THE SCIENCE OF MENTAL HEALTH

Fear and Anxiety

Edited by
Steven Hyman
The Science of Mental Health

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Fear and Anxiety
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The Science of Mental Health

Volume 10
Fear and Anxiety

Edited with introductions by
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ROUTLEDGE
New York/London
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Introduction

The word "emotion" is used in ordinary parlance to refer to subjective feelings, but at the level of brain and behavior emotions are critical survival mechanisms. In response to salient environmental or internal stimuli, "emotion circuitry" in the brain must rapidly appraise the significance of what is happening, and then activate output systems that prepare a person (or animal) to respond adaptively. These output systems produce changes in physiology and automatic patterns of behavior. They also produce changes in cognition and, indeed, accompanying subjective feelings that are congruent with the situation (LeDoux, 2000).

In addition to its immediate effects, emotion facilitates the formation of memories (Fendt and Fanselow, 1999). An important aspect of survival is the ability to learn environmental cues that predict danger as well as the necessities of life. Although humans exhibit many subtle forms of emotion, at a crude level emotions can be divided into two broad classes: "negative" emotions (such as fear), which under normal circumstances are elicited by aversive stimuli and which generally lead to avoidance, escape, or protective responses; and "positive" or "appetitive" emotions, which are elicited by rewarding stimuli and which lead to approach behaviors.

During the past decade there has been substantial progress in the understanding of one emotion in particular: fear (LeDoux, 2000). This progress has been possible, in part, because fear can readily be elicited and studied in the laboratory. This research is an important step toward a deeper understanding of one of our basic emotions. But it also has important implications for health. Fear and the closely related state of anxiety are core symptoms in common and debilitating mental disorders, including panic disorder, post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), social anxiety disorder (also called social phobia), and simple phobias (for example, phobias elicited by specific stimuli such as heights or spiders). Anxiety also commonly occurs in the course of major depression and may be severe. Panic disorder, PTSD, GAD, social anxiety disorder, and simple phobias are often grouped together as the so-called anxiety disorders. In some classifications, including that of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th edition, obsessive-compulsive disorder (OCD) is grouped with the anxiety disorders because, in addition to its core features of obsessions (intrusive, unwanted thoughts) and compulsions, intense anxiety may be a characteristic response to these obsessions and may be discharged by the performance of compulsive rituals. However, increasing evidence of the differences in the pathogenesis between the other anxiety disorders and obsessive-compulsive disorder has led many scientists
Introduction

to group the latter with Tourette's syndrome, a grouping reflected in these volumes.

As in other volumes in this series, there are descriptions of some of the clinical syndromes followed by sections on epidemiology, genetic and environmental risk factors, and natural history (course of illness). Because anxiety disorders so often co-occur with other mental disorders, there is a section devoted to this issue. The volume also includes an article on the evolutionary psychology of anxiety disorders (Marks and Nesse, 1994) and a long section on brain and behavior that, among other issues, illustrates current attempts to use new insights into fear circuitry in the brain to help investigate the pathogenesis of anxiety disorders. The volume ends with a section on treatment. In some sections there are articles on panic disorder, PTSD, GAD, social anxiety disorder, and, where appropriate, childhood anxiety disorders (which are not always readily separated into their adult forms). Because simple phobias cause relatively little harm or impairment compared with the other anxiety disorders, they are little discussed.

Fear generally represents a transient response to a specific stimulus that connotes danger. Anxiety differs from fear in that a stimulus is either not present or not immediately threatening. Nevertheless, negative effects and cognitions occur that are associated with danger or lack of control over events and that are accompanied by the types of arousal induced by fear. Because it is not stimulus-bound, anxiety may be prolonged. Although anxiety occurs as a core symptom in all of the anxiety disorders, the precise forms it takes differ across these disorders, as do prevalence (Kessler et al., 1999; Kessler et al., 1998), genetic and environmental risk factors, life course, pathophysiology, and treatment.

The central feature of panic disorder is the unexpected panic attack, a discrete period of intense fear accompanied by bodily symptoms that may include a pounding heart, sweating, trembling, perceived shortness of breath, chest pain, nausea, dizziness, and tingling of limbs. There may also be feelings of unreality or detachment, fear of losing control, and fear of dying. The diagnosis of panic disorder is made when panic attacks are recurrent and are accompanied by persistent fear of having additional attacks. People with panic disorder may progressively restrict their lives to avoid situations in which panic attacks have occurred or are feared. For example, people may avoid being in crowds, traveling, or being on a bridge or in an elevator and may ultimately avoid leaving the home altogether. When avoidance becomes pervasive, the diagnosis of agoraphobia is made. While this synopsis relates the two, panic disorder may occur without agoraphobia, and agoraphobia may occur without panic disorder (Katschinger and Amering, 1998; Bouton et al., 2001).

Post-traumatic stress disorder follows serious trauma. It is characterized by a sense of numbness, by intrusive reliving of the traumatic experience that is often initiated by otherwise harmless cues that serve as reminders of the trauma, by hyperarousal (for example, increased startle), and by disturbed sleep that may include nightmares. Generalized anxiety disorder (Yonkers et al., 1996) is characterized by unrealistic and excessive worry for more than six months, accompanied by specific anxiety-related symptoms such as motor tension, sympathetic hyperactivity, and excessive vigilance. Social anxiety disorder
Introduction

(Liebowitz et al., 1985) is characterized by serious persistent fear of social situations or performance situations (examples of the latter include stage fright) that expose a person to potential scrutiny by others. The affected person has intense fear that he or she will act in a way that will be humiliating. Attempts to separate social anxiety disorder (or social phobia) from more extreme temperamental shyness have led to the requirement in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, that the symptoms cause distress and interfere significantly with an individual's occupational or social role functioning. Despite such a requirement, the boundaries separating social phobia, avoidant personality disorder, and shyness are difficult to delineate.

There is less genetic data on anxiety disorders than on schizophrenia, bipolar disorder, or autism. Nonetheless, some family studies have been done on the genetic risks of anxiety disorders, with the most substantial investigations focusing on panic disorder, in part because the phenotype may be easier to define than that in other anxiety disorders (Biederman et al., 2001). Genetic linkage studies have been performed on panic disorder, but given the lack of convincing replication, none is included here. As in the case of all mental disorders, the data on panic disorder and other anxiety disorders suggest genetic complexity. This means that anxiety disorders do not appear to be "caused" by a single gene. Rather, multiple genes work as susceptibility factors, acting together with developmental and environmental factors to produce illness. Studies of children at risk for anxiety disorders have identified early markers of vulnerability (Merikangas et al., 1999; Kagan and Snidman, 1999); the search for specific risk factors is in its early stages. One interesting possibility is that early-onset anxiety disorders may create risk of subsequent alcoholism (Merikangas et al., 1998), as alcohol may serve as a misguided attempt at self-medication. Overall, the interaction among anxiety disorders, addictive disorders, and mood disorders is clinically significant and may provide opportunities for prevention of secondary disorders (Merikangas et al., 1998; Mineka et al., 1998; Regier et al., 1998).

Studies of brain and behavior have led to greater understandings of the neural substrates of both fear and anxiety (LeDoux, 2000; Kalin et al., 2001). There is a long way to go in relating these basic advances to the understanding of anxiety disorders, but research from several scientific traditions is already building bridges between neuroscience and clinical investigation (Gorman et al., 2000; Stein, 1998). One important strand of clinical investigation has been the careful analysis of individuals with informative brain lesions resulting from illness or injury. Studies have examined such individuals and can demonstrate in humans that different neural structures underlie the cognitive and conscious aspects of memory (hippocampus) versus the emotional and unconscious aspects that regulate physiologic responses (the amygdala). Such human studies extend the findings from animal studies in which invasive techniques such as placing of brain lesions permit a more detailed tracing of fear pathways (Fendt and Fanselow, 1999). A second approach that extends basic findings to the human situation is the use of noninvasive imaging. Studies are included here that investigate the neural circuits activated by fear in healthy volunteers (Phelps et al., 2001) and in individuals with
anxiety disorders such as PTSD. Other studies in normal volunteers examine different aspects of the encoding of fear-related memories (Buchel et al., 1998).

Many of the initial studies in humans have focused on the amygdala, a small but complex structure in the temporal lobes that plays a key role in fear and other emotions. It is already clear from basic investigation, however, that other brain regions, such as the prefrontal cerebral cortex, also play important roles in fear (García et al., 1999). Ultimately, the brain works not as a phrenologist might have imagined (brain regions functioning in isolation) but as distributed circuits across which specialized regions interact.

Another important aspect of research is the role of development in creating risk for anxiety disorders. There have been recent investigations of both temperamental factors (Kagan and Snidman, 1999) and environmental factors, especially the role of trauma.

Treatment of anxiety disorders involves both medication and cognitive-behavioral psychotherapies, or some combination of the two. In the Brain and Behavior section there is a review by Bouton et al. (2001) bringing a learning-theory perspective to the pathogenesis of panic disorder. This understanding has direct implications for understanding the use of cognitive-behavioral therapies (Barlow et al., 2000), which are highly efficacious in panic disorder and also in PTSD (Foa and Meadows, 1997) and simple phobias. The recognition that antidepressant drugs, initially the tricyclics, were efficacious for panic disorder was an important watershed for psychopharmacology (Klein, Klein, and Fink, 1962). These findings also had important implications for the classification of anxiety disorders. More recently, selective serotonin reuptake inhibitors (SSRIs) have proven efficacious in panic disorder, GAD, PTSD (Davidson et al., 2001), social anxiety disorder (Stein et al., 1998), and pediatric anxiety disorders (The Research Unit on Pediatric Psychopharmacology Anxiety Study Group, 2001). While benzodiazepines and anxiolytics can also be used effectively for a variety of anxiety disorders, the move to SSRIs reflects the fact that, unlike benzodiazepines, they do not produce dependence. This broad use of SSRIs is a reminder that the term "antidepressant" is a misnomer.

In summary, anxiety disorders are common and cause both distress and impairment. As will be seen from the articles in this collection, existing treatments are extremely useful but far from perfect. Thus the research progress in understanding fear and anxiety has created real excitement about the possibility of more effective interventions in the coming years.

References
The Science of Mental Health
Phenomenology and Course of Generalised Anxiety Disorder

KIMBERLY A. YONKERS, MEREDITH G. WARSHAW, ANN O. MASSION and MARTIN B. KELLER

Background. The diagnostic category of generalised anxiety disorder (GAD) was originally intended to describe residual anxiety states. Over the years clinical criteria have been refined in an attempt to describe a unique diagnostic entity. Given these changes, little is known about the clinical course of this newly defined disorder. This study investigates the longitudinal course, including remission and relapse rates, for patients with DSM-III-R defined GAD.

Method. Analysis of the 164 patients with GAD participating in the Harvard Anxiety Research Program. Patients were assessed with a structured clinical interview at intake and re-examined at six month intervals for two years and then annually for one to two years. Psychiatric Status Ratings were assigned at each interview point. Kaplan-Meier curves were constructed to assess likelihood of remission.

Results. Comorbidity was high, with panic disorder and social phobia as the most frequently found comorbid disorders. The likelihood of remission was 0.15 after one year and 0.25 after two years. The probability of becoming asymptomatic from all psychiatric symptoms was only 0.08.

Conclusions. This prospective study confirms the chronicity associated with GAD and extends this finding to define the one and two year remission rates for the disorder. Likelihood of remission for GAD and any other comorbid condition after one year was half the annual remission rate for GAD alone.

Generalised anxiety disorder (GAD), a disorder characterised by extreme anxiety and worry, was introduced as a category in DSM–III–R (American Psychiatric Association, 1980). It develops insidiously between the late teens and early twenties and some investigators (Anderson et al, 1984; Barlow et al, 1986), but not all (von Korff et al, 1985), find it develops before other anxiety disorders such as panic disorder. Stress plays a role in the genesis of GAD (Barlow et al, 1986) but genetic factors cannot be ruled out (Kendler et al, 1992). Retrospectively collected data show that the course of generalised anxiety is protracted and average illness duration may be as long as 20 years (Barlow et al, 1986). Few remissions occur after illness onset (Anderson et al, 1984). The remission rate for patients with anxiety neurosis, an older diagnostic category that includes patients with panic disorder and GAD, was only 12% after six years (Noyes et al, 1980).

A notable feature of GAD is the high degree of comorbidity with other psychiatric disorders (Massion et al, 1993). Community studies (Blazer et al, 1991; Wittchen et al, 1994) show frequent co-occurrence with major depression and panic. Studies using clinical cohorts also document extensive comorbidity (Barlow et al, 1986; Breier et al, 1986; Fava et al, 1988; Garvey et al, 1988; Brawman-Mintzer et al, 1993) which generates questions regarding the diagnostic integrity of the category (Massion et al, 1993). Because most data on GAD utilise older diagnostic systems and are retrospective in nature, it is unclear how accurate this information is for patients meeting the newer DSM–III–R definition. Prospectively collected information regarding comorbidity and longitudinal course of patients with DSM–III–R defined GAD would be useful in distinguishing it from other anxiety disorders and establishing its diagnostic integrity.

Methods

The Harvard/Brown Anxiety Research Program (HARP) is a prospective, naturalistic, longitudinal study of patients with DSM–III–R defined anxiety disorders. The design of the study has been described in detail elsewhere (Keller et al, 1994). Patients were recruited voluntarily from eleven Boston area hospitals with current or past diagnoses of: panic disorder (with or without agoraphobia); agoraphobia without a history of panic disorder; generalised anxiety disorder, or social phobia. Patients were at least 18-years-old and free of any organic mental
disorder, schizophrenia, or psychosis for the six months prior to intake. The intake diagnostic evaluation included a structured interview with the SCAL-UP (Keller et al., 1987a), which combines the Structured Clinical Interview for the DSM-III-R Patient Version (Spitzer et al., 1988) and the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (Endicott & Spitzer 1978). Follow-up was conducted at six month intervals for the first two years and annually thereafter, using the Longitudinal Interval Follow-Up Evaluation (LIFE; Keller et al., 1987b). Information on psychosocial treatment was collected using the Psychosocial Treatment Inventory (Perry et al., 1993). The majority of interviews were conducted in person by experienced clinical interviewers, who were closely supervised by the site project director. Clerical errors were corrected before inclusion in the computer master file. This paper includes an analysis of 164 patients with an active diagnosis of GAD at intake. Of these, 153 (93%) were interviewed at one year, 141 (86%) at two years and 112 (68%) at three years.

**Psychiatric status ratings**

The LIFE was used to collect information on the severity of symptoms during the study. Psychopathology is rated on a six-point Psychiatric Status Rating (PSR) scale which is scored on a week by week basis at each interview. The greatest severity of illness for GAD, a PSR of six, requires full DSM-III-R criteria as does a PSR of five, although functioning is not disrupted. A PSR of four is assigned when worry is present most days with three to five symptoms or worry less than 50% of the time and six symptoms. A PSR of three includes three symptoms and worry less than 50% of the time. Occasional worry is designated by a PSR of two and lack of symptoms, a PSR of one.

**Definition of remission**

Remission is defined as symptom improvement for eight consecutive weeks. This time period detects noticeable changes in morbidity and minimises transient changes in psychopathological state. Full remission requires improvement to a PSR of two or less. A partial remission is defined as a decrease in symptoms to a PSR of three. Also examined was improvement marked by loss of full criteria, i.e. decrease to a PSR of four during an eight week interval. Relapse was defined as a return to PSR of five or six for any length of time.

Patients were considered to be in an episode at intake if they met full criteria (PSR = 5 or 6) for GAD at any point during the previous six months and had not been well for eight consecutive weeks or longer at the time of intake. Because of this definition, some patients who were considered 'in episode' at intake did not meet full criteria at that time.

**Psychosocial treatment**

The Psychosocial Treatment Inventory (Perry et al., 1993) was administered at the first six month follow-up. Patients were scored as receiving treatment if they reported undergoing at least one of its constituent modalities at the 'frequent' level (0 = never, 1 = sometimes and 2 = frequent).

**Statistical analysis**

All statistical analyses were conducted using SAS Version 6.07 (SAS Institute, 1990) using PROC freq, PROC NPARIWAY, PROC t-test and PROC LIFE test. Longitudinal data were analysed using standard survival analysis techniques (Kalbfleish & Prentice, 1980). Kaplan-Meier life tables were constructed for times to remission and relapse for varying definitions of remission.

**Results**

**Subject characteristics**

Seventy-two per cent of patients with GAD were female and the average intake age was 41 (range 19-75). The age of onset for GAD varied between 2 and 61 years, with a mean of 21 years. The average length of illness by retrospective report was 20 years.

**Comorbidity with other anxiety disorders and depression**

Sixty per cent of the patients gave a history of only one episode of GAD during their lifetime while remaining patients had multiple episodes. Thirty-five per cent had experienced psychiatric hospitalisation, but not necessarily for GAD. Eighty-seven per cent had a lifetime history of another anxiety disorder and 83% had another anxiety disorder active at intake. Nearly one-quarter (23%) had two additional anxiety disorders active at intake and another 16% had three or four other active anxiety disorders. The most frequently seen coexisting anxiety disorders were panic disorder with agoraphobia (PDA) and social phobia (Table 1). Both were target diagnoses; simple phobia was the most frequently found non-target anxiety disorder. Over one-third of patients with GAD also had major depression.
One hundred and forty-nine patients had a concurrent anxiety disorder diagnosis. Of those, 47% (70/149) reported the first onset of GAD before the comorbid disorders, 13% (20/149) reported the first onsets occurring within four weeks of each other, with the remaining 40% (59/149) reporting first onset of GAD after the other anxiety disorders.

**Gender**

Women with GAD were more likely than men to have a lifetime history of an additional anxiety disorder (95% vs. 80%, $\chi^2 = 7.93, P = 0.005$). In particular, they were more likely to have histories of PDA (56% vs. 28%, $\chi^2 = 10.46, P = 0.001$). There was no gender difference for history of major depressive disorder. The (in episode) comorbidity rates at intake were equivalent for men and women.

**Course**

**Remission**

At study intake, 135 of 164 patients met full criteria for GAD. As shown in Table 2 the remission rate at one year was 0.15 and increased to 0.25 by two years. Less rigorous definitions of remission were associated with higher rates of remission.

At intake, a subset of GAD patients, 18% (29/164), only met partial criteria for GAD even though they had been at full criteria sometime during the preceding six months. Patients meeting partial criteria at intake had essentially the same probabilities of remission at one year (0.14 for full criteria and 0.17 for partial criteria). At two years, the probability of remitting for both groups was 0.25.

We also investigated remission from GAD plus concurrent psychiatric disorders for patients who entered the study meeting either full or partial criteria. At 26 weeks, the likelihood of full remission from GAD was 0.11 but the probability for remission from both GAD and coexisting anxiety disorders diminished to 0.03 during this same interval. The chances of becoming asymptomatic from GAD and other anxiety disorders increased slightly by one year and was flat after that (Table 3). Adding the requirement of concurrent remission from MDD does not further effect the remission rate.

Given the low probability for remission, we examined the general symptom status for the group over this initial six month period. In any given week, the majority of patients had anxiety more days than not and at least six DSM-III-R symptoms without a major disruption in functioning (PSR = 5). Figure 1 shows the distribution of PSRs among patients in episode of GAD at three time points. Although there was a trend toward some amelioration of symptoms over the 26 weeks, most patients remained stably symptomatic: 88% stayed at the same PSR during the first six months of follow-up, 9% changed by one level and only 3% changed by two or three levels (Fig. 1).

**Relapse**

Relapse was examined in the 42 patients who achieved a full remission (PSR < 3 for eight weeks). The risk of relapse was 0.07 after six months and 0.15 after one year. The risk of relapse was higher for the 43

<table>
<thead>
<tr>
<th>Week</th>
<th>Full remission (PSR&lt;3 for 8 wks)</th>
<th>Partial remission (PSR&lt;4 for 8 wks)</th>
<th>Loss of criteria (PSR&lt;5 for 8 wks)</th>
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<th>Week</th>
<th>GAD (only) (n=164)</th>
<th>GAD &amp; other anxiety disorders (n=164)</th>
<th>GAD, MDD &amp; other anxiety disorders (n=164)</th>
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patients who had a partial remission (PSR of 3 or 4 = 0.34 at one year) and for patients who had comorbid anxiety (0.23 at one year) or depressive disorders (0.28 at one year).

Treatment

Psychotherapy treatment data are available for 131 patients, and 88% of this group described involvement with some psychosocial treatment. Techniques consistent with psychodynamic psychotherapy were reported by 50%, 24% reported cognitive therapy, 15% reported behavioural therapy and 14% indicated treatment consistent with relaxation or meditation techniques.

Somatic treatment data were available for 163 of 164 patients. Eighty-four per cent of the group received pharmacological treatment during the first six months of the study. Thirty-five per cent of patients took one medication, 31% took two and 18% took more than two psychoactive agents during this six month interval. The majority (69%) received a benzodiazepine anxiolytic while 31% received tricyclic antidepressants. The most frequently reported drugs were alprazolam (51/163 = 31%), clonazepam (37/163 = 23%) and fluoxetine (30/163 = 18%). Sixteen per cent (8/51) of patients taking alprazolam, 14% (5/37) of those taking clonazepam and none of those taking fluoxetine reported PRN usage.

Discussion

Comorbidity

In prior reports, we note that solo anxiety disorder diagnoses are rare (White et al., 1992; Massion et al., 1993). For patients with GAD, 90% had a lifetime history of another anxiety disorder and 83% had at least one other anxiety disorder diagnosis active at intake. A recent study (Brawman-Mintzer et al., 1993) finds slightly lower rates (74%) of comorbidity in a clinical sample of patients with GAD. One would wonder whether these high comorbidity rates occur because clinical cohorts versus community samples, are likely to be more ill and to suffer from multiple conditions. However, data from the National Comorbidity Study (NCS) finds lifetime comorbidity rates of 90% and one month comorbidity rates of 66% (Wittchen et al., 1994). In that study, the most likely comorbid diagnoses are dysthymia, panic disorder, mania and major depression. Comorbidity rates in our study were influenced by intake criteria and thus high rates for mania were not seen. These reports suggest that patients requesting treatment for generalised anxiety should be carefully screened for comorbid psychiatric disorders.

The comorbidity between the various anxiety disorders suggests shared predisposing biological and developmental factors, as previously proposed (Massion et al., 1993; Brown et al., 1994).
GAD was constructed to encapsulate residual and prodromal anxiety and the symptoms of GAD are commonly found among the other anxiety disorders (Barlow et al., 1986). Modifications in DSM-III-R appear not to have changed this characteristic. In fact, eliminating the DSM-III-R hierarchical exclusions with agoraphobia and obsessive–compulsive disorder (OCD), or lessening exclusions when GAD co-occurs with simple phobia, panic disorders and social phobia, have increased the apparent comorbidity in a clinical study (Boyd et al., 1984) but did not appreciably change rates in the NCS (Wittchen et al., 1994).

Course of illness
Retrospective report of average illness length was 20 years, similar to other reports (Barlow et al., 1986). The average age of illness onset is also consistent (Garvey et al., 1988; Kendler et al., 1992). After one year, the chance of experiencing complete remission was only 0.15, a rate reported by a number of groups (Schapira et al., 1972; Noyes et al., 1980; Wittchen, 1988). The full remission rate at two years, 0.25, is considerably higher than that found in other studies. Perhaps the rate found by others reflects remission rates from both GAD and other psychiatric disorders which is only 0.17 in HARP. Studies which assess anxious symptomatology rather than symptom clusters, might well find that few patients become asymptomatic. Partial remissions and loss of full criteria were far more likely (0.23–0.41 at one year). Huxley (1979) found rates of 0.30 in patients using 50% improvement criteria and Kedward & Cooper (1966) found improvement in 24% of their group. These rates are remarkably similar to our remission rates despite differences in diagnostic criteria between studies.

Despite improvement in GAD, many of our patients continued to have other psychiatric symptoms as evidenced by a lower remission rate from GAD together with other anxiety disorders. In a separate paper, we report that one-third of patients with GAD (and no comorbid panic) were never married and 17% were separated, widowed or divorced (Mension et al., 1993). Patients were also under-employed and 37% had received public assistance. Thus, GAD may be a marker for chronicity and functional impairment.

Brown et al. (1994) note problems with diagnostic reliability but also describe features of GAD which differ from other anxiety disorders. Data on course of illness can contribute to this discussion of diagnostic reliability and validity. Our group finds a one year remission rate from panic disorder of 0.37 (Keller et al., 1994). The unique course for GAD as shown in this study shows some differentiation between this diagnostic category and other anxiety disorders. This means but it does not rule out the possibility that GAD, which begins earlier and has a lower remission rate, shares psychobiological features with other anxiety disorders such as panic. It also does not eliminate the possibility that GAD is a prodromal substrate or residua of other anxiety disorders.

Over 80% of the group received either pharmacotherapy or psychotherapy with the majority of patients receiving both treatments. Despite this, patients infrequently remitted. Inspecting data for somatic treatment suggests under treatment (median daily doses for alprazolam and clorazepam were 1.4 and 1.0 mg respectively). Future research should more thoroughly investigate the intensity and types of treatment received to understand whether this is a factor in so few individuals becoming asymptomatic.

Clinical Implications
- Generalised anxiety disorder is associated with extensive comorbidity.
- Remission from generalised anxiety is rare (0.15 at one year) and the majority of patients remain stably symptomatic.
- Even if patients remit from generalised anxiety disorder, approximately one-half will continue to have symptoms associated with a comorbid anxiety disorder.

Limitations
- Data from clinical samples may be representative of patients with more severe, comorbid, chronic illnesses.
- Observational data which does not control treatment may underestimate the likelihood of remission compared to controlled, adequately treated cohorts.
- The existence of comorbid illness in patients with generalised anxiety disorder may have affected the likelihood of remission from generalised anxiety disorder.

Acknowledgements
Supported by the Upjohn Company, the Harvard/Brown Anxiety Disorders Research Program is conducted with the participation of the following investigators: M. B. Keller, Chairperson; S. Rasmussen, Co-Chairperson; R. Stout; M. Weinsten, P. Alexander, A. Gordon, Butler Hospital, Brown University School of Medicine; J. Risch, Brown University School of Medicine; K. White, J. Curran, Veterans Administration Hospital, Providence, Brown University School of Medicine; P. Lavori, Stanford University;
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xu Introduction Other studies in normal volunteers examine of the encoding of fear-related memories (Buchel et al., 1998). of the initial studies in humans have focused on the amygdala, a It is already clear from basic investigation, however, that other ofM ental

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(First received 27 March 1995, final revision 31 July 1995,
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Journal of Clinical Psychopharmacology

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The Long-Term Course of Panic Disorder and
Whereas lifetime prevalence rates of panic disorder—as established in epidemiologic surveys—range between 1.6 and 3.5%, 1-month rates usually amount to much less than one half of the lifetime rates. This finding indicates that a substantial proportion of patients who had panic disorder at some stage in their life must have remitted. In contrast to these results, clinicians tend to regard panic disorder as a chronic condition because, as a rule, they see panic patients only several years after onset of the disorder. A number of small, prospective, long-term studies of such clinical populations indicate that after several years, between 17 and 70% of patients still have panic attacks, and between 36 and 82% have phobic avoidance. In the largest and longest follow-up study published to date, 45% of all patients showed an unremitting—although in a certain proportion waxing and waning—course, 24% followed a pattern of remissions and relapses, whereas 31% went back into a stable remission. The evidence of factors predicting the course of panic disorder in
clinical populations suggests that long duration and agoraphobia at baseline—not the severity and frequency of panic attacks—are predictors of an unfavorable course. Additional studies are needed to determine whether personality factors, depression, and other variables are also of predictive relevance. Also, factors working during follow-up, such as positive and negative life events, coping behaviors, and treatment, should be considered in future studies. (J Clin Psycho pharmacoI1998jI8[suppI21:68-118)

QUALITY-OF-LIFE ISSUES are becoming increasingly important in medicine today. In psychiatry, therefore, long-term outcomes of patients with mental disorders are becoming of equal interest as outcomes of short-term pharmacologic trials. Comprehensive data bases of long-term outcomes exist for some psychiatric disorders, such as schizophrenia. However, for many other psychiatric disorders, similar databases are not as well established, often for the simple reason that the disorder was defined a relatively short time ago. Panic disorder, which only emerged as a specific illness entity in 1980 (DSM-III), is one of these latter disorders. In this article, we present evidence that we have collected regarding the course of panic disorder beyond the usual 6 or 8-week clinical trial period. We also attempt to answer the clinically most relevant question: Is it possible to identify, at an early stage of panic
ilisorder, those persons who are at risk for an unfavorable course? The usual clinical description of panic ilisorder begins with unexpected panic attacks, then expected or situational panic attacks develop, then phobic avoidance, and finally full-blown agoraphobia. Comorbid conditions, such as depression and substance abuse, often complicate the clinical pictures of the patients we usually see as clinicians, and comorbidity is often so prominent that the original disorder is not recognized. Approximately 80% of panic ilisorder patients seen by psychiatrists in clinical settings also have agoraphobia, and the average illness duration is approximately 5 years. Therefore, if psychiatric practitioners draw conclusions from the patients they typically see, they will regard panic ilisorder as a chronic condition. However, only prospective stuilies can prove or ilisprove that the pattern of chronicity seen in clinical patients is valid for most or all patients who start having unexpected panic attacks. Unfortunately, not many prospective stuilies have been conducted so far, and those that have been had methodologic ilisadvantages in one respect or another, such as small sample sizes, short duration of follow-up, insufficient outcome criteria selection, etc. In this article, we attempt to sketch a picture of the course of panic ilisorder, beginning with a startling epidemiologic observation, going on to describe the results of prospective stuilies, and finishing by essaying the task of identifying preilictors of source and outcome once 82

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panic disorder has developed. Although the attempt is ambitious, we feel that it is justified in the effort to con

centrate the ever-shrinking health care resources on

those patients who need them most. Conclusions About Course and Outcome of Panic Disorder from Cross-Sectional Epidemiologic Data

Epidemiologic data suggest that it is an oversimplifi
cation to regard panic disorder as a chronic condition. This is demonstrated in the comparison of lifetime, 12

month, and 1-month prevalence rates from the two
large U.S. epidemiologic studies conducted over the last 15 years. Although all the rates in the more recent National Comorbidity Survey (NCS)2, 3 are more than twice as high as those in the older Epidemiological Catchment Area (CECA) study,5 the relationship between lifetime, 12-month, and 1-month prevalence rates is strikingly similar. As shown in Figure 1, the 1-month prevalence rates are less than half of the lifetime prevalence rates. More precisely, the 1-month rate is less than one third of the lifetime rate in the ECA study, and approximately two fifths of the lifetime prevalence rate in the NCS. Therefore, according to the results of these large epidemiologic studies, at least three fifths to two thirds of those who had panic disorder at some period in their lives did not experience it during the month before the intake interviews.

Figure 1. Prevalence of panic disorder. (Sources: Regier DA, Boyd .ill, Burke JD Jr, Rse DS, Myers JK, Kramer M, Robins LN, George LK, Kamo M, Locke BZ. One-month prevalence of mental disorders in the United States. Arch Gen Psychiatry 1988;45:977--86; Eaton WW, Dryman A, Weissman MM. Panic and phobia: the diagnosis of panic dis
order and phobic disorder. In: Robins LN, Regier DA, eds. Psychiatric disorders in America: the Epidemiologic Catchment Area study. New York: The Free Press, 1991:155-79; Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H-U, Kendler K Ufe tUne and 12-month prevalence of DSM-ffl.R psychiatric disorders in the United States: results from the national comorbidity study. Arch Gen Psychiatry 1994;51:8-19; Eaton WW, Kessler RC, Wittchen HU, Magee WJ. Panic and panic disorder in the United States. Am J Psychiatry 1994;151:418-20. In a second approach to drawing conclusions about the course of panic disorder from prevalence data, lifetime prevalence data from the ECA study, as analyzed by Weissman· and Klerman and associates,’ can be interpreted as providing the following hypothetical "longitudinal" picture: although approximately 10% of the general population experience at least one panic attack at some stage in their lives, only one in six of these persons fulfills diagnostic criteria for panic disorder (1.6% lifetime prevalence). One third of the latter group also had agoraphobia (i.e" in an epidemiologic sample, two thirds did not seem to develop agoraphobia) while fulfilling criteria for panic disorder, which is just the opposite of the picture seen in clinical samples-usually approximately 80% of those presenting for treatment of panic disorder have developed agoraphobia, 1 However, hypothetical constructs notwithstanding, actual longitudinal data from epidemiologic studies are not available, We therefore have to rely on clinical populations when studying the course and outcome of panic disorder, Data on these populations are nevertheless useful as a guidance for clinicians, although selection criteria for inclusion into such studies vary to a considerable degree, and most studies use clinical trial populations as a starting point, which usually constitute a highly selective group, Choosing Outcome Criteria The
epidemiologic studies just cited used operational diagnostic criteria, and we drew our conclusions from the presence or absence of these full criteria. But diagnostic criteria are crude, do not reflect the complex and varied structure of the disorder in individual patients, and usually do not say anything about severity. Diagnostic criteria may also miss relevant psychopathology. For instance, Katschnig and Amerling, in reference to data published by Weissman and Klerman and associates, I have stressed that of all persons assessed in the ECA study, 1.2% experienced panic attacks with agoraphobia without fulfilling diagnostic criteria for panic disorder. These persons obviously were not included in the ECA prevalence data, but their daily life was nevertheless quite likely impaired to some degree. Therefore, when following up a group of panic disorder patients to assess course and outcome, one inevitably is challenged by the great complexity of panic disorder. Spontaneous panic attacks, anticipatory anxiety, situational panic attacks, phobic avoidance, disabilities, comorbid depression, and substance abuse have to be considered. Some of these phenomena are persistent, others are not, as clinical experience shows. For instance, the outcome of "zero panic attacks" at 83 follow-up is much more frequent than that of remission of other symptoms. 9 • 10

Many methodologic questions remain open today: Which of the different phenomena complicating panic disorder should be considered most important in assessing course and outcome? Furthermore, what are the critical time intervals? How often must panic attacks occur for the disorder to be considered active rather than remitted? Every day? Once a week? Once a month? What about two panic attacks within a single year? Furthermore, what about the disappearance of panic attacks because disabling avoidance behavior has
Because of the great complexity of these variables, Roy-Byrne and Cowley\textsuperscript{1} and Shear and Maser,\textsuperscript{11} as well as Starcevic,\textsuperscript{12} indicate that it is necessary to use multiple measures in assessing outcome.

In view of these complex outcome criteria, simple conclusions, such as that panic disorder is or is not a chronic condition, are problematic. Panic disorder may be chronic in one respect but not in another (e.g., a patient might still be experiencing panic attacks but not have agoraphobia, or is agoraphobic but experiences no panic attacks). Also, because combinations of so many possible outcome criteria may lead to many different patterns, large samples are needed to properly describe at least the most frequent patterns.

Prospective Studies in Clinical Populations

Twenty-five years ago, Marks and Lader\textsuperscript{13} reviewed six follow-up studies of anxiety neurosis, observing that between 41 and 59\% of patients were considered uncovered after an average of 19 years. The results of these early studies cannot be generalized, both because of the less stringent research methodology at that time and because the diagnosis of anxiety neurosis was a mixture of today's general anxiety disorder and panic disorder. Marks and Lader, however, certainly brought
up the idea of chronicity.

In a recent review of 16 prospective studies, which fulfilled minimum methodologic standards, Roy-Byrne and Cowley concluded that "despite the availability of effective antipanic treatments, panic disorder remains a chronic condition." We contend that this is an oversimplification. According to the Roy-Byrne and Cowley review, between 17 and 70% of patients (mean, 46%) still had panic attacks at follow-up, and between 36 and 82% had phobic avoidance (mean, 69%). Disabilities were still present in every second patient. However, these results also mean that between 30 and 83% of patients ceased to experience panic attacks, and between 18 and 64% were not agoraphobic at follow-up." Clearly, there is a subgroup of panic disorder patients whose condition is "chronic," but there is also a large subgroup whose condition is not. Also, given that multiple outcome criteria have to be used, there is clearly a need for a differentiated view, and the terms "chronic" and "not chronic" need specification. Therefore, instead of aiming at gross generalizations, we contend that our task is to identify and describe subgroups of panic disorder patients to determine the characteristics of patients who might be expected to undergo a more or less unfavorable course. Questions to be answered in this regard are the following: Are there two or even more types of panic disorder? Does choice of treatment during follow-up make a difference, or does it not? Furthermore, what is the effect of adverse experiences during the follow-up period on course and outcome? Sample sizes in the studies reviewed by Roy-Byrne and Cowley are rather small (5 studies with enrollment of up to 40 patients, 14-18 8 studies with between 41 and 77 patients, 19-26 1 study with 89 patients, 27 and 1 study with 107 patients”). Only one of these studies was large enough for detailed analysis (N =
394)29 and in that study, 55% of patients who had panic disorder with agoraphobia and 68% of patients who had uncomplicated panic disorder were panic-free after 1 year. If one considers the variable proportions of patients lost to follow-up in the most recent study more than 50% of the original group could not be followed up30—there is little room left for describing subtypes of course and outcome. Despite these methodologic drawbacks, which Roy-Byrne and Cowley painstakingly analyze and identify in most of their 16 reviewed studies, they nevertheless come to the abovementioned conclusion that "panic disorder remains a chronic condition." The largest and longest follow-up study of panic disorder, which because of the large number of patients allowed for the definition of possible subtypes of course and outcome, was carried out by Katschnig and associates 10 In this study, 423 patients (a 1-in-4 sample of all patients who had taken part in a clinical drug trial) were followed up over nearly 4 years on average. This study also assessed fluctuations over time; only 2 of the 16 studies reviewed by Roy-Byrne and Cowley actually addressed this question. 26 • 27 Figure 2 shows the subtypes of course we identified (as defined by DSM-III-R criteria at a given point in time). In 45% of all patients, panic disorder had not remitted in the clinical drug trial and had persisted throughout follow-up, although in many patients there was a fluctuation in severity. Two fifths (18.6% of the total sample) of this group had a severe chronic course. On the other hand, 31% of the total group remitted and stayed well. Approximately one quarter had an episodic course with free intervals. These find- 84

Predicting Long-Term Course N = 220, Follow-up@4 Years

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<th>Remitted</th>
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<td>31%</td>
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FIG. 2. Patterns of course of panic disorder in Cross-National Collaborative Study. (Source: Katschnig H, Amering M, Stolk JM, Klerman GL, Ballenger JC, Briggs A, Buller R, Cassano G, Garvey M, Roth M, Solyom C. Long-term follow-up after a drug trial for panic...
disorder.

ings were reflected in the analyses of status at follow
up, with roughly one in five patients performing badly
on most outcome criteria, especially on disability mea
sures.

Our study confirms the finding from other studies
that the course of panic disorder over the long term can
best be described as following different patterns in dif
ferent subgroups of patients. But which patients do
well, and which do not? The answer to this question, ap
plied to early-stage patients, would be of considerable
practical importance. Predicting the Course and Outcome
of Panic Disorder

Both unforeseeable external influences, such as neg
ative and positive life events and other stressors, and
unpredictable changes in personal coping behavior (be
cause of new experiences) do not allow for the exclu
sive use of baseline variables as predictors of course
and outcome in disorders such as panic disorder or
schizophrenia.

The "vulnerability stress model"31 and the "interac
tive developmental model"2 are more in accordance
with these observations than the "natural history"
model. For instance, Teich and associates" and Mavis
sakalian' 4 have convincingly shown that self-exposure
to phobic stimuli is therapeutic for patients with panic disorder with agoraphobia, and it is unclear to what extent patients inadvertently or purposely practiced such exposure during follow-up. Another variable that we cannot control in naturalistic follow-up studies is the use of therapeutic resources by the patients, let alone the quality of their treatments. When trying to identify the predictors for course and outcome of panic disorder, one has to keep these caveats in mind.

Unfortunately, there is a paucity of follow-up studies that monitor course and study external influence during the long-term development of the disorder, as well as treatments. O'Rourke and associates analyzed 25 outcome studies. Twelve of these studies were conducted before the publication of the DSM-III and are therefore not strictly comparable with DSM-III studies. O'Rourke and associates found that the most consistent predictors of unfavorable course and outcome were severity of illness at baseline, personality disorder, chronicity, comorbid states of depression, alcohol and substance abuse, and clinical status on discharge. They also conducted their own 5 to 6-year follow-up study of 79 patients who had received drug and behavioral counseling in a clinical trial; they found that 34% of all patients followed up went into remission and remained asymptomatic throughout follow-up. The authors could not confirm the prognostic value of severity at baseline, but showed that personality disorder was a factor. Long duration at baseline was a significant but weak predictor of an unfavorable outcome. In the prospective Harvard Brown Anxiety Disorders Research Program study of 412 subjects who were in episodes of DSM-III-R panic, Warshaw and associates found that panic severity at intake was not predictive of time to remission, but that severity of agoraphobia was. Follow-up duration was between 6 months and 5 years. Depression was not found to be predictive of outcome if other variables were controlled for, a finding also reported by Maier and Buller. Most of these
findings are in accordance with our own results in 423 panic disorder patients followed up over an average of 46.5 (± 10.3) months. Panic attack frequency at baseline, which is often taken as an indicator of severity, was not predictive of any outcome measure at follow-up, neither of occurrence of panic attacks, nor phobic avoidance, nor disabilities in everyday life. Agoraphobia at baseline, however, predicted agoraphobia and disabilities at outcome. Longer duration of illness at baseline predicted a worse phobic avoidance outcome. Disabilities at baseline were predictive of disabilities at follow-up, but these were only domain-specific, e.g., work disabilities at baseline predicted work disabilities at follow-up, etc. In this study, intermittent treatments received during the follow-up period were also recorded. Because this was a naturalistic follow-up study, treatments were not randomly allocated. One unexpected finding, that contact with or treatment by a psychiatrist or a psychologist was related to an unfavorable outcome, may thus be a consequence of patient self-selection, i.e., only the most severely ill might have used services. Also, the fact that continuous psychotropic medication was not related to a better outcome might be explained by the naturalistic design of the follow-up.

Usually panic disorder patients still wait many years before receiving state-of-the-art, specialized clinical treatment. As a result, clinicians see an overwhelming proportion of patients with a long duration of their disorder and therefore tend to regard panic disorder as a chronic condition. In retrospect, these patients do in deed follow a course progressing from unexpected to situational panic attacks, phobic avoidance, and full blown agoraphobia, with disabilities in several life domains and comorbidity from depression and substance abuse. Today we know that these patients constitute a
biased sample of all persons suffering from panic disorder. This observation is supported by the finding that although four of five panic disorder patients in clinical samples have agoraphobia, this percentage is only one third in panic disorder samples of the general population.

Research in recent years has shown that panic disorder tends to follow the pattern shown for the long-term course of schizophrenia. Although Kraepelin, who derived his knowledge from observing asylum patients, assumed that a chronic and progressive course was characteristic of the disorder (his "dementia praecox" concept), later research identified several types of long term course, including a large proportion of patients with full remission.

The fact that panic disorder was only defined in 1980 prevents us from conducting studies on its lifelong course. The available evidence for shorter follow-up periods (up to 6 years) suggests that full remission might occur in approximately one third of patients who have undergone clinical treatment, i.e., in patients with rather long duration and higher severity. From comparing lifetime and 6-month prevalence data in epidemiologic studies, it can be concluded that the remission rate in general population samples is greater than one
third. At the other end of the spectrum, in those panic
disorder patients who have received specialized psy-
chiatric care, it seems that approximately one in five fol-
lows an unremitting and severe chronic course.
The identification of those panic patients who might
follow such a severe chronic and unremitting course is
an important challenge, especially now, when health
care resources are becoming more and more re-
stricted. Unfortunately, empirical data about the pre-
diction of the course and outcome of panic disorder
are only available for clinical samples and are still
missing for primary care patients and panic sufferers
identified in general population surveys. Taken to
gether, the results of long-term studies suggest that the
frequency and intensity of panic attacks at baseline
have no predictive importance. Instead, a longer duration
of the disorder and the presence of agoraphobia at
baseline seem to be connected with a less favorable
course and outcome. Results regarding the predictive
value of comorbid depression and personality disorder are
ambiguous. As Roy-Byrne and Cowley' have shown, many
methodologic issues are unresolved or treated differently
in different studies, and many questions regarding the
long-term course and outcome of panic disorder have not
yet been properly addressed. These issues include the
following: • The selection of patients to be followed up
Those who have participated in a clinical drug trial?
Unselected consecutive clients of a specialized anxiety
clinic? Patients of general practitioners? General
population samples? • The choice of outcome domains
Panic attacks? (Unexpected, situational?) Agoraphobia?
Disabilities? Anticipatory anxiety? Quality of life? •
The outcome measure Mean values? Proportions of patients
having reached a certain level of outcome, e.g., zero
panic attacks? • The design Prospective follow-up
studies with regular, frequent assessments to actually describe the course? Outcome measures recorded only at follow-up? • The influence of different treatments during follow-up Pharmacologic? Cognitive? Self-selection of those receiving treatment during follow-up in naturalistic studies? • The influence of life changes on course and outcome As long as there is no uniformity in these and other issues of design and method, conclusions about the long term course and outcome of panic disorders must remain tentative. One thing, however, is already clear: panic disorder is not a uniformly chronic and progressive disorder. Rather, it follows a course pattern known to us from many psychiatric and somatic disorders (for instance, hepatitis); a substantial proportion of patients achieve complete remission, whereas another group has a clearly unfavorable course. What happens to the group in-between probably depends largely on therapeutic efforts. Therefore, we require not only more naturalistic long-term follow-up studies with a uniform methodology, but also more long-term clinical trials, contrasting and combining pharmacologic and behavioral/cognitive treatments.


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COMORBIDITY OF ANXIETY AND UNIPOLAR MOOD DISORDERS

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KEY WORDS: depression, anxiety, comorbidity

ABSTRACT Research on relationships between anxiety and depression has proceeded at a rapid pace since the 1980s. The similarities and differences between these two conditions, as well as many of the important features of the comorbidity of these disorders, are well understood. The genotypic structure of anxiety and depression is also fairly well documented. Generalized anxiety and major depression share a common genetic diathesis, but the anxiety disorders themselves are genetically heterogeneous. Sophisticated phenotypic models have also emerged, with data converging on an integrative hierarchical model of mood and anxiety disorders in which each individual syndrome contains both a common and a unique component. Finally, considerable progress has been made in understanding cognitive aspects of these disorders. This work has focused on both the cognitive content of anxiety and depression and on the effects that anxiety and depression have on information processing for mood-congruent material.

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Fear and Fitness: An Evolutionary Analysis of Anxiety Disorders
Isaac M. Marks Institute of Psychiatry, London Randolph M. Nesse University of Michigan Medical School, Department of Psychiatry, Ann Arbor This article reviews the evolutionary origins and functions of the capacity for anxiety, and relevant clinical and research issues. Normal anxiety is an emotion that helps organisms defend against a wide variety of threats. There is a general capacity for normal defensive arousal, and subtypes of normal anxiety protect against particular kinds of threats. These normal subtypes correspond somewhat to mild forms of various anxiety disorders. Anxiety disorders arise from dysregulation of normal defensive responses, raising the possibility of a hypophobic disorder (too little anxiety). If a drug were discovered that abolished all defensive anxiety, it could do harm as well as good. Factors that have shaped anxiety-regulation mechanisms can explain prepotent and prepared tendencies to associate anxiety more quickly with certain cues than with others. These tendencies lead to excess fear of largely archaic dangers, like snakes, and too little fear of new threats, like cars. An understanding of the evolutionary origins, functions, and mechanisms of anxiety suggests new questions about anxiety disorders. KEY WORDS: Fear, phobias, anxiety disorders, obsessive-compulsive disorder, agoraphobia, social phobia, prepotency, preparedness

INTRODUCTION Nearly everyone recognizes that anxiety is a useful trait that has been shaped by natural selection. Even good things, however, cease to be good when they become excessive. Too much anxiety can be disabling. If a drug were found that abolished all anxiety for all time
always aversive and can even be pleasurable. Millions flock to be thrilled by horror movies, the big wheel, tightrope walkers, and the like. Perhaps this a form of play behavior, like so many other enjoyable games that help us deal time in play that teaches them the game of life (Smith 1982). Hypotheses to The four defensive strategies noted earlier—escape, aggression, freezing, and submission—are deployed to varying degrees in different subtypes of anxiety, in accordance with their utility. Examples include the greater promi-

flight in blood/injury phobias. Predictions yet to be tested include these hypotheses: (a) Submission more marked in social than animal phobias, (b) more pronounced in fear of animals than in fear of heights. Close matching of testing of many such predictions. This major research program is likely to CONCLUSION of the mediating mechanisms we if we knew every connection of every neuron, of every transmitter, our understanding would remain inadequate of anxiety without major side effects or


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Brain Systems Mediating Aversive Conditioning: an Event-Related fMRI Study

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Summary We have used event-related functional magnetic resonance imaging (fMRI) to characterize neural responses associated with emotional learning. Employing a classical conditioning paradigm in which faces were conditioned by pairing with an aversive tone (US), we compared responses evoked by conditioned (CS+) and nonconditioned (CS-) stimuli. Pairing 50% of the CS+ with the US enabled us to constrain our analysis to responses evoked by a CS+ not followed by a US. Differential evoked responses, related to conditioning, were found in the anterior cingulate and the anterior insula, regions with known involvement in emotional processing. Differential responses of the amygdalae were best characterized by a time by stimulus interaction indicating a rapid adaptation of CS+ -specific responses in this region.

Introduction

In classical conditioning paradigms, a previously neutral stimulus (conditioned stimulus or CS) comes to elicit a behavioral response through temporal pairing with an unconditioned stimulus (US). In many paradigms, the US is aversive and the behavioral response is measured in terms of changes in skin conductance (skin conductance response SCR) or galvanic skin response GSR, pupil diameter, or some other measure such as freezing behavior (LeDoux, 1996). Hence, classical conditioning is a form of associative learning involving linkage between a neutral stimulus and a stimulus with high intrinsic behavioral
Classical conditioning embodies elements of memory and emotional processing, a fact reflected by the associated functional anatomy. Lesion studies suggest a critical role for medial temporal lobe structures, especially the amygdala, in the acquisition of conditioned emotional responses (laBar and LeDoux, 1996). For example, lesions restricted to bilateral amygdalae impair the acquisition of conditioned autonomic responses but leave declarative knowledge of stimulus contingencies intact. The opposite dissociation has been reported in association with bilateral hippocampal damage (Bechara et al., 1995).

In classical conditioning, the close temporal proximity of US and CS pairings is essential. To achieve selective conditioning of some stimuli but not others, the intertrial interval (ITI) between neutral and conditioned stimuli has to be long compared to the time between CS and US. Several functional neuroimaging studies have investigated human classical conditioning (Fredrikson et al., 1995; Schreurs et al., 1997). Positron emission tomography (PET) functional neuroimaging (Morris et al., 1997) has implicated an extended system including the pulvinar, medial thalamic nuclei, and amygdala in aversive classical conditioning of emotionally expressive faces. Notably, functional imaging studies, using PET and functional magnetic resonance imaging (fMRI), employ blocked designs, in which subjects undergo an initial conditioning block by presenting the CS with the US and the effect is then assessed in a (test) second block by presenting the CS alone (Morris et al., 1997). Unfortunately, this procedure is confounded by the fact that during the test block, when the CS is always presented alone, there may also be an extinction component where the associated functional neuroanatomy may differ from that of conditioning per se (Rolls et al., 1994). The optimal prerequisites for studying the neurobiology of classical conditioning in humans, using functional neuroimaging, are met by event-related (mixed/single trial) fMRI technique (Buckner et al., 1996; Dale and Buckner, 1997; Josephs et al., 1997). This novel technique resembles that used to record event-related potentials in electrophysiology, where different stimuli are presented repeatedly over time. Recent methodological advances (Josephs et al., 1997) have enabled us to study evoked hemodynamic responses for the whole brain to conditioned and neutral stimuli in a manner compatible with mixed trial classical conditioning paradigms. In this study, we used a partial reinforcement strategy in which one half of the CS + presentations were paired with the US (CS + ......) and the other half were not paired (CS+,
...... ), to compare evoked hemodynamic responses elicited by the CS+ in the absence of the US. Results We chose four neutral faces, two male and two female, taken from the Ekman series (Ekman, 1982). Faces were presented for 3 s. Subjects were scanned during two distinct phases: in an initial familiarization phase, all four faces were presented in randomized order (52 faces were presented over 10 min), and in a second conditioning phase, two (one male, one female) of the four faces were paired with an unpleasant tone (1 kHz) and consequently became CS+. The amplitude of the tone was adjusted to 10% above each subject's aversive threshold (~100 dB; estimated by self report during gradient switching). The 500 ms tone followed at the end of the 3 s presentation time of the face (Figure 1). Faces presented during the first and second phases of the experiment were identical.
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Abstract After a few pairings of a threatening stimulus with a formerly neutral cue, animals and humans will experience a state of conditioned fear.
when only the cue is present. Conditioned fear provides a critical survival-related function in the face of threat by activating a range of protective behaviors. The present review summarizes and compares the results of different laboratories investigating the neuroanatomical and neurochemical basis of conditioned fear, focusing primarily on the behavioral models of freezing and fear-potentiated startle in rats. On the basis of these studies, we describe the pathways mediating and modulating fear. We identify several key unanswered questions and discuss possible implications for the understanding of human anxiety disorders. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Conditioned fear; Fear-potentiated startle; Conditioned stimulus; Unconditioned stimulus; Periaqueductal gray; Amygdala; Freezing

J. Introduction Acute fear can be one of the most potent emotional experiences of our lifetime. The strength of this subjective experience may be because fear serves a function that is critical to the survival of higher vertebrates. It can be thought of as activation of a defensive behavioral system [I] that protects animals or humans against potentially dangerous environmental threats. For a small vertebrate such as a rat, an example of such an environmental threat would be predation. These threats may be innately recognized or learned (2,3). For example, in the presence of a cat or a stimulus that predicts potential injury, a rat will become
completely motionless and freeze, no movements except those associated with respiration are observable [4-6].

Furthermore, the rat shows a fear-potentiated startle response [7-9], analgesia [10], a host of autonomic changes [11,12] and increased release of several hormones [13]. In humans, these responses are correlated with a subjective state of fear [14-17]. The brain and body are dedicated to fast and effective defense to increase the chances of survival. Therefore, we use the term "fear" to refer to the activation of the defensive behavioral system that gives rise to this constellation of reactions to threatening stimuli. There are three major reasons why scientists investigate the neuronal basis of fear. First, they use fear-modulated behaviors as models to understand how emotions influence behavior. Second, the investigation of the neuroanatomical and neurochemical basis of fear and anxiety is a prerequisite to develop strategies to treat and cure anxiety disorders. Anxiety disorders, such as specific phobias (agoraphobia, social phobia, etc.), panic disorder, post-traumatic stress disorder and generalized anxiety disorder are among the most common psychopathologies in the industrial states. Third, fearful experiences are rapidly learned about and long remembered. Hence, fear-conditioning has become an excellent model for trying to unravel the processes and mechanisms underlying learning and memory. The development of several reliable behavioral tasks for investigating fear has led to major developments in our understanding of the neuronal basis of fear and anxiety in just the last decade. These behavioral tasks fall into two general
classes: learned and unlearned. Tests of unlearned fear rely on stimuli that naturally provoke fear even when the animal has had no prior experience with the stimulus. The most frequently used stimuli in these tasks are natural predators (e.g., [18]) and exposure to a novel place (especially one that is brightly lighted [19] or elevated [20]). Approaches using learned fear examine conditioned behaviors provoked by stimuli that have become associated with something aversive, usually an electric footshock. These Pavlovian fear stimuli provoke many of the same behaviors that innate fear stimuli do. For example, rats freeze to both cats and conditioned stimuli associated with shock.

To measure the conditioned fear, a number of specific responses can be easily quantified such as fear-potentiated startle [7,8], freezing [3,21], tachycardia [22], conditioned defensive burying [23] and ultrasonic vocalization [24-26]. Alternatively, conditioned fear can be measured as a disruption of ongoing behaviors (e.g., conditioned suppression [27,28] and conflict tests [29,30]).

Validity for this approach to fear is obtained when a variety of stimuli that present clear threats to the subject generate a consistent set of behaviors that are tailored to protect against the threat. Additionally, these perceptual-motor organizations should have a common neuronal basis that overlaps considerably with the neural systems that
mediate human fear and anxiety. Furthermore, the potency of drugs that modulate human fear and anxiety should correlate with their effectiveness in altering the behavior in these animal models.

The present review will primarily compare two specific responses to learned fear, freezing and fear-potentiated startle because these are most clearly identified with specific neural mechanisms that mediate between environmental stimulus and behavioral response. We go on to describe a hypothetical neuronal circuit which characterizes conditioned fear and helps organize existing knowledge about several conditioned defensive behaviors. Finally, we indicate what we feel to be some of the most critical open questions remaining for the analysis of fear.

2. The fear-conditioning procedure

Fear-conditioning is a form of Pavlovian conditioning where a subject is trained to associate a neutral stimulus (e.g. a 10s presentation of light) with an aversive, unconditioned stimulus (US), such as an electric footshock. After such pairings, the light alone predicts the occurrence of the shock and acts as a conditioned stimulus (CS), eliciting a state of fear. Tones, lights, odors and tactile stimuli have been used as CS in fear-conditioning experiments. These stimuli range from a few seconds to a few minutes in dura
tion and because of this brevity are called discrete CS. However, the subject also has fear responses conditioned to the setting in which the discrete CS and shock US was presented. Such stimuli, which are less temporally restricted and are made up of many separate features, are referred to as contextual stimuli. The fear of contextual and discrete CS can be acquired as rapidly as a single trial.

When examining the neural circuitry mediating fear learning, there are three different time-points at which experimental manipulations can be made. Manipulations during the training procedure affect the acquisition of conditioned fear, while manipulations during the testing procedure affect the expression of conditioned fear. If consolidation of a fear memory is to be targeted, the manipulation is made after acquisition, but before testing. If a brain structure were lesioned, the time-point when the lesion was carried out can help us to make a statement about the influence of this lesion on the acquisition or on the expression of conditioned fear. If this brain structure were only involved in the acquisition of conditioned fear, only pretraining, and not post-training lesions would affect the measure of fear. On the contrary, if this brain structure was only involved in the expression of conditioned fear, both the preand post-training lesions should affect conditioned fear. Manipulations that affect consolidation are usually temporally graded such that the greatest effect occurs when the manipulation is carried out immediately after training. Obviously, reversible treatments provide the most powerful tools for separating acquisition, consolidation and expression processes. 2.1.
Fear-potentiated startle A startle response is elicited by a sudden acoustic, visual or tactile stimuli and is found in every mammal studied so far [31]. A typical startle response is composed of a fast, sequential muscle contraction, with the most prominent reaction around the face, neck and shoulders [15,31]. Possible functions of the startle response are to reduce the latency of a flight reaction [32] and/or a protection from a predator’s attacks from behind by contraction of the dorsal muscles [33]. The electromyographically measured latency of the startle response in rats is only 510 ms [34,35], indicating a relatively short neuronal startle pathway with only a few central synapses. The elementary startle pathway was initially described by Davis and co-workers [36], and further detailed by Lingenhübel and Friauf [37,38] and Lee and co-workers [39]. It includes the cochlear root neurons, the giant neurons of the caudal pontine nucleus of the reticular formation (PnC) and spinal motorneurons. Yeomans and Frankland [33] suggested a further parallel pathway additionally including the ventrolateral pons and spinal interneurons. In the last decade, the startle response became a valuable model for investigating behavioral modulations such as habituation [40,41], sensitization [42,43], prepulse inhibition [44,45] and Pavlovian conditioning [7,8]. Furthermore, appetitive emotions weaken the startle response [17,46,47], while aversive emotions such as fear or anxiety enhance the startle response [7,8,13,17,41]. The fear-potentiated startle paradigm was initially described by Brown, Kalish and Farber [7]. Rats are given several pairings of a light CS and footshock. After this procedure, the mean amplitude of the acoustic startle response to a loud noise is usually 50-100% higher in the presence of the light CS than to the noise alone [8,48]. The difference between these two trial types (light-noise and noise alone) represents the fear-potentiation of the startle response and acts as a measure of fear. Fear-potentiated startle is very sensitive to drugs that are known to modulate the state of fear: norepinephrine antagonists [49], benzodiazepine agonists [50], dopamine antagonists [8], opioid agonists [51], 5-HT 1A agonists [52], 5-HT3 antagonists 224 M. Fendt. M.S. Fans/o/owl Neuroscience and Biobehavioral Reviews 23 (1999) 743-760 745 corticotropin-releasing factor antagonists [54], cholecystokinin antagonists [55], neuropeptide Y agonists [56], NMDA-associated glycine receptor antagonists [57],
NMDA antagonists [57] and ethanol [58,59] block or reduce the fear-potentiation of the startle response after systemic injections (reviewed in Refs. [8,60]). Most of these drugs were also tested in humans and had an anxiolytic effect [61-65].

Sensitization of the acoustic startle response is another approach used to investigate the effects of aversive stimuli on reflexes. Sensitization of the startle response is the immediate enhancement of startle amplitude after shock [42]. Initially this excitatory effect of footshock on startle was thought to be an unconditioned response to footshock [42]. Recent work indicates that sensitization reflects a rapid conditioning to the test environment [66,67]. Therefore, it is suggested that the mechanisms underlying the sensitization of the startle are largely identical to those that mediate fear potentiated startle [68].

2.2. Freezing

Over a century ago, Darwin recognized that fear produces a profound suppression of activity in several species (see [69, p. 260]). Small [21] reported freezing as a characteristic fear response of rats and Griffith [5] reported that rats would
show pronounced freezing in the presence of a cat. While freezing was reported to occur in aversive conditioning experiments using shock, it was initially considered a nuisance variable (e.g. [70]). Earlier studies of Pavlovian conditioned fear used measures such as bar press suppression that relied on what the rat was not doing (i.e. it had stopped eating [71,72]). Investigation of direct observational measures of freezing (e.g. [4,73]) and crouching [74] to shock associated cues began in earnest in the early 1970s, but these typically looked at reactions to contextual cues. Direct measures of freezing to discrete CS such as tones and lights began in Robert Bolles’ laboratory in the late 1970s (e.g. [75,76]). Bouton and Bolles [77] showed that direct visual observation of freezing to tones paired with shock provided a measure that correlated highly with, but tended to be more sensitive than, other measures such as conditioned suppression. There tends to be no baseline freezing in control rats that have not received shock. There is reliable freezing with even a single brief (0.75 s) mild (0.5 mA) shock conditioning trial, and more robust training parameters can easily result in freezing levels near 100% (e.g. [78]). For rats, freezing is a highly selected response because movement makes the rat more detectable
to predators and because predators are much more likely to attack moving than still prey. In other words, movement acts as a releasing stimulus for predatory attacks. This is probably why freezing is observed even in situations that afford the opportunity for other behaviors such as escape (see [79] for a review).

2.3. Other behavioral indices

There are certainly other behavioral manifestations of fear in aversive Pavlovian conditioning situations. Obviously, there are profound changes in autonomic function. Defecation covaries with other measures of fear [80] and blood pressure shows a reliable increase (e.g. [81-84]). While fear CS influence heart rate as well, these changes are much less consistent than the hypertensive effects of fear stimuli [84]. Both tachycardia (e.g. [22]) and bradycardia (e.g. [85,86]) have been reported. What determines the direction of the heart rate change is not clear at this time, but whether or not the rat is restrained [86,87], the type of conditioning control one uses [88] and the baseline heart rate (e.g. [85]) appear to contribute and possibly interact. There are, of course, other responses that characterize the fear response. For example, rats show ultrasonic vocalizations (e.g. [24-26]) and a loss in pain sensitivity [89,90]. Such responses add to the validity that the fear state is related to a species typical survival function (e.g. [10,91,92]).

3. The role of the amygdala

It is now well established that the amygdala plays a pivotal role in fear. The initial hints of this were provided by Brown and Schaffer [93] who reported that large lesions of the temporal lobe tamed previously ferocious monkeys. Kluver and Bucy [94] characterized the rather widespread emotional disturbance caused by such brain damage and this psychopathology became known as the Kluver-Bucy syndrome. Weiskrantz [95] reported that many aspects of the Kluver-Bucy syndrome could be produced by damage restricted to the amygdala. Fuster and Uyeda [96] were the first to show that there were cells within the amygdala that selectively respond to a CS paired with shock. Subsequently, it has been confirmed that cells in both the central [97] and lateral nuclei [98] of the amygdala show short latency CS specific activity. The fact that these neurons in the amygdala will show increased responsiveness to stimuli after they were paired with shock indicates
that the structure is sensitive to the convergence of the CS and US information. The dorsal subdivision of the lateral amygdala may be important for the processing of this convergence as it has cells that respond to both tones and footshock [99]. Stimulation of afferent pathways to the amygdala can lead to an enhanced responsiveness of cells in the amygdala; in other words, the amygdala shows long-term potentiation (LTP [100-103]). Using lateral amygdala slices, Huang and Kandel [102] showed that LTP depends on post-synaptic depolarization and calcium influx into the post-synaptic cell. As this LTP includes paired-pulse facilitation, Maren and Fanselow suggested that the potentiation was expressed through a pre-synaptic mechanism [103]. Huang and Kandel [102] have subsequently confirmed this observation.

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Glutamate receptors, particularly NMDA receptors, play a critical role in these responses [102-104]. Indeed, fear conditioning itself can potentiate amygdala responses [105,106]. Together these electrophysiological data indicate that the amygdala has the potential to be a point where the CS and US converge to produce fear-conditioning. Therefore, in the next sections we examine the amygdala’s contribution to two specific behavioral indices of conditioned fear, freezing and fear-potentiated startle.

3.1. The amygdala and fear-potentiated startle

The first studies investigating the neuroanatomical basis of fear-potentiated startle were carried out in the mid 1980s.

A series of studies by Davis and colleagues showed that the pathway from the amygdala to the PnC is essential for the potentiation of the startle response by conditioned fear.
First, they showed that fear-conditioning potentiates the startle response at the level of the PnC [107,108]. Second, lesions of the amygdala blocked fear-potentiated startle using a visual CS [109] or an auditory CS [110], while lesions of other nuclei (e.g. the cerebellum or the red nucleus, which are both known to be involved in Pavlovian conditioning of reflexive responses [111,112]) had no effect.

Third, destruction of the direct pathway from the central nucleus of the amygdala to the PnC—the ventral amygdalofugal pathway [113]—blocked fear-potentiation of the startle response [114]. Thus, the amygdala is necessary to observe fear-potentiation of startle.

Activity in the amygdala is sufficient for potentiation of startle as electrical stimulation there increases the amplitude of the startle response [115-117]. Koch and colleagues showed a strong short-latency potentiation of the startle amplitude after injections of glutamate into the central nucleus of the amygdala [118], confirming that it was the activity of neurons intrinsic to the amygdala that potentiated the response. A longer latency increase of startle amplitude could be produced when selective metabotropic glutamate receptor agonists were applied to the amygdala [119].

3.1.1. Acquisition of/ear-potentiated startle
To test the hypothesis that NMDA receptor-dependent LTP in the amygdala mediates fear-conditioning, Davis and colleagues micro injected NMDA receptor antagonists (AP-5 and AP-7) and pertussis toxin into the basolateral nucleus of the amygdala. These LTP-impairing treatments blocked acquisition, consistent with the suggestion that NMDA receptors in the basolateral nucleus of the amygdala are involved in the plasticity underlying fear-conditioning [120-122]. Interestingly, the elimination of fear-potentiated startle during extinction is an NMDA-dependent process, as well. Injections of AP-5, but not of the non-NMDA receptor antagonist CNQX into the basolateral amygdala blocked extinction of fear-potentiated startle [123].

Gewirtz and Davis [124] extended these results to second-order conditioning. This occurs when a previously conditioned CS (first-order CS) is paired with another CS (second-order CS). The first-order CS functions like a US, giving the second-order CS the ability to produce a conditioned response. Injections of AP-5 into the basolateral nucleus of the amygdala during the acquisition of second-order fear-conditioning blocks the acquisition of fear-potentiation to the second-order CS. Interestingly, the expression of fear-potentiation by the first-order CS was slightly increased during testing. One explanation of this finding is that AP-5 blocked the extinction of the first-order CS that normally occurs during second-order training. A lesion study by Tischler and Davis [125] led to the initial hypothesis that the amygdala receives information about a visual CS via a pathway from the retina to the dorsal lateral geniculate nucleus to the visual cortex to the deep layers of the superior colliculus and down to the elementary startle pathway. Further extensive lesion studies by the Davis group [126-129] suggested that the basolateral and/or the lateral nucleus of the amygdala receives CS information from the perirhinal cortex. Auditory CS are mediated from
the cochlea via different subnuclei of the auditory thalamus to the perirhinal cortex, while visual CS are mediated from the retina via the lateral geniculate body to the perirhinal cortex. There are several routes by which information about shock can reach the amygdala, but it seems unlikely that any single one of these pathways is necessary and sufficient as a US pathway for conditioning. Fendt and colleagues [130] suggested that US information for fear-potentiated startle is carried from the spinal cord, through the nucleus paragigantocellularis and the locus coeruleus to the amygdala. This was based on the finding that the locus coeruleus is activated by footshock via the nucleus paragigantocellularis [131-133], which in turn projects to the amygdala. The locus coeruleus-amygda pathway uses noradrenaline as a transmitter [134] and a reduction of noradrenaline release in the amygdala blocks the enhanced startle seen immediately after footshock [130]. However, the hypothesis that noradrenaline release in the amygdala mediates the reinforcing aspects of the US was contradicted by the finding that a blockade of amygadaloid \(\alpha_{3}\)-adrenergic receptors has no effect on the acquisition of fear-potentiated startle [122]. The central nucleus of the amygdala also receives nociceptive information via a projection from the nucleus parabrachialis [135, 136]. The transmitters of this projection are mainly neuropeptides but also noradrenaline [137]. While this pathway may make a contribution to conditioning the fact that, at least in rat, there do not appear to be projections from the central nucleus to the lateral nucleus suggests that this pathway cannot support the CS-US convergence found in the lateral nucleus [138]. Based on anatomical tracing and electrolytic lesions experiments, Shi and Davis [139,140] recently suggested that two parallel pathways can provide the amygdala with nociceptive input. Footshocks information is conveyed from the spinal cord to the basolateral nucleus of the amygdala 226 M. Fendt. M.S. Fanselow I Neuroscience and Biobehavioral Reviews 23 (1/999) 743-760 747 aversive unconditioned stimulus acoustic stimulus visual auditory conditioned conditioned stimulus stimulus startle response

Fig. I. Hypothetical circuit mediating fear-potentiated startle. Abbreviations: CRF, corticotropin-releasing factor; Glu, glutamate; NA, noradrenaline; NP, neuropeptides; Som, somatostatin.

via a direct pathway that synapses in the posterior intrala
minar nucleus. An additional indirect pathway includes synapses in the ventral posteriolateral thalamic nucleus, the posterior thalamic nucleus, the posterior intralaminar nucleus, the areas SI and S2 and the caudal insular cortex.

Acquisition of fear-potentiated startle was only blocked when both the direct and indirect pathways were lesioned, thus either one is sufficient to support conditioning. As combined lesions in these pathways affected acquisition but not expression of fear-potentiated startle they may indeed function as parallel US pathways. However, the pattern of data also leaves open the possibility that these pathways modulate memory storage within the amygdala.

3.1.2. Expression of fear-potentiated startle
Injections of the non-NMDA receptor antagonist CNQX [141] or NBQX [142] but not of the NMDA receptor antagonist AP-5 [120] into the central or the basolateral nucleus of the amygdala blocked the expression of fear potentiated startle. This suggests that fear-potentiation is mediated by a projection from the lateral and/or basolateral nucleus of the amygdala to the central nucleus of the amygdala activating non-NMDA receptors. As intra-amygdaloid injections of the CCK receptor agonist pentagastrin [143,144] increased the baseline startle amplitude and systemic injections of CCK. antagonists blocked the fear-potentiated startle [55], amygdaloid CCK. receptors seem to be involved in the expression of fear-potentiated

startle, as well. The central nucleus of the amygdala is the origin of a direct pathway to the elementary startle pathway [113,118,145], mediating the expression off ear-potentiated startle [114]. Koch and Ebert [146] showed that the effect of amygdaloid stimulation on the activity of PnC neurons can be blocked by microiontophoretic applications of the NMDA receptor antagonist AP-5 into the PnC. These results and the fact that AP-5 microinjections into the PnC block fear-potentiated startle [147] suggested that the direct pathway from the central nucleus of the amygdala to the PnC mediates fear-potentiated startle, uses glutamate as a transmitter and acts via NMDA receptors. This hypothesis is supported by previous studies, showing that NMDA receptors in the PnC are involved in the up-modulation of the startle response, while the non-NMDA receptors are involved in the direct mediation of the startle response [148-150]. Anatomical experiments showed that the direct pathway from the central nucleus of the amygdala to the PnC uses the neuropeptide corticotropin-releasing factor (CRF) as a transmitter [145]. Microinjections of CRF receptor antagonists into the PnC block the expression of fear-potentiated startle [145], while injections of CRF into the PnC increased the baseline startle response [151]. Conditioned inhibition of fear-potentiation of startle occurs when a second stimulus (e.g. a tone) signals that the CS (e.g. a light) will not be followed by the usual foot shock during training [152]. Conditioned inhibition was not blocked by amygdaloid lesions suggesting that conditioned inhibitors acts through another brain structure [153].

3.1.3. Summary The amygdala is a critical structure for
the acquisition of fear-potentiated startle. Information about the CS and the US converge in the lateral, and perhaps basolateral amygdala (Fig. I). A direct pathway from the central nucleus of the amygdala to the PnC uses CRF and glutamate as a transmitter and modulates the primary startle circuit to produce fear-potentiation.

3.2. The amygdala and freezing
The involvement of the amygdala in freezing to shock associated cues was first demonstrated by Blanchard and Blanchard [2], who found that large lesions of the amygdala abolished freezing to a context associated with shock.

LeDoux and colleagues extended this earlier findings by showing that selective destruction of cells within the lateral amygdala block freezing to auditory CS [154]. This critical role of the amygdala has been confirmed for virtually all CRs to fear stimuli as blood pressure [154], heart rate [155], analgesia [156,157] and ultrasonic vocalizations [158] are blocked by amygdala lesions. Fig. 2 indicates a circuit responsible for the mediation of two of these fear CRs, freezing and opioid analgesia.

3.2.1. Acquisition of freezing
The basolateral complex of the amygdala, particularly the lateral and basolateral nuclei, appears to be critical for acquisition of freezing. Blockade of NMDA receptor
activity [159-161] or enhanced GABAergic inhibition [162-164] within the amygdala during acquisition blocks the expression of freezing in the undrugged state. Consistent with the electrophysiological and fear-potentiated startle data reviewed before, the lateral and/or basolateral nuclei seem to be the important site of CS-US convergence and neural plasticity as AP-5 prevented acquisition when given to the basolateral complex but not when injected into the central nucleus [159]. Extinction of fear-induced freezing to both the discrete and contextual CS is also prevented by administering AP-5 to the basolateral complex [160]. Although fear-potentiated startle studies have typically used a light as a discrete CS, freezing experiments have typically used tone. Information about the discrete CS, provoking freezing, appears to arrive at the amygdala via direct thalamo-amygdala and also thalamo-cortico-amygdala projections [154]; either pathway appears to be sufficient for mediating a conditioned freezing response to tone. The primary pathway mediating freezing to a discrete CS appears to be the direct thalamo-amygdala pathway. The cortico-amygdala pathway may serve more complex fear-related information-processing, and also provide a redundant pathway capable of supporting simple conditioning as well [165-167]. The properties of freezing make it ideal for analyzing fear of more static, or contextual cues [78,168]. The hippocampal formation appears to play a critical role in providing the amygdala with information about contextual CS [86,103,169]. As with fear-potentiated startle, the nature of the pathway carrying US information is not clear, even though footshock is known to evoke responses in the lateral amygdala [99]. Currently, the best candidate is the spinothalamic tract, which carries somatosensory information about the shock US to the posterior intralaminar nucleus (PIN) of the thalamus. The PIN is immediately ventromedial to the areas of the medial geniculate that carry auditory CS information [170,171]. Tone footshock pairings result in altered tuning curves of cells in the medial geniculate [172] and electrical stimulation of the PIN can serve as an US for conditioned bradycardia in rabbits to auditory stimuli [170]. It is not clear if this specific pathway or some analogue supports conditioning in other CS modalities. Additionally, because lesions that damaged the PIN did not prevent acquisition of...
freezing to a tone paired with footshock, other US pathways must be sufficient. As was shown with fear-potentiated startle, the insular cortex may be the redundant pathway [140], but that has yet to be tested for freezing. In a more general sense, GABA antagonism has been found to function as an US for Pavlovian fear-conditioning [173] and as mentioned before, GABAergic agonists block acquisition of conditioned fear. Transgenic mice with the \( \beta \), subunit of the GABA \( A \) receptor deleted show an impairment in the acquisition of conditioned freezing [174]. Therefore, it seems possible that a reduction in tonic GABAergic inhibition at the amygdala acts as the ultimate effect of the US to promote conditioning. There is a serious conceptual problem with any potential US pathway for fear-conditioning iff ear-conditioning is to be linked to a mechanism of cellular plasticity like LTP. The LTP analogy suggests that a CS cannot initially activate cells that can produce fear, but it acquires the ability to do so because it is paired with a US that can effectively depolarize these cells. This would suggest that the US should be capable of generating the constellation of ear responses that the LTP is presumed to support. However, while CS paired with shock readily produce freezing as a conditioned
response, the shock US itself has no ability to provoke freezing [80,168]. Future research will need to reconcile this discrepancy between behavior and cellular mechanism.

but the neural basis of how the US fosters learning currently stands as the most open question in the acquisition of Pavlovian fear.

3.2.2. Expression of freezing

As with fear-potentiated startle, the amygdala is important for expression of conditioned fear-induced freezing. If a rat is trained with an intact amygdala, excitotoxic lesions of the structure abolish expression of freezing to both tone and contextual CS even when a substantial consolidation period is given between training and testing [175]. Amygdala application of lidocaine, muscimol and diazepam all block expression of freezing [156,162,163]. AP-5 blocks expression of freezing to both discrete [160] contextual stimuli [161], and this contrasts with the lack of effect of AP-5 on the expression of fear-potentiated startle to a fear-inducing tone [120] or light [122]. However, these effects of AP-5 are consistent with the finding that AP-5 also blocks evoked potentials in the lateral and basolateral nuclei in response
to electrical stimulation of the pathways carrying information about contextual [103] and discrete CS to the amygdala [104].

As with fear-potentiated startle, the central nucleus acts as an output pathway to brain structures that generate freezing. However, for freezing these projections from the central nucleus terminate in the midbrain rather than the brainstem. 3.3. Other models The involvement of the amygdala in several other indices of Pavlovian fear appears to be consistent with the data from freezing and fear-potentiated startle. Kapp and colleagues [155] were the first to show that amygdala lesions blocked autonomic responses to Pavlovian fear stimuli—in this case it was conditioned bradycardia in rabbits. Iwata et al. extended this finding to arterial hypertension in the rat [154]. Conditioned fear-induced analgesia is also blocked by amygdala lesions [176]. In humans, damage to the amygdala precludes fear-conditioning as assessed by changes in skin conductance [177,178]. While the emotional component fear of conditioning was blocked in these patients, as long as the hippocampus was intact they remembered the events that happened during training. This indicates that the amygdala is specifically involved in learning the emotional aspects of the fear-conditioning experience. Other, non-emotional information is encoded in parallel by other brain systems. The data reviewed above indicate four important points: (I) a large number of very different indices of conditioned fear are abolished by amygdala lesions; (2) this structure receives convergence of CS and US information; (3) pharmacological manipulations targeted at neural plasticity in this structure also abolish learning; and (4) evoked activity in this structure shows changes following Pavlovian fear conditioning. When these are taken together, the inescapable conclusion is that the amygdala is a crucial structure for the learning of fear. The central nucleus may be the end of the common pathway mediating fear as "fear state" and it appears that different efferents from the central nucleus mediate different fear responses. Central nucleus projections to the PnC mediate the fear-potentiation of startle. However, efferents to the lateral hypothalamus [179] and medulla, e.g. [180],
mediate autonomic responses. Finally, projections to the periaqueductal gray (PAG) are critical for freezing and analgesia [81,179,181]. but may be important for the expression of fear-potentiated startle, as well [48,181-183]. Indeed. second to the amygdala, the PAG may be the most critical area in the brain for fear and defensive behaviors [184,185].

4. The role of the periaqueductal gray

4.1. The periaqueductal gray

and ear-potentiated startle Cassella and Davis [186] first showed that the PAG is involved in the modulation of startle responding. They reported that electrolytic lesions of the dorsal PAG enhanced baseline amplitude, habituation and sensitization of the startle response. Although these lesions increased the sensitization of the startle response, no influences on the potentiation of startle by conditioned fear could be observed [186]. Some of Cassella’s and Davis’ data were supported 229

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later by Barszcz et al. [187], showing that electrolytic lesions of the ventrolateral PAG enhance both short-term and long-term habituation. Chemical PAG lesions by Fendt and co-workers [184] totally blocked the sensitization of the startle response without affecting the baseline startle amplitude. Furthermore, anatomical data of this study showed a possible indirect pathway from the central nucleus of the amygdala via the lateral PAG to the PnC mediating the effects of aversive stimuli on the startle response. A follow-up study showed that PAG lesions prevent fear potentiated startle [48], suggesting that the PAG is involved in the mediation of fear-potentiated startle too. In both lesion studies, mainly the lateral and the dorsal part of the
PAG was lesioned. Walker and Davis [188] chemically lesioned the dorso lateral PAG more rostrally than the lesions of Fendt and colleagues, and found that these lesions did not block fear-potentiated startle if the rats were trained with moderate footshock (0.6 mA). If strong footshocks (1.6 mA) were used, fear-potentiated startle was reliable only in lesioned rats but not in control rats. Furthermore, chemical stimulation of the dorsolateral PAG reduced fear-potentiated startle without affecting baseline startle amplitudes. The authors suggested that the dorsolateral PAG is activated by particularly aversive events and this activation may interfere with the expression of fear-potentiated startle. These data suggest that different regions of the PAG differentially influence fear-potentiated startle. For example, weak chemical stimulation of the lateral PAG enhances fear-potentiated startle [182] and electrical stimulation of the same area increases the startle baseline amplitude [189], while chemical stimulation of the ventrolateral PAG attenuates the expression of fear-potentiated startle [182].

4.1.1. Expression of fear-potentiated startle Fendt and colleagues [48] lesioned the PAG before and after the fear-conditioning training procedure. Both the pre
and post-training lesions prevented fear-potentiated startle, indicating that the PAG is certainly involved in the expression of fear-potentiated startle. However, these experiments do not rule out a potential role of the PAG in the acquisition of fear-potentiated startle. Further experiments are necessary to resolve this question.

4.1.2. Inhibition of fear-potentiated startle

Anatomical and electrophysiological experiments revealed a somatostatinergic projection from the ventrolateral PAG to the PnC, which may act to reduce the excitatory effects of glutamate on tone-evoked activity of the PnC [190]. Weak chemical stimulation of the ventrolateral PAG led to a decrease of fear-potentiated startle [181,182] and injections of somatostatin into the PnC dose-dependently reduced fear-potentiation of the startle response [190]. These results suggested that this somatostatinergic projection from the ventrolateral PAG to the PnC is involved in the inhibition of fear-potentiated startle. Recent results suggest that inhibition of fear-potentiated startle by the ventrolateral PAG is not involved in conditioned inhibition of fear-potentiation of startle as chemical stimulation of the ventrolateral PAG decreased the fear-potentiated startle, but did not affect the conditioned inhibition of fear-potentiated startle [182]. In contrast, there are indications that the dorsal PAG is involved in the mediation of conditioned inhibition, as chemical stimulation of the dorsal PAG reduces conditioned inhibition of fear-potentiated startle [182].

4.1.3. Summary

A pathway from the central nucleus of the amygdala to the PnC via the lateral PAG is involved in the mediation of the effects of conditioned fear on the elementary startle circuit. Additionally, the ventrolateral PAG has a somatostatinergic projection to the elementary startle circuit, which is involved in the
inhibition of ear-potentiated startle. 4.2. The periaqueductal gray and freezing As stated earlier, the PAG is absolutely critical for freezing. Liebmann et al. [191] discovered the PAG’s involvement in this response when they found that rats with large lesions of the PAG did not freeze following an extended series of strong shocks. Lesions of the PAG eliminate freezing of rats not only to conditioned fear stimuli but to cats as well [92]. These lesions attenuate conditioned freezing when made either before or after training [192]. The ventrolateral PAG seems to be the region critical for freezing. First, lesions of the PAG that completely spare the tissue ventral and ventrolateral to the aqueduct do not reduce freezing [193]. Furthermore, lesions of the dorsal raphe that spare the surrounding ventral PAG also fail to reduce freezing [194]. Carrive and colleagues [185] examined Fos immunoreactivity in rats following exposure to a context previously paired with shock. They found that these rats both froze and showed the greatest number of Fos stained nuclei in the ventrolateral column of the PAG compared to the control. As with fear-potentiated startle, dorsolateral PAG lesions have a modulatory effect on freezing. Dorsolateral PAG lesions made before, but not after training, will enhance the level of freezing observed on testing [192,193]. However, this enhancing effect is confined to training parameters that show paradoxically reduced freezing because of very dense shock schedules. Within the PAG, expression of the unconditioned response and the conditioned response to shock can be doubly dissociated [181]. Lesions of the dorsolateral PAG reduce the unconditioned burst of activity produced by the shock, but do not reduce the conditioned freezing. Ventrolateral regions have the opposite effect; they reduce conditioned freezing but do not affect the unconditioned activity [182]. M. Fendt, M.S. Fanselow I Neuroscience and Biobehavioral Reviews 23 (1999) 743-760 751

burst. This dissociation further illustrates the profound separation of the CR and the UR in Pavlovian fear-conditioning.

4.3. Other models

While direct stimulation of the PAG can have pronounced autonomic effects [195], it has been repeatedly demon
strated that the autonomic reactions to conditioned fear stimuli do not depend on the PAG [81,179]. However, like freezing, fear-induced analgesia depends on the PAG as lesions of this structure block the reduction in pain sensitivity produced by conditional fear [81]. Within the PAG, freezing and analgesia are dissociable as injections of the opioid antagonist naltrexone into the ventral PAG block analgesia but not freezing [196]. This conditioned fear induced analgesia is realized from projections from the PAG to the rostral ventromedial medulla [81]. Fig. 2 summarizes this information.

5. Other brain regions

Although the amygdala and PAG play a central role in the acquisition and expression of fear-related behavior, certainly several other brain regions play an important role as well. In the ensuing paragraphs, we will discuss the two brain regions that have been shown to play a role in fear-potentiated startle and freezing, the tegmental area and the hippocampal formation, respectively.

5.1. Tegmental nuclei

The tegmental nuclei play a role in fear-potentiated startle, but this area is yet to be examined for freezing response. Sensitization of the startle response after application of foot shock is blocked by microinjections of substance P antago
nists into the PnC [197]. This indicates that the laterodorsal tegmental nucleus is involved in the potentiation of the startle response by fear, as the laterodorsal tegmental nucleus is the only brain structure providing substance Pergic input to the PnC [198]. Electrolytic lesions of the midbrain tegmental area (including the lateral tegmental nucleus) blocked fear-potentiation of the startle response [114].

Frankland and Yeomans [199] made chemical lesion of the rostrolateral midbrain, a brain area including the lateral tegmental nucleus, and showed that these lesions also block fear-potentiated startle. They suggested that a further parallel pathway from the amygdala via the rostrolateral midbrain (the lateral tegmental nucleus?) to the brainstem is involved in the mediation of fear-potentiated startle. Anatomical tracing studies showed that the amygdalofugal pathway (including the direct pathway from the amygdala to the PnC) cross the midbrain tegmental nuclei but there is also a projection from the central nucleus of the amygdala terminating in this area [113,183]. The ventral tegmental area (VTA) plays a role in fear-potentiated startle [189]. Chemical lesions of the VTA blocked the expression of fear-potentiated startle. Electrical stimulation of the VTA enhanced the baseline startle amplitude and increased the fear-potentiation of the startle response, while micro injections of the Dm receptor antagonist quinpirole into the VTA totally blocked the fear-potentiated startle [190]. Injections of CCK-8S, a CCK receptor agonist, into
the PnC increase the baseline startle amplitude [200], suggesting that an excitatory CCK-ergic projection to the PnC is involved in the expression of fear-potentiated startle. The VTA, the central nucleus of the amygdala and the PAG show a high density of CCK containing neurons [201] and project to the PnC, so any or all of these projections may use CCK as a transmitter. 5.2. Hippocampus As might be expected from its role in spatial [202] and/or configural [203] learning, the hippocampus plays a disproportionate role in the fear acquired in the situation where fear-conditioning occurred. When tones were paired with shock, lesions of the hippocampus blocked freezing to the contextual cues associated with shock, but the same rats froze normally to the tone [204,205]. Lesions of the hippocampus made shortly after training produce a severe retrograde amnesia for contextual fear [169,206]. If the lesions are made prior to conditioning, anterograde amnesia is also observed, although it seems to be less pronounced than retrograde amnesia [206-208]. Retrograde amnesia for conditioned freezing to contextual cues is time-limited, as the interval between training and lesion increases the retrograde amnesia decreases [169,206,208]. The effects of hippocampal lesions on freezing to contextual cues are remarkably selective, in a way that accords well with the human amnesic syndrome [209]. Some forms of memory are drastically impaired (context conditioning), while the others are spared (conditioned freezing to auditory cues) and the type of memory that is lost shows a temporal gradient for retrograde amnesia [210]. McNish et al. [211] reported that while lesions of the hippocampus disrupt freezing to contextual cues, they do not affect the fear-potentiated startle to the same contextual cues. Unfortunately, a flaw in this study makes it premature to conclude that the hippocampus plays a different role in these two measures of contextual fear. McNish et al. did not include an assessment of the effects of hippocampal lesions on baseline startle magnitude. As the hippocampal lesions have been reported to increase the baseline startle response [212], the effects of hippocampal lesions on fear-potentiated startle would be masked by any increases in baseline startle response. It should be noted that the specificity of the deficit in the contextual freezing described before, indicates that hippocampal lesions do not affect the rat’s ability to freeze [207,209]. Given the very selective effects of hippocampal lesions, it is unlikely that the deficit is due to a nonspecific species-specific danger signals... lateral...
lesions on fear and its more general role in memory, it seems likely that its function is to convey a configural or spatial memory of context to the amygdala, where it can be associated with shock [103]. This places the hippocampus on the input side of fear-conditioning.

6. Summary, a neural circuitry and open questions

The studies reviewed here suggest a certain neural circuitry and this is shown in Fig. 3. This circuit goes a long way in integrating and summarizing the extensive data on Pavlovian fear-conditioning. As shown in the figure, the amygdala plays the central role in the acquisition and expression of fear to the conditioned stimulus [136,213-216]. The amygdala is the interface between the sensory system that carry information about the CS and US, and the different motor and autonomic
systems that control the conditioned reactions. If anyone structure is to be associated with the acquisition of conditioned fear, it is the lateral and/or basolateral amygdala. It seems likely that the cellular mechanism underlying this learning is NMDA-receptor dependent long-term potentiation (LTP) [106,217-219].

The amygdala receives information about the US from several sources that act in parallel. How they act to foster association formation is unknown. The problem arises because in fear-conditioning the conditioned and the unconditioned response are different; the US conditions responses it does not normally activate.

The CS pathway to the amygdala seems well characterized. As is shown in Figs. 2 and 3, the lateral and basolateral amygdala receive direct input from the thalamus as well as cortically processed input via the perirhinal cortex and hippocampal formation. What function do each of these pathways serve? As has been described earlier, for the hippocampus the case seems clear; information processed by the hippocampus normally functions to provide contextual information to the amygdala [169,205]. However, the available data does not provide any clear picture for a differential role of cortico- and thalamo-amygdala projections in
excitatory fear-conditioning to discrete CS. The pathways seem to function somewhat redundantly as either route seems sufficient to support fear-conditioning on its own [126,167,220]. The sorts of discriminations, such as sound localization, considered to depend on the auditory cortex have yet to be tested with fear-conditioning [221-223]. After sufficient overtraining, fear-potentiated startle seems to peak at the point when the US is nonnally delivered [224]. Such temporal encoding is likely to require processing in cortical regions such as the perirhinal cortex [225]. There also seem to be pharmacological differences in the pathways that carry CS information to the amygdala. Projections from the hippocampal formation [103] and medial geniculate body [104,226] use both the NMDA and the AMPA receptors for normal synaptic transmission, as NMDA antagonists reduce evoked potentials in the amygdala produced by stimulation of these structures. On the contrary, AMPA and not NMDA antagonists [104,226] reduce amygdala responses to activity in auditory cortex. Expression of freezing to conditioned tone and contextual stimuli is reduced by NMDA antagonists applied to the amygdala of rats trained in the absence of drug [160,161], but expression of fear-potentiated startle to a tone CS is not affected by NMDA antagonists [120]. The most straightforward explanation of this pattern is that fear-potentiated startle depends on a cortico-amygdala glutamatergic pathway that requires only AMPA activity to drive action potentials. However, thalamo- and hippocampo-amygdala glutamatergic pathways that require both the NMDA and the AMPA currents for the generation of action potentials may drive freezing. Note that the Campeau et al. [120] study used a relatively large number of training trials and examined a response that is well
timed [224]. The freezing study used few trials and a response that is not particularly well-timed [161]. Thus, the pattern of data is consistent with the idea that cortico-amygdala projections are particularly important for temporal encoding that is revealed when very discrete fear responses are observed in overtrained animals. Certainly, this hypothesis is in need of further analysis. Given the schema presented here and the generally devastating effects of amygdala lesions on Pavlovian conditioned fear, one might expect that rats with amygdala lesions might never express fear-related behavior. While this seems to be the case under normal training conditions, recent data suggests that fear may be present when extensive overtraining is given. Kim and Davis [227] found that while rats given extensive overtraining completely lost fear (as measured by fear-potentiated startle) following amygdala lesions, fear could be reacquired by these overtrained rats. Reacquisition of fear-potentiated startle progressed to near normal levels. Using the freezing preparation, Maren [228] found a similar pattern. However, reacquisition was only complete in animals that had partial lesions of the basolateral nucleus. Animals with total basolateral lesions still showed a large, albeit incomplete, deficit despite pre-lesion overtraining. Maren went on to show that this same pattern was obtained when the lesions were made before training. Including the central nucleus in the lesion did not alter the pattern of behavior. Thus, pre-training while intact does not appear to be the critical variable in the survival of fear following amygdala lesions. Rather the two crucial factors are the amount of spared amygdala tissue and the amount of training. With the freezing measure there is significant acquisition in a single trial and freezing is asymptotic at about six trials. In animals with complete basolateral lesions, freezing was abolished even with 25 training trials and was still significantly impaired at 35 trials. Killcross and co-workers [229] gave far more extensive training in a complex discrimination task and found that while some components of the fear response reached near normal levels, others were still dramatically impaired. Thus, without an 233

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amygdala fear responses never appear completely normal, although very extensive overtraining allows some expres
sion of the standard fear measures (fear-potentiated startle and freezing). It remains to be demonstrated what brain structures allow this residual fear-related behavior.

Within the present framework, the amygdala is playing the role of sensory-motor interface for fear. The simplest translation of this theory would suggest that when the amygdala is functional, all the fear responses it is essential for should occur in concert. Data on the ontogeny of ear calls this most parsimonious version into question [85,229,231]. Fear to tones, lights and contexts first develops at different ages with tone appearing first and context appearing last [85,231]. This is true for at least three measures of fear (freezing, fear-potentiated startle and heart rate changes). However, these different measures of fear also appear at different ages; with freezing appearing first and fear-potentiated startle appearing last [85,230]. Thus, a 23-day-old rat can freeze and show fear-potentiated startle to a tone associated with a shock, but only freezing and not fear-potentiated startle, is observed to a light associated with shock [85]. This ontological pattern suggests that the sensory motor organization within the amygdala and its afferent structures is quite complex. Note that this pattern cannot be due simply to maturation of structures afferent to the
amygdala (i.e. sensory information) as there is an age at
which rats will respond with freezing to a light CS, but
not show fear-potentiated startle to the same stimulus.
However, the pattern cannot be simply maturation of
response pathways either. Rats will show fear-potentiated
startle to a tone before they can show it to a light.
Obviously, there are different pathways mediating the
expression of conditioned fear. The PAG seems to be
involved in the expression of several measures of condi-
tioned fear (e.g. analgesia, freezing and fear-potentiated
startle). Whether the different fear responses have common
or separated processing in the several regions of the PAG,
should be a question of further study. Another important aim
of future investigation should be elucidation of neurochem-
ical differences in the different pathways from the amygdala
to the other brain structures mediating different fear
responses. For example, the parabrachial nucleus mediates
changes in respiration, the lateral hypothalamus and parts
of the medulla oblongata mediate cardiovascular responses.
The bed nucleus of the stria terminalis mediates stress reac-
tions and the ventral tegmental area and the paraventricular
hypothalamus seem to be involved in the modulation of
arousal and vigilance by conditioned fear (reviewed in
Refs. [136,213-216]). Once the amygdala recognizes that
the situation predicts danger, it generates the constellation of fear responses through multiple parallel and sometimes redundant channels. These pathways may mediate slightly different aspects of fear, allowing fine-tuning of the ultimate behavioral response to fear-provoking stimuli under a variety of external and internal conditions. This implies that


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Meanwhile, the prefrontal cortex, another area involved in decision-making and emotion regulation, showed significant changes in the pattern of activity. Specifically, there was increased activation in the medial prefrontal cortex and reduced activity in the lateral prefrontal cortex. These changes were associated with improved decision-making performance and better emotional regulation.

Furthermore, the study also revealed that these brain changes were not limited to the present moment but extended to future decision-making scenarios. The participants showed enhanced ability to consider the long-term consequences of their actions, which is a critical aspect of emotional intelligence.

In conclusion, the findings suggest that emotional intelligence can be developed and improved through targeted training and practice. The enhanced neural substrates of emotional intelligence, as revealed by fMRI studies, provide a potential mechanism for the observed improvements in decision-making and emotional regulation.

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