in the neurobiology of gSAD. Female gSAD patients completed a self-report survey with questions regarding the menarche, menstrual cycle, oral contraceptive use, pregnancy, lactation, postpartum period and menopause. Women that did report an influence of these phases on gSAD symptoms were asked to rate the severity of gSAD symptoms in these variable hormonal phases. We aimed to find that the fluctuations of female reproductive hormones might influence symptoms of gSAD in women.

The summary, conclusions and discussion of this thesis will be presented in **chapter 8**, including the incorporation of these data in a neurobiological model of gSAD.

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