



Modulating amygdala responses to emotion: Evidence from pharmacological fMRI

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ABSTRACT

The use of functional MRI (fMRI) in combination with pharmacological challenges has increased exponentially in recent years, motivated by the idea not only to elucidate the neurochemical foundations of human emotional and cognitive faculties, but also to optimize human brain function in healthy individuals and identify novel drug targets, with the ultimate goal to design more specific pharmacological therapies for the various disorders of human emotion and cognition. In particular, emotional responding of the amygdala has become a central interest, and pharmacological fMRI has been used to specifically probe, and modulate, amygdala activation in response to facial expressions of emotion and emotionally laden scenes. This article reviews recent fMRI experiments manipulating the amygdala's physiological response to such stimuli by pharmacological means and lays a particular focus on monoaminergic, glutamatergic, GABAergic, and hormonal/peptidergic challenges.

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1. Introduction

1.1. The amygdala: structure and connectivity

The amygdala, or 'almond' as its Latin etymology depicts, has become one of the focal centers in research surrounding emotional processing. What was once thought of as a solid, almond shaped mass within the limbic system continues to expose itself as a conglomerate of nuclei and subnuclei, collectively referred to as the amygdaloid complex and distinguished on the basis of cytoarchitectonics, chemoarchitectonics, and fiber connections (Brockhaus, 1938, 1940). The amygdala's subregions have been described using different parcellation schemes (LeDoux, 2007). One of the most widely accepted classification schemes distinguishes the superficial (cortico) subregion from the centromedial subregion and the laterobasal complex (basolateral amygdala, BLA) (Amunts et al., 2005; Heimer et al., 1999).

The flow of information within the amygdala is modulated by a large variety of neurotransmitter systems. Receptors for these neurotransmitters are differentially distributed across amygdala subregions. Also differentially distributed are receptors for various steroid hormones, including glucocorticoid and estrogen

hormones. Numerous peptide receptors are also present in the amygdala, including receptors for opioid peptides, oxytocin, vasopressin, corticotropin releasing factor and neuropeptide Y, to name a few. An important challenge is to understand how these neurochemical systems act together to set the overall tone of the amygdala and thereby modulate activity in interconnected brain regions (LeDoux, 2007).

In a comprehensive quantitative analysis including amygdala connectivity, it was found that the amygdala is richly interconnected with almost all cortical areas analyzed (Young, Scannell, Burns, & Blakemore, 1994), suggesting that, in addition to its well-established role in fear conditioning (LeDoux, 2007), it is fully capable of integrating and modulating multiple emotional processes (Pessoa, 2008; see also Barbas, 1995; Swanson, 2003). In fact, the numerous reciprocal connections of the amygdala form an intricate network supporting a large variety of emotional behaviors related to fear, reward, and motivation. The amygdala has also been implicated in emotional states associated with aggressive, maternal, sexual, and ingestive behaviors (LeDoux, 2007). In addition, the amygdala is involved in the emotional modulation of cognitive functions, such as perception, attention, declarative (explicit) learning and memory, and decision making (Aggleton, 2000; Seymour & Dolan, 2008; LeDoux, 2007; Phelps, 2004; Swanson & Petrovich, 1998). The amygdala's contribution to the detection of emotional events and the production of appropriate responses to these events, is the most extensively investigated and best understood function of this brain region. Recently developed

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cytoarchitectonic probability maps based on histological analysis of post-mortem human brains (Amunts et al., 2005) have even made it possible to shed light on the *in vivo* intra-amygdalar functional organization with functional magnetic resonance imaging (fMRI) and hypothesize about the particular role of human amygdala subdivisions in specific behaviors. Animal models focusing on a crucial role of the BLA subregion in responding to social–emotional stimuli have been expanded via these maps to include other amygdala regions in humans as well, such as the superficial amygdala (Goossens et al., 2009).

1.2. *Imaging drug effects on amygdala activation*

fMRI studies examining amygdala function in the face of emotional stimuli have evolved from clinical studies focusing on brain lesion, substance abuse, and affective disorder patients, to in more recent years using single or combined pharmacological challenges to exploit amygdala reactions in healthy individuals. There are several advantages to studying healthy subjects with pharmacological fMRI (phMRI). Honey and Bullmore (2004) mention for example the ability to discern the pharmacodynamics of the drug, as well as the ability to identify the neurochemical players involved in emotional and cognitive functions during various tasks; selective drug action can help to isolate the contribution of specific neuroreceptors (Honey & Bullmore, 2004). Studies listed in this review focus on single-drug challenges as well as combination drug challenges that target the interaction of multiple neurochemical pathways.

Another benefit to using phMRI in healthy individuals is the ability to identify potential biomarkers of behavioral changes, useful in applying to mental disorders, by inducing such changes with one drug or a combination of drugs. The utility of biomarkers stems from their potential to provide reliable and precise data regarding the probability and course of a disease. Following genetic and environmental factors, biological events often precede clinical pathologies (see for example Bonassi & Au, 2002), and are furthermore better predictors of disease than self-reports (Goldman, 2007), resulting in a more objective and reliable diagnosis and thus earlier treatment. In proof of concept studies, specifically in the preclinical and phase I development stages, biomarkers can help to identify the most ideal candidate pool in terms of toxicity and drug interactions (see for example Kuhlmann and Wensing, 2006). Research shows that by making use of biomarkers identified by pharmacological models in healthy volunteers, treatment development can be greatly enhanced in the first stages (Gilles & Luthringer, 2007). In a review of imaging in drug development, Wong, Tauscher, and Gruender (2009) noted that phMRI can be viable in studies on dose response and development of treatment. This field is dominated by positron emission tomography (PET) because of the necessity in most cases to determine dose-dependent receptor occupancy and thus mechanism of action. However, phMRI poses a viable option of measuring response to drugs for which the mechanism of action is known or possibly not dependent on receptor occupancy or enzyme activity (see Wong et al., 2009). Moreover, some drug responses are driven by a second or third messenger effect which cannot be easily measured with traditional PET (see Wong et al., 2009). The advantage of phMRI in this field lies in its ability to fill the void left by PET, when considering target engagement or receptor occupancy, in that it can measure intrinsic activity at the target. For instance, fMRI has led to the identification of brain regions associated with given symptoms on the basis of invoking activation or deactivation (Wong et al., 2009). In this vein, phMRI can allow researchers to isolate functional and behavioral changes with less risk of measuring artifacts or confounding factors caused by a relatively subjective clinical picture in patients, who often show symptoms of more than one illness (comorbidity), through the selective hypo- and hyper-sensitization of the amygdala in

healthy volunteers. PhMRI can in this case act as a pre-biomarker when the proof of concept of the target is unknown or uncertain (Wong et al., 2009).

1.3. *Experimental paradigms*

There are two basic approaches to eliciting amygdala responses used in the phMRI studies discussed below. One method is to ask participants to view, rate, or identify a set of emotional scenes, such as those from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1995) or facial expressions of emotion from various databases. The first paper here, by Hariri et al. (2002), used an alternative approach which engaged participants in a faces matching task. In this task, participants are instructed to match the angry or fearful face on top to one of two faces below displaying the same emotion. Importantly, this task engages amygdala–prefrontal cortex circuitry, which has led authors to explore amygdala connectivity under different pharmacological conditions, as presented in the following review. Since this original task, authors have created several variations of this paradigm, including matching the sex of the face or varying the emotions. For each study below, the specific type of phMRI paradigm is named. Another approach to measuring amygdala response to different emotions is to mask faces shortly after presentation. In this type of paradigm, faces showing a specific emotion are presented for a fraction of a second (e.g., 30 ms) and subsequently replaced by a neutral facial expression. This can have the effect that participants report only seeing a neutral face, but that the amygdala is despite this differentially activated according to the previous emotion. The concept of examining emotional processing of faces and scenes in healthy individuals has critical implications for patient studies, especially in affective disorders such as major depression, of which approximately 17% of US Americans suffer during their lifetimes (Kessler et al., 2003; see also Andrade et al., 2003). Already, research has shown a cognitive bias in depressed patients towards negative and away from positive facial emotions (see Leppänen, 2006). Contrasting such reactivity patterns between healthy individuals and patients, and furthermore pharmacologically reproducing such biases in healthy individuals can lead to more effective and honed treatments both in terms of pharmacological intervention as well as cognitive behavioral therapy (CBT).

1.4. *Aims and structure of the review*

This review is a summary of >30 published journal articles published up until May 2010, containing the criteria pharmacological modulation of emotional processing of faces and scenes in the amygdala. Search methods included an extensive search of PubMed with search criteria including 'amygdala', 'drug', 'emotion', 'fMRI', 'healthy', and 'human'. Included are only pharmacological challenge studies on healthy individuals. Studies reviewed are divided according to the following pharmacological challenges: serotonergic, dopaminergic, noradrenergic, glutamatergic, hormonal/peptidergic, and GABAergic.

2. **Overview**

2.1. *Serotonergic system*

Serotonergic neurotransmission can be influenced by serotonin (5-HT) reuptake inhibitors (SSRIs), which act by blocking 5-HT reuptake via the presynaptic 5-HT transporter (5-HTT or SERT). This increases the intrasynaptic concentration of 5-HT and the interaction with pre- and postsynaptic 5-HT receptors. Clinically, this mechanism of action is extremely relevant to treat major depressive disorder and anxiety disorders, including

obsessive–compulsive disorder (OCD) and post-traumatic stress disorder (PTSD); effective treatment, however, can take up to several weeks to take effect. As of yet, there is no consensus as to why this is the case. Escitalopram, and to a lesser degree citalopram, are the most selective SSRIs with very little affinity for other monoamine transmitter receptors, including those of dopamine (DA) or noradrenaline (norepinephrine, NE) (Benkert & Hippus, 2007). Only a few of the available SSRIs, citalopram, escitalopram, fluvoxamine, and one tricyclic agent, clomipramine, have been used to influence amygdala activation in pHMRI studies of healthy individuals.

2.1.1. Fluvoxamine

The first attempt to influence the amygdala's emotional response with an SSRI was by Takahashi et al. (2005), who administered a 50 mg single oral dose of fluvoxamine 5 h prior to scanning. Fluvoxamine has a mean serum half-life of 16 h (the shortest of the SSRIs) and a T_{max} of 2 h. Clinically, patients are usually prescribed 100–300 mg/day. In the experiment, amygdala response to neutral and unpleasant IAPS scenes was measured in a single-blind, randomized, crossover design in 13 males (mean age 29.2 ± 5.1 years). Participants were required to subjectively rate scenes according to unpleasantness during scans. Fluvoxamine resulted in reduced response to unpleasant scenes in the left amygdala.

2.1.2. Escitalopram

Escitalopram is an enantiopure compound (S-(+)-stereoisomer) of the racemic mixture citalopram and the most selective of the SSRIs. Importantly, an effective dose of escitalopram is about half of that of citalopram. It has a mean serum half-life of 30 h and a T_{max} of 4 h. Clinically, patients are usually prescribed 10–20 mg/day (Benkert & Hippus, 2007). Arce, Simmons, Lovero, Stein, and Paulus (2008) administered escitalopram to 13 women (mean age 22.4 ± 2.4 years) for 21 days total (5 mg for the first 3 days, 10 mg for the next 18 days) in a crossover design, using an emotion matching task with the facial expressions fear, anger, and happiness. Escitalopram showed no effect on emotional processing in the amygdala compared to placebo when including all study participants. The authors mention difficulties in participant compliancy as a major reason for their results. Windischberger et al. (2010) examined 18 subjects (6 females, mean age 24.8 ± 2.5 years; 12 males, mean age 28.9 ± 6.7 years) in a double-blind, crossover design comparing 20 mg/day citalopram (see results below), 10 mg/day escitalopram, and placebo over 3 scan sessions (Windischberger et al., 2010). Drugs were administered for 10 days each. Participants completed an emotional matching task (happy, angry, fearful, sad, surprised, disgusted, and neutral). Results showed that escitalopram reduced activation in the right amygdala to faces.

2.1.3. Citalopram

Citalopram has a mean serum half-life of 33 h and a T_{max} of 3 h. Patients are usually prescribed an oral dose of 10–60 mg/day (Benkert & Hippus, 2007). Del-Ben et al. (2005) examined 12 male volunteers (mean age 24.7 ± 5.8 years) receiving either placebo or 7.5 mg citalopram infused intravenously 45 min prior to a gender recognition task (anger, disgust, fear, and neutral) in a randomized, balanced order, single blind study design on two separate occasions. Participants showed decreased response in the right amygdala after citalopram to aversive vs. neutral faces compared to placebo. Harmer, Mackay, Reld, Cowen, and Goodwin (2006) studied short-term SSRI treatment using 24 healthy individuals (10 males, 14 females; mean age 26 ± 8 years) over 7 days (20 mg/day). Participants were then required to give the gender of masked emotional (happy or fearful) faces; none of the participants reported seeing an emotional face. Results showed that citalopram reduced bilateral amygdala response to fearful faces compared to placebo.

A further double-blind, randomized, placebo-controlled, parallel-group treatment study (20 mg/day over 7–10 days) (Norbury et al., 2009) in 28 male and female participants (mean age 23 years, range 19–32 years) with fearful and happy faces, on the other hand found that citalopram treatment had no effect on amygdala response to fearful faces, but that it increased bilateral amygdala response to happy faces. The authors concluded that these results illustrate a fast-acting mechanism for reversing the negative cognitive bias characteristic of major depressive disorder and anxiety disorders. They furthermore cited differing results of their previous study (Harmer et al., 2006, described above) as being a product of the amygdala's automatic response mechanism: whereas the automatic threat response system would be activated by masked or implicit stimuli, the explicit stimuli would not activate this system. Interestingly, citalopram has also shown robust results after a single dose. The first study used a single dose (7.5 mg/30 min) of citalopram on two separate occasions intravenously infused in 12 males (mean age 24.7 ± 5.8 years) to examine aversive amygdala response to emotional faces (angry, fearful, disgusted, and neutral) while subjects completed a gender judgment task (Anderson et al., 2007). Scanning took place 60 min after the end of infusion. The authors found that citalopram reduced amygdala response on the left to disgusted faces, whereas in the right amygdala, citalopram lead to reduced activation to fearful faces. No change in amygdala activation was shown compared to placebo for angry faces. One limitation in this study is that the study design was single-blind.

Another study examined the differences in amygdala responsiveness after a single oral dose of 20 mg citalopram to both masked (fearful, happy, and neutral faces, masked after 17 ms) and unmasked faces in a double-blind, randomized, between-subjects design while 26 (13 males, 13 females; mean age 24.2 years, range 19–30 years) participants judged the sex of the face (Murphy, Norbury, O'Sullivan, Cowen, & Harmer, 2009). Citalopram resulted in reduced response to fearful, unmasked faces in the right amygdala. These results conflict with Harmer et al. (2006) (see above), because here citalopram had no effect on fear response to masked, but instead only to unmasked, stimuli. The authors deduce that because the placebo group showed no differences in response to fearful vs. neutral or happy faces, the results regarding citalopram's effect on unconscious threat processing are too inconsistent to serve as a base for conclusion.

In a study examining the cumulative effects of a single dose of intravenous citalopram (20 mg/30 min), Bigos et al. (2008) studied 8 males (mean age 28 years, range 19–50 years) in a double-blind, randomized, cross-over design by measuring participants' responses to emotional faces (angry, fearful, surprised, and neutral) over three stages of drug administration (pre-administration, at the start of, and at T_{max} at the end of administration). Participants completed both a gender and emotional matching task. Responsiveness overall was increased early in the infusion in the right amygdala, and bilaterally at the end of drug administration. Importantly, the placebo condition showed the opposite effect, resulting in decreasing responsiveness throughout administration. The authors did not differentiate between valences and concluded that acute SSRI administration increases amygdala reactivity. They additionally concluded that the difference in results between the above mentioned chronic administration (Harmer et al., 2006) and their own illustrated a homeostatic shift between the amygdala and the prefrontal cortex, which has been shown to more slowly respond to increased 5-HT.

Windischberger et al. (2010) examined 18 subjects (6 females, mean age 24.8 ± 2.5 years; 12 males, mean age 28.9 ± 6.7 years) in a double-blind, crossover design comparing 20 mg/day citalopram, 10 mg/day escitalopram (results listed above), and placebo over 3 scan sessions. Drugs were administered for 10 days each. Participants completed an emotional matching task (happy, angry, fearful,

sad, surprised, disgusted, and neutral faces). Results showed that citalopram reduced task-related activation in the right amygdala.

2.1.4. Clomipramine

Clomipramine is a tricyclic agent, used to treat major depressive disorder and OCD, with an elimination half-life of 16–60 h. It is an antagonist/inverse agonist at 5-HT, DA, and NE receptors (among others) and blocks presynaptic 5-HT, DA, and NE reuptake. Because of tolerability, the dose must be increased from 25 mg/day up to 100 mg/day during the first two weeks and then up to a maximum dose of 225–300 mg/day in adults (Benkert & Hippus, 2007). de Almeida et al. (2009) gave 12 healthy volunteers (3 males, 9 females; mean age 33.5 ± 6.9 years) an increasing dose of up to 40 mg/day clomipramine over two weeks, which was then sustained for another 2 weeks in a longitudinal experiment. Subjects then underwent an fMRI during which they were presented with different sets of IAPS pictures (each set comprised happy, fearful, or angry emotions, with neutral pictures interspersed) and an emotion induction statement (e.g. 'you are being robbed' after a fearful set). Subjects then rated sets for arousal. Two scans were completed: first directly following the four week drug administration and second following a four week washout period. Results showed that clomipramine had no effect on pictures sets during happy or neutral control picture sets. The fear condition showed reduced activity in the left amygdala during induction as well as reduced right amygdala activity for neutral pictures. In the anger condition, reduced right amygdala activity was shown during emotion induction.

2.2. Dopaminergic system

2.2.1. Sultopride

Despite its approval by the U.S. Food and Drug Administration (FDA), the benzamide derivative and selective DA D2/D3 receptor antagonist sultopride was suspended as an atypical antipsychotic due to cardiac side-effects. It has a mean serum half-life of 3–5 h and a T_{max} of 0.5–2 h. Takahashi et al. (2005) examined 13 participants' reactions to IAPS scenes in the above described single-blind, randomized, crossover experiment using a 25 mg single oral dose of sultopride 2 h before scanning. The drug was found to decrease response to unpleasant pictures in the left amygdala, an effect that may be related to its dose-dependent pharmacodynamic profile.

2.2.2. Levodopa

Levodopa (L-DOPA), the biological forerunner to DA, NE, and adrenaline, is used to increase DA concentrations in the treatment of Parkinson's disease (PD) and dopa-responsive dystonia (DRD). It is capable of crossing the blood-brain barrier (BBB), whereas DA itself cannot. Once L-DOPA has entered the central nervous system (CNS), it is converted into DA by the enzyme aromatic L-amino acid decarboxylase (AADC), also known as DOPA decarboxylase (DDC). Delaveau, Salgado-Pineda, Wicker, Micallef-Roll, and Blin (2005) used 100 mg L-DOPA to examine passive emotional processing of faces in 10 elderly volunteers in a crossover study design. Results showed reduced bilateral activation to faces overall in the L-DOPA group compared to the control group, and reduced activation in the L-DOPA group between emotional and control conditions. The authors suggest an inverted parabolic relationship between amygdala activation and DA concentration. In a further experiment, the authors again used a 100 mg dose to examine reactivity in an emotional matching task (fear and anger) in 16 participants (8 males, 8 females; mean age 58.2 ± 9.1 years) (Delaveau, Salgado-Pineda, Micallef-Roll, & Blin, 2007). The study was conducted as a double-blind, randomized, crossover design over two scans. The authors observed a reduction in right amygdala activation under L-DOPA compared to placebo, and suggest that these results are compatible

with earlier indications of the relationship between DA concentration and activation.

2.2.3. Dextroamphetamine

An earlier psychostimulant study by Hariri et al. (2002) used the monoaminergic agonist dextroamphetamine (DXT). Clinically, DXT is used to treat attention-deficit hyperactivity disorder (ADHD) and narcolepsy. DXT most likely indirectly triggers the release of DA and NE at a ratio of 3.5:1, as well as inhibits the presynaptic reuptake of DA, NE, and 5-HT. DXT has a half-life of 12 h on average and a T_{max} of 3 h. In the periphery, DXT also triggers the release of adrenaline. Hariri et al. (2002) studied 12 participants (5 males, 7 females; mean age 33 years) in a randomized, double-blind, crossover design. The authors used an emotional matching task (fear and anger) and the DXT in a dose of 0.25 mg/kg body weight to measure amygdala response. The authors found that DXT increased right amygdala response to faces across fear and anger categories, which implicates the amygdala in mediating the "fright-flight-fight" effects of amphetamine.

2.3. Noradrenergic system

The two substances used so far for studying the influence of NE on amygdala-mediated emotional processing are reboxetine and propranolol.

2.3.1. Reboxetine

Reboxetine is a selective NE reuptake inhibitor (NARI). In healthy people, it has a half-life of 13–30 h and a T_{max} of 2 h. Reboxetine is clinically used to treat an acute major depressive episode; the normal starting dose is 2 mg twice a day for 3 days followed by two days of 4 mg/day. The first study used reboxetine treatment (4 mg twice a day for 7 days) in 24 participants (12 males, 12 females; mean age 24.5 ± 5.7 years) and a gender judgment task for fearful, happy, and neutral faces in a double-blind, randomized, between subjects design (Norbury, Mackay, Cowen, Goodwin, & Harmer, 2007). Participants in the reboxetine condition activated the right amygdala significantly less in response to fearful faces than those in the placebo condition. The authors concluded that this confirms Harmer's et al. (2006) study, which suggested that decreased response to masked faces (covert stimuli) suggests an antidepressant effect on automatic response. However, a second study using a 4 mg single dose of reboxetine found the opposite activation pattern: Onur et al. (2009) studied 18 participants (9 males, 9 females; mean age 24 years, range 19–33 years) in a within-subjects comparison with 4 mg reboxetine and engaged subjects in a gender judgment task while measuring responses to professional actors filmed displaying dynamic fearful, happy, and neutral expressions. The authors observed an increase in right amygdala response to fearful faces and reduced response to neutral faces; using cytoarchitectonic probabilistic brain maps based on histological analysis of ten postmortem brains (Amunts et al., 2005), activation changes were located to the BLA. The probabilistic mapping to the BLA is promising because of its congruency with rodent models demonstrating that the BLA is sensitive to a modulation of NE signaling through pharmacological agents (McGaugh, 2000). According to the authors, the results suggest that stress-induced increases in NE signaling are required to convert a subset of BLA neurons into a 'fear module'.

Another study used 62 participants (32 males, 30 females; mean age 24.2 years) in four arms in a randomized, double-blind, parallel-group design to test for differences in response to dynamic facial stimuli (also happy, fearful, or neutral) with either 4 mg reboxetine, 30 mg hydrocortisone (results detailed below in hormonal challenges), reboxetine and hydrocortisone together, or placebo while participants were involved in an emotion discrimination

task (Kukolja et al., 2008). In the combined reboxetine–cortisol condition, the authors observed greater response to fearful faces than to happy or neutral faces, but not in the reboxetine-only or cortisol-only groups. Interestingly, in the placebo group the highest activations were found in response to neutral, and not fearful or happy, faces. This could be interpreted as a tendency of the amygdala toward pre-caution when confronted with ambiguous stimuli such as neutral faces. The authors concluded that elevated NE signaling modulates response particularly in the presence of elevated cortisol levels, suggesting an interdependence of NE and cortisol. Furthermore, the authors suggest that contradictions in activation patterns to neutral faces could be indicative of greater ambiguity when confronted with neutral faces; this is supported by other studies (see for example Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006; LaBar, Crupain, Voyvodic, & McCarthy, 2003; Sergerie, Chochol, & Armony, 2008; Van der Gaag, Minderaa, & Keysers, 2007) and in this study by greater response latencies to neutral dynamic stimuli compared to other valences.

2.3.2. Propranolol

Propranolol is a BBB-penetrating nonspecific β_{1-3} - (nor)adrenergic receptor antagonist. In healthy people, it has a half-life of 3–4 h and a T_{max} of 1–2 h (Hurlemann, Walter, et al., 2010). Propranolol has traditionally been used in psychiatry to treat performance anxiety, particularly stage fright in musicians (Brantigan, Brantigan, & Joseph, 1982; Tyrer, 1988), test anxiety (Faigel, 1991), anxiety in dental phobic patients (Liu, Milgrom, & Fiset, 1991), and avoidance behavior in panic disorder patients (Ravaris, Friedman, Hauri, & McHugo, 1991). Other studies, however, failed to find robust effects of propranolol on subjective anxiety in phobic subjects (Fagerstrom, Hugdahl, & Lundstrom, 1985) or expression of cued fear conditioning in healthy volunteers (Grillon, Cordova, Morgan, Charney, & Davis, 2004). The observation that propranolol improved cognitive ability under stressful conditions (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007; Faigel, 1991) suggests potential use of the drug as an adjunct to exposure-based CBT for anxiety disorders. Specifically, diminishing excessive stress during repeated exposure with propranolol might reduce dropout rates in CBT (Rodriguez-Romaguera, Sotres-Bayon, Mueller, & Quirk, 2009). Considering evidence-based medicine criteria, propranolol is indicated to treat lithium-induced tremor, antipsychotic-induced akathisia/tardive dyskinesia, withdrawal syndromes, and (auto)aggressive behavior with temper outbursts (Kornischka, Cordes, & Agelink, 2007).

Van Stegeren et al. (2005) used an 80 mg single oral dose of propranolol in a randomized, double-blind, crossover study design over two consecutive days to examine 28 participants' responses to IAPS pictures (rated according to IAPS norms as category 1, neutral, to category 4, extremely unsettling) while participants rated the photos according to emotional arousal (intensity). Interestingly, propranolol attenuated amygdala response to category 3 pictures compared to placebo, whereas the authors found no difference in activation between drug conditions to more or less emotional pictures. The differential effects of propranolol across emotional categories led the authors to suggest that blockade of NE signaling selectively affects emotional, and not neutral, stimuli, but only to a specific point of arousal.

Hurlemann, Walter, et al. (2010) used dynamic stimuli (fearful, happy, and neutral faces) with 18 volunteers (9 males, 9 females; mean age 23 years, range 19–31 years) for a gender judgment task. The study was a double-blind, randomized, placebo-controlled design to test subjects in two scan sessions with a 40 mg single oral dose of propranolol. The authors found reduced amygdala response in the propranolol condition to all facial emotions, a pharmacological effect that probabilistically mapped to the BLA. The authors suggest that this study successfully translates animal models show-

ing anxiolytic effects of β -noradrenergic blockade in the BLA with propranolol (Buffalari & Grace, 2007) to humans.

2.4. Hormonal and neuropeptide actions

A further promising strain of research relies on hormonal and neuropeptidergic pathways. In this grain, studies have used oxytocin (OT), testosterone, vasopressin, and an NK₁ receptor antagonist to examine their modulatory effects on amygdala function.

2.4.1. Oxytocin

OT is a hypothalamic peptide secreted by the posterior pituitary (neurohypophysis) and is traditionally known for its role in lactation and parturition, but primarily acts as a neurotransmitter (Lee, Macbeth, Pagani, & Scott Young, 2009). Substantial evidence from behavioral-pharmacological studies implicates OT in facilitating human bonding, trust, social learning, and emotional empathy (Hurlemann, Patin, et al., 2010; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Consequently, OT is by far the most widely studied neuropeptide in human pHMRI. It has become indispensable to emotion research in part because of animal models showing a high availability of the OT receptor (OTR) in the amygdala (Huber, Veinante, & Stoop, 2005), and which link OT's actions to social recognition effects in animals (Ferguson, Aldag, Insel, & Young, 2001). Studies examining endogenous OT plasma levels have found correlations between low levels and social and affective dysfunction associated with developmental (autism) (Green et al., 2001; Modahl et al., 1998) and psychiatric conditions such as schizophrenia (Goldman, Marlow-O'Connor, Torres, & Carter, 2008).

Kirsch et al. (2005) were the first to find oxytocinergic amygdala effects in emotional processing: 15 male subjects (26.7 ± 3 years) were given 27 IU OT or placebo before a scan in a double-blind, crossover design with both an emotional faces matching task (angry and fearful faces) and an emotional scenes matching task (fearful and threatening scenes). OT proved to reduce amygdala activation in response to both faces and scenes compared to placebo, whereby the greatest reduction was observed in the left amygdala, with faces producing a greater change than scenes. Furthermore, the authors observed reduced functional connectivity between the amygdala and the upper brainstem under OT. The authors concluded that the amygdala is an important site in mediating OT's anxiolytic effects.

Domes et al. (2007) were the next to explore this area, using 24 IU OT and placebo in a gender recognition task with morphed faces (fearful, happy, and angry) in a double-blind, within-subjects study involving 13 males (25.7 ± 2.9 years). The authors found reduced activation in the right amygdala across valences under OT. A newer study by Domes et al. (2009) tested the effects of OT for the first time in females. Sixteen women (24.2 ± 2.5 years), receiving either placebo or 24 IU OT participated in a double-blind, within-subjects, crossover design, exhibited very different results: when asked to rate faces (angry, fearful, happy, and neutral) for arousal, participants in the OT group showed increased response to fearful faces in the left amygdala. An interesting finding that the authors present to explain this contrasting evidence is the lack of OT's effect on fixation pattern, which has been consistently affected in studies involving male participants. Furthermore, the authors suggest enhanced processing of social cues and possible OT receptor differences in men and women as probable reasons for these discrepancies between studies.

A recent study by Gamer, Zurowski, and Buechel (2010) examined 46 males (mean age 25.0 ± 3.7 years) in an emotion recognition task (happy, fearful, and neutral faces) 45 min after receiving either placebo or 24 IU OT. Results showed that while OT decreased left amygdala response to fearful faces, it also increased response to

happy faces compared to placebo, further substantiating the view that OT facilitates social approach behavior.

2.4.2. Testosterone

Testosterone is produced in the ovaries, testes, and adrenal cortex. It is the precursor to estradiol, which is synthesized in the CNS and is important in neurotransmission to the hypothalamus. Clinical use includes treating low sex drive, however this is not wide-spread and its side-effects are not yet clearly established (Benkert & Hippus, 2007). Testosterone has been used in two pHMRI studies to examine emotional processing. Hermans, Ramsey, and van Honk (2008) administered 0.5 mL testosterone tablets to examine response in 12 women (mean age 22.6 years) over three scan sessions (the first without drug administration, the second and third as a double-blind, crossover design) to viewing angry and happy faces. Participants in the testosterone condition showed greater activation with angry compared to happy faces, and interestingly, that the greater the testosterone-endogenous cortisol ratio, the greater the signal change with angry compared to happy faces. Furthermore, responses to angry faces in the testosterone condition were not as quickly habituated as in the placebo condition. A limitation of this study is that 10 of the 12 women were using hormonal contraceptives at the time of the study. According to the authors, the results indicate testosterone as being crucial to impulsive aggression. The second study using testosterone also studied women, this time comparing responses in 25 middle-aged (mean age 42 years) and 17 younger women (mean age 23 years) (Van Wingen et al., 2009). Subjects were administered 0.9 mg intranasal testosterone in a double-blind, crossover design on two scan dates and tested with an emotional matching task (angry and fearful faces). The authors found that testosterone resulted in elevated amygdala response to both emotions bilaterally, but more so in the left amygdala. The end result indicated that amygdala response levels in the middle-aged women under testosterone equaled those of untreated young adult women.

A more recent study by Van Wingen, Mattern, Verkes, Buitelaar, and Fernandez (2010) investigated the effects of 0.9 mg testosterone on 25 middle-aged women (mean age 42 years, range 37–50 years) in a double-blind, crossover design 30 min before a scan on amygdalar connectivity to more distant brain regions. Participants completed an emotional matching task (angry and fearful faces). Results showed decreased functional connectivity from the left amygdala to the orbitofrontal cortex, whereas a positive coupling was seen in the placebo condition; probabilistic maps placed the effect mainly in the centromedial and superficial nuclear groups. Furthermore, there was increased coupling of the bilateral amygdala with the thalamus under testosterone. Testosterone also led to negative coupling of the right amygdala to the anterior cingulate.

2.4.3. Cortisol

Circadian release of the stress hormone cortisol is orchestrated by the hypothalamus. The modulatory effects of cortisol on amygdala neuronal activity peak at 1–2 h after oral intake (Czock, Keller, Rasche, & Haussler, 2005). These effects of cortisol appear to be primarily mediated by genomic actions via intracellular gluco- and mineralocorticoid receptors (Joels, 2006). Kukulja et al. (2008) administered either 30 mg hydrocortisone (synthetic cortisol), 30 mg hydrocortisone plus 4 mg reboxetine, 4 mg reboxetine, or placebo 1 h 45 min previous to scanning (reboxetine results detailed above under noradrenergic system, reboxetine) in a randomized, double-blind, between-subjects experiment involving 62 volunteers to test for differences in response to dynamic facial stimuli (also happy, fearful, or neutral). A 30 mg single oral dose of hydrocortisone was chosen to elevate cortisol activity to levels ranging between moderate (20 mg) and extreme (40 mg) acute stress (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson,

2003). Participants completed an emotion discrimination task. In the combined reboxetine-cortisol condition, there was greater response to fearful faces than to happy or neutral faces, but not in the cortisol-only groups. The authors concluded that elevated NE signaling modulates amygdala response particularly in the presence of elevated cortisol signaling, suggesting an interdependence of NE and cortisol.

2.4.4. Vasopressin

In terms of chemical structure, arginine vasopressin (AVP) is very similar to OT, both being hypothalamic nonapeptides differing in two amino acids; both act as hormones and neuropeptides and are released by the posterior pituitary into the bloodstream as well as directly into the brain. As a hormone it promotes resorption of water through the kidneys. In the brain, studies have found that it can increase male aggression; the AVPR1a RS3_334 bp allele has been correlated with differential activation in the left amygdala to threatening faces (Meyer-Lindenberg et al., 2009). Vasopressin nasal spray has a T_{max} of 2–8 h, and a half-life of 10–20 min. Zink, Stein, Kempf, Hakimi, and Meyer-Lindenberg (2010) tested 20 Caucasian male participants (mean age 28.6 ± 5.9 years) using AVP in a face matching task, a variation of the emotional matching task in which participants matched the emotional upper face (fearful and angry) with the identical one below it. Volunteers were given 40 IU of AVP or placebo intranasally over two scans one week apart; the drug was counterbalanced across subjects. Results showed no direct effect of AVP in the amygdala. However, the authors found changed functional connectivity between the amygdala and the mPFC. Previous studies showed an activation loop from the amygdala, subgenual cingulate, supragenual cingulate, and back to the amygdala (Pezawas et al., 2005; Stein et al., 2007). Zink et al., 2010 showed that while a positive connection existed between the sub- and supragenual cingulate, this became negative in the placebo condition. The authors based this finding on the amygdala being regulated by the mPFC, and that AVP suppressed the normal decrease in subgenual cingulate activity shown during fearful stimuli. Furthermore, the authors suggest that mPFC regulation under AVP leads to a reduction of negative feedback to the amygdala, which in turn would facilitate sustained response to threatening stimuli.

2.4.5. Other neuropeptides

The neurokinin 1 (NK₁) receptor is a G protein-coupled receptor and is found in both the central and the peripheral nervous system. Aprepitant, a highly selective substance P NK₁ nonpeptide antagonist, is the first NK₁ receptor antagonist approved for use with corticosteroids and 5-HT₃ receptor antagonists in preventing chemotherapy-induced nausea and vomiting. Mixed results have been shown in depression trials. It has a half-life of 9–13 h and a T_{max} of 4 h. McCabe, Cowen, and Harmer (2009) used a 125 mg single dose of the NK₁ receptor antagonist aprepitant in 24 healthy participants (13 males, 11 females; mean age 25.8 ± 4.3 years) in a between-groups, double-blind experiment to explore the effects of the peptide on reaction to fearful and happy faces in a gender identification task. Facial emotions were categorized as high, medium, and low intensity. Subjects were scanned 4 h after drug administration. Results showed that aprepitant increased right amygdala response to happy facial expression, especially at high intensity levels. This study did not include a neutral control condition, but instead measured activation in response to happy vs. fearful faces.

2.5. GABAergic system

γ -Aminobutyric acid (GABA) is a pre- and postsynaptic inhibitory neurotransmitter. Benzodiazepine receptor ligands work closely with GABA to hyperpolarize the neuron by docking

onto the GABA_A receptors and increasing GABA inhibition, resulting in a sedative and anxiolytic effect. They are relatively quick to take effect once administered and are used in a wide spectrum of clinical settings, despite the relatively high risk of tolerance and addiction. They are mainly used to relieve anxiety, muscle tension, hypervigilance, sleep disorders, akathisia, and tardive dyskinesia. Lorazepam is one of the benzodiazepines mainly used to treat anxiety, and the only benzodiazepine tested with pHMRI. It is relatively quickly absorbed, and has a half-life of 8–24 h and a T_{max} of 1–2.5 h. In an outpatient setting, the approximate dose is usually between 0.25 and 5.0 mg spread out over 2–4 administrations (Benkert & Hippus, 2007). Paulus, Feinstein, Castillo, Simmons, and Stein (2005) examined dose-dependency of response to an emotional matching task (angry, fearful, and happy) using 0.25 mg and 1.0 mg of lorazepam on three separate occasions (at least one week apart). Fifteen subjects (9 males, 6 females; mean age 27.6 ± 1.4 years) in a double-blind, randomized, between-subjects design completed the task 1 hour after drug administration. In accordance with their a priori dose-dependency hypothesis, bilateral amygdala activation was significantly reduced across all emotion categories after 1.0 mg compared to both placebo and 0.25 mg.

2.6. Glutamatergic system

The N-methyl-D-aspartate (NMDA) pathway has for the most part been the focus of learning and memory studies involving NMDA receptor-dependent long-term potentiation (LTP), this being the leading synaptic model of associative learning in amygdala and hippocampus (Bliss & Lomo, 1973). Consistent with this model, the NMDA receptor glycine-site partial agonist D-cycloserine (DCS) has been shown to improve performance of hippocampus-dependent learning and memory-related tasks (Hood, Compton, & Monahan, 1989; Onur et al., 2010; Thompson,

Moskal, & Disterhoft, 1992). DCS (D-4-amino-3-isoxazolidone) is an antibiotic effective against *Mycobacterium tuberculosis* and has a T_{max} of 3–4 h and a half-life of 8–12 h. Fear conditioning has provided the learning aspect NMDA research with a clinical setting in terms of acquisition and extinction of fear memories in the amygdala. Kalisch et al. (2009), for example, showed DCS-augmented recall of conditioned memory to electric shocks, illustrating a possible NMDA receptor activation in fear memory consolidation. Fear extinction research has shown that DCS increases the effect of fear extinction and exposure therapy in anxiety patients and animals (Norberg, Krystal, & Tolin, 2008), and that it may facilitate exposure therapy in phobic patients (see Davis, Ressler, Rothbaum, & Richardson, 2006). Britton et al. (2009) gave 14 males (mean age 30 ± 8.7 years) 500 mg of DCS or placebo 1.5 h prior to viewing fearful and happy faces in a randomized, double-blind, parallel-group study. DCS led to a significant reduction of right amygdala response to faces in general, with the left amygdala showing a trend towards reduced response over the course of the experiment. Unexpectedly, the authors also found that the placebo group exhibited significantly more habituation to the faces than DCS, which they interpreted as an antagonizing effect of DCS in the amygdala (Tables 1 and 2).

3. Discussion

3.1. Serotonergic system

Overall, there emerge some clear and robust patterns, as well as some discrepancies. The SSRI group is unique as it holds three distinct categories of experimental designs, including measurements after repeated or single-dose oral administration, or as intravenous infusion.

Table 1
Review of literature on emotional faces processing.

Faces				Facial emotions					
Neurochemical affinity	Drug	Administration	Author	Happy	Angry	Fearful	Disgusted	Neutral	Global
Serotonergic	Citalopram	Single	Del-Ben et al. (2005)	–	0	0	0	0	↓ right
		Repeated	Harmer et al. (2006)	0	–	↓ bilateral	–	–	0
		Repeated	Norbury et al. (2009)	↑ bilateral	–	0	–	–	0
		Single	Bigos et al. (2008)	–	0	0	–	0	↑ bilateral
		Single	Murphy et al. (2009)	0	–	↓ right	–	0	0
		Single	Anderson et al. (2007)	–	0	↓ right	↓ left	0	0
	Escitalopram	Repeated	Windischberger et al. (2010)	0	0	0	0	0	↓ right
		Repeated	Arce et al. (2008) ^a	0	0	0	–	–	0
		Repeated	Windischberger et al. (2010)	0	0	0	0	0	↓ right
		Repeated	Windischberger et al. (2010)	0	0	0	0	0	↓ bilateral
Dopaminergic	Levodopa	Single	Delaveau et al. (2005)	–	0	0	–	–	↓ right
		Single	Delaveau et al. (2007)	–	0	0	–	–	↑ right
Noradrenergic	Dextroamphetamine	Single	Hariri et al. (2002)	–	0	0	–	–	↑ right
		Single	Hurlmann et al. (2010a)	0	–	0	–	0	↓ left
	Reboxetine	Repeated	Norbury et al. (2007)	0	–	↓ right	–	0	0
		Single	Onur et al. (2009)	0	–	↑ right	–	0	0
Hormonal/peptidergic	Reboxetine + Cortisol	Single	Kukulja et al. (2008)	0	–	↑ right	–	0	0
		Single	Kukulja et al. (2008)	0	–	0	–	0	0
	Oxytocin	Single	Domes et al. (2007)	↓ right	↓ right	↓ right	–	–	↓ right
		Single	Domes et al. (2009)	0	0	↑ left	–	–	0
		Single	Kirsch et al. (2005)	–	0	0	–	–	↓ bilateral
		Single	Gamer et al. (2010)	↑ left	–	↓ left	–	0	0
		Single	Van Wingen et al. (2009)	–	0	0	–	–	↑ left
		Single	Van Wingen et al. (2010)	–	0	0	–	–	0
	Testosterone	Single	Hermans et al. (2008)	0	↑ right	–	–	–	0
		Single	Zink et al. (2010)	–	0	0	–	–	0
Vasopressin	Single	McCabe et al. (2009)	↑ right	–	0	–	–	0	
	Single	McCabe et al. (2009)	↑ right	–	0	–	–	0	
Benzodiazepine	Lorazepam	Single	Paulus et al. (2005)	0	0	0	–	–	↓ bilateral
		Single	Britton et al. (2009)	0	–	0	–	–	↓ right
NMDA	D-Cycloserine	Single	Britton et al. (2009)	0	–	0	–	–	↓ right

0, response to individual face emotion categories was collapsed into an overall category faces (result shown in the 'Global' column), or no change was found.

^a A further analysis by the authors included only those participants with sufficient drug concentration in urine to be detected by the assay threshold. This second analysis showed decreased response to fearful and angry faces, and no change to happy faces, compared with placebo.

Table 2
Review of literature on International Affective Picture System (IAPS) pictures processing.

IAPS								
Neurochemical affinity	Drug	Administration	Author	Valence				
				Happy	Angry	Fearful	Unpleasant	Neutral
Serotonergic	Fluvoxamine	Single	Takahashi et al. (2005)	–	–	–	↓ left	–
	Clomipramine	Repeated	de Almeida et al. (2009)	0	↓ right	↓ left	–	↓ right
Dopaminergic	Sultopride	Single	Takahashi et al. (2005)	–	–	–	↓ left	–
Noradrenergic	Propranolol	Single	Van Stegeren et al. (2005)	–	–	–	↓ bilateral	–
Hormonal/peptidergic	Oxytocin	Single	Kirsch et al. (2005)	–	–	–	↓ bilateral	–

Results for escitalopram seem to be contradictory, although both available studies administer escitalopram repeatedly: while the first study reported no effect of escitalopram (Arce et al., 2008), the second study found that the drug decreased right amygdala response to emotional faces (Windischberger et al., 2010). However, when taking into account only those subjects whose urine showed drug levels well above the assay detection threshold, the first study yielded a citalopram effect in the form of decreased amygdala response to angry and fearful faces decreased (Arce et al., 2008). Here, methodological inconsistencies across studies prevent a clear conclusion regarding escitalopram.

Results for repeated administration of citalopram are split: whereas one study found reduced bilateral amygdala activation to fear after 7 days of administration (Harmer et al., 2006), the other found no change in response to fear but an increased response to happy faces after 7–10 days (Norbury et al., 2009). The authors postulate that the methodological differences between these two studies are crucial. Harmer et al. (2006) used masked stimuli, which could activate the automatic threat response and be blocked by citalopram. Under conditions of repeated viewing of fearful faces, however, the authors suggest that citalopram has no effect on fearful response, and furthermore increases the salience of positive emotions, i.e. happy faces, for emotional processing. This interpretation is supported by the findings of Windischberger et al. (2010), who documented decreased activation bilaterally to emotional faces after repeated administration.

Results after a single-dose administration of citalopram consistently illustrate lowered amygdala activation to negative emotions, such as negative pictures or angry, fearful, and disgusted faces, whereby findings are split between left, right, and bilateral amygdala response. Interestingly, however, this picture is reversed when one examines the time course of citalopram effects. Amygdala activity on the right is actually increased at early administration and spreads to the bilateral amygdala as administration continues. One can thus observe an interesting pattern of acute versus delayed amygdala response to SSRI action. Chronic administration of the tricyclic clomipramine by de Almeida et al. (2009) showed a similar picture of reduction to aversive pictures during presentation of both fearful and angry IAPS photos, indicating that both tricyclics and SSRIs work to lower amygdala reactivity to threatening or negative stimuli, be they faces or scenes.

The consistency of the SSRI studies is a first step in presenting evidence that increased 5-HT signaling has a direct modulatory effect on amygdala response. Future studies expanding on 5-HT neurotransmission, such as the above study examining the effect of clomipramine (de Almeida et al., 2009), are needed to elaborate on the exact relationship between 5-HT signaling and amygdala response.

3.2. Dopaminergic system

The DA group shows inconsistent results. A 25 mg dose of sultopride demonstrates a lowered amygdala response in the left amygdala (Takahashi et al., 2005) to emotional pictures. When

levodopa and faces are used, results are split between decreased bilateral (Delaveau et al., 2005) and right (Delaveau et al., 2007) amygdala response to fearful and angry faces. On the other hand, a DA receptor agonist showed the opposite activation pattern, including increased right amygdala response to fear and anger (Hariri et al., 2002). These results suggest a more complicated relationship between DA neurotransmission and amygdala response to negative emotions. Unfortunately, the number of studies manipulating DA signaling limits any strong conclusions concerning biomarkers, and this direction should therefore be developed in the future.

3.3. Noradrenergic system

The NE group, including both the NARI reboxetine and the β -blocker propranolol, presents a somewhat mixed picture, in terms of methodology and results. On the one hand, when using dynamic versus static stimuli, the traditional view of a genuine amygdala response bias to fear was replaced by increased baseline responsiveness to all emotions. Using a single dose of reboxetine in this context, the hyperresponsiveness to fear returned. Interestingly, however, this activation disappeared under repeated administration (such as at the beginning stages of therapy), suggesting a duration-dependent normalization of amygdala activity. Clinically, the varying activation patterns carry over to suggest varying behavioral response to therapy: the antidepressant reboxetine, for example, most likely leads to elevated anxiety levels for the first few administrations, but normalizes within a week to two weeks. This is congruent with rodent models of reboxetine treatment which show duration-dependent activation: whereas a single dose increases anxiety-related behavior, repeated administration over one week decreases this behavior (Inoue, Nakagawa, Izumi, Kitaichi, & Koyama, 2006; see also Miyata et al., 2007). Propranolol, in light of its blunting effects across emotions, could be effective as an add-on agent to SSRIs in cases where performance anxiety, cardiovascular symptoms, and tremor dominate the clinical phenotype (Brantigan et al., 1982; Tyrer, 1988; Liu et al., 1991) or as an adjunct to CBT in battling anxiety disorders, especially as the drug does not seem to block response to extremely intense subjective emotional response, meaning that the danger of navigating the world without fear would not exist.

The NE pathway thus seems to play a key role in the traditional idea of amygdala response as a yardstick for fear, and NE appears to modulate both the reactivity (sensitivity) and the operating characteristics (specificity) of the BLA when confronted with dynamic stimuli. Under propranolol conditions and reduced NE input, the BLA is inactive, whereas it is active under placebo conditions and moderate NE input, and hyperactive under a single dose of reboxetine and elevated NE input. Together, these data converge on NE as a key modulator of BLA response sensitivity. In addition, BLA response specificity appears to vary as a function of NE in that reboxetine-induced elevation of NE increased BLA responses to fearful faces but decreased BLA responses to neutral faces (Onur et al., 2009), perhaps by preferentially augmenting

the signal-to-noise ratio for fearful faces at the cost of neutral faces (see also Aston-Jones & Cohen, 2005; Berridge & Waterhouse, 2003; Woodward, Moises, Waterhouse, Yeh, & Cheun, 1991) and thus converting the BLA into a 'fear module'. Based on these findings, the authors suggest that elevations of NE evoked by stressful stimuli elicit a shift in BLA responsivity towards these stimuli. In terms of potential biomarkers, the noradrenergic experiments listed here present a clear picture of amygdalar hypersensitivity resulting in a bias in amygdala reactivity towards negative stimuli under conditions of increased NE. The finding that the amygdala shows decreased response to fearful faces under repeated administration of the NARI reboxetine indicates that targeting NE signaling is a valid direction for therapy.

3.4. Hormones and neuropeptides

The hormonal category presents a relatively consistent picture, however with some interesting twists. OT given to males proved to lower amygdala (left, right, and bilateral) response to faces in general. In females, however, this pattern is reversed, illustrating an increase in left amygdala response to fear. This is similar to activation patterns in women after testosterone administration: after a single dose women show greater activation levels for faces, whereby one study (Hermans et al., 2008) finds this regardless of valence and the other (Van Wingen et al., 2009) to be especially true of angry versus happy faces. These results suggest specific social manifestations in behavior: behavioral studies show increased prosocial behavior after OT administration in males. This could be a result of the lowered amygdala sensitivity shown in the study mentioned here. Furthermore, OT is also a hormone with strong parental behavior associations. Female hypersensitivity to fearful faces after OT administration could mean that in females, the fear response overrides the blunting effects of OT, which would have strong implications in terms of OT's evolutionary utility. The seemingly conflicting results of Domes et al. (2009) and Gamer et al. (2010) show that while in women OT increases response to fearful faces, it decreases this response in men. This conflict, however, is in tune with elementary findings showing sex differences in the correlation between OT and aggression, with females showing increased maternal aggression and males showing decreased aggression after OT administration (see for example Lee et al., 2009; Nephew, Bridges, Lovelock, & Byrnes, 2009). That OT increased response to happy faces in males (Gamer et al., 2010) adds strength to the hypothesis of prosocial behavior in males being dependent on OT (Hurlmann, Patin, et al., 2010).

A further hormone, cortisol, showed no effect on emotional processing when independently administered, but increased amygdala response to fearful faces when coupled with NE. This could shed light on an important facilitatory role of cortisol: when coupled with NE, cortisol enhances amygdala response to negative stimuli. This enhancement could be crucial to other areas of emotion research, including emotional memory: stress-related modulation by NE and cortisol in the BLA, for example, has been shown to enhance memory consolidation (Rooszendaal, McEwen, & Chattarji, 2009). In terms of anxiety disorders, downregulating an enhanced consolidation under stress conditions and subsequent hyperactive response, such as in post-traumatic stress disorder, could hold promise for treatment (Hurlmann et al., 2007; Hurlmann, 2008; Rooszendaal et al., 2009).

Substance P NK₁ receptor antagonism was shown to increase amygdala response to intense, happy faces. Earlier findings report that NK₁ receptor antagonists potentiate the antidepressant effects of repeated doses of the SSRIs citalopram and paroxetine (Chenu, Guiard, Bourin, & Gardier, 2006). Furthermore, substance P injected directly into the medial nucleus of the amygdala has shown

to evoke an anxiogenic effect in rats (Ebner, Rupniak, Saria, & Singewald, 2004). The study presented here, too, shows initial findings that the NK₁ receptor antagonist aprepitant could be effective in depression research.

Testosterone levels are higher in males. However, when females are administered with testosterone, they show heightened activation of amygdala response to threatening faces; this could thus be interpreted as testosterone converting the amygdala into a protection mechanism against hostile others. The decrease in functional coupling between the upstream orbitofrontal cortex and the increase in coupling to the more downstream thalamus in women also indicates testosterone's role in vital reflexes and stimulus processing.

The finding that AVP leads to an altered connectivity between the mPFC and the amygdala during threatening stimuli, leading to sustained response to these stimuli, suggests that AVP converts the amygdala into a defense module by increasing response to aversive stimuli. AVP has indeed been shown to play a role in male-typical social behaviors, such as aggression and pair-bond formation (see Heinrichs, von Dawans, & Domes, 2009), as well as increased electrophysiological response to neutral faces (Thompson, Gupta, Miller, Mills, & Orr, 2004).

The hormonal studies presented deliver some consistent results which could help in identifying biomarkers. OT administration, for example, consistently results in decreased amygdala response to negative faces in males. Interestingly, other findings in clinical populations of depressed patients show elevated levels of OT, lending strength to the hypothesis that OT dysregulation could be a biomarker of abnormal social relations seen in depression (Parker et al., 2010). Taken together, the findings here in healthy patients showing decreased response to negative stimuli after OT administration as well as the latter findings showing elevated OT levels in depressed patients, characterized in part by increased response to negative stimuli, could indicate an OT receptor dysfunction in depression. It could also indicate a dysfunction of an intermediate modulatory process which influences OT neurotransmission.

4. Conclusion

Overall, the amygdala is clearly an important center for emotional processing research, and one which needs further study to develop neurochemical models of its various functions. Pharmacological models in healthy humans are helpful because they eliminate artifacts created by genomic variations in diseases, especially when these produce phenotypical similarities difficult to distinguish in a clinical setting. Furthermore, biomarkers of different illnesses can be identified by pharmacologically producing known behavioral symptoms. However, one of the most important points shown in this review is that the amygdala *per se* is not a single static structure in the brain, but rather that the left and right sides, and indeed separate subregions, carry out very different tasks. This is important for specific drug development in a clinical setting; the measurement of reactivity to emotional faces and scenes in a laboratory setting, however, also carries strong implications for the neurobiology of anxiety disorders, depression, schizophrenia, and autism, which affect a great number of patients currently in therapy by allowing for a better understanding of how to more exactly target dysfunctional areas and circuitries in the brain. Furthermore, the developed state of research on some neurochemical pathways allows important conclusions concerning the validity of neurotransmission as a biomarker for disease, e.g. the serotonergic pathway and the correlation to depression. This point, however, is underdeveloped due to lack of studies in other neurochemical systems, and should be considered in future research.

Directions for future research

PhMRI has grown exponentially in the field of emotional processing research, as shown by this review of the literature. The following is a short list of the most important factors needing to be considered when discussing the future of phMRI:

- (a) **Repeated vs single dose; duration of administration.** Only two of the above mentioned drugs have been tested under both conditions, i.e. citalopram and reboxetine. These studies have shown that there are clear differences in resulting brain activations, implying very different mechanisms of action over the course of time. Unfortunately, a clear picture of conflicting mechanisms of action or the end results, if any, in varying conditions cannot be gained from the other drugs discussed here, even though these conflicts are crucial to understanding how the drugs work and how to administer them more effectively.
- (b) **Males vs females, especially in hormonal and peptidergic challenges.** Currently, only the effects of oxytocin have been differentially examined for men versus women; these results showed that the effects of the peptide in men were vastly different than those in women. The other substances presented here have examined either only men, only women, or men and women combined into one group. There is thus no full picture of gender-specific effects.
- (c) **Disease modeling.** Changes in neural response in healthy individuals similar to abnormal response patterns seen in patient populations can be pharmacologically induced. For instance, when given a combination of reboxetine and cortisol, participants showed a bias towards aversive stimuli, which was not present at the placebo baseline (Kukolja et al., 2008). Such a finding is crucial to developing treatment for anxiety or mood disorders characterized by pathologically elevated stress levels.
- (d) **Biomarkers.** Biomarkers can be used to save resources and increase precision. In a clinical setting, they can serve as better predictors of disease than self-reports (Goldman, 2007); therefore, even when confronted with highly heterogeneous phenotypes, such as those presented by often overlapping symptoms in anxiety and mood disorders, treatment options can be narrowed down. Biomarkers can furthermore help to identify the most ideal candidate pool (Kuhlmann & Wensing, 2006). PhMRI will eventually be used as a tool to exploit biomarkers in both treatment research and diagnosis in translational research, and thus more effectively prevent and treat mental disorders.

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References

- Abercrombie, H. C., Kalin, N. H., Thurow, M. E., Rosenkranz, M. A., & Davidson, R. J. (2003). Cortisol variation in humans affects memory for emotionally laden and neutral information. *Behavioral Neuroscience*, 117, 505–516.
- Aggleton, J. P. (2000). *The amygdala: A functional analysis*. Oxford: Oxford University Press.
- Alexander, J. K., Hillier, A., Smith, R. M., Tivarus, M. E., & Beversdorf, D. Q. (2007). Beta-adrenergic modulation of cognitive flexibility during stress. *Journal of Cognitive Neuroscience*, 19, 468–478.
- Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N. J., et al. (2005). Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: Intersubject variability and probability maps. *Anatomy and Embryology*, 210, 343–352.
- Anderson, I. M., Del-Ben, C. M., Mckie, S., Richardson, P., Williams, R., Elliott, R., et al. (2007). Citalopram modulation of neuronal responses to aversive face emotions: A functional MRI study. *Neuroreport*, 18, 1351–1355.
- Andrade, L., Caraveo-Anduaga, J. J., Berglund, P., Bijl, R. V., De Graaf, R., Vollebergh, W., et al. (2003). The epidemiology of major depressive episodes: Results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. *International Journal of Methods in Psychiatric Research*, 12, 3–21.
- Arce, E., Simmons, A. N., Lovero, K. L., Stein, M. B., & Paulus, M. P. (2008). Escitalopram effects on insula and amygdala BOLD activation during emotional processing. *Psychopharmacology*, 196, 661–672.
- Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus–norepinephrine function: Adaptive gain and optimal performance. *Annual Review of Neuroscience*, 28, 403–540.
- Barbas, H. (1995). Anatomic basis of cognitive–emotional interactions in the primate prefrontal cortex. *Neuroscience & Biobehavioral Reviews*, 19, 449–510.
- Benkert, O., & Hippus, H. (2007). *Kompendium der Psychiatrischen Pharmakotherapie*. Heidelberg, Germany: Springer Medizin Verlag Heidelberg.
- Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus–noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, 42, 33–84.
- Bigos, K. L., Pollock, B. G., Aizenstein, H. J., Fisher, P. M., Bies, R. R., & Hariri, A. R. (2008). Acute 5-HT reuptake blockade potentiates human amygdala reactivity. *Neuropsychopharmacology*, 33, 3221–3225.
- Bless, T. V., & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology*, 232, 331–356.
- Bonassi, S., & Au, W. W. (2002). Biomarkers in molecular epidemiology studies for health risk prediction. *Mutation Research*, 511, 73–86.
- Brantigan, C. O., Brantigan, T. A., & Joseph, N. (1982). Effect of beta blockade and beta stimulation on stage fright. *American Journal of Medicine*, 72, 88–94.
- Britton, J. C., Gold, A. L., Feczko, E. J., Rauch, S. L., Williams, D., & Wright, C. I. (2009). D-cycloserine inhibits amygdala responses during repeated presentations of faces. *CNS Spectrums*, 12, 600–605.
- Brockhaus, H. (1938). Zur normalen und pathologischen Anatomie des Mandelkerngebietes. *Journal für Psychologie und Neurologie*, 49, 1–136.
- Brockhaus, H. (1940). Die Cyto- und Myeloarchitektonik des Cortex claustralis und des Claustrum beim Menschen. *Journal für Psychologie und Neurologie*, 49, 249–347.
- Buffalari, D. M., & Grace, A. A. (2007). Noradrenergic modulation of basolateral amygdala neuronal activity: Opposing influences of alpha-2 and beta receptor activation. *Journal of Neuroscience*, 27, 12358–12366.
- Chenu, F., Guiard, G. P., Bourin, M., & Gardier, A. M. (2006). Antidepressant-like activity of selective serotonin reuptake inhibitors combined with a NK1 receptor antagonist in the mouse forced swimming test. *Behavioral Brain Research*, 172, 256–263.
- Czock, D., Keller, F., Rasche, F. M., & Haussler, U. (2005). Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clinical Pharmacokinetics*, 44, 61–98.
- Davis, M., Ressler, K., Rothbaum, B. O., & Richardson, R. (2006). Effects of d-cycloserine on extinction: Translation from preclinical to clinical work. *Biological Psychiatry*, 60, 369–375.
- de Almeida, J. R., Phillips, M. L., Cerqueira, C. T., Zilberman, M., Lobo, D., Henna, E., et al. (2009). Neural activity changes to emotional stimuli in healthy individuals under chronic use of clomipramine. *Journal of Psychopharmacology*, 24, 1165–1174.
- Del-Ben, C. M., Deakin, J. F. W., Mckie, S., Delvai, N. A., Williams, S. R., Elliott, R., et al. (2005). The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: An fMRI study. *Neuropsychopharmacology*, 30, 1724–1734.
- Delaveau, P., Salgado-Pineda, P., Micallef-Roll, J., & Blin, O. (2007). Amygdala activation modulated by levodopa during emotional recognition processing in healthy volunteers: A double-blind, placebo-controlled study. *Journal of Clinical Psychopharmacology*, 27, 692–697.
- Delaveau, P., Salgado-Pineda, P., Wicker, B., Micallef-Roll, J., & Blin, O. (2005). Effect of levodopa on healthy volunteers' facial emotion perception: An fMRI study. *Clinical Neuropharmacology*, 28, 255–261.
- Domes, G., Lischke, A., Berger, C., Grossmann, A., Hauenstein, K., Heinrichs, M., et al. (2009). Effects of intranasal oxytocin on emotional face processing in women. *Psychoneuroendocrinology*, 35, 83–93.
- Domes, G., Heinrichs, M., Gläscher, J., Büchel, C., Braus, D. F., & Herpertz, S. C. (2007). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biological Psychiatry*, 62, 1187–1190.

- Ebner, K., Rupniak, N. M., Saria, A., & Singewald, N. (2004). Substance P in the medial amygdala: Emotional stress-sensitive release and modulation of anxiety-related behavior in rats. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 4280–4285.
- Fagerstrom, K. O., Hugdahl, K., & Lundstrom, N. (1985). Effect of beta-receptor blockade on anxiety with reference to the three-systems model of phobic behavior. *Neuropsychobiology*, *13*, 187–193.
- Faigel, H. C. (1991). The effect of beta blockade on stress-induced cognitive dysfunction in adolescents. *Clinical Pediatrics*, *30*, 441–445.
- Ferguson, J. N., Aldag, J. M., Insel, T. R., & Young, L. J. (2001). Oxytocin in the medial amygdala is essential for social recognition in the mouse. *The Journal of Neuroscience*, *21*, 8278–8285.
- Fitzgerald, D. A., Angstadt, M., Jelsone, L. M., Nathan, P. J., & Phan, K. L. (2006). Beyond threat: Amygdala reactivity across multiple expressions of facial affect. *NeuroImage*, *30*, 1441–1448.
- Gamer, M., Zurowski, B., & Buechel, C. (2010). Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 9400–9405.
- Gilles, C., & Luthringer, R. (2007). Pharmacological models in healthy volunteers: Their use in the clinical development of psychotropic drugs. *Journal of Psychopharmacology*, *21*, 272–282.
- Goldman, M., Marlow-O'Connor, M., Torres, I., & Carter, C. S. (2008). Diminished plasma oxytocin in schizophrenia patients with neuroendocrine dysfunction and emotional deficits. *Schizophrenia Research*, *98*, 247–255.
- Goldman, N. (2007, June 12–14). Future directions in integration of biological and social theories. In *Presentation to the Chicago workshop on biological measures in population-based health and aging research*.
- Goossens, L., Kukulja, J., Onur, O. A., Fink, G. R., Maier, W., Griez, E., et al. (2009). Selective processing of social stimuli in the superficial amygdala. *Human Brain Mapping*, *30*, 3332–3338.
- Green, L., Fein, D., Modahl, C., Feinstein, C., Waterhouse, L., & Morris, M. (2001). Oxytocin and autistic disorder: Alterations in peptide forms. *Biological Psychiatry*, *50*, 609–613.
- Grillon, C., Cordova, J., Morgan, C. A., Charney, D. S., & Davis, M. (2004). Effects of beta-blocker propranolol on cued and contextual fear conditioning in humans. *Psychopharmacology*, *175*, 342–352.
- Hariri, A. R., Mattay, V. S., Tessitore, A., Fera, F., Smith, W. G., & Weinberger, D. R. (2002). Dextroamphetamine modulates the response of the human amygdala. *Neuropsychopharmacology*, *27*, 1036–1040.
- Harmer, C. J., Mackay, C. E., Reld, C. B., Cowen, P. J., & Goodwin, G. M. (2006). Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biological Psychiatry*, *59*, 816–820.
- Heimer, L., de Olmos, J. S., Alheid, G. F., Pearson, J., Sakamoto, N., Shinoda, K., et al. (1999). *The human basal forebrain. Part II. The primate nervous system. Part III. Elsevier*, pp. 57–226.
- Heinrichs, M., von Dawans, B., & Domes, G. (2009). Oxytocin, vasopressin, and human social behavior. *Frontiers in Neuroendocrinology*, *30*, 548–557.
- Hermans, E., Ramsey, N. F., & van Honk, J. (2008). Exogenous testosterone enhances responsiveness to social threat in the neural circuitry of social aggression in humans. *Biological Psychiatry*, *63*, 263–270.
- Honey, G., & Bullmore, E. (2004). Human pharmacological MRI. *Trends in Pharmacological Sciences*, *25*, 366–374.
- Hood, W. F., Compton, R. P., & Monahan, J. B. (1989). D-Cycloserine: A ligand for the N-methyl-D-aspartate coupled glycine receptor has partial agonist characteristics. *Neuroscience Letters*, *98*, 91–95.
- Huber, D., Veinante, P., & Stoop, R. (2005). Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. *Science*, *308*, 245–248.
- Hurlmann, R. (2008). Noradrenergic–glucocorticoid mechanisms in emotion-induced amnesia: From adaptation to disease. *Psychopharmacology (Berlin)*, *197*, 13–23.
- Hurlmann, R., Matusch, A., Klingmüller, D., Kölsch, H., Maier, W., & Dolan, R. J. (2007). Emotion-induced retrograde amnesia varies as a function of noradrenergic–glucocorticoid effects. *Psychopharmacology (Berlin)*, *194*, 261–269.
- Hurlmann, R., Walter, H., Rehme, A. K., Kukulja, J., Santoro, S. C., Schnell, K., et al. (2010). Human amygdala activity is diminished by the beta-noradrenergic antagonist propranolol. *Psychological Medicine*, *27*, 1–10.
- Hurlmann, R., Patin, A., Onur, O. A., Cohen, M. X., Baumgartner, T., Metzler, S., et al. (2010). Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *The Journal of Neuroscience*, *30*, 4999–5007.
- Inoue, T., Nakagawa, S., Izumi, T., Kitaichi, Y., & Koyama, T. (2006). Effect of combined treatment with noradrenaline and serotonin reuptake inhibitors on conditioned freezing. *European Journal of Pharmacology*, *540*, 91–95.
- Joels, M. (2006). Corticosteroid effects in the brain: U-shape it. *Trends in Pharmacological Sciences*, *27*, 244–250.
- Kalisch, R., Holt, B., Petrovic, P., De Martino, B., Klöppel, S., Büchel, C., et al. (2009). The NMDA agonist D-cycloserine facilitates fear memory consolidation in humans. *Cerebral Cortex*, *18*, 187–196.
- Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., et al. (2003). The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *The Journal of the American Medical Association*, *289*, 3095–3105.
- Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., et al. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of Neuroscience*, *25*, 11489–11493.
- Kornischka, J., Cordes, J., & Agelink, M. W. (2007). 40 Years beta-adrenergic blockers in psychiatry. *Fortschritte der Neurologie-Psychiatrie*, *75*, 199–210.
- Kosfeld, M., Heinrichs, M., Zak, P., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, *435*, 673–676.
- Kuhlmann, J., & Wensing, G. (2006). The applications of biomarkers in early clinical drug development to improve decision-making processes. *Current Clinical Pharmacology*, *1*, 185–191.
- Kukulja, J., Schlaepfer, T. E., Keysers, C., Klingmueller, D., Maier, W., Fink, G. R., et al. (2008). Modeling a negative response bias in the human amygdala by noradrenergic–glucocorticoid interactions. *The Journal of Neuroscience*, *28*, 12868–12876.
- LaBar, K. S., Crupain, M. J., Voyvodic, J. T., & McCarthy, G. (2003). Dynamic perception of facial affect and identity in the human brain. *Cerebral Cortex*, *13*, 1023–1033.
- Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1995). *International affective picture system: Technical manual and affective ratings*. Gainesville, FL: Center for Research in Psychophysiology, University of Florida.
- LeDoux, J. (2007). The amygdala. *Current Biology*, *17*, R868–874.
- Lee, H.-J., Macbeth, A. H., Pagani, J. H., & Scott Young, W. 3rd. (2009). Oxytocin: The great facilitator of life. *Progress in Neurobiology*, *88*, 127–151.
- Leppänen, J. M. (2006). Emotional information processing in mood disorders: A review of behavioral and neuroimaging findings. *Current Opinion in Psychiatry*, *19*, 34–39.
- Liu, H. H., Milgrom, P., & Fiset, L. (1991). Effect of a beta-adrenergic blocking agent on dental anxiety. *Journal of Dental Research*, *70*, 1306–1308.
- McCabe, C., Cowen, P. J., & Harmer, C. J. (2009). NK1 receptor antagonism and the neural processing of emotional information in healthy volunteers. *International Journal of Neuropsychopharmacology*, *12*, 1261–1274.
- McGaugh, J. L. (2000). Memory – A century of consolidation. *Science*, *287*, 248–251.
- Meyer-Lindenberg, A., Kolachana, B., Gold, B., Olsh, A., Nicodemus, K. K., Mattay, V., et al. (2009). Genetic variants in AVPR1A linked to autism predict amygdala activation and personality traits in healthy humans. *Molecular Psychiatry*, *14*, 968–975.
- Miyata, S., Shimoi, T., Hirano, S., Yamada, N., Hata, Y., Yoshikawa, N., et al. (2007). Effects of serotonergic anxiolytics on the freezing behavior in the elevated open-platform test in mice. *Journal of Pharmacological Sciences*, *105*, 272–278.
- Modahl, C., Green, L., Fein, D., Morris, M., Waterhouse, L., Feinstein, C., et al. (1998). Plasma oxytocin levels in autistic children. *Biological Psychiatry*, *43*, 270–277.
- Murphy, S. E., Norbury, R., O'Sullivan, U., Cowen, P. J., & Harmer, C. J. (2009). Effect of a single dose of citalopram on amygdala response to emotional faces. *The British Journal of Psychiatry*, *184*, 535–540.
- Nephew, B. C., Bridges, R. S., Lovelock, D. F., & Byrnes, E. M. (2009). Enhanced maternal aggression and associated changes in neuropeptide gene expression in multiparous rats. *Behavioral Neuroscience*, *123*, 949–957.
- Norberg, M. M., Krystal, J. H., & Tolin, D. F. (2008). A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biological Psychiatry*, *63*, 1118–1126.
- Norbury, R., Taylor, M. J., Selvaraj, S., Murphy, S. E., Harmer, C. J., & Cowen, P. J. (2009). Short-term antidepressant treatment modulates amygdala response to happy faces. *Psychopharmacology*, *206*, 197–204.
- Norbury, R., Mackay, C. E., Cowen, P. J., Goodwin, G. M., & Harmer, C. J. (2007). Short-term antidepressant treatment and facial processing. *The British Journal of Psychiatry*, *190*, 531–532.
- Onur, O. A., Walter, H., Schlaepfer, T. E., Rehme, A. K., Schmidt, C., Keysers, C., et al. (2009). Noradrenergic enhancement of amygdala responses to fear. *Social Cognitive and Affective Neuroscience*, *4*, 119–126.
- Onur, O. A., Schlaepfer, T. E., Kukulja, J., Bauer, A., Jeung, H., Patin, A., et al. (2010). The N-methyl-D-aspartate receptor co-agonist D-cycloserine facilitates declarative learning and hippocampal activity in humans. *Biological Psychiatry*, *67*, 1205–1211.
- Parker, K. J., Kenna, H. A., Zeitzer, J. M., Keller, J., Blasey, C. M., Amico, J. A., et al. (2010). Preliminary evidence that plasma oxytocin levels are elevated in major depression. *Psychiatry Research*, *178*, 359–362.
- Paulus, M. P., Feinstein, J. S., Castillo, G., Simmons, A. N., & Stein, M. B. (2005). Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotional processing. *Archives of General Psychiatry*, *62*, 282–288.
- Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., et al. (2005). 5-HTTLPR polymorphism impacts human cingulate–amygdala interactions: A genetic susceptibility mechanism for depression. *Nature Neuroscience*, *8*, 828–834.
- Pessoa, L. (2008). On the relationship between emotion and cognition. *Nature Reviews Neuroscience*, *9*, 148–158.
- Phelps, E. A. (2004). Human emotion and memory: Interactions of the amygdala and hippocampal complex. *Current Opinion in Neurobiology*, *14*, 198–202.
- Ravaris, C. L., Friedman, M. J., Hauri, P. J., & McHugo, G. J. (1991). A controlled study of alprazolam and propranolol in panic-disordered and agoraphobic outpatients. *Journal of Clinical Psychopharmacology*, *11*, 344–350.
- Rodriguez-Romaguer, J., Sotres-Bayon, F., Mueller, D., & Quirk, G. J. (2009). Systemic propranolol acts centrally to reduce conditioned fear in rats without impairing extinction. *Biological Psychiatry*, *15*, 887–892.
- Roosendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nature Reviews Neuroscience*, *10*, 423–433.
- Sergier, K., Chochol, C., & Armony, J. L. (2008). The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *32*, 811–830.
- Seymour, B., & Dolan, R. J. (2008). Emotion, decision making, and the amygdala. *Neuron*, *58*, 662–671.

- Swanson, L. W. (2003). The amygdala and its place in the cerebral hemisphere. *Annals of the New York Academy of Sciences*, 985, 174–184.
- Swanson, L. W., & Petrovich, G. D. (1998). What is the amygdala? *Trends in Neuroscience*, 21, 323–331.
- Stein, J. L., Wiedholz, L. M., Bassett, D. S., Weinberger, D. R., Zink, C. F., Mattay, V. S., et al. (2007). A validated network of effective amygdala connectivity. *Neuroimage*, 39, 548.
- Takahashi, H., Yahata, N., Koeda, M., Takano, A., Asai, K., Suhara, T., et al. (2005). Effects of dopaminergic and serotonergic manipulation on emotional processing: A pharmacological fMRI study. *Neuroimage*, 27, 991–1001.
- Thompson, L. T., Moskal, J. R., & Disterhoft, J. F. (1992). Hippocampus-dependent learning facilitated by a monoclonal antibody or D-cycloserine. *Nature*, 359, 638–641.
- Thompson, R., Gupta, S., Miller, K., Mills, S., & Orr, S. (2004). The effects of vasopressin on human facial responses related to social communication. *Psychoneuroendocrinology*, 29, 35–48.
- Tyrer, P. (1988). Current status of beta-blocking drugs in the treatment of anxiety disorders. *Drugs*, 36, 773–783.
- Van der Gaag, C., Minderaa, R. B., & Keysers, C. (2007). The BOLD signal in the amygdala does not differentiate between dynamic facial expressions. *Social Cognitive and Affective Neuroscience*, 2, 93–103.
- Van Stegeren, A. H., Goekoop, R., Everaerd, W., Scheltens, P., Barkhof, F., Kuijer, J. P. A., et al. (2005). Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. *Neuroimage*, 24, 898–909.
- Van Wingen, G. A., Zyllicz, S. A., Pieters, S., Mattern, C., Verkes, R. J., Buitelaar, J. K., et al. (2009). Testosterone increases amygdala reactivity in middle-aged women to a young adulthood level. *Neuropsychopharmacology*, 34, 539–547.
- Van Wingen, G. A., Mattern, C., Verkes, R. V., Buitelaar, J., & Fernandez, G. (2010). Testosterone reduces amygdala–orbitofrontal cortex coupling. *Psychoneuroendocrinology*, 35, 105–113.
- Windischberger, C., Lanzenberger, R., Holik, A., Spindelegger, C., Stein, P., Moser, U., et al. (2010). Area-specific modulation of neural activation comparing escitalopram and citalopram revealed by pharmacofMRI: A randomized cross-over study. *Neuroimage*, 49, 1161–1170.
- Wong, D. F., Tauscher, J., & Gruender, G. (2009). The role of imaging in proof of concept for CNS drug discovery and development. *Neuropsychopharmacology*, 34, 187–203.
- Woodward, D. J., Moises, H. C., Waterhouse, B. D., Yeh, H. H., & Cheun, J. E. (1991). Modulatory actions of norepinephrine on neural circuits. *Advances in Experimental Medicine and Biology*, 287, 193–208.
- Young, M. P., Scannell, J. W., Burns, G. A., & Blakemore, C. (1994). Analysis of connectivity: Neural systems in the cerebral cortex. *Reviews in the Neurosciences*, 5, 227–249.
- Zink, C. F., Stein, J. L., Kempf, L., Hakimi, S., & Meyer-Lindenberg, A. (2010). Vasopressin modulates medial prefrontal cortex–amygdala circuitry during emotion processing in humans. *The Journal of Neuroscience*, 30, 7017–7022.