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# Sensitivity, Specificity, And Probability Calculations For 6 Tests Of Attention With A Mood Disordered Population

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**Sensitivity, specificity, and probability calculations for 6 tests of attention with a mood  
disordered population.**

**By**

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**Submitted in partial fulfillment of the requirements of the Degree of Doctor of  
Philosophy  
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**2001**

## Dedication

To my parents,  
who were always first to buy tickets  
to my three ring circus

To my children,  
Natan-el, Micheal, & Liam  
who grew to be beautiful souls  
despite my studies

To Michal,  
who balanced my Ying  
with an enthusiastic Yang

To Dr. Keith D. Cicerone  
who, with great generosity,  
taught me the work  
that suited my soul

And to my husband, Yossi  
who makes me laugh,  
who protects me, supports me  
and loves me; no matter what

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## Chapter I

### INTRODUCTION:

In recent years, the literature has demonstrated the presence of wide-range neuropsychological deficits in individuals suffering from mood disorders with impairments in attention, memory and executive functions (Zakzanis et al 1998: Arnett et al,1999; Lemelin, et al 1997a) It has generally been established that both unipolar and bipolar disorders are associated with cognitive change (Beats et al, 1996: Austin et al,1999; Lemelin et al, 1997a; Murphy et al, 1999). However, few studies have explored the diagnostic accuracy of neuropsychological tests with mood disorders despite both the prevalence and co-morbidity with other neuropsychological disorders.

Depression is clearly a prevalent disorder, affecting one in seven of the normal population at some time in their lives (DSM-IV; 1994). The symptoms that help to classify clinical depression encompass major areas of functioning including affect, psychomotor speed and cognition. These symptoms can often resemble or coexist with many neuropsychological illnesses. In fact, it is been estimated that as much as 50% of the patient populations of stroke victims, Alzheimer's, Multiple Sclerosis, and Parkinson's disease will suffer from clinical depression during the course of their illnesses. (Sweets, Newman and & Bell; 1998; Arnett, Higginson Voss, Wright, Bender, Wurst, & Tippin (1999). Varney, Martzke & Roberts (1987) investigated depression and head trauma, and found 77% of this patient population with clinical depression, however, only 18% spontaneously reporting symptoms.

Neuropsychological evaluation is often used in an attempt to differentiate depression from other neuropsychological conditions, whether as a primary diagnosis

or secondary to other conditions. This distinction becomes important when considering treatment options. Accurate differentiation of depression from other neuropsychological conditions aids in treatment, and allows for a realistic evaluation of rehabilitation as well as an understanding of a patient's psychological characteristics. Patients suffering from depression will often have cognitive complaints such as difficulties in concentration, difficulties with memory and a general feeling of mental listlessness (DSM-IV, 1994). These symptoms can all potentially reflect significant findings on a neuropsychological assessment.

The difficulty in delineating depression from other neurologic disorders is a result of a number of reasons. To begin with, depression often has symptoms that resemble other neurologic diseases and/or trauma. Equally, depression can be secondary to many neurologic and medical conditions. Moreover, depression can arise as a result of the injury site itself (right hemisphere) producing a confusing, complex profile (Heilman and Valenstein; 1993).

Furthering the understanding of the neuropsychology of depression has been complicated both by the issues mentioned above as well as the methodological inconsistencies found in the literature. There are many studies that look at the neuropsychological elements of mood disorders, however, there are discrepancies in the measures used, the populations studied as well as the many and often subtle subtypes of depression explored. Even more importantly, the literature that does exist does not provide information that is helpful in making the most accurate diagnosis with an individual case in the typical clinical setting.

In a typical neuropsychological assessment, a patient will be given a battery of potentially 20 tests that will aid in understanding the cognitive strengths and weaknesses of that individual. Based on the patient's performance, the cut off criteria used, and the literature that supports certain deficits aligning with certain neuropathologies, the clinician will attempt to assimilate the data into a potential diagnosis. If the pattern is clear and the history supports the findings, a diagnosis can be made with some sense of accuracy. Often, however, the data do not readily align with one specific diagnosis, the data provide conflicting evidence, or the imaging results will be contrary to the neuropsychological testing results. A natural response to this dilemma would be to ask which test results are more likely to be accurate in a particular diagnosis. Or, which test has been more accurate in diagnosing a certain disease in the past? What combination of tests will be the best predictor of a certain diagnosis? If you begin to search for data in response to these questions, you'll find that there is very little research in the neuropsychological literature investigating the diagnostic accuracy of neuropsychological tests with specific populations. Further, there is only one study, to this author's knowledge, that explores the general diagnostic accuracy of neuropsychological assessment measures with a mood disordered population (Zakzanis et al, 1998).

The typical research studies of this subject matter attempt to illustrate the neurocognitive differences between depressives and other psychiatrically impaired or normal groups in order to create a profile distinguishing neuropsychological performance differences between groups. To this extent, there is data to support neuropsychological impairment with unipolar and bipolar depression. Typical profiles



include memory, attention, reaction time, inhibitory deficits, and some visual spatial dysfunction. Further, much of the literature comparing neuropsychological performances within groups of bipolar and unipolar patients found no differences (Bulbena & Berrios, 1993; Goldberg et al, 1993). Despite markedly different presentations, the literature suggests that the cognitive impairments found in the mood disordered subsets are similar processes rather than discrepant, contrary to expectations (Johnson & Magaro, 1987).

Conclusive understanding of the neuropsychological deficits of mood disorders remain obscure due to a number of issues including the severity and type of depression, age as well as the various measures used; all of which have influenced the level of clarity in the literature (Purcell et al, 1998). Further, when significant differences are found, they typically are analyzed through standard parametric measures that demonstrate the statistical significance between groups in order to create a sense of the cognitive deficits that might be seen with certain conditions.

These studies, however, do not address the value of using some tests over others, whether a neuropsychological test is sensitive and/or specific to certain psychological conditions; nor can they address the diagnostic accuracy of the neuropsychological measurements currently being used (Ivnik Smith, Petersen, Boeve, Kokmen, & Tangalos; 2000).

#### Need for the Study

The ability to accurately diagnose different neurologic illnesses is a primary goal of neuropsychological assessment. Often neuropsychologists are asked to differentiate between patients who are brain impaired and patients who are suffering

from affective disorder. When a patient is able to clearly provide symptoms that delineate a mood disorder, the process is generally straightforward. When a patient presents with neurocognitive difficulties and an undifferentiating diagnosis, the need for precise diagnostic tools becomes more evident. Potential misdiagnoses whether false positives or false negatives have important treatment implications. For example, a patient who is incorrectly diagnosed with depression, when in fact may be suffering from a subtype of dementia, (false positive) will not only receive potential treatment such as antidepressants and psychotherapy that would be ineffective, they will also be missing out on the effective treatment. This inaccuracy could cost the patient valuable treatment time as well as potentially irreversible damage. Reifler, Teri, Raskind, Veith, Barnes, White, & McLean (1989) found that AD patients treated with antidepressants (imipramine) showed additional cognitive decline not found in a placebo treated Alzheimer's Dementia group; Another study found that patients not treated with a cholinergic inhibitor two years post diagnosis declined more rapidly than those treated with a drug such as Aricept; illustrating the importance of diagnostic accuracy and treatment accuracy (Salmon & Bondi, 1995). Likewise, if a patient is suffering from Major Depressive Disorder, although misdiagnosed as normal (false negative) the implications are clear; continued psychological deterioration, cognitive decline, and potentially life-threatening complications.

Unfortunately, the present methodology of much of the literature explores group differences that can be found using neuropsychological instruments without accurately providing information as to which contributes to the diagnosis of a disorder in a given individual. Few studies have attempted to use neuropsychological testing as

a discriminative tool. Typically, an "impaired" score is established, referred to as below the major part of a normal distribution, and measured either through percentile ranks or multiple standard deviations from the mean; an interpretation is based on the distribution of scores under a normal curve (Spren & Strauss, 1998). A single neuropsychological test performance is then comparatively assessed based on the normative sample. This process is helpful to understanding the differences resulting from a certain neuropathology, but does not provide more precise diagnostic clinical information when considering individual treatment.

As the options for treatment increase, diagnostic precision is of greater importance. Several years ago, the diagnosis of an Alzheimer versus a Vascular dementia would not delineate vastly different treatment options. Today there are psychopharmacological treatments that are specific for Vascular versus an Alzheimer dementia. Likewise, there are different treatments suggested for mild versus a moderate dementia. Thus, with the increasing demand for diagnostic accuracy, the old method of using the current literature available and sound clinical judgment are no longer able to withstand today's demand of diagnostic proof in the face of changing treatment options.

There is another area of interpretations that is based more on the clinical data. "Clinical Epidemiology" is a research discipline that is concerned with the distribution and determinants of disease populations. Briefly, this area of study is concerned with observations that are representative of some defined group of people or "population" (Sackett, et al, 1991). Epidemiologists are more concerned as to whether something occurs rather than how it occurs in sub-groups of people. Therefore, due to the

unique characteristics and environmental qualities that are inherently part of human research, their decisions are often based on probabilities (Fletcher, et al, 1982). The probability calculations are best estimated by means of past experience with similar patients, and are formulated by mathematical calculations specifically used to reflect human research design (Fletcher, et. al., 1982)

Generally speaking, clinical observations are measured in nominal, ordinal or interval scales. They are found to vary because of error of measurement, differences of individuals from time to time and differences among individuals. Clinician's will attempt to simplify data by calling them abnormal or normal, in order to delineate a select course of action. Unfortunately, there is no inherent cut off between normal and abnormal and often there will be overlap between these so-called "distinct" groups. The choice point for which normal becomes abnormal is derived from data concerning the consequences of possessing a given value for the measurement in question and the base rate of a behavior.

Thus, on the comparison of scores found in actual samples of normal subjects and abnormal groups, there is typically an overlap of scores when the two groups are compared. The relationship between a diagnostic test and the actual presence of disease can be addressed when the groups are considered to be truly separate with minimal misclassification in both groups. For example, when using a given instrument, subjects correctly classified with depression given an "impaired performance" reflects the level of sensitivity and normals classified as such is the specificity of a measurement. Thus, *sensitivity* refers to the probability that a subject obtains an impaired test score, given that the disorder is present ( $TP/TP + FN$ ). *Specificity* refers

to the probability that a subject obtains a non-impaired test score, given that the disorder is absent ( $TN/TN + FP$ ). The overall *Efficiency, Accuracy or hit rate* of a test is then determined by the number of subjects correctly classified ( $TP + TN/N$ ).

Both sensitivity and specificity refer to the characteristics of the testing instrument, when the identities of the subjects according to the presence or absence of the disorder in question are known. When choosing a diagnostic test, one should take into account issues of sensitivity and specificity. When the penalty for missing the disease is great, such as a life threatening disease, a sensitive measure should be used over a specific one (Sackett, et al, 1991). Another clinical decision would be exploring the possibility of having a disease when the risk was low. The choice would then be to use a specific test since they are useful for confirming a diagnosis that has been suggested by other data. This is because a highly specific test is rarely positive in the absence of the disease. Optimally speaking, it would be best to have measures that are highly sensitive and specific. Unfortunately, there is often a trade off between sensitivity and specificity data when clinical data changes in cut-off criteria. Therefore as the cutoff criteria changes for abnormal versus normal, one characteristic can be increased (sensitivity) at the expense of another (specificity). The trade off between sensitivity and specificity can be demonstrated in the *Receiver Operator Characteristic* of a test (ROC curves)(Sackett et al , 1991). It appears that the best way to address this trade off is to use the results of several tests together. Unfortunately, these values are determined given that the disease is a known determinant. There are another set of calculations that can offer predictions when the disease existence is unknown. Routinely, the neuropsychological investigator is being asked to determine the

probability that a disorder is present based on their test performance. *Positive Predictive Value* refers to the probability that the disorder in question is present, given an impaired test score ( $TP/TP+FP$ ). *Negative Predictive Value* refers to the probability that the disorder in question is absent, given a non-impaired test score ( $TN/ TN+FN$ ). Unfortunately, these values will be effected by underlying prevalence of the disease in the population being tested (Sackett,1991). For example, if this research supported the usage of 6 tests of attention as excellent diagnostic predictors of mood disorders in an outpatient psychiatric population, other neuropsychological clinics might decide to also incorporate these tests as well. The problem is this population might be only 50 % in a neuropsychology outpatient clinic as opposed to a psychiatric outpatient clinic were the prevalence may be as high as 90%. Just by the fact that the proportion of patients who may have depression decreased will automatically effect the predictive value, even while the sensitivity and specificity remain the same. *Likelihood ratios* may be defined as given the disorder in question is present, what is the probability the individual will have an impaired test score on a given measure; or what are the chances (the likelihood) that a person who has depression will get an impaired score on the CPTA? (Ivnik et al, 2001).

Another probability ratio, the Odds Ratio ( $o'$ ) may be considered an overall index of diagnostic accuracy, and is derived from the ratio of correct to incorrect classifications (Bieliauskas, 1997). According to Bieliauskas et al (1997) the odds ratio may be interpreted as a statement that a subject scoring below a selected cut off score (where  $x=o'$ ) is more likely than that for people scoring in the unimpaired range of the same test (Bieliauskas et al 1997). Using the lower limit of the 95% confidence

interval to represent the value of  $x$ , one could interpret an impaired score to indicate that we can be 95% (one-tailed) confident that a person who obtains a score below the selected cutoff is  $x$  times more likely to have the disorder in question than a person who scores above the cutoff. Bieliauskas and his colleagues (1997) suggest that odd ratios over 3 indicate a positive association.

There are a limited number of studies that have investigated the clinical sensitivity of neuropsychological measures. Cicerone (1997) addressed this issue with a mild head injury population. His findings suggested that there is a significant degree of variability between measures of attention that might exist due to their varying degrees of sensitivity. Specifically, he found that both the Continuous Performance Test of Attention (CPTA) and the Paced Auditory Serial Addition Test (PASAT) were both more sensitive measures of impairment after mild traumatic brain injury (Cicerone, 1997). This study further facilitated the understanding that the varying levels of sensitivity alludes to the varying components of attention (Cicerone, 1997). Cahn et al (1995) successfully separated groups of 238 normal elderly subjects, 77 at risk for Alzheimer's patients, and 45 with Alzheimer patients using the Trail Making Test A (TMT A) and Trail Making Test B (TMT B) and found a sensitivity of 69% and specificity of 90% for Trails A and 87% and 88% for Trails B. These sensitivity findings are not only beneficial for gaining a clinical understanding of the more sensitive measures of attention with this population, the results suggest that the spatial shifting, more complex attention task may be a more diagnostically accurate measure for a dementing population, which is supported by the literature. Bieliauskas et al (1997) also used a population of 26 community dwelling adults with either possible or

probable Alzheimer's disease and 25 matched volunteers to explore the diagnostic probabilities of certain neuropsychological measures. Although his study used primarily tests of memory, his study illustrated the value of exploring data using sensitivity, specificity and probability calculations as beneficial to understanding the individual's performance and therefore potentially clarifying the individual's diagnosis (Beilaukas, et al, 1997). Comparatively speaking, his usage of a more simple attention (Digit Span) showed group differences when using typical parametric testing ( $t=4.20$ ) was likewise the least indicative that an impaired Digit Span scored would be clinically significant of the disease (CII  $\phi' = .6-.27.8$ ) Beilaukas et al (1997). Both Beilaukas (1997) and Cahn et al (1995) support the notion that less complex attention measures appear less diagnostically accurate with an Alzheimer population. Likewise, Cicerone (1997) proposes that both the CPTA and the PASAT share the usage of externally paced stimuli as a key factor in their significant sensitivity to the mild TBI population. The sustained and/or working memory element of these tasks may be another. Ivnik et al's (2000,2001) studies have focused on demonstrating the diagnostic accuracy of using sensitivity and specificity and probability calculations over the more traditional parametric tests. In his initial study, Ivnik et al (2000) argued more firmly for the added usage of odd ratio calculations as a useful tool in understanding the neuropsychological data presented from cognitively impaired dementia spectrum patients. However, more recently, he also suggests the value of using likelihood ratios as helpful in understanding the specific individual's performance (Ivnik, et al, 2001). As mentioned earlier, the odds ratio value speaks to chances (probability) of having the target disease given a certain performance on a measure as



compared to those who performed below or above that certain performance, while Likelihood ratios discuss whether a person, who has the disease will be accurately categorized. For example, one could evaluate the probability of having Alzheimer's using APOE 4 gene test whose cut off is having 2 of the #4 alleles being at risk for Alzheimer's. The patients who has 2 of the # 4 alleles is x times more likely to have Alzheimer's as opposed to having 1 of the #4 alleles (Odds ratio), as opposed to given the presence of Alzheimer's, what is the probability that a person will have 2 #4 alleles (Likelihood ratio). Thus, the odds ratio calculations address the risk probability of having the disorder in question for those whose performance meets a certain cut off as compared to those people whose cut off score suggest they should not have a disorder. This speaks more to the increased chances of having a target disease based on a performance criteria. In comparison, a Likelihood ratio is the probability of having the disorder with an impaired score over the probability of not having the disorder with an impaired score; speaking to the individual's performance being correctly classified (Ivnik, et al., 2001).

Likewise, the question of how depression is accurately diagnosed using neuropsychological testing has not been thoroughly explored, only one study was found questioning the sensitivity of measures to depression. Zakzanis et al (1998) used a meta- analysis to explore the effect sizes of different tests using depressives and also calculated the sensitivity of these same measures using Cohen's U2 calculations. Their findings suggest intermediate effect sizes on tests of psychomotor speed and tests that required sustained attention (Zakzanis, 1998). Likewise, sensitivity measures of attention tests were as follows; Trails B, 64%, Stroop interference, 64%, Stroop Color

naming 59%, PASAT, 56% and Trails A 54%, suggesting that those attention tests having working memory, sustained attention components as well an externally paced element went from an intermediate to below median level of sensitivity (Zakzanis,1998).

Using the same theoretical investigative premises proposed by Cicerone, Ivnik, and Beiliaskas, this study will examine the clinical sensitivity, specificity and probability calculations of six commonly used attention measures in a sample of patients diagnosed with a mood disorder, either unipolar or bipolar. The goal of this study is to provide sensitivity specificity and probability calculations on several measures of attention using both a bipolar and unipolar population. The goal of this study is to provide an evaluation of specific attention measures' contribution to identifying attention impairments in a mood disordered population, and advance diagnostic accuracy in neuropsychological assessment of depression. Finally, a study of this nature may inadvertently facilitate the understanding of specific subtypes of attention impairments found in both bipolar and unipolar depression.

#### Significance of Study

The prevalence of mood disorders is extensive enough to warrant the exploration of cognitive characteristics of attention and to further the understanding of depression and its impact on cognition both for diagnostic and treatment issues. Assessing the results using sensitivity, specificity, and probability computations can be contrasted to the limitations of traditional statistical values. Typical parametric findings cannot be interpreted with any diagnostic value and sensitivity and specificity

scores allow for clinical interpretation of much smaller sample sizes (Bieliauskas et al,1997). Likelihood ratios allow for predictive criteria for the individual while odds ratios show differences that would not be significant in more traditional p values and thus would remain undetected, and allow for comparisons across studies irrespective of sample sizes (Ivnik et al, (2001). Therefore, this study will contribute to the diagnostic accuracy of attention tests with unipolar and bipolar disorder population as well as adding to the understanding of attention impairments secondary to mood disorders.

#### Theoretical Rationale of the Study

There are two underlying theoretical principles upon which this research is based. The first addresses the value of using sensitivity, specificity, and probability computations, over the more traditional statistics. The goal of this research is to provide specific clinical information that will further assist the neuropsychologist in accurately diagnosing patients with depression. Specificity, sensitivity, and probability calculations are useful to hypothesis testing and meaningful even when studying very small populations. Further, there is an inherent clinical and interpretable meaning above and beyond typical group comparisons used through traditional statistical testing (Bieliauskas, Fastenau, Lacey &Roper, 1997). Ivnik, Smith, Petersen, Boeve, Kokmen, & Tangalos (2000) suggest that the neuropsychological evaluation has been assessed as being a valued service provided by neuropsychologists with the detriment of having very little research examining the neuropsychological tests' diagnostic accuracy when applied to individual's with a range of potential neurologic conditions.

Rather than using the more common statistical analysis which provide statistical evidence of group differences, this study will use sensitivity, specificity, and probability computations. These calculations provide information with regards to the individual and the accuracy of the instrument in correctly classifying impaired and non-impaired subjects respectively. This study will also explore the conceptual understanding of the sub-components of attention in clinical depression.

The second theoretical basis underlying the design stems from the background research of cognitive psychology whose principles have extended recently into neuropsychology. It is these prepositions that have shaped the perspective and development of the instruments and more importantly, the interpretation of what is actually being measured. Prior to investigating what component of attention each measure will be quantifying, it is first necessary to discuss how attention is currently viewed.

#### Theoretical Underpinnings of Attention:

In order to understand the nature of attention impairment in depression, attention will need to be defined. Unfortunately, there is no unequivocal and universal definition of attention; instead there are several different theoretical positions used to define attention and its sub-processes. The lack of agreement appears to stem from the diversity of processes underlying the attention system and the complexity and variation of what occurs under a rather diverse set of operations called "attention". In any case, there are strong theoretical constructs that have been generated to classify and define the different processes that would explain how the organism becomes receptive to stimuli. Further there are theories to explain how it may begin processing

incoming stimuli to consciousness, ignore unwanted stimuli and maintain receptivity (continue to be open to new information coming in).

Posner & Boies (1971) suggest three major topics in attempting to conceptualize the different attention capacities. First is the notion of alertness or vigilance as well the "fore-period" that allows one to prepare to take in information. They propose the ability to select one type of information over another as a second type of attention and suggest this possibility through a filtering mechanism, which block or attenuate input (Posner & Boies, 1971) and as such, a necessary sub-component of the selective process. Further, this selecting process may diminish the capacity to process and maintain alertness in other modes (Posner & Boies, 1971). The third element of attention relates to the concept of a "central processing capacity" which suggests that any two operations requiring this main processor sometimes referred to as "working memory" will interfere with each other (Posner & Bioes, 1971).

Schneider and Shiffrin (1977) indirectly expand on this limited capacity concept by suggesting a two-process theory of processing; one is automatic and does not stress the capacity nor requires the attention demands of the system. This operation is suggested to occur through a set up of sequential configuration of nodes that are generated as a response to either an external or internal process and can be activated without active control (Schneider and Schiffirin, 1977). They suggest that limitations exist only in the speed of reception which if exceeds capacity (ie. speed of presentation-too quickly to even be processed) will hamper a complete processing operation (Schneider and Schiffirin, 1977). Schneider & Shriffrin (1977) further

delineate the automatic process as having a reflexive attention response, directing attention to the target regardless of concurrent inputs or memory load, which enable correct detection to occur. They also suggest a second process that is more relevant to the idea of limited capacity or working memory. They suggest the conceptualization of a temporary sequence of nodes activated under control of and through attention by the subject and thus only one sequence can be controlled or attended unless the speed of presentation is drastically reduced. They further distinguish divided attention from focused attention by suggesting the former is the control of information processing so that one input is perceived or remembered over another. The latter is defined as using the same set of resources to inhibit or ignore unwanted stimuli in order to more effectively attain to a specifically chosen stimuli (Shneider & Shiffrin, 1977). Mirsky, Bruno, Duncan, Ahearn, & Kellam (1991) propose a 4 component model for describing attention incorporating several different summative principles. They suggest that attention is based on a group of processes, is a resource with limitations, has a clear delineation between automatic processes and controlled processes which has different characteristics and places different demands upon the system (Mirsky et al, 1991). Their factor analysis suggest that Trail Making, Digit symbol, Stroop Interference and Letter Cancellation load on a focus and execute factor, while a Continuous Performance test load on a vigilance factor and a Digit Span measure load on an encode factor (Mirsky et al 1991). Their model consists of 4 elements shifting, focus-execute, sustain and encode that are components of attention, also proposing neurological substrates necessary for these processes to occur (Mirsky, et al, 1991). Finally, Mateer & Mapou (1996) attempt to integrate different models and propose a

separating attention into two different elements. The first is deployment- which describes an individual's ability to channel and focus attention resources and encompasses arousal, focused and sustained attention; and encoding - which refers to the individual's ability to hold information and then process it even if distracted or required to divide attention (Mateer & Mapou, 1996). Thus, in integrating the earlier models with some of the later paradigms there are several common threads that appear to describe with the greatest accuracy, the processes that occur for successful attending to one or more stimuli (external/internal). These include speed of processing, selectivity and inhibitory operations, and capacity limitations (working memory) intimately connected to controlled- more limited by the complexity of the stimulus, and automatic processes- which are more reflexive.

The measures chosen in this study reflect both the areas that have been theorized in the subject of attention theory as well as the measures commonly use in the literature of depression and attention. Schmidt, Trueblood, & Merwin (1994) assessed 12 tests of attention using a strict factor analysis. Their results suggest that these measures do not factor on one single component of attention and thus provide little insight into attention processes (Schmidt et al, 1994). Further, they argued that the current tests of attention most commonly used are not in fact base on any true theoretically based model of attention (Schmidt et al,1994). The most logical compromise is to use the models of attention to lay the theoretical ground-work for what these tests may be measuring. Recognizing that although there may be a primary attention process occurring with a certain measure, there will naturally be an overlap of several different secondary processes as well. Using the validity and factor loadings

provided by the authors of the tests themselves, this research will attempt to bridge the gap between theory and clinical tests of attention in order to gain some clinical understanding of the attention deficits, secondary to mood disorders. The tests used are first described with regards to their theoretical constructs, and later described more completely in Chapter Three.

The Digit Span subtest of the Wechsler Memory Scale-Revised - has been generally accepted as a basic auditory attention measure with an added component of working memory needed for digit span backwards. This measure does not employ a speed of processing demand and thus deficits found on this test generally suggest difficulties in maintaining vigilance and holding information in working memory irrespective of speed (Lizak, 1994).

Paced Auditory Serial Addition Test (PASAT) is an auditory attention measure with a speed component. It requires vigilance as well as freedom from distractibility. This measure is thought to primarily measure central processing capacity (working memory) as well as information processing speed (Spren & Strauss, 1998) Generally, deficits in this measure will suggest difficulties with more rapid and externally paced processing, as well as maintaining information in working memory (Cicerone, 1997) Further, performance is thought to be compromised by anxiety; reduction in the rate of speech, and to those patients with math deficits (Spren & Strauss, 1998).

Continuous Performance Test of Attention (CPTA)(Cicerone, 1997) is an auditory attention measure developed to measure processing speed at several different levels of complexity. Further, the test demands both a simple stimulus discrimination process as well as more complex stimuli processing (Cicerone, 1997). Deficits on the



CPTA typically denote difficulties with sustained processing and maintaining vigilance (Cicerone, 1997).

Trail Making Tests A and B are tests of both simple and complex visual scanning with a motor component developed to measure processing speed combined with motor speed agility. Trails A requires the subject to visually scan and connect consecutively numbered circles on one worksheet. Trails B requires the subject to connect consecutively numbered circles alternating with consecutive lettered circles on a second work sheet. The fact that on Trails B, subjects are required to hold or inhibit their more automatic response and instead shift to a second set of stimuli has further been described as tapping the selective-inhibitory process of attention (Reitan; 1989).

The Stroop Test (Golden, 1978) again is suggested to examine both simple processing speed in translating a string of color printed XXX's into a verbal word, as well as measuring the change in processing speed that occurs with the additional demand of inhibiting a more automatic response of reading a printed word, and instead to state the color of the ink used to print the word. As with Trails B, this test is thought to measure processing speed and selective inhibitory attention.

The Ruff 2 & 7 Test the developed to measure sustained and selective aspects of visual attention. The comparison of *automatic detection* versus *controlled processing* conditions is intended to assess selective attention to external stimuli with minimal demands on internal processing of information or immediate memory (Ruff, 1982).

Thus general components to be addressed in this study include attention measures that measure sustained attention, automatic and controlled attention,

selective or divided attention with the added component of working memory, processing speed, and the ability to inhibit attending one element over another.

#### Statement of the Problem

Although there have been numerous studies examining depression and the group differences found using attention measures with major depressive disorder, few studies have attempted to document levels of sensitivity, specificity, and diagnostic accuracy of attention measures with a depressive population. The purpose of the present study is to ascertain with a more scientific level of certainty the sensitivity and specificity of certain attention measures in correctly classifying patients with unipolar or bipolar Disorder. In doing so these tests, based on the nature of the attention impairment they are measuring, will also provide a clearer pattern of attention impairment in depression. This study will calculate the sensitivity and specificity efficiency, as well as probability calculations for the Stroop Color, Color Word, Pasat, Digit Span forward and backward, CPTA, Ruff's 2 & 7, and Trails A & B.

#### Hypothesis of the Study

Unlike the more traditional research calculations typical hypothesis statements do not hold the same value as when calculating significance levels. In evidence based medicine or Epidemiological measures the goal is to gain an understanding how certain groups will be categorized and how successfully this will be done, facilitating an understanding both about the population and the measures used. Thus, there are no significance levels that would allow one to reject or accept the null hypothesis based a priori hypotheses.

Instead, there are some theoretical constructs that could be argued based on the literature and the findings thus far; some trends that are expected based on the earlier research which lend themselves to several "hypotheses". First, based on the literature, it appears obvious that depressives will in fact have an unimpaired performance on tests of attention. Further, the attention measures will reflect varying levels of sensitivity and specificity with a mood disordered population. As with the Cicerone study (1997), the variation will be reflective of the different sub-components of attention that the measures assess. It will be possible to derive some measure of diagnostic accuracy for of a mood disordered population by using neuropsychological attention measures used in this study. Other hypotheses that can be made based on the literature and the sensitivity findings thus far (Zakzanis,1998) would suggest that attention measures that have a sustained and/or set shifting and/or inhibitory factor will generally be better diagnostic tools in differentiating a mood disordered population from controls. Conversely, those measures that factor on basic attention processes such as "focus" and "vigilance" will be less likely to accurately classify the affectively impaired group from controls. Finally, it is hypothesized that the severity of the depression will not be related to the cognitive impairments (Purcell,1997, Jest et al, 1996:Nelson et al, 1998)

### Definition of Terms

#### Unipolar Depression:

For the purposes of this study, the definition of depression will be solely based on the diagnostic criteria of the DSM-IV (1994 publication). DSM-IV (1994

publication) presents a criteria for Major Depressive Disorder in which five or more of the following symptoms have been present during the same 2 week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood; or (2) loss of interest or pleasure. The other 7 of the nine symptoms are as follows: (3) significant weight loss or increase or decrease in appetite; (4) insomnia or hypersomnia nearly everyday; (5) psychomotor agitation or retardation nearly everyday (observable by others, not merely a subjective feelings of restlessness or being slowed down); (6) fatigue or loss of energy nearly everyday; (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional ) nearly every day; (8) diminished ability to think and concentrate; or indecisiveness, nearly every day (either by subjective account or as observed by others); (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide (DSM-IV, p. 327;1994) Further, the symptoms cannot meet the criteria for a Mixed Episode; they must cause clear significant distress or impair social, occupational, or other areas of functioning; the symptoms cannot be due to any direct physiological effects of a substance abuse or a general medical condition and the symptoms are not better accounted for by bereavement.

Bipolar Disorder I- The essential feature of the clinical course is characterized by the occurrence of one or more Manic Episodes or Mixed Episodes as well as one or more depressive episodes (DSM-IV, American Psychiatric Association,1994).

#### Attention

Generally, attention refers to the capacity an organism has to become receptive to a certain stimuli over other stimuli and begin processing in a relevant manner (Lisak,1995).

#### Automatic Attention Processes

There are a variety of definitions for this term, however, Scheiner & Shiffrin (1977) best described this process as typically referring to a sequence of neural responses that are activated by certain associations, without control or intention. Because this process is reflexive there is little demand made on the short- term store capacity.

#### Controlled Processes

This process is dichotomous to automatic in that it is activated and consciously directed by the organism. In addition, the need for constant attentiveness makes this process capacity limited and connected to the limitations of short-term store.

#### Short term store

This term refers to a limited capacity in temporary memory store, unitary in nature (Atkinson and Shiffrin; 1968).

#### Working Memory

Working memory was originally thought to be the same as short term store but has evolved into the assumptions that it also contains several subsystems and can be involved in a number of tasks that require more sophisticated manipulations including learning, reasoning and comprehension (Baddley;1992).

#### Selective or Divided Attention

An element of the general attention process, which allows for the decision to choose one source of stimuli over another. The choice may either be a controlled choice or an automatic one. Further, it suggests a type of filtering system that must be in place in order for this process to occur smoothly. Further it speaks directly to the concept of limited capacity (Posner,1971)

#### Attention Resources

This term suggests that the ability to attend is limited in capacity and thus two simultaneous operations requiring attention will interfere with each other.

#### Distracter Inhibition

The ability to inhibit responding or attending to a concurrent or conflicting stimuli, while attending to another (Cicerone)

#### Sustained Attention

This term refers to the ability to maintain vigilance or alertness to external stimuli over a period of time (Posner,1971).

#### Psychomotor/Cognitive Retardation

Slowed cognitive processing, emotional expressiveness and motor abilities.

## Chapter II

### LITERATURE REVIEW

The purpose of this chapter is to examine previous research on mood disorder, and its influence on the performance of neuropsychological tests of attention. The literature suggests that the neuropsychological deficits found in unipolar and bipolar disorders are similar (Bulbena & Berrios, 1993; Goldberg et al, 1993; Brown et al, 1994; Murphy et al 1999;). Not only were group differences not found in these studies, bipolar patients assessed in their manic phase were found to be impaired on tests of attention (Bulbena & Berrios, 1993). In fact, the literature frequently does not make the distinction between a unipolar and bipolar population; even including psychotics in their testing group, a group which has presented with some performance distinction. (Golinkoff & Sweeney, 1989; Brown et al, 1994 Further, Newman & Silverstein (1987) specifically assessed 6 subtypes of depressives using the Luria-Nebraska Neuropsychological Battery. Their results suggested no differences between groups other than the psychotic depressives, whose performance was impaired on 8 out of 10 subtests (Newman & Silverstein, 1987).

Despite these findings, effort has been made to delineate the groups being discussed and reporting any differences that might have been influenced by the different subtypes of depression. In general, the majority of the literature simply focuses on the impact that depression can have on neuropsychological performances, specifically in the areas of attention. The research has been categorized in what appears to be several general areas of study: the nature of attention impairment in

depression, the severity of depression and /or age and it's relationship to performance on tests of attention, and the relationship between depression and various illnesses and their impact on attention.

#### Nature of Attention Impairment In Depression:

In reviewing the literature on attention capacities in depressives, studies appeared to cluster around 3 different areas of attention processes: selective attention-including sustaining, inhibiting and shifting, psychomotor retardation as an underlying mechanism of attention processing, and automatic versus controlled processes.

#### Selective Attention: Sustaining/Inhibiting/Shifting :

Selective attention is important to the functioning of an individual. It allows one to focus and smoothly shift focus as necessary for successful processing to occur. It also allows one to ignore unwanted information and maintain focus on selected stimuli. A selective attention deficit will not only affect one's ability to focus and concentrate on a variety of different stimuli, but will impact functioning on a fundamental level. Impaired selective attention and the ability to successfully shift and sustain attention have been implicated in clinical depression. Purcell, Maruff, Kyrios, and Pantelis (1998) found set shifting impairments in a group of patients with unipolar depression . Purcell, et al (1998) compared cognitive functioning in patients with Obsessive Compulsive Disorder with matched patients with unipolar depression, panic disorder and healthy controls in an attempt to establish a specific neuropsychological profile in OCD. 20 unipolar depressives (screened and excluded for ECT, comorbid disorder, bipolar disorder) were assessed using the Cambridge Neuropsychological Test Automated Battery(CANTAB) with the severity of



depression measured using the Hamilton Depression Scale (HAM-D) of 22.6; a score which reflects moderate depression. Findings were not significant for depressives on any measure other than attentional set shifting (Purcell et al 1998); specifically, this task assessed the subject's ability to maintain attention to different examples within reinforced stimulus dimension and then to shift attention to previously irrelevant stimulus dimension (Purcell et al, 1998). The analysis suggested that although 25 out of 30 controls (83%), 21 out of 30 patients with panic disorder, (70%), 18 out of 30 patients with OCD (60%) only 10 out of 20 patients with depression (50 %) completed all 9 stages successfully. Patients were then compared noncumulatively (only subjects that attempted each stage were included in analysis) and no differences were found between groups suggesting that motivation (or the absence of) could not account for the differences between groups (Purcell, et al 1998).

These findings support an earlier study by Purcell, Maruff, Kyrios & Pantelis(1997) which specifically attempted to explore the cognitive deficits in 20 younger ( $M = 37.5$  years) adult depressives. Using the same neuropsychological testing (and apparently the same depressed population group), depressed patients were found to be significantly impaired as compared to controls on the ED/ID set shifting task. 85 % of the controls were able to complete all stages successfully compared to only 50% of depressives and patients were found to need more trials to reach criterion (to move to next level) as compared to controls. There was no correlation between patient's age or severity of depression and the ability to shift attention, although in separating the depressed group between impaired and unimpaired, the impaired were more likely to report previous hospitalization for the treatment of depression than the

unimpaired group. Thus, Purcell summarizes his results by suggesting young depressed patients with impaired attention set shifting ability, may be more evident among patients with a history of a more severe illness that required in-patient treatment (Purcell, et al. 1997).

Austin , Mitchell, Wilhelm. Hickie, Brodaty, Chan, Eysers, Milic , & Hasdzipavlovic (1999) also explored set shifting abilities and compared 28 controls to 77 depressed patients who were considered moderately depressed on the Hamilton Rating Scale. Austin's group (Austin et al 1999) found no differences among the entire depressed group on digit span forwards and backward; not surprising since it has been suggested as being an insensitive measure of attention (Veil,1997;Cicierone,1997); There was however, significant findings on Trails A and Trails B which were found to be impaired; even when reaction time for Trails B was covaried with Reaction Time A, a test which relates to the psychomotor speed component and was found to be impaired, there remained a deficit (Austin et al, 1999). There was no significant impairment found on Stroop and Digit Symbol substitution task (also timed tasks) and no interference effect (no difficulty in selective inhibition) nor difficulties found in "set shifting" or any other element of the WCST, verbal fluency or similarities task (Austin et al, 1999).

Other studies have also explored the issue of selective attention and potential deficits with depressives. Mialet, Pope, & Yurgelun-Todd(1996) attempted a rigorous review of the neuropsychological literature on attention impairment seen in depression. His comprehensive description of his findings was to conclude that on tasks requiring speed, depressed patients exhibit a "non-specific impairment of

selective attention". Mialet et al (1996) further suggest a decreased overall intensity of attention, rather than deficits in the focus or modification of the direction of attention. He elaborates on the term "attention intensity" by citing a review by Ellgring (1989) who suggests the notion of a global reduction of both eye movements and speech production which are best indicators of a subjects attention to his environment (Mialet et al ,1996). Gotlib et al's (1988) study helps to clarify the visual attention consideration referenced against Ellgring's suggestion of decreased eye movements in depression. Gotlib and his colleagues (1988) dispelled the notion that depressed patients suffered from visual attention biases. Conversely, he found that depressives did not have biases for visual stimuli, instead they were unable to attend to specific stimuli; attending to all the depressed, neutral and manic stimuli equally, as compared to controls who only attended to the manic- content stimuli (Gotlib, 1988).

Several meta-analyses repeatedly found attention tests most valuable in measuring performances with depression. Although they did not discuss the theoretical underpinnings of the tests and why they chose certain tests to represent certain types of sub-components of attention, their results are consistent with deficits of selective attention. Veiel (1997) attempted to derive a profile of cognitive deficits (absolute and relative size of the differences) between depressed and nondepressed groups through meta-analysis calculated by using a weighted average of single standardized scores across studies. He found on both the Trails B and Color-word score of the Stroop Test, with Single Standardized Differences ranging from 1.31 to 2.4, a variability among the depressed that is almost twice that of controls (Var Index=1.67) ; suggesting considerable and consistently impaired performances in

depressed patients with more than half (50.2%) having scores that were in the defective range Veiel (1997). Ironically, under the category he termed as attention and concentration which included Digit Span and Block Span (Richards & Ruff) found no differences between depressives and controls (Veiel,1997).

A second meta-analysis also attempting to depict a specific pattern of neurocognitive functioning in depressives found that that attention tests including letter cancellation(.68), Trails B (.64) and Stroop (.63)interference, were above the median effect sizes; all tests which have a selective as well as inhibitory component(Zakzanis et al, 1998). Their findings with regards to processing speed and working memory were less consistent with other studies (Veil,1997 ) as Stroop Color naming (.58), Trails A (.54) and PASAT (.56) measures effect sizes below the median suggested poor discrimination (sensitivity scores included in parentheses) (Zakzanis, Leach, and Kaplan, 1998).

Being able to ignore certain external or internal stimuli is also a necessary element of the attention process. The inability to ignore distracting information can slow mental processing as well as detract from the ability to attend to important stimuli. In reviewing the literature, the relationship between depression and this subcomponent of selective attention appears to be one of the most highly investigated. For example, Lemelin, Baruch, Vincent, Laplante, Everett, (1996) used the Stroop specifically to explore depressive's distracter inhibition disturbance. They proposed this deficit as one main hypothesis to account for depressives' attention disturbance, a notion initially purposed by Ellis & Ashbrook, (1988). 30 unmedicated depressed patients (psychotic depressives excluded, although it is not clear whether bipolars were

included) with a HDRS score of 25.6 were compared with 30 healthy controls using a computerized version of the SCWT and the Visuo-Spatial Interference Test (Lemelin et al., 1996). Results indicated that depressives presented longer Choice Reaction Times (CRT) and higher interference scores than did normals (Lemelin, et al, 1996). It was further noted that CRT showed a large within group variability with no correlation between the HDRS and the attention measure performances (Lemelin et al, 1996).

In addition, Lemelin et al (1996) controlled for psychomotor retardation in the depressed groups and found significant results on the VSIT and approaching significance on the Stroop Color Word Test (SCWT) suggesting further that selective attention deficit can exist without clear signs of psychomotor retardation. It was concluded that the lack of correlation between severity of depression and CRT increase, coupled with the fact that the less demanding task (VSIT) also produced higher interference with depressives implied an inhibitory deficit (Lemelin et al, 1996). An older study by Raskin (1982) also found impaired performance on the Stroop interference task with depressives, which was supported by the conclusions of Lemelin et al (1996).

Lemelin, Baruch, Vincett, Everett, and P. Vincent, (1997a) in a more recent study, further explored whether the slowed RT time of color naming of depressives and the increased interference score of depressives really stem from a distractor inhibition disturbance or as consequence of a more general processing deficit used to explain the deficit observed in the condition without distractors (color naming only task). Lemelin et al (1997) proposed two hypotheses to explain this phenomenon, one

derived from Hasher and Zacks (1979) which suggests a reduction of the total amount of processing resources resulting in an impairment on all tasks requiring more than the resources available and thus a considerable slowing down in the presence of distractors. A second hypothesis suggests that a distractor inhibition disturbance (external and internal) results in inappropriately allocated resources of attention. Thus the increased interference score of depressives would originate from a distractor inhibition disturbance and the slowed color naming speed would derive from the secondary decreased resource availability for the task-related processing (Lemelin et al 1997a). Using a second Stroop like test with non-conflicting distractors (Table printed in red) as compared to GREEN printed in red) proposed to be less distracting because they are not as conflicting, 33 depressed were compared as a whole group (HDRS of 26.4) to 30 controls (Lemelin et al,1997a). The analysis of the 3 interference scores derived from the modified Stroop test favored the hypothesis of distractor inhibition while a correlational analysis associated the increased interference to a processing resource deficit, however when the depressed groups were further separated based on their RT times, there appeared to be, in fact, two distinct attention disturbances to account for the apparent Stroop deficit seen in depression (Lemelin et al.,1997a).

#### Psychomotor Retardation

In an attempt to shed some light on the possibility of other cognitive processing deficits to account for variation found in potential attention deficits within depressives, this study used four different attention measures; Stroop, Simple RT Test, Divided Attention Test and the Visuo-Spatial Interference Test which would also

assist in exploring the cognitive component of psychomotor retardation (Lemelin & Baruch,1997a). Their findings suggested that while the severity of depression (HDRS) could not be correlated with attention performance measures, higher scores on clinical psychomotor retardation assessed by the Depression Retardation Rating Scale, could be correlated with slowed performances on the Divided Attention Test, SCWT, and the VSIT which tapped several components of attention (Lemelin & Baruch,1997a). The interference score on the SCWT was found to be significantly higher when comparing retarded to non-retarded depressives, while the interference score on the VSIT showed no significant difference, although non-retarded when compared to controls showed significantly higher interference scores on the VSIT and a higher interference score on the SCWT although not sufficiently significant (Lemelin & Baruch,1997a). Overall this study suggests that those depressives with psychomotor retardation appear to have more marked attention disturbances while nonretarded depressives have difficulty maintaining attention under certain circumstances and appear to have a deficit in distractor inhibition (Lemelin & Baruch,1997a). Thus, this study implicates the diagnosis of psychomotor retardation as a symptom of depression connected in some manner to the more marked attention deficits, including distractor inhibition and selective attention. This reflects Austin's & associates (1998) findings in which those patients diagnosed with psychomotor retardation were found to have more pronounced selective attention deficits.

Channon & Green (1998) also explored response suppression somewhat mirroring Lemelin's earlier cited work exploring inhibitory deficits in depression using executive functioning tasks as an investigative tool. They used 3 tasks, memory for

categorized words, Response suppression task, and Multiple scheduling task, where depressives were assigned to either a strategy or non-strategy aid (Cannon & Green, 1998). The population of depressives excluded bipolars. 13 of the 23 participants were medicated, with a mean score on the Beck of ( 24.3) and performed significantly impaired on all three tasks . Further the subjects qualitatively thought to make less use of performance strategies (Cannon & Green,1998). Specific to this present study was the finding that depressives made more errors than controls in completing sentences with nonsensical words on the response suppression task, and were also slower in this part of the task, although their performance was not compromised when they needed to complete sentences with sensible words; suggesting a specific inhibitory deficit, that was not overcome despite a strategy aid (Cannon & Green,1998).

Katz, Wood Goldstein Auchenbach & Geckle (1998) also found that the PASAT, CVLT and Stroop Test were most able to discriminate among ADHD and Depressive subgroups. Particularly, these tests aided an 82.1 % accurate discriminability for ADHD and identified 40% accuracy for depression and categorized depressives as ADHD 60% of the time suggesting potentially two subtypes of depressives both with identifying performances (Katz et al (1998). Veiel (1997) and Zakzanis (1998) et al also found both the color word and interference scores of the Stroop test as an important measure to be used with depressives and more sensitive and with a higher discriminability than most tests of attention with this population.

Psychomotor disturbance could theoretically also be called processing speed deficit as they both imply that the impairment lies in the slowed execution and



manipulation of information while all the sub-components of the attention system are intact; although lacking in speed. The discussion of psychomotor disturbance or processing speed deficits lacks distinction due to the cyclical argument presented by Hasher and Zacks (1979). They suggest that a reduction of the total amount of processing resources will result in an impairment on all tasks requiring more than the resources available which in turn causes considerable slowing; thus, a resource deficit. The contradictory argument would be that the lack of speed in processing decreases the ability to handle incoming information at a pace adequate to encompass a more complicated task or large amounts of information. Therefore the distinction between processing speed deficit and a resource deficit are difficult to separate or may in fact be one in the same.

As early as 1975, Miller attempted to explore the relationship between psychomotor retardation and cognitive deficits. Miller (1975) suggested that psychomotor retardation is more likely to be an index of the severity of the depression and found on that tests of speed depressives were significantly slower than other psychiatric groups or controls. Veil et al (1997) also found results consistent with psychomotor deficits or impaired processing speed with depressives as being the second largest difference found; although he termed the category "Visual-motor tracking" in which he included Trails A and Digit Symbol (Veiel, 1997). The Standardized Difference was .93 with a Var. Index of 1.14 again suggesting deficits of scores of depressed individuals on tests tapping processing speed, as well as tests tapping inhibitory ability consistent with previously cited studies. Veiel's meta-analysis on choice reaction time studies found consistently slower reaction with depressed

subjects (although he rejected many studies due to the variation in measuring reaction times) as compared to controls and argues for a response-process deficit (Veiel,1997). Mialet and associates (1996) upon reviewing the literature on neuropsychological studies of depression and attention also concur with the notion of a psychomotor slowing and suggest that patients of major depression have attention capacities that are "impoverished and slowed" and generally lacking in efficiency.

As cited earlier, Austin et al (1999) initially found only differences in the selective attention processing evidenced by the Trails B performance. They then, however, regrouped the depressives into subgroups based on the on the CORE melancholic scale and Newcastle scale assessing objective psychomotor disturbance in order to arrange the groups based on a more restricted definition of melancholia (Austin et. al. 1999). When depressed groups were then subdivided based on CORE and Newcastle scores, some of the findings did change; significant differences were found with CORE defined melancholic patients on the WCST perseverative response in comparison to controls; while Newcastle subgroup (Psychomotor retardation) were found impaired on Trails A,B, WCST perseverative responses and digit symbol substitution; although a weakness in the study is the number of psychotics (13) found only in this subgroup (Austin,et al,1999). The interpretation of the results further highlights the connection between psychomotor disturbance as a diagnosis and deficits in attention.

Lemelin also proposed in their 1997 study to validate the notion of a processing resource deficit, potentially some element of slowing, as color naming task shows response latencies in depressives even without interference. Their findings

supported a processing resource deficit with slower depressives and a specific distractor inhibition with non or mildly retarded depressives (Lemelin, et al, 1997).

### Automatic versus Controlled Processing

Automatic and controlled processing is another component of attention that enables several different well-learned tasks to be completed in a more reflexive manner and therefore allows more resources towards less familiar tasks. Aligning with this notion of effortful processing versus automatic processing, Thomas, Goudemand & Rousseaux (1998) attempted to assess attentional resources using Reaction Times on 10 depressed patients, finding that indeed, depression does appear to interfere with more effortful tasks (decision making tasks) than with automatic processing. Thomas et al (1998) further noted a dissociation of the cross modal effect that occurred in the choice but not in the dual task condition in which depressives appeared to improve in their performance, attributing this phenomena to a practice effect or an increased ability to mobilize previously captured resources. Zakzanis et al. (1998) supports this notion and also found that effortful or attention demand processing yielded effect sizes that were almost completely capable of discriminating depressives from controls. Conversely, Ronald Ruff (1994) explored the role depression plays in the performance of automatic and effortful (controlled) processing. He recruited 27 subjects from an outpatient clinic with a Beck Depression Inventory-II of 28.93, indicating severe depression. The average percentile rank for the entire sample fell within the unimpaired range both for processing and accuracy (Ruff,1994). His general conclusions supported the notion that depressives are not effected in their ability to

process automatically, and further concluded that depression does not lead to a reduced accuracy rate (Ruff, 1994). He did find a sub-sample (3 patients who had deficient speed scores which he attributed to psychomotor slowing as these same 3 patients also performed slowing on the Finger tapping Test and Grooved Peg Board, both tests which measure motor speed(Ruff 1994).

#### Severity of Depression:

Relationship between impaired neuropsychological performance on tasks of attention and patient characteristics have also been explored. Specifically, age, severity of depression and any combination of the two have been implicated in effecting neuropsychological changes. Jeste, Heaton, Paulsen, Ercoli, Harris, and K. Heaton (1996) compared psychotic depression, nonpsychotic depression, and schizophrenics who were all comparable in age and education. Results suggested that despite the severity of depression, nonpsychotic patients performed better and within normal limits as compared to the psychotic depressives on tests of attention including Trails A & B, And Wais-Digits Symbol (grouped under psychomotor speed); Grooved Peg Board (under Motor Skills) and Wais-R digit span and digit vigilance (under attention) (Jeste,1996). Although it should be noted that the results may have been confounded by the fact that both the psychotic and schizophrenic group were taking a significantly greater amounts of neuroleptic medications than the nonpsychotic depressives. Nelson, Kenji, Sax, & Strakowski(1998) examined Continuous Performance Test scores of patients with depression with and without psychosis and

with normals. There was no difference between the severity of depression of those with psychosis versus those without. However, results indicated that depressives with psychosis performed similar to schizophrenics on the Computerized Continuous Performance test as compared to depressives and controls, with psychotic depressives and schizophrenics performing significantly worse (Nelson et al,1998). Basso & Bornstein (1999) using a population >45, further support the findings that severity of depression does not correlate with deficits in neurocognitive functioning while the presence of psychosis presents a broad range of deficits in neuropsychological testing. Basso and Bornstein(1999) found interestingly that on Trails A non-psychotic depressives did worse and on Digit Span backward their performance was similar. Further, on Trails B, although the psychotic group performed more poorly, the non psychotic group also performed in the impaired range and were more impaired than the psychotic group on their Trails A performance (Basso & Bornstein,1999a). On a second study Basso & Bornstein (1999b) compared first episode and recurring episodic depressives and found no difference on Trails A & B and Digit Span forward and Backward, finding differences between groups only on the CVLT for recurring depressives, contrary to the findings of their initial study. Although this study focused primarily on memory, insofar as recurrent depressive episodes are associated with worse memory, recurrent depression may reflect increasing cerebral dysfunction, and thus it very well could be the elder patients with recurrent episodes may be more likely to show greater impairment. Further, Post (1992) suggests that fundamental neurochemical changes occur as a function of each successive depressive episodes and because of these changes subtle cerebral dysfunction increases, which in turn decreases

the threshold for the onset of subsequent depressive episodes. Inadvertently, this may put some perspective on Crews, Harrison, & Rhodes' study (1999) which suggested that young (  $M=20.3$  ) outpatient depressed (BDI-M=27.93) women when tested on Trails A & B and Stroop Color and Word Test did not perform any differently than matched controls, although the education level(14.37) may have also diminished the impact of depression on the neuropsychological test performances. King, Cox, Lyness & Caine (1995) attempted to explore the influence of age and depression on neuropsychological performance with subjects 50+ with Hamilton rating score of  $M=28.91$ . There were ten psychotic depressives and 34 nonpsychotic depressives in their sample and although contrary to earlier cited research, there was no difference found on neuropsychological test performance (King et al,1995). There were however, differences found between depressives and controls in that depressives performed more poorly on tests of attention, word generation, immediate and delayed verbal recall and constructional praxis; specifically, it was found that depressives scored lower on the attention concentration weighted sum of the WMS-R and took significantly more time to complete Trails B after age 59 (King et al,1995)

Boone, Lesser, Miller, Wohl, Berman, Lee, Palmer, & Back, (1995) explored cognitive functioning in older depressives, with varying degrees of severity in depression. Boone et al's (1995) findings suggest that there is an association between the increasing severity of depression with mild weaknesses in information processing speed which included Trails A & B, Stroop, and Digit Symbol of the WAIS-R and executive skills testing including Stroop test, WCST, COWAT, and ACT (Auditory Consonant Trigrams. Specifically, when depressed groups were subdivided into

moderate HAM-D scores of > 19 and mild whose scores were < 18, moderately depressed subjects performed significantly more poorly than both the mildly depressed group and controls on tests of information processing, performance IQ, visual memory, and executive skills. Significant between group differences were found on all visual memory tests, Stroop tests, and in the executive domain FAS, WCST, Stroop C, and ACT (Boone et al 1995).

Bieliaukas (1994) also explored depression in the elderly and found a different subtype of depression with the elderly that was less typical and characterized by the maintenance of self-esteem. Interestingly enough depressed patients with a reported loss of self-esteem and guilt had significantly slower reaction times, as compared to patients who did not.

#### Effects of Other Medical Illness Versus Depression:

Mood disturbance has long been acknowledged to accompany the diagnosis of many illnesses as well as neurologic trauma. It is reasonable to assume that patients faced with serious illness or physical trauma would have emotional responses that could impact their level functioning. For example, neuropsychological testing is well established as the most reliable and valid method for detecting cerebral HIV-related cognitive impairments (Butters et al, 1990). However, there has been confusion as to what elements of cognitive impairment stem from depression rather than the illness itself. More recent studies suggest that the neurocognitive complaints were related to the depression rather than the HIV status, and thus act as a diagnostic indicator.

Rourke, Halman, & Bassel,(1999) attempted to explore the relationship between

neuropsychological impairments, particularly in the areas of attention and working memory (Digit span forward and backward) and simple and complex psychomotor speed (Trail Making Test, Parts A and B). Their design allowed them to quantify the degree to which depressive symptoms contribute to neurocognitive complaints and found that neuropsychological measures which reflect attention, working memory, psychomotor efficiency and recall of verbal information correlated significantly with neurocognitive complaints. Further, depressive symptoms accounted for the majority of variance in neurocognitive complaints although this study was still unable to parcel out the contributions of neuroimpairments as a contribution of HIV status versus mood disturbance. Richardson's study also attempted to study depression and HIV status among African American men although their findings were geared more towards self report of depression and neuropsychological performance measures with no independent effects found (Richardson, Satz, Meyers, Miller, Bing, Fawzy & Maj, (1999). Likewise, Arnett, Higginson, Voss, Bender, Wurst & Tippin (1999) attempted to explore Multiple Sclerosis and Depression. They found by removing the MS symptoms that overlapped with depression, they were able to determine those MS patients suffering from depression and those MS patients who were not depressed (Arnett et al.; 1999). Interestingly, Arnett and associates (1999) found that those MS patients who scored highest on symptoms of depression using a depression scale insensitive to medical illnesses, showed significant difficulties with tasks involving working memory-attention demands, a reading span task, predictive of other working memory tasks including the PASAT. These results corroborate earlier cited studies suggesting that it is the major depression impacting the deficits in controlled



processing rather than the illness. In addition, in an earlier design Arnett, Higgins, Voss, Bender, Wurst & Tippin(1999a) investigated the relationship between depressed mood and working memory defined as capacity demanding tasks of memory and attention. Arnett and his associates(1999a) used the PASAT, Visual Elevator Test, and the Symbol Digit modalities (which reverses digit symbol, with just symbols and orally given numbers) and found that those patients with depressed mood performed significantly worse on speeded attention tasks of working memory similar to non-MS depressive literature.. Likewise, their results (Arnett et al; 1999a) for capacity non-demanding tasks such as CVLT recognition measure were not significant and factors such as low motivation and potential demographic differences were not significant between the groups.

### Conclusions

This review of the literature on depression and attention capacities has some discrepancies in the overall results. These discrepancies actually appear to be more related to the methods of the investigations, rather than to contradictory results. Specifically, it appears that the age, type of depression, number of previous hospitalizations, medication, agreement as to what cognitive process is being measured, as well as the accurately operationalizing the same process with the appropriate task have all impacted the results. Thus, the studies are actually less contradictory and instead, a body of varied and complex investigations that have been grouped together by two very broad and loose terms: attention and depression. That said, the attempt to encapsulate this body of information has led to the following summarization: First, there appears to be three different types of attention measures

that will be most sensitive to major depression. Measures that assess attention when the need for working memory is involved, when speed of processing is necessary for success, when there is a need for suppression or an inhibitory element to a selective attention process. Conversely, attention measures more automatic, that do not require a capacity demand (working memory element) and are not speed dependent are less likely to be sensitive to a depressive illness. Second, the variation of depression that impacts neuropsychological test performance appears to be connected to prior hospitalizations and/or the length of illness and less related to the severity of illness, or to diagnoses of unipolar or bipolar depression.

### Chapter III

#### METHOD

##### Participants

The subjects for this study were male and female patients from a local outpatient clinic who were recruited based on a diagnosis of major depression 296.xx Axis code (including both unipolar and bipolar). The diagnoses were made by licensed Psychiatrists. 500 subjects generated from the computer records with the primary DX of 296.xx. 400 of those subjects did not have a comorbid psychiatric illness. Letters were sent out to all patients briefly describing the study and the option to participate (see Appendix A). Letters include a contact phone number that they could call to explore participation. Psychiatrists at the clinic were also given a copy of the consent form as well a brief letter describing the study in order to facilitate a level of comfort in speaking about the study with interested patients (see Appendix B). All patients between the ages of 18-60 were recruited. Any patient who participated in this study completed a consent form (see Appendix C). Exclusion criteria included (1) History of developmental disorder, learning disability or attention deficit disorder (2) History of prior head trauma, (3) history of neurologic illness, (4) history of a comorbid psychiatric illness (5) other significant systemic medical illness. From the 61 subjects who responded positively to the letter, 31 were included in the study. Subjects were then matched with controls, and a final total of 24 subjects were included. 14 were diagnosed with Major Depressive Disorder and 10 were diagnosed with Bipolar I disorder, 7 of which reported having had a last episode or currently experiencing depression, 2 presented with some symptoms of a manic stage, while denying any

imbalance in their affective functioning, and one patient was hospitalized with a manic episode, one day subsequent to testing. Medications included SSRI's, Tricyclics, and lithium. The age of the patients ranged from 28 to 61 with a mean age of 42. The educational level of the patients ranged from 9 years to 15 with a mean educational level of 13. 22 out of 24 had been diagnosed at least four years prior to testing. 22 subjects had at least one psychiatric hospitalization, one patient was hospitalized one day subsequent to the testing.

Control subjects were recruited from local community volunteers. Exclusion criteria for the normal control subjects included: (1) no history of developmental disorder, learning disability, or attention deficit disorder. (2) no history of prior head trauma, (3) No history of neurologic illness. (4) No history of psychiatric illness. (5) No other significant medical illness at the time of testing. Normal control subjects were reimbursed for travel and meal expenses related to their participation. The age of the control subjects ranged from 18 to 60 years (mean =33.3 SD=2.3) and education ranged from 12 to 20 years (mean = 14.8, SD=2.3).

#### Test Materials

All tests were measured in single test sessions lasting between 1 to 2 hours. The tests were always presented in the same sequence. Due to the concern that potential diurnal variation of mood could have a significant effect on neuropsychological performance (Mafoot et al 1994) attempts were made to test patients at approximately the same time of day. All patients were tested between 9 a.m. and 4 p.m. Six measures of attention were administered that were considered to measure a variety of attention elements. These included the following:

### *The Stroop Color Word Test-*

This test consists of three subtests which require that the subject perform as quickly as possible to read color names (Stroop word), name colors, (Stroop color) and name colors that are themselves various color words (Stroop color-word) (Golden,1978). The first task is a well- trained response and thus does not require a controlled response. The second task, once considered to be an automatic process, has been instead evidencing on a continuum of automatic to controlled processes, as closer to a more controlled process (Hartlage,1993)(Cicerone & Azulay; in print) while the third process requires the subject to inhibit the more automatic task or reading the word in order to perform the task of naming the colors. There is a working memory component as the subject must constantly keep in mind the purpose of the task, which is not indicated on the task stimuli. The test performance is measured in the number of items correctly identified in 45-second intervals, which are then converted into age corrected T scores according the manual.

Factor analytic studies of the Stroop test suggests that speed of processing and conceptual abilities contribute to the performance on the color naming( Spreen & Struass, 1998). Sherman et al (1995) found that the response to the interference trial was moderately related to the Perceptual organization ( $r = .37$ ) and Freedom From Distractability ( $r = .29$ ) factors of the WAIS-R. Further there is evidence to suggest that the interference score moderately correlates with the PASAT (MacLeod and Prior, 1996).

The Continuous Performance Test of Attention is an auditory continuous performance test with five conditions incorporating different types of attending

processes (Cicerone,1997). It consists of a series of audio taped letters presented at a rate of one per second. The first three conditions vary in target sizes, while the fourth condition necessitates an inhibitory process while the fifth condition necessitates the need to shift between letters and numbers. The raw scores were based on the total number of errors, which were corrected for age and education (one error was subtracted from the raw score of subjects ages 40 through 59 with 15 or less years of education; one error was added to the raw score for ages 18 through 39 with 16 or more years of education). The total error scores were then converted to linear transformed z-scores based on the initial normative sample (Cicerone,1997).

The Paced Auditory Serial Addition Test- The Paced auditory is a version provided by H.S. Levin (Levin et al,1987) and consisted of four sets of 50 single items each presented at inter-stimulus intervals of 2.4, 2.0, 1.6., and 1.2 seconds. The participant is asked to add consecutively to the last number given by the speaker on the tape. Thus, the test forces an externally paced process and high demands on working memory, since the person must hold the numbers presented while performing addition. The total number of correct responses on all four trials was selected for analysis.

In terms of construct validity, the PASAT is moderately correlated to other tests of attention, including the Stroop Test, Visual Search Test of attention (VASAT), Trigams and Digit Span (O'Donnell, et al, 1994). Bases on a factor analysis of WAIS-R factor scores of head injured adults, Sherman et al (1995) found the PASAT to have .30 correlation with verbal comprehension factor, .23 with the perceptual organization, and .46 with the Freedom from Distractibility factor. Roman

(1991) suggests that the PASAT is highly correlated with education and mathematical ability, although the correlation with age is insignificant until age 50 where there is an age-related decline in performance. There is some data to suggest that the PASAT may be overly sensitive to excessively anxious patients (Spreeen & Struass, 1998).

Trail Making Test (TMT) A & B were administered according to the procedures described by Reitan and Wolfson (1993) with the number of seconds to complete each part used in the analysis. Trail Making A is assessing a speed of visual and motor processing since the participant is asked to draw lines from one circle to the next simply following the numbers in sequential order. Trail Making B is equal to the visual and motor processing abilities of Trails A but is more complex in that it requires an added shifting task that demands a participant to consecutively shift between the sequence of the alphabet with the sequence of the numbers in a connect the dot fashion similar to Trails A.

According to Heilbronner et al (1991) the correlation between Trails A and Trails B is only .49, which suggests that they are tapping into different cognitive components which actually concurs with the theory behind these two tests. A factor analysis of Trails B, Category Test, WCST, VSAT, and PASAT in a group of neuropsychiatric patients examined by O'Donnell et al (1994) suggested that TMT B loaded on "focused mental processing speed" along with the PASAT and VSAT, while it did not share variance with WCST and Category Test. This finding may suggest that while it shares a working memory element, it does assess a full executive process. Shum et al (1990) found Trails A & B to load on a visual- motor scanning, while Mirsky et al (1991) found Trails to load on a focus and execute factor.

Digit Span Forward and Backward subtest from the Wechsler Memory Scale – Revised (Wechsler, 1987) was administered and the raw scores for Digit Span forward and backward were normed separately. They were selected for analysis to provide a simple common auditory attention measure. An earlier version was used to avoid the risk of losing information when the forward and backward scores are combined. Shum, McFarland, & Bain (1990) suggest that both digits forward and backward load significantly on a factor of visual/auditory spanning. While Schmidt et al (1994) suggest that Digit Span is not very accurate in classifying cognitively impaired patients, the “attention” factor accounts for much of the high variability which is reflected by the fairly high communality.

Ruff's 2 & 7 Test- A visual test of cancellation used to assess differences between automatic (obvious distractors) using random letters with digits and controlled (less obvious distractors) using randomly mixed digits. The test consists of twenty 3 lined blocks of alternating “automatic” or “controlled” search conditions. Ruff's (1982) factor analysis found speed of visual attention, visual processing, immediate attention, and response accuracy as the principle components. Ruff (1982) applied a principle component analysis and concluded that there was a distinct pattern for the 2 & 7 of selective attention factor that did not overlap with any other tests of attention. He further suggested that right hemisphere involvement may affect the overall speed and accuracy of target selection due to the spatial/ visual component (Ruff, 1982).

Two self-report questionnaires were also administered. The first was a newer attention rating measure scale (ARMS) that consists of 15 statements that address



different attention deficits that subjects might be experiencing. Each statement can be rated on a continuum from NEVER (1) to ALWAYS (5) and enables a sense of perceived versus actual attention deficits as well as the types of deficits reported. This test is in the process of being validated.

The Beck Depression Inventory II, which has been proven to be a valid and reliable measure of depression is a 21 item measure that screens for depression through self-report (Beck, 1987). This measure is a commonly used screening tool administered to measure the current level of depression since most are receiving psychopharmacological treatments, and many have had changes in the level of severity of their depression.

All of the mood disordered subjects and controls were administered the measures of attention as well as the objective measures of attention and depression described earlier. Subjects as well as controls were typically administered the attention measures in the same order within 1 1/2 to 2 hour sessions. The variables used in the analysis were selected to reflect scores commonly used in clinical practice. Raw scores were demographically corrected whenever possible and converted to either T or z scores using available clinical norms. PASAT totals scores were transformed using extended norms reported by Roman, Edwall, Buchanan, and Patton (1991) and missing age categories were extrapolated to extend all appropriate age reference. Likewise, Digit Span subtest norms from the Wechsler Memory Scale-Revised were also converted to the appropriate age-referenced group and missing age groups norms were extrapolated from the standardized sample. The Trail Making Test, Parts A and B were first corrected for gender, age, and education according to the procedures and

norms provided by Heaton, Grant, and Mathew (1991), which are then converted to T scores. For the CPTA, the distribution of error scores were demographically corrected for age and education and then transformed into z scores. The Ruff's 2 & 7 have several variables that can be used, however, for simplification purposes only the total speed and total accuracy were analyzed and demographically corrected for age and education according to the procedures described in the Ruff 2 & 7 Selective Attention Test Manual (Ruff, 1978). The cutoff criteria for both the control and the affectively impaired group were determined using three criteria of -1.0, -1.5 and -2.0 z and T scores of equal to and less than 39, 34 and 29. Using the calculations presented earlier, sensitivity, specificity, positive predictive value, negative predictive value, efficiency (hit rate), likelihood ratio and odds ratios were calculated using guidelines provided by Sackett et al, 1991, Ivnik et al, 2001, and Bieliuakas, 1997. The Odds Ratio and a 95% confidence interval was determined for each of the measures according to the procedures outlined by Bieliauskas et al. (1997) using the median criteria z-scores less than -1.5 or T scores of equal to and less than 34.

For the purposes of this study, the tests were grouped a priori to cluster around the following areas of attention, as suggested by the literature and the theoretical analyses of the measurements. Digit Span and Ruff 2 & 7 were considered to be simple or more automatic tests of attention processing. Trails A and Stroop C are thought to have a sustained component of attention, although lacking complexity. Trails A also has a motor component, while Trails B is mildly more complex, with an added shifting process. Stroop C also has a choice process not present in Trails A. CPTA, PASAT,

and Stroop CW are grouped as more complex attention measures, having a working memory component, inhibitory component, as well as a selective attention component.

## IV

### RESULTS

The final sample consisted of 24 controls and 24 mood disordered subjects, resulting in a total of 48 participants. Of the mood disordered, 14 were diagnosed with unipolar depression, and 10 were diagnosed with Bipolar I disorder. The mood disordered patients were all currently being treated with psychopharmacological medications including SSRI's, tricyclics, and lithium and 4 of the participants were currently receiving psychotherapy. Of the unipolar depression, 12 currently reported a moderate to severe depression using the cutoff score of 18 On the BDI-II self-report scale (Spren & Strauss, 1995). Likewise, of the 10 bipolar subjects, 5 reported a moderate to severe depression (18+), 2 reported a minimal depression (10-15) and 3 reported in the normal range (0-9). Only 8 controls received the BDI-II all within normal range, aligning with the general psychiatric screening. The final sample of the Control group consisted of 15 females and 9 males.

Table one presents demographic information about all participants. The control and data sets were matched such that there were no significant differences between age, education, and gender (see table 2). Although male to female ratio within groups may limit the ability to apply the findings to other populations. This difference may be relevant with regards to the affective diagnosis since depression is found significantly more in women than men and the comparison to a control group that has equal numbers of males to females may impact the current results.

**Table 1**

**Means, Standard Deviations, and Sample Sizes of Control and Mood disordered groups**

<b>Group</b>	<b>Gender</b>	<b>Age</b>	<b>Education</b>
<b>Mood disordered :</b>	<b>Mean</b>	<b>42.04</b>	<b>14.25</b>
	<b>18 females 6 males SD</b>	<b>8.7</b>	<b>2.3</b>
<b>Controls :</b>	<b>Mean</b>	<b>39.70</b>	<b>13.20</b>
	<b>15 females 9 males SD</b>	<b>7.9</b>	<b>2.2</b>
<b>Total</b>	<b>Mean</b>	<b>40.87</b>	<b>13.72</b>
	<b>N</b>	<b>48</b>	<b>48</b>
	<b>SD</b>	<b>8.34</b>	<b>2.34</b>

TABLE 2

Independent samples T-Test depicting no significant differences in age and education between mood disordered and controls.

## T-Test

## Group Statistics

	group	N	Mean	Std. Deviation	Std. Error Mean
age	CONTROL	24	39.7083	7.9863	1.6302
	3.00="DD"	24	42.0417	8.7002	1.7759
EDUCATON	CONTROL	24	14.2500	2.3820	.4862
	3.00="DD"	24	13.2083	2.2454	.4583
gender	CONTROL	24	1.3750	.4945	.1009
	3.00="DD"	24	1.2500	.4423	9.029E-02

## Independent Samples Test

		Levene's Test for equality of Variance		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence interval of the Mean	
									Lower	Upper
age	Equal variance assumed	.055	.816	-.968	46	.338	-2.3333	2.4107	-7.1858	2.5191
	Equal variance not assumed			-.968	45.667	.338	-2.3333	2.4107	-7.1868	2.5201
EDUCATON	Equal variance assumed	.522	.474	1.559	46	.126	1.0417	.6682	-.3033	2.3867
	Equal variance not assumed			1.559	45.840	.126	1.0417	.6682	-.3035	2.3868
gender	Equal variance assumed	3.286	.076	.923	46	.361	.1250	.1354	-.1476	.3976
	Equal variance not assumed			.923	45.439	.361	.1250	.1354	-.1477	.3977

Using the cut off criteria of -1.0, -1.5, and -2.0, it was found that there are several measures that are of the greatest sensitivity as compared to the other measures of attention (see table 3). The results suggest that the CPTA (95.83%) PASAT(91.30%) and Stroop C (62.50%) and CW(70.83%) adequately classified depressives at the -1.0 cutoff as compared to controls. At a more stringent cutoff (1.5) the Stroop was less able to distinguish depressives performance from a control. Both the CPTA and the PASAT, however, still maintained adequate sensitivity at 91.66% and 73.91 %, respectively. At the 2.0 cut off, only the CPTA maintained adequate sensitivity (91.66%), while the PASAT dropped to 56% (a little more than half of the depressives were grouped accurately). Clinically, when choosing tests, sensitivity and specificity need to be considered. Generally, there is a trade-off between the sensitivity and specificity of a diagnostic test. Because the data are presented on an interval scale, the increase in sensitivity can only be decreased at the expense of specificity and visa versa. Naturally, the goal is to have tests that have both high sensitivity and specificity. Table 3 shows that as suggested most of the tests which had low sensitivity had high specificity; this includes Digit span backwards and forwards, Trail making tests A and B and Ruff's 2 & 7 total speed and accuracy. These results suggest that a positive finding on any of these tests would highly suggest the presence of a disorder with the population since a highly specific test is rarely positive in the absence of the disorder. The findings also suggested that the CPTA, PASAT, Stroop C and CW also had adequate specificity along with significant sensitivity. The efficiency of the number of subjects correctly classified by the diagnostic tests naturally aligned with the tests of greatest sensitivity and specificity

such that the CPTA and PASAT maintained the highest hit rate at all three cut-off values, while the Stroop C and CW maintained efficiency at the -.1 level but at the more stringent criteria, the subtests were less efficient and reflected the level of efficiency relatively equal to the remaining tests of attention. The Positive Predictive Value and Negative Predictive Value become more difficult to interpret because they are going to be dependent on the prevalence of the population actually having the disorder. So for example, this population represents an outpatient group who were predetermined to have an affective disorder based on the cut off scores set up for this study. A general neuropsychology outpatient unit could have a completely different prevalence rate for depression and therefore have completely different Positive and Negative Predictive Values than the numbers presented in table 3. The more specific a test is, the better the predictive value. Thus, the 2 & 7 Total Speed measure (100%) and the Stroop Color (94%) had the highest Positive Predictive Value. Likewise, the Stroop CW (85%) Trails B (81%) and the PASAT (80%) were the group of measures to have the second highest Positive Predictive value at a -.1 criteria. At the most stringent criteria(-2.0), the measures having the highest positive predictive value became the Trails A(100%), Trails B (100%) the Stroop CW (100%) and the PASAT (93%). Said in another manner, these findings suggest that the probability of a patient having the disease (depression) given a -2. z cutoff on either the Trails A, Trails B or Stroop CW is 100% and there is a 93% chance they have an affective disorder if they score below a T of 29 on the PASAT. Conversely, the Negative Predictive Value is going to be highly connected to the sensitivity of the measure. Thus, the more over inclusive a test, the greater the likelihood that a normal score has the greatest chance



of accurately predicting the absence of the disorder. In this case the CPTA which was by far the most sensitive even at the most stringent cutoff (92% sensitivity @ -.2) equally had the greatest Negative Predictive Value at the most stringent cutoff (91%). Actually, in reviewing the data in table 3, Stroop C Stroop CW, PASAT and the CPTA have solid positive and negative predictive values, which are elements that are desired. It is good to keep in mind that these calculations change given the change in the prevalence of a disease, thus it is important to focus on the likelihood ratios as calculations irrespective of the prevalence.

The likelihood ratio is probably one of the more important odd ratios a clinician will want to consider. Likelihood ratios speak to the diagnostic capabilities of a certain cut off score of a certain test with regards to the specific patient in question at risk for the specific condition (Ivnik, Smith, Cerhan, Bradley, Boeve, Tagalos, & Peterson, (2001). Therefore, it "...expresses the odds that a given level of a diagnostic test result would be expected in a patient with {depression} as opposed to one without the disorder."(Sackett, p120;1991). The results suggest that the Stroop CW at a -.1 (T>39) and -1.5 (T> 34) cut off scores is 13.7 times as likely to come from a patient with depression as without. At the -2.0 z, the PASAT had a likelihood ratio of 13.3 and the CPTA has a likelihood ratio of 7.33. This suggests that a patient with an impaired performance on the CPTA is 7.3 times as likely to come from patients with a mood disorder as from normals.

Both the Stroop C and Stroop CW did not have a likelihood ratio for a -2.0 cutoff simply because the specificity was at 100%, that is, no controls were incorrectly

classified at that level of impairment, therefore no calculations could be made for this group.

**Table 3- sensitivity, specificity, and probability ratios****for mood disordered population**

Sensitivity	DIGIT FOR	DIGITS BK	TRAILS A	TRAILS B	CPT	PASAT	2&7 SPD	2&7 ACC	STRP C	STRP CW
-1	0.41	0.27	0.38	0.37	0.96	0.91	0.12	0.33	0.64	0.71
-1.5	0.32	0.14	0.17	0.21	0.92	0.74	0.04	0.25	0.38	0.42
-2	na		0.04	0.08	0.92	0.57		0.09	0.21	0.25
		Na					na			
<b>Specificity</b>										
-1	0.83	0.92	0.87	0.92	0.71	0.79	1	0.79	0.96	0.86
-1.5	0.87	0.96	1	1	0.79	0.96	1	0.83	0.96	0.91
-2	0.92		1	1	0.88	0.96	0	0.96	1	1
		Na								
<b>Efficiency</b>										
-1	0.63	0.6	0.62	0.64	0.83	0.85	0.55	0.55	0.78	0.78
-1.5	0.61	0.56	0.58	0.6	0.85	0.85	0.5	0.53	0.65	0.65
-2	0.5		0.52	0.54	0.89	0.77	0	0.51	0.59	0.61
		Na								
<b>PPR</b>										
-1	0.69	0.75	0.75	0.82	0.77	0.81	1	0.62	0.94	0.85
-1.5	0.7	0.75	1	1	0.82	0.94	1	0.6	0.94	0.83
-2	0	0	1	1	0.88	0.93	0	0.67	0	1
<b>NPR</b>										
-1	0.61	0.57	0.58	0.56	0.94	0.91	0.52	0.53	0.7	0.73
-1.5	0.58	0.54	0.54	0.56	0.91	0.79	0.5	0.51	0.54	0.83
-2	0.5	0	0.51	0.52	0.91	0.7	0	0.5	0	0.55
<b>LR</b>										
-1	2.45	3.57	3	4.49	3.28	4.3	0	1.53	13.74	5.19
-1.5	2.54	3.27	0	0	4.39	17.59	0	1.43	8.33	4.57
-2	0	0		0	7.33	13.33	0	2.07	0	0
			na							
<b>OR</b>										
-1.5	2.97	2.81	7.53	13.82	31.9	42.17	0.45	1.52	5.93	5.93
<b>95% CI</b>	(.72 - 12.3)	(.38 - 20.7)	(1.5- 99.6)	(.23 - 854)	(6.4 - 159)	(6.5- 276)	(.50 - 3.16)	(.39 - 5.9)	(1.6 - 49.4)	(1.3 - 27.4)

(PPV=positive predictive value, NPV= negative predictive value, LR= likelihood ratio, OR=

odds ratio, CI= confidence interval)

The relationship between depression severity and cognitive impairment was analyzed using Spearman rank correlations. The Spearman statistic was chosen as a conservative measure of agreement that is free from the multiple parametric assumptions inherent in the use of a Pearson product –moment correlation coefficients (Kirk, 1995). Failure to find significant correlations was consistent across all measures excluding the Digit Span backward (see table 4). These findings were then evaluated again using the sensitivity, specificity, and odd ratio calculations exploring the severity of depression with a cut off on the BDI-II of 18 (Beck,1982) on Table 5. The findings reflected those found in the correlation analysis, although the findings were more explicit to the utility of each of the tests. For example, the PASAT (.75) and Stroop CW (.76) were found to be the most sensitive for severe depression, although in general, these tests, are not specific; (.29 and .43 respectively). Moreover, the Likelihood ratios, that is, the odds that those with a severe depression are likely to have a performance reflecting the cutoff criteria used, were very low across tests.

The odds ratio calculations for the severity of depression, which would suggest that given the cut off score of a certain test, the patient will be x times more likely to have a severe depression, only Trails A and Stroop Color offered significant probabilities at a 95 % CI that patients with this performance are 6.6 times as likely to have a severe depression. Finally, the odds ratio calculations for the study suggested that Trails B (13.82), CPTA (31.9) and The PASAT (42.17) were the best overall measures for predicting whether a patient would have a mood disorder. For example, a patient with –1.5 cut off on the PASAT, at the lowest range of a 95% CI would be at least 6.5 times more likely to have depression.

**Table 4. Correlations between cognitive measures and depression rating****Spearman correlations between measures**

<b>Measure</b>	<b>n</b>	<b>Mean</b>	<b>SD</b>	<b>Strength of corr w/ BDI-II score</b>	<b>Sig @.01</b>
<b>Speed score</b>	<b>28</b>	<b>48.17</b>	<b>8.96</b>	<b>.2050</b>	<b>.864</b>
<b>Accur Score</b>	<b>28</b>	<b>42.75</b>	<b>10.87</b>	<b>.0977</b>	<b>.639</b>
<b>Stroop C</b>	<b>28</b>	<b>39.42</b>	<b>9.75</b>	<b>.0958</b>	<b>.397</b>
<b>Stroop CW</b>	<b>28</b>	<b>36.07</b>	<b>8.93</b>	<b>.2019</b>	<b>.670</b>
<b>CPTA</b>	<b>28</b>	<b>-2.13</b>	<b>.50</b>	<b>.0066</b>	<b>.784</b>
<b>PASAT</b>	<b>28</b>	<b>-2.06</b>	<b>1.03</b>	<b>.2757</b>	<b>.791</b>
<b>Digits B</b>	<b>28</b>	<b>-.59</b>	<b>.96</b>	<b>.3407</b>	<b>.001</b>
<b>Digits F</b>	<b>28</b>	<b>1.09</b>	<b>8.2</b>	<b>-.1355</b>	<b>.172</b>
<b>Trails A</b>	<b>28</b>	<b>42.7</b>	<b>9.35</b>	<b>.0650</b>	<b>.232</b>
<b>Trails B</b>	<b>28</b>	<b>42.5</b>	<b>10.13</b>	<b>.1900</b>	<b>.420</b>
<b>BDI-II Score</b>	<b>28</b>	<b>26.53</b>	<b>14.72</b>		

Table 5

**Analysis of the relationship between severity of depression with the BDI-II cut off score of 18, using sensitivity, specificity, and probability calculations**

	<u>Digit F</u>	<u>Digit B</u>	<u>Trails A</u>	<u>Trails B</u>	<u>CPTA</u>	<u>PASAT</u>	<u>StrpC</u>	<u>StrpCW</u>	<u>SPD</u>	<u>ACCR</u>
<u>SEN</u>	.54	.18	.42	.24	.29	.75	.42	.76	.59	.18
<u>SPEC</u>	.80	1	1	.86	0	.29	1	.43	1	.57
<u>EFF</u>	.45	.36	.5	.42	.63	.61	.5	13.6	.33	.29
<u>PPV</u>	.86	1	1	.8	.68	.71	1	.77	1	.50
<u>NPV</u>	.27	.26	.37	.32	0	.33	.37	.43	.30	.22
<u>LR</u>	0	0	0	1.6	.29	1.0	0	.02	0	.42
<u>OR</u>	1.7	2.7	6.6	1.4	0	1.2	6.6	2.3	1.4	.31
<u>95</u>	(.2-13)	(2-60)	(.32-6.6)	(.19-11.3)	(0)	(.21-6.8)	(.32-709)	(.4-11.2)	(.05-37)	(.03-7)

(Sen= sensitivity, Spe= specificity, Eff= efficiency ratio, PPV= positive predictive value, NPV= negative predictive value, LR= likelihood ratios, OR= odds ratios, 95= 95% confidence interval)

TABLE 6

Sensitivity & Specificity Calculations for Bipolar versus Unipolar at -1.5

	<u>Digit F</u>	<u>Digit B</u>	<u>Trails A</u>	<u>Trails B</u>	<u>CPTA</u>	<u>PASAT</u>	<u>Strp C</u>	<u>Strp CW</u>	<u>SPD</u>	<u>ACCR</u>
<u>SEN</u>	.05	0.5	.05	.05	.94	.5	.3	.4	0	.05
<u>SPE</u>	.18	.3	0	.08	.91	.58	.4	.5	.3	.08

## CHAPTER V

### DISCUSSION

The goal of this research was to examine the diagnostic accuracy of neuropsychological tests of attention in accurately separating patients with mood disorders from controls. Inherent in this question is whether patients suffering from affective disorders, specifically unipolar and bipolar II depression can accurately be categorized based on their performance on neuropsychological tests. The first conclusion that can be drawn from the results of this study is that the patient's attention processes were sufficiently impaired in a manner that can be measured and differentiated from a control group. More importantly, the probability ratios calculated appear to offer useful information in predicting the likelihood of a patient suffering from an affective disorder, and more specifically, this study illustrated the point that certain measures of attention will be more accurate in diagnosing depression over other measures. This information then becomes applicable when choosing a battery of neuropsychological tests. Certain measures of attention will be more useful in classifying an affective disorder when a diagnosis is in question.

The results of this study strongly support the previous literature discussing the sub-types of attention disorders experienced by a mood disordered subject. Moreover, the usage of sensitivity, specificity, and probability calculations allow for unique categorizations of the measures. The ability to categorize tests based on diagnostic accuracy inadvertently offers insight into as to the prospective attention deficits found



in a mood-disordered population, while simultaneously offering insight in the construct of these measures.

The present results provide evidence that neuropsychological measures may be useful as diagnostic delineators of the global and often diffuse cognitive deficits found in a mood disordered population. The fact that there was little correlation (only Digits B) between the severity of the depression and the cognitive impairment suggests that other factors may be related to the level of cognitive impairment, including chronicity and prior hospitalizations (Purcell,1998: Nelson et al,1989). There appears to be a significant range of diagnostic accuracy to the impaired attention performance of this population among the 6 measures of attention used in this study. This apparent difference reflects the fact that the measures are assessing different aspects of attention as supported by Schmidt and his colleagues (1994). For example, as consistent with the literature (Austin et al, 1999), Digit Span forwards and backward were not accurate in differentiating the affectively impaired group from the controls. This becomes important when considering the standardization for the development of norms for the WAIS-III & WMS-III. In reviewing the standardization process, it is assumed that there were no depressives in the normative population, however, it is not clear how exact the exclusion criteria was for depressives. The WAIS-III & WMS-III manual does clearly indicate that bipolars were excluded as were an subjects currently taking anti-depressant medication (Psychological Corporation:1997). Likewise, subjects with head injury requiring hospitalization for less than 24 hours were included. Thus, the possibility exists that both mild head injuries and mild depressives, not currently medicated, may have been included as part of the initial samples, and

therefore less likely to be diagnostically classified as impaired (Psychological Corporation:1997). Thus, it is still questionable whether Digit Span is insensitive to this population due to potentially blurred norms, or whether this test remains insensitive to a depressed population and to mild head injury due to the subcomponent of attention that is assessed; the latter suggested by the results of this study.

As presented in Table 3, Trails A was also relatively weak in its ability to accurately classify depressives from controls. This finding supports the earlier research of Schmidt et al (1994) whose findings suggest that both Trails A and Digit Span were less likely to correctly classify patients as impaired (17%) and (18%). His study further suggested that for Trails A, attention accounted for little of the variance (Schmidt et al, 1994). Likewise, the lack of diagnostic accuracy for the speed and accuracy scores of the 2 & 7 test replicated the earlier study by Ronald Ruff (1994). These findings become equally relevant when testing a patient. Given that this patient population's performance did not differ in a way that allowed for a separate classification from controls, the likelihood that a patient who has an impaired performance is more likely to have an affective diagnosis is increased (Specificity rules in diagnoses). Moreover, when considering the factor loadings presented in the testing manual (Ruff, 1982) which was speed of visual attention, visual processing, immediate attention, and response accuracy, there appears to be a pattern emerging with regards to the type of attention spared in mood disorders. Generally speaking, the tests that had the weakest efficiency and likelihood ratios were the tests that loaded on what might be termed simple attention processing. Included in these factors are simple speed of processing, immediate attention, and simple attention spanning. Factors that were

found within all three of the measures; 2 & 7 (Ruff, 1994) Digits Span (Schmidt, 1994) and Trails A (Heilbronner et al, 1991) (Schmidt, 1994).

Trails B was one test that did not easily align with the relatively strong diagnostic classifiers, while it was more efficient than either Digit Span or Trails A. This finding concurs with those of Schmidt et al (1994) who found similarly that while Trails B correctly classified only 26% of the neurocognitively impaired subjects, it was mildly improved over the Trails A (17%) and Digit Span (18%). Theoretically, in looking at the studies that attempt to consider what factors account for the variance of Trails B, Schmid et al's factor analysis (1994) concurs that Trails B loads heavily on attention (.61 communality). Other studies support Trails B as a solid measure of attention that examines other components as well (Zakzanis, 1998; Austin, 1999).

One potential argument to support the psychomotor component of affective disorders impacting the performance to account for its intermediate efficiency of Trails B, cannot be adequately defended because it should hold for Trails A as well. Thus, the psychomotor component of the attention process does not appear to be supported by the theoretical argument that measures requiring a processing speed /motor component could enhance diagnostic accuracy with a mood-disordered population. The factor that has been found to make Trails B slightly different from Trails A is the "set shifting component" (Pontius & Yedowitz, 1980). Further, low correlations found between the Trails A & B (.49) support the argument that the two measures are assessing different components of attention (Heilbronner et al, 1991). Further, both Veiel et al (1997) and Lemelin et al (1998) found Trails B along with Stroop CW as having the highest degree of variability with depressives. Thus, the integration of

earlier studies along with the current findings, suggests that Trails B has several secondary components that factor on some components of simple attention and having some components that make it a more complex measure. Unfortunately, these factors don't make up enough of the variance, or are complex enough or do not align strongly enough with the subcomponents of attention found impaired with this group that would make it a strong diagnostic tool with mood disordered population. Interestingly enough, Cahn et al (1995) found Trails B to be both sensitive and specific with Alzheimer's dementia, potentially suggesting different deficits (or breakdowns) in the visual attention processes between dementia and mood disordered groups. The classic Pet scan presentation for Alzheimer's patient would be hypometabolic activity in the parietal temporal lobes. Conversely, for depressives, hypometabolic activity was found in the anterior cingulate cortex and left dorsal lateral prefrontal cortex (Brown, 1994.) Therefore, it might be assumed that the visual spatial and visual search elements implicated by the parietal deficits may be effected with a dementia patient while the complex working memory implicated by an anterior cingulate deficit differently impacting the task.

Overall, the inefficient diagnostic abilities found with the Digit Span, Ruff's 2 & 7, Trails A as well as the mediocre diagnostic accuracy of the Trails B support the notion that the attention deficits found in the mood disordered population tend to be more complex.

The next group of measures that had the relatively greatest efficiency and likelihood ratios were the PASAT, Stroop C, Stroop CW and CPTA, in that order at a cut off of  $-1.5$ . The PASAT and the Stroop CW being solid diagnostic tests were

supported by the literature presented earlier (see Chapter II). The Stroop CW performance had been found to be consistently impaired with depressives (Veiel et al, 1997; Lemelin et al, 1997; Zakzanis, 1998). Moreover, both Veiel et al (1997) and Zakzanis et al (1998) found the CW scores of the Stroop as important differentiating measures for depressives; reflected in these findings. Thus, there appears to be evidence to support the notion that not only is impaired inhibition a primary cognitive symptom of depression, likewise, tests that assess this function will have strong diagnostic accuracy.

An interesting finding was proposed by Murphy et al (1999), who suggested that impaired inhibitory processes are found both in unipolar and bipolar depression with subsets of different types of inhibitory dysfunction (Murphy et al 1999). Their findings suggested that the only difference between bipolar and unipolar depression is their affective attention biases, and found that manic and depressed patients performed differently on affective shifting tasks only; postulating localizations of impairment (Murphy et al 1999). They suggest the ventromedial prefrontal cortex is impaired with bipolars, which tends to be activated in mania and believed to subserve affective attention tasks, as opposed to dorsal lateral prefrontal cortex believed to subserve cognitive shifting and is impaired with unipolars (Murphy et al, 1999).

The PASAT is also a test that has been suggested to be highly sensitive test with mild Traumatic Brain Injury and generally sensitive to cognitive deficits (Cicerone, 1997; Schmidt, 1994). In fact, sensitivity and specificity calculations in a more recent study of attention measures with mild TBI, suggests that PASAT has solid diagnostic accuracy with both groups, potentially indicating that the

neuropsychological attention deficits in mood disordered and mild TBIs are similar or that the TBI patients may have suffered from depression; more likely the former (Cicerone & Azulay, in press). Interestingly enough, Zakzanis et al (1998) found the PASAT (56) equally sensitive at a  $-2.0$  z supported by this studies (56.52), despite the usage of different calculations. She and her colleagues interpreted these findings to suggest that the diagnostic accuracy for the PASAT was below the median for effect size, although as the predictive calculations suggest, the sensitivity of the measure is only one element of a measure's diagnostic capabilities (Zakzanis et al,1998).

The findings of the color reading portion of the Stroop test are interesting and perhaps counter intuitive but not surprising given the literature. The stroop Color portion is simply reading the XXX and naming a color, which sounds relatively simple and potentially falling in the realm of a simple processing attention task, similar to that of Trails A. However, in recalling the literature review, many of the studies found Stroop Color naming to be as highly discriminative of depressives as the CW portion of the Stroop (Zakzanis et al 1998, Lemelin et al,1997a ;Lemelin et al 1997b). Likewise, several of the studies on the choice reaction times (CRT) of depressives were found to be consistently slowed (Thomas & Rousseaux,1999; Massiouo & Lesevre,1988; Thomas, et al, 1999;Baribeau- Braun and Lesevre,1983). Lemelin (1997a) and her colleagues argue that the Stroop Color reading task has a choice reaction time component in which the subject is forced to choose between the three colors offered the one that the XXX 's represent. She concluded that depressives can have two different attention deficits of either a distractor inhibition disturbance or in processing resources (choice reaction time). The present study also reflected similar

findings in that both the Stroop C and CW were strong diagnostic indicators of depression. The fact that the Stroop Color appeared to be diagnostically stronger than Color Word may suggest that this group of mood disordered patients may have better fit the spectrum of process resource deficit over distractor inhibition deficit postulated by Lemelin et al(1997a) as evidenced by the differences in Likelihood ratios.

Since the CPTA is a relatively new test, one can only speculate as to the prospective subcomponents it may assess. Cicerone (1997) suggested the development of the CPTA was intended as a measure of speed of processing at several levels of complexity which theoretically could entail a choice reaction time as part of an attention resource deficit. However, theoretically speaking, other sub-components of attention may be involved as well. A working memory component is needed in order to keep in mind the changing rules of each subsection since the stimuli does not provide any cues; similar to the conjectured working memory component of the PASAT or the Stroop. Again, in both of these measures the task rules are given and then must be held in working memory by the subject throughout the remainder of the task. Another component of the CPTA, is the prospective inhibitory element involved through out the task. Since the rules change at each subsection, the subject is than forced to inhibit responding to the previous rules that he had been primed to respond to earlier and instead respond to the newer set of rules that follow. Thus, the CPTA appears to share the inhibitory, working memory, and choice reaction time (CRT), sub-components of attention shared along with the Stroop C and CW, as well as the PASAT.

There are other elements found in these measures that might also contribute to their sensitivity with this particular population. The Stroop is internally paced while the PASAT and CPTA are externally paced, a factor which has been implicated in relation to the overall neurologic impairment and proposed as having implications for diagnostic sensitivity with the mild head injury patients (Cicierone,1997). Thus, the added diagnostic value of the Stroop C and CW may afford information regarding the different impairments between the mood disordered patients and mild TBI, that will be diagnostically invaluable.

In summary, the tests that afforded the greatest diagnostic accuracy included the PASAT, CPTA, Stroop C and Stroop CW. These tests are believed to assess sub-components of attention including speed of processing, working memory, and inhibitory processes. These findings are consistent with the evidence of impairments of distractor inhibition, (Lemelin et al 1997a) attentional resource allocation expressed in choice reaction time (Thomas et al; 1997) and the working memory component (Bassel, 1999; Arnett et al 1999; Zakzanis, et al,1998) found in the mood disordered population.

#### Limitations of This Study

The patients studied here were a mix of bipolar and unipolar subjects, which clearly may have confounded the presentation of attention deficits, despite the literature suggesting the contrary (Murphy et al,1999; ) In an effort to explore this potential effect, sensitivity and specificity contingency tables were calculated between the groups, using the unipolar depressives as the target population (see Table 6). The findings did support this studies' results by illustrating that these measure were not



able to correctly differentiate between unipolar and bipolar groups based on their performances using the 6 measures of attention. The CPTA, which found 11 out of 12 (91) bipolars impaired and 17 out of 18 unipolar depressives impaired (94%) was the only measure that differentiated through sensitivity and specificity calculations. This speaks to the "over" sensitiveness (the likelihood of true positives) of this measure, rather than the differences between groups.

Another concern is the potential negative or positive impact of psychotropic medications. At the inclusion of this study, all patients were receiving psychopharmacological treatments and 4 were receiving psychotherapy. This raises the question of the possible influence of these drugs on subject performance. Numerous studies reported no negative effects with specific tests of attention with patients taking anti-depressive (Berger et al 1989; Jones et al 1996). However, more recent reviews of mood stabilizers and anti-psychotic medication suggest the potential for medication confounding memory and attention (Martimer, 1997). Although the results found in this study are consistent with data reported by studies with comparative within group drug versus drug-free patient studies (Murphy, 1999; Austin et al, 1998), these concerns should be kept in mind when reviewing the results.

Of course, the fact that the volunteers were compensated for their participation raises the issue of a population subtype. Many of the subjects expressed financial concerns, potentially suggesting that the level of functioning may have been inferior to a more random sample. Finally, the history of hospitalizations and the level chronicity of most of the patients suggest that these data are representative of a more chronic

mood disordered population, and thus the results may be limited to an equal population.

### Implications for Future Research

For years it has been accepted in the literature that depression causes global cognitive deficits, specifically in the areas of attention and memory. This research has further demonstrated the irrelevance of severity with regards to cognitive dysfunction, and instead has illustrated that chronicity and prior hospitalizations may be risk factors for long term and potentially irreversible cognitive damage. Thus, one subject area of future research would be to explore chronicity with regards to neurocognitive impairment. To back through the data and explore relationships between the length of diagnosis and the impairment on tests of attention would be useful information.

It has long been accepted that emotional deficits and motivational changes occur in depression and that these changes are treated with psychotherapy and psychopharmacological treatments. One element that has not been considered is viewing chronic depressives as brain injured patients. The potential exists that chronic depression or long term deficits in neurochemical levels may result in anatomical changes, perhaps mirroring the hippocampal deterioration found in long term PTSD patients (Nusbaum conference, 2001). Thus, the culmination of long term depression may in fact be equal to any other neurological insult or disease, ultimately resulting in cognitive deficits. Trichard et al(1995) examined 23 severely depressed patients using the Stroop and the Verbal Fluency Test. After patients had been treated with anti-

depressives, the depressed group of unipolars and bipolars were reassessed. Results suggested that only the Verbal Fluency measure showed improvement, while the Stroop measure remained impaired (Trichard et al 1995).

This research clearly points to the diagnostic accuracy of certain tests, tests that appear to align with difficulties in very discreet areas of attention. Diagnostic accuracy becomes of greatest importance when it can be matched with equally important treatment options. The assumption that patients once treated for depression, no longer presenting with affective signs of depression does not address the issue of the potential cognitive changes. There is acknowledgement of neurocognitive deficits in depression and there is equal research to support the use of cognitive rehabilitation for specific deficits. It appears that one treatment that has not been considered or utilized with chronic depressives is the opportunity to receive treatment that might improve their cognitive functioning; both psychopharmacological and cognitive rehabilitation. Thus, one area of future study would be the potential treatment benefits of certain chronic depressives who are cognitively impaired.

Other areas of study that would be potentially improve the understanding the cognitive deficits of depression would be to explore other measures using evidenced based statistics. As there is an increase in research assessing the diagnostic accuracy of neuropsychological measures with different populations, the benefit will be an improved neuropsychologic assessment with increased diagnostic clarity, resulting in more specific treatments.

The lack of studies using these types of calculations, does not allow for comparative dialogue with these results. Having a sense of what is a significant

likelihood as opposed to a minimal likelihood is less clear. Ivnik et al (2001) in his discussion of evidence based calculations gives likelihood ratios ranging from 1.9 to .7 without ever discussing what the numbers represent. Future studies are needed to help develop criteria for a better description of the results presented in this study.

A final notion to consider would be to gain a better understanding of the possibility of combining tests to obtain the greatest diagnostic accuracy. More than just the parallel or serial notion presented by Sackett,(1991) and Fletcher, (1982). Logarithms for combining tests so that there can be accumulative advantage needs to be explored. For, example, if you have a PET scan; an allele test; a neuropsychological battery, and an MRI, all with contradictory results, which should hold more weight or what combination has the greatest diagnostic predictability? These are the studies to be considered for the future.

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**Appendix A**

September 7, 2000

Dear Consumer:

You have been selected to participate in a study that measures attention and Major Depression. Such participation will not effect your treatment in any way and will be kept confidential. The purpose of this study is to evaluate cognitive functioning in clinically depressed adults. The results will be used to better understand cognitive difficulties found with depression and the results of the evaluation will remain confidential with regards to any publications as a result of the study.

The testing will take approximately 1-2 hours and participants will be asked to fill out questionnaires concerning physical, emotional, and cognitive problems you may be having. You will also be given a number of verbal and paper and pencil tests to measure how well you pay attention, learn and remember words, sentences, designs, and solve problems. You may elect to discontinue participation at any time and will suffer no penalty or benefits to which you are otherwise entitled should you decide not to participate. Upon completion of the testing, you will be reimbursed \$20.00 to defray the cost of travel or other expenses associated with your participation in the study.

If you feel you might be interested, please call and leave a message. We can discuss the study in greater length, go over questions you may have and you can determine if you would like to participate. Thank you for your time. (732-235-3907).

Sincerely,

Joanne Azulay  
Researcher

## Appendix B

My name is Joanne Azulay and I previously worked as a consulting therapist and externed at Preferred Behavioral Health as part of my clinical training for my Doctorate at Seton Hall University.

Currently, I am working on research as part of my dissertation requirements that Michael Blatt and the board reviewed and approved. I hoped to start testing as many patients as possible over the summer before I begin interning at UMDNJ in the fall. I am assessing with a short battery of mostly neuropsychological tests of attention with patients diagnosed with a DSM-IV 296.xx Diagnostic code.

Briefly, my goal is to calculate sensitivity, specificity, and probability statistics on the performances of depressives. Using these calculations on their performances would allow for better diagnostic and predictive capabilities of neuropsychological tests. The tests are mostly pencil and paper tests, for the most part easily completed, and non-intrusive. The testing process typically takes about an hour but could run longer depending on the individual. I will be reimbursing each patient \$20 to defray the cost of travel expenses.

I was looking to you for assistance in the recruiting process by answering there questions and /or encouraging them to call me for further information. I would also welcome any questions or comments you might have as well.

Thank you,

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Joanne Azulay, Ph.D. Candidate- (732) 370-9898

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Janet Pisani, MD

## Appendix c

### CONSENT TO PARTICIPATE IN RESEARCH

Protocol: Neuropsychological functioning in Clinically Depressed adults.  
Principal Investigator: Joanne Azulay, Ph.D. Candidate at Seton Hall  
University

**Research Participant Information:** The purpose of this study is to evaluate cognitive functioning in clinically depressed adults without known neurologic disease. As a participant in this study, you will be given a number of verbal and paper-and-pencil tests to measure how well you can pay attention, learn and remember words, sentences and designs, and solve problems. You may also be asked to respond to questionnaires which will ask about any physical, cognitive, or emotional symptoms or problems you may be having. Testing will take approximately 1 to 2 hours. The tests are as follows: CPTA- an auditory listening test where you are to tap your finger when hearing a certain letter; Trails A & B - connecting letters and numbers in sequential order; 2 & 7 cancellation test - crossing out 2 & 7 's among other letters and numbers; PASAT- sequentially adding numbers in order; Digit Span- repeating orally presented numbers in a certain order; Rey Copy- copying a figure from a presented drawing, Stroop- reading colored words as quickly as possible; Block Design- producing designs based on a picture as quickly as possible; Mazes; Vocabulary; COWAT- naming as many words possible beginning with C, F, & L; Ruff figural Fluency- making different figures by connecting dots; and WCST- sorting cards based on different principles of form color and number.

**Risks and Benefits:** There are no physical risks involved in procedures used in this study. On occasion, some people may experience frustration during portions of the testing. If this occurs, you may stop testing and you will be given the opportunity to speak with a professional regarding your response to the testing.

The benefits of this study are primarily to understand the potential cognitive changes that may occur as a result of depression. There are no direct benefits to you as a result of your participation in the study. However, you will be given the opportunity to review your performance with the principal investigator.

Your identity as a participant and the results of your participation will remain confidential with regards to maintenance of test results and any publications as a result of this study.

**Terms of Participation:** Participation in this study is voluntary. You may elect not to participate in this study at any time and will suffer no penalty nor loss of benefits to which you are otherwise entitled should you decide not to participate. There will be no cost to you for participating in the study. Upon completion of the

testing, you will be reimbursed \$20.00 to defray the costs of travel or other expenses associated with your participation in the study.

**Contact Person:** For more information regarding any aspect of the study, you may contact Joanne Azulay, telephone 732-616-0609.

**Authorization:**

I authorize Joanne Azulay to obtain information regarding my health and socioeconomic status as given by me or through medical records, and to administer psychometric tests of attention, learning and memory, cognitive functioning and emotional status.

\_\_\_\_\_  
Initial here

I acknowledge that I have read and understand, or had explained to me in a language I understand, information regarding my participation as well as any benefits, risks or discomfort which may be reasonably expected as a result of my participation in this study. I have had the opportunity to ask any questions I have had and all the questions I asked were answered to my satisfaction.

\_\_\_\_\_  
Initial here

**Liability Disclaimer:** In the event that injury occurs as a result of my participation in the study, treatment for injury will be available. I understand, however, that such treatment will be provided to me at my own expense or at the expense of my health care insurer, I will not be provided with free medical care nor receive other compensation from Seton Hall University, its students, or Preferred Behavioral Health.

\_\_\_\_\_  
Initial here

I confirm that I have read the foregoing authorization and consent to participate in the research as described above.

\_\_\_\_\_  
Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Principal Investigator

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

This project has been reviewed and approved by the Seton Hall University Institutional Review Board for Human Subjects Research. The IRB believes that the research procedures adequately safeguard the subject's privacy welfare, civil liberties,

and rights. The Chairperson of the IRB may be reached through the Office of Grants and Research Services. The telephone number of the Office is (973) 275-2974.

I have read the material above, and any questions I asked have been answered to my satisfaction. I agree to participate in this activity, realizing that I may withdraw without prejudice at any time.

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Signature of Subject

Date

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