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Attention Mechanisms in Bipolar Depression

by

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A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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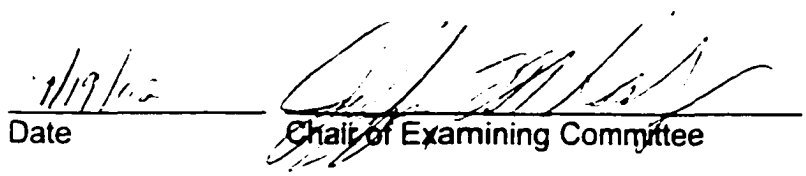

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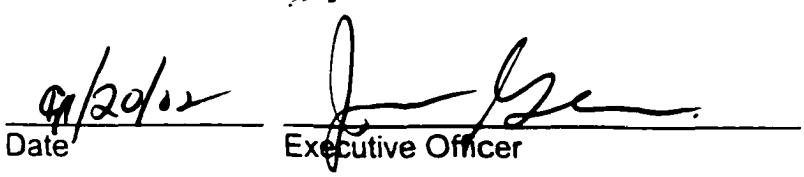

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Abstract

ATTENTION MECHANISMS IN BIPOLAR DEPRESSION

by

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Background: Bipolar disorder affects approximately 6.5% of the population and consists of both manic and depressive episodes, often resulting in chronic psychosocial impairment. Cognitive deficits are common among patients with bipolar disorder during acute episodes of depression and mania (Reitan & Wolfson, 1997). Among the commonly observed deficits are psychomotor abnormalities and attentional dysfunction (Goodwin & Jamison, 1990). Few studies to date have investigated the underlying information-processing deficit within the attentional domain in patients with bipolar depression. The current study will quantify attentional deficits as they relate to the severity of the depression and the degree of psychomotor retardation in a group of patients with bipolar depression.

Methods: 23 medicated, non-psychotic, depressed outpatients meeting DSM-IV criteria for Bipolar I or Bipolar II disorder were compared with 27 age-matched, non-psychiatric control subjects on a neuropsychological battery of psychomotor

and attentional tasks to further evaluate the nature, extent, and potential correlation of attention and psychomotor disturbances in this population. Psychopathological severity was concurrently measured to establish its relationship to cognitive dysfunction.

Results: Results indicate a significant difference between groups on measures of executive attention, suggesting an impairment in inhibitory processes in patients with bipolar depression. No group differences were seen on the primary variables of a double-key version of Posner's covert orientation of visual attention designed to measure automatic, non-executive attention; however, secondary analyses suggest a deficit in the normal pattern of inhibition of return (IOR) in patients with bipolar depression. Depressive severity was not significantly correlated with executive attentional impairment. Psychomotor variables demonstrated a weak relationship with attention deficits.

Discussion: The present research provides preliminary evidence identifying impairment of the executive anterior attention network in depressed subjects with BP disorder. Additionally, there may be some dysfunction in the executive control of the automatic aspects of the dynamic deployment of attention (posterior attention network) in depressed subjects with BP disorder. Severity of depression was not significantly correlated with attentional impairment. Psychomotor retardation was only weakly correlated to executive attention deficits. Future studies in larger samples are needed to confirm and clarify the current findings.

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BACKGROUND

Introduction

Bipolar disorder is an affective disorder characterized by both manic and depressive episodes. In the course of the illness, patients suffer not only from the lows of depression, but they must also endure the exaggerated optimism and destructive impulsivity of mania (Goodwin & Jamison, 1990). Recent information puts the lifetime prevalence of bipolar disorder up to an astounding 6.5%, with medical costs of up to $476,000.00 per year, per patient (Post, 2002). Adding to the financial burden is the grim fact that 25 to 50% of those diagnosed with bipolar disorder attempt suicide (Post, 2002).

It is widely held that patients with bipolar disorder demonstrate diffuse cognitive deficits during acute phases of the illness. Psychomotor and attention deficits are among the most frequently reported in bipolar disorder, particularly during periods of depression, yet studies looking into the specific qualitative aspects of these deficits are sparse. Further investigation of cognition in patients with bipolar disorder is necessary, with a specific focus on elucidating the nature and extent of these deficits.

Rationale

The current study assessed 23 patients with bipolar I or bipolar II disorder in the depressed phase of illness on a detailed neuropsychological battery of attention tasks, in an attempt to further characterize the deficits that are

commonly found in patients with bipolar depression. Furthermore, a careful assessment of motor behavior was performed, in order to establish the extent to which psychomotor retardation may be playing a role in the attention deficits.

Patient inclusion criteria for the current study was: 1. Confirmed diagnosis of bipolar I or bipolar II disorder by DSM-IV (American Psychiatric Association, 1994) criteria; 2. Current major depressive episode, of moderate to severe intensity by DSM-IV criteria; 3. Age 18-55; and 4. Stable, therapeutic dose of either lithium, carbamazepine, or valproate. Exclusion criteria included: 1. Current psychosis; 2. Major medical illness; 3. Comorbid Axis I diagnosis; 4. Antidepressant or neuroleptic (typical or atypical) medications; 5. History of rapid-cycling; and 5. History of neurological disorder, including seizures or head injury. An equal number of sex and age-matched, non-psychiatric control subjects were also tested. The final resulting sample was not matched one-to-one due to the exclusion of both patients and controls for reasons described in the Methods section of this paper.

Studies have shown that patients with bipolar depression have significantly more psychomotor retardation than patients with unipolar depression (Mitchell, Wilhelm, Parker, et al., 2001; Benazzi, 2000). Furthermore, recent evidence suggests that patients with bipolar disorder might perform as poorly as schizophrenic patients on tests of executive function (Hoff, Shukla,

Aronson, Cook, Ollo, Baruch, et al., 1990; Maurice, 1990). These findings taken together suggest prefrontal dysfunction, which has been supported by neuroimaging studies in patients with bipolar disorder (Benabarre, Vieta, Martinez-Aran, Reinares, Colom, Lomena, et al., 2002).

Previous studies investigating the attention deficits that are common in patients with depression, both unipolar and bipolar, have linked some components of attention to frontal lobe and dopaminergic dysfunction. Depressed patients, in general, demonstrate reduced performance on attention tasks as the demands of the task increase (Hartlage, Alloy, Vasquez, & Dykman, 1993). This attention decline is considered, by many, to be a central component of the cognitive deficits seen in depression (Brown, Scot, Bench, & Dolan, 1994; Channon, Baker, & Robertson, 1993). In addition, recent studies have correlated attention disturbances in depression with the degree of psychomotor retardation seen in the sample; however, these deficits have not been specifically characterized (Lemelin & Baruch, 1998). The anterior attention system, described by Posner (1980), was the focus of the current study because of its involvement in executive attention control (conscious attention) and its relationship with brain areas related to psychomotor functioning. (Posner & Petersen, 1990.) The following hypotheses were tested:

Hypotheses

a) Depressed patients with bipolar disorder (BP) demonstrate significantly greater attention deficits, selectively in the executive attention domain, as compared with a non-psychiatric control (NC) group.

b) Executive attention deficits seen in the BP group are not related to severity of depressive symptoms.

c) The degree of psychomotor slowing in the BP group is positively correlated with executive attention deficits.

Review of Literature

Bipolar Disorder-DSM-IV criteria

Bipolar I disorder is defined by the Diagnostic and Statistical Manual of Mental Disorders-4th Revision (DSM-IV) (APA, 1994) as a recurrent affective illness characterized by both full manic and major depressive episodes. A manic episode is described as a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week (or any duration if hospitalization is required). During this period of mood disturbance, at least three of the following symptoms must have persisted (four or more if mood is only irritable) and have been present to a significant degree: 1) inflated self-esteem or grandiosity, 2) decreased need for sleep, 3) increased rate or amount of speech, 4) flight of ideas or subjective feeling that thoughts are racing, 5) distractibility (attention too easily drawn to external stimuli), 6) increased goal-directed activity (socially, occupationally, or

sexually) or psychomotor agitation, and 7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. unrestrained buying sprees, sexual indiscretions, or foolish business investments). Furthermore, mania must be sufficiently severe to cause marked interference with occupational functioning, social activities or relationships with others, or necessitate hospitalization to prevent harm to self or others, or there are psychotic features. The symptoms described above must not be due to direct physiological effects of a substance (e.g. drug of abuse, a medication, or other treatment) or a general medical condition (APA, 1994).

Depressive episodes are defined in the DSM-IV (APA, 1994) by five or more of the following symptoms (at least one of which must be depressed mood or loss of interest or pleasure) that must be present for at least two weeks and represent a change from previous functioning: 1) depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others, 2) markedly diminished interest or pleasure in all, or almost all, activities all day, or most of the day, nearly every day (by subjective report or observation of others), 3) significant weight loss when not dieting or weight gain (e.g. change of >5% body weight in a month), or decrease or increase in appetite nearly every day, 4) insomnia or hypersomnia nearly every day, 5) psychomotor agitation or retardation nearly every day (must be observable by others), 6) fatigue or loss of energy nearly

every day, 7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely guilt about being sick), 8) diminished ability to think or concentrate, or indecisiveness, nearly every day, 9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. The symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and cannot be due to a substance or general medical condition. In addition, these symptoms may not be due to basic bereavement (e.g. over the loss of a loved one).

According to the DSM-IV (APA, 1994) bipolar II disorder is characterized by periods of major depression and hypomanic episodes. Hypomania differs from mania in both severity and duration. When the criteria for a full manic episode is not met but hypomania is present, a diagnosis of bipolar II disorder is given. Hypomania is defined by a distinct period similar to that described for mania but lasting for at least four days and consisting of at least three (instead of four) manic symptoms. Hypomanic episodes are not severe enough to cause marked impairment in functioning, or necessitate hospitalization, and there are no psychotic symptoms (APA, 1994).

Bipolar disorder differs from major depressive disorder (MDD) predominantly due to the presence of manic or hypomanic episodes, which do not occur in

major depressive disorder. The term "unipolar" depression, which was utilized in the DSM-III-R (APA, 1987) to define major depressive disorder, has since been dropped in favor of MDD in the DSM-IV (APA, 1994). The current paper will use the term unipolar to distinguish between samples when reviewing previous studies of depression that have grouped both unipolar and bipolar depressed patients together or have compared them directly.

The primary focus of this dissertation will be the depressed phase of the illness and specific psychomotor and attention abnormalities in depressed patients with bipolar disorder. Depression, in both unipolar and bipolar patients, is often characterized by a slowing of almost all aspects of behavior and emotion including decreased rate of speech, decreased energy, decreased libido and anhedonia (Nelson & Charney, 1993). Mental and physical slowing are nearly always present in bipolar depression, are more frequent than in unipolar depression (Wolff, Putnam, & Post, 1985), and can be manifest as pronounced psychomotor retardation. There is frequently a marked slowing of thought processes and indecisiveness (Parker, Hadzi-Pavlovic, Brodaty et al., 1993). Similarly, activity and behavior are almost always slowed in bipolar depression (Wolff et al., 1985).

In a qualitative study of 21 bipolar patients by Winokur and colleagues (1969), eighty-five percent of patients experienced a gradual onset of depressive symptoms and virtually all of the patients were classified as melancholic, with

91% reporting poor concentration, diminished clarity of thought and diminished speed of thought. One-half reported memory problems. Fatigue and psychomotor retardation were seen in three-fourths of the bipolar patients studied and sleep and appetite difficulties were pervasive (Winokur, Clayton, & Reich, 1969).

Diffuse cognitive deficits have been reported among patients during either manic or depressive episodes (Teasdale, 1983; Mialet, Pope, & Yurglen-Todd, 1996; Reitan & Wolfson, 1997). Attention deficits and impairment in executive functioning have been consistent findings in bipolar patients (Clark, Iversen, & Goodwin, 2002; Martinez-Aran, Vieta, Colom, et al., 2000) and can be linked to the integrity of the prefrontal cortex, which has been one of the structural abnormalities seen in bipolar patients (Soares & Mann, 1997). More specific information on the nature of the neuropsychological deficits may provide a clearer picture of the functional networks that are abnormal in bipolar disorder and suggest a link to symptomatology. In clarifying some of these issues, we hope to enable more informed treatment strategies in a group of patients for whom treatment is often inadequate (Post, 2002).

Treatment considerations

The treatment of bipolar depression represents a unique challenge and is limited by several factors including the fact that drug development is focused on the treatment of mania, there are no FDA approved treatments for bipolar

depression, and there is a high risk of destabilization from antidepressant therapy in bipolar patients (including the possible induction of mania or rapid-cycling) (Post, 2002). According to experts in the field (Calabrese, Frye, & Goldberg, 2002), adequate treatment of bipolar depression is one of the greatest unmet needs. In a review, Judd and colleagues (in press) found that depressive episodes are more frequent than manias and last longer, relapse most often occurs in the direction of depression, and 90% of completed suicides are in the depressed or mixed (mania concurrent with depression) phases of the illness (Judd et al, In Press).

Current treatment of bipolar depression focuses on maintaining mood stability through the use of a mood stabilizer (i.e. lithium, valproic acid), while concomitantly introducing an antidepressant to target the depressive symptoms. The most common type of antidepressant prescribed today falls within the selective serotonin reuptake inhibitor (SSRI) family and works via the serotonergic system in the brain (Bezchlibnyk-Butler & Jeffries, 1998). The role of dopamine in depression pathogenesis has received less attention than either serotonin or noradrenaline (Perugi, Toni, Ruffolo, Frare, Akiskal, 2001); however, clinical evidence suggests that dopamine may have a role in the development and treatment of depression (Willner, 1983). Novel approaches in treating bipolar depression have recently been investigated with this in mind, with results suggesting safe and effective adjunctive treatment with dopamine agonists in patients with treatment-resistant

depression (Goldberg, Burdick, & Endick, 2001; Lambert, Johansson, Agren, & Friberg, 2000; Perugi et al., 2001).

The identification of psychomotor retardation and the corresponding cognitive impairment has prognostic implications, including prediction of response to medication. Psychomotor retardation has been shown to accurately predict good response to tricyclic antidepressant medications in patients with both bipolar and unipolar depression (Joyce & Paykel, 1989; Ranelli & Miller, 1981). Motor symptoms in depression may indicate abnormalities in specific structures and pathways in the brain. Neurological disorders affecting motor performance such as Parkinson's disease (Cummings, 1992), Huntington's disease (Jeste, Karson, & Wyatt, 1984), Progressive Supranuclear Palsy (Albert, Feldman, & Willis, 1974), Wilson's disease (Akil, Schwartz, Dutchak, et. al., 1991), and basal ganglia calcifications (Trautner, Cummings, Read, &Benson, 1988), often result in higher rates of clinical depression than is expected in the general population or in the medically ill population. This has led to the suggestion that basal ganglia disorders may shed light on some of the neuroanatomical correlates of affective disorders, specifically involving symptoms such as psychomotor changes (Peyser & Folstein, 1990).

With this in mind, the current study focused specifically on the psychomotor and attention functioning of patients with bipolar disorder in the depressed phase of illness. A priori hypotheses included a predicted deficit specifically in

"executive" attention and not in other areas of attentional function ("non-executive"). This followed from evidence of overlapping neuroanatomic regions affected by psychomotor deficits and executive impairment, in addition to recent findings correlating psychomotor functioning with attentional deficits on neuropsychological measures (Lemelin & Baruch, 1998). Executive attention refers to attention processes used when tasks require planning, error detection, novelty, difficult processing, or conflict (Posner & Di Girolamo, 1998). Executive attention includes such areas of study as selective attention, divided attention, and inhibition of distractors. Tasks used in the literature to measure executive attention in the visual domain include measures requiring the distribution of attention over two or more tasks at the same time and measures requiring the inhibition of highly learned responses in favor of a more novel response. Performance on such tasks of executive attention has previously been linked to frontal midline areas, which receive dopaminergic input from the basal ganglia (Posner & DiGirolamo, 1998). Specific deficits in executive attention in patients with bipolar disorder may serve as a potential predictor for treatment response to dopaminergic agents, or other specific data-driven treatment options in bipolar patients.

In contrast, non-executive attention is predominantly described as automatic attention, such that conscious processing is not necessary in order to elicit a response. For example, the sudden appearance of a stimulus within the visual field automatically elicits an orienting of attention to that stimulus,

without requiring specific thought in doing so (Posner & Petersen, 1990). Non-executive attention is frequently measured in tasks utilizing a target detection paradigm (Posner & Cohen, 1984), or in visual search tasks that have highly dissimilar distractors allowing for a 'pop-out' of the target stimuli (i.e. red squares in a field of green triangles) (Treisman & Gormican, 1988). The distinction between executive and non-executive attention as it relates to the current study will be described below in relation to the measures used in this study.

Neural Network Model of Attention

There are several different models that describe the mechanism of visual attention. While there is no single model that is accepted universally, there are many models that have furthered our understanding of a very complex cognitive mechanism (LaBerge & Brown, 1989; Desimone & Duncan, 1995; Steinman & Steinman, 1997). One specific, well-studied paradigm that attempts to distinguish executive from non-executive attention is described by Posner and colleagues, who utilized a cued target detection task to measure non-executive attention and the Stroop Task to measure executive attention (Posner, 1986). The focus of the current study is based on the attention model of the neural networks involved in visual attention proposed by Posner and Petersen (1990).

Posner and Petersen (1990) described a commonly cited neuroanatomical model of visual attention, which can be identified as a spotlight model of attention. Cognitive neuroscience has allowed for the linkage between cognition and a system of anatomical areas, forming a neural circuitry that is necessary for the selection of visual information for conscious processing. This model includes both top-down and bottom-up processes; similar to those described by Desimone and Duncan (1995). Posner and Petersen (1990) attempted to describe how voluntary control is exerted over more automatic brain systems. The model described attention mechanisms on both the level of cognitive operations as well as at the level of neuronal activity. Posner's model suggests the following: 1) The attention system is anatomically separate from the brain systems responsible for the operations of data processing. 2) Attention is carried out by a network of specific anatomical areas and is not a function of a single center or the brain as a whole. 3) The brain areas involved in visual attention carry out different functions and can be separated in cognitive terms.

Posner described visual attention as being composed of three components; orienting, detecting and vigilance. Each of these components involves different neuroanatomical areas. The detecting network is consistent with Posner's description of an anterior attention network and is commonly thought of as responsible for executive attention, or controlled processing. The orienting and vigilance networks combine to form the basis of Posner's

posterior attention network, which functions more automatically and is not otherwise involved in controlled processing (Posner & Petersen, 1990).

Orienting can be defined as the foveation of a stimulus; however, this definition only describes what is known as overt orienting. Humans are also capable of covert orienting, which involves the movement of attention without the movement of the eyes or the head. Orienting to a stimulus increases the efficiency of processing targets (Mountcastle, Motter, Steinmetz, Duffy, 1984). This is measured by reduced reaction time, increased scalp activity, and decreased threshold in target detection tasks and has been shown to occur in overt orienting tasks within the first 150ms, before the eyes have moved to the target (Goldberg & Wertz, 1972). This suggests that the orienting component of visual attention may serve the purpose of programming, or guiding, the eye to the appropriate area of the visual field and is not restricted to the observable movement of the head or eyes to a target. Areas of the brain that have been shown to be involved in orienting include the posterior parietal lobe, the lateral pulvinar of the thalamus, and the superior colliculus (Posner & Raichle, 1994).

A review of lesion studies in monkeys (Petersen, Robinson, & Morris, 1987; Posner & Cohen, 1984) illuminates the specific function of each of these brain areas. Lesions of the posterior parietal lobe result in problems of disengagement from a stimulus that is being attended to on the side opposite

the lesion (Posner, Walker, Friedrich, Rafal, 1984). Lesions of the superior colliculus impair the computation involved in moving attention and are closely linked to problems with saccadic eye movement (Posner & Cohen, 1984). Lateral pulvinar lesions result in difficulty in covert orienting, particularly the ability to engage attention on a newly presented target (Petersen, Robinson, Morris, 1987). Patients with lesions in the latter area are not helped by cueing, while patients with lesions in the former two areas still benefit from cueing (Petersen et al., 1987). In general lesion studies have supported Posner's model confirming different functions for different areas within the attention system. Furthermore, lesion studies suggest a circuitry involved in covert orienting to spatial locations. The posterior parietal lobe is responsible for disengagement from current fixation. The midbrain and the superior colliculus are in charge of moving the attention spotlight to the area of the target and finally, the pulvinar reads out the data from the attended location (Petersen et. al. 1987; Posner & Cohen, 1984).

Vigilance, sometimes referred to as alerting, is the ability to prepare and sustain alertness to process high priority signals (Posner, 1978). An alert state decreases reaction time but increases error rate such that the selection of a response is quicker but it is based on lower quality information. Therefore, alertness does not affect the build up of information in the sensory or memory systems, but does affect the rate at which attention can respond

(Posner, 1978). Areas of the brain that are involved in vigilance include the right midline prefrontal cortex and the locus coeruleus.

Vigilance depends heavily on the integrity of the right hemisphere (Posner & Petersen, 1990). Lesions in several locations (i.e. posterior parietal lobe, basal ganglia) in the right hemisphere lead more commonly to neglect than lesions in the left hemisphere (Coslett, Bowers, Heilman, 1987). This led to the idea that the right hemisphere controlled all spatial attention but this seems only to be true in tasks that depend upon an alert state. Studies using split brain patients, lesion studies, and PET studies suggest that right hemispheric abnormalities result in deficits in vigilance but not in other measures of cognition, such as semantic tasks or visual imagery tasks (Posner & Petersen, 1990). Vigilance deficits result in corresponding impairments in other attention functions, including orienting and detecting, as a consequence of an impaired state of alertness. The right midline prefrontal cortex is most active during states of vigilance. Cohen, Sample, Gross, Holcomb, Dowling, et al., (1988) found increased prefrontal and anterior cingulate cerebral blood flow during vigilant states. Norepinephrine (NE) has been the key transmitter studied in relation to vigilance. Robinson (1985) demonstrated that, in rats, lesions of the right but not the left hemisphere led to decreased production of NE on both sides with the strongest effect when the lesion is closest to the frontal pole. Morrison and Foote (1986) mapped major NE innervation to the posterior parietal lobe, pulvinar and the superior

colliculus, consistent with the brain regions involved in the posterior attention system. There is a weaker NE innervation in the geniculo-striate and along the ventral stream that targets pattern recognition. Therefore, the NE path likely provides the basis for maintaining an alert state and acts most strongly on the posterior attention system of the right cerebral hemisphere (Posner & Petersen, 1990).

Detection is the third component of attention that is described by Posner and Petersen (1990). Detection is controlled by the anterior attention system and is predominantly involved in conscious, executive, or focal attention. Unlike a state of vigilance when any target that is intense enough will summon attention, the executive (anterior) attention system consciously searches for a known target and utilizes expectancy. The posterior and anterior systems do not act completely independently of one another. Goldman-Rakic (1988) found that the posterior parietal lobe projects to the lateral and medial frontal cortex, implying a potential link between the posterior and anterior attention systems. Increased cerebral blood flow in the anterior cingulate occurs as the number of targets to detect increases (Posner et al., 1988). The anterior cingulate has alternating bands receiving input from the posterior parietal cortex and the dorsolateral prefrontal cortex, suggesting that the anterior cingulate is a likely candidate involved in the conscious processing of the anterior attention system in executive attention tasks (Goldman-Rakic, 1988).

Also described in Posner and Petersen's review of the neural mechanisms of attention (1990) is the debate surrounding automatic versus conscious processing, which is likened to non-executive versus executive attention processing. The ventral visual stream is involved in the search of a complex visual display for single feature (i.e. red square targets in the presence of blue square distractors) and can occur in parallel, with little detriment as the number of distractors increases (Treisman & Gormican, 1988). When a conjunction search occurs (with more than one feature to detect-i.e. red squares in the midst of red triangles and blue squares) search becomes slow, requires attention, and is serial (Duncan & Humphreys, 1989). In the current study, a serial search task is utilized as an additional measure of executive attention and will be described in greater detail below.

There currently exist several models of human mechanisms of attention, with some components that overlap and others that contradict each other (LaBerge & Brown, 1989; Desimone & Duncan, 1995; Steinman & Steinman, 1997). Many of the various attempts to describe attention in the context of a unified model have extended our knowledge of the underlying brain mechanisms and the cognitive components involved in attention. It seems likely that parts of each of these models hold importance for future study with the hope of incorporating the relevant information into a consolidated model. The current study attempted to utilize a visual attention paradigm based on one of the existing models (Posner & Petersen, 1990) within a group of

patients with bipolar depression, in order to further elucidate the nature of attention deficits seen in this population.

Why propose a deficit in executive Attention in Bipolar Depression?

Characterizing the attention deficit in depressed patients has been challenging and has raised the question of whether it is a specific or global deficit. Mialet et al. (1996) demonstrated a non-specific impairment of selective attention on tasks requiring speed, supporting an impoverished, slowed, decreased overall intensity of attention rather than a deficit in the direction or focus of attention. This suggests that the global slowing of information processing found in depressed patients might represent a common "deficit state" found throughout many diagnostic entities, perhaps reflective of a dysfunction of the fronto-subcortical axis (Robbins, Joyce, & Sahakian, 1992).

Consistent with this hypothesis, Hawkins, Hoffman, Quinlan, Rakfelt, Docherty, et al. (1996) compared a group of bipolar patients, schizophrenic patients and normal controls on a variety of neurocognitive tasks. In comparing patient groups, specific differences were seen predominantly in the severity of impairment, placing patients with bipolar disorder significantly superior to patients with schizophrenia on 12 of 12 neuropsychological variables; however, both patient groups' performance was significantly impaired relative to the non-psychiatric controls. Interestingly, after

corrections for multiple comparisons were made, a statistically significant difference was no longer present when comparing the 2 patient groups, while both groups remained impaired relative to the control group. Specifically, processing speed impairment characterized both patient groups, possibly revealing a generalized deficit state that is differentially sensitive to psychometric measures (Hawkins et al., 1996).

More recently, studies directly addressing the neuropsychological functioning in bipolar patients have begun to attempt to define more specifically the type of deficit seen in the domain of attention. Clark and colleagues (2002) compared 30 euthymic bipolar patients with 30 non-psychiatric control subjects on measure of executive function and attention. Several differences were demonstrated on a Continuous Performance Test (CPT), indicating impaired sustained attention and psychomotor speed. Executive deficits were seen on a task of intradimensional-extradimensional shifting and learning deficits were indicated on the California Verbal Learning Test (CVLT). Despite the exclusion of patients with clinically significant symptoms, all differences in performance in bipolar patients were eliminated when analyzed using measures of psychopathology as covariates, with the exception of the sustained attention deficit on the CPT. This finding suggests that some of the executive deficits may reflect subsyndromal clinical symptomology in euthymic bipolar patients; however, attention impairment in this sample was

not related to the severity of depression or mania at the subsyndromal level and may represent a more stable trait (Clark et al., 2002).

In contrast, Liu and colleagues (2002) detected a deficit in sustained attention in patients with bipolar disorder on a CPT measure but only during acute manic and mixed episodes, requiring hospitalization. The authors compared patients with schizophrenia, major depressive disorder with psychotic features, MDD without psychotic features, bipolar disorder with psychotic features, and bipolar disorder without psychotic features on a degraded stimulus CPT. Results indicate comparable performance between schizophrenic inpatients and bipolar inpatients at the time of admission, which was significantly impaired as compared with normal controls. However, bipolar patients' performance improved substantially such that at the time of discharge they were comparable with the normal control subjects, while schizophrenics maintained the deficit in sustained attention from admission to discharge (Liu, Chiu, Chang, Hwang, Hwu, et al., 2002). This implies a trait-related deficit in patients with schizophrenia that appears to be a deficit related to clinical state in bipolar patients. The discrepancy in results likely reflects methodological differences in the studies, including measures used, statistical analyses, and patient characteristics.

Neuroanatomical studies in bipolar disorder suggest structural and functional brain abnormalities that likely contribute to the pathogenesis of the clinical

symptoms involved in mood dysregulation, and are related to cognitive impairment (Ali, Denicoff, Altschuler, Hauser, Li, et al., 2000). Post mortem studies yield evidence primarily from patients with mood disorders who have completed suicide and may represent a somewhat biased sample; however, findings suggest prefrontal changes including decreased cortical and laminar thickness in the dorsolateral prefrontal cortex in both bipolar disorder and major depressive disorder (Rajkowska, 1997). Medial prefrontal cortex and anterior cingulate regions have been shown to have reduced volume in familial mood disorders (Drevets, Ongur, & Price, 1998). Additionally, a layer-specific reduction of interneurons has been detected in the anterior cingulate in patients with bipolar disorder (Vincent, Todtenkopf, & Benes, 1997). Post mortem evidence of reduced volume in the basal ganglia is also relevant to the current study, with the left nucleus accumbens demonstrating the greatest reduction (Baumann, Denos, Krell, et al., 1999).

Ali and colleagues (2000) looked specifically at the relationship of neuropsychological performance to certain neuroanatomic structures in bipolar disorder, associating impairment in sustained attention, verbal working memory, and verbal fluency with enlargement of the right hippocampus. Their study unfortunately did not obtain volumetric measures of the frontal lobes and imaging techniques were not sensitive enough to investigate possible changes in the basal ganglia; therefore, they could not clarify the potential role of all key areas in executive functioning.

In an attempt to correlate neuropsychological performance with specific brain regions, the current study includes the Stroop Task as one of the executive attention variables, based on previous evidence linking Stroop performance with activation of the anterior cingulate. Activation of the anterior cingulate is confirmed by several neuroimaging studies utilizing the Stroop (Bench, Frich, Grasby, Friston, et al., 1993; Carter, Mintun, & Cohen, 1995; George, Ketter, Parekh, Rosinski, Ring, et al., 1994; Pardo, Pardo, Janer, & Raichle, 1990; Taylor, Kornblum, Lauber, Minoshima, &Koeppe, 1997). The d2 Test of Attention (Brickenkamp & Zilmer, 1998) was used as an additional executive attention measure but has not been as well studied as the Stroop. Additional psychometric properties are described in the Methods section of this paper.

Neurochemical abnormalities in patients with mood disorders also shed additional light on the pathogenesis of both mood dysregulation and cognitive impairment. The catecholamine deficiency hypothesis of mood disorders was driven by the observation that norepinephrine uptake-blocking agents serve as effective antidepressants (Schildkraut, 1965). However, since not all depressed patients respond adequately to these medications, it is not plausible to attribute all of the clinical symptoms of depression to the activity of noradrenergic neurons.

Homovanillic acid (HVA) levels are reduced in the cerebrospinal fluid of suicidal and non-suicidal patients with depression, suggesting a direct role for dopamine in the etiology of depression (Brown & Gershon, 1993). However, very few studies have focused on the role of dopamine in mood disorders from and neuroimaging standpoint. Sparse research indicates reduced binding of the D1 receptor in the nucleus accumbens in suicide victims with major depression (Bowden, Theodorou, Cheetham, et al., 1997).

As the basal ganglia are the source of dopamine input to the anterior cingulate, these two structures are closely linked. The basal ganglia is important in switching sets during a cognitive task, with patients who have basal ganglia damage or disease demonstrating difficulty in initiation of behavior and set shifting (Hayes, Davidson, Keele, & Rafal, 1995). Studies of visual attention provide specific hypotheses on how subcortical and cortical structures are coordinated in the act of orienting attention (Posner & Dehaene, 1994), describing the interrelationship of non-executive attention and executive attention.

Does depressive severity correlate with attention impairment?

Depression has been associated with impairment in memory, semantic encoding and attention. In some studies, these deficits have been found to correlate with severity of depression and psychomotor retardation (Sackheim and Steif, 1989; Blackburn et al., 1990; Austin et. al., 1992) while others have

found no relation to severity of depressive symptoms (Lemelin & Baruch, 1998; Degl'Innocenti et al., 1998). The discrepancy is likely due to the use of a wide variety of neuropsychological tests, which vary in sensitivity and measure a range of different cognitive functions. Additionally, patient characteristics play a role in discrepant findings, with studies sampling heterogeneous groups of patients, including diagnostic, age, gender, medications, and severity of pathology differences.

Executive deficits in major depression were studied using tests of verbal fluency, Wisconsin Card Sorting Test, and the Stroop Color Word Test, by Degl'Innocenti & Backman (1998). Findings indicated executive deficits across a range of tasks, with one important result that is in contrast with previous reports. Normal attention performance was seen on the interference trial of the Stroop test, suggesting intact inhibitory processes, but with overall slowed processing speed on the congruent trials. In this study, depressive severity was not correlated with executive cognitive deficits (Degl'Innocenti & Backman, 1998).

Improvement in clinical state can often result in alleviation of cognitive deficits, including attention, concentration, rapid mental processing, and spontaneous verbal elaboration and memory. In general, depressive states, in both unipolar and bipolar disorder, result in impairment in effortful processes (sustained effort, use of controlled processes, increased cognitive

effort) selectively, with relative sparing of the more automatic processes (facilitated recall, recognition and repetition priming) that require less effort and rely on automatic activation of information (Hartlage, et al., 1993). The effortful processes deficit has been attributed to an overall reduction in cognitive resources, an impairment in the allocation of these resources, or a strategy for cognitive economy aiming to reduce effortful processing (Georgieff, Dominey, Michel, Marie-Cardin, & Daley, 1998) and is state-related, implying a direct relationship to severity of illness.

Significantly more research has been conducted on patients with unipolar depression, or without specification of disorder, than has been done in bipolar disorder. Bipolar illness may represent a more complicated disorder, as a number of clinical factors may bear on the cognitive profile of bipolar patients, including diagnostic subtype (i.e., bipolar I vs. II), rapid cycling, chronicity, number of episodes, duration of remissions, and comorbid conditions including substance use disorders. Denicoff, Ali, Mirsky, et al. (1999) found that neuropsychological deficits in bipolar patients were associated with a longer duration and more severe prior course of illness, as reflected by number of episodes of mania and depression and number of hospitalizations. Specifically, increased number of episodes was significantly correlated with impairment in memory and abstraction tasks, while increased number of hospitalizations and longer duration of illness was associated with select deficits in attention and concentration measures (Denicoff et al., 1999). The

current study included both bipolar I and bipolar II subtypes but excluded patients with rapid-cycling and comorbid Axis I pathology, including substance use disorders. Analysis of patient characteristics that may play a role in cognitive deficits in our sample is discussed in the Results and Discussion sections of this paper.

Does psychomotor retardation correlate with attention impairment in depression?

Psychomotor retardation is a defining feature of the depressed phase of bipolar illness. It may be an important symptom in identifying a possible subgroup of depressed patients that may respond more favorably to treatments that focus on reducing these symptoms. The reduction in motor activity in depressed patients has been linked to a disruption in the basal ganglia and frontal lobe connections (Peyser & Folstein, 1990), as it shares many characteristics with disorders that are known to be, at least in part, due to damage to the striate and the depletion of dopamine (i.e. abulia, parkinsonism) (Bhatia & Marsden, 1994; Cummings, 1993; Fischer, 1983). With new, more sensitive scales that have been developed to rate the psychomotor symptoms in depression (Motor Agitation and Retardation Scale-MARS), we are now able to classify a heterogeneous population into more homogenous subgroups (Sobin, Mayer, & Endicott, 1998). Efforts to assess the central processing deficits associated with motor agitation and retardation await further investigation. The current study attempted to this by

evaluating performance on measures of both psychomotor and attentional functioning in patients with bipolar depression and non-psychiatric controls.

Bipolar depression undoubtedly affects the ability to think, concentrate, form ideas and remember. The nature and extent of these difficulties is less clear. Subjective complaints of slowed thinking are common in bipolar depression and are thought, by many, to be central to the depressive state. Nelson and Charney (1981) compared patients with unipolar, bipolar and reactive depression, demonstrating that bipolar patients are more likely to manifest psychomotor retardation (86%), while patients with unipolar depression are more likely to display psychomotor agitation (38%).

The term psychomotor has been applied to almost every observable manifestation of slowing (retardation) or increased activity (agitation) seen in the depressed state (DSM-IV). Several measures of motor activity have been shown to be reliably different in psychiatric versus non-psychiatric control populations, including gross motor movements, speech, and motor reaction time (Nelson & Charney, 1981).

A review by Sobin and Sackheim (1997) provides a detailed account of previous studies attempting to delineate the features of these common symptoms in depression, namely psychomotor retardation. Overall motor activity has been measured in patients with depression, investigating both

retardation and agitation, by utilizing continuous activity monitors over a 24-hour period, which allows for the measurement of diurnal variation of motor activity in an individual (Post, Stoddard, Gillin et al., 1977). Patients with bipolar depression have shown reduced motor activity as compared with non-psychiatric controls, while patients in manic episodes demonstrate increased activity (Wolff, Putnam, & Post, 1985). Furthermore, studies indicate that changes in motor activity precede the more abrupt changes in mood state in patients with bipolar disorder, highlighting the potential clinical utility that monitoring motor activity may have (Post et. al. 1977). Bipolar patients have been shown to have less overall motor activity during depressed phases, as compared to manic or euthymic periods (Wolff et. al. 1985).

Motor speed has frequently been measured in patients with depression, with varying efforts to delineate the cognitive and motor components of reaction time measures. The separation of decision and movement time in reaction time paradigms has allowed for specific analyses of depression-related deficits (Greden, 1993). In patients with high clinical ratings of agitation, motor components of reaction time are found to differentiate patient and normal controls samples (Lapierre & Butter, 1980). In depressed patients with psychomotor retardation, both motor and decision times significantly differ between patient and control samples. A study by Cornell, Suarez, and Berent (1984), suggested that melancholic and non-melancholic depressed patients differed from normal controls with regard to motor slowing, while only

melancholic patients differed on measures of cognitive slowing. A review of psychomotor studies in depression revealed that psychomotor slowing had the highest and the most consistent loadings on the melancholic/endogenous factor (Nelson & Charney, 1981).

Differentiation between psychomotor slowing seen in patients with depression and patients with schizophrenia was investigated in a study by van Hoof, Jogems-Kosterman, Sabbe, Zitman, and Hulstijn (1998), using a computerized version of the Digit Symbol Test (DST). Findings suggest that schizophrenia primarily affects the higher processes such as retrieval of motor programs and initiation, typically correlated with hypofrontality. In contrast, depression not only affects the higher processes mentioned above, but also motoric processes.

Visible slowing can be measured experimentally with a number of different tasks, most commonly through reaction time testing. It is important to note, however, that motor reaction time testing alone, with no cognitive component, often fails to differentiate depressed samples from non-psychiatric controls (Cornell et al., 1984: Gerhard & Hobi, 1984), suggesting the importance of cognitive retardation as a separate entity to generalized motor slowing. The slowed thought processes cannot be measured as readily because they are not clinically visible; however, certain paradigms allow for the separation of motor slowing and cognitive slowing (Cornell et al., 1984).

Caliguiri and Ellwanger (2000) studied aspects of motor slowing in depressed patients in an effort to distinguish between motor and cognitive components of retardation. Motor retardation was found to be an essential feature of major depressive disorder, with many patients demonstrating deficits in the programming of movement velocity as well. Findings of this study suggest that bipolar patients' motor retardation more closely resembles that of parkinsonian bradykinesia than the motor retardation seen in unipolar depression. The authors found that nearly all of the subjects with bipolar depression (80%) demonstrated abnormalities on a velocity scaling measure (designed to measure neuromotor programming deficits), while only 1/3 of the subjects with unipolar depression had such deficits. These results suggest that patients with unipolar depression have both motor and cognitive retardation, while patients with bipolar depression demonstrate a more specific motor programming deficit, similar to the bradykinesia seen in parkinsonism (Caliguiri & Ellwanger, 2000). This implies basal ganglia involvement in the etiology of psychomotor slowing seen in patients with bipolar depression, while areas related to cognitive slowing (i.e. prefrontal regions) may not be directly affected. One major limitation to interpretation of these results is the small sample size, including only 5 patients with bipolar disorder.

The Posner paradigm of covert orienting of attention to visual stimuli (Posner, 1980) measures a robust 'cost' of deprogramming and reprogramming visual attention when stimuli are preceded by an invalid cue, measuring the cognitive processing time necessary to perform the attentional shift. The motor component can be inferred from the overall response times at the different stimulus onset asynchronies (SOAs), which can be differentiated from the cognitive speed. The non-motor (cognitive) component of shifting of preparation is best measured by the difference between the neutral and invalid conditions, also referred to as the 'cost' of invalid cueing (Posner, 1980). In many clinical and normal control samples, an improvement in response time with increased SOAs has been demonstrated (Posner, Early, Reiman, Pardo, & Dhawan, 1988).

Subjects with depression continue to demonstrate an improvement across increased SOAs but overall response time is slower on each SOA, as compared with non-psychiatric control subjects, indicating the common phenomena of motor slowing (Smith et al., 1998). Increased 'costs' in patients with depression, when comparing neutral and invalid conditions, allows for the separate demonstration of slowed mentation, or preparation of motor response (Smith, Brebion, Banquet, & Cohen, 1995). These results were consistent with previous findings (Kupfer, Weiss, & Forest, 1974; Flint, Black, Campbell-Taylor, Gailey, & Levinton, 1993), that patients with depression demonstrate slow and inaccurate performance on psychophysical tests.

Longer response times on all conditions (Valid, Invalid) and on all SOAs, without significant interaction with these factors was seen in the depressed sample, suggestive of overall motor slowing. Additionally, maximum cost in the invalid condition was reached at longer latency for patients with depression than for non-psychiatric control subjects, suggesting that there was a delay in the engagement of the specific hand preparation prior to the response itself, indicating cognitive slowing in addition to motor slowing.

Additionally, Smith and colleagues (1995) found that overall slowing and measured cognitive differences were not correlated with the severity of depressive symptoms. This is consistent with several other studies of this type (Miller, 1975; Johnson & Margo, 1987) and may be at least partially attributed to the fact that the scales used to rate depressive severity incorporate many symptoms of depression, psychomotor retardation being only one of them.

Lemelin and Baruch (1998) attempted to investigate the underlying information-processing dysfunction involved in psychomotor retardation in patients with depression. Their findings suggest that while depression severity is not correlated with attentional dysfunction, clinically rated psychomotor retardation correlated with almost every attention variable. Clinical ratings of psychomotor retardation did not correlate with 2 simple reaction time tasks (which measured motor slowing with no cognitive

component) but did correlate with every reaction time measure with cognitive involvement, regardless of the aspect of attention involved. Lemelin and Baruch (1998) used continuous and categorical analyses to establish whether a linear relationship may exist with psychomotor retardation and attention dysfunction. Their results suggest a link between psychomotor retardation and a global attention difficulty. When dichotomized, patients with depression and psychomotor retardation performed significantly worse on attention measures than did patients with depression but without psychomotor retardation. This study confirmed the hypothesis that the subgroup of patients with psychomotor retardation in depression would experience particularly severe attention deficits, based on the shared role by the frontal lobes in psychomotor disturbance and attention control, whereas patients with depression, without psychomotor slowing, would not.

Functional neuroimaging has shed light on possible changes in brain areas relative to clinical symptoms and cognitive deficits in bipolar disorder. Dolan, Bench, Liddle, et al. (1993) investigated the prominent feature of psychomotor slowing using PET and found decreased activity in the dorsolateral prefrontal cortex in both patients with bipolar disorder and schizophrenia who were experiencing psychomotor deficits. Abnormalities in regional brain metabolism have been found to be present in patients with bipolar disorder, despite clinical improvement. Specifically, hypometabolism and hypoperfusion

are present in the prefrontal cortex, anterior cingulate and basal ganglia (Martinot, Hardy, Feline, et. al., 1990; Bench, Frackowiak, & Dolan, 1995).

Lesion studies offer support to the hypothesis that the basal ganglia and specifically its links with the anterior cingulate area, may be correlated with several of the behavioral symptoms seen in mood disorders (See Review in Bhatia & Marsden, 1994). For example, lesions in the caudate, and/or globus pallidus can cause apathy, loss of initiative, and loss of emotional reactivity. Putamen and globus pallidus damage often results in a dystonic motor deficit. Lesions in the basal ganglia-anterior cingulate circuitry can result in post-stroke mania, implying a fundamental role in mood regulation (Soares & Mann, 1997). Movement disorders associated with damage to the basal ganglia/thalamo-cortical circuit can be differentiated based on lesion location. Specifically, lesions to the caudate are linked with movement disorders, while lesions in the basal ganglia/anterior cingulate circuitry result predominantly in apathy syndrome (Bhatia & Marsden, 1994). Laplane and colleagues (1989), hypothesized that mood disorders may be associated with structural or functional anomalies of the dorsolateral prefrontal/basal ganglia circuit.

Additional evidence from functional MRI studies indicate higher rates of white matter hyperintensities in the circuitry of the basal ganglia/thalamo-cortical loop in affective patients. Lesions have been noted in the basal ganglia in patients with depression, as well as decreased volume of the putamen and

caudate nuclei, when compared with non-psychiatric control subjects (Stoll, 2000). Functional imaging also supports a role for basal ganglia and cingulate structures in affective dysfunction. Specifically, decreased blood flow has been reported in the caudate nucleus, anterior cingulate and the dorsolateral prefrontal cortex (Bench et. al, 1992).

Martinot and colleagues (2001) describe a relationship between dopaminergic dysfunction and psychomotor retardation in patients with depression through the use of MRI and PET. Their study investigated presynaptic dopamine function in depressed patients, with a specific focus on the clinical distinction of patients with and without psychomotor retardation. Results indicate significantly lower levels of dopamine uptake in the left caudate of patients with psychomotor retardation but not in depressed patients without psychomotor retardation. The caudate is a part of a neural loop involving the basal ganglia, anterior cingulate, thalamus, and prefrontal cortex that has been hypothesized to modulate mood (Swerdlow & Koob, 1987) and appears to be a key area involved in psychomotor symptoms in depression.

Reduced levels of homovanillic acid in the CSF of patients with depression has been a consistent finding, with this reduction most pronounced in depressed patients with psychomotor retardation (van Praag & Korf, 1971). This supports the hypothesis that central dopamine function might be impaired in patients with depression and psychomotor retardation.

Significance of Current Study

Recent studies (Smith et al., 1995; Lemelin & Baruch, 1998) indicate that specific symptomology (i.e. psychomotor retardation) may predict the likelihood of cognitive disturbance in a subgroup of depressed subjects better than the extent or severity of depression itself. The current study aimed to better identify attentional dysfunction in a group of bipolar patients with depression by using an attention paradigm, for which the involved anatomy is fairly well-known that allowed for the separate measurement of executive and non-executive attention functioning. A systematic investigation of psychomotor symptoms was also performed, in an attempt to identify a possible subgroup of patients exhibiting deficits in these areas. Results from the current study may carry treatment implications and add to existing evidence of a possible shared neurophysiological basis for psychomotor and cognitive impairment in depression. Severity of depression was also measured to determine its effect on attention and psychomotor disturbance.

Primary hypotheses:

A) Bipolar (BP) depressed patients demonstrate significantly greater attention deficits, selectively in the executive attention domain, as compared with a normal control (NC) group.

B) Executive attention deficits seen in the BP group are not related to severity of depressive symptoms.

C) The degree of psychomotor slowing in the BP group is positively correlated with executive attention deficits.

These hypotheses were tested by administering a detailed neuropsychological battery of attention tasks and motor tests to a group of subjects with bipolar disorder meeting DSM-IV criteria for a current major depressive episode, of moderate to severe intensity. An equal number of sex and age-matched non-psychiatric control subjects were also tested. The final sample included a greater number of non-psychiatric control subjects than patients, due to the exclusion of three patients (described in detail later).

Secondary Hypotheses

Age and gender effects on attentional performance were described in secondary analyses. Additional analyses were also conducted on the cued target detection (CTD) paradigm looking specifically at the nature of a phenomenon known as inhibition of return, which is described in more detail later in this paper. The current study focused on this in the secondary analysis section, although no a priori hypotheses were made.

METHODS

Subjects

Twenty-three patients meeting DSM-IV criteria for Bipolar I (65%) or Bipolar II (35%) disorder, in the depressed phase of the illness (14 men and 9 women), derived from the Bipolar Disorders Research Center at the New York Presbyterian Hospital-Weill Medical College of Cornell University and twenty-seven age-matched normal controls (10 men and 17 women) participated in this study. Participants were between the ages of 18 and 55 and were assessed to have capacity to sign informed consent. Written informed consent was obtained prior to any study procedures being performed. Approval from the Institutional Review Board (IRB) was granted from the NY Presbyterian Hospital-Weill Medical College of Cornell University as well as from the Queens College IRB prior to the conduction of the study.

All patients had a minimum score greater than or equal to 18 on the first 17 items of the 31-item Hamilton Depression Scale (Hamilton, 1960), indicating moderate to severe depression. Patients were excluded if there was a presence of substance abuse within one month or substance dependence within six months prior to participation in the study (DSM-IV definition), if they were pregnant, lactating or planning to become pregnant (due to the potential need to change or withdraw mood stabilizing medications during pregnancy and lactation), or if they were medically unstable (i.e. presence of a life-

threatening medical illness or were required to take medications on a daily basis to treat a medical problem). Patients currently taking an antipsychotic medication were excluded from participation, due to the high probability of motor effects of such medications. In addition, if patients had been exposed to antipsychotic medications within two weeks prior to starting the study, a physician-rated assessment of movement disorder was performed and patients with any signs of lasting motor effects from exposure to neuroleptics were excluded from the study. The presence of any comorbid primary Axis I diagnosis also excluded patients from participating (as assessed by the Structured Clinical Interview for the DSM-IV, SCID-I) (First, Spitzer, Gibbon et al., 1997). Patients with a history of rapid-cycling were also excluded. A series of prescreening questions were asked prior to scheduling the full screening process to limit the number excluded after the full interview was conducted. Approximately ten subjects failed to meet criteria for normal control status during the prescreening portion, predominantly due to a history of either neurological injury (TBI of any type including past concussion was ruled out) or previous psychiatric treatment. Of the subjects brought in for screening purposes, only one was excluded due to current psychopathology that was not evident during the prescreening phone session.

Patients were recruited through the Bipolar Disorders Research Center of the New York Presbyterian Hospital-Weill Medical College of Cornell University. They had a mean age of 39.39 years, (SD= 9.3), and an average of 15.8

years of education, (SD=2.2). All patients were assessed using the Structured Clinical Interview of the DSM-IV (SCID-IV) to confirm a diagnosis of Bipolar I or Bipolar II, with moderate to severe depression. Clinical characteristics of the patient sample suggested that the majority of patients had a more severe course of illness than expected in a typical bipolar sample. Only 2 of 23 patients had a typical duration of the current depressive episode, while the remainder had been depressed for long periods of time, with an average duration of 8 months (SD= 2.6), prior to enrolling in the current study. The average age of onset was, however, typical for bipolar I patients, with an average age of onset of 21.4 years (SD=8.2) in the current sample. In contrast, the current sample differed from the typical bipolar sample with regard to substance abuse history. In our patient group, only 3 of 23 patients met criteria for a history of substance abuse or dependence by DSM-IV criteria. This is inconsistent with recent estimates of greater than 50% of all patients with bipolar disorder having a substance use disorder at some time in their lifetimes. This is likely due to the exclusion of patients with current substance use disorders, as well as the age restrictions for entry.

All patients were on one of three mood stabilizer medications (lithium, valproate, or carbamazepine) at a therapeutic dose, confirmed by blood levels. Unfortunately, this sample was highly heterogeneous with regard to their treatment histories, with the majority of patient's having been on multiple medications in the past, often in combination therapy. Their status as a

predominantly treatment-resistant group did not allow for further analyses of past treatment, as the sample was too diverse. Approximately 7 of 23 patients were started on a mood stabilizer with specific intent to enroll in a related treatment study and had only been on the mood stabilizing medication for approximately one month prior to testing. Dosing and blood levels had been stable for at least two weeks prior to testing. It is important to note that while the current sample is typical of a clinical sample of patients with bipolar disorder, the possible influence of medication on both depressive severity and cognition was taken into account in interpreting the results.

The effects of the allowable medications on neurochemical functioning are complicated and diffuse; however, a very brief description of the mechanism of action is provided here for clarification purposes.

Lithium is a monovalent cation and belongs to the group of alkali metals together with sodium, potassium and other elements with which it shares some of its properties. The mechanism whereby lithium controls manic episodes and possibly influences affective disorders is not yet known. It does not possess general sedative properties. There is evidence, however, that lithium alters sodium transport and may interfere with ion exchange mechanisms and nerve conduction. Lithium enhances the uptake of norepinephrine and serotonin into the synaptosomes, thus reducing their

action. It reduces release of norepinephrine from synaptic vesicles and inhibits production of cyclic AMP (Bezchlibnyk-Butler & Jeffries,1998).

Valproate's mechanism of action is also unknown but it probably works by affecting the metabolism of GABA. It may cause competitive inhibition of GABA-transaminase leading to increased brain levels of GABA. There is evidence that it acts at multiple levels of GABA synthesis, degradation, and effect (Bezchlibnyk-Butler & Jeffries,1998).

Similarly, carbamazepine's precise mechanism of action unknown. It depresses synaptic transmission in spinal trigeminal nucleus and transmission from the VA nucleus of the thalamus. It is known to block sustained repetitive firing in a frequency dependent manner. As with similar anticonvulsant agents, this is due to blockade of voltage-sensitive sodium channels and is believed to be largely responsible for its action (Bezchlibnyk-Butler & Jeffries,1998).

Cognitive side effects seen with the use of these medications were extensively reviewed by Goldberg and Burdick (2001). In summary, although results are somewhat equivocal, recent studies imply very mild cognitive impairment including a lack of practice effects seen on repeat testing, suggestive of a mild learning decline. Psychomotor slowing has been one of the more consistent findings in patients taking lithium; however, dosage was

often overlooked, with very minimal effects seen within the therapeutic range. Furthermore, mild attention deficits were seen with the administration of these three medications but predominantly in patients taking these medications in combination with other agents. For more extensive review, see Goldberg and Burdick (2001).

The current study included only patients taking one of these three medications, with no concomitant medications allowed. The potential for side effects was also lessened by requiring a stable, therapeutic level of medication prior to testing. Dosage remained stable at least two weeks prior to study participation. Regardless of the attempts to limit the impact of medication on performance, it was deemed unethical to discontinue medication for participation; therefore, the potential influence of medication was considered in the interpretation of the findings.

Normal control subjects were recruited from local advertisements and postings. They had a mean age of 34.85 years, (SD= 9.8) and an average of 16.6 years of education, (SD=2.4). All control subjects were originally recruited by matching for sex and age (within 5 years) individually to the patient sample. Due to limiting the original patient sample to include only patients that completed all key assessments and omitting three normal controls because of significant outliers and undetected pathology, it was not possible to match one-to-one; therefore, statistical analyses were conducted

to verify that the samples did not significantly differ on demographic variables. Results of preliminary analyses revealed no significant differences between groups on any of the demographic variables.

Normal controls underwent a SCID-IV interview to verify that there were no current or past psychiatric diagnoses. A list of all current non-psychotropic medications was obtained and any person taking medication on a daily basis for the treatment of a medical condition was excluded from the sample of normal controls, due to the unknown potential impact of such medications on cognition. In addition, a Hamilton Depression Rating Scale (HamD, 31 item) was completed for each control subject to rule out any current subsyndromal depressive symptoms, such as appetite or sleep disturbances. The 31-item HamD assesses both typical (i.e. loss of appetite, insomnia) and atypical (i.e. increased appetite, hypersomnia) symptoms of depression, while shorter versions of the same scale (HamD 17 item, and HamD 24 item) assess only typical symptoms. The cutoff for inclusion was set at HamD<8.

Measures

Table 1: Measures and Variables Used

Diagnostic/ Symptom Severity
Structured Clinical Interview (SCID-IV)
Hamilton Depression Rating Scale (HamD)
Young Mania Rating Scale (YMRS)
Positive and Negative Symptoms Scale (PANSS)
Psychomotor Functioning
Finger Tapping Test (FTT)
Grooved Pegboard (GPB)
Simple Reaction Time (SRT)
Decision time (SRDT)
Movement time (SRMT)
Total time (SRTT)
Choice Reaction Time (CRT)
Decision time (CRDT)
Movement time (CRMT)
Total time (CRTT)
Motor Agitation Retardation Scale (MARS)
Non-Executive Attention
Cued Target Detection (CTD)
Cost 100msec
Cost 400msec
Cost 800msec
Benefit 100msec
Benefit 400msec
Benefit 800msec
Executive Attention
Stroop Interference
d2 Accuracy
d2 Concentration

Psychopathological Assessment

Severity of depression was measured by the 31-item Hamilton Depression Rating Scale (HamD) (Hamilton, 1960). Total scores were derived from a sum over 31 clinician-rated items. In an attempt to reduce the impact that

psychomotor symptoms has on total Hamilton scores, a variable labeled Ham-mood was derived by subtracting out 6 items that involve direct evaluation of cognitive and motor slowing. Mania symptoms were measured by the Young Mania Rating Scale (YMRS) (Young, Biggs, Meyer, 1978) and were measured as a total score on eleven clinical items indicating severity of mania. Psychosis was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay, Opler, Lindenmayer, 1989), again utilizing a total score across items measuring severity of psychotic processes. Both the YMRS and the PANSS were used only as screening measures to rule out current psychosis and current mania in the study population.

A trained rater, meeting inter-rater reliability standards for several unrelated pharmaceutically sponsored clinical trials completed all ratings (HamD, YMRS, PANSS).

Motor Assessment

The Motor and Agitation Rating Scale (MARS) (Sobin, Mayer, & Endicott, 1998) was used to assess psychomotor symptoms of agitation and retardation. The MARS is a 19 -item clinical scale that is clinician rated as the patient is seated describing the course of his/her medication and treatment. The scale is intended to measure agitation and retardation as separate, continuous variables. Scores were calculated by separating retardation items

from agitation items and summing each subscale to provide a total retardation score and a total agitation score.

Clinical ratings were conducted by a trained, clinician, meeting inter-rater reliability with the creator of the scale. Ratings of items include 5 individual areas of focus including: 1. Body, 2. Hands, Legs, and Feet, 3. Face, 4. Eyes, and 5. Voice. Each area of evaluation is subdivided into several specific typical manifestations of psychomotor functioning.

Reaction Time testing

Motor speed was assessed using a simple reaction test (SRT), where each patient was administered five practice trials followed by fifteen test trials. Each trial consisted of the patient responding with his/her dominant hand to a red light presented in the center of the visual field.

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Choice reaction time testing (CRT) was obtained by the same method with the addition of green and blue lights that were presented as non-target stimuli, while the patient was instructed to respond to the red light only.

The current study utilized the "fixed foreperiod" paradigm for both SRT and CRT. In this method, each trial began with the subject pressing down a "home" key in order to initiate each trial, using his/her dominant hand. A timer started as the target was presented and stopped when the subject lifted

his/her hand from the "home" key. When the first timer stopped (set to measure decision time, variables labeled SRDT and CRDT), a second timer started and stopped when the subject hit the response key (set to measure movement time, variables labeled SRMT and CRMT). The sum of these 2 measures was recorded as total reaction time (Variables labeled SRTT and CRTT). This paradigm allowed for the separation of the cognitive processing (or motor programming) time, utilizing the time it took for the subject to lift his/her hand off of the lever, and the actual motor response time, looking at the time it took for the subject to move his/her hand to the response key.

Speed of finger oscillation

The Finger-Tapping Test (FTT) (Reitan, 1969) was used to assess motor speed and differences in laterality on motor tasks. Using a specially adapted tapper, subjects were instructed to tap as quickly as possible using the index finger, without moving the arm or hand. Subjects must place their hand palm down with fingers extended and the index finger on the tapping key.

A practice trial was given, on each hand, to familiarize the subject with the "feel" for the test. Each subject was administered ten trials (5 on each hand) of 10 seconds each, with mean number of taps per 10 seconds as the variable of interest. Due to the potential for fatigue, a brief resting period was given after each trial, with a longer (1-2 minute) resting period between the third and fourth trials.

Administration time for the task was approximately ten minutes.

FTT performance is quite stable over time, with reliability coefficients ranging from .58 to .93 in both normal control and neurological samples (Dodrill & Troupin, 1979; Gill, Reddon, Stefanyk, & Hans, 1986; Goldstein and Watson, 1989; Ruff and Parker, 1993). FTT measures are frequently utilized clinically to detect subtle motor impairment and are sensitive to the laterality of brain lesion (Barnes and Lucas, 1974; Bigler and Tucker, 1981; Hom and Reitan, 1982; Reitan and Wolfson, 1996). Extensive normative data has been collected on this measure (Bornstein, 1985).

Finger and Hand Dexterity

Patients were asked to place key-like pegs into a board (Grooved Pegboard) (Psychological Assessment Resources, 2002) as quickly as they could, starting at the top left-hand corner of the board, using their dominant hand. Subjects were instructed to pick up one peg at a time and to complete the board in succession, without skipping over any of the holes. Total time to complete the board was used as variable of interest, measuring fine motor speed and dexterity on the dominant hand only. Typically, performance on each hand is measured for purposes of lesion localization (laterality sensitive); however, the purpose of the current use was merely to measure fine motor speed and therefore, performance on the dominant hand was

sufficient. Extensive normative data are available for this measure, as well (Bornstein, 1985).

Attention Assessment

Non-executive attention: Cued Target Detection

A computerized task (PRECUE) was administered that produces an orienting and alerting index of attention (Psych/Lab, 1999). This measure, a version of the "Posner" precuing paradigm known as the Cued Target Detection (CTD), is a target detection task in which patients were asked to detect the presence of an "x" inside of one of two boxes while keeping his/her eyes fixated on a central "+". Just prior to the target appearing in the box, the patient was instructed to watch for a cue, indicating that the target is likely (80%) to appear in that box, and therefore prepare to answer toward that side of the display. Response was made by pressing a key on the side of the keyboard corresponding with the side of the screen on which the target appeared (i.e. if the target appeared on the left side the subject responded using his/her left hand hitting the "z" key as quickly as possible and if it appeared on the right the subjects responded using his/her right hand and hitting the "/" key on the keyboard).

Cues were of varying types, including valid (target appeared in the same location as the preceding cue), invalid (target appeared opposite the preceding cue), and neutral (cues appeared on both sides, giving no prior

information regarding target location). The subject was explicitly told that there is an 80% chance that a cue would be valid. The total number of blocks per trial was 50, using 5 blocks per testing session. The inter-trial interval was set at 500 msec, with an interval between display onset and cue was 1000 msec. The order of conditions within a block, and the locations of the stimuli were determined randomly. Only correct trials were analyzed and the maximum allowed reaction time was set at 3000 msec.

This task continued with various stimulus onset asynchronies (SOAs) of 100, 400, and 800ms. The entire task lasted for approximately 8-10 minutes. SOAs were defined as the time between the onset of the cue and the onset of the target.

Variables that were derived included 'Costs', as measured by mean reaction time on neutral cue conditions minus the mean reaction time on invalid cue conditions and 'Benefits', measured by neutral cues minus valid cues. Additionally, differential performance across SOA and cue type (Valid, Invalid, Neutral) was measured.

There are several version of the CTD paradigm. This particular two-key version (with a single cue) allows for the simultaneous investigation of the motor component of global response time, as well as the non-motor phenomena (e.g. the preparation of the specific hand, and the

disengagement, shifting of attention, and reprogramming of the responding hand in the invalid cue condition) (Posner, 1986). The purely motor component is best assessed by the overall response time at the different SOAs, while the non-motor component is evaluated by looking at the difference between the neutral and the invalid cue conditions (defined above as the Cost of reprogramming motor response) (Smith et al., 1995).

Executive Attention Variables: Stroop and d2 Test of Attention

Stroop Color Word Test

The Stroop Color-Word Test (SCWT) (Stroop, 1935) is a commonly used task measuring selective attention and inhibitory control. This test is designed to measure the ease with which a person can shift his/her perceptual set to conform to changing demands and suppress habitual response in favor of a more effortful one (Spreen & Strauss, 1998).

The standardized version used in the current study was first described by Golden (1978). The SCWT has three conditions: 1) Word Series-100 stimuli consisting of color names printed in black. Subjects are instructed to read the printed words as quickly as possible and to continue until told to stop. 2) Color series-100 stimuli of five colored Xs and the subject had to name the color (red, blue, and green) of the Xs, again instructed to name as quickly as possible and to continue until told to stop. 3) Color-word series-100 stimuli consisting of color words printed in incongruent colored ink. For example, the

word "green" will be printed in red ink. The subject is instructed to ignore the word that is printed but say the color of the ink that the word is printed in. Subjects read each series aloud as quickly as they can for a total of 45 seconds. An interference score is calculated by subtracting the predicted Color-Word (CW) score from the actual CW score. The following formula is used to calculate predicted CW scores: SCRxSWR/SCR+SWR. The interference score is reflective of "pure" interference corrected for speed factors.

The Stroop Test yields four basic scores. The Word (SWR) score is the number of items completed on the first page, within the 45-second interval. The Color (SCR) score is the number of items completed on the second page. The Color-Word (CW) score is the number of words completed on the third page. Errors are tracked and subtracted from the total number of items processed. Interference scores are calculated using the above mentioned formula and are designed to control for speed, while providing an index of inhibitory control. (Golden, 1976)

Scores are corrected for age in subjects above the age of 45. Scores are frequently translated to T-scores for consistency in interpreting; however, variables used in the current study were raw scores after correction for age. Interference scores were transformed by adding a constant in order to quantify scores using positive numbers only. In the current study, a constant

of 18 was chosen because the minimum interference score in the sample was −18.

The reliability of the Stroop is highly consistent across different versions of the test. Test-retest reliabilities have been studied over intervals from one minute to 10 days. Golden (1976) reported reliabilities of .86, .82, and .73 (N=30) for the individual version.

d2 Test of Attention

The d2 Test of Attention (Brickenkamp, 1981) is a paper-pencil test intended to measure selective attention and mental concentration. This task is a basic cancellation task where patients must cross out targets that include a "d" and two dashes, in any distribution (dashes can be two above, two below or one above and one below the d). The patient continues for 20 seconds on each of 14 lines of text and is told when 20 seconds is up to continue on the next line until the task is completed (Brickenkamp & Zilmer, 1998).

Data suggest high internal reliability for the d2 test among U.S. samples, using both the split-half method and Cronbach's alpha. In almost all studies the scores of the d2 test are very highly reliable (>.90), independent of the statistics used or the sample (Brickenkamp & Zilmer, 1998). The d2 yields six scores (Brickenkamp & Zilmer, 1998). TN is the total number of items processed, both relevant and irrelevant. TN is a highly reliable and normally

distributed measure of attention allocation, processing speed, amount of work completed, and motivation. Total number of errors, E is equal to E1+E2, where E1 is errors of omission and E2 is errors of commission. E1 is relatively sensitive to attention control, rule compliance, accuracy of visual scanning and quality of performance. E2 is sensitive to inhibitory control, rule compliance, accuracy of visual scanning, carefulness and cognitive flexibility. E% is the percentage of errors and it measures the qualitative aspect of performance. TN-E is the total number of items scanned minus the error scores. TN-E is normally distributed, highly reliable (test-retest reliabilities range from .89 to .92) (Spreen & Strauss, 1997) and provides a measure of attention and inhibitory control, related to the speed and accuracy of performance. CPR, Concentration Performance, is derived from the number of correctly cancelled relevant items (hits) minus the errors of commission. CPR provides a reliable index of coordination of speed and accuracy of performance. FR is the fluctuation rate and is measured by the difference between the line with the maximum number of items cancelled and the line with the minimum number of items cancelled. FR assesses the stability of performance and high FR may suggest poor motivation.

Variables utilized as measures of executive attention for the current study included TN-E and CPR. TN-E will be referred to as "Accuracy" and CPR will be referred to as "Concentration" for purposes of clarity in the text to follow. These two variables are designed to measure slightly different constructs

within the domain of selective attention but have been shown to be highly correlated to one another (r= .89), suggesting some level of redundancy, which will be taken into account in interpretation of the findings.

Both Accuracy and Concentration scores were utilized because they are measuring slightly different cognitive functions, although they tend to be highly correlated with one another (Brickenkamp & Zillmer, 1998). Accuracy and Concentration scores have been compared with measures of executive function with significant correlations, suggesting a common neuropsychological construct. The test manual reviews the correlational studies conducted, with highest relationships seen on tasks such as those seen below in Table 2. All correlations presented were significant at the p< .01 level (Brickenkamp & Zillmer, 1998).

Table 2: d2 Variables Correlations to Executive Measures

Accuracy / Executive Measures	*r*
Trails B	-.29
Symbol Digit Modalities	.47
Stroop Interference	.34
Tower of London	.44
Concentration/Executive Measures	
Trails B	-.36
Symbol Digit Modalities	.47
Stroop Interference	.34

Furthermore, d2 Accuracy measures have been used successfully to distinguish depressed patients from other clinical samples (Regal, Krause, Ruhmling, 1987; Rauchfleisch, 1983).

Procedures

Prior to neuropsychological testing, each participant underwent a structured clinical interview (SCID-IV) to confirm diagnosis of bipolar disorder. Control subjects also underwent diagnostic screening to rule out any Axis I pathology. Mood rating scales were conducted by a trained research assistant prior to cognitive testing, including the Young Mania Rating Scale (YMRS), Positive and Negative Symptoms Scale (PANSS), and the Hamilton Rating

Depression Scale (HamD). PANSS and YMRS scores were only used to rule out psychosis and mania in bipolar patients. Any scores indicating the presence of such symptoms resulted in patient exclusion. Clinical assessment typically took approximately one to two hours to complete, generally shorter in duration for healthy control subjects.

All subjects underwent approximately 1 1/2 hours of neuropsychological testing. Patient subjects were usually enrolled into a separate but related treatment study at the Bipolar Disorders Research Center after completion of cognitive testing, receiving at least 8 weeks of free treatment in exchange for participation. Patients did not necessarily have to participate in the current study in order to enroll in the treatment study. Control subjects were paid $30 for their participation in the study.

Data Analysis

Statistical analyses were carried out using Statview software (Abacus Concepts, 1996). The following hypothesis testing was conducted:

A) Bipolar (BP) depressed patients demonstrate significantly greater attention deficits, on measures of executive attention, as compared with a normal control (NC) group.

The variables utilized to define "executive attention" were the variables Accuracy and Concentration from the d2 Test of Attention, and the Stroop Interference score, therefore Hypothesis 1 will be supported if:

1. BP Accuracy< NC Accuracy
2. BP Concentration<NC Concentration
3. BP Stroop Interference< NC Stroop Interference
4. BP "Cost" from CTD (SOAs100, 400, and 800msec) = NC "Cost" from CTD (SOAs100, 400 and 800msec)
5. BP "Benefits" from CTD (SOAs100, 400, and 800msec) = NC "Benefits" from CTD (SOAs100, 400, and 800msec)

Multiple independent t-tests comparing groups were conducted in analyzing the above variables when all parametric assumptions were met. Log transformations were applied, when necessary, and if parametric testing continued to be inappropriate Mann Whitney tests were run. In order to control for elevated alpha-levels due to multiple comparisons, a more stringent significance level was set at $p \leq .01$.

B) Executive attention deficits seen in the BP group are not related to severity of depressive symptoms.

Executive attention variables included: d2 Accuracy, d2 Concentration, and Stroop Interference scores therefore, hypothesis testing included:

Pearson's correlation matrix using the above named variables and the total mood score from the Hamilton Depression Rating Scale (Ham-Mood). Significance was set at $p \leq .01$ to control for elevated alpha levels resulting from multiple comparisons.

C) The degree of psychomotor slowing in the BP group is positively correlated with executive attention deficits.

Variables of interest measuring psychomotor slowing included: Clinician rated MARS Retardation Total (MRET), Finger Tapping Mean (FTT), Grooved Pegboard Mean (GPB), and all three variables from both Simple and Choice Reaction Time measures (SRDT, SRMT, SRTT, CRDT, CRMT and CRTT). All of the above variables were utilized as "psychomotor" measures including both aspects (cognitive and motor) of psychomotor functioning. The division between motor and cognitive aspects of these measures is discussed further in the Discussion section of this document.

The executive attention variables were d2 Accuracy, d2 Concentration, and Stroop Interference scores. Hypothesis testing included:

Pearson's Correlation matrix with above named variables. Significance level was set at $p \leq .01$ to control for multiple comparisons.

RESULTS

One bipolar patient was dropped prior to analyses due to extreme variability in response and significant outliers on nearly all reaction time measures, rendering unequal variances between groups on nearly all measures of interest. The removal of this 48 year old, female patient allowed for homogeneity of variance (HVF) on several measures of interest. Those measures that continued to fail to meet the HVF assumption were analyzed with nonparametric tests. Additionally, three normal control subjects were dropped prior to analyses. One subject was dropped because post-test abnormal social behaviors (i.e. repeated paranoid phone messages to the experimenter) suggested that she did not meet the criteria for a non-psychiatric control. Two additional normal control subjects were removed due to neuropsychological performance that fell significantly outside the range of normative scores on motor measures, suggestive of neurological impairment.

Table 3 presents demographic data separately for the bipolar and control groups. Chi Square analyses indicated that the groups did not differ significantly in gender distribution (Chi Square= 2.826, p= 0.0927), or handedness (Chi Square=2.719, p= .0992). Unpaired t-tests were run and no significant differences were found between groups on age (t=-1.6, df=48, p=.1014), or education (t= 1.3, df=48, p= .1990); however, due to the trend

toward significance of age difference between groups, age and gender effects were explored in secondary analyses.

Table 3: Demographic characteristics of the sample

	Normal Control (N=27)	Bipolar Depressed (N=23)
	Mean (SD)	**Mean (SD)**
Age	34.85 (9.75)	39.39 (9.32)
Education	16.63 (2.40)	15.78 (2.15)
	Percent (%)	**Percent (%)**
Female	62.9	39.1
Right-Handed	88.9	100.0

Prior to hypothesis testing, means and standard deviations were examined on all variables of interest. Table 4 is included below for descriptive purposes.

Table 4: Descriptive statistics of variables of interest

	Measure	Mean	SD	Minimum	Maximum
NC	**FTT**	53.8	8.3	38.0	67.8
BP	**FTT**	52.5	10.5	28.8	71.3
NC	**GPB**	63.3	6.0	55.0	76.0
BP	**GPB**	69.4	11.2	50.6	100.0
NC	**d2 Accur**	509.1	80.6	351.0	642.0

Table 4: Descriptive statistics of variables of interest-continued

BP	**d2 Accur**	441.0	98.4	257.0	584.0
NC	**d2 Conc**	210.9	42.8	137.0	291.0
BP	**d2 Conc**	174.8	45.8	98.0	241.0
NC	**Stroop I**	23.1	9.1	3.0	42.0
BP	**Stroop I**	20.0	6.4	4.0	36.0
NC	**SRDT**	280.5	61.4	197.0	450.9
BP	**SRDT**	314.1	57.0	239.2	426.8
NC	**SRMT**	226.0	62.6	110.0	376.6
BP	**SRMT**	237.6	74.5	46.2	367.8
NC	**SRTT**	439.7	108.1	263.5	691.1
BP	**SRTT**	509.1	124.0	322.2	738.2
NC	**CRDT**	374.2	58.1	256.7	475.1
BP	**CRDT**	476.0	109.3	324.5	690.1
NC	**CRMT**	228.5	73.3	102.5	434.1
BP	**CRMT**	264.6	92.8	26.9	431.2
NC	**CRTT**	531.0	108.1	368.7	804.2
BP	**CRTT**	689.8	179.1	440.7	1121.3
NC	**Ham 31**	3.0	2.6	0.0	8.0
BP	**Ham 31**	33.3	6.9	24.0	52.0
NC	**Mars-Ret**	10.9	1.0	10.0	14.0
BP	**Mars-Ret**	14.4	3.5	10.0	22.0

Hypothesis Testing

Hypothesis 1 posited that patients with bipolar depression (BP) would perform more poorly on measures of executive attention as compared with normal controls (NC).

Independent t-tests were run to detect group differences in performance on executive attention measures that met all assumptions of parametric analyses. These included the Stroop Interference and the d2 Accuracy scores. The d2 Concentration variable was transformed to meet assumptions of t-tests, using log transformation, and then compared using an independent t-test. Differences were considered significant at the $p \leq .01$ level to control for the elevated alpha level resulting from multiple comparisons. The results are presented in Table 6.

Preliminary to analyzing the CTD measure, mean reaction times and standard deviations were examined. Table 5 is included for descriptive purposes only, to demonstrate the reaction times seen in each group at the varying SOAs and as a function of cue validity. Groups differed at or near significance at every SOA and on all cue conditions, suggesting slower motor reaction time in patients with bipolar depression. Additionally, in testing for homogeneity of variance (HVF), it was determined that the bipolar group was significantly more variable in their performance on three of the trials presented (Neutral 800msec, Invalid 100msec, and Invalid 400msec). Log transformations were

unsuccessful in equalizing the variance to meet assumptions for t-tests; therefore, for those CTD measures comparing groups, Mann Whitney tests were used. The results are presented in Table 6.

Table 5: Mean reaction times on CTD measure in groups

SOA-Cue type	***NC (N=27)***	***BP (N=23)***	***t*-value**	***p*-value**
	Mean (SD)	**Mean (SD)**		
100 msec-Valid	*399.5 (62.0)*	*440.6 (69.3)*	*-2.16*	*.0361*
400 msec-Valid	*386.1 (53.3)*	*429.2 (63.9)*	*-2.55*	*.0143*
800 msec-Valid	*391.9 (68.9)*	*437.7 (84.9)*	*-2.06*	*.0449*
100 msec-Neutral	*434.8 (58.4)*	*486.3 (78.1)*	*-2.62*	*.0120*
400 msec-Neutral	*406.5 (54.4)*	*462.8 (63.4)*	*-3.31*	*.0018*
800 msec-Invalid	*380.7 (60.8)*	*454.6 (88.2)*	*-3.44*	*.0013*
	Mean rank	***Mean rank***	***Mann Whitney z-value***	***p*-value**
800 msec-Neutral	*20.41*	*29.76*	*-2.30*	*.0216*
100 msec-Invalid	*20.85*	*29.19*	*-2.05*	*.0406*
400 msec-Invalid	*20.26*	*29.95*	*-2.38*	*.0173*

Comparisons between groups on the non-executive measures of Cost and Benefit from the CTD at varying SOAs were done utilizing Mann Whitney U Tests, due to the failure of homogeneity of variance on both raw and log transformed variables. It was noted that this statistical procedure is far less

sensitive than utilizing parametric statistics and is considered in the Discussion section of this paper. These results are also presented in Table 6.

Table 6: Mean Differences on Attention Variables (BP vs. NC)

Variable	Normal Control (N=27)	Bipolar Patients (N=23)	*t*-value	*p*-value
EXECUTIVE	***Mean (SD)***	***Mean (SD)***		
Stroop-Interference	*23.12 (9.14)*	*20.00 (6.41)*	*1.36*	*.1791*
d2-Accuracy	*509.07 (80.59)*	*441.04 (98.42)*	*2.69*	*.0099**
D2-Concentration Log Transformed	*2.319 (.091)*	*2.227 (.121)*	*2.93*	*.0052**
NON-EXECUTIVE	***Mean rank***	***Mean rank***	***Mann-Whitney z-value***	***p-value***
Cost 100 msec	*24.70*	*24.24*	*-.114*	*.9090*
Cost 400 msec	*23.70*	*25.52*	*-.447*	*.6550*
Cost 800 msec	*23.30*	*26.05*	*-.675*	*.4994*
Benefit 100 msec	*22.41*	*27.19*	*-1.17*	*.2403*
Benefit 400 msec	*23.30*	*26.05*	*-.68*	*.4994*
Benefit 800 msec	*23.30*	*26.05*	*-.68*	*.4994*

*$p \leq .01$

Executive Attention measures:

Among the 3 executive attention measures, d2 Accuracy and d2 Concentration were found to significantly distinguish between the two groups such that the bipolar group was significantly less accurate in their performance and had worse concentration. No significant group differences were found for Stroop Interference scores.

Non-executive Attention measures:

Measures from the Cued Target Detection task (CTD) that were analyzed consisted of calculated variables of Cost and Benefit.

Analyses were conducted on the calculated Costs (for orienting attention towards the falsely indicated location) for each subject. The mean Cost was determined by subtracting the mean reaction time of invalid trials from neutral trials.

Measures of Cost (see Table 6) did not result in significant differences between groups. This suggests that bipolar patients do not incur greater costs (as seen in increased reaction time to target) than normal controls, when their attention is directed to an incorrect location, resulting in the necessity to shift attention to an uncued location. Costs were comparable at all SOAs, indicating an equivalent level of cortical arousal in bipolar subjects as compared to normal controls.

The Benefit measure was determined by subtracting the mean reaction time of the valid trials from the neutral trials. There were no significant differences found comparing normal controls and bipolar patients on Benefits of valid cueing. This suggests that bipolar patients gained comparable advantage of detection, when correct cues are given prior to target presentation. This comparable benefit was seen in both groups, across all SOAs. (See Table 6).

Hypothesis 1 was partially supported with significant differences found on two of the three executive attention measures (Accuracy and Concentration variables from the d2 Cancellation Task) and no significant differences were found on any of the measures of non-executive attention. (See Table 6.)

Hypothesis 2 posited that executive attention deficits in the BP group would not be correlated with severity of depressive symptoms.

Pearson's correlational analyses were conducted to determine the relationship of severity of depression, using Ham-Mood (HAMD Total minus the specific psychomotor items from the Hamilton), to the variables of executive attention (d2 Accuracy, d2 Concentration, Stroop Interference) in the BP group.

Results indicate that depressive severity was not correlated with the attention deficits seen in the bipolar group at a $p \leq .01$ significance level for the d2 Accuracy measure ($r = -.174$, $p = .4321$) or for the d2 Concentration measure ($r = -.125$, $p = .5756$). In contrast, correlation of depressive severity showed a trend toward significance with Stroop Interference scores in the BP group ($r = -.480$, $p = .019$).

Hypothesis 3 posited that the degree of psychomotor slowing in the BP group would be positively correlated with executive attention deficits.

Variables measuring psychomotor slowing were: Clinician rated MARS Retardation Total, Finger Tapping (FTT) Mean, Grooved Pegboard (GPB) Mean, and all three variables from both Simple and Choice Reaction Time measures (SRDT, SRMT, SRTT, CRDT, CRMT and CRTT). Executive attention variables were the d2 Accuracy measure, the d2 Concentration measure and the Stroop Interference. Pearson's correlations were run on the above variables in the BP group only. The results are presented in Table 7.

Table 7: Correlation: Psychomotor & Executive Attention
Bipolar Subjects (N=23)

Variables	Correlation	*p*-value
d2 Accuracy		
SRDT	-.345	.108
SRMT	-.463	.025†
SRTT	-.539	.007*
CRDT	-.174	.431
CRMT	-.335	.119
CRTT	-.401	.057
FTT	.292	.178
GPB	-.518	.010*
MRET	-.039	.861
d2 Concentration		
SRDT	-.342	.111
SRMT	-.433	.038†
SRTT	-.521	.009*
CRDT	-.217	.325
CRMT	-.327	.129
CRTT	-.420	.045†
FTT	.240	.273
GPB	-.529	.008*
MRET	.010	.963
Stroop-Interference		
SRDT	.438	.036†
SRMT	-.004	.985
SRTT	.051	.818
CRDT	.303	.162
CRMT	.059	.791
CRTT	.606	.002*
FTT	.019	.932
GPB	.041	.853
MRET	-.185	.403

* $p \leq .01$
† $p \leq .05$

Only two of eleven psychomotor variables were found to be significantly correlated with d2 Accuracy and d2 Concentration, with one additional variable correlating significantly with Stroop Interference. This does not strongly support Hypothesis 3, suggesting that the executive attention deficits detected in the bipolar group were not significantly correlated with most of the

objective measures of psychomotor retardation in patients with bipolar disorder. The 2 motor measures that did correlate significantly with observed deficits were Grooved Pegboard and Simple Reaction Time Total Time. Several additional variables revealed a trend toward significance and may be representative of impoverished statistical power, due to an inadequate number of subjects.

Exploratory Analyses

The following analyses were done solely for exploratory purposes and to generate hypotheses for further study.

Age

Although age range was limited to participants under 55 years of age, given the recent evidence of the impact that duration of illness may have on the neuropsychological functioning of patients with bipolar disorder, in an attempt to distinguish the effect that age had on performance in our sample, exploratory analyses were run on significant measures.

To determine if the older subjects' performance was significantly different than that of the younger subjects, independent t-tests were then conducted on the total sample and subsequently split by patient groups. A dichotomous (grouping) variable was formed to separate the oldest quartile of subjects (48 years or older) from the rest of the sample. No significant difference was

found in severity of depression (HamD 31) between older and younger subjects. In contrast, results suggest that the older subjects did, in fact, perform significantly more poorly on the d2 Accuracy and the d2 Concentration measures, as compared with younger subjects. (See Table 8).

Table 8: Total sample grouped by age

Variables	Subjects<48 (N=39)	Subjects≥48 (N=11)	*t*-value	*p*-value
	Mean (SD)	Mean (SD)		
HamD 31	16.2 (16.1)	19.3 (16.6)	-.551	.5840
d2 Accuracy	497.7 (91.3)	407.2 (72.4)	3.023	.0040*
d2 Concentration Log Transformed	2.300 (.105)	2.184 (.098)	3.268	.0020*

*$p \leq .01$

Further analyses were run to determine whether this age effect occurred differentially in the patient or normal control group. See Table 9.

Table 9: Sample grouped by age and patient group: d2 Accuracy and Concentration

Group	Young	Old	*t*-value	*p*-value
	Mean (SD)	**Mean (SD)**		
d2 Accuracy				
BP	458.6 (103.8) (N=17)	391.2 (63.9) (N=6)	1.483	.1530
NC	527.9 (68.4) (N=22)	426.4 (84.6) (N=5)	2.874	.0081*
d2 Concentration Log Transformed				
BP	2.248 (.122)	2.167 (.103)	1.460	.1591
NC	2.340 (.070)	2.205 (.099)	3.607	.0013*

*$p \leq .01$

The differences in performance on the d2 measures as a function of age grouping failed to reach significance in the bipolar sample but were found to be significant in the normal control sample. This may suggest that in our normal control sample, age factors affect performance on the d2 Accuracy and d2 Concentration measures, while the impairment in performance on the same measures in the patient sample may be better accounted for by other factors. Due to the limited size of the sample, this may more accurately reflect a power issue.

Gender

Although preliminary Chi Square analysis did not detect a significant difference in gender distribution between groups (Chi Square= 2.826, p= 0.0927), since gender has been found to be relevant in research involving reaction time and neuropsychological measures (Spreen & Strauss, 1998). Exploratory analyses were therefore conducted, utilizing gender as a grouping variable. Initially, comparisons were made within the entire sample (See Table 10). Subsequently, the effect of gender was investigated within groups, separating the BP group from the NC group (See Tables 11 & 12). There were no significant differences found between male and female participants on any of the demographic variables (education, age), level of depressive symptomology (Ham31), or clinical ratings of psychomotor retardation (MARS-R). As the d2 Accuracy and d2 Concentration measures were the only variables to detect significant differences between groups, the effect of gender was investigated for those measures only. This resulted in no significant differences between men and women in either group (BP vs. NC). Independent t-tests were used to compare groups on the both variables, following log transformation for the d2 Concentration variable.

Table 10: Gender Effects on the Total Sample

Measure	Male (N=24)	Female (N=26)	*t*-value	*p*-value
	Mean (SD)	Mean (SD)		
Age	35.7 (8.2)	38.1 (11.0)	-.856	3964
Education	16.1 (2.0)	16.4 (2.6)	-.335	.7388
HamD 31	21.2 (17.1)	12.9 (14.3)	1.869	.0677
d2 Accuracy	462.1 (107.0)	492.2 (81.2)	-1.126	.2657
d2 Concentration Log Transformed	2.25 (.13)	2.30 (.09)	-1.277	.2078
MARS-R	12.1 (2.8)	13.0 (3.3)	.984	.3301

Table 11: Gender Effects in Control Subjects

Measure	Male (N=10)	Female (N=17)	*t*-value	*p*-value
	Mean (SD)	Mean (SD)		
Age	31.6 (4.2)	36.8 (11.6)	-1.34	.1911
Education	17.4 (2.7)	16.2 (2.7)	1.29	.2077
HamD 31	2.6 (2.5)	2.9 (2.6)	-.24	.8089
d2 Accuracy	525.5 (64.3)	499.4 (89.2)	.81	.4274
d2 Concentration Log Transformed	2.338 (.067)	2.301 (.103)	1.016	.3193
MARS-R	10.8 (1.3)	10.9 (0.7)	-.36	.7237

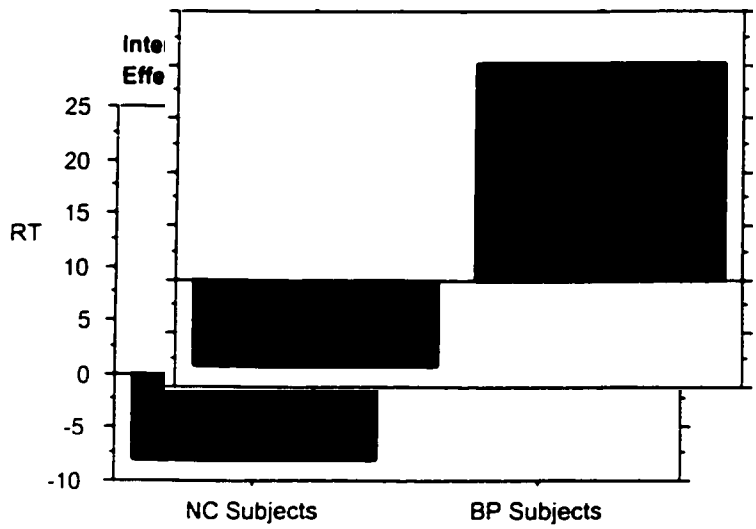
Table 12: Gender Effects in Bipolar Subjects

Measure	Male (N=14)	Female (N=9)	*t*-value	*p*-value
	Mean (SD)	Mean (SD)		
Age	38.6 (9.2)	40.6 (9.9)	-.472	.6418
Education	15.2 (1.8)	16.7 (2.4)	-1.64	.1161
HamD 31	34.4 (8.0)	31.6 (4.6)	.95	.3531
d2 Accuracy	416.9 (110.0)	478.7 (66.1)	-1.51	.1454
d2 Concentration Log Transformed	2.193 (.136)	2.280 (.072)	-1.753	.0942
MARS-R	14.5 (3.4)	14.3 (3.8)	.109	.9140

Inhibition of Return (IOR)

While analyzing the CTD 'benefits' measure at 800 msec, it was noted that BP subjects were continuing to show facilitory effects of cueing at 800 msec SOA, suggesting blunted or absent IOR effects, while NC subjects demonstrated the expected negative effect of valid cueing at the longer (800 msec) SOA. (See Figure 1).

Figure 1: IOR in BP versus NC Subjects



This result indicates an atypical response pattern in BP subjects that is consistent with previous literature in other clinical samples including obsessive- compulsive disorder (OCD) (Nelson, Early, Haller, 1993) and schizophrenia (Huey & Wexler, 1994). Results from an independent t-test revealed a trend toward significance of Benefit 800msec measures between groups (t=-1.685, df=46, p=.09). Potential implications will be discussed briefly in the following section.

DISCUSSION

Patients with bipolar depression (N=23) were compared with non-psychiatric adults (N=27) in the current study in an attempt to identify and to further classify psychomotor and attention deficits seen in bipolar depression, as well as their relation to one another. Well-studied attention tasks that have been associated to varying degrees with specific regions of brain function were used to facilitate the characterization of attention abnormalities. It was hypothesized that patients with BP disorder would demonstrate particular difficulty on measures determined to tap "higher-level", executive (anterior) attention processing. In contrast, performance on less demanding attention tasks (i.e. CTD) was expected to be unimpaired, reflecting the sparing of the "lower level", non-executive (posterior) component of visuospatial attention. Furthermore, a relationship between executive attention deficits and psychomotor retardation was predicted, while no significant relationship between executive attention deficits and the severity of the depressive symptoms was hypothesized.

On the most common measure of executive attention, the Stroop Interference Task, results demonstrated no significant impairment in depressed patients with bipolar disorder. This was a somewhat surprising finding based on previous studies indicating deficits in depressed patients on the Stroop task, which requires the inhibition of a preponent response, in favor of a novel

response (Lemelin & Baruch, 1998; Gotlib & McCann, 1984). However, some recent studies, consistent with our results, have found comparable Stroop interference scores in depressed patients and normal controls (van Gorp, Altschuler, Theberge, Wilkins, Dixon, 1998; Degl'Innocenti & Backman, 1998). The discrepancy may be due, in part, to different methodologies of score calculation on the Stroop task, different patient samples, and varying medication status. The Interference score is reflective of a measure of a subject's ability to selectively attend to the relevant color of the ink, while suppressing the processing of the irrelevant word meaning. The Stroop task is highly dependent on psychomotor speed but in the method of calculating the interference scores used in the current study, psychomotor speed is controlled for, by utilizing a predicted score for the incongruent trial (calculated based on reading and color naming speed from the first two trials), as it compares with true performance.

In contrast, results from the d2 Test of Attention suggest that depressed patients with bipolar disorder demonstrate executive attention deficits as compared with healthy adults. Two measures of executive attention from the d2 Test of Attention (d2 Accuracy and d2 Concentration), revealed significant group differences. This discrepancy may be related to reliance on psychomotor speed on the d2 test, which is not controlled for, as it is on the Stroop interference measure. Discrepant results may be explained by interpreting the deficit seen in the patient sample as a result of an additive

effect of motor slowing and executive attentional impairment, resulting in the differences seen between groups on the d2 variables that were not seen on Stroop Interference Scores. Because subsequent analyses indicated that the d2 variables did not strongly correlate with the majority of the motor measures in the patient sample, this explanation may not be an adequate one.

An alternative explanation is to suggest that the d2 may be more accurately classified as a visual search task, involving the posterior attention system, that is more closely linked to target detection similar to that measured on the CTD. This explanation has supporting evidence with regard to other visual search tasks. In fact, cognitive studies suggest that the spatial attention mechanism in visual search may be the same as the one involved in covert orienting and shifting of attention in response to location cues (Parasuraman, Greenwood, & Alexander, 1995; Prinzmetal, Presti, & Posner, 1986). Imaging studies confirm an overlap of neuroanatomical location in covert orienting tasks and conjunction search, but not feature-only search, indicating the role of the superior parietal lobule in both tasks (Corbetta, Shulman, Miezin, & Petersen, 1995).

However, this explanation seems unlikely because the level of difficulty of the d2 task is high, as the distracters presented are highly similar to the targets. This type of cancellation task requires serial search utilizing higher-level processing, unlike some cancellation measures which clearly measure more

automatic processing through parallel search and 'pop out' phenomena (Treisman & Gormican, 1988). Furthermore, d2 Accuracy and Concentration scores have been shown to be significantly correlated with other tasks of executive function (i.e. Trails B, Symbol Digits Modalities, Stroop, and Tower of London) (Brickenkamp & Zilmer, 1998), implying its shared neuropsychological construct, or similarity to measures corresponding to the cognitive domain it is intended to measure.

It may be suggested that the d2 task best assesses the interplay of both the anterior and posterior attention systems, without measuring the performance of either in isolation. Regardless, results of the current study suggest that subjects with bipolar depression were impaired on an executive attention task that was intended to measure the effortful, inhibitory controlled processing of the anterior attention system.

Automatic attention (non-executive) was investigated utilizing a cued target detection task in the current study. Covert attention has been extensively studied in the context of location cueing tasks, in which an advance visual cue directs attention to a location while eyes remain fixated on another location. Research indicates that precues enhance sensory processing at the attended location, as measured by improved reaction time to subsequent targets appearing in the cued location (Benefits). In contrast invalid, or misleading cues result in degradation of performance (increased RT), presumably due to

the necessity to shift location from a cued location to a different one (Costs). Considerable evidence exists to suggest that the specific requirements of shifting attention during a CTD can be mapped to different neuroanatomical areas forming a circuitry of visual orienting of attention.

Analysis of the variables from the cued detection task (CTD) resulted in no significant differences between groups, as was predicted. Results of the current study indicate that reaction times of patients with bipolar depression on a cued target detection task are slower than those of the non-psycihiatric control group, with results reaching or approaching statistical significance, in all conditions (Valid, Neutral Invalid) and at all SOAs (100msec, 400 msec, and 800msec). Despite this overall slower reaction time, patients with bipolar disorder, like non-psychiatric controls, respond more quickly when presented with a valid cue than with a neutral or invalid cue. As expected, this indicates that bipolar depressed subjects' basic ability to orient attention to a target is not substantially compromised.

The "benefits" gained from correct location cueing are present in our bipolar sample and do not differ significantly from non-psychiatric controls. This benefit was seen at each of the SOAs, indicating an ability to maintain attention automatically drawn to a location by cueing, regardless of the interval following the cue and preceding the target. Because the longest SOA utilized in the current study was 800msec, we are unable to state with

confidence that this is indicative of intact vigilance, or sustained attention; however, this does imply unimpaired phasic alertness, or cortical arousal in our sample of patients with bipolar depression.

Cost, or the disadvantage of orienting attention to an incorrect location prior to target onset, was calculated by subtracting the mean reaction time of invalid cue trials from the neutral cue condition. As with the measure of benefits, patients with bipolar disorder exhibited comparable costs of reorienting attention following an invalid cue, as compared with non-psychiatric controls. This is consistent with our hypothesis and previous studies demonstrating that automatic attention processing is intact in patients with depression.

Another important goal of the current study was to address the question of how depression severity correlates with attention deficits. Findings in previous studies investigating the potential correlation between the severity of depression and cognitive impairment have been equivocal, with some indicating a relationship (Hartlage et al., 1993) while others evidence no significant correlation (Lemelin, Baruch, Vincent, Laplante, Everett, et al., 1996; Trichard, Martinot, Alagille, Masure, Hardy, et al., 1995; Degl'Innocenti et al., 1998). The results of the current study suggest that the severity of depression in this group of patients with bipolar depression does not significantly correlate with the impaired functioning seen on the d2 Accuracy and Concentration measures. Stroop Interference scores did not differentiate

patients from controls; however, results indicate that performance on the Stroop interference measure was correlated to depressive severity at a level approaching statistical significance. It is possible that measures on which psychomotor speed is controlled for may be more impacted by severity of depressive symptomology. This is supported by the fact that subsequent analysis of the incongruent condition (SCWR), measuring interference prior to controlling for speed, demonstrated a weaker correlation (-.409, p=.05) to Ham Mood scores than the calculated Interference scores did (-.480, p=.02).

Previously discrepant results may be due, in part, to the use in this study of the 31-item Hamilton Depression Rating Scale (Hamilton, 1960). Many studies use the 17 or 24-item versions, which do not include items designed to measure the atypical symptoms of depression, that weigh heavily on motor and cognitive retardation. The 31-item version has several additional items measuring psychomotor variables, weighting the total score more heavily on psychomotor function. Due to the nature of the current study, psychomotor and cognitive items were subtracted from the total Hamilton score before analyses were conducted, thereby limiting the effect that these deficits may have on total ratings of depressive severity.

Additionally, there is evidence to suggest that bipolar depression may represent a different entity than the depression seen in major depressive disorder, with a different course of illness, as well as methods of treatment

(Wolfe et al.,1987). Several of the previous studies have looked at groups of subjects with depression whom are either diagnostically diverse (i.e. both bipolar and unipolar) or only patients with major depressive disorder.

This raises the important question of what, if anything, might be related to attention deficits in our sample, if it is not depressive severity? Previous research indicates that psychomotor retardation may be directly related to the degree of cognitive impairment in depressed patients (Lemelin & Baruch, 1998). Our results indicate significant correlations between measures of psychomotor retardation and executive attention deficits on only two of nine motor tasks in relation to the d2 variables in the bipolar group. This is somewhat inconsistent with recent evidence suggesting that attention deficits in depression are related to psychomotor impairment and not to the severity of the depression itself (Lemelin & Baruch, 1998). In the current study the variables that did correlate with executive attention impairment were objective measures of motor functioning (i.e. Grooved Pegboard and Simple Reaction time), while clinical ratings of psychomotor retardation (MARS-R) did not correlate with attention impairment. Lemelin & Baruch (1998) did not investigate measures of pure motor speed from an objective standpoint, but did find clinician-rated psychomotor assessments to accurately predict attention impairment. The discrepancy may be due, in part, to different instruments used to assess attention and psychomotor functioning. Their measures of attention all had reaction time components, which would imply a

relation to psychomotor functioning from the outset. The clinician rated scale used in their study, the Depressive Retardation Rating Scale (DRRS) directly assesses the clinician's as well as the subject's own experience of cognitive impairment, again confounding the relationship between psychomotor function and cognition (Widlocher, 1983). The current study found that clinician-rated psychomotor retardation was not related to deficits in executive attention; however, unlike the DRRS, the MARS instrument does not directly assess any cognitive component of psychomotor functioning, but rather looks at it as an isolated phenomena of motor behavior. In light of these methodological differences, the discrepant findings are not surprising.

In addition, it is noteworthy that several additional correlations of psychomotor variables and executive attention variables demonstrated a trend toward significance in our sample. Multiple comparisons necessitated use of a more stringent p-value and may have resulted in fewer significant findings. The relatively large correlation values, in conjunction with a small sample size, implies positive findings, regardless of the resulting p-values. In breaking down the specific variables that demonstrated a strong relationship, it was noted that the two measures with the highest correlations were the Grooved Pegboard (GPB) and the Simple Reaction Time Variables (SRMT, SRTT). In addition, the Choice Reaction total time variable (CRTT) demonstrated a strong, although not statistically significant, correlation. The Grooved Pegboard test requires the use of fine motor skills in a timed setting and it

additionally incorporates a visual requirement to aid in identifying the appropriate orientation of the peg and the peg-hole. Therefore, correlation of this measure with the d2 variables may his reflect the combined effort of the motor and visual attention systems. Likewise, both the Simple and Choice reaction Tests require the rapid action of the motor system in response to the detection of a visual stimulus. The psychomotor measures that did not correlate as strongly, such as the Finger Tapping Test, make no demands on visual processing. Replication of the current study in a larger sample would help to clarify the strength of the relationship between psychomotor retardation and executive attention impairment.

Results indicated a relationship between attentional deficits on the d2 measures and specific objective psychomotor variables. In contrast, the subjective clinician-rated measure of psychomotor function did not demonstrate a strong correlation. This finding is very interesting, providing evidence that the subtle psychomotor disturbance in psychiatric patients cannot easily be detected by observation alone and may be better assessed using objective neuropsychological measures.

In secondary analyses, the effect of age was considered, despite the limited age range of the current sample. Due to a small sample size, these exploratory results must be interpreted with caution. By separating the "older" subjects in our sample (as defined by the oldest quartile, with age$\geq$ 48 years),

we were able to look at the effect age had on the variables of interest, namely the d2 Accuracy and d2 Concentration measures. Results indicated that there was a significant difference in older and younger subjects across the entire sample on both measures of executive attention. Furthermore, when separating patients from non-psychiatric controls, age differences in d2 performance remained significant in the non-psychiatric control group only. This finding suggests that in our sample, age has a greater effect on performance in the control group than it has in the patient group, with the implication that the executive attention deficits seen in the bipolar group are likely due to factors other than age. Again, this finding was present within a very small number of subjects and may be due, in part to limited statistical power. A similar study with a larger sample size is necessary to confirm this finding. In a larger sample, patient characteristics such as age of onset, duration of illness, and severity of course may be better predictors of deficits than age alone.

Another variable of interest in neuropsychological research is gender, as gender differences are seen on many tests of cognitive functioning (Spreen & Strauss, 1998). Exploratory analyses were run on the current sample, resulting in no significant differences between gender groups on any of the variables of interest. Furthermore, after splitting the total sample by patient group, gender differences failed to reach significance in either patients with bipolar depression or non-psychiatric control subjects.

Results from the exploratory analyses focused largely on the CTD paradigm and the model of attention proposed by Posner and colleagues (Posner & Petersen, 1990). There are two well-studied forms of cueing in a CTD; one presenting the cue in the periphery, is thought to automatically orient attention to the cued location, with little cognitive processing necessary. The second cue, called an endogenous cue, presents a cue in the central fixation area (i.e. an arrow pointing in the direction of the intended target), and is believed to require more effort on the part of the participant in identifying the meaning of the cue. The current study utilized an exogenous cue, presented in the periphery, as a measure of automatic visual orienting. The resulting data from peripheral (exogenous) cueing paradigms have been thought of as measures of automatic visual orienting, which is believed to be subcortical in nature (Posner & Petersen, 1990).

An interesting finding, that was not an a priori hypothesis, involves a well-established phenomenon called inhibition of return (IOR), which typically occurs at longer SOAs (i.e. > 500msec) and is explained as an individual's automatic resistance to return attention to a recently attended location, once attention has shifted elsewhere (Posner, et al., 1985). In general, healthy subjects detect a visual target more quickly at a cued location than at an uncued location in the visual field, provided the interval between onset of cue and onset of target is less than approximately 500 msec (Posner, Rafal,

Choate, & Vaughn, 1985). That is, the cue has a facilitory effect on target detection. However, if enough time has elapsed between cue and target presentation, subjects will detect a target more slowly at a cued location as compared with an uncued location in the visual field. This is known as the inhibition of return (IOR) affect. IOR is believed to be an important component function in the normal deployment of attention, serving as a filtering mechanism of information that operates early in stimulus processing, likely mediated by the superior colliculus (Posner et. al., 1985).

In the current study, an exploratory analysis indicated that typical patterns of IOR are seen at the 800msec interval for non-psychiatric control subjects only. This is seen as longer reaction times to valid cues than to invalid and neutral cues. Interestingly, patients with bipolar disorder in our sample, do not exhibit IOR patterns, rather they continue to gain benefit from valid cues at longer SOAs, as seen in decreased reaction times on valid trials. This is similar to results that have been seen in other clinical samples, including Obsessive-Compulsive Disorder (OCD) (Nelson et al.; 1993), Schizophrenia (Posner, et al., 1988), and Attention Deficit Hyperactivity Disorder (ADHD) (Swanson, Posner, Potkin, Bonforte, & Youpa, et al., 1991) and is generally described as a specific deficit in disengagement of attention from a cued location. This unexpected finding may indicate a deficit in the orienting component of the neural network model of attention described by Posner and Petersen (1990) and implies impairment of the functions of the posterior

attention system in our bipolar depressed sample. This finding appears to be the first of its kind and is extremely interesting but somewhat inconsistent with the theory that automatic processing remains intact, while more effortful processing is impaired in affective populations, at least when looking specifically within the attention domain.

As the posterior attention system is outlined in Posner and Petersen's neural network model of attention (1990), it involves three specific neuroanatomical areas that can be dissociated based on function in an orienting task, such as the CTD administered in the current study. The function of overt and covert orienting involves the posterior parietal lobes in the disengagement of attention, the superior colliculus in moving attention to a new location, and the pulvinar of the thalamus in engaging attention at a new location. The process of covert orienting is thought to be controlled by subcortical structures only and requires no cortical involvement when attention is being studied in location detection only. When a subject is required to discriminate features of a target, cortical processing is summoned. Additionally, if endogenous cueing is used (i.e. central arrow pointing to one side giving information as to where the target will appear), cortical involvement is also assumed and IOR effects are typically not seen (Posner & DiGirolamo, 1998).

The current study specifically attempted to reduce any chance of cortical involvement and was interested in looking solely at the automatic, subcortical

processing of the posterior attention system and therefore utilized exogenous cueing. Furthermore, the two-key version of the CTD, allowed for the investigation of not only the motor component of response time but also the cognitive programming time in response to the preparation of the specific hand, and the disengagement, shifting of attention, and the reprogramming of the responding hand in the invalid condition (Posner, 1986). The motor component can be surmised by overall response time at the different SOAs, while the non-motor (cognitive) component is best measured by the difference between the neutral and invalid conditions, reflecting the 'cost' of the shift in preparation. While results indicate a slowing of motor speed, evident in higher mean reaction times in the patient group, there was no significant difference between groups on the measure of Cost at any of the SOAs. Again, this implies a motor slowing that is not accompanied by a specific deficit in the posterior attention system involved in orienting of attention.

One possible explanation for this result is to attribute the IOR impairment to a deficit in the posterior attention system as a direct result of a low level of arousal or a vigilance deficit. The posterior attention system relies heavily on the vigilance network, predominantly influenced by the norepinephrine innervation from the locus coeruleus (Harley, 1987). Depression is commonly thought of as a state of low arousal and motivation; therefore making this explanation an attractive one. In fact, several previous studies have found a global attention deficit in depressed subjects, typically described within the

context of low levels of vigilance, demonstrating an increasing impairment as the demands of the tasks increase (Mialet et al., 1996). This is not consistent with our current findings. There are no indications within the current data to imply impairment of the vigilance network. In fact, BP subjects' ability to benefit from cueing indicates an adequate level of arousal, particularly at longer SOAs.

Finally, an alternate hypothesis for the results may be to attribute the seemingly automatic attention deficit to summoned cortical processing, not normally believed necessary for performing this orienting task. In fact, Henderson (1991) has suggested that some versions of the CTD may involve both exogenous and endogenous cueing (and therefore involve both the posterior and anterior attention systems), when expectancy is introduced to the participants. Carter, Robertson, Chaderjian, Celeya, and Nordahl (1992) explained that by proposing a bias toward valid cueing (i.e. telling subjects that 80% of the time the cue will be valid) an endogenous cue (expectancy) is summoned. It is well established that exogenous cueing elicits IOR, while endogenous cueing rarely does (Posner et al., 1985). Therefore, the IOR deficit seen in the subjects with BP disorder in the current study may be attributed to a malfunction in the oculomotor system's responses to exogenous and endogenous information, resulting in a breakdown of the gating mechanism allowing normally ignored, exogenous stimuli to occupy endogenous resources, as suggested by Nelson et al. (1993) in OCD

patients. The problem with such an explanation in the current study is the presence of IOR in the non-psychiatric control subjects. If expectancy summons cortical involvement, making IOR less likely, then why is IOR still seen in the NC group?

In taking all of the current results together, the best possible explanation appears to be a modification of this last interpretation. The CTD task was likely confounded by the directive given to the subjects in advance, which indicated the value of the cue. This summoned endogenous resources by introducing expectancy, rendering the "automatic" orienting task partially controlled by the executive anterior attention system. There is evidence to suggest that endogenous and exogenous orienting of covert attention interact, such that impairment in the endogenous orienting (executive attention) will have deleterious effects on exogenous orienting to peripheral stimuli (Allport, 1992; Maruff & Currie, 1995; Rafal & Henik, 1994). Executive attention processes are necessary to inhibit unwanted or unnecessary exogenous attentional processes (Rafal & Henik, 1994). Research utilizing an antisaccade task has been used to demonstrate executive control over exogenous orienting, requiring subjects to inhibit a reflexive saccade toward a sudden onset peripheral stimulus but must attend to and utilize information contained in the stimulus to accurately control eye movement in the opposite direction (Currie, Ramsden, McArthur, Maruff, 1991). It has recently been demonstrated that patients with bipolar disorder are impaired on an

antisaccade task, demonstrating an inability to inhibit a reflexive saccade toward an irrelevant stimulus (Tien, Ross, Pearlson, Strauss, 1996). This type of deficit would explain the results in the current study in light of the bipolar groups' inability to inhibit the return of attention to the cued location. The confounding factor introducing endogenous processing was the instruction prior to administration of the task, notifying subjects of expectancy (80% Valid) to the cues.

This explanation is consistent with the executive attention deficit seen on the d2 variables, implying a specific impairment in inhibitory processes. The fact that the Stroop Interference scores did not result in significant differences between groups is difficult to understand; however, the inhibition deficit seen on the d2 measures and in the lack of IOR on the CTD may represent a specific inhibition deficit related to visual scanning or oculomotor programming rather than a general inhibition deficit.

Frontal cortex damage in humans results in an inability to suppress involuntary automatic saccades towards targets and an apparent inability to control volitional saccades (Fischer & Breitmeyer, 1987; Guitton, Buchtel, Douglas, 1985). A recent PET study in humans has confirmed the involvement of prefrontal cortex and parietal cortex during a task requiring the maintenance of information during a delay period about spatial locations for later action (Jonides, Smith, Koeppe, Awh, Minoshima, Mintun, 1993). In a

review of PET studies, Corbetta (1998) described a superior frontal region in the dorsolateral prefrontal cortex (DLPC) near the frontal eye fields (FEF), located near Brodmann's area 6, as a likely candidate for encoding and holding spatial information over a delay. Imaging studies indicate that this region is activated during locational working memory (Smith, Jonides, Koeppe, Awh, Schumacher, Minoshima, 1995) and during endogenous shifts of spatial attention (Corbetta, Miezin, Schulman, Petersen, 1993). These regions may represent an important component of the interaction of the neural networks of posterior and anterior attention. Goldman-Rakic (1988) illustrated the connections from the posterior parietal lobe to the FEF in the superior frontal cortex. It is plausible to attribute the deficits seen in the patients with bipolar depression in the current study to impaired functioning of this neuroanatomic region, although this clearly requires further investigation.

The results from the current study suggest an intriguing pattern of neuropsychological performance in patients with bipolar depression. While executive attention appears to be intact on classic measures that activate the regions of the brain involved in Posner and Petersen's anterior attention system (Stroop interference), patients with bipolar disorder showed evidence of a deficit in inhibitory processes specific to the control of the posterior attention network on tasks requiring orienting and shifting of attention.

Limitations and future direction

The current study had several methodological limitations including the small sample size, limiting the power of statistical analyses. The effect of medication on neuropsychological performance must also be taken into account, although ethical considerations prevent the possibility of taking bipolar patients off of their medication for purposes of neuropsychological assessment. The acceptable medications were significantly limited in this study, with no allowance for antipsychotic medications, antidepressants, or any of the newer anticonvulsant mood stabilizers (i.e. lamotrigine, gabapentin). Patients were included only if they were taking one of the three most common treatments (lithium, valproate, or carbamazepine) and had been on a stable, therapeutic dose for at least 6 weeks. Furthermore, the common use of benzodiazepines (antianxiety) medications in this population, such as lorazepam, was not permitted within 10 hours of testing. Most importantly, bipolar patients taking medications represent a very common, if not typical, clinical situation. Unfortunately, there was no subgroup of patients that could be analyzed separately due to the small sample size and the heterogeneity of treatments.

A thorough review of the literature (Goldberg & Burdick, 2001) suggests that the three most commonly used mood stabilizers, valproate, lithium and carbamazepine have very mild neurocognitive effects on neuropsychological performance (typically seen as a lack of practice effects over repeated

testing), when drug levels are in the therapeutic range, limiting the degree to which medications may account for the results of this study. Psychomotor slowing has been attributed to the use of valproic acid and lithium in previous studies, although not consistently so. In contrast, carbamazepine does not seem to have any deleterious effects on motor performance. Of note, many of the previous studies identifying negative cognitive effects of these medications often investigated patients on combination therapy, which is known to result in an increased likelihood of all side effects. For a more thorough review, see Goldberg & Burdick (2001). Additionally, the results of primary interest are the intergroup differences on specific measures and are not consistent with a global decrement in performance as might be seen from sedation, motor slowing, or other general medication effects. The potential impact of medication on performance cannot, however, be ruled out as a possible explanation for some of the results, particularly due to the heavy reliance on psychomotor performance on tasks used in the current study.

A small sample size, with a majority of patients with bipolar I disorder (65%) did not allow for splitting patients by bipolar type (BPI vs. BPII), which may have different implications on clinical and cognitive functioning. A larger sample with equivalent numbers of BPI and BPII patients would be useful in differentiating patient subtypes on the basis of severity of symptomology and course of illness.

Additionally, the patient group evaluated was likely a subset of bipolar patients who have been treatment resistant in the past, as they were recruited in the context of a medication trial using a novel pharmaceutical agent. Severity of the course of illness may have biased the sample and resulted in more severe cognitive deficits than might be seen in a more heterogeneous group of bipolar patients. A selection bias may also be present as this was a voluntary study, recruiting from the community and offering free psychiatric treatment.

Because age can have effects on motor and cognitive functioning, the current study was limited to investigating subjects under the age of 55. Thus, it is not possible to generalize the results of this study to older subjects. Older bipolar patients may experience additional cognitive difficulties due to normal aging effects, increased duration of illness, increased exposure to psychotropic medications and comorbid medical illnesses (Martinez-Aran et al., 2000).

The CTD paradigm used in the current study did not allow for the statistical differentiation between left-sided and right-sided targets for the identification of a potential hemispheric impairment, if one exists. Future studies focused on this paradigm would benefit from including variables to investigate preferential hemifield processing, particularly in light of the absence of IOR in the subjects with bipolar depression. There are alternative ways in which an IOR deficit can be interpreted and the clarification of whether preferential

hemifield processing has occurred is an important feature in attributing the IOR deficit to inhibitory deficits versus a disengagement deficit.

Another limitation of the CTD paradigm used is that it cannot determine the nature of the IOR deficit because it uses a single-cue rather than a double-cue CTD measure (Fuentes & Santiago, 1999). In utilizing a single-cue stimulus (one peripheral cue followed by target onset), the observed impairment in IOR could be attributed to a deficit in the processes that control intrinsic reorientation of attention rather than indicating a deficit in filtering information that appears at inhibited locations (Faust & Balota, 1997). In a double-cue paradigm, the initial cue is in the periphery and at longer SOAs a second cue appears at the central fixation location to exogenously draw attention away from the peripheral cue, facilitating reorientation of attention. Therefore, if normal patterns of IOR are seen in a double-cue paradigm, it can be assumed that the posterior attention system is relatively intact and that the inhibitory impairment arose at the level of cortical processing in the anterior attention system and is a specific, not a global, inhibition deficit.

Finally, the CTD paradigm used in the current study is an older version based on the original work by Posner (1984) and has since been updated. The most recent version includes a fourth cue-type that is referred as a no-cue condition, which can be used in comparison with the neutral condition as an index of alerting. Alerting, or vigilance was not adequately assessed in the

current study and utilizing a CTD paradigm with a no-cue condition would allow for direct measurement of the third component of Posner's neural network model of attention (Posner & Petersen, 1990).

Statisical analyses were limited by the failure of some variables to meet criteria for parametric testing. The Mann-Whitney U procedure used on three of the variables of the CTD task is a less sensitive test and may have reduced the likelihood of significant findings.

Significance

The cyclic nature of bipolar disorder has led to the implication that during periods of remission, complete recovery is established, yet growing evidence from modern studies now suggests that many, if not most, bipolar patients show persistent low-grade forms of psychopathology between full affective episodes (Keller, Lavori, Kane, et al., 1992; Coryell, Scheftner, Keller, et al., 1993; Gitlin, Swendsen, Heller, et al., 1995). , but very few studies have systematically investigated neuropsychological functioning during periods of wellness. Unfortunately, this does not allow for investigating trait-related deficits that may persist during affectively intermorbid periods of bipolar illness. Cognitive dysfunction seems to be associated with the severity and chronicity of illness, and lifetime duration of bipolar disorder has a negative impact on executive functions and memory (Martinez-Aran et al., 2000).

Neuropsychological deficits have been reported in euthymic bipolar patients (Martinez-Aran et al., 2000) and may be an important factor in understanding the high incidence of psychosocial difficulties during remission (Scott, 1995), despite apparent clinical recovery. The current study investigated attentional functioning of patients with bipolar disorder in the depressed phase of illness and has therefore added to our knowledge of neuropsychological deficits during affectively ill periods. The fact that attentional deficits in our sample were not significantly correlated with depressive severity may imply a trait-like deficit, rather than one seen as a result of the symptoms of the illness itself. A replication of the current study in euthymic patients with bipolar disorder would provide a clearer answer to the ongoing state vs. trait question as it relates to cognition in psychiatric patients.

In addition, illuminating the nature of attentional impairment by utilizing a paradigm with relatively well-understood neural correlates may serve as a tool in identifying neuroanatomic regions related to the neuropsychological deficits commonly seen in patients with bipolar disorder. Potential benefits in identifying regions and neurotransmitter systems involved include possible utility in predicting treatment response to antidepressants. As bipolar depression is a complicated and difficult to treat clinical state, advances in this area using non-invasive information would be highly beneficial. Additionally, identifying the presence of cognitive impairment in a patient in

clinical practice might help to steer the course of treatment. Patients with cognitive deficits may utilize psychotherapy to a lesser degree and treatment must be altered to incorporate possible cognitive limitations. Another important aspect of treatment is related to medication compliance. In schizophrenic patients, it has been shown (Liu et al., 2002) that cognitive impairment results in higher rates of non-compliance. Medication compliance is a particular challenge in bipolar patients and illuminating possible predictors of non-compliance would serve to improve overall treatment.

Psychomotor retardation is an important symptom in bipolar disorder and may serve as a predictor for relapse in a complex group of patients. Psychomotor changes often precede mood state changes and can serve as a useful tool in identifying cycling prior to full relapse. Although it appears that clinical observation alone may not be sensitive enough to detect subtle psychomotor changes, it would be beneficial to consider the use of a brief motor measure that might aid in monitoring psychomotor functioning over time.

Summary

By looking at the pattern of attention deficits in depressed subjects with BP disorder in comparison with healthy adults, we hoped to better understand the cognitive impairments of BP disorder. The present research provides preliminary evidence showing dysfunction of the executive anterior attention

network in depressed subjects with BP disorder. This impairment appears to be unrelated to the severity of the depressive symptomology, and only weakly related to the degree of psychomotor slowing in our sample. Additionally, there are indications that the early and automatic aspects of the dynamic deployment of attention may be directly affected by a specific impairment of inhibitory attentional processes, assumed to be under the control of the anterior attention system, in depressed subjects with BP disorder.

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