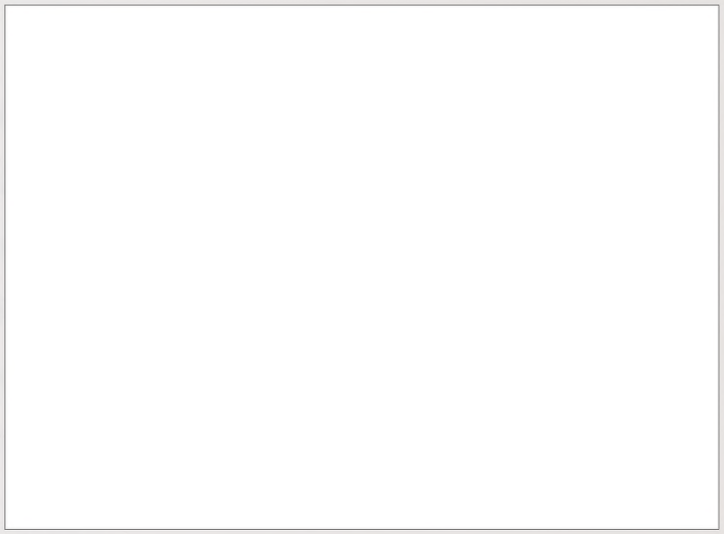
MEMORY FUNCTIONING IN PANIC DISORDER:
A NEUROPSYCHOLOGICAL INVESTIGATION



MEMORY FUNCTIONING IN PANIC DISORDER: A NEUROPSYCHOLOGICAL INVESTIGATION

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This dissertation is dedicated to my parents,

John Andrew Lucas and Maria Catapano Lucas,

whose love, support, and encouragement proved steadfast and invaluable.

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Recent psychological and neurological studies of patients with anxiety disorders suggest that memory functioning may be impaired in patients with panic disorder. The suggested means by which memory may be impaired, however, differs among the various areas of study. Some studies have reported attentional disturbances among patients with anxiety disorders, thus suggesting that memory may be impaired secondary to distractibility. Neuroimaging studies, on the other hand, have reported abnormalities in temporal lobe structures of patients with panic disorder who panic in response to sodium lactate infusion, suggesting that memory may be impaired secondary to temporal lobe dysfunction. Moreover, abnormalities reported by the majority of imaging studies have been lateralized to the right temporal lobe, suggesting that memory for visual material may be more impaired than memory for verbal material.

Twenty-five subjects with a primary diagnosis of panic disorder were administered a test battery consisting of neuropsychological measures of memory functioning, standard measures of intellectual functioning, and self-report measures of emotional functioning. Twenty-five normal subjects and 25 subjects with a primary diagnosis of major depression served as controls. Groups were matched for age, education, and gender. Multivariate analyses of memory test scores revealed that subjects with panic disorder performed significantly worse than normal controls on measures of visual learning, and significantly worse than both normal and depressed controls on measures of visual recall. Panic disorder subjects did not differ from normal controls on measures of verbal learning, verbal recall, or attentional capacity. Panic disorder subjects performed significantly better than depressed subjects on measures of verbal recall, but were no different on measures of verbal learning or attentional capacity. No relationship was found between test performance and the self-reported tendency of patients with panic disorder to focus attention on internal bodily sensations or concerns. Similarly, no relationship was found between memory test performance and severity of panic disorder; however, a significant negative relationship was found between attentional capacity and severity of illness. Results provide evidence for a neuropsychological correlate to panic disorder and are discussed within the context of recent psychological and neurological models of panic.

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Introduction

The phenomenon of panic has been recognized at least as far back as ancient Greece (Barlow, 1988). According to Greek mythology, the god Pan lived in the countryside and ruled over the fields, forests, wildlife, shepherds, and their flocks. Unlike most Greek gods, Pan was short and ugly, with the legs, ears and horns of a goat. Like a shepherd, he rested during the heat of the day, often taking naps in small mountain caves, or shrubbery near the roadside. Pan did not like to be disturbed from his rest, and if an unsuspecting traveller happened to awaken him, the god would display his anger by letting out an intense scream; it was rumored that Pan's scream could be so frightening, that one could actually be scared to death by it. People throughout the Greek countryside would often attribute startling or mysterious sounds to him, and it was believed that not even the gods themselves were immune to the terror invoked by his screams. Hence, the experience of sudden, overwhelming fear became known as "panic" (Barlow, 1988).

Although Pan has long since faded into myth, the phenomenon of panic remains today, and is experienced by millions of people on a daily basis (Barlow, 1988). Recently, the importance of understanding panic attacks and panic disorder has been underscored by a report from the National Institute of Mental Health Epidemiologic Catchment Area (ECA) Program survey, which revealed that anxiety disorders are currently the most prevalent psychiatric illnesses in the United States (Karno et al., 1987). Panic is common among all anxiety disorders, as well as other psychiatric conditions (Barlow et al., 1985); therefore, greater understanding of the nature, etiology,

and maintenance of panic may yield a greater understanding of these and other psychiatric conditions.

In recent years, phenomena associated with panic attacks and panic disorder have been studied with increasing intensity and from increasingly diverse perspectives. The following study represents an attempt to examine hypotheses regarding memory functioning in panic disorder derived from two diverse perspectives. Specifically, hypotheses regarding the role of attentional factors and brain mechanisms with regards to memory functioning in panic disorder are explored. To that end, a brief background of the nature of panic disorder will be presented first, followed by reviews of cognitive and neuropsychological models of panic disorder. A study of memory functioning in patients with panic disorder will then be presented, followed by discussion of the results and the implications of those results on our current understanding of panic disorder.

CHAPTER 1

The Nature and History of Panic Disorder

Although recognized for several centuries, panic symptoms have travelled through history under a variety of diagnostic labels. The following chapter examines the nosological history of panic, as well as the current diagnostic criteria, prevalence, and phenomenology of panic disorder.

Nosological History

Throughout much of medical history, panic was described as a symptom of "hysteria," a disorder characterized by chronic, recurrent physical complaints for which there is no apparent physical cause (Sheehan, 1982). Over the centuries, attempts were made to organize the various manifestations of hysteria into separate categories, based on distinguishing symptoms or etiological theories. In the late 19th and early 20th centuries, disorders such as "neurasthenia," "irritable heart," and "effort syndrome" were described as forms of hysteria in which the central features included nervousness and unexplained physiological arousal (Barlow, 1988; Sheehan & Sheehan, 1982). At approximately the same time, Freud attempted to distinguish "anxiety" from "hysteria;" he proposed that although both were caused by frustrated or incomplete discharge of sexual energy, anxiety was a purely physiological reaction, while hysteria was a purely psychological response (Thompson, 1950).

Later, Freud revised his theory and allotted a prominent position to the role of anxiety in the development of psychological disorders. According to Freud, anxiety could be characterized as either "normal" or "neurotic." Normal anxiety was considered

a natural reaction provoked by an objective danger, and was thus of little interest to the exploration of emotional disorders. Neurotic anxiety, on the other hand, was believed to signal that forces within the individual were threatening the sense of self (i. e., the Ego) and its relation to the external world. If the strength of these forces began to overwhelm the Ego, the affect associated with them was believed to detach from its source and either attach itself to an otherwise nonthreatening object-representation or idea, or remain in a "free-floating" state. While the former manifested as phobic or obsessional symptoms, respectively, the latter manifested as somatic excitation, called "anxiety-neurosis" (Thompson, 1950). Anxiety-neurosis could take the form of "expectant" anxiety or "anxiety attacks," the latter of which appears to correspond to the modern concept of panic (Freud, 1917, cited in Barlow, 1988).

Although Freud wrote specifically of "panic," he argued that the term should be reserved to describe a collective phenomenon, rather than a disorder exhibited by an individual. In a paper entitled: "Two artificial groups: The church and the army," he states:

> It is not to be expected that the usage of the word "panic" should be clearly and unambiguously determined. Sometimes it is used to describe any collective fear, sometimes even fear in an individual when it exceeds all bounds, and often the name seems to be reserved for cases in which the outbreak of fear is not warranted by the occasion. Fear in an individual is provoked either by the greatness of a danger or by the cessation of emotional ties (libidinal cathexes); the latter is the case of neurotic fear or anxiety. In just the same way, panic arises either owing to an increase of the *common* danger or owing to the disappearance of emotional ties *which holds the group together*. The latter case is analogous to that of neurotic anxiety (Freud, 1920, cited in Sims, 1988, p. 6, emphasis added).

It has only been within recent years that panic has been considered a nosological entity distinct from anxiety-neurosis. In 1967, Pitts and McClure reported that infusion with sodium lactate provoked panic episodes in patients who suffered from spontaneous anxiety attacks, but did not provoke such episodes in normal controls. Moreover, Klein

and his colleagues found that patients with discrete episodes of panic responded well to treatment with imipramine (a tricyclic antidepressant) more so than with benzodiazepine, the treatment of choice for other anxiety disorders (Klein & Fink, 1962; Klein, Zitrin, & Woerner, 1978; Zitrin, Klein, & Woerner, 1978). As a result of these and similar studies, the American Psychiatric Association (APA) introduced the diagnosis of "Panic Disorder" in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM III, APA, 1980).

According to DSM III, the essential feature of panic disorder was "the sudden onset of intense apprehension, fear or terror, often associated with feelings of impending doom" (APA, 1980, p. 230). DSM III diagnostic criteria for panic disorder are presented in Table 1.1. In order for a diagnosis to be made, it was necessary for a patient to report having at least three discrete episodes of apprehension or fear (i. e., panic attacks) within a three-week period, with each episode characterized by at least four of 12 symptoms. Eleven of the symptoms reflected physiological arousal (e. g., palpitations, trembling, sweating), while the remaining symptom reflected a cognitive appraisal (i. e., "fear of dying, going crazy, or doing something uncontrolled during an attack;" APA, 1980, p. 232).

Despite recognition of the specific nature of panic, DSM III applied a hierarchical rule to the diagnosis of panic disorder, excluding it if other mental disorders were present. Moreover, if phobic avoidance was present, the diagnosis of panic disorder was deferred in favor of a diagnosis of agoraphobia with panic attacks. With the advent of the revised third edition of the DSM (DSM III-R; APA, 1987), however, important changes were implemented in the diagnosis of panic disorder. These are discussed in the following section.

Table 1.1. DSM III Diagnostic Criteria for Panic Disorder.

A. At least three panic attacks within a three-week period in circumstances other than during marked physical exertion or in a life-threatening situation. The attacks are not precipitated by exposure to a circumscribed phobic stimulus.

B. Panic attacks are manifested by discrete periods of apprehension or fear, and at least four of the following symptoms appear during each attack:

(1) dyspnea
(2) palpitations
(3) chest pain or discomfort
(4) choking or smothering sensations
(5) dizziness, vertigo, or unsteady feelings
(6) feelings of unreality
(7) paresthesias (tingling in hands or feet)
(8) hot and cold flashes
(9) sweating
(10) faintness
(11) trembling or shaking
(12) fear of dying, going crazy, or doing something uncontrolled during an attack

C. Not due to a physical disorder or another mental disorder such as Major Depression, Somatization Disorder, or Schizophrenia.

D. The disorder is not associated with Agoraphobia.

Current Diagnostic Criteria for Panic Disorder

DSM III-R criteria for the diagnosis of panic disorder are presented in Table 1. 2. Although there are many similarities between DSM III and DSM III-R criteria, important differences also exist. The concept of "sudden onset," which appears in the DSM III definition of a panic attack, is defined more clearly in DSM III-R. According to the latter, at least one attack must be unexpected (i. e., must not occur in a situation that always provokes anxiety), and must occur in situations other than when the individual is the focus of other's attention. DSM III-R further specifies that, during at least one attack, four or more symptoms must develop suddenly and increase in intensity within 10 minutes after the first symptom is noticed. These criteria help distinguish individuals

Table 1.2. DSM III-R Diagnostic Criteria for Panic Disorder.

A. At some time during the disturbance, one or more panic attacks (discrete periods of intense fear or discomfort) have occurred that were (1) unexpected and (2) not triggered by situations in which the person was the focus of others' attention.

B. Either four attacks, as defined by (A), have occurred within a four week period, or one or more attacks have been followed by a period of at least one month of persistent fear of having another attack.

C. At least four of the following symptoms developed during at least one of the attacks:

(1) shortness of breath (dyspnea) or smothering sensations
(2) dizziness, unsteady feelings, or faintness
(3) palpitations or accelerated heart rate (tachycardia)
(4) trembling or shaking
(5) sweating
(6) choking
(7) nausea or abdominal distress
(8) depersonalization or derealization
(9) numbness or tingling sensations (paresthesias)
(10) flushes (hot flashes) or chills
(11) chest pain or discomfort
(12) fear of dying
(13) fear of going crazy or of doing something uncontrolled

D. During at least some of the attacks, at least four symptoms developed suddenly and increased in intensity within 10 minutes of the first symptom noticed in the attack.

E. It cannot be established that an organic factor initiated and maintained the disturbance (e.g., Amphetamine Intoxication , Hyperthyroidism, etc.).

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who suffer from generalized anxiety states from patients who experience discrete panic episodes.

The symptoms associated with panic are essentially the same in DSM III and DSM III-R; however, one new physiological symptom was added ("nausea or abdominal distress"), two DSM III physiological symptoms ("dizziness" and "faintness") were combined into one DSM III-R symptom, and the one DSM III cognitive symptom was separated into two DSM III-R symptoms ("fear of dying" and "fear of going crazy or of doing something uncontrolled"). These changes were implemented to allow more precise

identification of the physical symptoms and cognitive experiences associated with panic episodes (Barlow, 1988).

One of the most significant differences between DSM III and DSM III-R criteria for panic disorder is the required frequency of panic recurrence. As stated earlier, DSM III required at least three panic attacks within a three week period, with each attack accompanied by at least four symptoms. DSM III-R, however, allows one of two different panic frequencies to be met: either 1) four attacks within a four week period, or 2) one or more attacks followed by at least one month of persistent worry or fear of having another attack. This "worry" option, as well as the division of the one cognitive symptom into two, reflects the growing recognition of recent theoretical formulations, which have placed great importance on the role of cognitive appraisals and "anxious apprehension" in the development and maintenance of panic disorder (cf. Barlow, 1988). A more detailed discussion of this is presented in Chapter 2 (See pp. 32-34).

The final major distinction between DSM III and DSM III-R criteria is the elimination of the exclusion criterion employed by the DSM III hierarchical rule. According to DSM III-R, a diagnosis of panic disorder is excluded only if the attacks are initiated and maintained by organic factors, such as amphetamine intoxication or hyperthyroidism. One important consequence of this change is the alteration of the relationship between panic disorder and agoraphobia. DSM III-R notes that "in the majority of cases of 'agoraphobia' that are seen in clinical settings, the phobic symptoms are a complication of Panic Disorder" (APA, 1987, p. 422). Consequently, DSM III-R classifies varying degrees of phobic avoidance as subtypes of panic disorder. Further discussion of the relationship between panic disorder and phobic avoidance is presented in a later section (p. 15).

Prevalence

Epidemiological studies investigating the prevalence of panic disorder have recently appeared in the literature; unfortunately, due to the relatively recent arrival of DSM III-R, most published studies employed DSM III criteria to determine prevalence rates for panic disorder. As part of the National Institute of Mental Health Epidemiologic Catchment Area (ECA) Program, approximately 17,000 residents in five U. S. cities (Los Angeles, New Haven, Baltimore, Raleigh-Durham, and St. Louis) were interviewed with the Diagnostic Interview Schedule (DIS; Robins, Helzer, Croughan, Williams, & Spitzer, 1981). Based on data from this survey, the lifetime prevalence rate of DSM III-defined Panic Disorder in the United States was estimated at approximately 1.5% (Karno et al., 1987). Using the German Version II of the DIS (Wittchen & Rupp, 1981), the Munich Follow-up Study (MFS) reported a 2.4% lifetime prevalence of panic disorder in West Germany (Wittchen, 1986). The difference between the ECA and MFS prevalence rates for panic disorder is attributable to differences in the age ranges studied; when comparable age groups were examined, no significant difference was found between the two studies (Wittchen, 1986).

Although neither the ECA nor the MFS reported employing DSM III exclusion criteria in calculating prevalence rates, both studies classified panic disorder and agoraphobia as separate disorders. Consequently, the prevalence rates reported by these studies do not include individuals meeting what would currently be diagnosed as panic disorder with agoraphobia. Combining the rates reported for panic disorder and agoraphobia, which is consistent with DSM III-R criteria, yields lifetime panic disorder

prevalence estimates of 5.4% and 8.1% for the ECA and MFS, respectively (Robins et al., 1984; Wittchen, 1986).

To date, only one published study has examined the prevalence of panic attacks and panic disorder using DSM III-R criteria. Telch, Lucas, and Nelson (1989) surveyed a large sample of college students using a questionnaire designed to obtain information relevant for making DSM III and DSM III-R diagnoses of panic disorder (exclusion criteria were not employed in determining DSM III-defined panic disorder). The survey revealed a prevalence rate of approximately 2.4% for DSM III-defined panic disorder. This rate is considerably lower than the rates derived from the ECA and MFS (i. e., 5.4% and 8.1%), and likely due to the younger age and higher education of the sample studied.

Surprisingly, an identical lifetime prevalence rate of approximately 2.4% was obtained using DSM III-R criteria. The authors noted, however, that a significant interaction was found between gender and diagnostic criteria (Telch et al., 1989). When DSM III criteria were used, men and women did not differ significantly in their reported prevalence of panic disorder, although a nonsignificant trend for higher prevalence among women was evident. When DSM III-R criteria were used, an opposite pattern emerged, with a significantly higher proportion of men meeting criteria. The authors reported that the observed gender difference was likely due to the differences in frequency criteria. While women reported more discrete panic episodes than men, men were more likely to report being worried about panic recurrence. Thus, while the addition of the worry criterion in DSM III-R likely allowed a greater number of men to fulfill diagnostic criteria, the more stringent requirement of four discrete panic episodes

in a four week period (compared to three episodes in three weeks) may have reduced the number of women who met diagnostic criteria.

Recent evidence suggests that panic episodes are common in all anxiety disorders, as well as among other psychiatric disorders. Barlow et al. (1985) interviewed patients with various DSM III anxiety disorder diagnoses, and found that over 83% reported a history of at least one unexpected panic attack. Based on information gathered from the Los Angeles site of the ECA study, Boyd (1986) estimated that 15-25% of patients who met criteria for a major affective disorder, and 63% of patients meeting criteria for schizophrenia, reported at least one unexpected panic attack within the six-month period prior to their interview.

Surprisingly, a large number of otherwise healthy adults also report occasional panic attacks. In two separate studies, Norton and his colleagues found that approximately 35% of "presumably normal" young adults reported having experienced at least one panic attack in the year prior to the survey (Norton, Harrison, Hauch, & Rhodes, 1985; Norton, Doward, & Cox, 1986). This figure, however, includes panic attacks in common anxiety-provoking situations; the proportion of subjects reporting at least one unexpected panic attack within the previous year dropped to approximately 10%, a figure commensurate with the 9-14% life-time prevalence rates for unexpected panic reported by other studies (Salge, Beck, & Logan, 1988; Telch et al., 1989; Wittchen, 1986).

The Phenomenology of Panic Disorder

Although specific criteria for panic disorder have changed over time, the general definition of panic has remained essentially the same. According to Klein (1981)

three major components of panic disorder may be distinguished: the panic attack, anticipatory anxiety, and phobic avoidance. In addition, other features commonly associated with panic, including depression and cognitive dysfunction, have been suggested by the literature. Each of these will be discussed briefly below.

The Panic Attack

A panic attack is an innate, phylogenetic mechanism, that serves to protect the organism in the event of danger or threat by preparing it to respond with one of two actions: fight off the threat or try to escape from it (i. e., fight or flight; Groves & Schlesinger, 1982). Whichever course is taken, the physiological systems necessary to carry out the desired action must be engaged, and energy supplies must be diverted from nonessential systems to essential ones. Moreover, once the danger is gone, the body must return to a baseline level of functioning and conserve energy. These activities are controlled by a division of the nervous system called the autonomic nervous system.

The autonomic nervous system (ANS) has body-wide distribution, and exerts prime control in maintaining homeostasis (i.e., the constancy of the internal environment). Projections from the ANS innervate organs of many different bodily systems, including the circulatory, respiratory, excretory, endocrine, and exocrine systems. This enables the ANS to regulate the composition, volume, temperature, and distribution of bodily fluids. The ANS is comprised of two principal subdivisions: the sympathetic and the parasympathetic nervous systems. Many of the organs innervated by the ANS receive inputs from both the sympathetic and parasympathetic components, which operate in an antagonistic fashion. Typically, if the signals sent along the fibers of one system stimulate the organ to begin or accelerate activity, the impulses sent along the

fibers of the other system will stop or reduce activity. This dual innervation allows for the fine degree of control necessary to accomplish homeostatic regulation.

Sympathetic Nervous System (SNS). The sympathetic division of the ANS is responsible for preparing the body for action. It acts upon all target organs at once, thus being quick and multifaceted in its presentation. Sympathetic activation causes dilation of the blood vessels in the skeletal muscles, and constriction of the blood vessels in the skin, mucosa, and abdominal viscera. Heart rate increases, as does the force of contraction in cardiac muscle. The bronchioles in the lungs dilate and the ciliary muscle of the eye relaxes, causing the pupils to dilate. Sweat glands are stimulated, while salivation and gastrointestinal functioning are inhibited. The medulla of the adrenal glands is activated, causing epinephrine to be released into the blood. The epinephrine reinforces the increased cardiac output, and causes stored glycogen and fat to be broken down into glucose and free fatty acids.

Functionally, dilation of the bronchioles in the lungs improves oxygen delivery to the blood. The release of epinephrine makes large amounts of energy (i.e., glucose and fatty acids) available for metabolism. Increased cardiac output and dilation of blood vessels in the skeletal muscles increase the amount of blood available to the large muscle groups, ensuring quick delivery of energy and removal of waste products. Constriction of peripheral and nonessential blood vessels in the skin and viscera increases arterial blood pressure, ensuring delivery of blood to the vital organs, including the brain, heart, and lungs. Stimulation of the sweat glands promotes water evaporation, thus cooling the body. Dilation of the pupils aids in the detection of visual stimuli, thereby increasing vigilance to possible danger in the environment.

Parasympathetic Nervous System (PNS). The major role of the PNS is to conserve energy and to promote vegetative functioning in the body; thus, it is opposed to the functions of the SNS. In almost all instances, the PNS serves to counteract the effects of sympathetic arousal. Parasympathetic activation decreases heart rate, dilates blood vessels in the viscera, stimulates gastrointestinal functioning, contracts the bronchioles in the lungs, and constricts the pupils. It cannot, however, counter the effects of epinephrine which has been released in the bloodstream. Consequently, an increased level of physiological arousal (e. g., increased heart rate) is usually experienced even after activity in the SNS has ceased.

Anticipatory Anxiety

Panic is a natural, physiological response; consequently, psychologists who study panic disorder have focused less on the attacks themselves and more on why these attacks are triggered in the absence of objective danger. In addition to the sensations associated with sympathetic arousal (e. g., palpitations, sweating), patients with panic disorder often experience varying degrees of nervousness between attacks. Rather than returning to a baseline level of arousal after an attack, patients with panic disorder remain at a higher level of tonic arousal. In addition, they report fears of having another panic episode, a phenomenon known as anticipatory anxiety (Barlow, 1988; Klein, 1981). Recent theoretical formulations view this fear, as well as a related phenomenon known as "anxious apprehension," as crucial to the development of panic disorder (Barlow, 1988). This will be discussed in greater detail in the next chapter (See p. 32).

Phobic Avoidance

Phobic avoidance, or agoraphobia, is commonly associated with panic disorder. It is described in DSM III-R as a "fear of being in places or situations from which escape might be difficult (or embarrassing) or in which help might not be available in the event of a panic attack" (APA, 1987, p. 238). Because of this fear, individuals either avoid or severely limit their activities. Considerable research has been conducted on the relationship between panic and agoraphobia, and several hypotheses regarding this relationship have been proposed.

Several retrospective studies have yielded a temporal relationship between the perceived onset of panic and agoraphobia. This has led to the theory that agoraphobia is the second stage in a two-stage illness, with the first stage being the development of panic disorder. Garvey and Tuason (1984) noted that none of the 12 subjects in their study of patients with agoraphobia with panic attacks reported the occurrence of agoraphobic symptomatology prior to their first panic attack. Similarly, 31 of 32 agoraphobics studied by Uhde et al. (1985) reported that they had developed their phobic avoidance after the onset of their first panic. Moreover, Thyer and Himle (1985) reported that 79% of the patients who attended an outpatient self-help group for agoraphobia endorsed the statement "My panics caused my agoraphobia." These data, however, presuppose the accuracy of patient self-report and the ability of subjects to determine the etiology of their own psychiatric condition. More importantly, the two-stage hypothesis does not account for the considerable proportion of individuals in clinical and nonclinical populations who report recurrent panic, but do <u>not</u> develop phobic avoidance (Barlow et al., 1985; Craske, Sanderson, & Barlow, 1987; Telch,

Brouillard, Telch, Agras, & Taylor, 1989). Consequently, this theory has not been widely accepted.

A second hypothesis regarding the relationship between panic disorder and phobic avoidance posits that agoraphobia represents a more severe variant of panic disorder. Family studies of patients with panic disorder with and without agoraphobia provide evidence consistent with this hypothesis (e. g., Noyes et al., 1986; Noyes, Clancy, & Garvey, 1987); however, studies examining correlates to panic severity have been less supportive. Theoretically, if agoraphobia was a more severe variant of panic disorder, patients with phobic avoidance should exhibit greater panic severity than patients without avoidance behavior. No differences have been found, however, between panic disorder patients with or without agoraphobia on several measures of panic severity, including panic frequency, intensity of attacks, or number of symptoms experienced (Rapee & Murrell, 1988; Telch et al., 1989).

Recently models proposing that cognitive factors play an important role in the development and/or maintenance of phobic avoidance have been advanced (e. g., Beck, 1988). Telch et al. (1989) examined the relationship between cognitive appraisal and phobic avoidance among panic disorder subjects with and without agoraphobia and found that, although groups did not differ on measures of panic symptoms, frequency, or severity, patients with phobic avoidance reported more dysfunctional panic-related appraisals (e. g., anticipation of panic, perceived consequences of panic, and perceived self-efficacy of coping with panic) than patients without phobic avoidance. Continued research, however, is necessary to better understand the nature of phobic avoidance.

Depression

There is also much controversy over the nature of the relationship between panic and depression. Some have suggested that there may be a genetic link between panic disorder and depression (e. g., Leckman, Weissman, Merikangas, Pauls, & Prusoff, 1983). Others, however, have argued that panic disorder is a familial disease that is **not** associated with increased familial risk of depression. (e. g., Crowe, Noyes, Pauls, & Slymen, 1983; Moran & Andrews, 1985; Torgersen, 1983). The clinical evidence of overlap between the disorders, however, is compelling. Research has indicated that as many as 70% of patients with panic disorder report depressive symptoms (Uhde et al., 1985; Cloninger, Martin, Clayton, & Guze, 1981). Moreover, a study of 481 patients with panic disorder and agoraphobia found that 31% of the sample met criteria for a major depressive episode which developed after the onset of panic (Lesser et al., 1988).

It is not surprising that patients with panic disorder develop depressive symptomatology. Panic disorder is characterized by attacks that, in the patient's experience, occur without warning. Individuals who suffer from panic disorder over a prolonged period are therefore likely to perceive having little or no control over the attacks. This may cause feelings of hopelessness about attaining highly valued goals and, in turn, lead to feelings of low self-worth and depression (Alloy, Abramson, Metalsky, & Hartlage, 1988). The development of panic-related avoidance can further reinforce depressive cognitions by isolating the patient from interpersonal contact and reducing the number of pleasurable activities available to the patient. This is supported by the finding that panic disorder patients with phobic avoidance score significantly higher on the Beck Depression Inventory than patients without agoraphobia (Telch et al., 1989).

Memory Dysfunction

Although not studied directly, both psychological and neurobiological studies of anxiety suggest that memory functioning may be impaired in patients with panic disorder. Studies suggest that patients with anxiety disorders may process information differently from nonanxious individuals, and may attend selectively to threat-related stimuli at the expense of nonthreat-related material, thus reducing cognitive efficiency. Moreover, studies of the possible neurological substrates of anxiety and panic have implicated brain regions essential to memory functioning, suggesting that memory may be compromised in patients with panic disorder. The following chapter reviews the literature examining information-processing in patients with anxiety disorders. A review of the literature on the neurological substrates of anxiety is presented in Chapter 3.

CHAPTER 2

Mood and Memory: Information Processing in Panic Disorder

Psychologists first began to investigate the relationship between mood and memory in the early 20th century. The earliest studies typically reported that pleasant autobiographical events were recalled better than unpleasant experiences (e.g., Colgrove, 1899), that the speed of associations to positively-toned words was faster than negatively-toned words (e.g., Smith, 1921; Tolman & Johnson, 1918; Washburn, Giang, Ives, & Pollock, 1925), and that learning and recall of pleasant words was superior to that of unpleasant or neutral words (Bunch & Wientge, 1933; Silverman & Cason, 1934; Stagner, 1933; Tait, 1913; Thomson, 1930; Tolman, 1917).

The majority of early investigations studied normal subjects and examined mood as a property of test stimuli (i. e., positive vs. negative words). Later investigations, however, treated mood as a subject-variable and attempted to evaluate and manipulate it as part of the experimental design. In one of the first studies of this type, Postman and Brown (1952) asked subjects to view a series of slides containing various symbols, and to name all the symbols they could detect. Before each trial, subjects were asked to predict their performance level, and were later provided false feedback in order to create two experimental groups: one receiving feedback that frequently exceeded their expectations, and the other receiving feedback that fell short of their expectations. Immediately following experimental manipulation, subjects viewed words tachistoscopically, half of which were related to success and failure, half of which were neutral. Subjects evidenced a decreased recognition threshold for words commensurate with their experimental condition, which the authors suggested reflected an information-processing bias in favor of mood-congruent material.

The Network Theory of Affect

In order to explain the phenomenon of mood-congruent information-processing bias, Bower (1981) proposed the Network Theory of Affect, a model derived largely from Quillan's (1968, 1969) theories of the organization of information in semantic memory. According to Quillan (1968, 1969), information is represented in memory by combinations of three types of structures: units, properties, and pointers. Units represent objects, events, or concepts, and are analogous to nouns or noun-phrases in grammar. Properties are the descriptors of the unit, and act much like adjectives, adverbs, or predicates. Units and properties are considered to be places or "nodes" in memory, and are linked together by pointers, thus creating an enormous, interconnected network of related concepts (See Figure 2. 1).

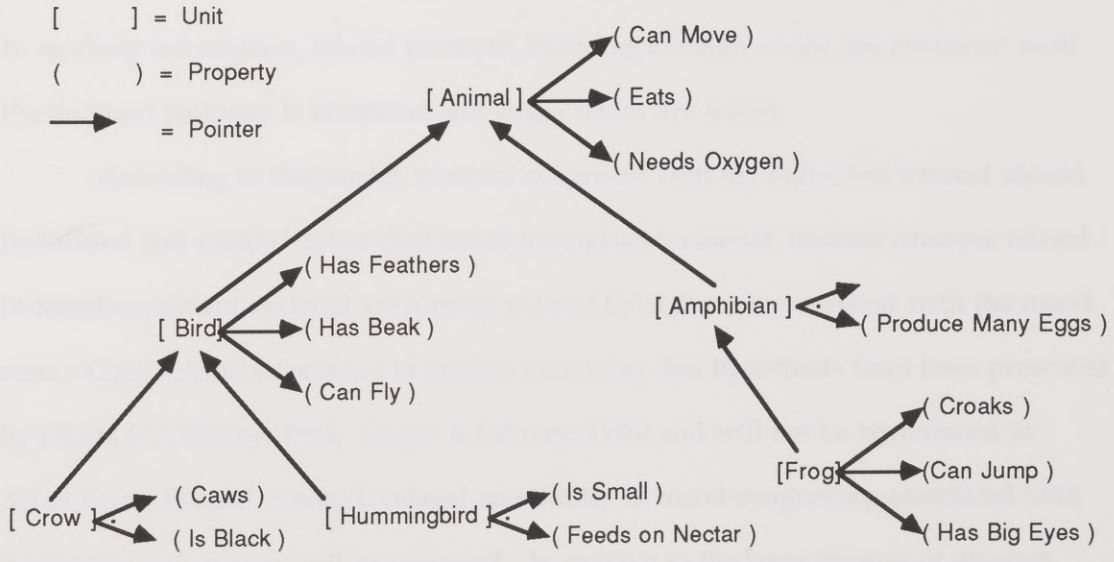

Figure 2.1. An Example of the Relationship Among Concepts in a Simple Semantic Network.

When information is learned or a semantic relationship is assessed, related concepts are activated in the network. Activation spreads outward from the target concepts along the pointers leading from them. Each time a pointer leads to a different concept (i.e. node), the node is "tagged." Recall is accomplished by activating related concepts and tracing the associations until the specified target is reached.

According to the Network Theory of Affect each distinct emotion is itself a node in memory, connected via associative links to related concepts and events, as well as to nervous system activity, muscular events, and expressive patterns (Singer & Salovey, 1988). Thus, information is learned and stored in memory not only in terms of the subject and object, but also in terms of emotional responses. As described above, information processing is a function of the activation of nodes within the network of memory. When information is encoded, nodes associated with the emotional content of the information, as well as the emotional state of the individual at the time of encoding, are activated. In recalling information, related concepts, including emotion nodes, are evaluated until the accurate pathway is identified and target nodes are found.

According to this model, material congruent with the individual's mood should be learned and recalled better than mood-incongruent material, because concepts related to mood-congruent material are already primed by activation associated with the mood state. Comprehensive reviews of studies examining this hypothesis have been presented by others (cf., Blaney, 1986; Singer & Salovey, 1988) and will not be reproduced in detail here. Instead, research related specifically to mood-congruency associated with depression and anxiety will be reviewed. In contrast to the large amount of research examining mood-congruent information-processing biases associated with depressed mood, the literature evaluating biases associated with anxious mood is relatively small.

Consequently, a brief overview of the recent research on depressed mood will be presented first, followed by a more extensive review of studies examining information-processing bias associated with anxious mood.

Mood Congruency and Depression

Several studies have yielded evidence supporting mood-congruent learning associated with depressed mood. Bower, Gilligan, and Monteiro (1981) hypnotically induced happy and sad states in subjects, and then asked them to read a story that described positive and negative characters and events. When the subjects were no longer in their induced mood, they were asked to recall the story. In general, subjects tended to recall more information about the characters and events that were congruent with their mood at the time they read the story, suggesting a learning bias. Similar results have been reported by studies using mood-induction statements (Velten, 1968) and self-generated imagery to induce mood (Nasby & Yando, 1982; Ellis, Thomas, & Rodriguez, 1984).

Studies examining recall bias associated with depressed mood have been less consistent. Several investigators have reported that, following induction of happy or sad mood via Velten (1968) statements, subjects tended to recall more mood-congruent autobiographical events than mood-incongruent memories (Madigan & Bollenbach, 1982; Mathews & Bradley, 1983; Snyder & White, 1982). Using a similar mood-induction procedure, Teasdale and his colleagues found that subjects took longer to recall mood-incongruent memories (e. g., happy memories while in a sad mood) than they took to recall memories congruent with their mood (Teasdale & Fogarty, 1979; Teasdale & Taylor, 1981). In contrast, several studies using hypnosis or self-generated imagery as a

means to induce mood states have failed to find recall bias associated with depressed mood (e.g., Bower et al., 1981; Gerrig & Bower, 1982; Nasby & Yando, 1982; Potts, Morse, Felleman, & Masters, 1986). Unlike the studies using Velten (1968) statements, these latter studies did not employ validity checks to verify appropriate mood-induction. Therefore, the inability of the latter studies to demonstrate recall bias may reflect a failure to induce appropriate mood states adequately.

Studies examining naturally-occurring depression further support the hypothesis of mood-congruent recall bias. Using an incidental learning paradigm, Derry and Kuiper (1981) examined recall of "depressive" and "nondepressive" adjectives in depressed psychiatric patients, nondepressed psychiatric patients, and normal controls. Before viewing words presented tachistoscopically, subjects were cued to respond to one of three properties of each word: a) whether the target word was in small letters (structural), b) whether it meant the same as a presented word (semantic), or c) whether it described them (self-referent). Free recall was assessed after all words were presented. Results showed that all groups demonstrated greater recall of self-referent words. In addition, the depressed group demonstrated greater recall of "depressive" words, but only in the self-referent condition. Bradley and Mathews (1983) reported similar results in a sample of eight patients with primary depressive disorder. Kuiper and Derry (1982) reported that normal subjects demonstrated superior recall of positive self-referent adjectives, while depressed subjects showed a recall bias for negative self-referent adjectives. Similarly, Mathews & Bradley (1983) demonstrated that depressed subjects were more likely to recall negative personality traits, and less likely to recall positive traits, than nondepressed subjects.

In summary, strong evidence can be found supporting mood-congruent learning and recall biases associated with depressed mood. Among clinically-depressed patients, however, these biases appear to be specific to autobiographical or self-referent material, and not to "depressive" material in general. This finding, along with the finding that normal subjects demonstrate bias for positive self-referent material, is consistent with the theories of Beck and his colleagues, who have suggested that all individuals attend to stimuli and conceptualize information via relatively stable cognitive structures, called "schemas" (e. g., Beck, Rush, Shaw, & Emery, 1979). Cognitive schemas are activated to screen, differentiate, organize, and respond to the vast number of stimuli present in the environment, thus allowing individuals to categorize and evaluate their experiences. According to Beck et al. (1979), depressed patients differ from normals in that the former selectively attend to stimuli congruent with their depressed mood and distort information to fit their negative self-concept.

Mood-Congruency and Anxiety

Compared to studies of depressed subjects, studies of information-processing in subjects with anxious mood have been relatively few in number. In one of the only published studies in which information processing was examined following induction of anxious mood in the laboratory, Norton and his colleagues asked college students with and without a history of panic attacks to read a story that was either panic-related, anger-related, or neutral in order to induce anxious, hostile, and neutral moods, respectively (Norton, Schaefer, Cox, Doward, & Wozney, 1987). Subjects were then presented a list containing either danger-related, anger-related, or neutral words, and later asked to recall the list. Subjects with a history of panic who read the panic-

related passage demonstrated a recall bias for danger-related words; no bias was found in nonpanickers who read the same passage or panickers who read a different passage. Unfortunately, mood at the time of learning was not verified, and mood at the time of recall was neither assessed nor manipulated. Consequently, it is not possible to distinguish the relative contributions of learning and recall bias to these results (Craske & Barlow, in press).

In a study of naturally-occurring anxious mood, Nunn, Stevenson, and Whalan (1984) asked agoraphobic subjects and normal controls to read five passages; three passages contained "phobic-related" material (e. g., going to a shopping mall) while the other two contained "neutral" information (e.g., eating breakfast). Subjects were later asked to recall as much as possible about the passages. Groups did not differ on the number of ideas recalled from neutral passages; however agoraphobic patients recalled significantly more material than controls from the phobic-related passages. In a second experiment, Nunn et al. (1984) presented a list of twenty words (10 phobic-related, 10 neutral) to subjects over four trials and assessed recall after each trial. Agoraphobic patients demonstrated superior recall of phobic words compared to neutral words, while controls demonstrated an opposite pattern.

These studies suggest mood-congruent learning and recall bias associated with anxiety; however, some have argued that differences in word-familiarity were not controlled, thus confounding the results (Mathews & Eysenck, 1987). Mogg, Mathews, and Weinman (1987) presented a series of adjectives matched on familiarity to 10 "generally anxious patients" and 10 normal controls. Each adjective was paired with one of two references (i. e., self or a person familiar to the subject), and subjects were asked to decide whether or not the adjective described the referenced person. Half the words

were positively-toned (e. g., secure, amused) and half were negatively-toned. Of the negative words, half were threatening (e. g., humiliated, trapped), half nonthreatening (e. g., bored, gloomy). Both anxious and control subjects demonstrated greater recall of self-referent and positive words, compared to other-referent and negative words. Although a group difference was also noted along the threat/nonthreat dimension, the pattern of results was opposite that expected, with anxious subjects recalling a greater number of nonthreat-related words and less threat-related words than control subjects. These results seemingly contradict the mood-congruent hypothesis with respect to anxiety.

Studies of patients with panic disorder, however, have supported the hypothesis of mood-congruent recall. McNally, Foa, and Donnell (1989) asked panic disorder subjects and normal controls to rate the self-descriptiveness of a number of anxious and nonanxious adjectives. Following a five minute delay, panic subjects recalled more anxiety-related than nonanxiety-related words, whereas the opposite pattern was found among controls. Cloitre and Liebowitz (1989) reported similar results, with the additional finding that panic subjects did not show a similar bias for emotionally-charged, positive words.

Mathews, Mogg, May, and Eysenck (1989) have suggested that, rather than reflecting a lack of mood-congruency associated with anxiety, the failure of Mogg et al. (1987) to demonstrate recall bias associated with anxious mood may reflect an artifact of the type of memory examined. Mathews et al. (1989) argue that studies of mood-congruency have assessed only *explicit* memory, that is, the ability to recall factual information upon demand (e. g., words from list), and have ignored a second type of memory, called *implicit* memory. Implicit memory refers to a process by which exposure

to information "can influence performance even when [subjects] cannot recognize the material as familiar" (Squire, 1987, p. 157).

A classic illustration of implicit memory is the phenomenon of semantic priming in amnesia. Shortly after learning a word-list, amnesic subjects demonstrate rapid forgetting and are unable to recall a significant number of words from the list (or even having learned the list at all). If, however, these patients are given a series of word-stems (i. e., the first two or three letters of a word) and asked to complete each stem with the first word that comes to mind, they will produce a greater number of list-words than patients who were never exposed to the list (Butters, 1984; Butters, Heindel, & Salmon, 1990; Squire, 1987).

Mathews et al. (1989) examined implicit and explicit memory in patients with Generalized Anxiety Disorder (GAD), normal controls, and former GAD patients who had successfully completed a six-month treatment program. Subjects were presented two lists containing both threat-related and nonthreat-related words. As each word was presented, subjects were asked to imagine themselves in a scene involving the word, and then asked to rate the pleasantness of the word. After all words were presented, implicit and explicit memory tasks were administered.

The implicit memory task consisted of a semantic priming task similar to that described above; the explicit task consisted of a cued recall procedure. Subjects were presented a series of three-letter word-stems and asked either to complete each stem with the first word that came to mind (implicit), or to recall the word from the list that began with each stem (explicit). No group differences were found on the explicit memory task; however, GAD subjects produced a significantly greater number of threat-related list-words, and less nonthreat-related list-words on the implicit memory task,

compared to control subjects. The authors concluded that anxious subjects demonstrate an implicit memory bias for threat-related material, but not an explicit memory bias. Although they go on to suggest that explicit and implicit memory operate independently from one another in anxious subjects with respect to processing threat-related information, they do not suggest why this would be so, nor do they address why normal and depressed individuals demonstrate explicit memory biases for mood-congruent material while anxious subjects do not.

Some have suggested that, unlike depressed and normal individuals, anxious subjects may divert attention away from mood-congruent material, rather than selectively process such information (Mathews & Eysenck, 1987; Williams, Watts, MacLeod, & Mathews, 1988). Although initial attention and processing is required to detect and recognize stimuli as threat-related, once detected, attention is believed to shift away, thus precluding continued processing and rehearsal of information. This may explain the finding of implicit memory bias in the absence of explicit memory bias, since exposure to the stimulus would be sufficient for implicit memory, while the more elaborative processing necessary for explicit memory is prevented. This hypothesis is examined further in the following section.

Attentional Bias and Anxious Mood

In general, studies of attentional biases in anxious populations have yielded consistent evidence suggesting bias <u>toward</u> threat-related (i. e., mood-congruent) material, rather than away from it. Parkinson and Rachman (1981) reported that mothers of children scheduled for surgery detected a greater number of concern-related words (e.g., bleeding) embedded in taped music than mothers of children who were not

hospitalized. Similarly, Burgess et al. (1981) found that, compared to normal controls, anxious patients detected a greater number of threat-related words and less nonthreat-related words presented in the unattended channel of a dichotic listening task.

These studies have been criticized for confounding perceptual selectivity and word-familiarity (cf. Williams et al., 1988); however, controlled studies have reported similar results. Using a method similar to Burgess et al. (1981), Mathews and MacLeod (1986) found that anxious patients were slower to respond to a visual probe when the words presented to the unattended ear in a dichotic listening task were threat-related than when they were nonthreat-related. Other studies have shown that when anxious subjects are asked to name the color ink in which words are printed (i. e., a Stroop (1935) paradigm), they are significantly slower than nonanxious controls when threatening, as opposed to nonthreatening words are present (Mathews & MacLeod, 1985; Mogg, Mathews, & Weinman, 1989; Richards & Millwood, 1989).

MacLeod, Mathews, and Tata (1986) presented pairs of words on a video screen to "clinically anxious" and normal control subjects. Each word-pair consisted of a threat-related and neutral word, one appearing above center and one below. Subjects were instructed to read the top word of each pair aloud. After the words disappeared from the screen, a dot would appear in either the top or bottom position; subjects were instructed to press a button as soon as they detected the stimulus. Probe detection among the anxious subjects was faster when the stimulus was in the location of the threat-related than the nonthreat word, while the opposite pattern was observed in normal controls.

Overall, these studies suggest that threat-related material commands increased attention and occupies a greater amount of information-processing resources in anxious

subjects than normal controls. Moreover, Mathews, May, Mogg, and Eysenck (1990) report that this bias is "an enduring feature of individuals vulnerable to anxiety, rather than a transient consequence of current mood alone" (p. 173). Martin, Williams, and Clark (1988), however, have argued that some of the aforementioned studies (e. g., Mathews & MacLeod, 1985; 1986) confounded emotional salience of threat-related words with attentional bias. Using a Stroop paradigm, these investigators showed that subjects with GAD responded as slowly to emotionally-charged, positively-toned words as to threat-related words. Watts and his colleagues, however, reported opposite results with a sample subjects with spider phobia (Watts, McKenna, Sharrock, & Trezise, 1986). Subjects were presented spider-related words (e.g., hairy, crawl), emotionally-matched, threat-related, nonspider words (e.g., crash, death), and neutral control words (e.g., clock, field) in a Stroop paradigm. In contrast to the findings of Martin et al. (1988), spider phobics were significantly slower to complete trials containing spider-related words than controls, but were no different from controls on trials of emotional or neutral words.

The difference in results between these two studies may be attributable to the populations examined. Whereas threat-related material for spider phobics is clearly circumscribed, that for GAD is quite diffuse. Thus, much like depressed subjects who demonstrate bias for depressive stimuli only in self-referent conditions, anxious subjects may selectively attend to threat material only when it is related to their specific fear. Indeed, several studies have suggested that patients with panic disorder exhibit attentional bias toward information related directly to their principal fears, but not toward threat-related information in general (McNally, 1990). Based on results of a Stroop-paradigm, Ehlers, Margraf, Davies, and Roth (1988) reported that panic disorder

patients and nonclinical panickers demonstrated significant perceptual interference from words related to physical threat, embarrassment, and separation, while normal control subjects demonstrated no such interference. Similarly, McNally, Riemann, and Kim (1990) found that panic disorder patients, but not normal controls, exhibited greater Stroop interference for words related to physical sensations, fear, and catastrophic events. Unlike panic disorder patients, patients with social phobia do not demonstrate Stroop interference when presented with words related to physical threat (Hope, Rapee, Heimberg, & Dombeck, 1990).

The phenomenon of selective attention to specific, fear-related cues has important implications for understanding panic disorder. The central fears of patients with panic disorder are the perceived consequences of having a panic attack (Telch et al., 1989). Thus, the specific, fear-related cues would be those which signal the advent of a panic episode. Given the physiological component of panic (See pp. 12-14), physical sensations are likely to hold increased threat-value for patients with panic disorder. Patients with panic disorder have been shown to be faster and more accurate than controls in determining whether they have been given a panicogenic compound or placebo (van den Hout, van der Molen, Griez, & Lousberg, 1987). Moreover, Barlow (1988) reported that selective attention to physical sensations is common in patients with panic disorder.

Self-focus and Narrowing of Attention

Research suggests that selective attention to physical sensations is closely associated with a tendency toward self-focus (cf. Barlow, 1988). Wegner and Guiliano (1980) found that physically active subjects produced more self-referent words on a

sentence completion task than subjects at rest. Others have reported that when physiological arousal become salient, individuals tend to reflect more intensely about themselves, and become increasingly sensitive to bodily sensations and self-evaluative concerns (Duval & Wicklund, 1972; Fenigstein & Carver, 1978). Moreover, individuals with high levels of self-focussed attention reportedly experience greater subjective intensity of laboratory-induced emotions, and demonstrate a slower rate of habituation to external stimuli, than less self-focused individuals (cf. Craske & Barlow, in press).

According to Barlow (1988) self-focused attention is accompanied by attention narrowing. As originally defined by Easterbrook (1959; cited in Barlow, 1988), attention narrowing is a preoccupation with mood-congruent material during an emotional reaction. This preoccupation varies as a function of emotional intensity; as intensity increases, self-focus becomes increasingly narrow. As self-focus narrows, attention to cues irrelevant to the current mood state is sacrificed. Such a process is consistent with the frequent clinical observation that individuals in a panic state often disregard or ignore competing, rational cognitive activity (Barlow, 1988).

A Model of Pathological Anxiety and Panic Disorder

Although self-focus and narrowing of attention are considered normal processes, they are believed to be central to the development and maintenance of pathological anxiety. Barlow (1988) has suggested that patients with pathological anxiety have been conditioned to attend to internal states, whereas nonanxious individuals ignore or do not detect minor variations in bodily responses. In addition, patients with pathological anxiety are believed to be preoccupied with the negative affect associated with anxious states. This preoccupation is referred to as "anxious apprehension," and is considered a

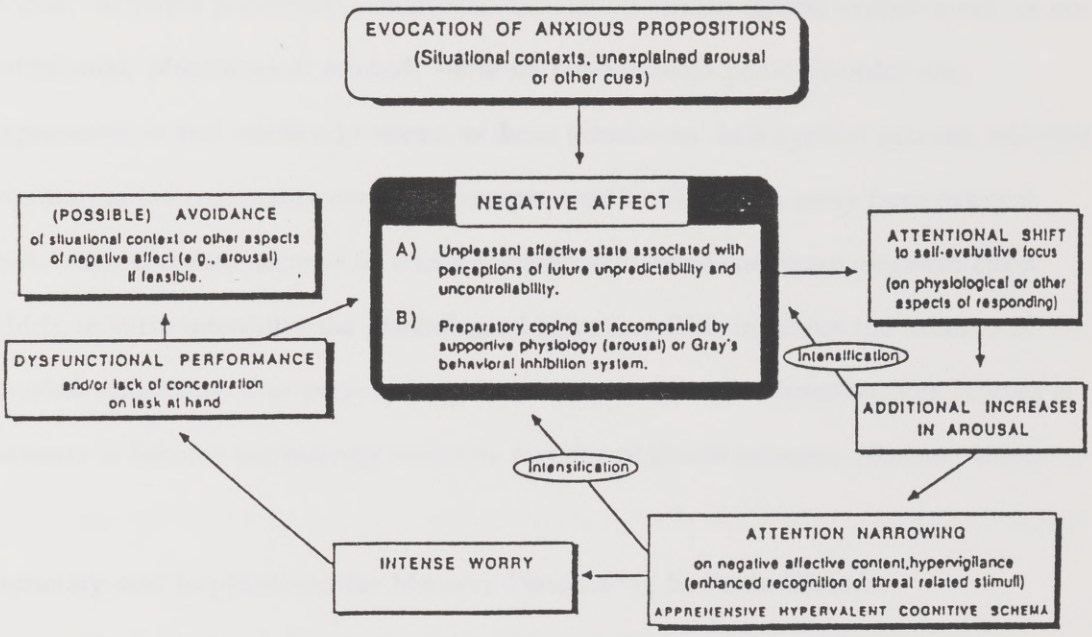

Figure 2.2. Barlow's Model of Anxious Apprehension. From Barlow, D. H. (1988). Anxiety and its disorders: The nature and treatment of anxiety and panic. New York: The Guilford Press, reprinted with permission.

central feature of all anxiety disorders; its relevance specifically to panic disorder will be discussed here.

Barlow's model of anxious apprehension incorporates many of the phenomena discussed in previous sections and is presented in Figure 2. 2. The negative affect at the center of anxious apprehension consists of two major components: the physical sensations associated with panic, and the perceived unpredictability and uncontrollability of future panic episodes. According to the model, this negative affect is evoked by panic-related situational contexts (e. g., agoraphobic stimuli, such as the thought of going to a supermarket) or the detection of physiological sensations. While these are not pathological in and of themselves, "what is pathological is [an] associated shift of attention [from the task at hand] to an off-task (i. e., internal) focus" (Barlow, 1988,

p. 255). As noted previously, nonanxious individuals tend to ignore, explain away, or not notice mild, physiological arousal, while individuals with panic disorder are hypersensitive and selectively attend to these sensations. In a cyclical process, selective attention to internal bodily concerns prompts a shift of attention away from external cues. Attention then narrows on cues associated with mood-congruent, negative affect which, in turn, intensifies the physiological response. This increases the salience of physical sensations, thus perpetuating the affective response. Moreover, this process is believed to become increasingly active as severity of illness increases (Barlow, 1988).

Summary and Implications for Memory Functioning in Panic Disorder

Theoretically, it has been suggested that patients with anxiety disorders selectively attend to cues related to their specific fears. In panic disorder, these cues are primarily physiological sensations associated with panic attacks, to which the individual has become hypersensitive. Given that patients with panic disorder experience elevated levels of physiological arousal between attacks (see p. 14), the likelihood that these patients will detect subjectively unexplainable physiological sensations is high. Once physiological arousal is detected, attention shifts to an internal, self-evaluative focus and narrows; stimuli relevant to the emotional state become increasingly salient at the expense of emotionally irrelevant stimuli.

Korchin (1964) reported that extreme narrowing of attention can result in distractibility, decreased cognitive efficiency, and impaired performance on tasks unrelated to the present concern. Although most individuals in an acute state of panic would likely exhibit impaired attention and memory compared to someone at rest, the literature reviewed in this chapter suggests that patients with panic disorder may

demonstrate such impairments while in a nonpanic state, due to their more chronic anxious apprehension and hypervigilance toward bodily cues. Specifically, the hypersensitivity of panic disorder patients to physical sensations, and the vulnerability of attention to be disrupted by concerns over internal events may cause attentional deficits in the absence of acute panic episodes, especially among patients with more severe panic disorder. Poor attention would impair memory ability, in that information may not be learned efficiently, and thus may be more susceptible to forgetting.

Recent neurobiological studies of panic disorder also provide evidence suggesting that memory functioning may be compromised in patients with panic disorder. A review of this literature is presented in the next chapter.

CHAPTER 3

The Neuropsychology of Panic Disorder

Neuropsychology is the study of brain-behavior relationships. One of the fundamental assumptions of neuropsychological science is that all behavior, including emotional behavior, is mediated by the central nervous system (Heilman & Satz, 1983). The present chapter reviews the literature of neurobiological studies related to panic disorder. An overview of the brain systems believed to be involved in anxiety will be presented first, and will include a discussion of the putative roles of both neuroanatomical and biochemical systems, based on data from both animal and human studies. The hypothesized roles of these brain systems in the manifestation of pathological anxiety and panic disorder will then be discussed, followed by a review of recent findings from human neuroimaging studies. Finally, the implications of these findings for memory functioning in patients with panic disorder will be addressed.

A Neuropsychological Model of Anxiety

Guided primarily by studies of the effects of anti-anxiety drugs on animal behavior, Gray (1982) proposed a model that attempts to delineate the psychological processes of anxiety and the neurological substrates that underlie those processes. This model is based on two important assumptions. The first assumption is that the "psychology" of anxiety is defined by the behaviors that are altered by anxiolytic drugs. At this level, the model attempts to identify the stimuli which bring about the behaviors associated with anxiety, the responses that arise from this state, and the mechanisms that relate responses to stimuli. The second assumption is that the behavioral changes caused by anxiolytic medications are due to alteration of neural

processes, and that the neural systems which underlie these behavioral changes represent the "neurology" of anxiety.

The Psychology of Anxiety

When healthy, unmedicated laboratory animals are confronted with stimuli that warn of punishment or frustrative nonreward, a specific combination of behavioral changes are elicited. These include inhibition of ongoing motor behaviors, increased physiological arousal, and increased vigilance to the surrounding environment (Amsel, 1962; Gray, 1975; Wagner, 1969). These behavioral changes are also noted when animals are confronted with novel stimuli (Sokolov, 1963), stimuli associated with species-specific danger (e. g., the innate fear of snakes among primates; Hebb, 1946), and threat-related stimuli that arise during social interactions among conspecifics (e. g., threatening looks or calls; Gray, 1971); they are also quite similar to anxiety-related behaviors in humans (Barlow, 1988).

Studies of laboratory animals have found that anxiolytic medications reliably block the behavioral changes made in response to the aforementioned stimuli; these medications do <u>not</u>, however, alter behaviors associated with other stimuli, such as those which signal reward or nonpunishment (Gray, 1975). Based on these data, Gray and his colleagues postulated that the behavioral responses to innate fear stimuli, novel stimuli, and stimuli associated with punishment or frustrative nonreward constitute "anxiety" (Gray, Feldon, Rawlins, Owens, & McNaughton, 1978). Moreover, they hypothesized that these responses are the function of a "behavioral inhibition system" (BIS), which monitors incoming stimuli and mediates behavioral output according to the type of stimuli detected (See Figure 3.1).

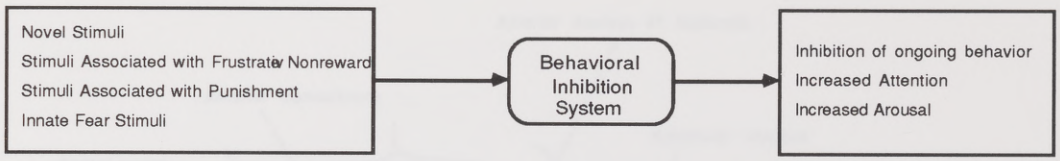

Figure 3.1. The Behavioral Inhibition System (BIS).

The Neurology of Anxiety

As described by Gray (1982), the BIS represents a functional system and not a specific brain structure or system. In an exhaustive review of the literature of lesion studies in laboratory animals, Gray & McNaughton (1983) noted that the behavioral syndrome produced by lesions to structures within the limbic system was remarkably similar to the effects of anxiolytic medications.

The limbic system is a phylogenetically older set of cerebral structures which forms a border or rim around the upper part of the brainstem. It consists of several subcortical nuclei, including the amygdala, hypothalamus, septal nuclei, and thalamus, as well as cortical areas, known collectively as the limbic lobe (the hippocampal formation and the subcallosal, cingulate, dentate, and parahippocampal gyri; See Figure 3. 2). The limbic system has long been implicated in the experience and expression of emotion, and is often referred to as the "visceral brain" (Papez 1937, Klüver & Bucy, 1939; Klüver, 1952). Simply stated, cortical and sensory input converge in the limbic system and trigger mechanisms which activate the visceral and somatic systems associated with the experience and physiological expression of emotion.

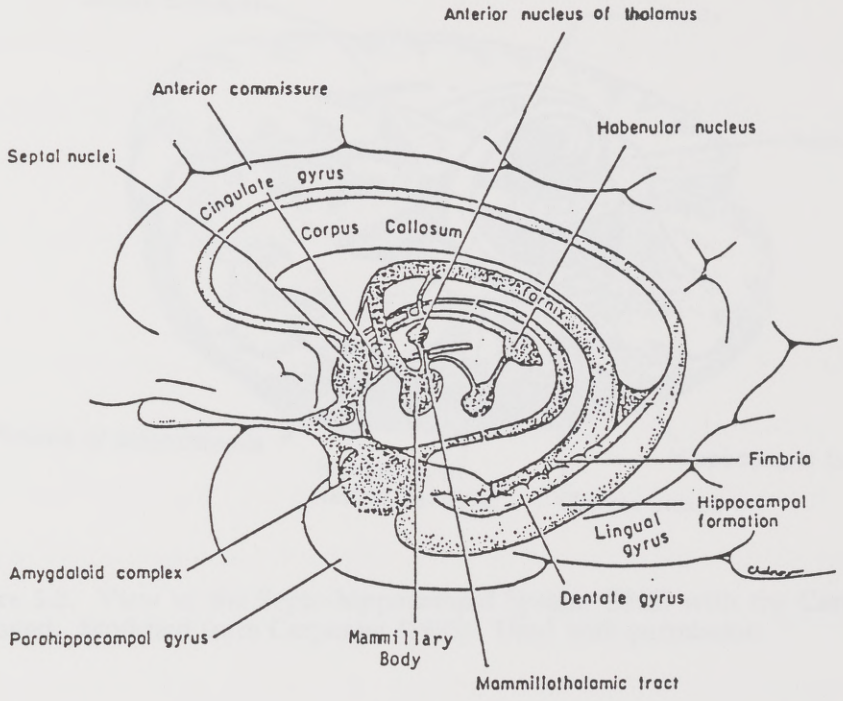

Figure 3.2. Medial View of the Structures Which Comprise the Limbic System. Modified from Carpenter (1985). Used with permission.

As mentioned above, lesions to specific structures within the limbic system produce behavioral effects similar to those associated with anxiolytic medications. These structures are the septal nuclei and the hippocampal formation, which, together with their interconnections, comprise the septo-hippocampal system (SHS; See Figure 3. 3). The septal nuclei and hippocampal formation are found in the medial portions of the cerebral hemispheres. The septal nuclei are located bilaterally in the basal forebrain, and consist of four major divisions: medial, lateral, ventral, and posterior (Swanson, 1978). The hippocampal formation is located bilaterally in the medial portion of the temporal lobes, and is comprised of several structures, including the hippocampus proper (areas CA1 - CA4), dentate gyrus, subiculum, entorhinal cortex, and several associated cortical areas, known collectively as the limbic neocortex (the

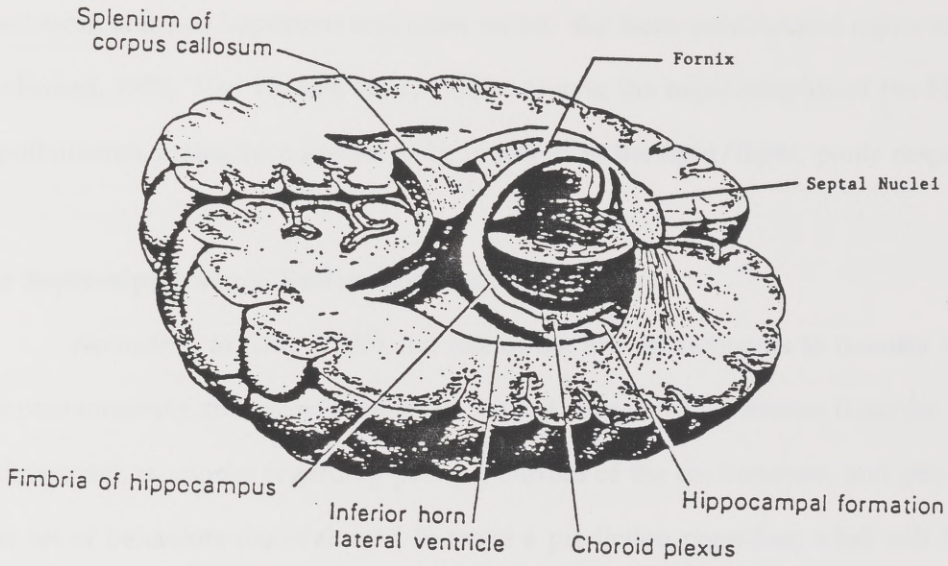

Figure 3.3. View of the Septo-hippocampal System (SHS) with the Cerebral Cortices Removed. Modified from Carpenter (1985). Used with permission.

cingulate gyrus, orbito-frontal cortex, and parahippocampal gyrus). Fibers connecting the septal nuclei and hippocampal formation travel via two neural tracts: the fimbria, which sweeps along the outside edges of the SHS, and the dorsal fornix, which keeps to the midline and follows the inferior surface of the corpus callosum.

The neural circuitry of the SHS is quite complex, and consists of a series of feedback loops, the majority of which begin and end within the SHS itself. By and large, the SHS makes contact with other brain systems at relatively few points. The major points of input to the SHS include the medial area of the septal nuclei, the entorhinal cortex, and the parahippocampal gyrus. The SHS receives information from all sensory systems, but only after this information has undergone extensive processing in cortical association areas (e. g., Jones & Powell, 1970; Van Hoesen, Pandya, & Butters, 1975); the SHS also receives input from the prefrontal cortex (a region implicated in planning behavior), the thalamus (a major relay center between cortical and subcortical

structures), and two important brainstem nuclei: the locus ceruleus and raphe nuclei (Beckstead, 1978; Van Hoesen et al., 1975). Among the major outputs of the SHS is the hypothalamus, a structure known to be involved in the fight/flight, panic response.

The Septo-hippocampal System and Anxiety

According to Gray (1982), the role of the SHS in anxiety is to monitor and compare incoming stimuli with expected stimuli. Sensory information from the current environment, memories regarding past regularities of the environment, and plans for the next set of behaviors are evaluated to make a prediction regarding what will happen next in the environment. The SHS compares this prediction with the next set of incoming sensory stimuli. If the sensory stimuli match the prediction, the SHS allows behavioral control to remain in the currently functioning brain systems, and another prediction is made (See Figure 3.4). If, however, incoming and predicted stimuli do not match (as when novel stimuli, or stimuli associated with nonreward are detected),

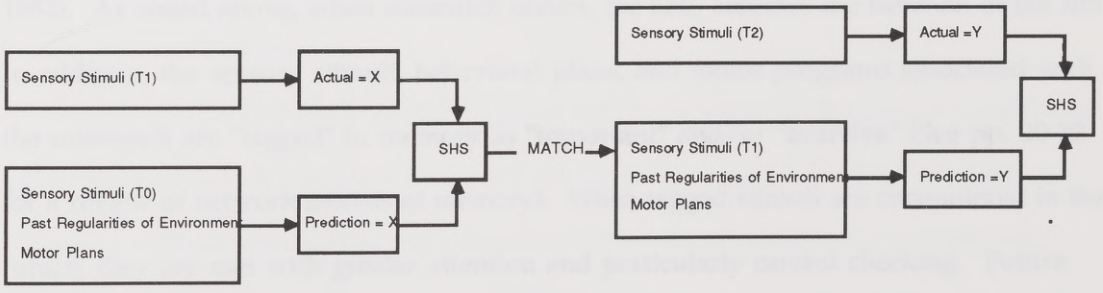

Figure 3.4. Septo-hippocampal System (SHS) Functioning Under "Match" Condition. Incoming sensory stimuli are compared with a prediction based on previous sensory stimuli, information regarding past regularities of the environment, and the next intended set of motor movements. If the incoming stimuli matches that which is predicted, it is used to generate the next prediction.

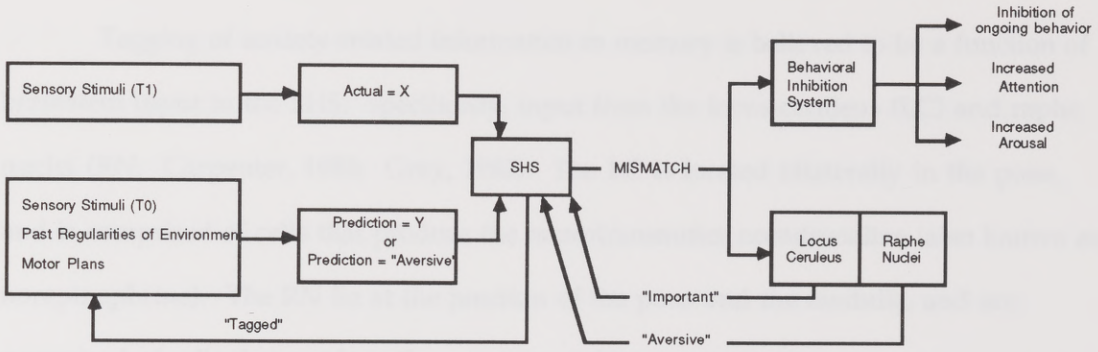

Figure 3.5. Septo-hippocampal System (SHS) Functioning Under Normal "Mismatch" Condition. Incoming sensory stimuli are different from those which were predicted, or the predicted stimuli are aversive. The "mismatch" is detected by the SHS, and the behavioral inhibition system is engaged. Moreover, input from the locus ceruleus and/or the raphe nuclei "tag" the information for future reference.

or the predicted event is aversive (as when innate fear stimuli or stimuli associated with punishment are detected), the process of generating predictions stops. The SHS then takes control and the behavioral changes associated with the BIS are engaged (See Figure 3.5).

Both the failure of incoming stimuli to match predicted stimuli and the prediction of aversive stimuli are subsumed under the inclusive term "mismatch" (Gray, 1982). As stated above, when mismatch occurs, the SHS assumes the function of the BIS. In addition, the sensory stimuli, behavioral plans, and motor programs associated with the mismatch are "tagged" in memory as "important" and/or "aversive" (See pp. 20-22 for a review of network models of memory). When tagged stimuli are encountered in the future, they are met with greater attention and particularly careful checking. Future engagement (or intention to engage) in activities associated with the tagged stimuli will be accompanied by increased vigilance, will be executed with greater restraint, and will be more readily abandoned in favor of other behaviors (Gray, 1982).

Tagging of anxiety-related information in memory is believed to be a function of brainstem input to the SHS; specifically, input from the locus ceruleus (LC) and raphe nuclei (RN; Carpenter, 1985; Gray, 1982). The LC is located bilaterally in the pons, and is comprised of cells that produce the neurotransmitter noradrenaline (also known as norepinephrine). The RN lie at the junction of the pons and the medulla, and are comprised of cells that produce the neurotransmitter serotonin.

Electrical stimulation of the LC in stump-tail monkeys elicits behaviors similar to those emitted spontaneously under conditions of threat (e. g., teeth grinding, hand wringing; Redmond, Huang, Snyder, & Maas, 1976). Conversely, ablation of the LC results in significant reductions of these behaviors, even in threatening situations (Redmond et al., 1976). Electrical stimulation of the RN in nonhuman primates causes intense, fear-like responses, including crouching, defecation, urination, and piloerection (Graeff & Silveira-Filho, 1978). Interference with serotonergic functioning in laboratory animals, either by the destruction of the RN, inhibition of serotonin synthesis, or blockage of serotonin receptor sites, results in hyperactivity and hypervigilance to environmental stimuli (Carpenter, 1985; Geyer, Puerto, Menkes, Segal, & Mandell, 1976; Srebro & Lorens, 1975).

All events that are potentially important to an animal's survival are associated with increased noradrenergic (LC) activity (e. g., Redmond, 1979), while reactions to stimuli associated with punishment are associated with increased serotonergic (RN) activity (e. g., Tye, Everitt, & Iverson, 1977). Increased noradrenergic and serotonergic activity are both associated with increased activity in the hippocampal formation (Gray, 1975). According to Gray (1982), the specific role of noradrenergic input to the

SHS is to tag information as "important," while serotonergic input adds the additional qualification that the information is associated with aversive or punishing consequences.

Neural Bases of Panic Disorder

Gorman, Liebowitz, Fyer, and Stein (1989) have incorporated much of Gray's work into a neuroanatomical model of panic disorder, which attempts to localize the three major components of panic disorder - the acute panic episode, anticipatory anxiety, and phobic avoidance - to various cerebral regions. These are summarized briefly below.

Acute Panic Episodes. Gorman et al. (1989) suggest that the LC and RN, along with carbon-dioxide (CO_2) sensitive nuclei in the medulla, are responsible for triggering panic episodes. Studies have shown that panic episodes can be elicited in the laboratory if patients with panic disorder are administered one of several pharmacological agents that act upon one or more of the above-mentioned brainstem regions. Three of these agents: sodium lactate, yohimbine, and CO_2, have been studied extensively. Sodium lactate infusion is related to increased serotonergic (i. e., RN) activity (Carr et al., 1986; Lingjaerde, 1985), while administration of yohimbine is related to increased noradrenergic (i. e., LC) activity (Charney, Heninger, & Breier, 1984, Charney, Heninger, & Redmond, 1983). Inhalation of CO_2 increases activity of CO_2 -sensitive receptors in the medulla. These, in turn, stimulate LC activity in a dose-dependent fashion (Elam, Yao, Thoren, & Svensson, 1981; Gorman & Uy, 1987; Gorman et al., 1988).

Cells of the LC and RN project extensively throughout the brain, and innervate regions known to be involved in the fight/flight response such as the hypothalamus and sympathetic nervous system neurons of the spinal cord (Carpenter, 1985). Under normal

circumstances, cortical and limbic input to the brainstem regulate LC and RN activity and thus control when the fight/flight (i. e., panic) response will be initiated. Based on the laboratory data presented above and the clinical observation that panic disorder patients experience spontaneous "storms of autonomic nervous system activity" (p. 150), Gorman et al. (1989) suggest that panic episodes associated with panic disorder are initially caused and maintained by random firing of hyperexcitable, "irritable foci" in the LC, RN, or CO_2 -sensitive regions of the brainstem.

Anticipatory Anxiety. Regardless of whether an acute panic episode is elicited by normal, cortico-limbic stimulation of brainstem regions, or by spontaneous firing of "irritable" brainstem foci, ascending projections from the LC and RN to the SHS are activated during panic (Gorman et al., 1989; Gray, 1982). It has been suggested that repeated stimulation of limbic structures by brainstem afferents lowers the threshold to further stimulation of the limbic system, a phenomenon known as the "kindling effect" (Goddard, 1983; Post & Uhde, 1985; Uhde & Post, 1984). Consequently, stressors that would not normally activate the SHS may reach the lowered threshold, and signal brainstem nuclei to trigger a panic episode. This, in turn, maintains the reduced limbic threshold and continues the cyclical process.

In terms of Gray's (1982) model, brainstem innervation of the SHS tags environmental stimuli as "important" and "aversive" for future reference. Although this is a normal response to "mismatch," random firing of hyperexcitable, "irritable foci" in brainstem regions would elevate noradrenergic and serotonergic input to the SHS regardless of whether match or mismatch is detected (See Figure 3.6; Gray, 1971; 1982). Consequently, innocuous "match" stimuli are tagged inappropriately, and treated as requiring careful checking. As more and more nonthreatening stimuli are tagged, BIS

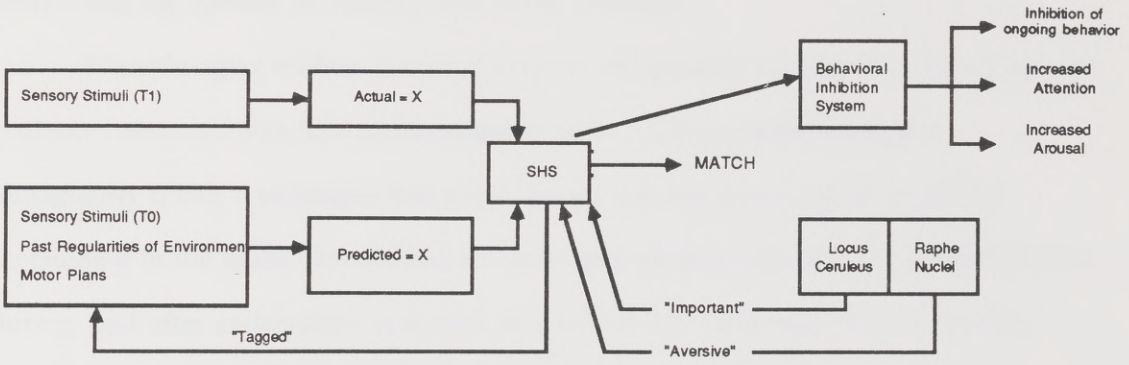

Figure 3.6. Septo-hippocampal System (SHS) Functioning in Conditions of "Pathological" Anxiety. Incoming sensory stimuli match the prediction generated; however, random firing of brainstem nuclei innervate the SHS, causing it to engage the behavioral inhibition system. In addition, stimuli are tagged as important and/or aversive, even though they may not be.

activation increases, and behavior becomes characterized by inappropriate shifts of attention and hypervigilance; similar behavioral manifestations have been noted in cognitive theories of anxiety (See pp. 32-34).

Phobic Avoidance. While panic episodes and anticipatory anxiety are believed to be functions of brainstem and limbic structures, phobic avoidance is believed to be a function of higher cortical regions (Gorman et al., 1989). Associations linking panic episodes to specific situations are believed to be made in the prefrontal cortex. Extensive anatomical connections are known to exist between the prefrontal cortex, the limbic system, and the brainstem (Nauta & Domesick, 1981; Rossi & Brodal, 1956); it is via these pathways that cognitions may cause anticipatory anxiety and panic (see Gorman et al., 1989).

Brain Imaging Studies of Anxiety and Panic Disorder

Neuroimaging studies of normal subjects and patients with panic disorder provide evidence consistent with SHS involvement in panic. Using positron emission tomography (PET), a technique that provides regional measurements of metabolic functioning in the brain, Reiman and his colleagues studied eight healthy subjects before, during, and after anticipation of electric shock (Reiman, Fusselman, Fox, & Raichle, 1989). Subjects were told that they would receive a painful electric shock sometime during the second of three measurement intervals, and that the severity of the shock would increase with the length of the time between the beginning of the second measurement and shock delivery. Results revealed significant increases in blood flow bilaterally in the temporal lobes during anticipation of shock.

Studies of patients with panic disorder have also noted abnormalities in temporal lobe metabolism compared to normal controls. Reiman and his colleagues measured cerebral blow flow in 10 patients with panic disorder and six normal controls at rest, after which all subjects received intravenous infusion of sodium lactate (Reiman, Raichle, Butler, Herscovitch, & Robins, 1984). Groups did not differ in whole brain or hemispheric measurements of cerebral blood flow; however, patients who panicked following lactate infusion showed a significantly lower blood-flow ratio between the right and left parahippocampal gyrus than normal controls or patients who did not respond to lactate. Recall that the parahippocampal gyrus is part of the hippocampal formation and is located in the medial temporal lobe. Reiman et al. (1986) extended this study to 16 patients with panic disorder and 25 normal controls and replicated the previous findings. Moreover, unilateral measurements suggested that the right/left asymmetry reflected an abnormal increase in regional cerebral blood flow (rCBF) in the

right parahippocampal gyrus. A study of patients during a panic attack, however, noted rCBF elevations bilaterally in the temporal lobes (Reiman, Fusselman et al., 1989). These studies suggest that panic disorder is distinct from normal forms of anxiety by the presence of a regional abnormality in the right medial temporal lobe (i. e., parahippocampal gyrus) in the nonpanic state (Reiman, Raichle et al., 1989).

Results of neuroanatomical studies of patients with panic disorder have thus far been consistent with metabolic studies. A recent published case study reported that "autonomic and experiential phenomena consistent with a diagnosis of panic disorder" were the only symptoms experienced by a patient with a neoplasm involving the right, medial temporal lobe (Drubach & Kelly, 1989). Panic episodes have also been reported in patients with focal, right temporal lobe meningioma (Ghardian, Gauthier, & Bertrand, 1986) and arteriovenous malformation (George, McLeod-Bryant, Lydiard, Kurent, & Zealberg, 1990; Wall, Tuchman, & Mielke, 1985). Moreover, a magnetic resonance imaging (MRI) study of 30 lactate-sensitive panic disorder patients and 20 normal controls found a significantly higher incidence of right medial temporal lobe abnormalities in panic disorder patients than normal controls (Ontiveros et al., 1989).

Electrophysiological evidence, although strongly suggesting temporal-limbic involvement in panic, have relied primarily on case studies and have been less consistent in terms of lateralization. It is well established that emotional responses associated with fear are common ictal phenomena in patients with temporal lobe seizures (e. g., Williams, 1956; Volkow, Harper, & Swann, 1986). Using brain electrical activity mapping (BEAM), Abraham (1986) noted temporal lobe abnormalities in psychostimulant abusers who later developed panic attacks. Weilburg, Bear, and Sachs (1987) presented one case of panic representing the aura of a complex seizure, and a

second case of nonictal panic which developed following the onset of a seizure disorder. The former case was associated with left temporal lobe seizure activity, while the latter was associated with right temporal lobe seizure activity. Edlund, Swann, and Clothier (1987) described a series of six patients with "atypical panic attacks," characterized by hostility, irritability, and severe depersonalization. Five of the six patients had abnormal electroencephalographic (EEG) measurements: two with right temporal lobe abnormalities, two with left temporal lobe abnormalities, and one with bilateral temporal abnormalities. A recent study of 35 medication-free patients with panic disorder, however, reported finding only five patients with abnormal EEGs (Stein & Uhde, 1989). One of the five patients displayed right temporal abnormality, and two displayed bilateral temporal abnormalities; the remaining two patients displayed abnormalities not specified by the authors with regard to laterality.

The lack of consistent electrophysiological support for right temporal involvement in panic disorder may be due to the relatively gross, insensitive measurements of current EEG and BEAM technology or may reflect the atypical nature of panic associated with seizure activity. In contrast, metabolic and neuroanatomical studies strongly suggest right medial temporal lobe dysfunction in panic disorder, most likely involving the right parahippocampal gyrus. Such involvement appears to be unique to panic disorder. Studies of patients with DSM III diagnoses of phobic disorder, generalized anxiety disorder, or obsessive-compulsive disorder have thus far failed to demonstrate similar abnormalities (Baxter et al., 1987; 1988; Mathew, Weinman, & Claghorn, 1982; Mindus et al., 1986; Mountz et al., 1989; Zohar et al., 1989).

Studies of patients with major depression have also failed to demonstrate consistent evidence of medial temporal lobe abnormalities. Over the past few decades,

several theories regarding cerebral localization of affective disorders have been advanced. Some have argued that depression reflects a predominantly right-hemisphere dysfunction, while others have suggested that it reflects left-hemisphere pathology (see Davidson, 1984; Tucker, 1981 for reviews); still others have suggested bilateral/diffuse cerebral involvement in major affective disorders (e. g., Kluger & Goldberg, 1990).

Using computerized tomography (CT) Robinson and his colleagues demonstrated that severity of depressed mood following stroke was positively correlated with the proximity of the infarct to the left frontal pole, and negatively correlated with proximity to the right frontal pole (Robinson, Kubos, Starr, Rao, & Price, 1984; Robinson & Price, 1982). These results suggest that depression is associated with decreased activity in the left anterior and/or right posterior cerebral regions.

Studies that have looked at metabolic asymmetry associated with depression have yielded somewhat inconsistent results. O'Connell et al. (1989) used single photon emission computed tomography (SPECT), a procedure similar to, but less precise than, PET, to study 22 patients with major depression. Patients demonstrated reduced blood flow in all cortical areas compared to normal and psychiatric controls, with most notable reduction bilaterally in cortical and subcortical regions of the frontal lobes. PET studies of depressed patients have also found significant frontal lobe hypometabolism compared to normal controls (Baxter et al., 1985; 1989; Martinot et al., 1990; Mathew et al., 1980; Phelps, Mazziotta, Baxter, & Gerner, 1984). Unilateral measurements from these studies strongly suggest lateralization to the left cerebral hemisphere. Moreover, studies have reported that frontal hypometabolism persists even after successful treatment of depression; however, the degree of left-right asymmetry diminishes significantly

(Baxter et al., 1985; Martinot et al., 1990). None of these studies reported evidence of right posterior involvement.

In contrast, Gur et al. (1984) and Uytdenhoef et al. (1983) found evidence of right posterior (i. e., parieto-occipital), but not left-frontal, hypometabolism in depressed patients. Post et al. (1987) reported evidence of decreased metabolism in the right temporal lobe of patients with affective disorders; however, these results have not been replicated. Still others have failed to find abnormalities in PET scans of depressed patients (Gustafson, Risberg, & Silfverskiöld, 1981; Silfverskiöld & Risberg, 1989).

A recent electrophysiological study of subjects with a previous history of major or minor depression (according to Research Diagnostic Criteria; Spitzer, Endicott, & Robins, 1978) found reduced left frontal and right posterior activation on EEG compared to subjects who had never suffered from depression (Henriques & Davidson, 1990). A study of patients with temporal lobe epilepsy, however, suggested a significantly stronger relationship between left-hemisphere pathology (i. e., left temporal epileptogenic focus) than either right hemisphere or bilateral pathology (Altshuler, Devinsky, Post, & Theodore, 1990).

Overall, the data from neuroimaging studies suggest that medial temporal lobe involvement is specific to panic disorder. This is consistent with the hypothesized role of the SHS in anxiety. As stated earlier, anticipatory anxiety associated with panic disorder is believed to be due to abnormal hyperactivity of the hippocampal formation, secondary to kindling from repeated brainstem activation. Metabolic studies have demonstrated increased cerebral blood flow in the parahippocampal gyrus of patients with panic disorder who panic in response to lactate, suggesting hypermetabolism in this region. Interestingly, abnormal increases in metabolic activity have been associated only

with the right parahippocampal gyrus. Many investigators have suggested that the right cerebral hemisphere subserves the processing and expression of emotional states (e.g., Ahern & Schwartz, 1979; Davidson, 1987; Sackheim et al., 1982), and has a greater role in the perception and processing of autonomic activity (Hantas, Katkin, & Reed, 1984; Montgomery & Jones, 1984; Wittling, 1990). Given this, it may be that SHS functioning is lateralized, with panic-related behaviors subserved primarily by right hemisphere structures. Consequently, abnormality in the right parahippocampal gyrus may represent a locus of dysfunction specific to panic disorder.

The Septo-hippocampal System and Memory

In addition to its proposed role in anxiety and panic, the hippocampal formation serves additional functions, including learning and memory (Butters & Cermak, 1975; Morris, 1983; Nadel & Morris, 1982; Olton, 1983; O'Keefe, 1983; Squire, 1982; 1983). The role of the hippocampal formation in memory was first recognized when it was observed that removal of the medial temporal lobe in patients with intractable epilepsy produced a profound, yet circumscribed amnesic syndrome. The best-known case of this type is HM, a patient with severe, intractable seizures who sustained bilateral resection of the medial temporal lobe, including the amygdala, uncus, parahippocampal gyrus, and the anterior two-thirds of the hippocampus proper (Scoville & Milner, 1957; Milner, 1966; 1972). Subsequent to his surgery, HM showed little disruption of general cognitive skills; however, he showed no ability to learn or recall new information.

Research on HM and other patients with medial temporal lobe resections, as well as studies of patients with cortical and subcortical dementias, suggests that the medial temporal lobe and its associated structures are essential to explicit memory

functioning (Butters, Heindel, & Salmon, 1990; Heindel, Salmon, & Butters, 1990). The distinction between explicit and implicit memory processes was introduced in Chapter 2 (See pp. 26-28). Briefly restated, explicit memory refers to the ability to recall information upon demand, while implicit memory refers to a process by which recently exposed stimuli may affect behavior in the absence of explicit recall. Unlike explicit memory, implicit memory does not appear to depend on any single cerebral location or structure (Squire, 1987). Rather than a discrete entity, implicit memory is a "collection of different abilities, each dependent on its own specialized processing system ... including motor skill learning, perceptual learning, classical conditioning, priming, habituation, sensitization, and perceptual after-effects" (p. 164). Consequently, dysfunction in a single area would not be expected to affect implicit memory to the same extent that a lesion in the hippocampal formation would affect explicit memory (Squire, 1987).

Studies of hippocampal and parahippocampal functioning in animals strongly support the role of these structures in explicit memory. Kesner and Connor (1972) showed that disruption of hippocampal functioning via electrical stimulation impaired long term memory capacity in rats. Using a Skinner box, rats were trained to press a bar in order to receive sugar-water. Once trained, the rats were given foot shock after each bar press. Rats receiving hippocampal stimulation following foot shock showed no suppression of bar pressing behavior 24 hours later, whereas control rats receiving no electrical stimulation, or stimulation to brain regions other than the hippocampus (e. g, the reticular formation), demonstrated significant behavioral suppression. Studies of the effects of hippocampal lesions on maze-learning in rats have yielded similar results (Becker, Walker, & Olton, 1980; Olton, Becker & Handleman, 1979; Olton, Collison, &

Werz, 1977; Olton & Samuelson, 1976; Olton, Walker, & Gage, 1978; Olton & Werz, 1978; Walker & Olton, 1979).

Using cryogenic probes, George, Horel, and Cirillo (1989) found that cooling of the parahippocampal gyrus in monkeys (*M. fascicularis*) resulted in a significant reduction in recall accuracy on a delayed match-to-sample test. In contrast, cooling of the posterior inferotemporal gyrus, the cortical region dorsal to the parahippocampal gyrus, had no significant effect on test performance, and cooling of both regions produced no greater deficits than cooling of the parahippocampal gyrus alone. Other researchers have found that lesions to the parahippocampal gyrus alone produce equal to greater impairment of delayed retention of object discrimination than lesions elsewhere in the hippocampal formation (Zola-Morgan, Squire, Amaral, & Suzuki, 1989; Zola-Morgan, Squire, & Amaral, 1989).

The parahippocampal gyrus and the hippocampus are believed to function as a unit, with the parahippocampal gyrus serving as a funnel for cortical input into the hippocampus (Van Hoesen, 1982). The posterior parahippocampal gyrus receives massive projections from all sensory association areas. This information is relayed to the entorhinal cortex, and ultimately, the hippocampus. Conversely, projections from the hippocampus relayed to the parahippocampal gyrus are known to innervate virtually every region of the association cortex (Halgren, 1985; Van Hoesen, 1982). Thus, the parahippocampal gyrus is considered important for both learning and recall of information.

Summary and Implications for Memory Functioning in Panic Disorder

Evidence from the psychological and neurological literature converge to suggest memory dysfunction in patients with panic disorder; however, different mechanisms for this dysfunction may be discerned. As reviewed in chapter 2, the prevailing cognitive model suggests that patients with panic disorder are hypersensitive to physiological arousal, and are prone to self-focussed attention when such arousal is detected. Attention is shifted from an external to an internal focus, and becomes increasingly narrow. Consequently, less and less information-processing resources are allocated to external cues.

The neuropsychological model reviewed in this chapter suggests that "anxiety" is a state caused by detection of innate fear stimuli, novel stimuli, or stimuli associated with punishment or nonreward, and is expressed by behavioral inhibition, increased physiological arousal, and hypervigilance to the environment. Information associated with anxiety-provoking stimuli are "tagged" and met with increased attention and careful checking when encountered again. In the case of panic disorder, innocuous stimuli are tagged inappropriately because of increased stimulation of the SHS by erratic, hyperexcitable brainstem nuclei. This causes increased BIS activation, which is characterized by hypervigilance and inappropriate shifts of attention.

With the exception of the direction of attentional shift (cognitive - internal shift, neuropsychological - external shift), these models of anxiety are quite similar; indeed, even this difference can be reconciled if direction of attentional shift is viewed as a shift toward the hypothesized location of threat, rather than as internal versus external. Behaviorally, off-task shifts of attention would likely impair one's ability to learn new information efficiently, thus interfering with memory. Simply stated, these models suggest that memory functioning in patients with panic disorder may be impaired

secondary to poor attention. A systematic review of the research literature has failed to reveal a study where this hypothesis has been tested.

Neuroimaging studies strongly support the hypothesis of memory disturbance in patients with panic disorder and suggest an alternative mechanism for this disturbance. Brain structures believed to be involved in mediating anxiety-related behaviors (i.e., the hippocampal formation) are also known to be essential to explicit memory processes. Recall from Chapter 2 (pp. 26-28) that anxious subjects, unlike normal and depressed individuals, fail to demonstrate explicit recall biases for mood-congruent material. Although it was suggested that this may be due to secondary avoidance strategies, studies of attentional processes associated with anxious mood did not support this hypothesis. An alternative explanation for the lack of expected explicit recall bias is that the mechanism for explicit memory may be impaired in anxious subjects. Metabolic, neuroanatomical, and electrophysiological studies of brain functioning reveal a significantly greater proportion of abnormalities in the medial temporal lobe of patients with panic disorder compared to controls, a finding consistent with hippocampal involvement. A number of studies of panic disorder patients demonstrate lateralization of involvement to the right medial temporal lobe; metabolic studies in particular have found specific involvement of the right parahippocampal gyrus. Studies of patients with other anxiety disorders and depressive disorders have failed to find similar abnormalities.

Medial temporal lobe abnormalities may interfere significantly with learning and recall of new information. It is generally accepted that, in right-handed individuals, the left cerebral hemisphere subserves verbal functions, while the right hemisphere subserves nonverbal functions (Bradshaw & Nettleton, 1981; Butters &

Miliotis, 1985; Cummings, 1985; Geschwind & Galaburda, 1985; Ross, 1981). Although the presence of extensive connections between cerebral hemispheres makes it unlikely that memory functioning is completely lateralized, the finding of predominantly right temporal lobe involvement in panic disorder patients at rest suggests that visual memory may be impaired to a greater extent than verbal memory in these patients.

The present study examined attentional capacity, as well as learning and recall of verbal and visual material among a sample of patients with panic disorder. Attentional capacity and memory were evaluated using standardized neuropsychological measures. Performance on these tasks was compared to that of normal control subjects. In addition, because depression is a common feature associated with panic disorder but has not been associated with right medial temporal lobe abnormalities, a sample of patients with major depression served as a psychiatric control group.

The following hypotheses were examined in the present study:

1) As suggested by models posited by Barlow (1988) and Gray (1982), subjects with panic disorder should demonstrate lower scores than normal control subjects on tests of attentional capacity. Panic disorder subjects should perform no differently from depressed controls on these measures.

2) Patients with panic disorder will demonstrate lower scores on tests of both verbal and visual memory as compared to control subjects.

3) As suggested by Barlow (1988), panic disorder subjects' performance on tests of attention and memory will be negatively correlated with increased tendency to focus on internal bodily sensations, as measured by a self-report instrument.

4) Moreover, both Barlow's (1988) and Gray's (1982) models of panic disorder suggest that frequency of attentional shifts is greater in patients with greater severity of illness. Consequently, a significant negative correlation should be observed between severity of panic disorder and performance on tests of attention and memory.

5) Alternatively, as suggested by neuroimaging studies, panic disorder subjects will demonstrate lower scores on tests of visual memory, but will demonstrate no difference on tests of verbal memory, than normal and psychiatric control subjects.

CHAPTER 4

Method

Subjects

Panic Disorder Subjects. Twenty-five, right-handed subjects (4 males, 21 females), ranging in age from 20 to 60 years (M = 35.5, SD=10.0), were recruited through local media as part of an ongoing panic disorder treatment study at The University of Texas at Austin. Potential subjects were administered a brief telephone screening interview. Those reporting panic attacks as their primary problem were invited to participate in a face-to-face, structured clinical interview (SCID - Non-Patient Version). Subjects with a history of a Bipolar Disorder, Psychotic Disorder, Psychoactive Substance Dependence Disorder, or Anxiety Disorder other than Panic Disorder were excluded from the study, as were subjects with current mood disorder (e. g., Major Depression, Dysthymia) or Psychoactive Substance Abuse Disorder. All subjects in the final sample met DSM III-R criteria for current Panic Disorder with or without Agoraphobia as their only Axis I condition. Fourteen subjects in the final sample were taking prescribed psychotropic medication to help control their panic. Eleven subjects were taking benzodiazepine, two subjects were taking a tricyclic antidepressant, and one subject was taking a monoamine oxidase inhibitor.

Normal Controls. Twenty-five, right-handed subjects (4 males, 21 females), ranging in age from 20 to 56 years (M = 35.0, SD=9.1), were recruited from the staff of the Austin Neurological Clinic and its associated facilities to serve as normal controls. Screening of control subjects was accomplished using a symptom checklist (SCL-90 Revised) and the Anxiety Questionnaire (AQ), a brief self-report panic disorder

assessment instrument (see Telch, Lucas, & Nelson, 1989). Subjects with current psychopathology, as measured by elevations on any of the SCL-90 clinical scales, or history of unexpected panic attacks, as determined by the AQ, were excluded from the study.

Depressed Controls. Twenty-five, right-handed, depressed outpatients (4 males, 21 females), ranging in age from 19 to 56 years (M = 39.8, SD = 9.5), were recruited from the patient population of the University of California, San Diego, Outpatient Mental Health Clinic. Potential subjects participated in a face-to-face, structured clinical interview (SCID - Non-Patient Version). Subjects with a history of Bipolar Disorder, Anxiety Disorder, Psychotic Disorder, or Psychoactive Substance Dependence Disorder were excluded from the study. Subjects with current Dysthymia or Psychoactive Substance Abuse were also excluded. All depressed control subjects in the final sample met DSM III-R criteria for current Major Depression as their only Axis I condition. Seventeen subjects in the final sample were taking prescribed psychotropic medication to help control their depression; nine were taking a tricyclic antidepressant, seven were taking fluoxetine hydrochloride (Prozac), and one was taking an MAO inhibitor.

All subjects in the final sample reported no history of significant central neurological illness, birth stress, learning disability, and previous neuropsychological evaluation. Subjects taking prescribed medications were included in the study only if they had been maintained on their medication for at least one month.

Materials

Clinical Memory Tests:

Wechsler Memory Scale (WMS; Wechsler, 1945). The WMS consists of seven subtests designed to assess various aspects of memory functioning. These include:

a) Personal and Current Information. Asks the subject's age and date of birth, as well as the names of current public figures.

b) Orientation to time (i. e., the date) and place.

c) Mental Control. Subjects are asked to count backwards, recite the alphabet, and perform serial calculations, all under time pressure.

d) Logical Memory (LM). Two brief passages are read to the subject. After each passage is presented, the subject is asked to recall as much information from the passage as possible.

e) Memory Span. Subjects are asked to repeat series of digits forward or backward.

f) Visual Reproduction (VR). Subjects study three cards containing two-dimensional geometric figures one at a time. After presentation of each card, they are asked to draw the figure from memory. Two cards contain one figure each; the third contains two designs presented side by side.

g) Paired Associate Learning (PAL). A list of word-pairs is read to subjects over three trials. After each presentation of the list, the examiner states the first word of a pair, and the subject must respond with its associate.

In addition to Wechsler's (1945) immediate recall procedures (described above), recall of LM passages, VR designs, and PAL word-pairs was assessed following a 15- and 45-minute delay period.

Several studies suggest that at least two, and possibly three, factors underlie the structure of the WMS. In most studies, LM, VR, and PAL load on a "memory" or "retention" factor, while Mental Control and Memory Span load together on a separate factor, often labelled "freedom-from-distractibility" or "attention/concentration" (cf. Erickson & Scott, 1977; Prigatano, 1978). When Information and Orientation subtests are included in the analyses, these subtests hold primary loadings on a separate "orientation" factor.

Larrabee, Kane, and Schuck (1983) factor analyzed the WMS together with subtests from the Wechsler Adult Intelligence Scale (WAIS), and found that the PAL and LM subtests loaded together on a factor which they labelled "verbal learning and recall." Macartney-Filgate & Vriezen (1988) reported modest intercorrelations between measures derived from the LM/PAL subtests of the WMS and learning ($\underline{r}$ = .35 - .67) and recall ($\underline{r}$ = .18 - .60) measures from the Rey (1964) Auditory Verbal Learning Test (RAVLT).

In contrast, the construct underlying the VR subtest has been the subject of some controversy. Some have argued that VR is too sensitive to verbal encoding, (e. g., Trahan & Larrabee, 1984; Trahan, Quintana, Willingham, & Goethe, 1988) and that it assesses visual-perceptual-constructional ability, rather than visual mnestic functioning (Larrabee et al., 1983; Larrabee, Kane, Schuck, & Francis, 1985). Most investigators agree, however, that use of a delayed recall procedure substantially mitigates these confounding effects (Larrabee et al., 1985, Trahan et al., 1988). Moreover, delayed recall

of the VR subtest has been shown to be sensitive to the effects of lateralized (i. e., right) cerebral involvement (Cullum & Bigler, 1986; see also Lezak, 1983).

Larabee et al.'s (1983) factor analysis of the WMS and WAIS subtests yielded a separate factor containing the WMS Memory Span and Mental Control subtests and the WAIS Arithmetic subtest (to avoid redundancy, WAIS Digit Span was not included). Consistent with previous research, this factor was labelled "attention/concentration" (cf., Erickson & Scott, 1977; Lezak, 1983; Prigatano, 1978).

With the exception of LM and VR, all WMS subtests were scored following standard procedures (Wechsler, 1945). Wechsler's rules for scoring LM stories and VR drawings have been criticized for being vague and involving overly subjective interpretation of performance (Loring & Papanicolaou, 1987; Power, Logue, McCarty, Rosenstiel, & Ziesat, 1979). Logical Memory stories are scored based on the average number of ideas recalled from each of the two passages; the subject receives one point for each idea recalled. Wechsler's (1945) scoring procedure calls for the examiner to "score according to number of ideas marked off in selection" (p. 9); however, scoring consistency across studies in the literature has varied considerably, depending on the interpretation of scoring rules (Loring & Papanicolaou, 1987). Some investigators require verbatim recall of ideas in order to receive credit for recall (this was presumably Wechsler's intent). Others give full credit if the "gist" of the idea is recalled. Still others give full credit for verbatim responses and half-credit for gist responses. Power et al. (1979) proposed a scoring system that allows half credit for semantic substitutions that do not alter the meaning of the phrase (e.g., "ship" for "liner") and for partial recall of an idea in which the omission of an adjective, adverb, or article only slightly changes the meaning of the phrase (e.g., "children" for "little children"). Using these criteria, inter-

rater reliability is reportedly high ($r \geq .95$; Power et al., 1979). Waddell and Squires (1987) scored 251 LM protocols using both Power et al.'s (1979) rules and verbatim scoring and found that the two scoring systems were highly correlated ($r = .96$). They concluded, however, that application of the half-credit system failed to add any information over and above that obtained using the verbatim method. In the present study, LM stories were scored using both verbatim and propositional scoring rules[1].

Scoring of the VR drawings using Wechsler's (1945) criteria is similarly problematic, and contain ambiguous terminology such as "nearly equal" and "in approximate proportion" (p. 9). In order to promote standardized scoring of designs, Dalton, Dizzonne, Wallace, Blom, & Holmes (1986), quantified Wechsler's rules and provided scoring samples. VR drawings in the present study were scored using these revised rules.

In addition to the use of more objective scoring criteria, LM stories and VR designs were randomized and scored with the examiner blind to group status (panic disorder vs. depressed control vs. normal control) and recall condition (immediate vs. delay) in order to mitigate possible experimenter bias.

Selective Reminding (SR). Selective reminding is a procedure developed by Buschke and his colleagues to evaluate memory within the context of information processing theory (Buschke, 1973; Buschke & Fuld, 1974). The procedure has found widespread appeal because it allows one to parcel "memory" into several components, including storage and recall, and has been implemented to assess both verbal (e. g., Ruff, Light, & Quayhagen, 1988) and visual (e.g., Fletcher, 1985) learning recall.

In verbal SR, subjects are asked to learn a list of 12 common words. The list is read aloud at a rate of one word every two seconds; the subject is then asked to recall as many words as possible, in any order. Next, subjects are reminded of the words they failed to recall, and asked again to recall as many words as possible from the list. The reminding procedure continues until the subject recalls all words on three consecutive trials or until 12 trials have been administered. The word list employed by this study is one of four (List 2) developed by Hannay and Levin (1985). In addition to learning trials, delayed recall was also assessed.

The test-retest reliability of the selective reminding procedure ranges from .50 to .65 (Hannay & Levin, 1985). Although this is somewhat low, some have argued that it is a promising level, since other well-known, widely-used neuropsychological tests have similar reliability coefficients (Morgan, 1982). Verbal SR correlates modestly ($\underline{r}$ = .51 to .78) with scores from other tests of verbal learning and recall (e. g., the RAVLT, LM, and PAL), supporting its validity as a measure of verbal memory (Macartney-Filgate & Vriezen, 1988).

Visual SR follows the same procedure and offers evaluation of the same memory variables as verbal SR. In this procedure, the subject is presented a card with eight squares, each of which contains five large dots in random positions. One dot in each square is pointed out to the subject at a rate of one every two seconds. After all dots have been designated, the subject is asked to recall each target dot in any order. The selective reminding procedure described above is employed until the subject recalls all dots correctly on two consecutive trials[2] or until 12 trials have been administered. Delayed recall of the target stimuli was also elicited. The stimulus card used by this study is an 8.5 x 11" enlargement of Fletcher's (1985) stimulus figure (p. 251). Target dots

in each square were chosen randomly. Although Visual SR is believed to be a nonverbal analog to verbal SR (Fletcher, 1985), reliability and validity measures of this technique are unavailable from the literature.

The verbal and visual selective reminding tests were scored according the procedure described by Buschke & Fuld (1974).

Benton Visual Retention Test (BVRT; Benton, 1974). The BVRT is a test of immediate memory for geometric designs, and consists of 10 cards, most of which contain three figures each: two large "main" figures and one small "peripheral" figure. Subjects are given 10 seconds to study each card, and are then asked to reproduce the figures from memory. The BVRT is scored for the number of cards correctly reproduced and the number and type of errors made.

Benton (1967, 1968) examined the psychometric properties of the BVRT and found that poor performances on immediate recall were associated with right-hemisphere lesions. Although Larrabee et al. (1985) reported that immediate recall of the BVRT loaded primarily on a visual-perceptual motor factor, and only secondarily on a memory factor, Moses (1986) demonstrated that copy scores from the BVRT loaded on a separate factor than immediate recall, arguing that BVRT recall is distinct from pure visual-perceptual motor ability.

The BVRT scoring manual provides precise scoring procedures (Benton, 1974). Each card is first scored as correct or incorrect. If a card is incorrectly reproduced, the number of errors are recorded. The number of designs correctly reproduced and the total number of errors are each summed to obtain total correct and total error scores. Inter-rater reliability for the BVRT has been calculated between .90 and .95 (Erickson & Scott,

1977; Wellman, 1987). BVRT designs were randomized and scored with the examiner blind to group status and recall condition.

Intellectual Tests

Wechsler Adult Intelligence Scale - Revised (WAIS-R; Wechsler, 1981). Four subtests of the WAIS-R were included in the test battery:

a) Picture Completion is a measure of visual reasoning ability. The subject is presented a stimulus card in which an essential detail is missing, and is asked to state the missing part under time pressure. According to the manual (Wechsler, 1981), this subtest correlates .79 with Performance IQ (PIQ) and .73 with Full Scale IQ (FSIQ).

b) Vocabulary measures the subject's knowledge of word definitions. It has the highest loading of all subtests on the Verbal Comprehension factor of the WAIS-R. It also has the highest correlation of all subtests with Verbal IQ (VIQ; .90) and FSIQ (.85).

c) Block Design is a measure of visuospatial constructional ability. Subjects must manipulate blocks under time pressure to reproduce designs similar to models presented by the examiner. Block Design has the highest correlation of all subtests with PIQ (.82), and correlates .74 with FSIQ.

d) Similarities measures verbal abstract reasoning ability by asking subjects to discern similarities between different concepts. It correlates .83 with VIQ and .80 with FSIQ.

Estimated IQ measures were prorated from these four subtests. Scores from the two verbal subtests were summed and multiplied by 3 to obtain an estimated verbal raw score. Similarly, the sum of the two performance subtests was multiplied by 5/2 to

obtain an estimated performance raw score. The estimated verbal and performance raw scores were summed to obtain an estimated full scale raw; values were then converted to IQ scores using Wechsler's (1981) conversion tables. The validity coefficient for this short-form version of the WAIS-R with FSIQ measures derived from the standard version is 0.93 (Sattler, 1988).

Self-Report Measures

Subjective Memory Questionnaire - Revised (SMQ - R). The SMQ-R is a brief, author-constructed, three-part questionnaire derived from the SMQ (Bennett-Levy & Powell, 1980). Items with the highest reliability coefficients were taken from the original SMQ, and the language was changed to replace British jargon with American equivalents. Part I contains 17 items which elicit one's perception of his/her memory ability for various things (e.g., names of people, telephone numbers) on a Likert-type scale ranging from "Very Bad" to "Very Good" (1 - 5). Part II contains five items, assessing one's perception of how often certain memory failures occur (e.g., forgetting to turn off the stove) on a scale from "Very Often" to "Very Rarely" (1 - 5). Parts I and II are summed to obtain a total score. Part III consists of a single question which asks the subject to rate his/her memory ability relative to age-related peers on a Likert-type scale ranging from "Much Worse" to "Much Better" (1 - 7).

The SMQ-R was administered to 415 college students at the University of Texas at Austin in partial fulfillment of their introductory psychology course requirement. The measure yielded adequate internal consistency, with alpha equal to .81. To date, no validity studies have been conducted on the SMQ-R; however, a study of the original

measure yielded a modest correlation between total score and ability to learn and recall names paired with faces (r = .41; Bennett-Levy & Powell, 1980)

State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1968). The STAI is a 40-item measure developed to assess the level of anxiety experienced at the moment, as well as in general. Subjects are presented 20 anxiety-related statements (e.g., "I feel tense," " I am worried," "I feel secure,") and are asked to indicate how they feel at that moment, on a Likert-type scale ranging from "not at all" to "very much so" (1 - 4). Next, subjects are presented 20 similar statements and are asked to indicate how they generally feel, on a scale ranging from "almost never" to "almost always" (1 - 4). Items are summed to obtain measures of "state" and "trait" anxiety.

Psychometrically, the STAI demonstrates high internal consistency (alpha ranging from .86 - .95; Chaplin, 1985) and correlates highly with other measures of anxiety, namely the IPAT Anxiety Scale (r = .75) and the Taylor Manifest Anxiety Checklist (r = .80).

Beck Depression Inventory (BDI; Beck, 1978). The BDI is a widely-used, self-report questionnaire consisting of 21 grouped statements reflecting depressive symptomatology. Subjects are asked to choose the statement in each group that best describes their recent feeling state. The BDI has adequate internal consistency (alpha = .86) and test-retest reliability (r = .93; Stehouwer, 1987). It correlates highly with the Depression Scale of the Minnesota Multiphasic Personality Inventory (r = .75) and with clinical ratings of severity of depression (r = .90; Stehouwer, 1987).

Neurological History Interview (NHI). The NHI is a semi-structured interview designed by the author to elicit neurologically-relevant information, including history of head injury, birth stress, learning disability, central neurological illness, etc. In addition, items from the handedness inventory of the Halstead-Reitan Lateral Dominance Examination (see Bigler, 1984) were included to assess hand preference.

Body Vigilance Questionnaire (BVQ; Curry, 1990). The BVQ is a 20-item scale that assesses the individual's perception of how quickly he/she perceives the onset of physiological sensations. Each statement is phrased affirmatively (e. g., "I am quick to notice pressure or tightness in my chest," "I am quick to notice irregularities in my heartbeat"), and subjects are asked to rate their level of agreement with each statement on a Likert-type scale from "Strongly Disagree" to "Strongly Agree" (1 - 6). Curry (1988) reported that the BVQ demonstrates adequate internal consistency (alpha = 0.85) and correlates highly with panic-related items of the Anxiety/Panic Scale (APS; Telch, 1989).

Global Disability Scale (GDS). The GDS is a 4-item questionnaire in which subjects are asked to rate the level of impairment they feel they have suffered in different spheres of daily functioning because of their psychological "problems" (see Sheehan, Raj, Sheehan, & Soto, 1988). Degree of impairment in the ability to work, carry out familial responsibilities, and enjoy social activities are rated on a scale from "not at all" impaired to "very severely" impaired (1 - 10). A fourth item asks subjects to rate their perceived global level of impairment from "No complaints, normal activity" to "Symptoms radically change or prevent normal work or social activities" (1 - 5).

Procedure

Subjects with panic disorder and major depression participated in structured clinical interviews (SCID - Non-patient Version) and completed the Body Vigilance Questionnaire (BVQ) and Global Disability Scale (GDS) in sessions prior to administration of the neuropsychological test battery. Normal control subjects completed a symptom checklist (SCL-90) and Anxiety Questionnaire (AQ) prior to testing. During the testing session, all subjects were administered the neuropsychological test battery according to the procedure described below.

Subjects were first asked to complete the Subjective Memory Questionnaire - Revised (SMQ-R), and were then administered the Wechsler Memory Scale (WMS). Standard procedures were followed in the administration of the WMS, with one exception: the order of subtest administration was changed, with the Memory Span subtest preceding, rather than following the LM subtest. Thus, the three WMS subtests from which delayed recall measures were obtained (LM stories, VR drawings, and PAL word-pairs) were administered in succession. The State-Trait Anxiety Inventory and Beck Depression Inventory were administered next, followed by the Neurological History Interview. Fifteen-minute delayed recall of the LM, VR, and PAL subtests of the WMS was then assessed. The Picture Completion, Vocabulary, Block Design, and Similarities subtests of the WAIS-R were administered next, in that order, followed by 45-minute delayed recall of the WMS subtests. The Verbal Selective Reminding (SR) procedure was then administered, followed by Visual SR and the Benton Visual Retention Test (BVRT). When the BVRT was completed, 15-minute delayed recall of the Verbal SR word-list and 10-minute delayed recall of the Visual SR stimuli were elicited. Testing required approximately 1-1/2 hours to complete.

CHAPTER 5

Results

Data Analyses

Demographic information, self-report data, and WAIS-R scores were evaluated using one-way analyses of variance, with group status (Panic Disorder (PD) vs. Normal Control (N) vs. Depressed Control (D)) as the independent variable. Post-hoc analyses of significant main effects were conducted using Tukey's method (alpha = .05).

Overall differences among groups in current use of psychotropic medication and history of neurological consultation were analyzed in 3 x 2 Chi-square analyses. Post-hoc comparisons of significant overall effects were analyzed in 2 x 2 Chi-square analyses.

Sixteen scores were derived from the memory battery and grouped into sets of variables reflecting learning, recall, and attentional ability, based on the literature (e. g., Bigler, 1984; Lezak, 1983). These are presented in Table 5.1. Learning variables included PAL scores from the WMS, Long Term Storage (LTS) scores from the SR procedures, and the number of learning trials required to meet criterion on the SR procedures. Recall variables included 15-minute delayed recall[3] of LM stories, VR drawings, and PAL word-pairs of the WMS, Long Term Retrieval (LTR) and Delayed Recall scores of the SR procedures, and BVRT error scores[4]. These variables were then divided into measures of verbal versus visual learning and recall. Scores from the Mental Control and Memory Span (digits forward and backward) subtests of the WMS were analyzed as measures of attention.

Multivariate analyses of variance (MANOVA) using planned comparisons (i. e., PD vs. N, PD vs. D, D vs. N) were conducted to evaluate group differences on measures of

Table 5.1. Measures of Memory Functioning Employed in Data Analyses.

Function Assessed	Measures Employed	Source of Measure
Verbal Learning	Paired Associate Learning	Wechsler Memory Scale
	Long Term Storage	Verbal Selective Reminding
	Trials to Criterion	Verbal Selective Reminding
Verbal Recall	Logical Memory Delay	Wechsler Memory Scale
	Paired Associate Learning Delay	Wechsler Memory Scale
	Long Term Retrieval	Verbal Selective Reminding
	Delayed Recall	Verbal Selective Reminding
Visual Learning	Long Term Storage	Visual Selective Reminding
	Trials to Criterion	Visual Selective Reminding
Visual Recall	Visual Reproduction Delay	Wechsler Memory Scale
	Long Term Retrieval	Visual Selective Reminding
	Delayed Recall	Visual Selective Reminding
	Error Score	Benton Visual Retention Test
Attention	Mental Control	Wechsler Memory Scale
	Digit Span Forward	Wechsler Memory Scale
	Digit Span Backward	Wechsler Memory Scale

verbal learning, verbal recall, visual learning, visual recall, and attention. Group membership served as the independent variable, and test scores as dependent variables. Multivariate F-statistics derived from Wilks' criterion were employed to determine statistical significance of results.

In order to examine the clinical significance of findings, subject's performances on several measures were categorized as impaired or unimpaired, based on normative data from the literature. Planned comparisons were carried out in 2 x 2 (group x impairment rating) Chi-square analyses with correction for continuity. Measures reflecting verbal learning (PAL and Verbal LTS scores), verbal recall (delayed recall of LM stories and Verbal Consistent LTR[5] scores), and visual recall (delayed recall of VR drawings and BVRT error scores) were included in the analyses; normative data for other memory

variables, including measures from the visual SR procedures, were not available in the literature.

Due to significant variability in the presentation and availability of normative data, different procedures were used to determine cutoff scores for "impaired" performances. These are summarized in Table 5.2. Means and standard deviations for various age cohorts were obtained for verbal SR, PAL, and LM delayed-recall scores (Abikoff, Alivar, & Hong, 1987; desRosiers and Ivison, 1988; Ruff, Light, and Quayhagen, 1988). In general, scores less than or equal to two standard deviations below the mean (i. e., 2nd percentile) were considered impaired. Normative data for delayed LM recall, however, contained exceedingly large standard deviations (e. g., $\underline{M}$ = 8.07, $\underline{SD}$ = 4.45 for ages 50-59; Abikoff et al., 1987); therefore, scores on this test were considered "impaired" if they were less than one standard deviation below the mean (16th percentile). Percentiles and recommended cutoff scores for impaired performance on delayed recall of the WMS VR subtest were obtained from Trahan et al. (1988). According to these norms, scores falling below the 10th percentile are considered impaired. In contrast, Benton's (1974) normative data for BVRT errors consists only of the number of errors "expected" for individuals of a certain age and intelligence level (i. e., FSIQ). In the present study, subjects who produced more errors than expected for their age and estimated FSIQ, were considered impaired.

The relationship between performance on memory tests and the tendency to focus on physiological sensations in panic disorder was evaluated via multiple correlation. Due to the small case-to-variable ratio (25 cases to 16 variables), data reduction was employed before running the analysis. All variables were transformed to standard scores and averaged to obtain single composite scores reflecting each of the five constructs of

Table 5.2. Criteria Used To Determine "Impaired" Performance on Selected Memory Measures.

Measure	Cutoff	Normed On	Source
Verbal Learning:			
Paired Associate Learning	-2 SD (2nd percentile)	age, sex	desRosiers & Ivison, 1988
Verbal SR Long Term Storage	-2 SD (2nd percentile)	age, educ, sex	Ruff, Light, and Quayhagen, 1988
Verbal Recall:			
Verbal SR Consistent Long Term Retrieval	-2 SD (2nd percentile)	age, educ, sex	Ruff, Light, & Quayhagen, 1988
Logical Memory Delay	-1 SD (16th percentile)	age	Abikoff, Alivar, & Hong, 1987
Visual Recall:			
Visual Reproduction Delay	10th percentile	age	Trahan et al., 1988
Benton VRT Errors	Below "expected"	age, IQ	Benton, 1974

interest (i. e., verbal learning, verbal recall, visual learning, visual recall, and concentration). A standard multiple correlation was then performed between BVQ scores and composite test scores.

The relationship between memory test performance and severity of panic disorder was evaluated in a similar fashion. Two measures of panic severity, namely panic frequency (i. e., the number of panic attacks experienced in one week) and symptom severity (i. e., SPRAS scores), were obtained from measures completed by subjects during a baseline evaluation session held within the week prior to neuropsychological testing. Data were transformed to standard scores and averaged to obtain a single "panic severity" score. A standard multiple correlation was then performed between the composite panic severity score and composite memory test scores.

Subject Characteristics

Subjects did not differ significantly in age [F (2, 72) = 1.95, NS] or years of formal education completed [F (2, 72) = 0.20, NS; See Table 5.3]. Subject performance on subtests of the WAIS-R , as well as pro-rated IQ scores, are presented in Table 5.4 . One subject with panic disorder reported having previous experience administering the

Table 5.3. Mean Age and Years of Education of Panic Disorder Subjects, Normal Controls, and Depressed Controls.

	Panic Disorder (n = 25)		Normal (n = 25)		Depressed (n=25)		
	M	(SD)	M	(SD)	M	(SD)	F
Age	35.5	(10.0)	35.0	(9.1)	39.8	(9.5)	1.95
Education	14.4	(2.3)	14.6	(1.7)	14.7	(2.2)	0.20

WAIS-R. Consequently, the Army Beta Examination - Revised (Kellogg & Morton, 1935) was administered in place of the WAIS-R subtests in order to obtain an estimated Full Scale IQ (FSIQ); Verbal and Performance IQ measures (VIQ & PIQ, respectively), however, could not be estimated for this subject. No significant differences were found among groups on the Vocabulary [F (2, 71) = 0.03, NS], Similarities [F (2, 71) = 0.63, NS], or Block Design [F (2, 71) = 0.98, NS] subtests of the WAIS-R. Groups did, however, differ significantly in their performance on the Picture Completion subtest [F (2, 71) = 4.12, $p < .03$]. Post-hoc analysis revealed that panic disorder subjects scored significantly lower on this test than either normal or depressed controls; the two control groups did not differ from each other. Not surprisingly, given the above results, pro-rated FSIQ scores [F (2, 72) = 0.77, NS] and VIQ scores [F (2, 71) = 0.28, NS] did not differ

Table 5.4. Mean Scores on Selected Subtests of the Wechsler Adult Intelligence Scale - Revised and Pro-rated IQ Scores for Panic Disorder Subjects, Normal Controls, and Depressed Ccontrols.

	Panic Disorder (n = 24)		Normal (n = 25)		Depressed (n=25)		
	M	(SD)	M	(SD)	M	(SD)	F
Vocabulary	10.9	(1.6)	10.9	(2.2)	11.0	(2.4)	0.03
Similarities	9.9	(1.9)	10.5	(2.0)	10.4	(2.1)	0.63
Picture Completion	8.8^{a}	(1.8)	10.6^{b}	(2.1)	$10.1^{a,b}$	(2.5)	4.12*
Block Design	9.3	(2.8)	10.3	(2.4)	9.6	(2.5)	0.98
Pro-rated Full Scale IQ	100.3	(8.8)	106.1	(13.3)	102.0	(24.5)	0.77
Pro-rated Verbal IQ	102.7	(10.3)	104.6	(12.4)	105.2	(13.8)	0.28
Pro-rated Performance IQ	97.5^{a}	(10.7)	107.4^{b}	(13.5)	$105.0^{a,b}$	(16.7)	3.32*

Note: Groups denoted with different letters differ significantly from each other.
* $p < .05$

significantly among groups, while significant group differences were found for estimated PIQ [F (2, 71) = 3.32, $p < .05$]. Again, panickers scored significantly lower than controls, who did not differ from each other.

Self-report data are presented in Table 5.5. Body vigilance and global disability data were collected from panic disorder subjects and depressed controls only. In addition, two panic disorder subjects failed to complete the "trait" items of the State-Trait Anxiety Inventory. Significant differences were found among groups on measures of state anxiety [F (2, 72) = 8.52, $p < .001$] and trait anxiety [F (2, 70) = 26.13, $p < .001$]. Panic disorder subjects and depressed controls scored significantly higher than normal control subjects on these measures; however, the two psychiatric groups did not differ from each other. Subject groups also scored significantly differently on the BDI [F (2, 72) = 24.90,

Table 5.5. Self-report Ratings for Panic Disorder Subjects, Normal Controls, and Depressed Controls.

	Panic Disorder (n = 25)		Normal (n = 25)		Depressed (n=25)		
	M	(SD)	M	(SD)	M	(SD)	F
Beck Depression Inventory	14.9[a]	(9.1)	5.7[b]	(5.1)	24.0[c]	(12.0)	24.90**
State Anxiety (Spielberger)	45.8[a]	(8.0)	36.8[b]	(8.6)	46.9[a]	(11.6)	8.52**
Trait Anxiety (Spielberger)[1]	49.8[a]	(11.5)	37.4[b]	(7.5)	56.6[a]	(9.4)	26.13**
Body Vigilance Questionnaire	88.6	(16.8)			72.2	(15.3)	13.04**
Sheehan Global Disability	3.9	(0.9)			4.2	(0.8)	1.39
Subjective Memory Questionnaire:							
Total (Parts I and II)	69.2[a,b]	(13.8)	73.3[a]	(7.4)	62.7[b]	(14.7)	4.66*
Part III	3.8[a,b]	(1.3)	4.5[a]	(0.9)	3.2[b]	(1.8)	5.15**

Note: Groups denoted with different letters differ significantly from each other.
[1] n = 23
* $p < .05$ ** $p < .01$

$p < .001$]. A post-hoc analysis revealed that depressed subjects scored significantly higher than panic disorder subjects, who, in turn, scored significantly higher than normal controls on this measure. Subjects with panic disorder obtained significantly higher scores on the Body Vigilance Questionnaire than depressed controls [F (1, 48) = 13.04, $p < .001$]. Panickers and depressed controls did not, however, differ significantly in their self-ratings of the degree of impairment in everyday functioning suffered as a result of their psychiatric disturbance, as measured by the Global Disability Scale [F (1, 48) = 1.39, NS].

Groups differed significantly in their perception of the frequency of memory disturbances they experience, as measured by the total score of the SMQ-R [F (2, 72) = 4.66, $p < .05$; See Table 5.5]. They also differed in self-ratings of their overall memory ability compared to age-related peers, as measured by Part III of the SMQ-R [F (2, 72) = 5.15, $p < .02$]. In each case, depressed subjects reported lower scores (i. e., worse memory ability) than both panic disorder subjects and normal controls. Panickers and normal controls did not differ significantly from one another on this measure.

Groups did not differ in the proportion of subjects who have sought neurological consultation in the past (X^2 (2, N=75) = 4.36, NS; See Table 5.6). A significant difference, however, was found among groups in current use of psychotropic medication (X^2 (2, N=75) = 23.4, $p < .001$). Not surprisingly, a significantly greater number of psychiatric subjects than normal controls reported taking psychotropic medication; psychiatric groups did not, however, differ from each other on this measure.

Table 5.6. History of Neurological Consultation and Current Use of Psychotropic Medication Among Panic Disorder Subjects, Normal Controls, and Depressed Controls.

	Panic Disorder (n = 25)		Normal (n = 25)		Depressed (n=25)		
	N	(%)	N	(%)	N	(%)	X^2
Neurological Consultation	12	(48%)	5	(20%)	9	(36%)	4.36
Current Medication	14[a]	(56%)	0[b]	(0%)	17[a]	(68%)	23.40*

Note: Groups denoted with different letters differ significantly from each other.
* $p < .01$

Group Differences in Memory Functioning

Verbal Learning. Results of planned comparisons between groups on measures of verbal learning and recall are presented in Table 5.7. One-way multivariate analyses of variance (MANOVA) yielded no significant difference between panic disorder subjects and normal controls [F (3, 70) = 1.77, NS], or panic disorder subjects and depressed controls [F (3, 70) = 1.28, NS] on combined verbal learning variables. A significant difference was found, however, between depressed and normal controls [F (3, 70) = 6.02, $p < .01$], with depressed subjects performing worse than normal subjects.

Verbal Recall. No difference was found between panic disorder and normal subjects on combined verbal recall variables [F (4, 69) = 2.11, NS]; however, panic disorder subjects demonstrated significantly worse performance on several univariate measures of verbal recall, including delayed recall of LM stories [F (1, 72) = 4.12, $p < .05$], delayed recall of the verbal SR list [F (1, 72) = 4.41, $p < .05$], and verbal SR Long Term Retrieval scores [F (1, 72) = 7.55, $p < .01$]. Depressed controls differed significantly from both panic disorder subjects [F (4, 69) = 2.83, $p < .03$] and normal controls [F (4, 69) = 5.44, $p < .01$] on multivariate measures, with depressed subjects demonstrating poorer verbal recall compared to the other groups (See Table 5.7).

Visual Learning. Panic disorder subjects performed significantly worse than normal controls on combined visual learning variables [F (2, 71) = 5.24, $p < .01$; See Table 5.8]. No other multivariate comparisons were significant; however, depressed subjects performed significantly worse than normal controls on one univariate measure of visual learning (i. e., Visual SR Trials to Criterion) [F (1, 72) = 4.09, $p < .05$].

Table 5.7. Planned Comparisons of Verbal Memory Variables Among Panic Disorder, Normal Control, and Depressed Control Subjects.

	Panic Disorder (N = 25)		Normal (N = 25)		Depressed (N=25)		Planned Comparisons		
							PD vs. N	PD vs. D	N vs. D
VERBAL LEARNING	M	(SD)	M	(SD)	M	(SD)	F	F	F
Associate Learning	17.1	(3.1)	18.5	(1.7)	15.9	(3.3)	3.21	2.45	11.27**
Verbal Selective Reminding:									
Long term storage	115.8	(18.9)	125.4	(9.6)	107.1	(24.1)	3.36	2.80	12.29**
Trials to criterion	9.7	(3.0)	8.2	(3.3)	10.7	(2.0)	3.48	1.86	10.42**
OVERALL VERBAL LEARNING [1]							**1.77**	**1.28**	**6.01****
VERBAL RECALL									
Logical Memory:									
Delayed recall	5.56	(2.7)	7.1	(2.7)	5.0	(2.4)	4.12*	0.57	7.77**
Associate Learning:									
Delayed Recall	9.5	(0.9)	9.8	(0.6)	8.9	(1.1)	2.07	5.76*	14.75**
Verbal Selective Reminding:									
Delayed recall	10.2	(1.8)	11.5	(0.9)	10.3	(2.0)	7.55**	0.03	6.64*
Long term retrieval	108.4	(22.0)	120.6	(12.7)	99.0	(24.9)	4.41*	2.60	13.77**
OVERALL VERBAL RECALL [1]							**2.11**	**2.83***	**5.44****

[1] Multivariate Analyses
*p < .05
**p < .01

Table 5.8. Planned Comparisons of Visual Memory Variables Among Panic Disorder, Normal Control, and Depressed Control Subjects.

	Panic Disorder (N = 25)		Normal (N = 25)		Depressed (N=25)		Planned Comparisons		
							PD vs. N	PD vs. D	N vs. D
VISUAL LEARNING	M	(SD)	M	(SD)	M	(SD)	F	F	F
Visual Selective Reminding:									
Long term storage	79.5	(13.1)	88.3	(5.4)	83.4	(9.8)	9.76**	1.95	2.98
Trials to criterion	8.0	(3.3)	5.4	(3.0)	7.1	(3.4)	7.50**	0.51	4.09*
OVERALL VISUAL LEARNING [1]							**5.24****	**1.00**	**2.16**
VISUAL RECALL									
Visual Reproduction:									
Delayed recall	8.0	(2.4)	10.2	(2.3)	9.5	(2.6)	9.05**	4.58*	0.75
Visual Selective Reminding:									
Delayed recall	6.6	(1.4)	7.8	(0.4)	7.4	(1.0)	15.58**	7.95**	1.27
Long term retrieval	75.3	(16.4)	86.7	(6.7)	78.0	(13.5)	9.89**	1.65	3.45
Benton VRT Errors	4.8	(1.8)	2.4	(1.9)	2.9	(2.3)	16.23**	10.21**	0.70
OVERALL VISUAL RECALL [1]							**7.32****	**4.30****	**0.93**

[1] Multivariate Analyses
*$p < .05$
**$p < .01$

Table 5.9. Planned Comparisons of Attention Variables Among Panic Disorder, Normal Control, and Depressed Control Subjects.

	Panic Disorder (N = 25)		Normal (N = 25)		Depressed (N=25)		Planned Comparisons		
							PD vs. N	PD vs. D	N vs. D
	M	(SD)	M	(SD)	M	(SD)	F	F	F
Mental Control	7.5	(1.5)	7.8	(1.3)	6.9	(2.4)	0.40	1.62	3.63
Digits Forward	6.8	(1.1)	6.7	(1.2)	6.4	(1.3)	0.12	1.66	0.88
Digits Backward	4.9	(1.3)	5.0	(1.2)	4.9	(1.2)	0.20	0.13	0.11
OVERALL ATTENTION[1]							**0.42**	**1.54**	**1.41**

[1] **Multivariate Analysis**

Visual Recall. On the combined measure of visual recall, panic disorder subjects performed significantly worse than normal [F (4, 69) = 7.32, $p < .01$] and depressed controls [F (4, 69) = 4.30, $p < .01$]; no difference was found between depressed and normal control subjects on these measures [F (4, 69) = 0.93, NS]. These data are presented in Table 5.8.

Attention. Results of comparisons on measures of attention are presented in Table 5.9. No significant differences were found between any groups on these measures.

Effects of State Anxiety and Depressive Symptomatology

Given the significant differences among groups in reported level of anxiety and depressive symptomatology at the time of testing (i. e., State Anxiety (SA) scores and BDI scores), multivariate analyses of variance were repeated holding SA scores as a covariate. Although a subject group was included specifically to control for depressive symptomatology in panic disorder, BDI scores were held as a covariate alone, and together with SA scores, in comparisons between panic disorder and normal control subjects. The assumption of homogeneity of covariance was met in all analyses.

Effects of group status on the dependent (i. e., memory) variables after adjustment for SA scores are presented in Table 5.10. Analyses were not repeated on the panic disorder versus depressed condition, since panickers and depressed controls did not differ significantly from each other on this measure. After statistically adjusting for differences in anxiety at the time of testing, the difference between panic disorder subjects and normal controls in overall visual recall remained; however, the main effect for combined visual learning variables was no longer statistically significant. The lack

Table 5.10. Univariate and Multivariate Results of Analyses of Panic Disorder Subjects Versus Normal Controls and Depressed Versus Normal Controls Holding State Anxiety (SA) Scores as a Covariate.

Variables	Panic Disorder vs. Normal Control	Depressed vs. Normal Control
	F	F
Verbal Learning:		
Paired Associate Learning	0.98	5.49*
Verbal SR Long Term Storage	1.66	7.54**
Verbal SR Trials to Criterion	2.65	7.97**
Verbal Recall:		
Logical Memory Delay	1.44[a]	3.22
Paired Associate Learning Delay	1.07	10.05**
Verbal SR Delay	5.85*	4.87*
Verbal SR Long Term Retrieval	3.88[a]	8.64**
Visual Learning:		
Visual SR Long Term Storage	5.49*	0.88
Visual SR Trials to Criterion	3.01[a]	0.88[a]
Visual Recall:		
Visual Reproduction Delay	4.63*	0.00
Visual SR Delayed Recall	10.21**	0.27
Visual SR Long Term Retrieval	5.33*	0.99
Benton VRT Errors	10.16**	0.01
Attention:		
Mental Control	0.00	1.14
Digits Forward	3.50	0.52
Digits Backward	0.64	1.10
Overall Verbal Learning[1]	0.97	3.70**
Overall Verbal Recall[1]	1.47	3.45**
Overall Visual Learning[1]	2.77[a]	0.53
Overall Visual Recall[1]	4.70**	0.24
Overall Attention[1]	1.25	1.17

[1] Multivariate Analysis

[a]Comparison was significant in unadjusted MANOVA, but lost significance in covariance analysis.

* $p < .05$ ** $p < .01$

of group differences between panic disorder and normal subjects on overall verbal learning, verbal recall, and attention remained unchanged when SA scores were held as a covariate. Moreover, significant differences on univariate measures of verbal recall were significantly reduced, with two of the three differences (LM delay and Verbal LTR scores) lost in the covariance analysis. Comparisons of depressed versus normal subjects after statistically adjusting for differences in anxiety at the time of testing yielded no significant changes in multivariate results; however, the significant difference between groups on the univariate measure of the number of learning trials to achieve criterion on the visual selective reminding test was lost in the covariance analysis (See Table 5.10).

Effects of group status on memory variables after adjustment for BDI scores are presented in Table 5.11. Multivariate results obtained after statistically adjusting for differences in depression at the time of testing were similar to those found in unadjusted analyses; group differences in visual learning and visual recall remained, while no differences were found between groups in verbal learning, verbal recall, or attention. Interestingly, adjusting for BDI scores had the same effect of reducing the significance of group differences on univariate measures of verbal recall as adjusting for SA scores (see above). Similar results were obtained when both SA and BDI scores were held together as covariates; however, the significance of the main effect for visual learning was reduced from .01 to .05 (See Table 5.11).

In addition to higher state anxiety scores and depressive symptomatology, panickers scored significantly lower than normal controls on the Picture Completion subtest of the WAIS-R. Consequently, comparisons between panic disorder subjects and normal controls were repeated holding Picture Completion scores as a covariate; no other comparisons were made, since depressed controls did not differ significantly from panic

Table 5.11. Univariate and Multivariate Results of Analyses of Panic Disorder Subjects Versus Normal Controls Holding Beck Depression (BDI) Scores and State Anxiety (SA) Scores as Covariates.

Variables	Adjusted for BDI	Adjusted for BDI and SA
	F	F
Verbal Learning:		
Paired Associate Learning	2.89	1.51
Verbal SR Long Term Storage	2.57	1.76
Verbal SR Trials to Criterion	3.45	2.90
Verbal Recall:		
Logical Memory Delay	1.85[a]	1.08[a]
Paired Associate Learning Delay	1.09	0.83
Verbal SR Delay	6.41*	5.68*
Verbal SR Long Term Retrieval	3.62[a]	2.59[a]
Visual Learning:		
Visual SR Long Term Storage	8.05**	5.97*
Visual SR Trials to Criterion	7.66**	4.87*
Visual Recall:		
Visual Reproduction Delay	5.79*	4.21*
Visual SR Delayed Recall	11.03**	9.21**
Visual SR Long Term Retrieval	8.22**	5.95*
Benton VRT Errors	10.62**	8.78**
Attention:		
Mental Control	0.01	0.03
Digits Forward	0.81	3.02
Digits Backward	0.01	0.48
Overall Verbal Learning[1]	1.60	1.13
Overall Verbal Recall[1]	1.59	1.38
Overall Visual Learning[1]	4.69**	3.30*
Overall Visual Recall[1]	5.09**	4.21**
Overall Attention[1]	0.45	1.06

[1] Multivariate Analysis

[a]Comparison was significant in unadjusted MANOVA, but lost significance in covariance analysis.

* $p < .05$ ** $p < .01$

Table 5.12. Univariate and Multivariate Results of Analyses of Panic Disorder Subjects Versus Normal Controls Holding Picture Completion Scores as a Covariate.

Variables	F
Verbal Learning:	
Paired Associate Learning	1.47
Verbal SR Long Term Storage	1.81
Verbal SR Trials to Criterion	2.21
Verbal Recall:	
Logical Memory Delay	2.19[a]
Paired Associate Learning Delay	1.24
Verbal SR Delay	7.45**
Verbal SR Long Term Retrieval	2.66[a]
Visual Learning:	
Visual SR Long Term Storage	5.75**
Visual SR Trials to Criterion	4.52*
Visual Recall:	
Visual Reproduction Delay	6.77**
Visual SR Delayed Recall	11.15**
Visual SR Long Term Retrieval	5.38*
Benton VRT Errors	11.17**
Attention:	
Mental Control	0.00
Digits Forward	1.35
Digits Backward	0.10
Overall Verbal Learning[1]	1.00
Overall Verbal Recall[1]	1.93
Overall Visual Learning[1]	3.05*
Overall Visual Recall[1]	5.27**
Overall Attention[1]	0.98

[1] Multivariate Analysis

[a]Comparison was significant in unadjusted MANOVA, but lost significance in covariance analysis.

* $p < .05$ ** $p < .01$

disorder subjects or normals on this measure. Results of these analyses are presented in Table 5.12. Multivariate results obtained after statistically adjusting for Picture Completion scores were similar to those found in the unadjusted analyses. Significant group differences were found in visual learning and visual recall; however, the the significance of the effect for overall visual learning was reduced from .01 to .05 in the analysis. Again, no differences were found between groups in verbal learning, verbal recall, or attention.

Medication Effects

The relationship between the use of psychotropic medication and memory test performance was examined within each psychiatric group in one-way multivariate analyses of variance, with medication status (medication vs. no medication) as the independent variable and memory test scores as the dependent variables. Differences in age, education, BDI scores, SA scores, global disability ratings, and IQ measures between the two levels of the independent variable were not statistically significant. Results yielded no main effect for medication usage on any of the combined dependent variables in either psychiatric group (See Tables 5.13 and 5.14).

Clinical Significance of Memory Findings

Differences in the proportion of subjects in each group with performances that would be rated as clinically impaired (See p. 73) were examined in 2 X 2 (subject group X impairment status) Chi-square analyses with correction for continuity. Results of these analyses are presented in Table 5.15. A significantly greater number of PD subjects

Table 5.13. Memory Variables by Medication Status in Patients with Panic Disorder.

	Medication (n = 14)		No Medication (n = 11)		
VERBAL LEARNING	M	(SD)	M	(SD)	F
Associate Learning	17.4	(3.2)	16.7	(3.0)	0.28
Verbal Selective Reminding:					
Long term storage	118.0	(16.7)	113.1	(21.9)	0.41
Trials to criterion	9.1	(3.0)	10.5	(3.0)	0.26
OVERALL VERBAL LEARNING [1]					**0.74**
VERBAL RECALL					
Logical Memory:					
Delayed recall	6.0	(2.8)	5.1	(2.7)	0.69
Associate Learning:					
Delayed Recall	9.4	(1.2)	9.6	(0.5)	0.56
Verbal Selective Reminding:					
Delayed recall	10.8	(1.4)	9.5	(2.0)	3.86
Long term retrieval	112.1	(19.6)	103.6	(24.9)	0.92
OVERALL VERBAL RECALL [1]					**1.13**
VISUAL LEARNING					
Visual Selective Reminding					
Long term storage	82.4	(7.7)	75.8	(17.5)	1.62
Trials to criterion	7.4	(3.3)	8.6	(3.3)	0.81
OVERALL VISUAL LEARNING [1]					**0.78**
VISUAL RECALL					
Visual Reproduction:					
Delayed recall	8.2	(1.9)	7.7	(3.0)	0.25
Visual Selective Reminding:					
Delayed recall	6.6	(1.3)	6.6	(1.6)	0.00
Long term retrieval	78.8	(11.1)	70.8	(21.1)	1.48
Benton VRT Errors	5.0	(2.1)	4.5	(1.5)	0.54
OVERALL VISUAL RECALL [1]					**0.67**
ATTENTION					
Mental Control	7.8	(1.4)	7.2	(1.5)	1.08
Digits Forward	7.0	(1.1)	6.5	(1.1)	1.02
Digits Backward	4.9	(1.4)	4.9	(1.3)	0.01
OVERALL ATTENTION[1]					**1.06**

[1] Multivariate Analysis

Table 5.14. Memory Variables by Medication Status in Patients with Depression.

	Medication (n = 17)		No Medication (n = 8)		
VERBAL LEARNING	M	(SD)	M	(SD)	F
Associate Learning	16.2	(3.4)	15.3	(3.5)	0.38
Verbal Selective Reminding:					
Long term storage	101.9	(25.8)	118.0	(16.0)	2.58
Trials to criterion	10.8	(2.1)	10.5	(1.82)	0.20
OVERALL VERBAL LEARNING [1]					**1.87**
VERBAL RECALL					
Logical Memory:					
Delayed recall	4.9	(2.6)	5.1	(1.9)	0.03
Associate Learning:					
Delayed Recall	8.9	(1.1)	8.8	(1.2)	0.16
Verbal Selective Reminding:					
Delayed recall	9.9	(2.3)	11.1	(1.1)	2.13
Long term retrieval	94.2	(27.1)	109.4	(16.3)	2.12
OVERALL VERBAL RECALL [1]					**1.08**
VISUAL LEARNING					
Visual Selective Reminding					
Long term storage	83.0	(10.2)	84.4	(9.4)	0.10
Trials to criterion	7.7	(3.7)	6.4	(3.7)	0.70
OVERALL VISUAL LEARNING [1]					**0.44**
VISUAL RECALL					
Visual Reproduction:					
Delayed recall	9.1	(2.5	10.3	(2.7)	1.05
Visual Selective Reminding:					
Delayed recall	7.2	(1.1)	7.9	(0.4)	2.57
Long term retrieval	78.5	(14.7)	83.1	(10.7)	0.64
Benton VRT Errors	3.3	(2.6)	2.1	(1.6)	1.4
OVERALL VISUAL RECALL [1]					**0.87**
ATTENTION					
Mental Control	7.1	(2.1)	6.5	(3.0)	0.29
Digits Forward	6.7	(1.3)	5.6	(0.9)	4.38*
Digits Backward	5.1	(1.3)	4.6	(0.7)	0.72
OVERALL ATTENTION[1]					**1.52**

[1] **Multivariate Analysis**
* $p < .05$

Table 5.15. Proportion of Subjects in Each Group with Impaired Performance on Selected Measures.

	Panic Disorder (N = 25)		Normal (N = 25)		Depressed (N=25)		Planned Comparisons		
							PD vs. N	PD vs. D	N vs. D
VARIABLES	N	(%)	N	(%)	N	(%)	X^2	X^2	X^2
Verbal Measures:									
Paired Associate Learning	0	(0%)	0	(0%)	0	(0%)	0.00	0.00	0.00
Verbal SR LTS	4	(16%)	0	(0%)	5	(20%)	2.45	0.00	3.56#
Verbal SR Consistent LTR	3	(12%)	0	(0%)	2	(8%)	1.42	0.00	0.52
Logical Memory Delay	9	(36%)	3	(12%)	12	(48%)	2.74	0.33	6.10*
Visual Measures:									
Visual Reproduction Delay	6	(24%)	0	(0%)	0	(0%)	4.74*	4.74*	0.00
Benton VRT Errors	15	(60%)	6	(24%)	11	(44%)	5.26*	0.72	1.43

*$p < .05$
#$p = .059$

than normal controls demonstrated impaired performances on measures of visual recall (VR delay, X^2 (1, N=50) = 4.74, p < .03; BVRT, X^2 (1, N=50) = 5.26, p < .02). The PD group also contained a significantly greater number of subjects with impaired performance on VR delay (X^2 (1, N=50) = 4.74, p < .03) than depressed controls. No significant difference was found in the proportion of PD and depressed subjects with clinically impaired performances on the BVRT. In contrast, more depressed subjects than normal controls demonstrated impaired performance on delayed recall of LM stories (X^2 (1, N=50) = 6.10, p < .02). Moreover, a nonsignificant trend toward a greater number of depressed than normal control subjects with impaired performance on verbal SR Long Term Storage scores was also found (X^2 (1, N=50) = 3.56, p < .06). No other group differences were observed.

Self-Focus and Memory

A standard multiple correlation analysis was performed on the sample of PD subjects, with self reported tendency to detect physiological sensations (i. e., BVQ scores) as the dependent variable, and verbal learning, verbal recall, visual learning, visual recall, and concentration composite scores as the independent variables. Table 5.16 displays the correlations between variables, R, R^2, and adjusted R^2. The multiple correlation for this analysis was not significantly different from zero [F (5, 19) = 0.67, NS].

Table 5.16. Multiple Correlation of Memory Variables on Body Vigilance Scores.

Variable	BVQ (DV)	Verbal Learning	Verbal Recall	Visual Learning	Visual Recall
Verbal Learning	0.09				
Verbal Recall	-0.02	0.84			
Visual Learning	0.25	0.16	0.03		
Visual Recall	0.03	0.25	0.07	0.72	
Attention	-0.11	0.47	0.35	0.09	0.41
					$R^2 = 0.15$
					Adjusted $R^2 = 0.00$
					$R = 0.39$

Panic Severity and Memory

A standard multiple correlation analysis was performed between the composite variable of panic severity as the dependent variable and verbal learning, verbal recall, visual learning, visual recall, and concentration composite scores as the independent variables. Table 5.17 displays the correlations between variables, R, R^2, and adjusted R^2. The multiple correlation approached, but did not achieve, significance from zero [F (5, 18) = 2.23, $p < .10$]. One independent variable (i. e., Attention), however, correlated significantly negatively with panic severity (r= -0.53). .

Table 5.17. Multiple Correlation of Memory Variables on Panic Severity.

Variable	Panic Severity (DV)	Verbal Learning	Verbal Recall	Visual Learning	Visual Recall
Verbal Learning	-0.13				
Verbal Recall	0.08	0.83			
Visual Learning	-0.06	0.13	-0.01		
Visual Recall	-0.28	0.24	0.06	0.72	
Attention	-0.53*	0.47	0.34	0.08	0.40
					$R^2 = 0.38$
					Adjusted $R^2 = 0.21$
					$R = 0.62$

* $p < .05$

CHAPTER 6

Discussion

In the present study, subjects with panic disorder (PD) demonstrated greater impairment on multivariate measures of visual learning and recall than normal control subjects. PD subjects were no different from normal controls on multivariate measures of verbal learning, verbal recall, or attentional ability. When compared to depressed control subjects, PD subjects exhibited significantly poorer performance on visual recall; however, no group difference was found for visual learning. In contrast, PD subjects performed significantly better than depressed controls on measures of verbal recall and were no different from depressed controls on measures of verbal learning or attention.

A similar pattern of results was found when a more stringent criterion of memory dysfunction was applied, namely, the proportion of subjects in each group exhibiting clinically impaired performances. Based on available normative data, a greater proportion of PD subjects than normal controls demonstrated performance below the 10th percentile for their age on delayed recall of the VR subtest of the WMS and committed a greater number of BVRT errors than expected for their age and estimated IQ. The number of PD subjects with impaired performance on these tests of visual recall also exceeded that of depressed subjects; however, groups differed significantly on only one of the two selected measures (i. e., VR delay). In contrast, the proportion of PD subjects with clinically impaired performances on selected measures of verbal learning and recall did not differ significantly from that of normal or depressed controls

Results of the present study are not likely attributable to group differences in visuoperceptual discrimination, as measured by the WAIS-R Picture Completion subtest

(Wechsler, 1981). Moreover, as will be discussed later, results cannot be attributed to use of psychotropic medication or level of depressive symptomatology, nor can they be fully explained by group differences in level of state anxiety. Instead, the presence and pattern of memory deficits among PD subjects in this study suggest a neuropsychological correlate to panic disorder consistent with neuroimaging studies, which have reported structural and metabolic abnormalities in right medial temporal lobe of patients with panic disorder (See Chapter 3). The temporal lobes are known to contain structures crucial to memory functioning (Squire, 1983; Butters, 1984). Moreover, studies of hemispheric specialization and lateralization have shown that, among right-handed individuals, visual memory functioning is subserved primarily by the right temporal lobe (cf., Geschwind & Galaburda, 1985). Disturbance in visual memory ability, with relative sparing of other areas of cognitive functioning, would be consistent with focal abnormalities in this region. Therefore, the finding that PD subjects perform significantly worse on composite measures of visual memory compared to normal and psychiatric controls, but do not perform worse than controls on composite measures of verbal memory and attention supports the hypothesis of right temporal lobe dysfunction associated with panic disorder.

Although, as stated above, PD subjects did not differ significantly from normal controls on composite measures of verbal recall, PD subjects performed significantly worse than normal controls on several univariate measures of verbal recall. These results appear inconsistent with cerebral involvement lateralized to the right temporal lobe. Despite the dominance of the left-hemisphere for verbal functioning, however, the right-hemisphere is not devoid of such functioning (Cummings, 1985; Zaidel, 1985). Given the incomplete nature of cerebral lateralization and the extensive interconnections

that exist between the two hemispheres, it is possible that right temporal lobe involvement may interfere with verbal, as well as visual, recall. The extent of verbal impairment, however, would be expected to be much less than that of visual memory impairment. Such a pattern is consistent with the present results.

A second possibility is that impaired performance on univariate measures of verbal recall among PD subjects reflects some degree of bilateral temporal lobe involvement in panic disorder. Although patients with panic disorder demonstrate focal, right temporal lobe abnormalities at rest (e. g., Reiman et al., 1986), abnormal metabolic elevations have been found bilaterally in the temporal lobes during panic episodes (e. g., Reiman, 1989). It is not uncommon for patients with panic disorder to experience panic episodes without others being aware that the episode is taking place (Barlow, 1988). Although not assessed directly, some of the PD subjects in the present sample may have experienced panic during the testing procedure. Consequently, these subjects may have had difficulty performing verbal as well as visual memory tasks, secondary to abnormal bilateral temporal lobe activity. It should be reiterated, however, that when the more stringent criterion of clinical impairment was applied, PD subjects did not differ significantly from normal controls on measures of verbal recall, but did differ significantly on measures of visual recall. These results more strongly support the proposed role of right temporal lobe involvement in panic disorder.

Memory Findings in Depressed Controls

Significant memory deficits were also found among subjects with major depression; however, these deficit were largely within the realm of verbal learning and recall, rather than visual learning and recall. When compared to PD subjects, depressed

subjects performed significantly worse on overall measures of verbal recall. When compared to normal control subjects, depressed subjects performed significantly worse on overall measures of both verbal learning and verbal recall, but were not significantly different from normals on overall measures of visual learning and recall. Depressed subjects did, however, require a significantly greater number of learning trials to achieve criterion on the Visual SR procedure as compared to normal controls. No differences were found between these two groups on delayed recall of the visual stimuli, suggesting relatively intact visual memory. Given the additional exposure to the test stimuli afforded to depressed subjects, however, overlearning may have occurred and confounded results of the delayed recall measure (see Underwood, 1966).

Based on available normative data, depressed patients demonstrated a greater number of clinically impaired performances on three of four selected measures of verbal memory; however, only one of these, a measure of verbal recall, obtained clinical significance (LM delay), while another, a measure of verbal learning, approached, but did not reach significance (Verbal SR LTS). Several depressed subjects also demonstrated impaired performance on a measure of visual recall (BVRT); however, the proportion of depressed subjects with such a performance was not significantly different from that of normal controls.

It has long been suggested that organic factors may play a role in many forms of depression. To date, however, neuropsychological studies have yielded inconsistent results with regards to cognitive functioning in depressed patients. Several authors have found no relationship between depression and neuropsychological impairment (see review by Heaton & Crowley, 1981), while others have found that depression can produce or exacerbate cognitive deficits on a number of neuropsychological measures (Fisher, Sweet,

& Pfaelzer-Smith, 1986; Miller, 1975; Sternberg & Jarvik, 1976; Sweet, 1983). Studies noting cognitive deficits among depressed patients have generally reported a variety of findings, including motor slowing (bradykinesia), reduced speed of cognitive processing (bradyphrenia), impaired verbal learning, impaired free recall, poor performance on spatial tasks, and reduced scores on intelligence tests (Fisher et al., 1986; Miller, 1975; Rush, Weissenburger, Vinson, & Giles, 1983). In a comprehensive review of the literature, Miller (1975) argued that despite "occasional" findings of cognitive deficits among depressed subjects, no study had been able to demonstrate a pattern of deficits in cognitive functioning unique to depression. McAllister (1983) reviewed several studies of memory functioning in depression, and suggested that depression impaired verbal learning, verbal recall, and visual recall. Although a recent study also suggested that depressed patients tend to demonstrate deficits in both verbal and visual memory functioning (Richards & Ruff, 1989), other investigators have demonstrated that depressed patients are essentially unimpaired on measures of learning and recall (e. g., Gass & Russell, 1986; Williams, Little, Scates, & Blockman, 1987).

The inconsistency of neuropsychological studies of depression in the literature is mirrored by the results of neuroimaging studies, which have been somewhat inconsistent in the localization of areas of cerebral dysfunction in depression (see pp. 50-51). Some have suggested that depression is associated with reduced functioning in the posterior (i. e., parieto-occipital) region of the right cerebral hemisphere and the anterior (i. e., frontal) region of the left cerebral hemisphere. Brain imaging studies have yielded some support for this hypothesis; however, the majority of metabolic studies have found reduced cerebral functioning bilaterally in the frontal lobes, with evidence of greater dysfunction in the left frontal lobe.

One possible reason for some of the inconsistencies seen within neuropsychological and neuroimaging studies is heterogeneity of the subject samples studied. Many of the brain imaging studies have examined relatively small samples comprised of subjects carrying a variety of depressive diagnoses, including Bipolar Mood Disorder, Dysthymia, Depressive Disorder Not Otherwise Specified (i. e., Atypical Depression) and Reactive Depression, as well as subjects meeting criteria for Major Depression. Consequently, Henriques and Davidson (1990) have suggested that inconsistencies across neuroimaging studies may reflect different subgroups of depression. A well controlled study of endogenous, unipolar depression, however, confirmed the finding of left frontal hypometabolism in such patients (Mazziotta & Phelps, 1985).

Heterogeneity of subject samples may also contribute to the inconsistency of results across neuropsychological studies of depression. Some studies (e. g., Williams et al., 1987) selected subjects on an ad hoc basis, while others (e. g., Gass & Russell, 1986) used a post-hoc method of selecting subjects. In addition, a significant number of published studies of neuropsychological functioning and depression have been conducted exclusively on elderly subjects in order to evaluate differences in cognitive functioning associated with normal aging, dementia, and "pseudodementia" (See Massman, 1990). Consequently, some cognitive deficits reportedly associated with depression may reflect dysfunction secondary to normal or abnormal aging. Finally, the methods employed to diagnose depression varies considerably across studies, with some verifying diagnoses based on face-to-face interviews (e. g., Williams et al., 1987) and others relying solely on results of psychometric tests, such as the Minnesota Multiphasic Personality Inventory and the Beck Depression Inventory (e. g., Gass & Russell, 1986).

In the present study, all depressed control subjects met DSM III-R criteria for current major depression without history of psychotic features. Subjects were recruited on an ad hoc basis through referrals from mental health professionals, and diagnoses were verified by clinical interview. Moreover, subjects were of ages not generally at risk for degenerative dementing illnesses. Results revealed that depressed patients performed significantly worse than normal controls on composite measures of verbal learning, and worse than PD subjects and normal controls on a composite measure of verbal recall. There is compelling evidence to suggest that, in right-handed individuals, verbal functioning is strongly lateralized to the left hemisphere (cf. Geschwind & Galaburda, 1985). Results therefore support the hypothesis that organic dysfunction associated with unipolar depression may be characterized by left-hemisphere disease. Although speculative, results may reflect verbal retrieval deficits consistent with left frontal lobe dysfunction (Mayes & Meudell, 1985). It should be noted, however, that depressed patients were no more likely than normal controls or PD subjects to demonstrate clinically impaired performance on at least two of four selected tests of verbal memory. Consequently, any hemispheric pathology that may be present is likely to be relatively mild. Despite this, results hold important implications for the relationship between PD and depression. Although significant overlap between panic and depression has been documented in the literature (e. g., Lesser et al., 1988), the finding of a double dissociation between PD and depressed subjects on memory test performance may provide an important distinction between these two disorders.

Interestingly, although both PD subjects and depressed controls demonstrated significant memory deficits compared to normals, only the depressed subjects rated themselves as experiencing memory problems on a self-report questionnaire (i. e.,

SMQ-R). In general, depressed patients rated their memory ability for everyday things (e.g., names of people, the color of cloth for matching) as slightly below average, and perceived that memory failures, such as forgetting to turn off the stove, occurred more often than panickers or normal controls. In addition, depressed subjects rated their overall memory ability as slightly below average compared to their age related peers, while panickers and normals rated their memory as average to slightly above average. These results may reflect a more accurate assessment of memory ability by the depressed patients than by the panic disorder patients, consistent with the theory of "depressive realism" (Alloy, 1988). It is also possible that verbal memory deficits are more readily perceived than visual memory deficits. Individuals with poor visual memory but intact verbal memory may employ verbal strategies to encode visual information for storage and future recall. The reverse, however, may not be as easy a strategy to employ. Consequently, deficits in visual memory may be relatively undetected in everyday functioning, while verbal deficits would be quickly noticed. Yet another possibility is that the SMQ-R is biased toward assessing perception of verbal memory ability, thus differentially affecting PD and depressed subjects. Part I of this measure consists of many more verbally-related memory abilities than visually-related abilities, thus biasing results of the total score. Part III of this measure, however, asks subjects to rate their overall memory ability compared to age-related peers. The persistence of the group difference on this rating in the absence of a modality-specific reference reduces the likelihood of the bias hypothesis; however, the verbal nature of the questions in Part I may have made the memory deficits of the depressed subjects more salient, thus biasing their responses to the overall rating item.

It has long been recognized that factors other than cerebral dysfunction may contribute to poor performance on neuropsychological tests (Adams, Boake, & Crain, 1983; Anthony, Heaton, & Lehman, 1980, Heaton, Grant, & Mathews, 1986). Subject characteristics such as age, education, and gender must be taken into account, as well as test-taking variables such as fatigue, psychological factors, medication usage, and freedom from distractibility. In the present study, group differences were not found for age or education, and subjects were matched for gender; therefore, it is unlikely that these variables are responsible for the observed findings. Moreover, given that both verbal and visual memory were assessed throughout the course of the one and one-half hour evaluation, it is unlikely that factors such as fatigue would differentially affect one memory modality compared to another, as was found in the present study. Additional factors, including level of anxiety and depression experienced during testing, effects of medication usage, and ability to sustain attention were evaluated to determine their effects on memory test performances.

Effects of State Anxiety and Depressive Symptomatology

When level of anxiety at the time of testing was controlled statistically, the main effect for visual learning between PD and normal control subjects was no longer significant. In addition, two of the three significant differences between PD and normal control subjects on univariate measures of verbal recall were lost, while the third was reduced from .01 to .05. The significant difference found between depressed and normal controls on a univariate measure of visual learning was also lost. In contrast, the main effects for visual recall between PD and normal controls remained significant, as did the

differences in verbal learning and recall found between depressed and normal control subjects.

Interestingly, controlling for depresssive symptomatology (i. e., BDI scores) had the same effect of reducing the significance of differences between PD and normal control subjects on univariate measures of verbal recall as controlling for state anxiety. The main effects for both visual learning and recall, however, were not significantly affected by depression. A similar pattern of results was found when both state anxiety and depression were controlled statistically, although the significance of the main effect for visual learning between PD subjects and normal controls was reduced from the .01 to .05 level.

Overall, these results suggest that state anxiety is strongly associated with the visual learning deficits found in PD subjects, but does not account for the significantly poorer visual recall among PD subjects or the verbal learning and recall deficits found in depressed patients. Although state anxiety appears to account for differences between PD subjects and normal controls in verbal recall, similar effects were seen on measures of verbal recall when depression was controlled statistically. Therefore, the difference between PD and normal subjects on these measures is not specific to anxiety. In addition, depressive symptomatology, as measured by the BDI, does not appear to contribute significantly to differences between PD and normal control subjects on measures of visual learning and recall. Consequently, the effect of state anxiety on visual learning in panic disorder appears to be unique.

The loss of the group difference in visual learning and the persistence of group difference in visual recall among PD subjects when state anxiety was controlled statistically is of particular interest. It appears, based on these findings, that visual

learning in patients with panic disorder is mediated by processes related to state anxiety, while recall of visual information is independent of such processes. Studies of amnesic patients suggest that the hippocampus may play a role specifically in consolidation and storage of information (i. e., learning), whereas other temporal lobe regions, such as the parahippocampal gyrus, may be more important to retrieval (cf., Butters & Miliotis, 1985). The hippocampus has also been implicated as a neuroanatomical substrate of anxiety (Gray, 1982). It may be that the role of the hippocampus in visual learning is secondary to its role in anxiety among patients with PD. Consequently, visual learning may be sacrificed or made less efficient during anxious activation. The specificity of these findings to visual learning (as opposed to verbal learning or visual recall) suggests that right hippocampal functioning may be more related to the experience of state anxiety than left hippocampal functioning. This is consistent with the recent finding that the right cerebral hemisphere has a greater role than the left-hemisphere in processing autonomic activity (Wittling, 1990).

Despite the high level of state anxiety reported by depressed controls at the time of testing, depressed subjects did not differ from normal controls on measures of visual learning. Moreover, verbal learning and recall deficits found among depressed patients compared to normal controls remained when state anxiety was controlled statistically. These findings suggest that state anxiety may affect cognitive functioning differently among patients with depression than patients with PD, and that the proposed relationship between state anxiety and hippocampal functioning may not be generalized to populations other than panic disorder.

Unlike the effect for visual learning, the main effect for visual recall between PD subjects and normal controls remained significant after state anxiety was controlled

statistically. This is consistent with studies that suggest that retrieval of information relies on processes distinct from those underlying learning (e. g., Butters & Miliotis, 1985). Squire (1987) has suggested that memory storage is widely distributed in the brain, with different loci storing different aspects of the whole. The extensive convergence of neural fibers from the neocortex on to the parahippocampal gyrus, and the functional relationship between the parahippocampal gyrus and hippocampus proper strongly implicate the parahippocampal gyrus in the function of retrieval of information from storage (e. g., Squire, 1987). Metabolic and neuroanatomical studies have reported abnormalities in the parahippocampal region of patients with panic disorder (See Chapter 3). If present, such abnormalities should affect recall regardless of the subject's mood state, and would account for the results observed in this study.

Medication Effects

Given the significant number of PD and depressed subjects receiving psychotropic medication, the possible effect of medication on the present results was addressed. Fifty-six percent of the PD subjects (n = 14) and 68% of the depressed subjects (n = 17) in the present study were taking psychotropic medication. Among the PD subjects, 11 were taking benzodiazepine (10 alprazolam, 1 lorazepam), one was taking a monoamine oxidase (MAO) inhibitor, and two others were taking tricyclic antidepressants. Among the depressed subjects, nine were taking a tricyclic antidepressant, seven were taking fluoxetine hydrochloride (Prozac), and one was taking an MAO inhibitor.

Studies have suggested that acute administration of benzodiazepine may significantly impair learning and memory (Lister, 1985; Block & Berchou, 1984; Wolkowitz, et al., 1987). Studies of chronic benzodiazepine use, however, have failed

to show similar effects. Bornstein, Watson, and Pawluck (1985) administered the WMS LM and VR subtests, as well as other neuropsychological measures, to subjects who had taken either benzodiazepine or placebo for seven days. Results showed no differences between groups on any measure. Similarly, Lucki, Rickels, and Geller (1986) found that patients who had been taking benzodiazepine for a mean of 60 months performed as well on a list-learning task while taking their medication as they did after their medication was terminated.

In contrast, studies of the effects of antidepressant medication on neuropsychological performance have yielded inconsistent results. Some have reported impaired performance on memory tests following treatment with imipramine (Legg & Stiff, 1976), while others have found no significant impairment in neuropsychological functioning associated with tricyclic use (Heimann, Reed, & Witt, 1968; Kendrick & Post, 1967). Still others have reported that use of antidepressant medication results in improved performance of depressed patients on tests of learning and memory (Stern & Jarvik, 1976).

Subjects taking psychotropic medications were included in the present study only if they had been maintained on their current dosage for at least one month. Thus, the likelihood of acute effects of medication on cognitive functioning was greatly reduced. Moreover, analyses revealed that, within each patient group, medicated and unmedicated subjects did not differ significantly with respect to attention or memory functioning. These results suggest that the findings of memory disturbances among PD and depressed subjects compared to normal controls are not likely due to use of psychotropic medication among subjects in the psychiatric groups.

Attentional Activity

The present study failed to find group differences on tests traditionally believed to measure attentional activity. This is inconsistent with the literature, which contains compelling evidence suggesting differences in attention between subjects with anxiety disorders and controls. Barlow (1988) has proposed that attentional shifts toward self-evaluation are central to all anxiety disorders. Moreover, studies exploring the role of attentional processes in anxiety have suggested that anxious subjects shift attention toward stimuli related to their specific fear (e.g., MacLeod, Mathews, & Tata, 1986; Mathews & MacLeod, 1985; Watts, McKenna, Sharrock, & Trezise, 1986; Ehlers, Margraf, Davies, & Roth, 1988; McNally, Riemann, & Kim,1990; Hope, Rapee, Heimberg, & Dombeck, 1990). The lack of differences in attention between PD subjects and controls is also inconsistent with Gray's (1982) model of anxiety, which, like Barlow's (1988) model, suggests that pathological anxiety is characterized in part by inappropriate shifts of attention.

Despite the lack of group differences on measures of attention, significant differences were found among groups on measures of verbal and visual memory. These results strongly suggest that the memory deficits found were not attributable to attentional capacity. Moreover, as stated earlier with regard to the possible effect of fatigue on memory test performance, it is unlikely that poor attention or attentional shifts such as those posited by Barlow (1988) and Gray (1982) would selectively impair one memory modality and leave the other modality relatively intact. Together with the results of analyses of anxiety, depression, and medication, these findings underscore the specific nature of PD with regard to visual memory deficits, as well as the specific

nature of depression with regard to verbal memory deficits, thereby strengthening the hypotheses of hemispheric dysfunction associated with these behavioral disorders.

The inconsistency between the present results of attention testing and the literature of attentional processes associated with anxiety disorders deserves comment. In neuropsychology, attentional activity is generally conceptualized in terms of three related constructs: attention, concentration, and conceptual tracking. The construct of attention refers to the capacity for selective perception, while concentration is characterized as an effortful state of attention in which irrelevant stimuli are inhibited from awareness; conceptual tracking, on the other hand, involves concentrating on a line of thought over a period of time (Lezak, 1983). While the tests of attentional activity used in the present study are often casually referred to as measures of "attention" (e. g., Erickson & Scott, 1977; Larrabee et al., 1983; Prigatano, 1978), it may be more accurate to conceptualize these tasks as measures of "concentration" and/or "conceptual tracking." This distinction of terminology and concepts may reconcile the discrepancy between the present findings and those of studies from the literature, most of which appear to have examined perceptual selectivity (i. e., "attention") rather than concentration or conceptual tracking abilities.

Perhaps a better test of the relationship between "attention" and memory test performance lies in the examination of the hypotheses concerning self-focused attention and panic severity. Given the proposed nature of anxious apprehension and tendency of patients with PD to focus on internal states (See chapter 2), it was hypothesized that memory functioning among PD subjects would be correlated negatively with the tendency to focus on physiological sensations. Results, however, revealed no relationship between self-focus and memory test performance. Again, this result appears contradictory to the

theoretical model of panic disorder suggested by Barlow (1988), and runs counter to the evidence in the literature which suggests that perceptual selectivity of threat-related stimuli can impair cognitive processing of nonthreat related information. It is possible that the negative result obtained in this analysis reflects a limitation of the methodology employed to examine the hypothesis. The present study relied exclusively on self-report data to evaluate tendency to focus attention on internal bodily sensations. Given that the nature of self-focus, as described by Barlow and others (e. g., Barlow, 1988; Craske & Barlow, in press), is automatic and not necessarily available to conscious appraisal, subjects may not be able to report shifts of attention associated with the perception of physiological sensations accurately. Consequently, a more objective measure of subjects' tendency to shift attention in response to physiological sensations is needed to examine this relationship adequately.

The relationship between memory functioning and severity of panic disorder was also examined. Results again revealed no significant relationship between panic severity and the combined memory measures; however, the relationship between panic severity and performance on tests of concentration was significantly negatively correlated. This finding is consistent with the proposed models of attentional processing in panic disorder. These results may suggest that the processes suggested by attentional models may be appropriate only for more severe cases of panic disorder. An alternative interpretation of results, however, is that the measures of attentional activity employed in this study may not be sensitive to deficits in attentional abilities associated with milder forms of panic disorder, and can only detect more gross attentional deficits that may be associated with more severe panic disorder. Nevertheless, no significant

relationship was found among panic severity and memory measures, suggesting that visual memory deficits among PD subjects are independent of panic severity.

Limitations of the Present Study and Directions for Future Research

In addition to those mentioned previously, several other limitations of the present study should be addressed. First, the absence of imaging techniques in the present study precludes firm conclusions regarding memory processes and involved brain regions. Moreover, as Butters and Miliotis (1985) point out, application of information processing models to neuropsychological studies of cognitive functioning is a relatively new venture, and has proven quite complex. Relationships between cognitive processes and neuropsychological performances are not always straightforward and are often difficult to interpret without confirming information, such as metabolic or neuroanatomical studies. On the other hand, neuropsychological results can often reveal cognitive disturbance in the absence of detectable imaging abnormalities. Considerable additional research, including imaging as well as neuropsychological data, is necessary to clarify the relationship between psychiatric conditions such as panic disorder and their underlying neural mechanisms.

Although the presence of neuropsychological deficits in PD subjects suggests temporal lobe involvement, this in no way confirms that temporal lobe dysfunction is of etiological significance in panic disorder. It is quite possible that the memory deficits observed in the present study, as well as the temporal lobe abnormalities reported by imaging studies are concomitants or consequences of panic disorder. This also applies to the finding of verbal memory deficits and suggestion of left-hemisphere dysfunction in

depressed patients. Prospective studies are needed to clarify whether neuropsychological deficits are present prior to the onset of panic disorder or depression.

Several issues regarding the neuropsychological measures included in the test battery must also be addressed. Although most of the memory tests employed by the present study are widely used in clinical neuropsychological practice and research, very few established measures of nonverbal memory exist that do not have a significant visuoconstructional component or that cannot be performed by using verbal strategies. Although two of the three nonverbal memory tests used in the present study (i. e., VR delay & BVRT) have been shown to be sensitive to nondominant (i. e., right) temporal dysfunction (cf. Rausch, 1985; Benton, 1967; 1968), the Visual SR procedure, which has no visuoconstructional component and minimal pull for verbal encoding, lacks data regarding its psychometric properties. Moreover, given that this is the only measure of nonverbal learning employed in this study, conclusions based on results of this test in particular must be viewed cautiously.

The lack of adequate normative data with which to compare the clinical significance of results is another limiting factor in interpretation of the current results. Unfortunately, systematic normative information for many widely used neuropsychological measures is unavailable, and data from tests of verbal and visual memory are seldom adequately standardized using subjects common to each test (Loring, Lee, Martin, & Meador, 1989). Moreover, the composition of non-neurologic reference groups used in normative studies vary considerably, and include college students, optimally healthy volunteers, non-neurological medical patients, and psychiatric patients, among others. Consequently, use of published normative data may

systematically underestimate or overestimate verbal and visual memory relative to each other when evaluating individual subjects (Loring et al., 1989).

In the present study, it was necessary to establish different cut-off scores reflecting "impaired" performance for different memory tests. Most notably, performances below one standard deviation from the mean were designated as impaired on delayed recall of LM stories, and the presence of a greater number of errors than "expected" was designated as impaired on the BVRT. These cut-off scores, although made necessary by constraints of the available normative data, likely produced a large number of Type I error classifications. This is illustrated by the relatively large number of subjects across groups who were classified as "impaired" on these tests compared to the measures from which more stringent cut-off scores of 10th and 2nd percentile performances could be obtained. Therefore, conclusions drawn from impairment classifications of these two measures must be viewed cautiously.

While the neuropsychological tests of memory employed by this study measured learning and explicit recall, additional aspects of memory functioning, such as remote memory and implicit memory (e. g., priming effects), were not assessed. Also, the test battery did not include other measures of neuropsychological functions, such as language, psychomotor speed, or cognitive flexibility. Use of a comprehensive neuropsychological battery is required to determine if visual memory is affected selectively in PD subjects and verbal memory is affected selectively in depressed patients, or if impaired memory functioning is just one facet of a constellation of neuropsychological deficits found in these groups.

Tests traditionally used in neuropsychological batteries to measure "attention" were employed in this study. The construct measured by these tests, however, appears

distinct from that measured by tests of attention (i. e., perceptual selectivity) employed by studies of cognitive processing in anxious and nonanxious subjects reviewed in Chapter 2. Conclusions regarding the role of "attention" in panic disorder based on the present results must therefore be viewed within this context. Although PD subjects did not differ from normal controls on these measures, this does not necessarily suggest that no differences in attentional processes exist between PD and normal subjects. It should be made clear that attentional *processes* were not examined in the present study. Rather, ability to sustain attention on a task (i. e., concentration and conceptual tracking) was examined. Studies incorporating more sensitive measures of attentional processes are needed to clarify the relationship between such processes and neuropsychological functioning in panic disorder.

Appendix A

Explanation of Footnotes

[1] Although both verbatim and propositional scores were obtained for Logical Memory, these were very highly correlated for all three conditions (immediate recall $\underline{r}$ = 0.95; 15-minute recall $\underline{r}$ = 0.98; 45-minute recall $\underline{r}$ = 0.97). Consequently, only one measure (verbatim) was included in the analyses.

[2] Although the verbal selective reminding procedure is discontinued when three consecutive error-free trials are obtained (Buschke & Fuld, 1974), the visual selective reminding procedure as described by Fletcher (1985) discontinues the procedure after two error-free trials. Although not explicitly stated, this may be because only eight stimulus items are to be learned in the visual task, compared to 12 in the verbal task. Despite this, both procedures continue through 12 trials if the subject fails to demonstrate complete retention of all items.

[3] Fifteen-minute delayed recall of Logical Memory, Visual Reproduction, and Paired Associate Learning was chosen to be the delayed recall measure of these subtests in the analyses. All three subtests showed very high correlations between 15- and 45-minute recall (Logical Memory $\underline{r}$ = 0.89; Visual Reproduction $\underline{r}$ = .87; Paired Associate Learning $\underline{r}$ = .81); thus, only one delayed recall measure was included.

[4] Scoring of the BVRT for both number correct and number of errors has been shown to be statistically redundant (Moses, 1986); consequently, only one of these measures was included. Error scores were chosen because they offer greater discrimination between performances. For example, two subjects who each correctly reproduce eight figures would receive the same "number correct" score; however, one subject may have scored only one error per design (error score = 2) while the other may have made several errors on each design (error score > 2).

[5] Although CLTR scores were not used in the multivariate analyses, they correlate highly (r = .92 in the present study) with LTR scores (a measure included in analyses). Consequently, CLTR scores were used in analyses of the clinical significance of results.

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