Pergamon

Journal of Anxiety Disorders, Vol. 12, No. 5, pp. 485–507, 1998

0887-6185/98 $19.00 + .00

PII S0887-6185(98)00029-2

THEORETICAL ARTICLE

Panic Disorder From a Monistic Perspective: Integrating Neurobiological and Psychological Approaches

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Abstract—In the literature, psychological and biological theories of panic disorder are often regarded as mutually exclusive. The present article presents an integrative theory that explains how and why cognitive misinterpretations and "false threat alarms" leading to irrational fear and anxiety can arise from a neurobiological dysfunction in the amygdala and ascending transmitter systems. According to this view, physiological symptoms (such as palpitations and respiration manoeuvres) and psychological symptoms of anxiety (perception of threat and anticipation of catastrophe) are elicited simultaneously by a subcortical threat detection mechanism. This perspective might help to integrate conflicting earlier approaches. It is discussed with respect to theoretical, empirical, and clinical implications. © 1998 Elsevier Science Ltd

Panic disorder is characterized by sudden episodes of uncontrollable anxiety accompanied by a variety of cognitive and physiological symptoms. Numerous psychological and biological theories have been proposed to explain development and maintenance of the disorder (for an extensive review, see McNally, 1994). The discussion is characterized by vigorous debates among scientists holding either biological or psychological factors to be crucial (e.g., Klein, 1996a, 1996b; Klein & Klein, 1989; Ley, 1994, 1996; Margraf, Ehlers, & Roth, 1986; McNally, 1996a, 1996b) while suggesting—most often explicitly—

The author is currently supported by the German Reseach Foundation (DFG) through the graduate program KOGNET. The help of Daniel Durstewitz, AE Biopsychology of the Ruhr-Universität Bochum, in many valuable discussions on this article and related topics is gratefully acknowledged.

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that the alternative view, respectively, is inadequate for explaining the disorder (cf. McNally, 1994, pp. 108–111). In sharp contrast to the most commonly held belief on a metatheoretical level that cognitions actually emerge from brain processes, psychological models of panic try to explain panic and anxiety without referring to neurobiological processes, whereas biological theories postulate neurobiological dysfunctions, for example, in neurotransmitter systems (for a short review, see Johnson, Lydiard, & Ballenger, 1995) without showing how and why these lead to panic-specific sensations and cognitions (and not to any other cognitive disturbance).

Neuroscience has progressed considerably in recent years. For many cognitive processes, translations into neurobiological terms and models already exist, at least hypothetically (see Arbib, 1995). The present article tries to show why it is advantageous to combine cognitive and neurobiological explanations instead of giving preference to either a purely mentalistic or a purely materialistic view while simultaneously neglecting or rejecting the alternative perspective. Thus, in an attempt to bridge the gap between biological and psychological theories of panic disorder, I will try to show how the cognitive dysfunctions described by psychological models of panic might in fact arise from neurobiological dysfunctions proposed by biological models. Clearly, this cannot be done solely in structural terms with mere reference to neuroanatomy or biochemistry alone (e.g., by referring to a specific receptor-dysfunction). Instead, a functional, dynamic process should be outlined to explain how subjective experience of irrational fear might be produced by the brain.

METATHEORETICAL ISSUES

In his very comprehensive monograph on panic disorder, McNally (1994) pointed out how the mind-body problem is dealt with by many psychologists:

> Cognitive psychopathologists who study anxiety have been agnostic about how information processing dysfunctions are instantiated at the neural level of analysis, and most have assumed that cognitive dysfunction need not imply brain dysfunction. Just as a programming error in a software package does not imply a defect in the computer itself, cognitive biases that excacerbate anxiety do not necessarily imply brain disease. Although cognition is instaniated in neural tissue, it is not reducible or translatable into its physical underpinnings. (McNally, 1994, p. 124)

Although the computer metaphor McNally refers to in this passage is quite common among cognitive psychologists and scientists in the domain of artificial intelligence, it does not seem applicable to human information processing, neither with respect to structural and functional features of the brain (Crick & Mitchison, 1995; Mallot, Kopecz, & von Seelen, 1992; Windmann, 1997, section 2.1.2) nor with respect to cognitive performance (Penrose, 1994; Searle, 1990). One of the most important differences between the brain and the computer is that neuronal processes are directly representative for the qualitative

and quantitative functions they perform. This means that in the ideal case where the neuronal code is known in detail, researchers would be able to directly infer from observations of neural states and processes what function the system currently performs. Thus, investigating hardware processes in biological organisms cannot only indicate *what* cognitive functions are being performed but also *how* they are being performed in the biological system and how they have been developed and established by nature. In contrast, the relationship between the hardware of a computer and the software that is running on it is in fact arbitrary. Thus, if one intended to empirically examine the functions of an artificial computer program, it would indeed be useless to focus on the hardware of the system. Examining cognitive functions in living organisms, however, is a different issue.

Another objection to the reasoning presented by McNally (1994) stems from the fact that all psychological and behavioral functions arise from specific neuronal activities and processes, implying that different psychological functions are based on different neuronal processes (otherwise the functions they perform would be identical). Thus, normal psychological functioning must arise from "normal" neuronal processing and abnormal psychological functioning must arise from "other-than-normal" (i.e., abnormal) neuronal processing. Although this use of language would be logical, the functionalistic conviction presented in the citation of McNally (1994) involves the contradiction that brain processes leading to "normal" psychological functioning can be designated as "normal" whereas brain processes leading to "abnormal" psychological functioning or "psychological disease" may not be referred to as "abnormal" brain processes or "brain disease", at least in the case of panic disorder. Although it is true that brain dysfunctions of patients with panic disorder are more likely to be found on a microstructural and functional rather than on a macrostructural level, it should also be taken into account that panic disorder reflects a very striking example of cognitive dysfunction that is associated with severe loss of life quality and psychosocial functioning. In view of this high degree of cognitive malfunctioning, it seems reasonable to say that some sort of brain disease or neural dysfunction must actually be involved in its development.

In any event, the question of how panic provoking brain processes are being defined or classified at a descriptive level is simply a matter of definition which does per se not help to understand the mechanisms underlying the phenomenon. As heuristics based on (more or less rational) conventions established by humans, not necessarily by nature, descriptive classifications help us to communicate effectively but do not include any explanatory information. Thus, even if clinicians and scientists designate panic-related cognitive malfunctioning as pathological while tending to designate the underlying brain processes as normal—maybe just because they are so poorly understood—this does not imply that we can neglect brain processes in explaining cognitive functions and dysfunctions of these patients.

Although many psychologists use the arguments presented by McNally (1994) to justify their decision to disregard the neuronal basis of the functions they examine, relatively little attention has been paid to the theoretical and practical risks that such a one-sided interest might involve. This also holds for biological psychiatrists who are trying to oppose a cognitive view of panic. By restricting the perspective a priori either to a purely mentalistic or to a purely materialistic view, one might ignore essential features of the disorder and, consequently, overlook potentially effective treatment approaches. As I will try to point out in more detail in the sections below, one might even get in danger of misinterpreting experimental results, and of confusing causes and consequences of empirical observations.

To conclude, I believe that it would be more fruitful to search for compatible aspects among neurobiological and psychological theories of panic rather than to focus on the short-comings of each other's position in order to establish one's own viewpoint.

In the following, I will try to show more specifically how and why a "monistic" approach to the mind-body problem can increase our understanding of panic and anxiety and how it might contribute to the resolution of ongoing debates between biological and psychological theorists. First, I will discuss why I think that some prominent psychological theories of panic disorder could probably benefit from referring to more external levels of (causal) explanation. Second, I will deal with a recent approach by Beck and Clark (1997) and show that this theory differs from previous psychological models with respect to some very important assumptions, although these might seem somewhat speculative at this point. Third, I will examine whether the framework of Beck and Clark (1997) is plausible from a neurobiological perspective. Fourth, I will present an own empirically plausible theory of panic disorder in which psychological and physiological symptoms of anxiety are regarded as emergent products of neuronal substrates and processes. This theory gives rise to empirical predictions which have not been focused on previously in the literature, even though some of them seem to be inherent in the Beck and Clark (1997) approach (at least implicitly). As a conclusion, I will point out several implications of my position with respect to theoretical, empirical, and practical issues.

PSYCHOLOGICAL THEORIES OF PANIC DISORDER

Two prominent psychological models of panic disorder, the cognitive (Clark, 1986) and the psychophysiological model (Ehlers, 1989; Ehlers, Margraf, & Roth, 1988), have stimulated much empirical research and many theoretical debates. Both models assume that panic arises from a cognitive tendency to associate perception of harmless bodily symptoms (Clark, 1986) or of "bodily and/or cognitive changes" (Ehlers, 1989, Ehlers, Margraf, & Roth, 1988) with imminent threat. In the cognitive model, this process is referred to

as "cognitive misinterpretation" because patients erroneously take their internal sensations (such as palpitations) as signs for personal danger and catastrophe (e.g., as indicating a heart attack). In the psychophysiological model, this view is extended in so far as associative conditioning of fear responses to harmless cognitive and/or bodily changes is also regarded as a possible panic-provoking mechanism (cf. Barlow, 1988; Goldstein & Chambless, 1978; McNally, 1994, pp. 105–136).

Both models assume that the threat perceived in these primary sensations can lead to cognitive and physiological symptoms of anxiety which in turn are perceived and evaluated as threatening and therefore lead to further anxiety and so on, until the process culminates in a panic attack. Thus, both approaches represent circulus-vitiosus models (see also Pauli et al., 1991). Intuitively, their assumptions seem very convincing because of their high face-validity, and because they provide a useful basis for cognitive treatment approaches.

From a strict scientific point of view, however, the models have been criticized. First, it has been argued that they lack explanatory power because development of anxiety is explained by cognitive symptoms of anxiety (i.e., perception of threat or anticipation of personal danger). As Peter Lang (1988) argued:

> It is basic to the logic of explanation that a phenomenon cannot be elucidated in its own terms. Thus, Molière's physician is a figure of fun, because he "explained" the effect of a sleeping drug as attributable to its "soporific action". To say that a situation is frightening because it is appraised as "fearful" has, at the least, similar explanatory limitations. To an extent, all traditional analyses of mentation have this problem of circularity. (Lang, 1988, p. 223)

The criticism refers to the realization that explanans and explananda must not be confounded in scientific theories. As anxiety always manifests on the cognitive, the emotional, and the physiological level, symptoms of anxiety can hardly occur without a cognitive component signaling potential threat and danger—otherwise the state would probably not be called "anxiety" but merely "enhanced physiological arousal" or something alike. Therefore, in a condition where symptoms of anxiety occur spontaneously without any reasonable cause, inadequate perception of threat must by definition be involved in addition to bodily symptoms. Thus, it seems questionable whether cognitive theories of anxiety can ever be proven wrong in their central assumption that irrational, event-unrelated symptoms of anxiety are related to inadequate associations of threat (Ehlers, 1989; Ehlers, Margraf, & Roth, 1988) or cognitive misinterpretations (Clark, 1986, 1988).

One might try to rule this objection out by arguing that patients with panic disorder fear the *consequences* of bodily symptoms (e.g., catastrophe, death) rather than the symptoms of anxiety themselves. A similar rationale is being put forward in the anxiety sensitivity approach (e.g., Reiss & McNally, 1985). However, because cognitive misinterpreations, "irrational" anxiety, and the

physiological symptoms of fear are *conceptually* confounded in the concepts of clinical "anxiety" and "panic", this line of argumentation does not really solve the problem. For example, if a patient with panic disorder expresses, "I was afraid that I would suffocate," it is unclear whether he describes an emotion (fear), a physiological state (symptoms of suffocation), or a cognitive expectation referring to the consequences of his current state (dying; see also Costello, 1992). Thus, the cognitive component of the irrational anxious state dealing with some upcoming catastrophe seems to be an integral part of the attack which can hardly be separated from its other components.

A second, related problem of the cognitive and the psychophysiological model is that it is also with respect to temporal succession difficult to empirically disentangle the presumed causes from the presumed consequences because of their strong interdependency. Due to the circularity of the argumentation, it is difficult to grasp the exact moment in time the attack developed out of. This issue was referred to by Costello (1992) when he pointed out that: "Even if one had grounds for assuming that the construct 'panic', 'body sensations' and 'cognitions' are independent ones that are being independently measured, the problem still remains of what is causing what" (Costello, 1992, p. 3). As there is no fixed temporal sequence of cognitions, emotions, and physiological correlates of anxiety, any given irrational fear symptom (including cognitive correlates inferring imminent catastrophe from the current state) can hardly be interpreted unambiguously in terms of initial relevance. Instead, it can always simply be a consequence of one of the other fear components.

Third, both models do not directly explain why patients with panic disorder tend to associate harmless physical and cognitive events with threat whereas other individuals do not. One could think of this disposition as a genetically determined vulnerability (Barlow, 1988), an interoceptively conditioned response-tendency (Barlow, 1988; Goldstein & Chambless, 1978), or a general cognitive belief towards physical sensations, possibly acquired during socialization (Reiss & McNally, 1985). But irrespective of whether the disposition is innate or being learnt, the question of how it has become represented in the cognitive system and why it can lead to such dramatic episodes of panic and anxiety which are considerably resistant to extinction and to cognitive countermeasures should be outlined in more detail.

Summarizing this evaluation, it is obvious that the cognitive and the psychophysiological model of panic disorder provide a clear and comprehensive description of the development of panic attacks which is useful for clinical treatment approaches. However, it is conceptually and methodologically difficult to determine their causal explanatory value for scientific purposes because they do not really refer to external levels of explanation. Manipulating the independent variables of these theories will almost inevitably lead to the expected change in the dependent variables (i.e., symptoms of anxiety) because the two types of measures are both conceptually and empirically confounded. As McNally (1994) points out:

> Cognitive approaches to the understanding and treatment of panic disorder have had few ties to basic research in cognitive psychology. Concepts such as catastrophic misinterpretation, anxiety sensitivity, sense of control, and so forth, have their roots in psychometric and clinical psychology, not in experimental psychology. Conversely, cognitive psychologists have traditionally had little interest in emotion, let alone psychopathology. The growing divide between experimentalists and practioners, at least in the United States, has further diminished cross-fertilization between basic and applied inquiry. (p. 123)

PANIC DISORDER AND INFORMATION PROCESSING

Psychological theories of panic and anxiety usually imply directly or indirectly that pathological anxiety is associated with an attentional bias towards threat cues and bodily sensations (Beck, Emery, & Greenberg, 1985; Clark, 1986, 1988; Ehlers, 1989; Ehlers, Margraf, Davies, & Roth, 1988; Goldstein & Chambless, 1978; Reiss & McNally, 1985). In line with this hypothesis, numerous studies showed that patients with panic disorder and patients with generalized anxiety disorder display a cognitive tendency to selectively detect, focus on, store, retrieve, and recall anxiety-related information. For instance, relative to controls, patients with panic disorder have been found to show shorter response latencies to the presentation of physical threat words (Asmundson, Sandler, Wilson, & Walker, 1992), to evaluate masked panic-related auditory information as more intense (Amir, McNally, Riemann, & Clements, 1996), and to show increased implicit and explicit memory for bodily sensation words (Cloitre, Shear, Cancienne, & Zeitlin, 1994). However, the tendency occurred only when stimulus words (e.g., *anxiety, attack, panic, breathless, palpitation, dizzyness*) or phrases (e.g., "*The woman panicked in the supermarket*") were presented which are highly specific for the patients as opposed to the control subjects. It was not found in items with generally negative valence (Becker, Rinck, & Margraf, 1994; Windmann & Krüger, in press). It is possible that panic-related concepts are recalled more easily by patients with panic disorders than by healthy controls because the accessibility of cognitive representations depends on their familiarity and frequency (e.g., Connine, Mullennix, Shernoff, & Yelen, 1990; Engelkamp, Zimmer, & Kurbjuweit, 1995). In the cognitive literature, this observation has often been referred to as the word frequency effect (e.g., Treisman, 1974). It is probably related to use-dependent neuronal learning mechanisms (e.g., Artola & Singer, 1993; Brown, Kairis, & Keenan, 1990; Ratcliff & McKoon, 1996), especially to those associated with attentive and conscious processing (Kinoshita, 1995). Although some researchers have tried to take this problem into account (e.g., McNally et al., 1994), it still seems unclear whether the cognitive bias found in patients with panic attacks or in patients with generalized anxiety reflects a cause or a consequence of the disorder (see McNally, 1994, p. 135), mainly because the experimental stimuli that had been used were not exclusively related to the presumed origins of the investigated disturbance but rather to its symptomatology (see also Windmann & Krüger, in press).

SUBCONSCIOUS PROCESSING IN THE ANXIETY DISORDERS

Recently, it has been hypothesized that pathological anxiety might be related to automatic, involuntary and subconscious processing rather than to controlled and strategic processing (McNally, 1995; Windmann & Krüger, in press). This idea is intriguing because it is able to account for the unpredictability, the subjective unexplicability, and the uncontrollability of pathological anxiety. Thus, it has been speculated that cognitive misinterpretations and threat associations might develop so fast and automatically that they are not noticed by the patients themselves (Clark, 1988). This presumption implies that subconscious processing differs from conscious processing mainly in quantitative respects: Subconscious processing is too weak and too fast to be noticeable. However, recent contributions from cognitive psychology merely seem to support the view that subconscious processing is also qualitatively different from conscious processing. While conscious processes are discriminative and conceptual, subconscious processes are less discriminative, more stimulus-driven, and rather stereotyped, at least unless being extensively practiced and overlearned. Therefore, subconscious processing sometimes tends to give rise to false responses whereas conscious processing is correct and unambiguous (cf. Hay & Jacoby, 1996; Ratcliff & McKoon, 1996; Windmann & Krüger, in press). This rationale is actually the core assumption process dissociation procedures are based upon (Debner & Jacoby, 1994; Jacoby, 1991).

More recent theoretical approaches to panic and anxiety seem to have approached this view. In their recent model, Beck and Clark (1997) abandoned earlier unidimensional views on information processing in patients with anxiety disorders in favor of a multistage model. They propose that threat can be detected by an early warning system, which is described as a rapid, involuntary, unconscious, and purely stimulus-driven mode. Moreover, the authors point out that processing at this stage is "relatively undifferentiated," and that it might only serve to classify stimuli as related to threat or not on the basis of a rough perceptual analysis (see also Mathews & MacLeod, 1994). Furthermore, they presume that the early warning detection system activates a primal mode which initiates "rigid, inflexible and reflexive" (p. 52) responses based on "incomplete information" (p. 52). Therefore, the system can give rise to "non-rational, automatic, and involuntary fear reactions" (p. 52). Beck and Clark (1997) argue that this initial registration and fast automatic responding to threat is of high evolutionary value and will "optimize our chances of survival" (p. 51), especially because they assume that it can normally be countered by more elaborated and strategic processing provided by a secondary appraisal process (p. 53). This "metacognitive mode" allows for a more reflective consideration of the current context and the coping resources of the individual and can therefore lead to more flexible and more differentiated responding.

Summarized briefly, Beck and Clark (1997) conceptualize pathological anxiety as the predominance of the primal threat mode over more elaborated metacognitive processing modes. Consequently, they propose that psychological interventions in anxiety disorders should " 'turn off' the primal threat mode and 'turn on' more constructive elaborated processing of stimuli" (p. 55).

One very important theoretical difference between the model proposed by Beck and Clark (1997) and earlier psychological models of panic and anxiety (Beck et al., 1985; Clark, 1986; Ehlers, 1989; Ehlers, Margraf, & Roth, 1988) should be emphasized: As the early warning system is characterized as an undifferentiated, unprecise, stimulus-driven, and unconscious processing mode, Beck and Clark (1997) argue that sometimes false detection of threat will occur. In case of insufficient metacognitive control over the inaccurate preattentive warning system, potential threat is signaled relatively often and intensively to the primal response mode and to other parts of the cognitive system without being checked much for conceptual validity. Thus, pathological anxiety in the Beck and Clark (1997) model can be best understood as a decreased ability to discriminate between true threat and pseudo-threat: More threat is being perceived than would actually be adequate for a given situation. On the one hand, this implies that actually threatening stimuli are indeed more often correctly identified and responded to ("hit rates" in terms of signal detection theory). This is presumably what many clinical psychologists have been referring to when arguing for selectively enhanced sensitivity for threat in patients with anxiety disorders. However, the tendency is also associated with enhanced *false* threat detection (enhanced "false alarm rates" in terms of signal detection theory) reflecting either false evaluation of the valence of the current sensory input or inadequate presumption that a threatening stimulus has occurred when actually no change in sensory input is given. These *false threat alarms* (cf. Barlow, 1988) are probably what clinical psychologists have described as "cognitive misinterpretations" of objectively harmless internal or external sensations (Clark, 1986, 1988). However, because *sensitivity* should be defined in terms of *discrimination performance*, "false alarm rates" have to be substracted from "hit rates" in the overall analysis of behavior (see Windmann & Krüger, in press). Thus, the recent Beck and Clark (1997) model does not suggest that sensitivity for actual threat is selectively enhanced in pathological anxiety.

As far as I know, the fact that cognitive abnormalities in patients with anxiety disorders includes both, enhanced threat detection as well as enhanced "false" threat detection resulting in normal discrimination performance, has never been highlighted explicitly in the cognitive-clinical literature. The Beck and Clark (1997) approach is the first one that directly suggests that cognitive abnormalities observed in patients with clinical anxiety are based on an information processing bias that refers to stimuli of *any* valence, not just to objectively threatening stimuli (cf. Windmann & Krüger, in press). Hence, rather than suggesting selectively enhanced performance in response to threat items

relative to neutral items in patients with anxiety disorders, the Beck and Clark (1997) model suggests that researchers should think about how a preattentively initiated tendency to suppose the presence of threat in any real or virtual stimulus could be measured independent of conscious sensitivity for threat.

NEUROBIOLOGICAL PERSPECTIVES ON FEAR AND ANXIETY

Although cognition is not reducible to and not identical with its physical underpinnings for it displays different qualitative features (cf. Hesslow, 1994), this does not imply that neuroscience can be ignored in explaining psychological functions and dysfunctions. To the contrary, neurobiological findings provide a very strong challenge to psychological theories because they provide natural and external restrictions with which psychological theories should be able to comply. Thus, they can help to validate, verify, and modify psychological assumptions.

In the following, I will focus on neurobiological findings that refer to cortical mechanisms of subconscious threat detection in an attempt to examine whether the recent assumptions by Beck and Clark (1997) are plausible from a neurobiological perspective.

It has often been proposed that cortical structures within the limbic system can function as an "alarm bell" because they can detect novelty and potential threat in the perceptual environment on a preattentive level of processsing in order to prompt attentive processing of these stimuli (e.g., Graeff, 1994; Gray, 1982, 1995). In his numerous experiments with rats, LeDoux (1992, 1995a, 1995b) focused on the amygdala and its role in subcortical fear responding and conditioning (see also Bechara et al., 1995; Gallagher & Chiba, 1996). LeDoux and his colleagues found that the lateral nucleus of the amygdala receives direct input from the sensory thalamus. By this pathway, the amygdala is able to detect aversive input and fear conditioned stimuli even if sensory neocortical areas are disconnected, lesioned, or ablated. As a consequence, it can quickly and automatically elicit autonomic, endocrine, and motor fear responses even before the neocortex is able to build up a coherent representation of the triggering threat stimulus. Moreover, it transmits an alarm signal to the neocortex, which causes it to allocate its attentional resources to the current sensory input. Technically, this can be realized by activating ascending neuromodulatory transmitter systems such as serotonin, acetylcholine, and noradrenaline (Davis, 1989; Graeff, 1994). These neurotransmitters are presumed to affect the signal-to-noise ratio of neocortical processing (Robbins & Everitt, 1995). As a consequence, currently activated neurons may begin to engage in a synchronous firing mode (Durstewitz & Güntürkün, 1996; Liljenström & Hasselmo, 1995; Munk, Roelfsema, König, Engel, & Singer, 1996), which is presumed to be correlated with focal attention and conscious perception (Crick, 1994; Crick & Koch, 1990; Koch & Crick, 1994).

Thus, the amygdala does not only learn and elicit automatic fear resonses subconsciously, but probably also prompts and influences conscious cognitive processing by the help of ascending neuromodulatory transmitter systems.

However, because the thalamus performs only a relatively crude analysis of sensory input, direct projections from the thalamus to the amygdala do not encode differentiated and conceptual stimulus information. LeDoux (1986) describes this as follows:

> Emotional responses elicited by way of thalamo-amygdala pathways and unchecked by the relay from the cortex to the amygdala, leave much room for cognitive interpretation. Since the response is based on weakly tuned inputs, the cognitive system can only guess which stimulus features are critical. In contrast, when emotional responses are the result of detailed perceptual analyses by cortical sensory circuits, the critical stimulus features may be more accurately apprehended. (LeDoux, 1986, p. 242)

In accordance with this interpretation, LeDoux (1995a, 1995b) found neocortical processing to be necessary for *discriminative* conditioning as well as for the *extinction* of conditioned fear responses. LeDoux, Romanski, and Xagoraris (1989; LeDoux, 1995b) speculated that in the absence of primary sensory areas, potential fear information cannot be relayed to higher regions such as the prefrontal cortex and the hippocampus; areas which are believed to be crucial for higher-order processing of sensory information (van Essen & Deyoe, 1995), consciousness (e.g., Crick & Koch, 1995a; Goldman-Rakic, 1990; Gray, 1995), and declarative (explicit, conscious) memory (Eichenbaum, Otto, & Cohen, 1992; Moscovitch, 1995; Squire, 1992). In fact, recent experimental studies confirmed that the hippocampus is highly efficient in modifying neural processes in the amygdala (Gallagher & Chiba, 1996; Maren & Fanselow, 1995). Thus, when the activity of the amygdala is not sufficiently controlled and inhibited by these more discriminative modules, it tends to give rise to false threat alarms. LeDoux (1986) remarks that such default is very adaptive because a lack of responsiveness to actually existing threat stimuli can be fatal whereas false-positive responding to non-threatening stimuli does not involve any serious harm, especially as it can be modified later on by higher modules:

> The defensive reaction can be aborted once it is determined, on the basis of more detailed perceptual analysis (provided by the way of cortico-amygdala connections), that the threat is not real. Postponement of defense until the cortical sensory systems have analyzed the stimulus, however, could be costly. (LeDoux, 1986, p. 241)

Summarizing these findings, it seems that preattentive processing of potential threat tends to elicit false threat alarms which automatically activate both, physiological fear responses as well as attention directed to the current sensory input (leading to conscious perception and analysis). However, in the intact brain, both of these effects can be modified and extinguished by more discriminative and more elaborated modes of processing.

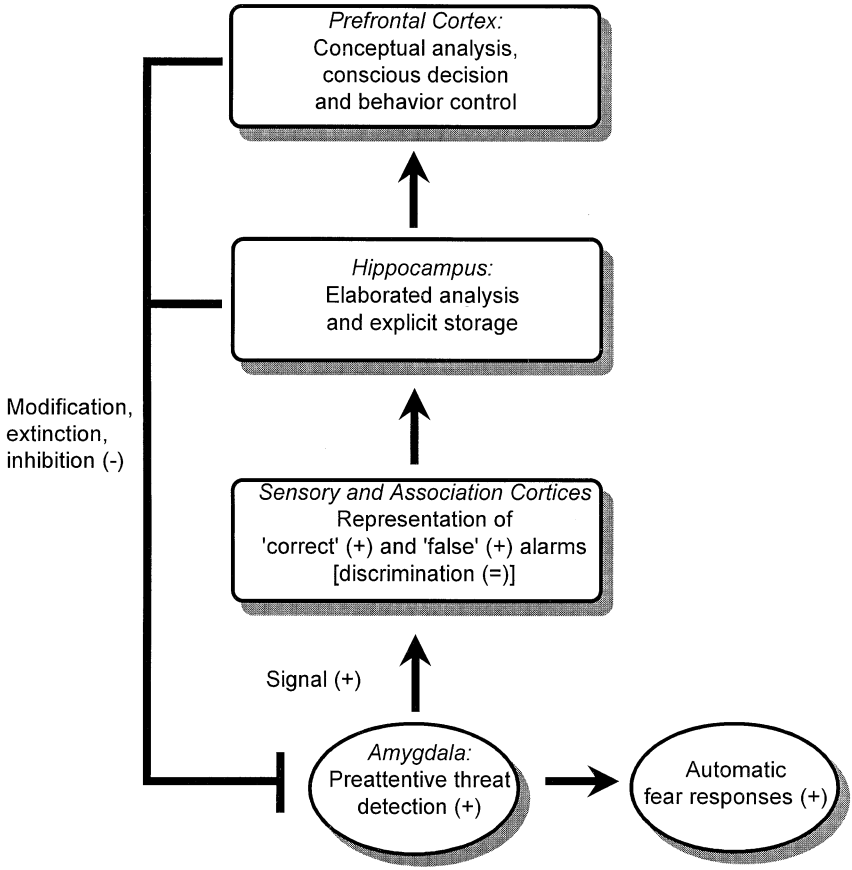

FIG. 1. A MODEL OF PREATTENTIVE DETECTION OF THREAT IN PATIENTS WITH PANIC DISORDER (+ INDICATES ENHANCED FUNCTIONING, − INDICATES REDUCED FUNCTIONING, AND = INDICATES NO OBSERVABLE ABNORMALITY). SEE TEXT FOR DETAILS.

FALSE-ALARM-THEORY OF PANIC DISORDER

The neurobiological perspective outlined above corresponds very well to the recent model of Beck and Clark (1997). Both perspectives suggest that preattentive detection of potential threat is performed by employing a liberal response criterion favoring false-positive responses to potential threat rather than false-negative ones. The mechanism reflects an automatic response-tendency concerning all types of stimuli, not a discriminative process referring to actually threatening stimuli only. However, it can normally be modified by more elaborative and more conceptual modes of processing.

In the following, I will suggest the following theoretical framework which might be called a "false alarm hypothesis of panic disorder" (see Figure 1; cf.

Barlow, 1988): Cognitive and physiological symptoms of panic and pathological states of anxiety arise from the hyperfunctioning of a preattentive alarm system whose structural basis is closely related to the amygdala and its connections to ascending neuromodulatory transmitter systems. The hyperfunction results in an irrational tendency to signal potential threat to the neocortex which is not adequately modified by more elaborated and more strategic modes of processing in patients with panic disorder, and possibly also in patients with generalized anxiety disorder. The conception includes both, an over*re*activity of the amygdala to actually neutral sensory input provided by thamalo-amygdala connections as well as the idea of an intrinsic, spontaneous, non-event-related overactivity of the amygdala when no stimulus is present in the external world that had provoked the response. In the latter case, the disorder would reflect a primary dysfunction of the amygdala, perhaps related to seizure-like processes in the temporal lobe (cf. Adamec, 1990; Dantendorfer et al., 1996; Helfer, Deransart, Marescaux, & Depaulis, 1996). However, both types of dysfunctions account for enhanced false alarm responding.

Correspondingly, inability of the cognitive system to modify these false threat alarms can in two ways be causally related to the malfunctioning of the preattentive detection mode. One possibility is that the preattentive alarm system receives an insufficient quantity or quality of differentiated, modifying (controlling) input from areas that are associated with higher order processing, conceptual analysis, and long-term-storage such as the hippocampus (cf. Dantendorfer et al., 1996; Maren & Fanselow, 1995; Phillips & LeDoux, 1992). The other possibility is that endogenous neural overactivity in the amygdala prevents conscious and strategic processing from being performed efficiently because newly incoming false threat alarms repeatedly require a shift in focal attention so that conscious stimulus processing cannot be developed up to a highly elaborated level.

It is important to note that neither one of my assumptions necessarily implies that the proposed dysfunction is genetically determined. The microstructures of even the adult brain are subject to extensive, experience-dependent structural and functional modifications. Thus, the presumed dysfunction can just as well result from learning and conditioning experiences. In my opinion, to say that a phenomenon is caused by psychological factors can never mean that brain processes are not involved. To the contrary, as many theories of computational neuroscience assume (e.g., see Arbib, 1995), individual experiences and response tendencies are stored in form of specific synaptic strengths and connection patterns, and neuronal computations take place as neurons integrate and respond to specific synaptic input patterns. Each individual cognitive process has its specific neuronal correlate; and psychological concepts are just more abstract descriptions of the underlying neuronal states and processes. Thus, the often found conceptual segregation of cognitive and neurobiological phenomena might simply reflect the fact that we cannot *feel* the neuronal processes underlying our subjective states of experience. We only

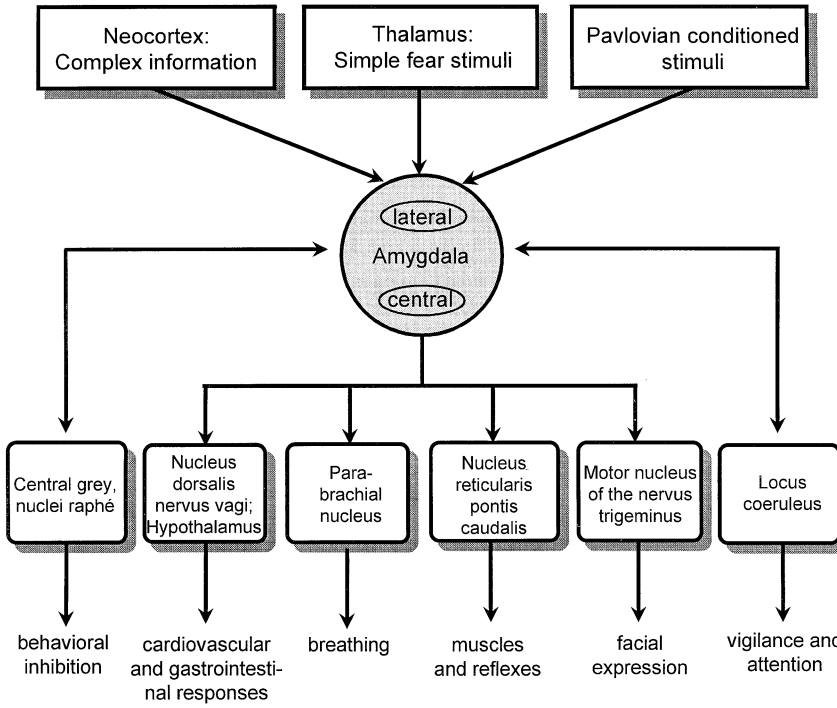

FIG. 2. COGNITIVE AND PHYSIOLOGICAL SYMPTOMS OF ANXIETY ELICITED BY THE AMYGDALA (MODIFIED AFTER DAVIS, 1989).

experience the output of the neuronal computations (Crick & Koch, 1995b). This, however, must not make us to believe that the neuronal processes determining this experience can be ignored when trying to understand how the cognitive system works.

Based on this monistic perspective, numerous cognitive and physiological symptoms which have been observed in anxiety and panic attacks can be explained within a single framework (see Figure 2) without encountering significant contradictions between biological and psychological findings. In the present context, I will focus primarily on the implications of my view for the cognitive (Clark, 1986) and the phychophysiological model (Ehlers, 1989; Ehlers, Margraf, & Roth, 1988) of panic.

Whenever the preattentive alarm system detects potential threat, it triggers physiological responses and activates attentional resources of the cognitive system. Thus, the cognitive system is informed about the presence of potential threat and consequently tries to focus on the triggering stimulus. However, in case of false threat alarms, there is no real danger. Hence, the cognitive system does not find any reasonable explanation for the threat alarms. Simultaneously, it becomes aware of the physiological responses which have also been

activated by the preattentive alarm system. Consequently, the individual registers bodily fear symptoms such as palpitations, feelings of suffocation, dizziness, and so on but "can only guess" (LeDoux, 1986, p. 242), what had caused these sensations. Because there is no actual environmental change which those responses can be meaningfully attributed to, the individual is left with "much room for cognitive interpretations" (LeDoux, 1986, p. 242). Searching for potential threat, the only sensory stimuli the conscious cognitive system can register at this moment are symptoms of autonomic arousal. Consequently, the individual might infer that these physiological symptoms *themselves* might have caused the feelings of anxiety, especially if the preattentive system continues to signal potential threat although no triggering threat event can be identified on a conscious basis. Thus, it is the mere *coincidence* of frequent and intense false threat alarms arriving in the neocortex and in subcortical nuclei of autonomic regulation at the same time that results in cognitive misinterpretations of harmless bodily sensations (Clark, 1986) and in inadequate associations of physical and cognitive changes with threat (Ehlers, 1989, Ehlers, Margraf, & Roth, 1988).

There are other observations on panic disorder which this theory sheds a somewhat new light upon (see Figure 2) although many of these can not be dealt with at length in the present article. First, antidepressant medication affecting ascending monoaminergic transmitter systems as well as unspecific sedatives such as benzodiazepines and alcohol should counteract the effects of the preattentive alarm system (Johnson et al., 1995). Probably, these pharmacological agents will inhibit the formation of synchroneous neural oscillations (Munk et al., 1996) as potential correlates of conscious representations and metarepresentations (Flohr, 1992; Koch & Crick, 1994), and will therefore reduce subjective experience of anxiety in addition to the reduction of physiological responses (Davis, 1989, 1992; see also Graeff, 1994). Second, because the amygdala is also connected with central nuclei of respiratory regulation (Davis, 1989; Graeff, 1994), it becomes evident why groundless respiration maneuvers can occur during panic attacks (Klein, 1993), often in coincidence with intense subjective feelings of threat and catastrophe (Ley, 1992). Third, the fact that there is considerable inter- and intraindividual variability in the phenomenology of panic disorder does not contradict the presumption of a circumscribed dysfunctional process in the brain. The human brain is a highly complex dynamic system characterized by countless forward- and backward-projections (Crick, 1994; Crick & Koch, 1995a) which form reentrant neuronal circuits (Amit, 1995). Thus, small perturbations in the initial conditions can lead to different computational results, at least to some extent. Hence, any functional and dysfunctional process can either be amplified or attenuated depending on the initial conditions of the system. In psychological terms, these different initial conditions can be referred to as actual sensory perceptions; current beliefs, imaginations, and anticipations; past experiences; attentional focus etc. (Clark, 1986; Ehlers, 1989; Ehlers, Margraf, & Roth, 1988; Ehlers,

Margraf, Davies, & Roth, 1988). Nevertheless, it is important to note that all of these cognitive events are implemented on a specific neuronal level and can thus have a direct influence on other neurobiological processes, including the presumed subcortical preattentive threat detection mechanism.

In general, the fundamentals of the theoretical framework presented here correspond well with many other findings dealing with the role of the amygdala in fear production. For example, it has been reported that experimental stimulation of the amygdala during surgical operation leads to experience of intense fear including visceral sensations and unpleasant cognitions and memories (Gloor, 1992). Conversely, lesions or cell death in the amygdala as in Klüver-Bucy (Klüver & Bucy, 1937) and Urbach-Wiethe syndrome (e.g., Cahill, Babinsky, Markowitsch & McGaugh, 1995) lead to a dramatic loss of emotionality which includes the inability to recognize emotional faces (Young, Hellawell, van de Wal, & Johnson, 1996), to remember emotional stories (Cahill et al., 1995), and to avoid stimuli that have previously been frightening (Aggleton, 1992).

To summarize, the conviction that the amygdala is responsible for fear production is well established in the neuroscience literature, suggesting that this region plays a crucial role for understanding pathological anxiety. It is amazing that it has been focused on so rarely in the context of clinical anxiety (but see Grillon, Ameli, Goddard, Woods, & Davis, 1994). Although the present hypothesis is only a first step aimed at the resolution of the apparent contradictions between biological and psychological perspectives, the next issue of primary interest for interdisciplinary research projects could be the question of how and why the amygdala (i.e., the preattentive warning system) might have become oversensitive, predominant, and disinhibited in patients with anxiety disorders.

EMPIRICAL IMPLICATIONS

The two most important empirical implications of the proposed hypothesis are based on the assumption that anxiety reflects an enhanced response-tendency to give rise to false alarm responses, irrespective of the objective valence and the exact features of the stimulus, and that this tendency is insufficiently modified by discriminative and elaborated processing. This assumption has two important implications for empirical predictions. First, when compared to healthy controls, patients with panic disorder should display an enhanced response-tendency (response-bias) in cognitive tasks requiring discrimination of threat and neutral stimuli. Because this bias is presumed to result from inaccurate preattentive processes, it should be independent of conscious identification and discrimination performance. Second, patients with panic disorder should display lower performance (i.e., sensitivity) scores than healthy controls in cognitive tasks which tap controlled and elaborated information processing (such as explicit memory tasks). Furthermore, relative to

healthy controls, patients should maintain their preattentively initiated response-bias quite rigidly across repeated presentations even when they are given the chance to process the stimuli consciously and elaboratedly. All these effects should be observed irrespective of the objective valence of the experimental stimuli.

However, these two predictions can be tested only if threat and neutral stimuli are used that are not specifically related to the symptomatology of the disorder, and only if signal detection analyses are applied to the data. No study has been published so far that meets these two criteria (but see Windmann & Krüger, in press).

Meanwhile, there are some other findings about panic disorder that the present hypothesis can integrate. First, heartbeat perception in patients with panic disorder as assessed by the mental tracking task has been found to differ from controls. In this task, subjects are instructed to count their heartbeats during a given time interval of about 20 to 45 seconds without taking their pulse. Patients with panic disorder have been shown to count more heartbeats than healthy controls. However, this effect was only observed when subjects were given the standard instruction asking them to count "all the heartbeats they felt in their body" (Ehlers, Breuer, Dohn, & Fiegenbaum, 1995, p. 71). Patients did not differ from controls when both groups were instructed to "only count the heartbeats that they had really felt in their body" and to "refrain from counting any heartbeats about which they were not sure and which would represent an estimated heartbeat rather than one really felt" (Ehlers et al., 1995, p. 71). Thus, these findings suggest that in the standard variant of the task, patients had adopted a more liberal response criterion than controls, allowing them to include heartbeats in their counting that represent estimated cardiac sensations rather than real heartbeat sensations. This tendency actually reflects a bias to risk more false-positive responses (leading to higher hit rates in the present context). It was obviously countered by the more strict instruction requiring patients to activate a more accurate and more discriminative processing mode. This interpretation is also able to explain why patients with panic disorder have never been able to show enhanced heartbeat perception in heartbeat discrimination procedures (Asmundson, Sandler, Wilson, & Norton, 1993; Barsky, Cleary, Sarnie, & Ruskin, 1994; Schonecke, 1993; Windmann, 1997). Performance on these tasks is analyzed by means of signal detection theory in order to separate sensitivity measures from response-biases.

Second, as mentioned above, the assumption that patients with panic disorder tend to process a given information less elaborately and less strategically as indicated by lower explicit memory performance seems to correspond with findings obtained by neuroimaging methods showing regional cerebral dysfunctions in hippocampal and temporal areas in patients with panic disorder (e.g., Friedman, 1992; George & Ballenger, 1992; Lucas, Telch, & Bigler, 1991; McNally, 1994, pp. 77–78). These areas are strongly believed to be involved in

higher-order processing of visual and auditory stimuli and in long-term memory (Eichenbaum et al., 1992; Squire, 1992). However, more specific findings with a primary focus on preattentive threat processing are required at this point. In general, much more interdisciplinary work is needed to test the specific assumptions of the present hypothesis.

PRACTICAL IMPLICATIONS

Finally, I would like to draw some conlcusions with respect to practical issues. In contrast to a commonly held belief I think that a neurobiologically founded theory on panic and anxiety need not imply that panic and anxiety disorders can be treated most efficiently by means of psychopharmacological medication. It is clear that pharmacological agents can be very helpful especially in cases of acute depression and strong avoidance behavior where it is often difficult to gain psychological access to the patients because they are relatively passive, demotivated, and immobile. However, because psychoactive medication always operates on a systemic basis in the brain, it will almost inevitably produce negative side-effects. Even though all types of abnormalities in behavior, physiology, and subjective experience have their specific correlates in brain structures or neuronal processes, in most cases there will be no chance to selectively take control over just these dysfunctions by means of pharmacological agents applied to the whole brain. As mentioned above, the microstructure of the brain is long known to be enormously plastic and modifiable by learning (Kandel, 1991; Rosenzweig & Leiman, 1989, Chapters 17 and 18, p. 750ff), especially when coincident or synchronous neural events act as specific triggers for synaptic modifications (Markram, Lubke, Frotscher, & Sakmann, 1997; Singer, 1993, 1994). These changes take place automatically when the neuronal connections are being used more frequently. Likewise, synaptic efficiency is being down-regulated when neural connections are used less frequently than before (Artola & Singer, 1993) or receive asynchronous input (Markram et al., 1997). Due to these learning principles, neural connections underlying dysfunctional fear responses and irrational experience of anxiety will be restructured and reorganized by enhanced use of different connections representing fear-incompatible behavior, experience, and imagination (as has been assumed by Foa & Kozak, 1986). Thus, even though I assume that antidepressants and benzodiazepines are effective in the overall suppression and sometimes even in the complete depletion of pathological anxiety, I conclude that the presumed hyperactive functioning of the preattentive alarm system can be modified more specifically and more effectively by means of cognitive behavioral therapy, at least in the long run.

CONCLUSIONS

In the present article I presented a monistic view on the etiology of panic disorder which might also be applicable to more generalized forms of pathological anxiety. The theory integrates neurobiological and psychological perspectives because it reconsiders how panic-related cognitions and symptoms

might be instaniated at the neural level. I assume that many psychological theories on panic and anxiety can be made stronger, more specific, and more verifiable when being formulated in compatibility with neurobiological findings. Conversely, neurobiological theories of panic and anxiety would be more convincing if they were not only making simple correlative statements between the disorder and certain biochemical agents or morphological features of neuronal cells. Instead, they should be able to explain how and why psychological symptoms such as cognitive misinterpretations can emerge from specific neurobiological dysfunctions or processes. Thus, I believe that multidisciplinary reflections on information processing in panic and anxiety can establish a more comprehensive view of the disorders without being restricted to a purely materialistic or a purely mentalistic view.

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