Vulnerability to Substance Abuse in Eating Disorders

Walter H. Kaye and Lucene Wisniewski

STATEMENT OF THE PROBLEM

Two types of eating disorders, bulimia nervosa in normal-weight bulimic (NWB) women and restricting-type anorexia nervosa (RAN), may provide insights into permissive or protective factors contributing to psychoactive substance use disorders (PSUD) in humans. These two eating disorders, while often grouped together, are at opposite extremes for rate of PSUD. Substance abuse is common in NWB patients and their family members, but rare in RAN patients. In addition, NWB and RAN are at opposite extremes in terms of pathologic feeding style and many behavioral traits (table 1). NWB individuals are impulsive, labile, may be overly sensitive to external cues, and have poor control of eating. In contrast, persons with RAN are rigid and perfectionistic, restrict eating, and are insensitive to internal and external cues.

Studies in humans at risk for PSUD have identified factors that may play a contributory role in the pathogenesis of PSUD. These factors include behavioral undercontrol, emotionality, and sensitization and tolerance to the reinforcing effects of drugs. Thus, NWB individuals may have many vulnerability factors for PSUD. It is provocative to speculate that factors that are the opposite of these vulnerabilities may protect RAN individuals from PSUD.

Specific Aim 1

This proposal characterizes factors that may contribute to the high rate of PSUD in NWB women. Specific Aim 1 will assess factors such as behavioral undercontrol; personality characteristics such as novelty seeking; and emotionality, especially unstable mood states. Four groups of women will be studied: NWB with a lifetime diagnosis of PSUD (+PSUD), NWB without a lifetime diagnosis of PSUD (-PSUD), RAN women, and healthy controls. This study hypothesizes that the behavioral factors are exaggerated in the +PSUD NWB women compared with the PSUD NWB women, and that both groups of NWB women have greater behavioral undercontrol and unstable moods than control women,

TABLE 1. Comparison of RAN and NWB women.

Restrictor AN (RAN)	Normal Weight BN (NWB)
Restricted eating	Binge eating
Denial of weight loss	Ashamed of bingeing
4+ fear of fat	1+ fear of fat
4+ exercise	Normal exercise
Rigid, obsessive, perfectionistic	Labile, mood extremes, impulsive
Substance abuse - rare	Substance abuse - common
Increased 5-HT activity	Reduced 5-HT activity

whereas RAN women have rigid and inflexible moods and enhanced self-control compared with control women or NWB women.

Specific Aim 1a. This study proposes to characterize which, of a number of paper-and-pencil self-assessment instruments, best quantifies the risk factors of impulsivity and personality in subgroups of women with eating disorders in terms of vulnerabilities to PSUD.

Specific Aim 1b. It also aims to improve the measurement of the constructs for this patient group by identifying the best items from existing scales in order to develop a revised behavioral under/overcontrol scale more specific for eating-disordered women.

Specific Aim 1c. In addition, this study will determine whether NWB women have disturbances of impulse control as reflected by laboratory assessments such as the Go/No-Go, Continuous Performance Test, and Matching Familiar Figures Test (MFFT). The ability to test behavioral undercontrol would be of much importance in future studies of the behavioral expression of risk factors in humans with PSUD.

Specific Aim 1d. This study also will test the hypothesis that NWB women will show much greater variance of negative and positive affects than RAN patients with respect to hourly ratings over a 2-day period. Unstable emotionality may be a contributory risk factor to PSUD in NWB women.

Specific Aim 2

The hypothesis is that the clinical presentation of disturbances of impulse control and mood stability reflects a more pervasive disturbance of reactivity in RAN and NWB subjects that may shed light on why differences in vulnerabilities to substance abuse occur.

Specific Aim 2a. Since preliminary data suggest that NWB women may become sensitized to the reinforcing effects of food intake. This study will replicate and extend this work, since the sensitization of reinforcing drug effects is central to current addiction theory. In contrast, this study hypothesizes that RAN women will rapidly habituate to food stimuli and thus may be insensitive to the reinforcing effects of food or drugs.

Specific Aim 2b. This study will also test the hypothesis that disturbances found as a response to a food stimulus will generalize to nonfood-related stimuli and NWB subjects will become sensitized (in terms of heart rate and skin conductance response) to nonfood stimuli such as auditory tone, whereas RAN subjects will show increased habituation.

Specific Aim 3

Other factors will be explored that may contribute to extremes of substance abuse in NWB subjects. These factors include NWB women's perception of their motivation, expectancy, and self-efficacy. In addition, the study will determine whether the severity of PSUD symptoms correlates with frequency of bingeing and purging and other eating disorder-related symptoms in NWB subjects.

BACKGROUND AND SIGNIFICANCE

The reasons that people engage in PSUD behaviors remain complex and uncertain. This study will develop the thesis that the eating disorders anorexia nervosa (AN) and bulimia nervosa (BN) may provide models for understanding permissive and protective factors underlying development of PSUD in humans. While AN and BN appear superficially similar, they are actually at opposite extremes in terms of behavioral characteristics. Behaviors in NWB individuals are consistent with some data about how pathophysiology may be related to risk for PSUD. In contrast, the study of behavior in RAN

individuals may generate insight into why some people are resistant to PSUD.

Since PSUD will likely prove to be a heterogeneous disorder, relationships between behavior and psychopathology may be obscured. In contrast, AN and BN are relatively homogeneous psychiatric disorders with stereotypic behaviors and relatively consistent physiologic abnormalities. Thus, the eating disorders may serve as an excellent model with which to understand and contrast a group of risk or protective factors.

Risk Factors for PSUD

While there is limited understanding of risk factors that contribute to the onset of PSUD, certain behaviors that occur in NWB individuals have been theoretically implicated.

Behavioral Undercontrol. Sher (1991) reviewed prospective and archival studies suggesting that traits related to behavioral undercontrol such as impulsivity, rebelliousness, and aggression also appear to characterize the prealcoholic male. These traits appear to be common in NWB women, although it is not certain whether they are associated with only those NWB subjects who develop PSUD or are also present in NWB subjects without PSUD.

Negative Mood States or Emotionality. A tendency to experience negative affective states has been associated with both clinical PSUD and a vulnerability to PSUD (Tarter 1988), particularly for women (Jones 1971). NWB patients commonly have negative mood states and tend to be mood unstable. Exaggerated ingestive behaviors (food, substance abuse) in NWB women may be an attempt to externally control mood states and suppress negative mood extremes that cannot be internally modulated.

Personality. Cloninger (1987a) has postulated that different types of alcoholism are associated with different personality profiles. Type I alcoholism is characterized by low novelty seeking, high harm avoidance, and high reward dependence; it is associated with binge drinking and may be more prevalent in females. Type II alcoholism is characterized by high novelty seeking, low harm avoidance, and low reward dependence; it is associated with antisocial behavior and may be more prevalent in males. Preliminary data from NWB subjects (Bulik et al. 1994) do not correspond to either type of alcoholism,

although NWB subjects with PSUD were higher in novelty seeking than NWB subjects without PSUD.

It is hypothesized that the clinical presentation of impulse control disturbances in NWB women is a reflection of a more pervasive cognitive disturbance that may shed light on why vulnerabilities to PSUD occur. NWB patients may be prone to binge eating and engage in substance abuse for several reasons. For example, they may be overreactive to environ-mental stimuli since they tend to be mood unstable. Exaggerated ingestive behaviors (food, substance abuse) may be an attempt to externally control mood states and suppress negative mood extremes that cannot be internally modulated. While this area is in its infancy and is somewhat controversial, there is evidence (Casper 1990; Casper et al. 1992) that other measures of personality may differentiate RAN from NWB subjects.

Sensitization. Preliminary data suggest that NWB subjects may have increased sensitization to the reinforcing effects of food intake. The intent is to replicate and extend this work since the sensitization of reinforcing drug effects is central to current addiction theory (Stewart et al. 1984; Wise and Bozarth 1987). In contrast, RAN subjects are rigid, perfectionistic, and insensitive to internal cues. It is hypothesized that RAN subjects will rapidly habituate to stimuli and thus may be insen-sitive to the reinforcing effects of food or drugs.

Differences Between Anorexia and Bulimia Nervosa

Patients with eating disorders can be subdivided by eating behavior and psychopathological characteristics (Garner et al. 1985; Halmi and Falk 1982; Herzog and Copeland 1985; Strober et al. 1982). The best known eating disorder is AN, whose most distinguishing characteristic is severe emaciation ("Diagnostic and Statistical Manual of Mental Disorders," 3d edition revised (DSM-III-R)) (American Psychiatric Association 1987). Two types of consummatory behavior are seen in AN. Restrictor anorexics lose weight by pure dieting, with no history of bingeing or purging, and are classified as restrictor anorexics in this proposal. Patients with BN remain at normal weight (i.e., NWB) and never become emaciated. That is, they maintain a body weight above 85 percent of average body weight (ABW) (Fairburn and Cooper 1982; Garner et al. 1985; Pyle et al. 1983). There are at least 10 times as many patients with BN as with AN (Halmi et al. 1981; Pope et al. 1983; Stangler and Printz 1980). These patients periodically binge and purge, usually by vomiting or laxative use. There is also a third group of BN patients with AN who

share attributes of both NWB and RAN, but they will be excluded from this study in order to characterize two most extreme subgroups.

Substance Abuse in Eating Disorders

Several lines of evidence suggest a link between NWB and PSUD (Vandereycken 1990). In contrast, AN appears to be associated with a much lower incidence of PSUD (Brisman and Seigel 1984 ; Hudson et al. 1983a; Laessle et al. 1989; Stern et al. 1985). Studies of NWB women using contemporary diagnostic criteria report a high incidence of PSUD (table 2). Hudson and colleagues (1983b) found a 22 percent incidence of alcohol abuse or dependence and a 31 percent incidence of any sub-stance abuse. Mitchell and colleagues (1985), in a study of 275 NWB women, found that 23 percent had a history of alcohol abuse and 18percent had prior treatment for chemical dependency. In other studies, the incidence of substance abuse has ranged between 23 percent and 49percent of NWB women (Bulik 1987b; Hudson et al. 1987; Laessle et al. 1989). Bulik and colleagues (1992) (table 3) found that NWB patients used significantly more licit (alcohol, cigarettes, laxatives, diuretics) and illicit drugs (amphetamines, cocaine, marijuana) than RAN patients. In comparison, PSUD is uncommon in women with RAN. For example, a 6percent lifetime prevalence of PSUD was found in RAN women, compared with 50 percent in BN ($p < 0.01$) (Bulik et al. 1992).

A number of studies have shown an increased rate of PSUD in relatives of BN or NWB patients. For example, in studies of relatives, Hudson and colleagues (1987) found that 16 percent of the first-degree relatives of BN probands had a history of alcohol abuse or dependence, significantly more than the controls (5 percent). Kassett and colleagues (1989) found alcoholism in 28 percent of first-degree relatives of BN probands, significantly more than the 14 percent incidence found in relatives of control women. In proband studies, most (Bulik 1987b; Mitchell et al. 1988) but not all authors (Stern et al. 1985) have reported that between 33percent and 83 percent of BN women have at least one close relative with alcoholism.

Bulik (1987a) studied 35 BN and 35 control women using a semi-structured family history interview. Significantly more (60 percent) BN patients had one or more first- and second-degree relatives with a history of alcoholism than controls (20 percent). While not as well studied, PSUD appears to be less common in family members of patients with RAN (Hudson et al. 1987).

TABLE 2. Incidence of alcohol abuse or dependency in patients with eating disorders.

STUDY	BN	AN	NC
Hudson et al. 1983a	22%	6%	N/A
Mitchell et al. 1985	23%	N/A	N/A
Hudson et al. 1982	36%	N/A	11%
Bulik 1987a	49%	N/A	9%
Laessle et al. 1989	19%	0%	N/A

KEY: N/A = not applicable (no data reported).

Clinical Phenomenology in NWB—Similarities to Substance Abuse

Clinically, many investigators have noted that NWB patients' thoughts about bingeing and purging resemble addiction-like behavior; such thoughts include craving, preoccupation with obtaining the food, loss of control, adverse social and medical consequences, ambivalence toward treatment, and risk of relapse (Bulik 1987a; Hatsukami et al. 1984;

TABLE 3. Comparison of licit and illicit substances.

	AN	BN	P
Number	27	42	
Age	20	22	NS
Cigarettes	6%	52%	0.002
Alcohol	11%	45%	0.003
Caffeine	74%	86%	NS
Laxatives	18%	62%	0.0001
Diuretics	7%	33%	0.01
Amphetamines	8%	30%	0.03
Cocaine	4%	14%	0.08
Marijuana	15%	45%	0.01

KEY: NS = not significant.

SOURCE: Bulik et al. 1992.

Mitchell et al. 1988). Bingeing behavior produces a brief reduction in stress and tension that is similar to intoxication (Johnson and Larson 1982; Kaye et al. 1986). One study of alcoholics with and without NWB reported that many NWB patients experienced negative emotions after binge eating or vomiting and felt that only drunkenness allowed them to sleep afterward (Suzuki et al. 1993). In another study (Rand et al. 1986), NWB patients reported that they drank alcohol to avoid eating, to blot out reality, and to feel calm and sexually relaxed.

Comorbid Behavior and Personality in Eating Disorder Patients

A considerable number of studies have found a high incidence of concurrent depressed mood in patients with RAN and NWB and a high rate of depression in their family members (Gwirtsman et al. 1983; Hatsukami et al. 1984; Herzog and Copeland 1985; Hudson et al. 1983a; Pope et al. 1983). Such findings have led investigators to hypothesize that eating disorders are a variant of major affective disorders (Hudson et al. 1983a, 1983b). However, it should be noted that other evidence such as clinical phenomenology, antidepressant response, biological correlates, course, and outcome yield limited support for the overarching hypothesis that RAN and NWB are variants of major affective disorders (Rothenberg 1988; Strober and Katz 1988; Swift et al. 1986). It is likely that a considerable number of the depression and anxiety symptoms found in ill RAN and NWB patients is secondary to malnutrition.

Recent data raise the hypothesis that there are certain traits of personality that persist in RAN and NWB (Kaye and Wisniewski, unpublished data). These traits are at opposite extremes. RAN individuals tend to be obses-sional and concerned with perfection, symmetry, and exactness. In com-parison, many NWB individuals tend to be more labile and impulsive. Such symptoms may contribute to different rates of PSUD in these two disorders.

The Anger, Irritability, Assault Questionnaire (AIAQ) (Coccaro et al. 1991), a measure of irritability, mood lability, and assaultive behavior, was administered to 24 NWB women and 10 controls (Weltzin 1993). NWB and control women were of similar ages (24±5 versus 22±4 years) and weights (101 percent versus 99 percent ABW). Bulimics reported higher levels of irritability/mood lability as children ($p < 0.02$), adolescents, and adults ($p < 0.01$), higher levels of assault as adolescents ($p < 0.01$), and a trend toward higher levels of assault as adults ($p < 0.07$) compared with controls. In addition, NWB women

with past suicide attempts (N = 7) showed a trend ($p < 0.06$) toward having higher irritability scores compared with NWB women with no past suicide attempt. Furthermore, the NWB subjects with a clinical diagnosis of borderline personality disorder (N = 5) had a trend toward higher mean scores on irritability/mood lability as adolescents (19±6 versus 12±3, $p=0.07$) and adults (19±5 versus 13±4, $p= 0.09$) than those without borderline personality disorder (N = 4). These data confirm that NWB women have higher ratings of irritability, mood lability, and aggressive behavior compared with controls.

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al. 1989), an interview that rates the severity and type of symptoms in patients with obsessive-compulsive disorder (OCD), was administered to patients with RAN-excluding symptoms (obsession, compulsion) pertaining to core RAN symptoms. In terms of impairment, interference, and intensity of current obsessive and compulsive symptoms, both ill (20±8) and recovered RAN women (9±8) had significant elevations in ratings for severity of OCD symptoms compared with controls (3±4), although recovered RAN women had lower scores than ill RAN women. However, both ill and recovered RAN women tended to have similar target symptoms of OCD that particularly concerned a need for symmetry and ordering/arranging, while these symptoms were rarely endorsed by control subjects. Furthermore, these target symptoms found in RAN are different from those found in patients with OCD or NWB. While NWB women have elevated Y-BOCS scores, those scores are significantly lower than ill RAN women and the patterns of symptoms are different. Whether such measures provide the best discrimination between RAN and NWB in terms of PSUD-related risk factors remains uncertain.

Habituation and Sensitization

One means of assessing an individual's responsiveness to stimuli is to measure the response to repeated stimulus presentations. Repeated exposure to a stimulus may result in one of two response patterns: habituation or sensitization. Habituation involves response decrements to repeated stimulus presentations and has been demonstrated with many types of stimuli and many response systems such as repeated visual stimuli on heart rate (Adkinson and Berg 1976), repeated auditory stimuli on the event-related potential (Lammers and Badia 1989; Megela and Teyler 1979; Polich 1989) and measures of skin conductance response (Kimmel and Bevill 1985), localized head-turning reflex (Zelazo et al. 1984), and heart rate (Chang and Trehub 1977). The response decrement indicative of

habituation can be recovered by the presentation of a novel stimulus (Wagner 1979). The demonstration of dishabituation or response recovery illustrates that the attenuated response over repeated presentations cannot be attributed to neural adaptation or fatigue. Sensitization, or response augmentation resulting from repeated stimu-lation, is also a universal phenomenon (Kalivas and Barnes 1988).

Habituation to food stimuli is consistent with the phenomenon of sensory-specific satiety (Rolls et al. 1988). In sensory-specific satiety, the pleasantness of a particular food decreases as it is eaten, but pleasant-ness remains for other foods having different sensory qualities. Previous research linking sensory-specific satiety and habituation has shown that repeated presentation of a food stimulus reliably results in habituation of both the salivary response and hedonic ratings in normal (control) men (Epstein et al. 1992a; Wisniewski et al. 1992) and women (Epstein et al. 1993a, 1993b). Related neurophysiological research in primates has shown that, in response to repeated presentations of food stimuli, food acceptance decreased. Likewise, neurons in the lateral hypothalamus, substantia innominate, and caudolateral orbitofrontal cortex decrease, and responsiveness of those neurons and food acceptability recover with presentation of a new food (Rolls et al. 1986, 1989). These electro-cortical response patterns are consistent with habituation and response recovery, which cannot be accounted for by sensory adaptation or fatigue.

Limited available data raise the possibility that NWB patients fail to develop habituation to food stimuli. Both Rolls and colleagues (1992) and Rodin and colleagues (1990) have found that NWB women do not experience a normal reduction in the pleasantness of a food after eating a large amount of it. Preliminary data also suggest that NWB women have disturbances in habituation to food stimuli. Control women (N = 15) had a significant decrease in the salivary response to food stimuli over eight trials compared to baseline secretion of saliva. In contrast, the NWB women (N=15) did not show such habituation. In fact, they showed a pattern more consistent with sensitization since saliva levels increased slightly. This difference between groups was significant [$F_{7,196} = 2.97$; $p < 0.006$].

This finding is of much potential interest in understanding why NWB women are vulnerable to PSUD and overeating. Clinically, it is common that NWB women describe losing control and "spacing out" when eating or abusing substances. It may be that they are

physiologically unable to inhibit their behavior because they do not habituate normally. Rather, they may become sensitized to reinforcing stimuli and thus vulnerable to overindulging in food and abusing substances.

There are fewer data examining these relationships in RAN patients. One study found that RAN patients reported a significant decrease in pleasantness after eating a food, but consumed less food than control subjects, suggesting it took less for RAN subjects to become satiated on a specific food relative to normal subjects (Rolls et al. 1992).

The intent is to replicate these preliminary data and extend these findings by determining whether such disturbances of habituation extend to other modalities and whether such disturbances persist after recovery.

Additional Characteristic Behaviors

Comparison of NWB With and Without PSUD. Bulik and colleagues (1994) compared the characteristics of 13 +PSUD NWB women and 19 -PSUD NWB women (table 4). These two groups were similar in terms of age, age at onset of NWB, and current weight. There were no differences between groups on the Eating Disorder Inventory (EDI) or on the Beck Depression Inventory (BDI). On Cloninger's Tridimensional Personality Questionnaire (TPQ), +PSUD NWB individuals scored significantly higher on novelty seeking but had similar scores for harm avoidance and reward dependence. In the NWB subjects, novelty seeking and harm avoidance scores were considerably higher in comparison with general population norms for caucasian women in this country. High novelty seeking is associated with thrill seeking, impulsivity, intolerance for monotony, and a quick temper. These data confirm clinical reports of impaired impulse control in NWB subjects and suggest that this characteristic is even more marked in NWB subjects with comorbid PSUD.

Matching Familiar Figures Test. It is important to determine whether standardized tests might measure perfectionism, exactness, and constraint in RAN, and impulse dyscontrol and lability in NWB. Thus, the MFFT was administered. In this paradigm, subjects are given a target picture of an object and are then asked to determine which of six or eight other pictures is the exact match of the target picture. All the matched pictures resemble the target picture. One picture is exactly the same as the target picture, and the rest have subtle differences. The subjects' time to determine a match (latency) and the number of mistakes (errors) are measured.

TABLE 4. Study design.

	Day A	Est time (min)	Day B	Est time (min)
8-11 a.m.	AIAQ, BDHI, MPS, MPQ, EDI, BDI, STAI	180	I7, AEQ, EDAS, TPQ, SSS, MFFT	180
2-5 p.m.	Habit-auditory	90	Habit-lemon	90
	Habit-yogurt	90	Go/No-Go	30
			CPT	30
q 1 hr	PANAS	3	PANAS	3

Ten RAN and nine NWB subjects were studied. (In this pilot study, control women were not studied.) Compared with NWB, the RAN patients took significantly longer to make a choice and made fewer errors. The differences on the MFFT may reflect increased impulsivity in NWB compared with RAN subjects.

Serotonin and Behavior

Serotonin (5-HT) is one neurotransmitter system of interest in explaining a potential link between risk for PSUD, impulse control, and other behaviors in patients with eating disorders.

Serotonin and Substance Abuse. Studies in animals and humans suggest that the augmentation of 5-HT neurotransmission attenuates alcohol consumption while 5-HT depletion enhances alcohol use (Sellers et al. 1992; Tollefson 1991). Animal studies have shown that agents that increase the synaptic availability of 5-HT reduce alcohol consumption (Hill 1974; Levy et al. 1989; Zabik et al. 1985). Conversely, destruction of 5-HT neurons increases alcohol consumption (Richardson and Novakowski 1978). In humans, a few short-term clinical trials of 5-HT uptake inhibitors in mildly to moderately alcohol-dependent individuals (Sellers et al. 1992) have shown a modest reduction in alcohol consumption. Interestingly, such responses are dose-related and onset is immediate, varying in magni-tude across the patient population. Other preliminary studies have shown that drugs with 5-HT activity decrease alcohol consumption (Bruno 1989; Monti and Alterwain 1991; Sellers et al. 1991). Limited data suggest that cerebrospinal fluid (CSF) measures

of 5-HT are decreased in many alcohol abusers (Borg et al. 1985; Eriksson and Humble 1990).

Regulation of Ingestive Behaviors. 5-HT neuronal systems contribute to the modulation of appetitive behaviors (Blundell 1984; Fernstrom and Wurtman 1971, 1972; Leibowitz and Shor-Posner 1986). Treatments that increase intrasynaptic 5-HT or directly activate 5-HT receptors tend to reduce food consumption. Conversely, interventions that diminish serotonergic neurotransmission or 5-HT receptor activation reportedly increase food consumption and promote weight gain. Theoretically, bingeing behavior is consistent with hyposerotonergic function. Alternatively, restricted eating in AN is consistent with hyperserotonin activity.

Mood and Personality. A disturbance of 5-HT activity has been suggested in a number of behavioral disorders. In this brief space, a comprehensive review of this complicated topic is not possible. Still, it is possible to raise a provocative hypothesis that 5-HT may be implicated in factors such as impulse control or mood modulation, which may cut across traditional diagnostic boundaries. Simplistically, reduced 5-HT activity may correlate with reduced impulse control and aggressive behaviors (Coccaro 1992; Siever and David 1991). In contrast, increased 5-HT activity may be related to obsessionality (Hollander et al. 1991; Zohar et al. 1988), inhibition (Cloninger 1987a, 1987b; Soubrie 1986; Spoont 1992), and/or anxiety and fear (Charney et al. 1990). In addition, there is pharmacological and physiological evidence that 5-HT function is altered in depression (Grahame-Smith 1992; Price et al. 1990; Siever et al. 1984).

Habituation and Sensitization. One potential lab test that may be influenced by 5-HT neuronal processes is habituation and sensitization. Geyer and Tapson (1988) noted that there is an extensive literature suggesting central nervous system (CNS) 5-HT neuronal systems are involved in modulating an organism's behavioral responses to environ-mental stimuli, particularly habituation and reactivity (Aghajanian and Sheard 1968; Davis 1980; Geyer and Tapson 1988). There appears to be an inverse correlation between 5-HT levels and startle reactivity. More-over, 5-HT type 1 (5-HT1) receptors influence reactivity, whereas 5-HT type 2 (5-HT2) receptors influence habituation.

Theoretical Perspective. Monoamine neuronal systems, including 5-HT, have a diffuse, widespread distribution, and can be argued to have

a threshold function for information processing independent of specific behaviors (Spoont 1992). Reviews have consistently postulated that 5-HT activity is inhibitory. Soubrie (1986) described the 5-HT system as enabling the organism to arrange or tolerate delay before acting. Cloninger (1987a, 1987b) described 5-HT as responsible for behavioral inhibition, specifically harm avoidance. Spoont (1992) stated that increased 5-HT activity locks in the system's phase, raising the threshold for perturbation by exogenous influences so that no new input is possible. In contrast, as reviewed above, reduced 5-HT activity is correlated with impulsive, aggressive behaviors.

According to Spoont (1992), 5-HT regulates or stabilizes the flow of information through a neural system. 5-HT neuronal activity prevents overshoot of other neurotransmitter systems and thus attenuates signal amplitude. In addition, it controls the sensitivity of the system to perturba-tions by new stimuli entering the system. Thus, 5-HT protects the brain from interference from nonsalient alternate signal sources and from sensiti-zation to potentially threatening stimuli. Therefore, increased 5-HT would result in regionally restricted cycles of information flow, redundant signal propagation and/or maintenance of prepotent response patterns, and hyper-rigid behaviors. In contrast, decreased 5-HT would impair the neural network's ability to maintain signal flow pattern integrity. This would result in increased switching, unstable and amplified signal passage, and impulsive and exaggerated stimulus reactivity.

Specifically, decreased 5-HT might cause behavioral instability by two mechanisms. First, there would be increased overshoot or magnitude of behavioral response (for example, increased feeding, sexual behavior, aggression, or startle response). There would be a decreased response to negative feedback (for example, insensitivity to satiety signals). There would also be a slower recovery time in response to initiated behavior (for example, increased exploring in response to novel stimuli). Second, the organism would have a decreased threshold for perturbation. It would be more susceptible to exogenous influences and would have compromised ability to maintain self-organization. There would be increased facilitation of switching to alternate signal sources and disruption of ongoing sequen-tial behavior. In other words, with decreased 5-HT, there would be behavioral instability. There would be an increased likelihood that a given response will occur, an increase in the magnitude of behavioral response, a slowing of the response recovery,

and an insensitivity to cues that would attenuate or inhibit the behavioral response.

Summary

There appear to be consistent findings regarding 5-HT, vulnerability to PSUD, and behaviors in women with eating disorders (table 4). That is, NWB patients, who may have reduced 5-HT activity, tend to have labile and impulsive behaviors, poor self-control of ingestive behaviors, and a high incidence of PSUD. In contrast, RAN patients, who may have increased 5-HT activity, tend to have restricted ingestive behaviors, inhibited and overcontrolled behaviors, and a low incidence of PSUD. Are rates of PSUD related to issues of ingestive behaviors, self-control, or negative mood states? These factors have been implicated in the patho-genesis of PSUD. Whether some or all of these factors are contributory and whether they are related to a disturbance of 5-HT activity are questions to be answered by appropriate followup studies.

DESIGN AND EXPERIMENTAL METHODS

Hypotheses

NWB individuals have a high rate of PSUD as do their families. It is hypothesized that this high rate of PSUD in NWB patients is related to the presence of the postulated risk factors contributing to development of PSUD. These factors include behavioral undercontrol, negative/unstable mood states, and sensitization to the reinforcing effects of drugs. In contrast, RAN patients have a low rate of PSUD. It is speculated that this low rate of PSUD is related to RAN patients' having opposite behavioral characteristics (behavioral overcontrol, rigid and inflexible mood states, and perhaps rapid habituation to the reinforcing effects of drugs) that may act as protective factors. Poor impulse control, exaggerated mood reac-tivity, and enhanced sensitization may make NWB patients vulnerable to the hedonic properties of substances of abuse. In contrast, RAN patients, who are serious and ascetic people with little ability to experience pleasure, may be insensitive to hedonic properties of drugs of abuse.

Subjects

NWB Women. Two groups of NWB individuals will be studied: 20NWB women with a lifetime history of PSUD and 20 NWB women without a lifetime history of PSUD. The reason for studying two groups of NWB

individuals is to determine whether -PSUD NWB women have the same risk factors as +PSUD NWB women. Methods of determining the presence or absence of PSUD are included in the description of the Schedule for Affective Disorders and Schizophrenia (SADS) interview below. To avoid any confounding effects on assessments, NWB women must not have used any substances of abuse or be on psychoactive medication for at least 30 days prior to the study. NWB women must have no lifetime history of major affective disorder, also to avoid con-founding influences. The NWB women must be ill for at least 4 years prior to study so as to have some substantial period of risk for developing PSUD. NWB women must be between 90 percent and 110 percent ABW. If NWB or RAN women have normal menses, they will be studied in the early follicular phase.

RAN Women. The proposed study will include 20 RAN patients who have no history of PSUD and who have never binged or purged. RAN women must have no lifetime history of major affective disorder and must not have used any psychoactive medication for at least 30 days prior to the study. RAN women must have been ill for at least 4 years prior to the study so as to have some substantial period of risk for developing PSUD or NWB. RAN women, if underweight and malnourished, must be renourished on an inpatient treatment unit for at least 30 days prior to the study and be above 85 percent ABW at the time of the study.

Control Women. The study will include 20 NC women who have no lifetime Axis I or II diagnoses or serious medical condition. Normal control women must have regular menses and will be studied in the first 10 days of the start of their menstrual cycle (early follicular phase) to control for confounding influences. NC women must be between 90percent and 110 percent ABW.

Study Design

All subjects will participate in an identical 2-day study (table 5). Prior to day 1 of the study, subjects will be psychologically and medically assessed. On the morning of days 1 and 2 (designated days A and B), subjects will complete a battery of self-rating psychological assessments. On the after-noon of days A and B, subjects will engage in a battery of performance studies. Studies on days A and B will be randomly counterbalanced.

Days A and B—Morning—Baseline Psychological Assessments. If the subject meets all the inclusion criteria, none of the exclusion criteria, and agrees to the study, she will enter the Eating Disorders

TABLE 5. Major dependent variables and predictions about response.

Assessment	Main Dept Variable	+PSUD	-PSUD	RAN
Behavioral under/over control				
Eysenck I7	Impulsivity	††	†	
Zuckerman	Sensation seeking	††	†	
AIAQ	Irritability, lability	††	†	
Buss-Durkee	Irritability	††	†	
MPS	Perfectionism	†	†	††
Y-BOCS target	Symmetry, exactness			††
Matching figure	Latency of response	¥¥	¥	†
	Errors	††	†	¥
Go/No-Go	Go signal			
	No-Go signal	††	†	
CPT	False alarms	††	†	¥
	Missed targets	††	†	¥
Personality style				
MPQ	Constraint			†
TPQ	Novelty seeking	††	†	¥
PDE (Axis II)	Cluster B, OC	B		OC

KEY: † = increased; ¥ = decreased compared to controls or other eating disorder patients.

Research Laboratory on the evening before day A. During the morning (8 a.m. to 11 a.m.) of days A and B, subjects will complete a battery of tests to assess behavior, mood, personality, and eating disorder-related symptoms. Because of the number of assessments, these assessments will be done over two 3-hour periods. All subjects will complete assessments in the same order. These data will be used to assess the presence and severity of symptoms in the patient versus the control population and to look at relationships with psychophysiological measures of impulse control and cognitive processes. The assessments to be completed are described as follows.

- Buss-Durkee Hostility Inventory (BDHI) (Buss and Durkee 1957). The BDHI is a 75-item true/false questionnaire related to aggression and hostility. The BDHI scales (irritability and assault) are found to correlate with indices of central 5-HT function, including CSF 5-hydroxyindoleacetic acid (5-HIAA) levels (Brown and Goodwin

1984), prolactin response to fenfluramine (Coccaro et al. 1989), m-chlorophenylpiperazine (mCPP) (Coccaro et al. 1989), and buspirone (Coccaro et al. 1990).

• Anger, Irritability, Assault Questionnaire (AIAQ) (Coccaro et al. 1991). The AIAQ is a 42-item self-report questionnaire that yields an assessment of irritability and assaultiveness with a focus on behaviors potentially related to reduced 5-HT activity. This scale has been empirically derived, in part, from the BDHI (Buss and Durkee 1957) and the Affect Lability Scale (Harvey et al. 1989). The authors have shown that this inventory discriminates between NWB and control women (unpublished data). There are three subscales to the AIAQ: behavioral irritability (readiness to explode with negative affect), three types of physical assaultiveness (direct, indirect, and verbal), and affective lability (impulsive dysregulation of anger). This instrument also rates along specific timeframes (past week, past month, adulthood, adolescence, and childhood).

• Multidimensional Perfectionism Scale (MPS) (Frost et al. 1990). This 35-item self-rating scale identifies 5 dimensions of perfectionism: concern over mistakes; high personal standards; parental expectations; doubt about quality of performance; and organization, order, and pre-cision. MPS measures have shown to be reliable and valid measures of different dimensions of perfectionism (Frost et al. 1993). This scale distinguishes differences in perfectionism between RAN and control women (Bastiani et al., in press; Srinivasagam et al., in press).

• Multidimensional Personality Questionnaire (MPQ) (Tellegen, unpublished data). The MPQ is a 300-item self-report questionnaire whose scales represent 11 primary personality dimensions (well-being, social potency, achievement, social closeness, stress reaction, alienation, aggression, control, harm avoidance, traditionalism, and absorption) and three higher order traits (positive affect, negative affect, and constraint). Casper (1990, Casper et al. 1992) showed that this assessment can distinguish differences in personality traits between RAN and NWB subjects. RAN subjects report greater self-control, lower impulsivity, and greater inhibition of emotionality and conscientiousness than NWB patients.

• Eating Disorder Inventory (EDI) (Garner et al. 1983). This 64-item, self-report, multiscale measure is designed for the assessment of psychological and behavioral traits common in women with eating

disorders. This scale is used extensively in the eating disorder field. Reliability has been established for all subscales.

- Beck Depression Inventory (BDI) (Beck et al. 1961). The BDI is a 21-item self-report inventory that correlates well with other established measures of depression.

- Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1970). The STAI is a widely used instrument that consists of separate self-report scales for measuring two anxiety concepts: state anxiety and trait anxiety.

On day B in the morning, subjects will complete the following tests.

- Eysenck (I7) (Eysenck and Eysenck 1975). The I7—a 90-item yes/no scale designed to assess impulsiveness and venturesome-ness—yields 7 factors: psychoticism, extraversion, neuroticism, lie score, impul-siveness, venturesome, and empathy.

- Alcohol Expectancy Questionnaire (AEQ). This is a 90-item, true/false questionnaire developed to assess subjects' beliefs about alcohol's effects in 6 domains using factors such as tension reduction, increased arousal, and performance impairment. Scores on this questionnaire have been shown to correlate with drinking style and the presence of problem drinking. The expectancies one holds about the effects of using alcohol or drugs may be important in determining future sub-stance use. For example, the expectancy that drinking alcohol will have a positive effect is correlated both with current (Goldman et al. 1987) and future drinking habits (Christiansen et al. 1989).

- Effects of Drinking Alcohol Scale (EDAS) (Leigh 1987). This is a 20-item, Likert-type scale designed to assess individuals' beliefs about the effects that alcohol has on their social behavior. This scale yields five factors: nastiness, cognitive/physical impairment, disinhibition, gregariousness, and depressant effects.

- Situational Confidence Questionnaire for Drugs and Alcohol (SCQD, SCQA) (Annis 1990). These are scales that measure self-efficacy, which refers to personal judgements of how well people can organize and implement patterns of behavior in situations that contain novel, unpredictable, and stressful elements. The alcohol scale has been validated (Miller et al. 1989); reliability and validation studies on the drug scale are in progress (Annis, personal communication,

February 1994). The drug scale contains 50 questions and the alcohol scale contains 39 questions. There are eight subscales: negative emotional states, negative physical states, positive emotional states, testing personal control, urges and temptations from intrapersonal deter-minants, interpersonal conflict, social pressure to use substances, and positive emotional states from interpersonal determinants. These scales are computerized so that each drug scale can be customized for each subject to ask questions about self-efficacy for up to three main drugs of abuse.

- Sensation Seeking Scale (Zuckerman 1971). This is a 40-item forced-choice scale developed to assess individual differences in optimal levels of stimulation and arousal. This scale yields four subscales: thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility. Scores on this measure have been hypothesized to be related to behavioral undercontrol and substance use. Personality characteristics indicative of behavioral undercontrol have been shown to be positively related to alcohol use (Earleywine and Finn 1991; Earleywine et al. 1990; Sher 1991).

- Tridimensional Personality Questionnaire (TPQ) (Cloninger 1987b). Three dimensions of personality (novelty seeking, reward depen-dence, and harm avoidance) have been hypothesized to be associated with brain monoamine systems. Specific patterns of these dimen-sions have been hypothesized to be associated with PSUD. Bulik and colleagues (1994) have found that +PSUD NWB women scored significantly higher on novelty seeking than -PSUD NWB women. While still in the early stages of clinical validation, this scale may be highly applicable to the study population.

- Matching Familiar Figures Test (MFFT). Subjects will be adminis-tered the MFFT. The subject is shown a series of 12 pictures, each containing a standard and 6 to 8 comparison figures. One of the comparison figures is identical to the standard, while each of the remaining figures subtly differs from the standard in some detail. The subject is asked which comparison figure is identical to the standard. Latency to first choice and number of errors (to a maxi-mum of two per item) are recorded. This test assesses impulsivity and reflectivity (Kagan et al. 1964).

Days A and B—Repeated Measures of Mood States and Mood Stability. It is hypothesized that NWB subjects have unstable, fluctuating, and overreactive mood states, whereas RAN subjects have rigid and inflexible mood states that are unresponsive to external

stimuli. To document such mood states, subjects will take the Brief Measure of Positive and Negative Affect Scale (PANAS) (Watson et al. 1988), a 20-item self-report inventory that measures positive affect and negative affect. High positive affect is a state of high energy, full concentration, and pleasurable engagement, whereas low positive affect is characterized by sadness and lethargy. High negative affect is a dimension of sub-jective distress and unpleasurable engagement, including anger, guilt, and fear, while low negative affect is a state of calmness and serenity. These scales have been shown to be highly internally consistent and largely uncorrelated. This scale is sensitive to changing internal or external circumstances and has been shown to be useful in quantifying an indi-vidual's mood fluctuations. Each subject will complete this scale at hourly intervals during the 2 days in the laboratory (except when engaged in other studies). It is hypothesized that variance in mood states in NWB subjects will be much greater than in RAN subjects.

Days A and B—Afternoon—Performance Assessments. These experiments will test several disturbances that have been conceptually implicated in the eating disorders: impulse control, response to stimuli, and habituation. Both performance and psychophysiological dependent measures (heart rate, skin conductance, and salivation) are assessed with this design. The tasks are a Go/No-Go reaction time task, a vigilance task (continuous performance test (CPT)), and several orienting/habituation series. Although all three functions are represented to some degree in all of the tests, the Go/No-Go reaction time serves as the primary impulsivity task and the CPT as the primary stimulus responsivity task. Three types of stimuli will be presented in the habituation task: a yogurt food, a lemon food, and an auditory tone.

- Go/No-Go task. The Go/No-Go task is a standard paradigm for the study of impulsivity (Troemmer et al. 1988) and has been used extensively. The Go/No-Go task requires a subject to respond as rapidly as possible to one set of signals (i.e., Go trials) and to withhold response to a second set (No-Go). A fixed foreperiod is typically used so that the subject develops a high state of readiness. In order to control for individual differences in reaction time, a 25-trial sample version of this task will be administered to subjects during baseline to evaluate subjects' average reaction times to the Go trials. For the experimental session, a reaction time will be calculated that is 70 percent of the subject's average, and subjects will be awarded a 5-cent incentive for each response to the Go trial that is equivalent to, or less than, this rate. This manipulation places an emphasis on speed and

accuracy and makes it more difficult for the subject to inhibit responding to the No-Go trials, thus ensuring that all subjects will have some failures to inhibit responses during No-Go trials.

Persons with disorders of inhibition typically show more inhibition failures to No-Go signals than controls (Patterson and Newman 1993). Psychophysiologically, the foreperiod induces heart rate deceleration and phasic skin conductance responses, as does success-ful inhibition. One hundred trials with 20 No-Go trials will provide sufficient data and require approximately 15 minutes.

Both behavioral and psychophysiological measures of impulsivity will be applied. With respect to the behavioral dependent measure, an elevated number of responses to the No-Go trials, also known as false alarms, are thought to indicate problems with impulsivity. It is expected that the NWB group will have a greater number of false alarms than the RAN or NC groups. RAN and NC will not differ from each other. The psycho-physiological measures are also expected to differentiate the groups. In RAN and NC groups, heart rate and skin conductance responses during the foreperiod will decelerate consistently over trials, indicative of appropriate attentional control of perceptual processing. NWB indi-viduals will show variable heart rate and skin conductance response during the foreperiod, indicative of a loss of appropriate attention.

• Continuous Performance Test. Vigilance requires maintained attention to the detection of a sensory stimulus; it provides a key test of a stimu-lus responsivity, but the test also has elements of performance test. The CPT is a computerized vigilance test that requires the subject to focus on an array of rapidly appearing stimuli and press a button every time a designated target appears (e.g., the number 9). To make the task more demanding, degraded visual stimuli (numbers covered by a cross-hatched grid) are used. Six blocks of trials are conducted and include two easy trials (blocks 1 and 6, stimulus duration of 101 milliseconds (ms)) and two hard trials (blocks 3 and 4, stimulus duration of 17ms). Reaction times to both correct and incorrect responses are recorded on disk. Stimuli are presented over a 9-minute period and subjects are not told about the variation in stimulus presentation rates. For each block, 20 percent of the stimuli are targets and the remainder are nontargets. Median reaction times are recorded for each block. Measures of d', an index of perceptual sensitivity, and beta, an index of response bias, are calculated for each block. Together, these measures provide estimates of vigilance and impulsivity. This task runs on an IBM-compatible

computer, and has been used to evaluate clinical patients having neuropsychological problems (Morrow et al. 1992).

It is expected that the NWB group will show greater heart rate and skin conductance responses to targets than the RAN and NC groups over trials, indicative of a disturbance in habituation. Further, the NWB group will have more false alarms and missed targets than both the NC and RAN groups. Extraversion has also been associated with more labile skin conductance during baseline conditions. If NWB subjects share respon-siveness and impulsivity characteristics with extraverts, then such a relationship might hold for the NWB group as well.

• Orientation/Habituation. Habituation and orienting to novel stimuli are basic processes that relate the stimuli of the external world to current knowledge. Preliminary data in 15 NWB women shows that their salivary response to food sensitizes with repeated presentations, compared to matched controls who show salivary habituation. Epstein and colleagues (1992a, 1992b) developed a basic paradigm to specifically study ingestive behavior. The pace of the habituation task is controlled by the necessity of salivary measurement. Dietary controls are also necessary, and will be standard for both days of testing.

Subjects will participate in two afternoon sessions between the hours of 2p.m. and 5 p.m. on both days. On day A, subjects will receive the auditory stimuli followed by the yogurt stimuli. On day B, subjects will receive the lemon juice stimuli followed by the Go/No-Go and CPT studies. On the days of testing, all subjects will consume a light lunch (approximately 350 kilocalories (kcal) from 11a.m. to 11:30 a.m.) and abstain from food and caffeinated beverages until this study is completed. Subjects must have at least a moderate liking (a rating greater than 50 on a 0 to 100 scale) for the food and taste stimuli used in the study.

Following specific instructions regarding the placement of dental rolls for salivation collection, two 2-minute baseline salivation measures will be taken. After these measures, the subject will rate (using a 100 millimeter (mm) line scale anchored by "very" and "not very") her initial degree of hunger, fullness, perceived pleasantness and intensity of the stimulus, desire to binge, and desire to purge before the study begins. The subject will then sit quietly for 3 minutes, after which she will be asked to insert new dental rolls.

The method of stimulus presentation for all groups is as follows: Immediately after insertion, a small amount of the taste stimulus (0.10milliliters (mL)) will be placed on the center of the tongue using a calibrated micropipette, and the salivary response to this taste will be collected for a 2-minute interval. After the stimulus is applied to the subject's tongue, a portion of the test food will be placed on the table in front of the subject and she will be instructed to look at the test food and to imagine eating it. The subject will be told explicitly that she will be asked to eat the test food after salivation collection, since it has been shown that the salivary response is attenuated when subjects do not expect to eat the presented food (Wooley and Wooley 1973; Wooley et al. 1976). After the 2-minute stimulus presentation, the subject will be instructed to remove the dental rolls from her mouth, place them in a plastic bag, and seal the bag. The plastic bag containing the dental rolls will be weighed within 10 minutes after removal. During each 3-minute intertrial interval, the subject will eat a portion of the test food; fill out self-report measures of hunger, fullness, pleasantness and intensity of the stimulus, desire to binge, and desire to purge; and rinse her mouth with water to remove any excess food debris.

In order to determine whether the impairment in salivary habituation demonstrated in NWB patients is generalizable to nonfood stimuli and other response systems, the subject's heart rate and skin conductance response to repeated presentations of an auditory stimulus will be evaluated. In this particular study, salivation will not be assessed since there will not be a significant salivary response to auditory stimuli. However, the auditory stimuli will be presented in a manner analogous to the salivary habituation paradigm. A sequence of eight stimuli will provide—just as in the food-related version—indices of habituation. Responsivity, via a dishabituating stimulus, causes the reinstatement of orienting; thus, the final stimulus identical to the first eight will also be examined. Rather than food bits, the generalization experiment uses 1,000 hertz (Hz) pure tones for standard stimuli, gated on with a slow rise time and presented for 2 minutes at 65 dB; the dishabituating stimulus is a 600-Hz tone presented for 2 minutes at the same dB.

The methodology for heart rate and skin conductance is common to all tasks. Interpretation of all these measures requires 10-minute resting baselines preceding the task battery and interspersed between the tasks. These measures are derived from surface electrodes, amplified, and then digitized by computer. To evaluate the phasic heart rate and skin con-ductance responses (SCR) to target stimuli in the CPT and Go/No-Go paradigms, the interbeat interval (IBI) and

SCR will be measured for 3seconds before, and 5 seconds after, the motor response to the target stimulus. The mean preresponse value for each measure will be sub-tracted from the mean postresponse value for each measure and for each target stimulus. The IBI and SCR responses to target stimuli will be averaged across subjects and between groups to obtain grand means for each target stimulus presented. In this study, skin conductance responses will be defined as those greater than 0.05 micro-Siemens occurring within 5 seconds after the motor reaction to the target stimulus. IBI will be defined as time between R-waves.

Analysis and Expected Results

The intent is to characterize permissive or protective factors that may contribute to the rates of PSUD in women with eating disorders. Four groups of female subjects will be studied: normal-weight bulimics with substance use disorder (+PSUD NWB); normal-weight bulimics without substance use disorder (-PSUD NWB); subjects with restricting anorexia (RAN); and normal controls (NC). Substance use is not crossed with RAN and NC. Very few individuals with RAN use substances of abuse, making inclusion of RAN subjects with and without PSUD impractical in this preliminary study.

Specific Aim 1. It is hypothesized that there are psychological factors that may permit or enhance the likelihood of developing PSUD, including behavioral undercontrol, personality factors such as novelty seeking; or negative, unstable mood states. Similarly, factors that are the conceptual opposites of these traits may protect against PSUD. These factors include increased self-control and DSM-III-R cluster C personality characteristics, perhaps characterized by perfectionism and obsessive need for symmetry and exactness; increased constraint or inhibition; and rigid, inflexible mood states. Analysis of variance (ANOVA) strategies will be used to test group differences of continuous measures of personality and behavioral traits and for the laboratory performance tests (the Go/No-Go and CPT tests). After multivariate analysis of variance (MANOVA) is conducted to confirm that measures differ from each other, univariate one-way ANOVA comparing the four groups (+PSUD NWB, -PSUD NWB, NC, RAN) will be con-ducted for each measure. Planned contrasts will be used to test the hypotheses that +PSUD NWB will show the greatest impulsivity, mood instability, and novelty seeking and the least perfectionism, inflexibility, and constraint, followed by -PSUD NWB, followed by NC, followed by RAN. For dichotomous variables, such as numbers of subjects who report a need for symmetry, chi-square

and Fisher exact tests will be used. It is likely that the chi-square requirement that at least five observations appear in each cell will not be met. If not, then Fisher exact tests will be used. Fisher exact tests can compare only two groups at a time (e.g., +PSUD NWB and -PSUD NWB); thus, it will be necessary to run multiple tests in order to make all of the comparisons of interest. Standard techniques to limit experiment-wise error will be applied; that is, tests will be conducted according to prior hypotheses and conservative p-values. Expectations are summarized in table 5.

Specific Aim 1a—Measures of Impulse Control and Other Risk Factors— Self-Assessment Paper-and-Pencil Tests. Measures of impulsivity have been developed primarily for aggressive, impulsive men. Such a conceptualization of the construct may not be completely appropriate for women with eating disorders. For example, there is an emphasis on the measurement of assault and, thus, there is less face validity in these measures for young women than is desirable. A major reason for this proposed study is to characterize the assessment tools that best quantify the risk factors for PSUD and discriminate between subgroups of eating disorders.

These tools have been chosen for several reasons. First, some instruments such as the Eysenck I7 or Zuckerman Sensation Seeking Scales (Sher 1991) have been shown to identify potential vulnerabilities in people at risk for developing PSUD. The intent is to determine whether these measures will discriminate NWB and RAN subjects. Second, preliminary studies suggest that some tools (e.g., TPQ, MPQ, MPS, Y-BOCS, and Axis II diagnoses) may discriminate characteristics related to impulse control, mood stability, or personality in patients with eating disorders. The intent is to determine whether these assessments are related to risk of PSUD. Third, certain assessments (BDHI, AIAQ) have been shown to be related to reduced 5-HT activity in studies mainly of aggressive, impulsive men. The intent is to determine whether differences exist between NWB and RAN subjects and how such measures may be related to risk for PSUD.

Specific Aim 1b—Construction of New Measures of Impulsivity From Old Scales. Since multiple measures of impulsivity are being used, it may be possible to improve the measurement for this patient group. As noted, measures of impulsivity have been developed primarily for aggressive, impulsive men, not women with eating disorders. Item-total correlations for each test will be used to ascertain which items best predict impulsivity in this population. Confirmatory factor

analysis will also be conducted. Members of the group will independently choose items across all scales that best characterize impulsiveness as expressed in NWB patients. Factor analysis will then be conducted. Items expected to measure impulsivity in NWB subjects that are shown by the factor analysis to group together will then be constructed into a new, revised scale. The properties of this scale will be tested on the experimental groups. The intent is to apply these techniques across the entire sample of eating-disordered women. However, the distributions across the groups will first be examined to ensure that combining across all four groups is appropriate.

Specific Aim 1c—Comparison of Laboratory Assessments of Impulse Control. Paper-and-pencil self-assessments of impulse control tend to measure how subjects have behaved in the past or how they per-ceive their behavior. Such measures tend not to be useful for assessment of "here and now" impulse control in brief laboratory studies. Traditional paper-and-pencil tests tend not to be designed to characterize short-term changes in impulse control and may be confounded by the artificial setting of the laboratory. Thus, the intent is to develop a lab test to characterize impulse control in women with eating disorders. It will be investigated whether NWB women have disturbances of impulse control as reflected by laboratory assessments such as the Go/No-Go, CPT, and MFFT. The ability to use a lab test of behavioral undercontrol will substantially benefit future studies of the behavioral expression of risk factors in humans with PSUD. For example, researchers could study whether agents that acted on specific neurotransmitter systems, such as 5-HT, altered behavioral undercontrol. Alternatively, the way that drugs of abuse or bingeing behavior altered behavioral undercontrol in NWB women could be studied in a laboratory setting.

Group differences in Go/No-Go, CPT, and MFFT will also be analyzed with ANOVA strategies. For the MFFT, latency of response and errors will serve as the primary dependent variables. For Go/No-Go, responses tothe No-Go signal will serve as the primary dependent variable. For CPT, false alarms and missed targets will serve as the primary dependent variable. Each dependent variable will be analyzed in a one-way ANOVA with four groups (+PSUD NWB, -PSUD NWB, RAN, and NC). As des-cribed above, it is expected that the groups will be ordered, with +PSUD NWB showing the most impulsive responses to each measure and RAN showing the least impulsive responses to each measure. Predictions for the order of the means will be tested with planned contrasts for each measure.

Specific Aim 1d—Negative Mood States and Unstable Mood. It has been suggested that increased negative emotionality may be a contributory risk factor for PSUD (Sher 1991). However, negative mood states in terms of depression and anxiety are of similar magnitudes in NWB and RAN patients. Therefore, negative mood states, per se, do not explain differences in rate of PSUD between NWB and RAN. Clinically, NWB patients have unstable moods and tend to be overreactive to stress and other stimuli. NWB women have a great deal of difficulty control-ling and tolerating extremes of negative affect. They often describe using bingeing or drugs to immediately reduce uncomfortable feelings they cannot otherwise control. Thus, it is hypothesized that a risk factor in NWB may be a vulnerability to unstable, overreactive, poorly modulated negative moods. In contrast, RAN women tend to be insensitive to internal and external cues, tolerate a great deal of physical and emotional distress, and take pride in their self-control and discipline. In fact, a hallmark of RAN is its ego-syntonic nature, with little insight or motiva-tion to change. It is hypothesized that RAN have rigid and inflexible mood modulation, are "stuck" in one mood state, and have little ability to experience or incorporate other perspectives such as pleasure.

This study will assess negative mood states. It is hypothesized that NWB and RAN women will have similar amounts of depression and anxiety in terms of DSM-III-R diagnoses and continuous measures (Beck et al. 1961, Hamilton 1959, Spielberger et al. 1970). The assessment of unstable mood is problematic. It is proposed to use the PANAS, which is a brief self-rating of negative and positive affective states that has been designed to be repeated multiple times during the day. It is hypothesized that NWB subjects will show much variance of negative and positive affects at ratings done hourly over a 2-day period. In contrast, RAN patients will have little change in mood. Group differences in mood stability will be tested by comparing the variance of hourly rated moods on the PANAS using the variance ratio test. Six variance ratio tests will be used to compare the four variances, and a Bonferroni-corrected p-value of 0.0083 will be used to assess significance in the differences of these ratios.

Specific Aim 2. It is hypothesized that the clinical presentation of disturbances of impulse control and mood stability reflect more pervasive characteristics of responsivity or reactivity to the environment in RAN and NWB subjects that may shed light on why differences in vulnerabilities to substance abuse occur. As Braff and colleagues (1992) noted, responses to stimuli and information processing are regulated by a cascade of operations including central

inhibition and selection, habituation, and traditional learning. Failure of some or all of these attentional functions might contri-bute to disturbances of impulse control and mood stability. The authors will test the possibility that people with eating disorders have disturbances in responding to novel stimuli (orienting response) or a disturbance of habituation (the decrement in the magnitude of the response over repeated presentations of the same initially novel stimulus). It is predicted that NWB subjects might fail to adequately habituate to the reinforcing effects of food or drugs of abuse. In comparison, it is hypothesized that hedonic stimuli have little reward value for RAN women because they rapidly habituate.

Specific Aim 2a. Preliminary data suggest that NWB subjects may have reduced habituation to the reinforcing effects of intake of a food such as yogurt. The intent is to replicate these findings using a yogurt stimulus and extend this study in several ways. First, other subjects groups will be investigated (+PSUD NWB versus -PSUD NWB, RAN). Second, a food (yogurt) will be compared with a neutral food stimulus (lemon) that should not elicit strong food associations. Each group of subjects is expected to show similar response patterns to both yogurt and lemon juice stimuli. It is hypothesized that such response is a trait characteristic of subjects and not just related to prior food-related experience or learning. It is predicted that RAN subjects will show the most rapid habituation, NC show intermediate habituation, and bulimic subjects show the slowest habituation. If there are differences between bulimics with and without PSUD, it is expected that bulimics with PSUD will show the slowest habituation of any group.

Specific Aim 2b. The hypothesis will be tested that such response disturbances to food stimuli generalize to nonfood-related stimuli. Thus, it is hypothesized that NWB subjects will have reduced heart rate and skin conductance response habituation to food stimuli (yogurt and lemon juice) and to nonfood stimuli (auditory tone and CPT). Eight trials of food and auditory stimuli will be used; CPT trials will be divided into blocks of eight for the purposes of the analysis. Two types of measures are extracted from the heart rate, skin conductance, and salivary variables.

- The tonic level describes the state of the variable during a baseline or performance of a task. For salivation, the tonic level is the total salivation volume for each trial. For heart rate, the average heart rate during baseline and task periods is calculated. For skin conductance, the average level of skin conductance is calculated and the number of responses within a baseline or task period is counted (a lability

measurement). These measures provide important context for the measures of event-related responsivity, phasic responsivity, which define the primary measures.

• The second type of dependent measure is phasic response. For salivation, the phasic measure is the pre- to posttrial difference in salivary volume. For heart rate, the phasic measure is the cardiac deceleration index formed by the difference between the longest pre- and poststimulus intervals. For skin conductance, the phasic measures are the amplitude of responses after an event compared to that before the event (typically assessed as zero for no response). As events do not elicit responses in all subjects for all stimuli, the probability of a poststimulus response (computed across subjects for a particular event) as a dependent variable will also be used; this will ensure that results are not measure-specific and not due to a small subset of subjects showing large amplitude responses.

The primary dependent phasic measures for salivation, heart rate, and skin conductance will be used. These measures are all predicted to show the same relationship to diagnosis over the eight trials, and thus a MANOVA will be applied first to show the overall result. Following the MANOVA, univariate tests for each of the dependent measures will be conducted. The tonic and phasic measures for heart rate and skin conductance will be subjected to a 4-way ANOVA by diagnosis (+PSUD NWB, -PSUD NWB, NC, and RAN), a 4-way ANOVA by stimulus (yogurt, lemon juice, auditory tone, and CPT), and an 8-way ANOVA by trials (or 8 trial blocks for CPT). Diagnosis will serve as a between-subjects factor, and stimulus and trial will serve as within-subject factors. First, the tonic measures of heart rate and skin conductance will be analyzed; if tonic effects are found, tonic measures will be used as covariates in the analyses of the phasic measures.

In the phasic measures, the expectation is to find main effects for diagnosis with RAN subjects showing the fastest habituation to all stimuli, followed by NC, followed by -PSUD NWB; +PSUD NWB subjects will show the slowest habituation, or perhaps sensitization, to all stimuli. Main effects with no interactions across the different types of measures would provide the strongest evidence that physiological habituation differentiates these groups. However, interactions may be present. It is anticipated that there will be interactions between patient group and trials, indicating differential habituation effects. The presence of interactions with the task factor would obscure the interpretation of the results, and it may be appropriate in this

exploratory grant to pursue a 4-way (+PSUD NWB, -PSUD NWB, NC, and RAN) ANOVA over 8 trials or trial-blocks separately for yogurt, lemon juice, auditory tone, and CPT habituation in order to best illuminate the pattern of results.

Orienting and habituation to novel stimuli are related processes. Clinically, NWB women tend to be overreactive to external stimuli. In contrast, RAN women tend to ignore internal stimuli (hunger) and external stimuli (feedback that they are too thin). It is hypothesized that NWB overrespond and RAN underrespond to stimuli and that this will be reflected in alterations in orienting response (increased in NWB, reduced in RAN). Orienting response will be assessed in the three habituation tasks (yogurt, lemon, and auditory tone) and in the CPT task. For the habituation tasks, there are two opportunities to observe orienting responses and thus test the basic responsivity of the different eating disorder groups: trial 1, initial orientation, and trial 9, the dishabituating stimulus. Relative to their habituated state, NWB subjects are expected to show greater orienting responses than RAN subjects and, to a lesser extent, the controls.

Habituation is only partially dependent on initial orienting. It is also expected that the hyperresponsivity of NWB subjects to be evident in a failure to habituate as well as initial hyperresponsivity. In pilot work, a sensitization over trials was seen in the NWB subjects. Habituation will be evaluated by examining the changes in the size of salivary, heart rate, and skin conductance responses over sequential stimuli. The slope over trials is a precise index of habituation. The slope should be most shallow for NWB, steeper for controls, and most steep for the RAN.

Specific Aim 3—Exploration of Other Factors Related to the Severity of PSUD in NWB. The opportunity provided by this research will be used to test whether substance use in NWB women is associated with some of the factors known to be associated with substance use in noneating-disordered populations. In particular, it is important to study the constructs of motivation, expectancy, and self-efficacy (which will be measured using the Alcohol Expectancy Questionnaire, the Effects of Drinking Alcohol Scale, and the Situational Confidence Questionnaire for Substance Abuse) as they relate to the presence of PSUD and degree of substance use among NWB women. As far as is known, little work has been done investigating such factors in NWB. These studies may shed light on understanding the relationship in NWB women between drug use and stress, tension reduction, interpersonal relationships, and social functioning.

Two types of analyses will be used to explore the relationship of motivation, expectancy, and self-efficacy to PSUD among NWB women. First, t-tests will be conducted for each measure to determine whether they differ between +PSUD NWB and -PSUD NWB women. For the second analysis strategy, presence or absence of substance use will be re-scored to reflect the degree of substance use as a continuous variable. In order to transform the diagnoses of PSUD to a continuous variable, the version of the SADS to be used has 125 summary questions that include DSM-III-R criteria for substance abuse and dependency. These questions quantify a wide range of drug use as well as alcohol use. The number of items endorsed will be a relative approximation of severity of drug and alcohol use for all 40 NWB women. That is, it is expected to find a range of scores of substance use degree within both groups, although the groups will not overlap; some women who do not meet the criteria for lifetime substance abuse or dependency will still have some drug or alcohol experience. It is expected that across the 40 NWB women, the range of scores of substance use will be fairly continuous. It is also expected that the distribution will reflect the genuine distribution within the eating-disordered population fairly accurately, despite the study sample selection of equal numbers of both groups. As far as is known, close to half of bulimic patients are also diagnosed with PSUD.

The correlation among motivation, expectancy, and amount of substance use will be calculated. It is anticipated that Spearman's correlations will be more suitable, as it is expected that substance use will be normally distributed. However, parametric or nonparametric strategies will be used as appropriate. Correlations will be calculated for all 40 NWB women and for +PSUD NWB women alone. Degree of substance use across all subjects may be predicted by different constructs than degree of sub-stance use within substance users alone. While direct tests of differences between the two tests would not be appropriate, methods such as these will be used to generate hypotheses for future work.

It is also important to determine whether extremes of substance abuse correspond with extremes of disordered eating behavior, that is, whether severity of eating disorder as measured by number of binge and purge episodes is associated with severity of substance use. First, it will be tested whether the number of binge and purge episodes differs for bulimics with and without substance use disorder. It is anticipated that the number of binge and purge episodes will not be

normally distributed, and this dif-ference will be tested with the Wilcoxon-Mann-Whitney rank sum test. Next, it will be tested whether binge and purge episodes are correlated with substance use across the two groups (using Spearman correlations for this test). Finally, the association of severity of eating disorder pathology and substance use in the substance use group alone will be examined. This group will be divided into high and low substance use based on a median split and into high and low binge/purgers based on a median split. A chi-square or Fisher exact test (depending on the distribution of frequencies among cells) will be used to test for the association of binge or purge episodes and substance use in this group.

In addition, the relationship of other demographic variables to PSUD in NWB women will be explored. These include current age, age of onset, duration of illness, current and past body weight, the presence of other psychiatric Axis I and II diagnoses, and previous treatment. The factors described in this aim will be correlated with the findings from specific aims 1 and 2 of the proposed study.

PUBLIC HEALTH SIGNIFICANCE

This study is intended to explore and develop a better understanding of risk factors for PSUD in women with eating disorders. First, this proposed study will focus on a better understanding of behaviors related to risk for PSUD in NWB and RAN women. Second, it will determine which psychological and psychophysiological assessments of impulse control may be the best reflection of risk factors for PSUD in NWB subjects. Third, it will attempt to develop a lab test that can be used to assess impulsiveness in the laboratory.

Limited data suggest that augmentation of 5-HT may attenuate alcohol consumption while serotonin depletion enhances alcohol use. NWB patients may have reduced 5-HT activity, whereas RAN patients may have increased 5-HT activity. Reduced 5-HT activity may contribute to impul-sive behaviors in NWB subjects, whereas increased 5-HT activity may contribute to obsessive exactness in RAN subjects. Uncontrolled over-feeding is consistent with reduced 5-HT activity, whereas restricted ingestive behaviors are consistent with increased 5-HT activity. However, a major impediment to understanding the relationship of 5-HT to psycho-logical measures of vulnerabilities is finding an accurate and reliable means of assessing the behavioral expression of risk factors in humans. This pro-posed study is intended to be a building block for future, more intensive, and larger

research studies. The long-term goal is to understand how disturbances of neurotransmitters, such as 5-HT, may play a permissive/ protective role in the development of PSUD in patients with eating disorders.

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AUTHORS

Walter H. Kaye, M.D.
Professor of Psychiatry
Director, Eating Disorders Module
Western Psychiatric Institute & Clinic
Room E-724
3811 O'Hara Street
Pittsburgh, PA 15213

Lucene Wisniewski
Doctoral Candidate, Clinical Psychology
University of Pittsburgh
Suite 300
Webster Hall
Pittsburgh, PA 15213

Click here to go to page 312