Amygdala compensation during short- and long-term changes in social-emotional and non-social-emotional contexts

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deprivation from smoking disrupts amygdala responses to fear. Hum Brain Mapp 33(6): 1407-16.
3. Eckstein M, Scheele D, Patin A, Preckel K, Becker B, Walter A, Domschke K, Grinevich V, Maier W, Hurlemann R (2016) Oxytocin Facilitates Pavlovian Fear Learning in Males. Neuropsychopharmacology 41(4): 932-9.

4. Bach DR, Talmi D, Hurlemann R, Patin A, Dolan RJ (2011) Automatic relevance detection in the absence of a functional amygdala. Neuropsychologia 49(5): 1302-5.
5. Talmi D, Hurlemann R, Patin A, Dolan RJ (2010) Framing effect following bilateral amygdala lesion. Neuropsychologia 48(6): 1823-7.

I. Zusammenfassung

Als Teil des limbischen Systems ist die Amygdala von großer Bedeutung für die Bildung und Aufrechterhaltung interpersoneller Beziehungen. Darüber hinaus dient die Amygdala mit ihrer starken Konnektivität zu anderen Hirnregionen als Zentrum der emotionalen Verarbeitung und vermittelt darüber hinaus kognitive Funktionen (Pessoa, 2008; LeDoux, 2007). Unser Verständnis von der Amygdala wächst kontinuierlich, da sowohl Bildgebungs- als auch Verhaltensstudien zunehmend verwendet werden, um die Rolle der Amygdala in klinischen Störungen zu untersuchen, und da die pharmakologische Modulation der Amygdala häufiger eingesetzt wird. Die Amygdala hat sich primär als Detektor sozialer und emotionaler Salienz herausgestellt.

Das Ziel dieser Dissertation ist zu untersuchen, wie die Amygdala zum einen in ihren sozio-emotionalen und zum anderen in ihrer nicht sozio-emotionalen Funktionen beeinflusst werden kann. Zuerst werden in einem Literaturreview die Aktivierungsmuster der Amygdala nach sozialen und nichtsozialen chemosensorischen Stimuli untersucht (Patin & Pause, 2015). Anschließend wird eine Reihe von Studien vorgestellt, in denen verschiedene sozio-emotionale und nicht sozio-emotionale Funktionen untersucht werden, inklusive Studien mit chemischer Modulation (Eckstein et al., 2015a; Onur et al., 2012), die eine kurzfristige, externe Modulation darstellen, und Läsionsstudien (Bach et al., 2011; Talmi et al., 2010), die eine langfristige, interne Modulation darstellen.

Die Publikationen zeigen, dass die Amygdala auf sozial und emotional relevante chemosensorische Stimuli unterschiedlich reagiert; die linke Amygdala häufiger auf sowohl angenehme, nicht soziale als auch soziale Stimuli und die rechte Amygdala häufiger auf unangenehme, nichtsoziale Stimuli (Patin & Pause, 2015). Wenn man die Wirkung kurzfristiger chemischer Modulation untersucht, zeigen Probanden Verhaltensdefizite und neurale Veränderungen (Eckstein et al., 2015; Onur et al., 2012), was darauf hinweist, dass ihre sozio-emotionale Rolle nach einer kurzfristigen, plötzlichen Funktionsblockade nicht kompensiert werden kann. Auf der anderen Seite kann jedoch eine langfristige Amygdala-Dysfunktion aufgrund kongenitaler, Amygdala-selektiver Läsionen vor allem in einem emotionalen Kontext (Bach et al., 2011), aber auch zum größten Teil in einer nicht emotionalen Situation (Talmi et al., 2010) kompensiert werden.

Insgesamt weisen die Ergebnisse darauf hin, dass die Amygdala eine komplexe Region darstellt, die die Fähigkeit besitzt, Stimuli nach der sozialen und emotionalen Relevanz zu durchsieben und differenzieren. Darüber hinaus scheint die bedeutsame Rolle der Amygdala in sozio-emotionaler Verarbeitung so groß zu

sein, dass eine sofortige Kompensation im Fall einer fehlenden Aktivität unmöglich ist. Auf der anderen Seite ist die Amygdala wichtig genug, dass sich langfristige Kompensationsmechanismen schließlich bilden.

II. Abstract

The amygdala, as part of the limbic system, provides a foundation for interpersonal relationships and serves as an emotional processing center through its rich connectivity to other brain regions, as well as allocates resources for certain cognitive functions (Pessoa, 2008; LeDoux, 2007). Our understanding of the amygdala is continuously growing, as both imaging and behavioral studies have increasingly been used determine its role in clinical disorders, and pharmacological modulation of amygdala function has become more common. The amygdala has emerged primarily as a detector of social and emotional salience, and social-emotional paradigms have dominated recent years of the literature.

The aim of this dissertation is to explore how the amygdala can be influenced in its social-emotional vs the nonsocial functions. To do this, an initial literature review illustrates the patterns of amygdala activation following both social and nonsocial chemosensory stimuli (Patin & Pause, 2015). Following this, a series of studies is presented examining different social-emotional and nonsocial-emotional functions, including both chemical modulation studies (Eckstein et al., 2016; Onur et al., 2012), representing a short-term, external modulation, and lesion studies (Bach et al., 2011; Talmi et al., 2010), which represent a long-term, internal modulation.

The publications show that the amygdala responds differently to social and emotionally valenced chemosensory stimuli, specifically that the left amygdala responds more frequently to pleasant nonsocial and social stimuli and the right more frequently to unpleasant, nonsocial stimuli (Patin & Pause, 2015). When the effect of chemical modulation on social paradigms is examined, the amygdala shows behavioral deficits and neural changes (Eckstein et al., 2016; Onur et al., 2012), indicating that its social-emotional role cannot be compensated for following a short-term, immediate block of function. On the other hand, long-term amygdala dysfunction following congenital, amygdala-selective lesions, can be compensated for, especially in an emotional context (Bach et al., 2011) but also to a great extent in a non-emotional setting (Talmi et al., 2010).

Overall, the results suggest that the amygdala represents a complex region with the ability to sift through and differentiate types of stimuli according to social and emotional relevance, but also that the vital role the amygdala plays in social-emotional processing is both large enough to make immediate compensation impossible in the event of its absence, but important enough that long-term mechanisms of compensation eventually form.

III. Theoretical and empirical background

III. 1. The amygdala

A focal point in research on social-emotional processing, the amygdala has transitioned from its image of a homogenous region in the basal ganglion to a conglomerate of integrated nuclei, fibrously and chemoarchitectonically linked to form the amygdaloid complex (Brockhaus, 1938, 1940). Nuclei and subnuclei work together in various constellations (LeDoux, 2007) to process emotional stimuli and influence other cognitive mechanisms (Pessoa, 2010). The amygdala's connections, for instance, first to the basal forebrain and on to the cortical mantle, and second to the visual cortex, provide the amygdala with a basis for modulating cognitive processes such as attention, value representation, and decision-making (Pessoa, 2010). Currently, many authors divide the amygdala into three categories: the superficial (corticoid) amygdaloid nuclei, the centromedial group, and the laterobasal complex (Heimer et al., 1999; Amunts et al., 2005).

The ability of the various amygdalar subregions to take on different roles in emotional processing is a result of the differential distribution of receptors for several neurochemical pathways, including but not limited to the dopaminergic, glutamatergic, and serotonergic pathways, as well as for hormonal pathways such as glucocorticoid and estrogen hormones, and neuropeptide pathways, for example oxytocin (OT), vasopressin, and neuropeptide Y (LeDoux, 2007). For the most part, the amygdala is activated by salient, relevant stimuli, and thus controlled by inhibitory mechanisms following its initial excitatory response (LeDoux, 2007).

A comprehensive quantitative analysis by Young and colleagues shows a remarkably large number of connections to many cortical areas (Young et al., 1994). Other authors have suggested that this may be the basis of the amygdala's ability to integrate and modulate various cognitive and emotional processes (Pessoa, 2008; see also Barbas et al., 1995; Swanson et al., 2003). These processes form a network of emotional behavior, including reactions to fear or reward, as well as motivation (LeDoux, 2007). Cognitive functions such as perception, attention, memory, declarative learning (Swanson & Petrovich, 1998; LeDoux, 2007; Aggleton, 2000), value representation, and decision-making (Pessoa, 2010) are also modulated via the amygdala. Furthermore, the amygdala has been implicated in more primal, social emotions relating to aggression, and maternal, sexual and ingestive behaviors (LeDoux, 2007).

III. 2. Chemosensory stimulation of the amygdala

As part of the primary olfactory cortex (POC), the amygdala receives direct olfactory and chemosensory input. As opposed to all other sensory modalities, chemosensation is not filtered prior to its arrival in the amygdala by the thalamus (Gottfried et al., 2006). This could be a main reason for why olfactory and gustatory stimuli most strongly invoke an amygdala response compared to other modalities (Costafreda et al., 2008) and why neocortical processing of chemosensory stimuli takes precedence over other emotional stimuli (Adolph & Pause, 2012). In accordance with the amygdala's position as part of the POC, abnormal chemosensory processing has been found in various pathologies in which the amygdala plays an important role, such as major depressive disorder (Pause et al., 2001), schizophrenia (Kohler et al., 2001; Moberg et al., 1999), and epilepsy (Kohler et al., 2001).

Following inhalation of a stimulus, the fila olfactoria (receptor cell axons, cranial nerve I) transmit the signal to the olfactory bulb and eventually, following a process of signal magnification (Adam & Mizrahi, 2010; Firestein, 2001; Su et al., 2009; Zou et al., 2009), on to the olfactory tract and the rest of the POC (Cleland & Linster, 2003), including the anterior cortical nucleus of the amygdala, the anterior olfactory nucleus, olfactory tuberculum, piriform cortex (PC), periamygdaloid cortex on the medial surface of the amygdala, and entorhinal cortex (EC) (Price, 2003; Wright, 1997). From there, signals are transmitted to the secondary olfactory cortex, namely the hippocampus from the EC; the orbitofrontal cortex (OFC), insular cortex, and thalamus from the PC; and OFC and hypothalamus from the amygdala (Carmichael et al., 1994; Cleland & Linster, 2003; Gottfried, 2006; Wilson & Sullivan, 2011).

Most of the POC is made up of three-layer paleocortex (Rubinstein et al., 1999), representing its role in one of the oldest regions of the brain; as the amygdala's volume increased throughout evolution, so did its role in olfactory processing (Barton & Aggleton, 2000; Gottfried, 2006). The route of transmission described above contrives the main olfactory system (Keller et al., 2009). Lesser understood is the route taken by social chemosensory stimuli, which in recent years has been associated with trace amine-associated receptors (TAARs) in the olfactory epithelium (Carnicelli et al., 2010; Horowitz et al., 2014; Liberles, 2009). In mice, amines released by predators evoke avoidance behavior (Dewan et al., 2013; Liberles, 2015; Liberles & Buck, 2006), indicating a crucial role for trace amines and the TAAR system in social judgments.

III. 3. The amygdala's evaluation of social-emotional stimuli

From almost the beginning of functional magnetic resonance imaging (fMRI) research, the amygdala has been one of the most examined regions for social and emotional processing. Emotional stimuli have been found to consistently activate the amygdala (Alpers et al. 2009; Schienle et al. 2007; Billot et al. 2017; Patin & Pause 2015). More recent findings show that the amygdala also responds to specifically social stimuli, as well (Adolphs, 2003; Patin & Pause, 2015). The newest studies have begun examining the intersection of these two realms, i.e. the social-emotional function of the amygdala. Initial studies have found that the amygdala reacts to neutral faces (Breiter et al., 1996), but also plays a role in low-level processing of the emotional aspect of faces, for instance through facial expression (Breiter et al., 1996; Critchley et al., 2000; Hariri et al., 2000) or by using faces with an emotional attachment to the participant (Seeck et al., 1993). Later findings have expanded the social-emotional spectrum to include functions from fear conditioning (LaBar et al., 1998) and emotional learning (Morris et al., 1998), to maternal and sexual behaviors (LeDoux, 2007).

In recent literature, the term social cognition has gained increasing popularity when describing the cognitive processing of emotions, even if the term itself is relatively difficult to precisely define (Adolphs, 2003). Functions described above, such as emotion recognition (Elfenbein & Ambady, 2002) or theory of mind, can be included in the concept of social cognition, but it can also be extended to encompass related areas, such as emotional empathy, the ability to infer feelings in another, cooperation, trust, social feedback-based learning (Patin & Hurlemann, 2015), and the ability to reciprocate social signals (Roepke et al., 2013). Findings from single cell studies have shown that the amygdala plays a vital role in emotion judgment (Wang et al., 2014), and even that it preferentially reacts to animals over humans (Mormann et al., 2011).

The higher level functions comprising social cognition are based in a diverse neural network, in which the amygdala (Adolphs, 2003; Haxby, 2000; Tudusciuc & Adolphs, 2013) works together with the prefrontal cortex (PFC), cingulate gyrus, fusiform gyrus, insula, somatosensory cortex, superior temporal sulcus, and supramarginal gyrus (Tudusciuc & Adolphs, 2013). Specific functions, such as static versus dynamic faces, are taken over by the fusiform gyrus and fusiform face area as well as the superior temporal sulcus, respectively (Adolphs, 2003; Haxby, 2000).

III. 4. Urbach-Wiethe Syndrome and its influence on amygdala function

Danial Tranel, in an interview with S.M., a patient with Urbach-Wiethe disease.: Tell me what fear is.

S.M.: Well, that's what I'm trying to - to be honest, I truly have no clue.

-- Excerpt from an interview presented on National Public Radio's *Invisibilia* (Spiegel & Miller, 2015)

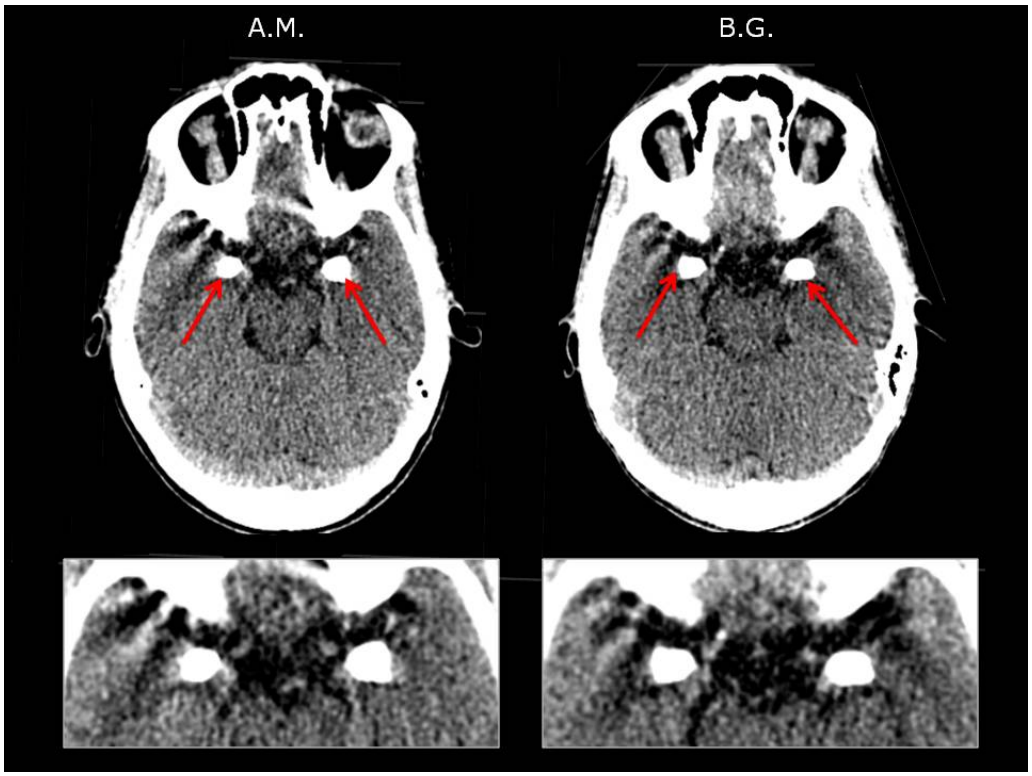

Fig 1: A cranial computer tomography scan of UW patients A.M. and B.G. shows bilateral calcification lesions located in the bilateral amygdala (Hurlemann et al., 2010a)

Urbach-Wiethe syndrome, otherwise known as lipoid proteinosis, is a rare autosomal recessive disorder; roughly 300 cases have been identified worldwide (Cordoro et al., 2011) since it was first introduced in 1929 by Erich Urbach and Camillo Wiethe (Urbach & Wiethe, 1929). The illness is characterized by cutaneous, mucosal, and visceral deposits of periodic acid-Schiff-positive hyaline (glycoprotein) material (Cordoro et al., 2011; Hamada, 2002), and roughly 50-75% of reported cases demonstrate selective bilateral amygdala calcification (Appenzeller et al., 2006; Hurlemann et al., 2007). Whether these deposits are a

primary or secondary phenomenon is unknown (Cordoro et al., 2011). Because the surrounding regions, including the hippocampus, remain intact (Hurlemann et al., 2007), the site of the lesions has made UW an advantageous basis for researching the effect of the amygdala on cognitive and emotional processes. Whereas in pharmacological studies a single target receptor or neurochemical pathway is chosen, in the case of UW, the entire amygdala is affected regardless of receptor, while other neural regions remain undamaged.

Early research described both the physical descriptions of the calcifications as well the neurophysiological symptoms (see for example Hofer et al., 1974; Wedrychowicz & Starzycki, 1978; Meenan et al., 1978). The literature evolved to show an increased focus on the neuropsychological and social-emotional consequences of the disease, specifically the absence of a fully functional fear center. Tranel and Hyman first focused on neuropsychological correlates and emphasized the damage to the amygdala over other physiological changes (Tranel & Hyman, 1990).

This opened up an exploration of the amygdala's social and emotional functions, and authors reported impaired emotional memory (Markowitsch et al., 1994), recognition of fearful faces, reduced anxiety in social contexts, and an impaired ability to acquire a healthy conditioned fear response (Adolphs et al., 1994, 1998, 2005). In a study including one of the largest participant groups of UW patients, Siebert and colleagues found that 10 UW patients showed impaired emotion recognition in an odor-figure association task and an emotional memory task, while they showed no impairments in cognitive tasks (Siebert et al., 2003), supporting initial findings of emotional recognition deficits (Adolphs et al., 1994). Social cognition studies have found that UW patients display a reduced ability to judge social attributes of an unfamiliar person (Adolphs et al., 1998) and an increased willingness to approach others (Harrison et al., 2015).

More recent findings have continued to address the traditional notion of UW patients being without fear (Bach et al., 2013; Becker et al., 2012; Feinstein et al., 2013; Klumpers et al., 2015; Mihov et al., 2013; Terburg et al., 2012) or an ability to perceive social threat (de Gelder et al., 2014). Other studies have branched out to include topics such as experience of emotion (Tranel et al., 2006), altruistic punishment of others (Scheele et al., 2012a), and social network size (Becker et al., 2012).

Over all studies, UW patients show several similarities, but interestingly, there is no one area in which all studies have found common ground. Even the realms of fear processing or emotion recognition, which belong to some of the most present of amygdala functions, show differences among studies. This could be, and in some cases most likely is, due to methodological differences in paradigms. Patients could also be

working from cognitive strategies developed over the years to evaluate stimuli. A third explanation, however, lies in neural plasticity, which is most likely responsibly for varied levels and areas of compensation for varied tasks, different in each UW individual. The amygdala is crucial to coordinating different cortical networks during emotional processing (Pessoa & Adolphs, 2010), a process which may start very early in life. Because amydala lesions in UW most likely correlate with disease duration (Appenzeller et al., 2006), other functional networks could become responsible for maintaining their function when the amygdala becomes absent. This variability is unsurprising, given how complex and varied human beings are: the concept of degeneracy states that, given a lesion, or degenerate region, interpersonal variation and funcitonal specialization within the brain determine which brain regions can or will take over which tasks (Price & Friston, 2002). Thus following, paradigms given to lesion patients may show deficits or may not (Price & Friston, 2002).

Included in this dissertation are two studies designed to examine the necessity of a functional amygdala for processing emotional stimuli in the first study (Bach et al., 2011) and non-emotional stimuli in the other (Talmi et al., 2010). Thirty-four-year-old monozygotic twin women A.M. and B.G., who have both been diagnosed with Urbach-Wiethe disease, were included in both studies. The disease was discovered after B.G. suffered a single epileptic grand-mal seizure at age 12; A.M. has never suffered an epileptic seizure. During neuropsychological screening for the studies, both patients showed average intelligence (LPS-4, Horn, 1983) and average performance on most neuropsychological tests during an extensive test battery. We included verbal learning and memory (Rey Auditory Verbal Learning Test, Helmstedter et al., 1981), executive function (Trail-Making Test, Reitan, 1955; Wisconsin Card Sorting Test, Kongs et al., 2000; Strooptest, Baeumler, 1985), and semantic fluency (Aschenbrenner et al., 2000). Both patients demonstrated minor impairments in short-term concentration (d2-Test, Brickenkamp, 1995). A.M. was impaired in figure learning and memory (Complex Figure Test, Osterrieth, 1944; DCS, Weidlich & Lamberti, 2001).

To date, they are the only known monozygotic twins to present with the disease. Against the backdrop of exactly equal genetic makeup and similar nurturing during their early lives as well as their adult lives (both twins decided to stay in the same area, marry, and have children) as well as their unwavering willingness to contribute to the growing body of UW research, they provide an unparalleled opportunity to create a model of neural plasticity and compensation in the face of an absent amygdala.

III. 5. Pharmacological modulation of the amygdala

The amygdala's central role in emotional and social processing has made it a popular region of interest in studying how the brain relates to emotional stimuli under varying conditions. Initial studies focused for the most part on substance abuse and patients with affective disorders, and have given way to an increased use of pharmacological modulation of the amygdala to examine its regulation of and by different neurochemical pathways (Patin & Hurlemann, 2010). Three of the most researched substances related to the serotonergic, noradrenergic, and oxytocinergic pathways.

Selective serotonin reuptake inhibitors (SSRIs), which are among the most widely used agents to explore amygdala function in healthy individuals, have been found to dampen amygdala response to negative emotions or imagery (Arce et al., 2008; Harmer et al., 2006; Outhred et al., 2015; Takahashi et al., 2005), as well as to increase amygdala response to positive emotions (Norbury et al., 2009). Recent work on the 5-HTTLPR polymorphism (serotonin-transporter-linked polymorphic region), which has been associated with increased serotonin transporter expression (Heils et al., 1995; Hu et al., 2006), showed that individuals with two long alleles showed no increased amygdala response to fear, whereas individuals with short variations responded differently to fearful and angry faces than to neutral faces (Fisher et al., 2015). Therefore, it appears that study results could be strongly dependent on underlying genetic variations within participant groups.

Noradrenergic substances appear to directly influence amygdala response in an opposite pattern to serotonergic influence (Outhred et al., 2013). Findings in single-dose studies showing reduced amygdala response following a noradrenaline (NA) block (Hurlemann et al., 2010b) and an increase in amygdala response following an increase in NA (Onur et al., 2009), indicating a direct reflection of amygdala activity based on noradrenergic input level. In a recent study, a decrease in NA induced a lower amygdala response to fearful faces in men, but an increased response in women (Schwabe et al., 2013), illustrating here, too, vast differences among participant groups. NMDA receptors additionally appear to play an important role in amygdala response, and been found to influence reward-based behavior, especially in the central nucleus of the amygdala (Kenny et al., 2009; but see also Onur et al., 2010).

III. 6. Aim and hypotheses of this dissertation

Against the background of the amygdala's role in emotional processing, as well as recent literature's focus on regulation of both the amygdala itself and by the amygdala of other regions, this dissertation aims to examine modulation of the amygdala according to social and social-emotional properties through external (chemical) and internal (lesion) influences. The following three hypotheses arose over the course of the five publications included in this dissertation:

1. The amygdala responds differently to social vs. nonsocial chemosensory stimuli. Pleasant, nonsocial stimuli preferentially activate the left amygdala, while unpleasant, nonsocial stimuli preferentially activate the right amygdala. Social stimuli tend to activate the left amygdala.

In a literature review, two core roles of the amygdala in stimulus processing are examined: first, its part in chemosensory stimulus processing as part of the primary olfactory cortex. Second, as part of the limbic system, the amydala processes emotional stimuli. In the review, the intersection of these roles and how the amygdala differentially responds to emotional, social, and other stimuli is examined by categorizing stimuli according to type (i.e. valence, intensity, social quality), method of delivery (i.e. sniff vs no sniff, stimulus duration, flow rate), paradigm (e.g. attention to stimulus), and other factors (e.g. age, gender, personality). Results are organized according to lateralization of activity in response to valence then in response to the social quality of the stimulus, and finally according to regions that were simultaneously activated alongside the amygdala. Overall, findings show that the left amygdala tended to respond to pleasant, nonsocial stimuli as well as social stimuli. The right amygdala tended to respond to unpleasant, nonsocial stimuli. This separation could illustrate a rapid, basic evaluation of potentially threatening chemosensory stimuli by the right amygdala, and a more laborous, slower, continued evaluation of stimuli in the left amygdala. An additional discussion of possible factors confounding amygdala activation is included following the discussion of the results.

2. Short-term, chemical modulation of amygdala activity is evident in a social-emotional context, i.e. during social-emotional experimental paradigms. This illustrates that social functions are dependent on the amygdala in healthy people, and these cannot be immediately compensated for in the event of changed amgydala function.

In Section III.3., the amygdala's role in social, emotional, and social-emotional functions is discussed. Because the amygdala plays such a strong role in these realms, the question arises, what are the consequences of a sudden dampening of amygdala activity during a social paradigm? To explore this

question, this dissertation includes two studies in which social-emotional paradigms are combined with a chemical or pharmacological challenge to dampen amygdala activity.

In the first study, designed to explore the effect of nicotine on the amygdala, amygdala response in smokers in both saturated and in deprived states was compared with that of nonsmokers (Onur et al., 2012). After showing participants pictures of emotional faces, saturated smokers showed similar response patterns when faced with threatening stimuli as non-smokers did, while the deprived smokers actually showed lower activation in the amygdala to fearful faces. In a second study, we explored oxytocin's effects on a Pavlovian fear conditioning paradigm which used social stimuli. Oxytocin was shown to facilitate fear conditioning, but unexpectedly, the paradigm did not significantly activate the amygdala. However, there was amygdala activation at an uncorrected level, suggesting that the amygdala was activated during fear learning.

In both studies, chemical modulation of the amygdala has a strong, apparent effect on paradigm results because other neural regions cannot immediately compensate for the changed amygdala activity.

3. Long term, internal amygdala modulation due to lesions can be used to illustrate compensation for missing amygdala function in both emotional and non-emotional paradigms. The level of compensation differs based on the cognitive resources needed to carry out the task and emotional content of the paradigm.

Given that the amygdala plays such a strong role in social and emotional processing (see Section III. 3.), and that patients with amygdala lesion often present with deficits in precisely these areas (see Section III. 4.), this dissertation aims to determine in which areas amygdala dysfunction can be overcome and furthermore how this normalization of amygdala activity could be related to long-term compensatory mechanisms.

The final two studies concentrate on two Urbach-Wiethe (UW) patients to explore the necessity of a functional amygdala in automatic relevance detection and a framing effect in risky decision-making. The first study (Bach et al., 2011) of automatic relevance detection for emotional stimuli found no difference between healthy controls and the patients, suggesting a possible compensatory mechanism for lesions acquired early in life. As Kennedy and Adolphs wrote in a recent review, "The amygdala, by itself, does nothing; instead, it is important to begin asking questions about the networks within which the amygdala participates – and of these there are many" (Kennedy & Adolphs, 2012).

The second study (Talmi et al., 2010) explored the framing effect with the subsequent propensity to gamble. UW patients showed a normal framing effect but an increased willingness to gamble compared to controls. In both studies, the patients demonstrated the ability to perform at the level of healthy controls. However, in the second study, their increased propensity to gamble suggests either that compensatory measures are not fully developed, or that even fully developed compensatory mechanisms cannot extend to the amygdala's modulation of other cognitive processes. Taken together, the two studies could further indicate that, while other regions can compensate for the amygdala's role in emotional paradigms, they do not compensate fully for its role in non-emotional paradigms.

Overall, the publications included here serve to present a balanced view of the amygdala's ability to discern different qualitative stimulus properties, including social-emotional or emotional content, and the ability of compensatory mechanisms to neutralize both sudden and long-term reductions in amygdala activity.

IV. Original studies

IV. 1. Amydgala response to nonsocial and social chemosensory stimuli

Study 1: Patin A, Pause BM (2015) Human amygdala activations during nasal chemoreception. Neuropsychologia 78: 171-94.

In a literature review, the effect of different olfactory and chemosensory stimuli on amygdala activation is explored. Because of its privileged position as part of the primary olfactory cortex, the amygdala receives direct chemosensory input without prior filtering by the thalamus (Gottfried, 2006), allowing for preferential treatment over other emotional stimuli (Adolph & Pause, 2012) and for the sidestepping of attentional processes found in other areas of sensory modulation (Albrecht & Wiesmann, 2006). Therefore, olfaction and chemosensory perception can be viewed as an ideal basis for exploring the most basic, but also most robust, functions of the amygdala. Smells can be entirely neutral; emotional, either due to an association in one's memory or due to the smell's innate characteristics, such as being extremely disgusting;

or even social, such as sweat produced by another human. This literature review, therefore, set out to explore the patterns of amygdala response given the different aspects of chemosensory and olfactory stimuli.

Methodology

A search was done on Pubmed including the search terms 'fMRI' or 'PET' in combination with either 'olfactory,' 'chemosensory,' 'odor,' 'odour,' 'smell,' or 'pheromone,' and the abstracts were read to identify studies that had concentrated on olfactory or chemosensory stimuli given to a population with healthy olfactory abilities. The studies which met these criteria were read and included in the review if they included results for amygdala activation as a result of an orthonasally presented stimulus alone and not in combination with a paradigm, such as a learning or memory task.

Data were collected regarding directed attention to stimulus (sniffing), stimulus concentration, duration of stimulus presentation, perceived intensity and pleasantness, and paradigm. Lateralization of amygdala activity was reported as well as other olfactory and non-olfactory regions activated simultaneously. Primary and secondary olfactory regions include the amygdala, piriform cortex, entorhinal cortex, OFC, insula, anterior (ACC) and posterior cingulate cortex, thalamus, and hippocampus. The borders of the OFC were set at x between +3/-3 and +49/-49, y +6 - +61, and z -5 - -32 (Zald & Rauch, 2006).

Studies used either an olfactometer (fMRI, with the exception of one study) or a glass bottle or cotton ball held near the participant's nose (PET, with the exception of one study) to deliver the stimuli.

Results and Interpretation

Main findings were that the amygdala responds differently depending on lateralization due to valence and on social quality of the sitmuli. Commonly used laboratory stimuli included vanillin, phenylethyl alcohol, and butanol, which resulted in bilateral and left amygdala activation. Pleasant stimuli resulted in left and bilateral amygdala activation (one study found right amygdala activation in a region of interest (ROI) analysis of chocolate odor (Small et al., 2005)). Unpleasant stimuli resulted in right and bilateral amygdala activation (a single study showed left response in males, but not in females (Royet et al., 2003)). The right amygdala, therefore, was shown to show a greater response to unpleasant chemosensory stimuli. Social stimuli showed mainly left amygdala response.

This is the first time a review of chemosensory literature has established the similar pattern of amygdala response as is found following emotional stimuli, such as faces or images (see for instance meta-analyses by Costafreda et al., 2008; Siebert et al., 2003). It is tempting to suggest that the right amygdala preferentially responds to unpleasant stimuli; however, this seemingly higher response is more likely a question of the temporal resolution of imaging methods. Instead of a constant period of amygdala response to a stimulus, several authors suggest that the two hemispheres somewhat independently evaluate novel stimuli: the right amygdala shows a rapid response, providing for a quick and superficial evaluation, while the left amygdala works to provide a more thorough evaluation, thereby giving off a more sustained signal (Costafreda et al., 2008; Glascher & Adolphs, 2003; Phillips et al., 2001; Sergerie et al., 2008; Wright et al., 2001). This longer evaluation by the left amygdala could be responsible for the classification of a stimulus according to its attractiveness, leading to the differential response of the right and left amygdala in imaging research (Glascher & Adolphs, 2003).

A study examining the effect of a positive vs. negative label on the same stimulus showed greater fMRI blood-oxygen-level dependent (BOLD) response to the positive labels (de Araujo et al., 2005), which is consistent with findings showing greater response to positive emotional, non-chemosensory, stimuli (Sergerie et al., 2008). A further factor in studies showing bilateral amygdala response was familiarity, which could be an effect of the previously shown corelation of familiarity with pleasantness (Delplanque et al., 2008; Distel et al., 1999; Engen & Ross, 1973; Lawless & Cain, 1975; Royet et al., 1999; Sulmont et al., 2002; Zajonc, 1968). This correlation could also add to the interpretation of findings showing right amygdala response to unfamiliar, neutral stimuli (Savic & Gulyas, 2000; Savic et al., 2000), in that unfamiliar stimuli could be interpreted as more unpleasant than neutral.

The left amygdala response found by studies using social stimuli could indicate several things. For one, social stimuli could require a more sustained evaluation than nonsocial stimuli, reflecting complexities within human friend-foe networks. This, however, would suggest that the amygdala does not posess a defense mechanism consisting of rapid judgment of social stimuli, which would not benefit survival during immediate threat. More likely, social stimuli are processed along a pathway separate to nonsocial stimuli with a greater dependency on TAARs. This is in accordance with previous literature illustrating that social stimuli are processed by more specialized networks, both within and outside of the amygdala (Adolphs, 2010; Dunbar, 2010; Goossens et al., 2009; Pause, 2012). These findings suggest that the evolutionary basis for amygdala response to social chemosensory stimuli is still present in everyday response.

Finally, the literature review presented here showed that the most common regions to be activated simultaneously to the amygdala were the OFC, the PC, and the insula, in order of frequency. Previous findings show greater connectivity between amygdala nuclei and the OFC in some cases than between nuclei within the amygdala (Nigri et al., 2013; Zald & Kim, 1996), illustrating an extremely close knit relationship of the amgydala to the OFC, possibly to influence behavior (Schoenbaum et al., 1998). It is theefore not surprising that it was the most activated region here. Also not surprising is the PC, which makes up a large part of the POC (Carmichael et al., 1994; Gottfried, 2006). Interestingly, the PC responses were overwhelmingly bilateral, suggesting that the right versus left hemisphere system of evaluation is specific to the amygdala, at least at the first moment of stimulus processing. Finally, the finding that insula activity so often correlated with the amygdala is interesting because of the insula's role in autonomic, interoceptive processing (Critchley et al., 2004; Craig, 2002). Chemosensory processing could therefore play a very strong role in interoception.

IV. 2. Short-term amygdala modulation within a social-emotional context

Study 2: Onur OA, Patin A, Mihov Y, Buecher B, Stoffel-Wagner B, Schlaepfer TE, Walter H, Maier W, Hurlemann R (2012) Overnight deprivation from smoking disrupts amygdala responses to fear. Hum Brain Mapp 33: 1407-16.

According to the American Heart Association, "nicotine addiction has historically been one of the hardest addictions to break." The strength of this addiction has tragic effects: of those who attempt to quit smoking, only 20-40% will be successful (Faller & Lang, 2006). Due to nicotine's short half-life, smokers turn to chain-smoking to ward off the withdrawal effects, which include nervousness, the inability to keep still, aggression, and concentration difficulties (Faller & Lang, 2006). The nicotinic acetylcholine receptor (nAChR) is located throughout the central and peripheral nervous system, more specifically in the ventral tegmental area (VTA), which leads to dopamine (DA) transmission in the nucleus accumbens (NAcc), PFC, and amygdala (Benowitz, 2010).

After only a matter of hours, studies have found an upregulation of binding to the nAChRs (see Govind et al., 2009). Isolating possible mechanisms of this upregulation remain difficult because of the large number of nicotinic receptor subtypes (Govind et al., 2009).

The behavioral effects of nicotine have been linked to the mesocorticolimbic DA system (Govind et al., 2009). The pathway begins in the VTA and progresses to the NAcc, amygdala, hippocampus, and into the prefrontal and frontal cortex (see Nestler & Aghajanian, 1997). Following nicotine exposure, this circuit plays a central role in the feeling of reward (Vezina et al., 2007). Rodent studies have shown that repeated injections of nicotine increase the drug's locomotor activating effects (Clarke et al., 1988; Ksir et al., 1985), as well as sensitize the amygdala's ability to increase NAcc DA release (Benwell & Balfour, 1992; Benwell et al., 1995; Schoffelmeer et al., 2002; Balflour et al., 1998). This sensitization appears to directly correlate with the length of withdrawal (Schoffelmeer et al., 2002; Benwell et al., 1995). Furthermore, rodents show increased drug self-administration after sensitization of midbrain DA neuron reactivity (Vezina, 2004; Vezina et al., 2002) . During withdrawal, nicotine is not as effective in activating NAcc DA release (Rahman, 2004), which could lead to an increase in drug-seeking behavior as an attempt to regain the feeling of reward.

Next to the DA circuit, glutamatergic NMDA receptors are also linked to the rewarding effect of nicotine consumption by increasing glutamatergic transmission in reward circuits (Kenny et al., 2009). Furthermore, NMDA receptors appear to be responsible for moderating the magnitude and valence (for instance the feeling of satisfaction or lack of) of nicotine effects on reward circuits, the effects being especially pronounced in the central nucleus of the amygdala (Kenny et al., 2009).

The study presented here was designed to examine the differences in amygdala response to emotional faces between nonsmokers, abstinent smokers, and satiated smokers.

Methodology

We tested 56 adults (28 females, 28 males), 28 of whom were chronic smokers (>15 cigarettes per day; 14 females, 14 males) and 28 of whom were nonsmokers (14 females, 14 males). We tested the participants prior to the task on verbal learning skills, working memory, and facial emotion recognition skills.

We compared amygdala response in two contexts: in a between-group analysis, satiated smokers were compared to nonsmokers, while in a within-group analysis we compared satiated and abstinent smokers (following overnight deprivation). For the second comparison, we completed two fMRI scans at least one week apart. Smokers alternately abstained from smoking for 12 hours prior to the scan (overnight deprivation) and smoked their last cigarette one hour prior to the scan (satiated state). Participants rated the

strength of their cravings as well as completed questionnaires on their current mood immediately prior to the scans. We also gave participants the Fagerström-test for nicotine dependence (FTND; Bleich et al., 2002; Heatherton et al., 1991), to rate the severity of their addiction.

A facial emotion paradigm, including pictures of fearful, neutral, and happy faces, was used to evoke amygdala response, compared to pictures of houses, with a fixation cross between each stimulus.

Results and interpretation

Smokers in a deprived state showed a lower amygdala response in the right amygdala to fearful faces. This response to fear correlated with addiction: the higher the smokers scored on the FTND, the lower their amygdala response to fearful faces during deprivation.

The cravings experienced during the fMRI scans were unprovoked, instead of stimulated by visual, auditory, or other cues, and based purely on the severity of feeling of deprivation. Based on probability maps (Amunts et al., 2005; Eickhoff et al., 2005), the abnormal amygdala activation found in this study could be traced to the basolateral amygdala (BLA). Animal studies showing that the BLA is active during fear detection (LeDoux, 2007) are in line with human studies showing that the amygdala is activated when presented with fearful faces (LaBar et al., 1998; Whalen et al., 2001). On the other hand, patients who have undergone a temporal lobectomy have shown a lower fear-conditioned startle response, showing the deficiency of amygdala absence (Funayama et al., 2001). Given these data, we can draw the connection between stunted amygdala activity during nicotine cravings and a lowered reaction to fear stimuli. This might mean that research showing amygdala hyperactivation and overexpression of fear responses (Quirk & Gehlert, 2003) is not valid when it comes to nicotine withdrawal.

The question arises, what might these findings say about nicotine dependence on a behavioral level? Our finding that nicotine withdrawal results in a lowered amygdala reaction to fear might be the reason for continued smoking in cancer patients with tracheostoma or in Buerger's Disease patients, despite characteristic peripheral ischemic tissue damage, which is often complicated by fatal ulcerations and gangrene (Malecki et al., 2009). Continued smoking despite such grave physical consequences could be a consequence of a stunted amygdala response to and in turn an impaired perception of stimuli which would otherwise cause fear-motivated avoidance of such threats.

The implication of such a lowered fear response might also be one reason that so few individuals who attempt to quit are successful (Benowitz, 2010; Faller & Lang, 2006). Previous research has shown that unprovoked, abstinence-induced nicotine cravings are a reliable predictor of relapse after an attempt to quit smoking (Killen & Fortmann, 1997; Shiffman et al., 1997). This might mean that the stronger the craving, the lower the ability or desire for self-preservation. This theory would complicate the effectiveness of public health awareness campaigns based on fear appeals, such as warning labels on cigarette packaging. Satiated smokers would perceive the threats, but this perception, and in turn desire for self-preservation, would diminish as soon as the abstinence-induced cravings set in.

In this study, the time span of one night of deprivation is apparently too short for the brain to completely compensate for the amygdala's compromised fear reaction. The importance of the amygdala is thus illustrated in this study, in that we can see the potentially tragic effects (e.g. lack of self-preservation) when it is not present. An interesting question to pursue further would be to determine, the direction of causality between amygdala hypofunction and smoking habits.

Study 3: Eckstein M, Scheele D, Patin A, Preckel K, Becker B, Walter A, Domschke K, Grinevich V, Maier W, Hurlemann R (2016) Oxytocin facilitates Pavlovian fear learning in males. Neuropsychopharmacology 228: 271-303.

Although oxytocin has a relatively long historical tradition of social research, starting with social bonding and sexual behaviors (Kendrick et al., 1987; Mahalati et al., 1991; Pedersen & Prange, 1985; Witt et al., 1990) and branching out into social cognition (Dantzer et al., 1987; Popik & Vetulani, 1991), it has become an indispensable tool for social neuroscience in recent years.

OT is produced mainly in the supraorbital and paraventricular nuclei of the hypothalamus, which transmit to the amygdala as well as the neurohypophysis, NAcc, and to other regions in central nervous system (Knobloch et al., 2012). Synthetic OT has been available since 1953, when it became the first sequenced and synthesized polypeptide hormone available (du Vigneaud et al., 1953, 1954). Although exact data regarding OT's ability to cross the blood-brain barrier are not available, initial findings suggest that intravenous OT crosses at a rate of only a fraction of a percent (Kendrick, 1991). On the other hand, intranasal administration of OT, which is by far the more common method used in human studies, has been shown to increase both plasma and cerebrospinal fluid OT levels (Striepens et al., 2013).

Newer studies of social cognition and behavior have shown that OT plays an important role in social group living and monogamous pair bonds in humans (Scheele et al., 2012b, 2013). Moreover, results show that OT reduces amygdala response to fear-inducing stimuli (Kanat et al., 2015; Sobota et al., 2015) and facilitate fear extinction in a Pavlovian fear paradigm (Eckstein et al., 2015). Given OT's effect on social stimulus processing as well as fear extinction, we therefore undertook this study to see what effect OT has on fear conditioning.

Methodology

We tested 97 healthy males (mean age 24.45 ± 4.02 years) in a randomized, placebo-controlled, double-blind, between-subject design. We used a Pavlovian fear conditioning paradigm which was adapted for use in an fMRI experiment (for details, see Becker et al., 2013). Neutral, condition stimuli (CS+) were either paired with an aversive, unconditioned stimulus (UCS) or left unpaired (CS-). The UCS consisted of an electric shock at 70% contingency. The conditioned stimuli consisted of faces and houses, allowing for the isolation of OT effects on a social and a nonsocial CS. Participants waited 30 min following OT (24 IU) or placebo administration to start the fMRI task. Stimuli were presented for 4000 ms each separated by 8 – 11 sec, 30 times total. Finally, skin conductance response (SCR) was measured in each participant.

Results and Interpretation

FMRI results showed that the CS+ (both social and nonsocial) activated the insula, cingulate cortex, and additional prefrontal areas. The contrast CS+ > CS- showed an increased response in the subgenual anterior cingulate cortex (sACC) in participants given OT. More specifically, an effect of sociality (faces versus houses) was found in the posterior midcingulate cortex (pMCC) in the OT condition as well. These results can be interpreted to mean that OT facilitated fear conditioning via potentiation of sACC response to fear-inducing stimuli overall, and via potentiation of the pMCC to social stimuli.

On a behavioral level, participants showed faster reaction times to the CS+ when given OT compared to placebo. Interestingly, participants given OT showed increased electrodermal response to the CS+ in the late phase of conditioning, but decreased electrodermal response to the electric shocks. This is in keeping with previous findings that OT reduced neural and psychophysiological response to electric shocks (Rash et al., 2014). Furthermore, this indicates that the physiological responses found here are not necessarily

coupled to the neural responses in the late phases of conditioning, meaning that OT's effect on increased conditioning is not due merely to an increased perception of pain.

Previous research has shown both the ACC (Hariri et al., 2003; for a review, see Milad et al., 2007; Sehlmeyer et al., 2009) and OT's modulation of it (Gorka et al., 2015; Scheele et al., 2014a) to play a role in fear processing. More unique are our findings of OT modulation of pMCC response to social stimuli. This could indicate that social stimuli are processed by an entirely different network than that which processes fear stimuli overall. However, the finding could also be a result of an OT-induced, heightened sensitivity to social stimuli. A second explanation could be a combination of an increased motivation, based in the pMCC, to orient oneself toward an aversive stimulus following OT (Vogt, 2005), as well as increased processing of social stimuli (Shahrestani et al., 2013). OT would thereby increase sensitivity to and processing of social stimuli during fear conditioning, which would accelerate learning and adaptation in social settings.

Interestingly, we did not find amygdala activation during fear conditioning, which is contradictory to previous findings suggesting an important role of the amygdala in fear conditioning. First, the lack of response could be indicative of a methodological artefact in our study. Although the region of interest analysis and the corrected whole brain analysis did not yield amygdala response, however, we did find a main effect of conditioning for both social and nonsocial stimuli at an uncorrected p-level in both the right ($p = 0.02$) and left ($p = 0.04$) amygdala. This would speak for the lack of amygdala activation reflecting a lack of power. Second, conditioning may not be dependent on the amygdala, but this would seem unusual considering that it has established itself in the literature as a prime region involved in fear conditioning (see for example reviews by (Greco & Liberzon, 2015; Keifer et al., 2015).

Our lack of amygdala activity could also indicate that OT effects are not amygdala-dependent. Further evidence for this can be found in a previous study, in which we found an isolated effect of OT on social, but not nonsocial, feedback during a learning task (Hurlemann et al., 2010a). Although this was a behavioral study and conclusions based on direct neural activity are difficult, we were able to indirectly show that the social condition was amygdala-dependent: on the one hand, we administered healthy males with OT and on the other, we tested twin women with selective bilateral amygdala lesions, A.M. and B.G. Social feedback was found to increase learning in males, and this effect was even greater following OT administration. Both A.M. and B.G., on the other hand, performed worse than healthy controls. The juxtaposition of the increase in learning by OT and the decrease in learning in the face of a missing amygdala indicate that learning in a social context is OT- and amygdala-dependent. Previous findings have

shown significant OT receptor density in the amygdala (Insel & Shapiro, 1992; Veinante & Freund-Mercier, 1997), specifically the basolateral and central regions (Boccia et al., 2013), and OT has been found to enhance memory in a social context (Guastella et al., 2008; Savaskan et al., 2008; Rimmele et al., 2009; Ferguson et al., 2001), all of which add support to our behavioral findings. Therefore, it is presumable that we could have found amygdala activation and OT modulation of this activation given a larger group of participants. A limitation of this study is that the subthreshold amygdala activity was found in response to conditioning, but not to faces versus houses, and that the effect of sociality is less clear than had we been able to clearly determine an isolated effect of faces. Despite this, the paradigm does present social stimuli during fear conditioning, and the reduction in amygdala activity following OT administration does therefore illustrate that the amygdala performed at a lower level during a paradigm with a strong social element.

IV. 3. Long-term amygdala modulation through bilateral lesions within an emotional and nonemotional context

Study 4: Bach DR, Talmi D, Hurlemann R, Patin A, Dolan RJ (2011) Automatic relevance detection in the absence of a functional amygdala. Neuropsychologia 49(5): 1302-5.

Several findings have indicated that the amygdala is a site of low-level judgment of stimuli (Bach et al., 2008; Critchley et al., 2000; Hariri et al., 2000, 2003) and that it allocates resources based on the relevance, e.g. arousal and motivational quality, of a stimulus (Pessoa, 2008; Zald, 2003). The reaction (BOLD response in fMRI paradigms) is greater when implicitly evaluating stimuli than when participants are required to explicitly react (Bach et al., 2008; Critchley et al., 2000; Hariri et al., 2000, 2003). Because of this reaction, the connection has been made of the amygdala as a basic, automatic system of detection (Scherer et al., 2001).

As opposed to the previous two studies examining a sudden chemical disruption of amygdala function, the following study examines automatic prioritized emotional processing in UW patients A.M. and B.G., described above (see section III.4.). Because the paradigm includes implicit processing of stimuli, which have been found to result in a large amygdala response (Bach et al., 2008; Critchley et al., 2000; Hariri et al., 2000, 2003), the paradigm is ideal for comparing a missing amygdala function with healthy controls.

Previous lesion studies have sought to address the amygdala's role in automatic prioritized emotional processing, specifically in patients S.P. and S.M. These studies, however, have been limited to only certain aspects of prioritized processing, and do not provide a comprehensive overview of relevance detection by the amygdala. The rationale of this study, therefore, was to determine the amygdala's role in automatic prioritization using an attentional blink paradigm.

Methodology

We used an attentional blink (AB) paradigm for recall facilitation of emotionally arousing stimuli. In a rapid serial visual presentation, two target stimuli and several distractor words are presented. The timing of the second target word (T2) determines its recall: if T2 falls shortly after the first target word (T1), its recall is impaired, and becomes less impaired with greater temporal lag between the two targets (Raymond et al., 1992). This could indicate that processing of the stimuli occurs across two stages: an early sensory stage, in which all stimuli are processed, and a later processing stage, in which there is competition between the T1 with distractor words (Chun & Potter, 1995). Therefore, the early processing of stimuli could result in attenuation in the AB, which is apparent when T2 is an emotionally arousing word (Anderson, 2005; De Martino et al., 2008b; Keil & Ihssen, 2004). The emotionally arousing target words are given preference over distractor words, and resource allocation is facilitated (Keil & Ihssen, 2004).

We tested UW patients A.M. and B.G. against age- and education-matched female controls as well as male university students (age 23.3 ± 4.6 years). The patients were impaired in the d2 Test; the male university students showed average scores. These results, however, did not co-vary with performance in the AB paradigm ($p < .20$).

Results and interpretation

The patients showed the same effect of lag and valence as the healthy controls, indicating that the patients showed recall facilitation for aversive items. Amygdala lesions, therefore, do not necessarily mean that relevance detection is impaired. This seems to contradict the view that the amygdala is vital to relevance detection (Sander et al., 2003), as it shows greater reaction to emotionally relevant stimuli (see Zald, 2003). The results indicate that the patients are demonstrating a compensation mechanism, which can only develop over the course of many years and in the context of a slow debilitation of the amygdala, as in UW.

Interestingly, the findings here reflect similar findings in another UW patient, S.M. (Tsuchiya et al., 2009). Previous findings suggest that subcortical, temporal structures could be important in compensation of the missing amgydala during low-level appraisal, including the pulivinar (Pessoa & Adolphs, 2010; Morris et al., 1998), which connects to several visual processing areas and the superior colliculus, for example (Morris et al., 1998). Based on the selectivity of the lesion's site being representative of UW (Hofer, 1973), it is imaginable that similar compensatory mechanisms can develop in different patients, as all other structures are spared and remain healthy. It is therefore probable that the patients here have developed the ability to compensate for their lack of an amygdala, especially given that the paradigm represents a fairly low-level, basic amygdala function that could presumably be more easily compensated for than other higher-level functions. (The concept of compensation in the twins is discussed in detail under section V.)

Study 5: Talmi D, Hurlemann R, Patin A, Dolan RJ (2010) Framing effect following bilateral amygdala lesion. Neuropsychologia 48(6): 1823-7.

In the final study, the UW twins described above (III.4.) were given a framing effect and risky gambling behavior paradigm. The framing effect explains the emotional bias shown by participants when risk-taking, i.e. when presented with a potential loss. At the core of the paradigm is the finding that healthy participants will more likely gamble than when presented with a potential win (Tversky & Kahneman, 1981).

In healthy participants, decisions are accompanied by a higher autonomic arousal (skin conductance response) in the loss than in the win frame (De Martino et al., 2008a). This emotional component has been traced to the amygdala, OFC, and ACC (De Martino et al., 2006; Roiser et al., 2009). Accordingly, amygdala lesions in animals show an impaired cost-benefit analysis (Ghods-Sharifi et al., 2009), and amgydala lesions in humans correlate with riskier and worse decisions in the Iowa Gambling Task and in the Game of Dice task (Bechera et al., 1999; Brand et al., 2006, 2007). Patients with anterior temporal lobe (including the amygdala) damage have shown an increased propensity to gamble when deciding between gains but a decreased propensity when deciding between losses (Weller et al., 2007). This indicates that the amygdala could play a role in separating the negative from the positive frames and in either increasing an individual's willingness to choose a sure gain or decreasing their willingness to take a sure loss.

Methodology

We tested the same two UW patients, A.M. and B.G., against 20 age- and education-matched healthy, female controls. Because of the patients' lower concentration scores, we used a shortened version of a previously published paradigm (De Martino et al., 2006). Using just the first of three sessions, however, showed no influence on the pattern of results, and no further correlations between intelligence, concentration, framing effect, or gambling frequency were found.

Over two decades ago, Tversky and Kahneman laid the groundwork for the framing theory of decisions, arguing that the context in which a decision is framed directly affects the probability that a person will choose one option over the other (Tversky & Kahneman, 1981). As part of the original experiment, participants chose between a sure gain or a gamble in one decision and a sure loss and gamble in the other. The sure amount was framed as either the amount a participant would keep out of the initial sum ('win frame'), or as the amount a participant would lose from the initial sum ('lose frame'). The gamble was therefore presented each time as either an opportunity to win or lose a set amount of money. In the gamble option, the magnitude of the win multiplied by the probability of winning (the expected win) was identical to the sure amount. In the gamble-weighted trials, the expected win was very clearly higher than the sure amount. In the sure-weighted trials, the expected win of gambling was very clearly lower than the sure amount. The decision was presented simultaneously on the screen, with the sure amount listed on one side and the gamble being shown in pie chart form.

Results and interpretation

Both the controls and the patients showed an intact framing effect, gambling more often in the lose frame than in the win frame. However, the patients gambled overall more often than controls: B.G. more often in both frames, A.M. only in the loss frame. In terms of decision latency, controls showed slower reaction times when gambling than when taking the sure amount. A.M. showed this same pattern, but was overall slower in her reactions. B.G. was overall faster than the controls, but showed the opposite reaction pattern, needing more time when taking the sure amount than when gambling.

These results showing intact framing but a propensity for gambling seem to contrast with previous studies showing that the amygdala is directly associated with the framing effect. For one, the amygdala could be reacting to the decisions compatible with the frame but not be additionally influencing the decision. This

influence could instead come from the ACC and/or OFC, which have previously been shown to both react more when participants make decisions incompatible to the frame, or the ACC and the amygdala, which interact more in this context (De Martino et al., 2006; Roiser et al., 2009). These decisions would have a more negative value than the frame-compatible ones. This negative versus positive evaluation is supported by research showing no differences in amygdala reaction to negative or positive facial expressions (Derntl et al., 2009; Fitzgerald et al., 2006; Winston et al., 2003), but impaired recognition of negative (fearful) faces in patients with bilateral amygdala lesions (Adolphs et al., 1999). This extra-amygdalar support in decision-making could be one explanation for the intact framing effect, yet increased gambling frequency, in A.M. and B.G. A second explanation is, as in the above studies, that the patients might have developed compensation mechanisms. (The concept of compensation in the twins is discussed in detail under section V.)

Our finding that the patients gambled overall more often than the controls is consistent with previous research showing increased risk-taking when the amygdala is compromised. Broken down over frames, the patients tended to take more risks in the win frame, whereas in the loss frame both patients and controls were equal risk takers. This could be because UW patients have an impaired ability to learn from social feedback (see for example Hurlemann et al., 2010a). This is supported by previous findings that amygdala lesion patients act irrationally when faced with risky decision-making after feedback, for example by choosing an option that had previously led to a negative outcome (Brand et al., 2006; see also Hampton et al., 2007).

Similarities between the patients and healthy controls, on the other hand, indicate that, as in findings regarding automatic relevance detection (IV.4.), patients also show signs of compensation in this experiment (see Section V. for further discussion). Aside from the amygdala, the ACC has been suggested to instruct and in turn modify decision-making circuits to make more cognitively efficient strategies (Botvinick, 2007). ACC activation is greater when deciding “against” the frame (De Martino et al., 2006); therefore, the ACC may play a role in censuring the amygdala and thus in shaping an individual’s willingness to choose one option over the other. In participants with a genetic variation in the 5-HT transporter-linked polymorphic region, causing them to be less susceptable to the effect of frame, findings have shown increased coupling between the ACC and amygdala (Roiser et al., 2009). Furthermore, the OFC correlates with deciding against the frame and shows strong coupling with the ACC (Kringelbach & Rolls, 2004), indicating that all three of the above areas work together to modulate the motivation towards certain decisions. These two regions could therefore be prime candidates in pathways for compensation during risky decisions.

V. General discussion

The ability of the amygdala to respond to both social as well as nonsocial stimuli reflects its primary role as a detector of relevant stimuli. While there is a bounty of literature describing mechanisms of amygdala modulation in an experimental setting, there has not yet been a description of whether this modulation depends on a social or emotional context and if yes, why. This dissertation is an attempt to answer these questions through three hypotheses:

1. **The amygdala responds differently to social vs. nonsocial chemosensory stimuli. Pleasant, nonsocial stimuli preferentially activate the left amygdala, while unpleasant, nonsocial stimuli preferentially activate the right amygdala. Social stimuli tend to activate the left amygdala.**

2. **Short-term, chemical modulation of amygdala activity is evident in a social-emotional context, i.e. during social-emotional experimental paradigms. This illustrates that social functions are dependent on the amygdala in healthy people, and these cannot be immediately compensated for in the event of changed amgydala function.**

3. **Long term, internal amygdala modulation due to lesions can be used to illustrate compensation for missing amygdala function in both emotional and non-emotional paradigms. The level of compensation differs based on the cognitive resources needed to carry out the task and emotional content of the paradigm.**

Regarding the first hypothesis, a literature review of chemosensory activation of the amygdala (see III.1.) showed that the amygdala tended to lateralize along both social and nonsocial lines, as well as along valence within the nonsocial category (Patin & Pause, 2015). Of the nonsocial stimuli, pleasant stimuli activated the left amygdala activation, whereas unpleasant stimuli showed a response in right amygdala (Patin & Pause, 2015). This lends support to the theory that the right amygdala is more involved in a rapid first response to stimuli, and the left in a more sustained response to stimuli (Glascher & Adolphs, 2003). The amygdala is, among other things, responsible for sorting stimuli according to relevance and emotional salience (Costafreda et al., 2008) and the right and left amygdala could act independently during odor detection to accomplish these tasks (Brand et al., 2001). Findings showing that while efferent connections are found mostly from the bilateral amygdala, the left amygdala receives most afferent connections (Nigri et al., 2013), thus suggesting a more involved, sustained processing by the left amygdala, seem to support this hypothesis. The finding that social stimuli, e.g. sweat samples, also activated the left amygdala most likely indicates that social stimuli are processed via a secondary, separate chemosensory route, perhaps involving TAARs in the olfactory epithelium (Carnicelli et al., 2010; Horowitz et al., 2014; Liberles, 2009).

Taken together, the results from this literature review provides a basis of support for a differential processing of social and emotional chemosensory stimuli in the amygdala.

For Hypothesis 2, two studies (Onur et al., 2012; Eckstein et al., 2016) were completed in order to examine the effect of sudden, external modulation of the amygdala in a social-emotional context. The first study examined smokers, in both a deprived and a satiated state, and non-smokers for amygdala response to emotional faces (Onur et al., 2012). We found that satiated smokers showed an amygdala response comparable to non-smokers, but that deprived smokers showed blunted amygdala response to fearful faces. This constellation of amygdala response suggests a model of nicotine withdrawal and amygdala activity: during times of withdrawal, reduced amygdala activation to negative stimuli would have the effect of removing emotional hurdles during drug-seeking and cause a smoker in withdrawal to perhaps undertake more risks while drug seeking. A reduced emotional evaluation of negative stimuli and increased risk-taking could be a driving force behind relapses during attempts to quit smoking. The second study studied the effect of OT on Pavlovian fear conditioning (Eckstein et al., 2016). Surprisingly, we did not find amygdala activation. However, when looking at the data closer, we did find that the amygdala was active at an uncorrected level, suggesting that our lack of amygdala activation was a statistical artefact, and that the paradigm did evoke amygdala activity. Because we used both social (faces) and nonsocial (houses) stimuli, it is feasible that OT modulates the amygdala in a social fear learning context, and not in a nonsocial context. Both studies therefore showed that the amygdala showed the effects of a short-term reduction of activity in a social context.

These two findings suggest that the amygdala plays a central, vital role to social-emotional processing. This could mean that too great a portion of the amygdala is dedicated to social-emotional processing, so that when it is altered, the rest of the amygdala cannot make up for the disruption. It could also mean that the amygdala plays too great a role in functionally connecting different neural regions to create a social-emotional processing network. As the amygdala has been suggested to be a hub of processing (Pessoa, 2008), and given that neural computation most likely rests on network and transmission between functionally connected regions instead of on isolated neural structures (Kennedy & Adolphs, 2012), the latter explanation is the more likely of the two. As is presented later in this section, the latter explanation also paves the way for the results of the lesion studies included in this review, which suggest functional compensation mechanisms in the face of a completely obliterated amygdala (see below).

In Hypothesis 3, I address the differences in amygdala disruption due to a short- versus long-term change of activity. Two studies were used (Bach et al., 2011; Talmi et al., 2010), both of which included the twins

A.M. and B.G., who have selective, bilateral amygdala lesions. The UW twins showed similar behavioral patterns during the studies presented here to healthy controls, and at times a further UW patient, S.M. Both of the studies included here were centered on nonsocial paradigms, so it is not possible to make a direct comparison within the framework presented in this dissertation. In addition, the comparison between short-term social/nonsocial differences and long-term lesion studies is difficult on a conceptual level: while chemical modulation provides for a sudden disruption of amygdala activity, the congenital lesions found in UW provide ample opportunity for compensatory mechanisms to be built along numerous neural pathways. Whereas the twins show no difference to controls in the emotional paradigm (Bach et al., 2011), they do show differences, albeit minor ones, in non-emotional cognitive domains (Talmi et al., 2010). The long-term studies do, however, differ in emotional content, allowing for a tentative differentiation of compensation potential according to emotional properties. While there are paradigms which explore relatively pure social or emotional stimuli without a crossover between the two (e.g. Schienle et al., 2007; Alpers et al., 2009; see Patin & Pause, 2015 for a review), the emotional words used in the attentional blink paradigm here included both social and nonsocial words, including for instance "victim" or "burgler" (Bach et al., 2011), meaning that there would most likely be some overlap between the findings in our study and expected findings had we used an entirely social-emotional word set.

The twins therefore seem to have compensated to a large degree for their amygdala lesions. Notably, the gambling task did reveal gaps in the twins' performance regarding propensity to gamble (Talmi et al., 2010). This could be due to the tasks nature: while low-level appraisal is an extremely basic task requiring few resources, the decision to gamble in the face of risk is a more involved process. Therefore, it could be that the more basic appraisal function of the amygdala was merely better compensated for compared to the higher level decision task. Furthermore, the emotional role of the amygdala could be given priority over non-emotional functions in the allocation of resources by other neural regions during compensation, so that non-emotional amygdala functions are less well compensated for in long-term dysfunction.

One point that must be mentioned, however, is that compensation mechanisms have not been consistently found in animal lesion models, nor have they been found in all UW patients. Animals given selective amygdala lesions at an early stage have shown vast disruptions in emotional reactivity (Thompson, 1981; Prather et al., 2001; Bauman et al., 2004a, b; Bliss-Moreau et al., 2011 Amaral et al., 2003; Raper et al., 2013) and HPA axis functioning (Raper et al., 2013). On the other hand, amygdala lesions given later in life have resulted in monkeys showing fewer deficits than their counterparts with early lesions (Amaral et al., 2003). UW patients, too, have shown strong amygdala deficits, including symptoms similar to Kluver-Bucy syndrome (Emsley & Paster, 1985; Kleinert et al., 1987). The twins, A.M. and B.G., have also

illustrated that they differ in their levels of compensation, with A.M. showing a higher level of compensation in a fear processing experiment than her sister (Becker et al., 2012).

One explanation is that the time of the lesion seems to play a role, in that if the lesion occurs during a period of high developmental vulnerability, behavioral effects could be more likely to develop (Raper et al., 2013). The other explanation depends on the concept of degeneracy (discussed above in III.4.). Because there is such large variation between subjects and between functional capabilities of unaffected neural regions, there will necessarily be variation in behavioral signs of the same type of lesion between patients (Price & Friston, 2002). This would explain why, even though the twins performed relatively normally compared to healthy controls in the tasks and neuropsychological profiles here, and even though they lead relatively average family lives, there are still missing parts not compensated for, such as their propensity to gamble in the framing task (Talmi et al., 2010). Because the framing effect was intact, the results of the study indicate that the twins' evaluation of the potential win or loss took place in the same framework as the healthy controls – they just differed on their decision on what action to take based on this evaluation, specifically whether to gamble or not.

Any compensatory mechanisms employed by the patients, therefore, might not fully developed and are still being formed. This could also, however, indicate that compensation involves a pathway separate from the network which modulates cognitive processes supported by the amygdala in a healthy person, and therefore involves regions that will remain only partly able to compensate. One possible route for compensation could involve the pulvinar, superior colliculus, and visual cortex regions, as these share rich connectivity to the amygdala and are crucial to emotional processing and relevance detection (Pessoa & Adolphs, 2010; Morris et al., 1998). Some authors suggest that the mirror neuron network could also be a site important for neural compensation (Becker et al., 2012).

Interestingly, one of the most consistently found gaps in the twins', and indeed in other UW patients' profiles (see for instance III.4.), concerns fear or threat processing, which one would expect to be a basic need for survival. An abnormally high willingness to step into potentially dangerous situations, for instance when faced with threatening persons (Bach et al., 2015; Becker et al., 2012; Harrison et al., 2015; Mihov et al., 2013), can be overcome in the real world by developing cognitive avoidance strategies, including those given down via parental guidelines. In a safe lab environment, such cognitive strategies would not come into play. This could explain why such a seemingly important instinct as fear appears to be less compensated than other areas, as it has been consistently found to be lacking in the twins and other UW patients.

Concluding remarks

To conclude, this dissertation has set out to provide an empirical basis for amygdala response to social versus nonsocial stimuli following immediate and long-term modulation. I have shown that the amygdala is highly relevant to processing both social and nonsocial chemosensory stimuli along different neural pathways, reflecting two evolutionarily separate but related systems. Second, I have shown that the role of the amygdala in social-emotional settings cannot be compensated for in the event of a sudden disruption. Finally, long-term amygdala disruption, on the other hand, does provide the opportunity to compensate for missing amygdala function in emotional processing, even though amygdala functions are not completely normalized.

VI. References

Adam Y, Mizrahi A (2010) Circuit formation and maintenance – perspectives from the mammalian olfactory bulb. Curr Opin Neurobiol 20(1): 134-40.

Adolphs R (2003) Is the human amygdala specialized for processing social information? Ann N Y Acad Sci 985: 326-40.

Adolphs R (2010) Conceptual challenges and directions for social neurosciences. Neuron 65: 752-67.

Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P, Damasio AR (2005) A mechanism of impaired fear recognition after amygdala damage. Nature 433: 68 –72.

Adolph D, Pause BM (2012) Different time course of emotion regulation towards odors and pictures: are odors more potent than pictures? Biol Psychol 91(1): 65-73.

Adolphs R, Tranel D, Buchanan TW (2005) Amygdala damage impairs emotional memory for gist but not details of complex stimuli. Nat Neurosci 8(4): 512-8. doi: 10.1038/nn1413

Adolphs R, Tranel D, Damasio AR (1998) The human amygdala in social judgment. Nature 393: 470–4.

Adolphs R, Tranel D, Damasio H, Damasio A (1994) Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 372: 669–72.

Adolphs R, Tranel D, Hamann S, Young AW, Calder AJ, Phelps EA (1999) Recognition of facial emotion in nine individuals with bilateral amygdala damage. Neuropsychologia 37: 1111–7.

Aggleton JP (2000) *The amygdala:A functional analysis*. Oxford:Oxford University Press.

Albrecht J, Wiesmann M (2006) [The human olfactory system. Anatomy and physiology]. Nervenarzt 77(8): 931-9.

Alpers GW, Gerdes AB, Lagarie B, Tabbert K, Vaitl D, Stark R (2009) Attention and amygdala activity: an fMRI study with spider pictures in spider phobia. J Neural Transm (Vienna) 116 (6): 747-57. doi: 10.1007/s00702-008-0106-8.

Amaral DG, Bauman MD, Capitanio JP, Lavenex P, Mason WA, Mauldin-Jourdain ML (2003) The amygdala: Is it an essential component of the neural network for social cognition? Neuropsychologia 41: 517–22.

American Heart Association. Why is it so hard to quit? Accessed 28.02.2012. <http://www.heart.org/HEARTORG/GettingHealthy/QuitSmoking/QuittingSmoking/Why-is-it-so-hard-to-quit_UCM_324053_Article.jsp#.T2SulF2Cn2Y>.

Amunts K, Kedo O, Kindler M, Pieperhoff P, Mohlberg H, Shah NJ, Habel U, Schneider F, Zilles K (2005) Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: Intersubject variability and probability maps. Anat Embryol 210: 343–52.

Anderson AK (2005) Affective influences on the attentional dynamics supporting awareness. J Exp Psychol Gen 134: 258–81.

Appenzeller S, Chaloult E, Velho P, de Souza EM, Araújo VZ, Cendes F, Li LM (2006) Amygdalae calcifications associated with disease duration in lipoid proteinosis. J Neuroimaging 16: 154 –6.

Arce E, Simmons AN, Lovero KL, Stein MB, Paulus MP (2008) Escitalopram effects on insula and amygdala BOLD activation during emotional processing. Psychopharmacology (Berl) 196(4): 661-72.

Aschenbrenner S, Tucha O, Lange KW (2000) *Regensburger Wortflüssigkeitstest.* Göttingen: Hogrefe.

Assini FL, Duzzioni M, Takahashi RN (2009) Object location memory in mice: Pharmacological validation and further evidence of hippocampal CA1 participation. Behav Brain Res 204: 206 –11.

Bach DR, Grandjean D, Sander D, Herdener M, Strik WK, Seifritz E (2008) The effect of appraisal level on processing of emotional prosody in meaningless speech. Neuroimage 42: 919–27.

Bach DR, Talmi D, Hurlemann R, Patin A, Dolan RJ (2011) Automatic relevance detection in the absence of a functional amygdala. Neuropsychologia 49: 1302-5.

Bach DR, Hurlemann R, Dolan RJ (2013) Unimpaired discrimination of fearful prosody after amygdala lesion. Neuropsychologia 51(11): 2070-4.

Bach DR, Hurlemann R, Dolan RJ (2015) Impaired threat prioritisation after selective bilateral amygdala lesions. Cortex 63: 206-13. doi: 10.1016/j.cortex.2014.08.017

Baeumler G (1985) *FWIT: Farbe-Wort-Interferenztest [The Stroop-Test]*. Göttingen: Hogrefe.

Balfour DJ, Benwell ME, Birrell CE, Kelly RJ, Al-Aloul M (1998) Sensitization of the mesoaccumbens dopamine response to nicotine. Pharmacol Biochem Behav 59: 1021–30.

Barbas H (1995) Anatomic basis of cognitive–emotional interactions in the primate prefrontal cortex. Neurosci Biobehav Rev 19: 449–510.

Barton RA, Aggleton JP, Grenyer R (2003) Evolutionary coherence of the mammalian amygdala. Proc Biol Sci 270: 539-43.

Bauman MD, Lavenex P, Mason WA, Capitanio JP, Amaral DG (2004a) The development of social behavior following neonatal amygdala lesions in rhesus monkeys. J Cogn Neurosci 16(8):1388-411.

Bauman MD, Lavenex P, Mason WA, Capitanio JP, Amaral DG (2004b) The development of mother-infant interactions after neonatal amygdala lesions in rhesus monkeys. J Neurosci 24(3): 711-21.

Bechara A, Damasio H, Damasio AR, Lee GP (1999) Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci 19: 5473–81.

Becker B, Mihov Y, Scheele D, Kendrick KM, Feinstein JS, Matusch A, Aydin M, Reich H, Urbach H, Oros-Peusquens AM, Shah NJ, Kunz WS, Schlaepfer TE, Zilles K, Maier W, Hurlemann R (2012) Fear processing and social networking in the absence of a functional amygdala. Biol Psychiatry 72(1): 70-7.

Becker B, Androsch L, Jahn RT, Alich T, Striepens N, Markett S, Maier W, Hurlemann R (2013). Inferior frontal gyrus preserves working memory and emotional learning under conditions of impaired noradrenergic signaling. Front Behav Neurosci 7: 197.

Behr J, Wozny C, Fidzinski P, Schmitz D (2009) Synaptic plasticity in the subiculum. Prog Neurobiol 89: 334-42.

Benwell ME, Balfour DJ (1992) The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. Br J Pharmacol 105: 849–56.

Benwell ME, Balfour DJ, Birrell CE (1995) Desensitization of the nicotine-induced mesolimbic dopamine responses during constant infusion with nicotine. Br J Pharmacol 114: 454–60.

Benowitz NL (2010) Nicotine addiction. N Engl J Med 362: 2295–303.

Bergado JA, Lucas M, Richter-Levin G (2011) Emotional tagging--a simple hypothesis in a complex reality. Prog Neurobiol 94(1): 64-76. doi: 10.1016/j.pneurobio.2011.03.004

Billot PE, Andrieu P, Biondi A, Vieillard S, Moulin T, Millot JL (2017) Cerebral bases of emotion regulation toward odours: A first approach. Behav Brain Res 317: 37-45. doi: http://dx.doi.org/10.1016/j.bbr.2016.09.027.

Bleich S, Havemann-Reinecke U, Kornhuber J (2002) *Der Fagerström-Test für Nikotinabhängigkeit (FTNA)*. Göttingen: Hogrefe.

Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361: 31-9.

Bliss-Moreau E, Bauman MD, Amaral DG (2011) Neonatal amygdala lesions result in globally blunted affect in adult rhesus macaques. Behav Neurosci 125(6): 848-58.

Boccia ML, Petrusz P, Suzuki K, Marson L, Pedersen CA (2013) Immunohistochemical localization of oxytocin receptors in human brain. Neuroscience 253: 155-64.

Botvinick MM (2007) Conflict monitoring and decision making: Reconciling two perspectives on anterior cingulate function. Cogn Affect Behav Neurosci 7: 356–66.

Brand M, Grabenhorst F, Starcke K, Vandekerckhove MM, Markowitsch HJ (2007) Role of the amygdala in decisions under ambiguity and decisions under risk: evidence from patients with Urbach-Wiethe disease. Neuropsychologia 45: 1305-17.

Brand M, Labudda K., Markowitsch HJ (2006) Neuropsychological correlates of decision-making in ambiguous and risky situations. Neural Netw 19: 1266–76.

Brand G, Millot JL, Henquell D (2001) Complexity of olfactory lateralization processes revealed by functional imaging: a review. Neurosci Biobehav Rev 25(2): 159-66.

Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, Strauss MM, Hyman SE, Rosen BR (1996) Response and Habituation of the Human Amygdala during Visual Processing of Facial Expression. Neuron 17(5): 875-87.

Brickenkamp R (1995) Aufmerksamkeitsbelastungstest 'd2', erweiterte und neu gestaltete Auflage. Diagnostica 41: 291–6.

Britton JC, Gold AL, Feczko EJ, Rauch SL, Williams D, Wright CI (2007) D-cycloserine inhibits amygdala responses during repeated presentations of faces. CNS Spectr 12(8): 600-5.

Brockhaus H (1938) Zur normalen und pathologischen Anatomie des Mandelkerngebietes. J Psychol Neurol 49: 1–136.

Brockhaus H (1940) Die Cyto- und Myeloarchitektonik des Cortex claustralis und des Claustrum beim Menschen. J Psychol Neurol 49: 249–347.

Cahill L, Haier RJ, Fallon J, Alkire MT, Tang C, Keator D, Wu J, McGaugh JL (1996) Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proc Natl Acad Sci U S A 93(15): 8016-21.

Cansino S, Maquet P, Dolan RJ, Rugg MD (2002) Brain activity underlying encoding and retrieval of source memory. Cereb Cortex 12: 1048– 56.

Carmichael ST, Clugnet MC, Price JL (1994) Central olfactory connections in the macaque monkey. J Comp Neurol 346(3): 403-34.

Carnicelli V, Santoro A, Sellari-Franceschini S, Berrettini S, Zucchi R (2010) Expression of trace amine-associated receptors in human nasal mucosa. Chemosens Percept 3(2): 99-107.

Chun MM, Potter MC (1995) A two-stage model for multiple target detection in rapid serial visual presentation. J Exp Psychol Hum Percept Perform 21: 109–27.

Clarke PB, Kumar R (1983) Characterization of the locomotor stimulant action of nicotine in tolerant rats. Br J Pharmacol 80: 587–94.

Cleland TA, Linster C (2003) Central olfactory processing. In RL Doty (Ed.), *Handbook of olfaction and gustation* (2ed., pp. 165-80). New York: Marcel Dekker.

Cooke SF, Bliss TV (2006) Plasticity in the human central nervous system. Brain 129: 1659-73.

Cordoro KM, Osleber MF, De Leo VA, Krafchik BR, Wells MJ, Libow LF, Quirk CM, Elston DM (2011) Lipoid proteinosis. Accessed 15.02.2012. http://emedicine.medscape.com/article/1103357-overview.

Costafreda SG, Brammer MJ, David AS, Fu CH (2008) Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. Brain Res Rev 58(1): 57-70.

Craig AD (2002) How do you feel? Interoception: the sense of physiological condition of the body. Nat Rev Neurosci 3: 655-66.

Critchley H, Daly E, Phillips M, Brammer M, Bullmore E, Williams S (2000) Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional magnetic resonance imaging study. Hum Brain Mapp 9: 93–105.

Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ (2004) Neural systems supporting interoceptive awareness. Nat Neurosci 7: 189-95.

Dantzer R, Bluthe RM, Koob GF, Le Moal M (1987) Modulation of social memory in male rats by neurohypophyseal peptides. Psychopharmacology (Berl) 91(3): 363-8.

Davis M, Ressler K, Rothbaum BO, Richardson R (2006) Effects of DSC on extinction: Translation from preclinical to clinical work. Biol Psychiatry 60: 369 –75.

De Araujo IE, Rolls ET, Velazco MI, Margot C, Cayeux I (2005) Cognitive modulation of olfactory processing. Neuron 46(4): 671-9.

De Gelder B, Terburg D, Morgan B, Hortensius R, Stein DJ, van Honk J (2014) The role of human basolateral amygdala in ambiguous social threat perception. Cortex 52: 28-34.

De Martino B, Kumaran D, Seymour B, Dolan RJ (2006) Frames, biases, and rational decision-making in the human brain. Science 313: 684–7.

De Martino B, Harrison NA, Knafo S, Bird G, Dolan RJ (2008a) Explaining enhanced logical consistency during decision making in autism. J Neurosci 28: 10746–50.

De Martino B, Strange BA, Dolan RJ (2008b) Noradrenergic neuromodulation of human attention for emotional and neutral stimuli. Psychopharmacology (Berl) 197: 127–36.

Du Vigneaud V, Ressler C, Swan JM, Roberts CW, Katsoyannis PG (1954) The synthesis of oxytocin1. J Am Chem Soc 76(12): 3115-21.

Du Vigneaud VD, Ressler C, Swan CJM, Roberts CW, Katsoyannis PG, Gordon S (1953) The synthesis of an octapeptide amide with the hormonal activity of oxytocin. Journal of the American Chemical Society 75(19): 4879-80.

Delplanque S, Grandjean D, Chrea C, Aymard L, Cayeux I, Le Calvé B, Velazco MI, Scherer KR, Sander D (2008) Emotional processing of odors: evidence for a nonlinear relation between pleasantness and familiarity evaluations. Chem Senses 33(5): 469-79.

Derntl B, Habel U, Windischberger C, Robinson S, Kryspin-Exner I, Gur RC (2009) General and specific responsiveness of the amygdala during explicit emotion recognition in females and males. BMC Neuroscience 10: 91.

Dewan A, Pacifico R, Zhan R, Rinberg D, Bozza T (2013) Non-redundant coding of aversive odors in the main olfactory pathway. Nature 497(7450): 486-9.

Distel H, Ayabe-Kanamura S, Martínez-Gómez M, Schicker I, Kobayakawa T, Saito S, Hudson R (1999) Perception of Everyday Odors—Correlation between Intensity, Familiarity and Strength of Hedonic Judgement. Chem Senses 24(2): 191-9.

Dunbar RIM (2010) The social role of touch in humans and primates: behavioural function and neurobiological mechanisms. Neurosci Biobehav Rev 34:260-8.

Easterbrook JA (1959) The effect of emotion on cue utilization and the organization of behavior. Psychol Rev 66(3): 183-201.

Eckstein M, Becker B, Scheele D, Scholz C, Preckel K, Schlaepfer TE, Grinevich V, Kendrick KM, Maier W, Hurlemann R (2015) Oxytocin facilitates the extinction of conditioned fear in humans. Biol Psychiatry 78(3): 194-202.

Eckstein M, Scheele D, Patin A, Preckel K, Becker B, Walter A, Domschke K, Grinevich V, Maier W, Hurlemann R (2016) Oxytocin Facilitates Pavlovian Fear Learning in Males. Neuropsychopharmacology 41(4): 932-9.

Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K (2005): A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25: 1325–35.

Elfenbein HA, Ambady N (2002) On the university and cultural specificity of emotion recognition: a meta-analysis. Psychol Bull 128(2): 203-35.

Ellison G (1995) The N-methyl-D-aspartate antagonists phencyclidine, ketamine and dizocilpine as both behavioral and anatomical models of the dementias. Brain Res Brain Res Rev 20: 250-67.

Emsley RA, Paster L (1985) Lipoid proteinosis presenting with neuropsychiatric manifestations. J Neurol Neurosurg Psychiatry 48(12): 1290-2.

Engen T, Ross BM (1973) Long-term memory of odors with and without verbal descriptions. J Exp Psychol 100(2): 221-7.

Faller H, Lang H (2006) *Medizinische Psychologie und Soziologie.* 2nd ed. Heidelberg: Springer Medizin Verlag Heidelberg.

Feinstein JS, Buzza C, Hurlemann R, Follmer RL, Dahdaleh NS, Coryell WH, Welsh MJ, Tranel D, Wemmie JA (2013) Fear and panic in humans with bilateral amygdala damage. Nat Neurosci 16(3): 270-2.

Ferguson JN, Aldag JM, Insel TR, Young LJ (2001) Oxytocin in the medial amygdala is essential for social recognition in the mouse. J Neurosci 21(20): 8278-85.

Firestein S (2001) How the olfactory system makes sense of scents. Nature 413: 211-8.

Fisher PM, Grady CL, Madsen MK, Strother SC, Knudsen GM (2015) 5-HTTLPR differentially predicts brain network responses to emotional faces. Hum Brain Mapp 36(7): 2842-51.

Fitzgerald DA, Angstadt M, Jelsone LM, Nathan PJ, Phan KL (2006) Beyond threat: amygdala reactivity across multiple expressions of facial affect. Neuroimage 30: 1441–8.

Flood J, Morley J, Lanthorn T (1992) Effect on memory processing by DSC, an agonist of the NMDA/glycine receptor. Eur J Pharmacol 221: 249 –54.

Funayama ES, Grillon C, Davis M, Phelps EA (2001) A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy. J Cogn Neurosci 13: 721–9.

Ghods-Sharifi S, Onge JRS, Floresco SB (2009) Fundamental contribution by the basolateral amygdala to different forms of decision making. J Neurosci 29: 5251–9.

Glascher J, Adolphs R (2003) Processing of the arousal of subliminal and supraliminal emotional stimuli by the human amygdala. J Neurosci 23(32): 10274-82.

Gomperts SN, Rao A, Craig AM, Malenka RC, Nicoll RA (1998) Postsynaptically silent synapses in single neuron cultures. Neuron 21: 1443– 51.

Goossens L, Kukolja J, Onur OA, Fink GR, Maier W, Griez E, Schruers K, Hurlemann R (2009) Selective processing of social stimuli in the superficial amygdala. Hum Brain Mapp 30: 3332–8.

Gorka SM, Fitzgerald DA, Labuschagne I, Hosanagar A, Wood AG, Nathan PJ, Phan KL (2015). Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. Neuropsychopharmacology 40: 278–86.

Gottfried JA (2006) Smell: central nervous processing. Adv Otorhinolaryngol 63: 44-69.

Govind AP, Vezina P, Green WN (2009) Nicotine-induced upregulation of nicotinic receptors: Underlying mechanisms and relevance to nicotine addiction. Biochem Pharmacol 78: 756-65.

Greco JA, Liberzon I (2015) Neuroimaging of Fear-Associated Learning. doi: 10.1038/npp.2015.255

Guastella AJ, Richardson R, Lovibond PF, Rapee RM, Gaston JE, Mitchell P, Dadds MR (2008) A randomized controlled trial of DSC enhancement of exposure therapy for social anxiety disorder. Biol Psychiatry 63: 544 –9.

Hamada T (2002) Lipoid proteinosis. Clin Exp Dermatol 27: 624–9.

Hampton AN, Adolphs R, Tyszka MJ, O'Doherty JP (2007) Contributions of the amygdala to reward expectancy and choice signals in human prefrontal cortex. Neuron 55: 545–55.

Hariri AR, Bookheimer SY, Mazziotta JC (2000) Modulating emotional responses: effects of a neocortical network on the limbic system. Neuroreport 11: 43–8.

Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR (2003) Neocortical modulation of the amygdala response to fearful stimuli. Biol Psychiatry 53: 494–501.

Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM (2006) Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. Biol Psychiatry 59(9): 816-20.

Harrison LA, Hurlemann R, Adolphs R (2015) An Enhanced Default Approach Bias Following Amygdala Lesions in Humans. Psychol Sci 26(10): 1543-55.

Haxby JV, Hoffman EA, Gobbini MI (2000) The distributed human neural system for face perception. Trends Cogn Sci 4(6):223–33.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO (1991) The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. Br J Addict 86: 1119–27.

Heils, A, Teufel A, Petri S, Seemann M, Bengel D, Balling U, Riederer P, Lesch KP (1995) Functional promoter and polyadenylation site mapping of the human serotonin (5-HT) transporter gene. J Neural Transm Gen Sect 102(3) 247-54.

Heimer L, de Olmos JS, Alheid GF, Pearson J, Sakamoto N, Shinoda K., Marksteiner J, Switzer RC (1999).The human basal forebrain. Part II. In: Bloom EE, Björklund A, Hökfelt T (Eds.) *Handbook of chemical neuroanatomy: The primate nervous system. Part III.* Elsevier.

Helmstaedter C, Lendt M, Lux S (1981) *VLMT Verbaler Lern und Merkfähigkeitstest.* Göttingen: Beltz Test.

Hofer PA (1973) Urbach-Wiethe disease (lipoglycoproteinosis; lipoid proteinosis; hyalinosis cutis et mucosae). A review. Acta Derm Venereol Suppl (Stockh) 53: 1-52.

Hofer PA (1974) Urbach-Wiethe disease (lipoglycoproteinosis; lipoid proteinosis, hyalinosis cutis et mucosae). A clinico-genetic study of 14 families from northern Sweden. Hereditas 77: 209-18.

Hofmann SG, Meuret AE, Smits JA, Simon NM, Pollack MH, Eisenmenger K, Shiekh M, Otto MW (2006) Augmentation of exposure therapy with DSC for social anxiety disorder. Arch Gen Psychiatry 63: 298 –304.

Horn W (1983) *L-P-S Leistungsprüfsystem.* Göttingen: Hogrefe.

Horowitz LF, Saraiva LR, Kuang D, Yoon KH, Buck LB (2014) Olfactory receptor patterning in a higher primate. J Neurosci 34(37): 12241-52.

Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, Xu K, Arnold PD, Richter MA, Kennedy JL, Murphy DL, Goldman D (2006) Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. Am J Hum Genet 78(5): 815-26.

Hurlemann R, Patin A, Onur OA, Cohen MX, Baumgartner T, Metzler S, Dziobek I, Gallinat J, Wagner M, Maier W, Kendrick KM (2010a) Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. J Neurosci 30: 4999-5007.

Hurlemann R, Walter H, Rehme AK, Kukolja J, Santoro SC, Schmidt C, Schnell K, Musshoff F, Keysers C, Maier W, Kendrick KM, Onur OA (2010b) Human amygdala reactivity is diminished by the beta-noradrenergic antagonist propranolol. Psychol Med 40(11): 1839-48.

Hurlemann R, Wagner M, Hawellek B, Reich H, Pieperhoff P, Amunts K, Oros-Peusquens AM, Shah NJ, Maier W, Dolan RJ (2007) Amygdala control of emotion-induced forgetting and remembering: evidence from Urbach-Wiethe disease. Neuropsychologia 45: 877– 84.

Kalisch R, Holt B, Petrovic P, De Martino B, Kloeppel S, Buechel C, Dolan RJ (2009) The NMDA agonist DSC facilitates fear memory consolidation in humans. Cereb Cortex 19: 187–96.

Kanat M, Heinrichs M, Mader I, van Elst LT, Domes G (2015) Oxytocin Modulates Amygdala Reactivity to Masked Fearful Eyes. Neuropsychopharmacology, 40(11), 2632-8.

Kaplan GB, Moore KA (2011) The use of cognitive enhancers in animal models of fear extinction. Pharmacol Biochem Behav 99(2): 217-28.

Karnath H, Thier P (2006) *Neuropsychologie: mit Glossar der wichtigsten Fachbegriffe*. 2nd ed. Heidelberg: Springer Medizin Verlag Heidelberg.

Keifer OP Jr, Hurt RC, Ressler KJ, Marvar PJ (2015) The Physiology of Fear: Reconceptualizing the Role of the Central Amygdala in Fear Learning. Physiology (Bethesda) 30(5): 389-401.

Keil A, Ihssen N (2004) Identification facilitation for emotionally arousing verbs during the attentional blink. Emotion 4: 23–35.

Keller M, Baum MJ, Brock O, Brennan PA, Bakker J (2009) The main and the accessory olfactory systems interact in the control of mate recognition and sexual behavior. Behavioural Brain Research 200(2): 268-76.

Kendrick KM, Keverne EB, Baldwin BA (1987) Intracerebroventricular Oxytocin Stimulates Maternal Behaviour in the Sheep. Neuroendocrinology 46(1): 56-61.

Kendrick K, Keverne E, Hinton M, Goode J (1991) Cerebrospinal fluid and plasma concentrations of oxytocin and vasopressin during parturition and vaginocervical stimulation in the sheep. Brain Res Bull 26(5):803–7.

Kennedy DP, Adolphs R (2012) The social brain in psychiatric and neurological disorders. Trends Cogn Sci 16(11): 559-72. doi: 10.1016/j.tics.2012.09.006

Kenny PJ, Chartoff E, Roberto M, Carlezon WA, Jr, Markou A (2009) NMDA receptors regulate nicotine-enhanced brain reward function and intravenous nicotine self-administration: role of the ventral tegmental area and central nucleus of the amygdala. Neuropsychopharmacology 34: 266-81.

Killen JD, Fortmann SP (1997) Craving is associated with smoking relapse: findings from three prospective studies. Exp Clin Psychopharmacol 5: 137–42.

Kleinert R, Cervos-Navarro J, Kleinert G, Walter GF, Steiner H (1987) Predominantly cerebral manifestation in Urbach-Wiethe's syndrome (lipoid proteinosis cutis et mucosae): a clinical and pathomorphological study. Clin Neuropathol 6(1): 43-5.

Klumpers F, Morgan B, Terburg D, Stein DJ, van Honk J (2015) Impaired acquisition of classically conditioned fear-potentiated startle reflexes in humans with focal bilateral basolateral amygdala damage. Soc Cogn Affect Neurosci 10(9): 1161-8.

Kohler, C. G., Moberg, P. J., Gur, R. E., O'Connor, M. J., Sperling, M. R., Doty, R. L. (2001). Olfactory dysfunction in schizophrenia and temporal lobe epilepsy. Neuropsychiatry Neuropsychol Behav Neurol, 14(2), 83-8.

Kongs SK, Thompson LL, Iverson GL, Heaton RK (2000) The Wisconsin Card Sorting Test (WCST-64): Computer Version 2 Research Edition. Odessa, FL: Psychological Assessment Resources.

Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH, Osten P, Schwarz MK, Seeburg PH, Stoop R, Grinevich V (2012) Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 73(3): 553-66.

Kringelbach ML, Rolls ET (2004) The functional neuroanatomy of the human orbitofrontal cortex: Evidence from neuroimaging and neuropsychology. Prog Neurobiol 72: 341–72.

Kukolja J, Thiel CM, Fink GR (2009a) Cholinergic stimulation enhances neural activity associated with encoding but reduces neural activity associated with retrieval in humans. J Neurosci 29: 8119–28.

Kukolja J, Thiel CM, Wilms M, Mirzazade S, Fink GR (2009b) Ageing related changes of neural activity associated with spatial contextual memory. Neurobiol Aging 30: 630–45.

Kushner MG, Kim SW, Donahue C, Thuras P, Adson D, Kotlyar M, McCabe J, Peterson J, Foa EB (2007) DSC augmented exposure therapy for obsessive-compulsive disorder. Biol Psychiatry 62: 835– 8.

Ksir C, Hakan R, Hall Jr DP, Kellar KJ (1985) Exposure to nicotine enhances the behavioral stimulant effect of nicotine and increases binding of [3H]acetylcholine to nicotinic receptors. Neuropharmacology 24: 527–31.

LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA (1998) Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. Neuron 20: 937–45.

Lawless HT, Cain WS (1975) Recognition memory for odors. Chem Senses 1(3): 331-7.

LeDoux J (2007) The amygdala. Curr Biol 17: R868–74.

Lee YS, Silva AJ (2009) The molecular and cellular biology of enhanced cognition. Nat Rev Neurosci 10: 126 –40.

Li F, Tsien JZ (2009) Memory and the NMDA receptors. N Engl J Med 361: 302–3.

Liberles SD (2009) Trace amine-associated receptors are olfactory receptors in vertebrates. Ann N Y Acad Sci 1170: 168-72.

Liberles SD (2015) Trace amine-associated receptors: ligands, neural circuits, and behaviors. Curr Opin Neubiol 34: 1-7.

Liberles SD, Buck LB (2006) A second class of chemosensory receptors in the olfactory epithelium. Nature 442(7103): 645-50.

Maguire EA, Vargha-Khadem F, Mishkin M (2001) The effects of bilateral hippocampal damage on fMRI regional activations and interactions during memory retrieval. Brain 124: 1156-70.

Mahalati K, Okanoya K, Witt DM, Carter CS (1991) Oxytocin inhibits male sexual behavior in prairie voles. Pharmacol Biochem Behav 39(1): 219-22.

Malecki R, Zdrojowy K, Adamiec R (2009) Thromboangiitis obliterans in the 21st century—A new face of disease. Atherosclerosis 206: 328–34.

Markowitsch HJ, Calabrese P, Würker M, Durwen HF, Kessler J, Babinsky R, Brechtelsbauer D, Heuser L, Gehlen W (1994) The amygdala's contribution to memory--a study on two patients with Urbach-Wiethe disease. Neuroreport 5: 1349-52.

McGaugh JL (2000) Memory--a century of consolidation. Science, 287(5451), 248-51.

McGaugh JL (2004) The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci 27: 1-28. doi: 10.1146/annurev.neuro.27.070203.144157

Meenan FO, Bowe SD, Dinn JJ, McCabe M, McCullen O, Masterson JG, Towers RP (1978) Lipoid proteinosis; a clinical, pathological and genetic study. Q J Med 47: 549-61.

Mihov Y, Kendrick KM, Becker B, Zschernack J, Reich H, Maier W, Keysers C, Hurlemann R (2013) Mirroring Fear in the Absence of a Functional Amygdala. Biol Psychiatry 73(7): e9-e11.

Milad MR, Quirk GJ, Pitman RK, Orr SP, Fischl B, Rauch SL (2007). A role for the human dorsal anterior cingulate cortex in fear expression. Biol Psychiatry 62: 1191–4.

Moberg PJ, Agrin R, Gur RE, Gur RC, Turetsky BI, Doty RL (1999) Olfactory dysfunction in schizophrenia: a qualitative and quantitave review. Neuropsychopharmacology 21(3): 325-40.

Monahan JB, Handelmann GE, Hood WF, Cordi AA (1989) DSC, a positive modulator of the N-methyl-D-aspartate receptor, enhances performance of learning tasks in rats. Pharmacol Biochem Behav 34: 649–53.

Mormann F, Dubois J, Kornblith S, Milosavljevic M, Cerf M, Ison M, Tsuchiya N, Kraskov A, Quiroga RQ, Adolphs R, Fried I, Koch C (2011) A category-specific response to animals in the right human amygdala. Nat Neurosci 14(10): 1247-9. doi: 10.1038/nn.2899

Morris JS, Ohman A, Dolan RJ (1998) Conscious and unconscious emotional learning in the human amygdala. Nature 393(6684): 467-70.

Myskiw JC, Izquierdo I, Furini CR (2014) Modulation of the extinction of fear learning. Brain Res Bull 105: 61-9. doi: 10.1016/j.brainresbull.2014.04.006

Nestler EJ, Aghajanian GK (1997) Molecular and cellular basis of addiction. Science 287: 58-63.

Nigri A, Ferraro S, D'Incerti L, Critchley HD, Bruzzone MG, Minati L (2013) Connectivity of the amygdala, piriform, and orbitofrontal cortex during olfactory stimulation: a functional MRI study. Neuroreport 24(4): 171-5.

Norberg MM, Krystal JH, Tolin DF (2008) A meta-analysis of DSC and the facilitation of fear extinction and exposure therapy. Biol Psychiatry 63: 1118 –26.

Norbury R, Taylor MJ, Selvaraj S, Murphy SE, Harmer CJ, Cowen PJ (2009) Short-term antidepressant treatment modulates amygdala response to happy faces. Psychopharmacology (Berl) 206: 197–204.

Onur OA, Patin A, Mihov Y, Buecher B, Stoffel-Wagner B, Schlaepfer TE, Walter H, Maier W, Hurlemann R (2012) Overnight deprivation from smoking disrupts amygdala responses to fear. Hum Brain Mapp 33(6): 1407-16.

Onur OA, Walter H, Schlaepfer TE, Rehme AK, Schmidt C, Keysers C, Maier W, Hurlemann R (2009) Noradrenergic enhancement of amygdala responses to fear. Soc Cogn Affect Neurosci 4: 119–26.

Onur OA, Schlaepfer TE, Kukolja J, Bauer A, Jeung H, Patin A, Otte DM, Shah NJ, Maier W, Kendrick KM, Fink GR, Hurlemann R (2010) The N-methyl-D-aspartate receptor co-agonist D-cycloserine facilitates declarative learning and hippocampal activity in humans. Biol Psychiatry 67: 1205-11.

Osterrieth PA (1944) Le test de copie d'une figure complexe. Arch Psychol 30: 206 –356.

Otto MW, Tolin DF, Simon NM, Pearlson GD, Basden S, Meunier SA, Hofmann SG, Eisenmenger K, Krystal JH, Pollack MH (2010) Efficacy of DSC for enhancing response to cognitive behavior therapy for panic disorder. Biol Psychiatry 67: 365–70.

Outhred T, Das P, Felmingham KL, Bryant RA, Nathan PJ, Malhi GS, Kemp AH (2015) Facilitation of emotion regulation with a single dose of escitalopram: A randomized fMRI study. Psychiatry Res 233(3): 451-7.

Outhred T, Hawkshead BE, Wager TD, Das P, Malhi GS, Kemp AH (2013) Acute neural effects of selective serotonin reuptake inhibitors versus noradrenaline reuptake inhibitors on emotion processing: Implications for differential treatment efficacy. Neurosci Biobehav Rev 37(8): 1786-800.

Patin A, Hurlemann R (2010) Modulating amygdala responses to emotion: evidence from pharmacological fMRI. Neuropsychologia 49: 706-17.

Patin A, Hurlemann R (2015) Social Cognition. Handb Exp Pharmacol 228: 271-303.

Patin A, Pause BM (2015) Human amygdala activations during nasal chemoreception. Neuropsychologia 78: 171-94.

Pause BM (2012) Processing of body odor signals by the human brain. Chemosens Percept 5(1): 55-63.

Pause BM, Miranda A, Göder R, Aldenhoff JB, Ferstl R (2001) Reduced olfactory performance in patients with major depression. J Psychiatr Res 35(5): 271-7.

Pedersen CA, Prange AJ Jr (1985) Oxytocin and mothering behavior in the rat. Pharmacol Ther 28(3): 287-302.

Pessoa L (2008) On the relationship between emotion and cognition. Nat Rev Neurosci 9: 148-58.

Pessoa L (2010) Emotion and cognition and the amygdala: from “what is it?” to “what’s to be done?”. Neuropsychologia 48: 3416-29.

Pessoa L, Adolphs R (2010) Emotion processing and the amygdala: from a low road’ to ‘many roads’ of evaluating biological significance. Nat Rev Neurosci 11: 773–83.

Phelps EA, LeDoux JE (2005) Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48(2): 175-87. doi: 10.1016/j.neuron.2005.09.025

Phillips ML, Medford N, Young AW, Williams L, Williams SC, Bullmore ET, Gray JA, Brammer MJ (2001) Time courses of left and right amygdalar responses to fearful facial expressions. Hum Brain Mapp 12(4): 193-202.

Popik P, Vetulani J (1991) Opposite action of oxytocin and its peptide antagonists on social memory in rats. Neuropeptides 18(1): 23-7.

Prather MD, Lavenex P, Mauldin-Jourdain ML, Mason WA, Capitanio JP, Mendoza SP, Amaral DG (2001) Increased social fear and decreased fear of objects in monkeys with neonatal amygdala lesions. Neuroscience 106(4): 653-8.

Price CJ, Friston KJ (2002) Degeneracy and cognitive anatomy. Trends Cogn Sci 6(10): 416-21.

Price JL (2003) Comparative aspects of amygdala connectivity. Ann N Y Acad Sci 985: 50-8.

Quartermain D, Mower J, Rafferty M, Hering R, Lanthorn T (1994) Acute but not chronic activation of the NMDA-coupled glycine receptor with DSC facilitates learning and retention. Eur J Pharmacol 257: 7–12.

Quirk GJ, Gehlert DR (2003) Inhibition of the amygdala: key to pathological states? Ann N Y Acad Sci 985: 263–72.

Rahman S, Zhang J, Engleman EA, Corrigall WA (2004) Neuroadaptive changes in the mesoaccumbens dopamine system after chronic nicotine self-administration: a microdialysis study. Neuroscience 129: 415–24.

Raper J, Wilson M, Sanchez M, Machado CJ, Bachevalier J (2013) Pervasive alterations of emotional and neuroendocrine responses to an acute stressor after neonatal amygdala lesions in rhesus monkeys. Psychoneuroendocrinology 38(7): 1021-35.

Rash JA, Aguirre-Camacho A, Campbell TS (2014). Oxytocin and pain: a systematic review and synthesis of findings. Clin J Pain 30: 453–62.

Raymond JE, Shapiro L, Arnell KM (1992) Temporary suppression of visual processing in an RSVP task: an attentional blink? J Exp Psychol Hum Percept Perform 18: 849–60.

Reitan RM (1955) The relation of the trail-making test to organic brain damage. J Consult Psychol 19: 393–4.

Ressler KJ, Rothbaum BO, Anderson P, Zimand E, Tannenbaum L, Hodges L, Davis M (2004) DSC, a putative cognitive enhancer, accelerates extinction of fear in humans. Arch Gen Psychiatry 61: 1136–44.

Richter-Levin G (2004) The amygdala, the hippocampus, and emotional modulation of memory. Neuroscientist 10(1): 31-9.

Richter-Levin G, Akirav I (2000) Amygdala-hippocampus dynamic interaction in relation to memory. Mol Neurobiol 22(1-3): 11-20. doi: 10.1385/mn:22:1-3:011.

Rimmele U, Hediger K, Heinrichs M, Klaver P (2009) Oxytocin makes a face in memory familiar. J Neurosci 29(1): 38-42.

Roepke S, Vater A, Preißler S, Heekeren HR, Dziobek I (2013) Social cognition in borderline personality disorder. Front Neurosci 6: 195.

Roiser, JP, De Martino B, Tan GC, Kumaran D, Seymour B, Wood NW, Dolan RJ (2009) A genetically mediated bias in decision making driven by failure of amygdala control. J Neurosci 29: 5985–91.

Royet JP, Koenig O, Gregoire MC, Cinotti L, Lavenne F, Le Bars D, Costes N, Vigouroux M, Farget V, Sicard G, Holley A, Mauguière F, Comar D, Froment JC (1999) Functional anatomy of perceptual and semantic processing for odors. J Cogn Neurosci 11(1): 94-109.

Royet JP, Plailly J, Delon-Martin C, Kareken DA, Segebarth C (2003) fMRI of emotional responses to odors: influence of hedonic valence and judgment, handedness, and gender. Neuroimage 20(2): 713-28.

Rubenstein JL, Anderson S, Shi L, Miyashita-Lin E, Bulfone A, Hevner R (1999) Genetic control of cortical regionalization and connectivity. Cereb Cortex 9(6): 524-32.

Rutishauser U, Schuman EM, Mamelak AN (2008) Activity of human hippocampal and amygdala neurons during retrieval of declarative memories. Proc Natl Acad Sci U S A 105(31): 11032.

Sander D, Grafman J, Zalla T (2003) The human amygdala: an evolved system for relevance detection. Rev Neurosci 14: 303–16.

Savaskan E, Ehrhardt R, Schulz A, Walter M, Schachinger H (2008) Post-learning intranasal oxytocin modulates human memory for facial identity. Psychoneuroendocrinology 33(3): 368-74.

Savic I, Gulyas B (2000) PET shows that odors are processed both ipsilaterally and contralaterally to the stimulated nostril. Neuroreport 11(13): 2861-6.

Savic I, Gulyas B, Larsson M, Roland P (2000) Olfactory functions are mediated by parallel and hierarchical processing. Neuron 26(3): 735-45.

Shahrestani S, Kemp AH, Guastella AJ (2013). The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis. Neuropsychopharmacology 38: 1929–36.

Scheele D, Mihov Y, Kendrick KM, Feinstein JS, Reich H, Maier W, Hurlemann R (2012a) Amygdala lesion profoundly alters altruistic punishment. Biol Psychiatry 72(3): e5-7. doi: 10.1016/j.biopsych.2012.01.028

Scheele D, Striepens N, Güntürkün O, Deutschländer S, Maier W, Kendrick KM, Hurlemann R (2012b) Oxytocin modulates social distance between males and females. J Neurosci 32(46): 16074-9. doi: 10.1523/jneurosci.2755-12.2012

Scheele D, Wille A, Kendrick KM, Stoffel-Wagner B, Becker B, Güntürkün O, Maier W, Hurlemann R (2013) Oxytocin enhances brain reward system responses in men viewing the face of their female partner. Proc Natl Acad Sci U S A 110(50): 20308-13. doi: 10.1073/pnas.1314190110

Scheele D, Kendrick KM, Khouri C, Kretzer E, Schläpfer TE, Stoffel-Wagner B, Güntürkün O, Maier W, Hurlemann R (2014a). An oxytocin-induced facilitation of neural and emotional responses to social touch correlates inversely with autism traits. Neuropsychopharmacology 39: 2078–85.

Scherer KR, Schorr A, Johnstone T (2001) *Appraisal processes in emotion: Theory, methods, research*. New York: Oxford University Press.

Schienle AA, Schafer A, Hermann S, Rohrmann S, Vaitl D (2007) Symptom provocation and reduction in patients suffering from spider phobia: an fMRI study on exposure therapy. Eur Arch Psychiatry Clin Neurosci 257 (8): 486-93. doi: 10.1007/s00406-007-0754-y.

Schoenbaum G, Chiba AA, Gallagher M (1998) Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nat Neurosci 1(2): 155-9. doi: 10.1038/407

Schoffelmeer AN, De Vries TJ, Wardeh G, van de Ven HW, Vanderschuren LJ (2002) Psychostimulant-induced behavioral sensitization depends on nicotinic receptor activation. J Neurosci 22: 3269–76.

Schwabe L, Höffken O, Tegenthoff M, Wolf OT (2013) Opposite effects of noradrenergic arousal on amygdala processing of fearful faces in men and women. Neuroimage 73: 1-7.

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosur Ps 20(1): 11.

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neuropsychiatry Clin Neurosci 12:103-13.

Seeck M, Mainwaring N, Ives J, Blume H, Dubuisson D, Cosgrove R, Mesulam MM, Schomer DL (1993) Differential neural activity in the human temporal lobe evoked by faces of family members and friends. Ann Neurol 34(3): 369-72. doi: 10.1002/ana.410340311

Sergerie K, Chochol C, Armony JL (2008) The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies. Neuroscience & Biobehavioral Reviews 32(4): 811-30. doi: http://dx.doi.org/10.1016/j.neubiorev.2007.12.002

Sehlmeyer C, Schöning S, Zwitserlood P, Pfleiderer B, Kircher T, Arolt V, Konrad C (2009). Human fear conditioning and extinction in neuroimaging: a systematic review. PLoS One 4: e5865.

Shiffman S, West R, Gilbert D, SRNT Work Group on the Assessment of Craving and Withdrawal in Clinical Trials (1997) Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. Nicotine Tob Res 6: 599–614.

Siebert M, Markowitsch HJ, Bartel P (2003) Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. Brain 126: 2627-37.

Small DM, Gerber JC, Mak YE, Hummel T (2005) Differential neural responses evoked by orthonasal versus retronasal odorant perception in humans. Neuron 47(4): 593-605.

Snell R (2010) *Clinical Neuroanatomy, 7th edition*. Baltimore, MD: Lippincott Williams & Wilkins.

Sobota R, Mihara T, Forrest A, Featherstone RE, Siegel SJ (2015) Oxytocin reduces amygdala activity, increases social interactions and reduces anxiety-like behavior irrespective of NMDAR antagonism. Behav Neurosci 129(4): 389-98. doi: 10.1037/bne0000074

Spiegel A, Miller L (2015) World with No Fear, Invisibilia: National Public Radio.

Striepens N, Kendrick KM, Hanking V, Landgraf R, Wüllner U, Maier W, Hurlemann R (2013) Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. Sci Rep 3: 3440. doi: 10.1038/srep03440

Su CY, Menuz K, Carlson JR (2009) Olfactory perception: receptors, cells, and circuits. Cell 139(1): 45-59.

Sulmont C, Issanchou S, Koster EP (2002) Selection of odorants for memory tests on the basis of familiarity, perceived complexity, pleasantness, similarity and identification. Chem Senses 27(4): 307-17.

Swanson LW (2003) The amygdala and its place in the cerebral hemisphere. Ann N Y Acad Sci 985: 174–84.

Swanson LW, Petrovich GD (1998) What is the amygdala? Trends Neurosci 21: 323–31.

Takahashi H, Yahata N, Koeda M, Takano A, Asai K, Suhara T, Okubo Y (2005) Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study. Neuroimage 27(4): 991-1001. doi: 10.1016/j.neuroimage.2005.05.039

Talmi D, Hurlemann R, Patin A, Dolan RJ (2010) Framing effect following bilateral amygdala lesion. Neuropsychologia 48: 1823-7.

Terburg D, Morgan BE, Montoya ER, Hooge IT, Thornton HB, Hariri AR, Panksepp J, Stein DJ, van Honk J (2012) Hypervigilance for fear after basolateral amygdala damage in humans. Transl Psychiatry 2: e115. doi: 10.1038/tp.2012.46

Thompson CI (1981) Learning in rhesus monkeys after amygdalectomy in infancy or adulthood. Behav Brain Res 2(1): 81-101.

Thompson LT, Moskal JR, Disterhoft JF (1992) Hippocampus-dependent learning facilitated by a monoclonal antibody or DSC. Nature 359: 638–41.

Tranel D, Gullickson G, Koch M, Adolphs R (2006) Altered experience of emotion following bilateral amygdala damage. Cogn Neuropsychiatry 11: 219-32.

Tranel D, Hyman BT (1990) Neuropsychological correlates of bilateral amygdala damage. Arch Neurol 47: 349-55.

Trepel M (2008) *Neuroanatomie mit Studentconsult-zugang: Struktur und Funktion.* Munich: Elsevier, Urban & Fischer Verlag.

Tsuchiya N, Moradi F, Felsen C, Yamazaki M, Adolphs R (2009) Intact rapid detection of fearful faces in the absence of the amygdala. Nat Neurosci 12: 1224–5.

Tudusciuc O, Adolphs R (2013) Social cognitive neuroscience: clinical foundations. In: Roberts DL, Penn DL (Eds.) *Social cognition in schizophrenia*. Oxford University Press, New York

Tulving E (1972) Episodic and semantic memory. In E Tulving and W Donaldson (Eds.) *Organization of Memory*. New York: Academic Press.

Tulving E (2002) Episodic memory: From mind to brain. Annu Rev Psychol 53: 1-25.

Tversky A, Kahneman D (1981) The framing of decisions and the psychology of choice. Science 211: 453–8.

Urbach E, Wiethe C (1929) Lipoidosis cutis et mucosae. Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin 273: 285–31.

Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M (1997) Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277: 376-80.

Veinante P, Freund-Mercier MJ (1997) Distribution of oxytocin- and vasopressin-binding sites in the rat extended amygdala: a histoautoradiographic study. J Comp Neurol 383(3): 305-25.

Vezina P (2004) Sensitization of midbrain dopamine neuron reactivity and the self administration of psychomotor stimulant drugs. Neurosci Biobehav Rev 27: 827–39.

Vezina P, Lorrain DS, Arnold GM, Austin JD, Suto N (2002) Sensitization of midbrain dopamine neuron reactivity promotes the pursuit of amphetamine. J Neurosci 22: 4654–62.

Vezina P, McGehee DS, Green WN (2007) Exposure to nicotine and sensitization of nicotine-induced behaviors. Prog Neuropsychopharmacol Biol Psychiatry 31: 1625–38.

Vogt BA (2005) Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci 6: 533–44.

Wang S, Tudusciuc O, Mamelak AN, Ross IB, Adolphs R, Rutishauser U (2014) Neurons in the human amygdala selective for perceived emotion. Proc Natl Acad Sci U S A 111(30): E3110-9.

Wedrychowicz W, Starzycki Z (1978) [Intracranial calcifications in Urbach-Wiethe disease (author's transl)] Pol Przegl Radiol Med Nukl 42: 299-301.

Weidlich S, Lamberti G (2001) DCS—Diagnosticum für Cerebralschädigung (DCS). Ein visueller Lern- und Gedächtnistest nach F. Hiller. Bern, Switzerland: Hans Huber.

Weller JA, Levin IP, Shiv B, Bechara A (2007) Neural correlates of adaptive decision making for risky gains and losses. Psychol Sci 18: 958–64.

Whalen PJ, Shin LM, McInerney SC, Fischer H, Wright CI, Rauch SL (2001) A functional MRI study of human amygdala responses to facial expressions of fear versus anger. Emotion 1: 70–83.

Wilhelm S, Buhlmann U, Tolin DF, Meunier SA, Pearlson GD, Reese HE, Cannistraro P, Jenike MA, Rauch SL (2008) Augmentation of behavior therapy with DSC for obsessive-compulsive disorder. Am J Psychiatry 165: 335–41.

Wilson DA, Sullivan RM (2011) Cortical processing of odor objects. Neuron 72(4): 506-19.

Winston JS, O'Doherty J, Dolan RJ (2003) Common and distinct neural responses during direct and incidental processing of multiple facial emotions. Neuroimage 20: 84–97.

Witt DM, Carter CS, Walton DM (1990) Central and peripheral effects of oxytocin administration in prairie voles (Microtus ochrogaster). Pharmacol Biochem Behav 37(1): 63-9.

Wong DF, Tauscher J, Gruender G (2009) The role of imaging in proof of concept for CNS drug discovery and development. Neuropsychopharmacology 34: 187–203.

Wright A (1997) *Neuroscience Online: An Electronic Textbook for the Neurosciences* J. H. Byrne (Ed.) Retrieved from http://nba.uth.tmc.edu/neuroscience/

Wright CI, Fischer H, Whalen PJ, McInerney SC, Shin LM, Rauch SL (2001) Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. Neuroreport 12(2): 379-83.

Young MP, Scannell JW, Burns GA, Blakemore C (1994) Analysis of connectivity: neural systems in the cerebral cortex. Rev Neurosci 5: 227–49.

Zajonc RB (1968) Attitudinal effects of mere exposure. J Pers Soc Psychol 9(2p2): 1.
Zald DH (2003) The human amygdala and the emotional evaluation of sensory stimuli. Brain Res Brain Res Rev 41: 88–123.
Zald DH, Rauch S (2006) *The Orbitofrontal Cortex*. Oxford University Press.
Zald DH, Kim SW (1996) Anatomy and function of the orbital frontal cortex: I. Anatomy, neurocircuitry, and obsessive-compulsive disorder. J Neuropsychiatry Clin Neurosci 8(2): 125-38.
Zou DJ, Chesler A, Firestein S (2009) How the olfactory bulb got its glomeruli: a just so story? Nat Rev Neurosci 10(8): 611-8.

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VIII. Original research articles

Patin A, Pause BM (2015) Human amygdala activations during nasal chemoreception. Neuropsychologia 78: 171-94.

Eckstein M, Scheele D, Patin A, Preckel K, Becker B, Walter A, Domschke K, Grinevich V, Maier W, Hurlemann R (2016) Oxytocin Facilitates Pavlovian Fear Learning in Males. Neuropsychopharmacology 41(4): 932-9.

Onur OA, Patin A, Mihov Y, Buecher B, Stoffel-Wagner B, Schlaepfer TE, Walter H, Maier W, Hurlemann R (2012) Overnight deprivation from smoking disrupts amygdala responses to fear. Hum Brain Mapp 33(6): 1407-16.

Bach DR, Talmi D, Hurlemann R, Patin A, Dolan RJ (2011) Automatic relevance detection in the absence of a functional amygdala. Neuropsychologia 49(5): 1302-5.

Talmi D, Hurlemann R, Patin A, Dolan RJ (2010) Framing effect following bilateral amygdala lesion. Neuropsychologia 48(6): 1823-7.

IX. Other publications not subject of this dissertation

Peer reviewed articles:

Onur OA, Schlaepfer TE, Kukolja J, Bauer A, Jeung H, Patin A, Otte DM, Shah NJ, Maier W, Kendrick KM, Fink GR, Hurlemann R (2010) The N-methyl-D-aspartate receptor co-agonist D-cycloserine facilitates declarative learning and hippocampal activity in humans. Biol Psychiatry 67(12): 1205-11.

Non-peer reviewed publications:

Patin A, Hurlemann R (2016) Behavioral Consequences and Compensatory Adaptations after Early Bilateral Amygdala Damage in Monozygotic Twins. In DG Amaral and R Adolphs (Eds.) *Living Without an Amygdala* (306-33). New York: Guilford Press.

Patin A, Hurlemann R (2015) Social Cognition. Handb Exp Pharmacol 228: 271-303.

X. Publications

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Patin A, Pause BM (2015) Human amygdala activations during nasal chemoreception. Neuropsychologia 78: 171-94.

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