Affective Bias, Chronophysiology, and Depression: Toward a Synthesis

by

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Per aspera ad astra.
To my parents, David, and my friends
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Abstract

Depression is associated with disruptions in affective processing and chronophysiology. However, the relationships between affective processing and chronophysiology are not well-described. This dissertation addresses critical gaps in the literature on affective bias in depression, the effects of circadian rhythms and sleep on affective processing, and organization of brain activity during sleep in depression.

First, anticipation for future affective events was examined in individuals with dysthyrmia (DYS) and controls. Warning stimuli forecasted the affective valence of subsequently presented adjectives, and participants indicated whether each adjective would describe them over the next two weeks. Controls expected fewer negative, and individuals with DYS expected fewer positive, adjectives to apply to them in the future. Event-related potentials (ERP) indicated increased physiological anticipation in controls prior to positive versus other adjectives. In sum, controls and individuals with DYS exhibit different behavioral and neurophysiological biases in anticipation for future affective events.

Second, the impact of time of day and sex on incentive-based decision making was assessed in controls. Participants completed the Iowa Gambling Task (IGT) either in the morning (08:00-10:00) or evening (20:00-22:00). Males had better IGT performance in the morning than evening. Furthermore, pre-session sleep duration was positively correlated with morning IGT performance in
females, but not males. Overall sex differences in IGT performance were not observed. In sum, chronophysiology predicts decision making, but does so differently for females and males.

Third, rhythms in bursts of beta- and delta-frequency activity during sleep were characterized in individuals with major depressive disorder (MDD) and controls. Period amplitude analysis (PAA) quantified the percent time in beta- and delta-frequency activity across a night of sleep, and power spectral analyses (PSA) applied to PAA results quantified the rhythmicity of activity bursts. Participant sex, rather than diagnosis, predicted PSA results. In sum, bursts in beta- and delta-frequency activity during sleep are less predictably organized in females than males.

Together, these studies provide a foundation for integrative research on affective processing, chronophysiology, and depression. They also indicate that sex differences in sleep and circadian rhythms are important to consider when evaluating decision making skill and organization of brain activity.
Chapter 1

Introduction

Unipolar depressive disorders, including major depressive disorder (MDD) and dysthymia (DYS), are highly prevalent and recurrent illnesses with profound socioeconomic consequences (see Appendix for MDD and DYS diagnostic criteria). First, approximately 16% of the population will experience MDD during their lifetime, and women are disproportionately affected by a ratio of about 2:1 (Kessler, 2002; Kessler et al., 2003). Furthermore, between half and two-thirds of individuals who have ever been clinically depressed will be in a depressive episode during any given year (Kessler et al.). Second, the high prevalence and recurrence of depression make it a leading cause of disability. In fact, unipolar depressive disorders were the third leading cause of worldwide disease burden, measured by years of healthy life lost, in the year 2004 (Mathers, Fat, Boerma, & World Health Organization, 2008). Depressive disorders are predicted to be the second leading cause of worldwide disease burden by the year 2020 (Mathers et al.). Third, depressive disorders carry a heavy financial burden. They result in a net economic loss of approximately $83 billion per year in the United States alone (Greenberg et al., 2003).

The burden of depression can be reduced with the application of effective treatments. Meta-analyses indicate that psychotherapy and anti-depressant medications are each effective at reducing depressive symptoms (Cuijpers, van
Straten, van Oppen, & Andersson, 2008; DeRubeis, Gelfand, Tang, & Simons, 1999; Elkin et al., 1989). However, treatment with either approach only results in remission of depressive symptoms for 40-60% of patients, and 30-50% of those who achieve initial symptom remission will relapse within a year (for review see DeRubeis, Siegle, & Hollon, 2008). There is room for progress in depression treatment, and it is dependent on advances in depression research. Two effective treatments for depression, cognitive therapy and chronotherapy, are reviewed here in the context of relevant research on cognitive bias and sleep and circadian rhythms. The synthesis of this literature is the foundation for the three studies presented in this dissertation.

One of the most well established treatments for depression is Aaron Beck’s “Cognitive Therapy” (Beck, 1979). Cognitive therapy is based on the hypothesis that emotions result from interpretations of life events (Beck, 1967). Depression can result when one has persistently negative interpretations of life events. For example, depressive cognitions in response to repeated failure to obtain a job might include, “I am worthless,” “I must not have what it takes to do these jobs,” and “I will always be a failure.” Alternatively, depression can result from repeated failure to make positive attributions (Abramson, Metalsky, & Alloy, 1989; Abramson, Seligman, & Teasdale, 1978). In this model, positive events are attributed to external factors that are unstable and specific to the circumstances of the event rather than to stable and general characteristics of oneself. For example, “I got the job because the person I interviewed with was having a good day, not because I am the most qualified person.” A major task in cognitive
therapy is to persistently challenge these automatic thoughts with the ultimate goal of changing emotions and behavior.

There is now a wealth of evidence that individuals with depression make more negative attributions (for review see Wisco, 2009) and fewer positive attributions (for meta-analytic review see Mezulis, Abramson, Hyde, & Hankin, 2004) than healthy individuals. Furthermore, cognitive researchers have delineated the mechanisms of affective bias in depression through studies of attention, memory, and executive functioning (for review of behavioral and neurophysiological evidence see Shestyuk & Deldin, in press). Biases in attention are most often present in tasks that allow for elaborative processing (Wisco). Tasks of mood-congruent memory bias, which generally allow for deeper processing of emotional stimuli than tasks of attention, provide reliable evidence that individuals with depression remember more negative and fewer positive events than healthy individuals (Matt, Vázquez, & Campbell, 1992). Furthermore, individuals with depression have difficulty removing negative information from memory (Berman et al., 2010; Joormann & Gotlib, 2008), but can learn to forget negative information when instructed to substitute it with positive information (Joormann, Hertel, LeMoult, & Gotlib, 2009). Thus, attention and memory biases are moderated by executive functioning: individuals with depression fail to appropriately disengage from negative stimuli or maintain attention and memory for positive stimuli without an explicit strategy. Challenging negative automatic thoughts in cognitive therapy may effectively enhance executive control of affective biases.
Another promising treatment for depression is chronotherapy. Chronotherapy is based on the hypothesized interaction between two biological drives: circadian rhythms and the sleep-wake homeostat (for review see Cajochen, Blatter, & Wallach, 2004). This is referred to as the “two-process model of sleep-wake regulation” (Borbély & Wirz-Justice, 1982; Daan, Beersma, & Borbély, 1984; see Figure 1-1). Circadian rhythms are 24 hr cycles in activity (process C). Process C is reflected in part by a peak in sleepiness late in the evening and a trough in sleepiness late in the morning. The sleep-wake homeostat (process S) moderates the depletion and repletion of sleep-need: the longer one is awake, the greater the need for sleep. Process S is reflected by increased sleepiness following a night of sleep deprivation despite a circadian trough in sleepiness. Ideally, circadian and homeostatic processes occur in synchrony with external time-cues called “zietgebers”. For example, decreases in light and daily activity should correspond to circadian peaks in sleepiness and homeostatic peaks in sleep-need.

There is extensive evidence that circadian rhythms and sleep are disrupted in MDD (for reviews see Armitage, 2007; Germain & Kupfer, 2008; McClung, 2007; Wirz-Justice, 2006). In fact, desynchronization between zietgebers, circadian rhythms, and homeostatic sleep-need may contribute to the onset and maintenance of depressive symptoms (Wehr & Wirz-Justice, 1981). Chronotherapy targets circadian and homeostatic processes by manipulating zietgebers that influence the timing of circadian rhythms, and temporarily restricting sleep to increase sleep-need. In theory, chronotherapy is effective at
reducing depressive symptoms because it helps synchronize circadian and homeostatic processes (Wehr & Wirz-Justice, 1982).

The most common form of chronotherapy for depression is time-limited total sleep deprivation (Pflug & Tölle, 1971). Decreases in depressive symptoms following sleep deprivation are seemingly paradoxical given the importance of sleep to biological and cognitive functioning. However, one night of total sleep deprivation results in a decrease in depressive symptoms in approximately 60% of patients (for review see Wirz-Justice & Van den Hoofdakker, 1999). Unfortunately, symptoms of depression increase again following recovery sleep for approximately 80% of those who respond initially (for review see Wu & Bunney, 1990). The short-lived effects of chronotherapy limit its use as general treatment for depression.

Partial sleep restriction and gradual shifts in the timing of sleep also have antidepressant effects (for review see Van den Hoofdakker, 1997). Cognitive-behavioral therapy for insomnia, which includes partial sleep-restriction and manipulation of circadian zeitgebers, reduces depressive symptoms in patients with MDD (Taylor, Lichstein, Weinstock, Sanford, & Temple, 2007; see Appendix for insomnia diagnostic criteria). Cognitive-behavioral therapy for insomnia also enhances treatment with antidepressant medications (Manber et al., 2008). Furthermore, most-antidepressant medications produce alterations in sleep and circadian rhythms (for reviews see Argyropoulos & Wilson, 2005; Casement, Arnedt, & Armitage, 2009; Winokur et al., 2001). These data indicate that standard treatments for depression may benefit from manipulations of the
circadian-homeostatic system (for review see Germain & Kupfer, 2008).

In fact, chronotherapy may help maximize the benefits of cognitive therapy for depression. There is growing evidence that sleep benefits encoding and consolidation of affective memories (for reviews see Diekelmann & Born, 2010; Walker & van der Helm, 2009). For example, preliminary data from Walker and Tharani (reviewed in Walker & van der Helm) demonstrated that individuals who were deprived of sleep for 36 hr prior to memory encoding had selective reductions in memory for positively-valenced words compared to individuals who were not sleep-deprived. Furthermore, consolidation of new learning may benefit from coherent rhythms in brain activity during wake and sleep (for reviews see Diekelmann & Born; Giuditta et al., 1995). More specifically, memories may be re-activated and strengthened by rhythmic oscillations in fast- and slow-frequency brain activity (Diekelmann & Born; Sejnowski & Destexhe, 2000; Steriade, 2003). Both circadian rhythms and the sleep-wake homeostat contribute to these ultradian rhythms in fast- and slow-frequency neural activity (Dijk & Czeisler, 1995). Thus, learning to challenge automatic thoughts and selectively enhance positive memories may be hastened by appropriate manipulation of the circadian-homeostatic system.

A model that describes the hypothesized interactions between affective processing and chronophysiology is presented in Figure 1-2. In this model, depression is represented by emotional-cognitive symptoms such as low mood and difficulty with attention and decision-making, as well as psychomotor symptoms such as impaired sleep and low energy. These symptoms are
included as diagnostic criteria for MDD and DYS (American Psychiatric Association, 2000). Affective processing, a target of cognitive therapy for depression, is represented by the component processes of attention, memory, action, and executive control. Executive control is the ability to select and manipulate information and behavior, and it regulates attention, memory, and action. Chronophysiology, the target of chronotherapy for depression, includes circadian rhythms and the sleep-wake homeostat. Disruptions in affective processing and chronophysiology are both causes and consequences of depression (Ising, Lauer, Holsboer, & Modell, 2004; Modell, Ising, Holsboer, & Lauer, 2002, 2005). Thus, targeting either process can reduce depressive symptoms. Furthermore, affective processing and chronophysiology interact with one another, so that targeting both of these processes in combination may enhance treatment effectiveness.

Additional research is needed to test components of this model. First, while there is evidence that individuals with depression have poor executive control of affective attention and memory, the functional consequences of these affective biases are less clear. Theoretically, biases in attention and memory could impact expectations for the future. Furthermore, biased anticipation of future affective events may impact decision making: determining the likely cost-benefit ratio of future choices relies on remembering the outcomes of previous decisions. Moreover, there is evidence that individuals with depression make less financially advantageous decisions than healthy individuals (Must et al., 2006). On a related note, while there is evidence that sleep benefits affective memory,
the relationship between chronophysiology and decision making is poorly defined. The timing of decisions and the amount of sleep that one gets may impact decision making skill. Third, while affective processing may be influenced by rhythmic oscillations in brain activity during sleep, and disruptions in chronophysiology may contribute to the onset and maintenance of depression, ultradian sleep rhythms in depression have not been fully characterized. Understanding the temporal pattern of fast- and slow-frequency brain activity during sleep may further elucidate the chronophysiological mechanisms of affective processing bias. The three studies included in this dissertation address these hypothesized interactions between affective processing and chronophysiology in depression.

The first study builds from research on cognitive bias in depression by comparing affective bias for future affective events between individuals with DYS and healthy controls. This is important because leading cognitive models posit that individuals with depressive disorders are more likely to anticipate future negative events, and less likely to anticipate future positive events, than healthy individuals (Abramson et al., 1989; Abramson et al., 1978; Beck, 1967). However, experimental evidence of future-oriented affective bias in depression is lacking despite ample evidence for mood-congruent memory bias (for meta-analytic review see Matt et al., 1992). Furthermore, there is a dearth of research about affective bias in chronic depressive disorders such as DYS. Notably, few differences have been found between individuals with DYS and those with chronic MDD (McCullough et al., 2003).
The second study examines the relationship between time of day, sleep, and incentive-based decision making in healthy controls. Circadian rhythms and sleep influence performance on a variety of executive functioning tasks (for reviews see Pilcher & Huffcutt, 1996; Schmidt, Collette, Cajochen, & Peigneux, 2007). However, there is very limited data about the relationship between circadian rhythms, sleep, and decision making. This study fills a gap in the literature on time of day, sleep, and decision making that can inform studies of circadian rhythms, sleep, and decision making in depression. It also builds from the first study in this dissertation, as decision making depends on expectations of reward and punishment.

The third study quantifies the strength of rhythms in beta- and delta-frequency activity during sleep in MDD. In contrast to previous studies that examine the amount and timing of sleep stages or frequencies of brain activity, this study examines whether bursts in beta- and delta-frequency activity are predictably organized across the night. Beta- and delta-frequency activity were selected for analysis a priori because activity within these frequency ranges is generally disrupted in MDD (Armitage, Hoffmann, Trivedi, & Rush, 2000; Tekell et al., 2005). Examining rhythms in brain activity in MDD is important because there is a long-standing notion that biological rhythm disruption may be involved in the pathogenesis of mood disorders (e.g., Healy, 1987), and organization of brain activity across the night may predict cognitive functioning (for reviews see Diekelmann & Born, 2010; Giuditta et al., 1995).
The latter two studies also examine the influence of sex. There is evidence that females make fewer positive and more negative self-attributions (e.g., Beyer, 1990; Parsons, Meece, Adler, & Kaczala, 1982), and perform less well on decision making tasks (e.g., Bolla et al., 2004; Overman et al., 2006; Reavis & Overman, 2001), than males. Females and males also have differential responses to sleep deprivation (Armitage, Smith, Thompson, & Hoffmann, 2001; Corsi-Cabrera, Sánchez, del-Río-Portilla, Villanueva, & Pérez-Garcì, 2003), and females with MDD have less coherent rhythms in brain activity compared to males with MDD and healthy individuals (Armitage et al., 1992; Armitage et al., 1999). The relationship between affective bias, chronophysiologicy, and sex is relatively unexplored. Therefore, the second study in this dissertation examines the role of time of day, sex, and sleep on decision making, and the third study compares the strength of rhythms in beta- and delta-frequency activity between females and males.

In summary, the three studies presented here address critical gaps in the literature on affective bias in depression, circadian-homeostatic effects on affective processing, and organization of brain activity during sleep in MDD. In combination, these studies provide a foundation for further research on affective bias and circadian-homeostatic influences in mood disorders. This is important because research that delineates the relationship between affective processing and chronophysiology may result in greater synthesis between depression treatments such as cognitive therapy and chronotherapy.
Figure 1-1. Two process model of sleep-wake regulation (Borbély, 1982). Circadian rhythms (process C) are 24 hr cycles in activity. Process C is reflected by a peak in sleepiness late in the evening and a trough in sleepiness in the morning. The sleep-wake homeostat (process S) moderates the depletion and repletion of sleep-need: the longer one is awake, the greater the need for sleep. Process S is reflected by increased sleep pressure following a night of sleep deprivation despite a circadian trough in sleepiness.
Figure 1-2. Model of the hypothesized interaction between affective processing and chronophysiology in depression.
Appendix

Diagnostic Criteria for Major Depressive Disorder, Dysthymia, and Primary Insomnia (American Psychiatric Association, 2000)

Major Depressive Disorder

The diagnosis of Major Depressive Disorder requires:

A. Presence of a single Major Depressive Episode

B. The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode. Note: This exclusion does not apply if all the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of a general medical condition.

Criteria for a Major Depressive Episode:

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.

(4) insomnia or hypersomnia nearly every day
(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(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 self-reproach or guilt about being sick)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

**Dysthymia**

The diagnosis of dysthymia requires:

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years. Note: In children and adolescents, mood can be irritable and duration must be at least 1 year.

B. Presence, while depressed, of two (or more) of the following:

   (1) poor appetite or overeating
   (2) Insomnia or Hypersomnia
(3) low energy or fatigue
(4) low self-esteem
(5) poor concentration or difficulty making decisions
(6) feelings of hopelessness

C. During the 2-year period (1 year for children or adolescents) of the disturbance, the person has never been without the symptoms in Criteria A and B for more than 2 months at a time.

D. No Major Depressive Episode has been present during the first 2 years of the disturbance (1 year for children and adolescents); i.e., the disturbance is not better accounted for by chronic Major Depressive Disorder, or Major Depressive Disorder, In Partial Remission.

Note: There may have been a previous Major Depressive Episode provided there was a full remission (no significant signs or symptoms for 2 months) before development of the Dysthymic Disorder. In addition, after the initial 2 years (1 year in children or adolescents) of Dysthymic Disorder, there may be superimposed episodes of Major Depressive Disorder, in which case both diagnoses may be given when the criteria are met for a Major Depressive Episode.

E. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode, and criteria have never been met for Cyclothymic Disorder.

F. The disturbance does not occur exclusively during the course of a chronic Psychotic Disorder, such as Schizophrenia or Delusional Disorder.

G. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**Primary Insomnia**

The diagnosis of primary insomnia requires:

A. The predominant symptom is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month.

B. The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.

D. The disturbance does not occur exclusively during the course of another mental disorder (eg, major depressive disorder, generalized anxiety disorder, a delirium).

E. The disturbance is not due to the direct physiological effects of a substance (eg, drug abuse, medication) or a general medical condition.
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Chapter 2
Anticipation of Affect in Dysthymia: Behavioral and Neurophysiological Indicators

Cognitive theories posit that individuals with unipolar mood disorders have biased processing of affective events (Abramson et al., 1978, 1989; Beck, 1967, 1987). In particular, individuals with depressive disorders may expect to experience more negative outcomes and fewer positive outcomes than psychologically healthy individuals. Mood-congruent processing of past or current affective events has been demonstrated using measures of both behavior (for meta-analysis see Matt et al., 1992) and brain activity (for review see Shestyuk & Deldin, in press). However, there is less empirical evidence that expectations for future affective events are biased in mood disorders. The present research evaluates future-oriented affective biases in individuals with dysthymia (DYS) and healthy controls using both behavioral and neurophysiological indices. Cognitive biases are particularly pronounced in individuals with chronic mood disorders such as DYS (McCullough et al., 1988, 1994; Riso et al., 2003), and the continuation of depressive symptoms over a period of years may be especially likely to change expectations for future affective experience.

Participants in this study completed a two-stimulus imperative response task. A symbol forecasted the affective valence of a subsequently presented adjective (“+”, positive; “=”, neutral; “-”, negative), and participants indicated whether each adjective would likely describe their general feeling about
themselves over the next two weeks. The percent of positive, neutral, and negative adjectives anticipated to be self-referent provided a behavioral measure of future-oriented affective bias, and the time taken to make these judgments provided a behavioral measure of response uncertainty. Existing research using a similar procedure indicates that individuals with major depression expect more negative and fewer positive adjectives to apply to them than healthy controls, but the amount of time taken to make self-reference judgments didn’t vary significantly as a function of depressive state or adjective valence (Serfaty et al., 2002).

Event related potential (ERP) components elicited during the response task were examined to determine the extent of neurophysiological biases in affect anticipation and response uncertainty. In particular, potential biases in affective stimulus anticipation and response preparation were examined using the contingent negative variation (CNV) component preceding an imperative stimulus (for a review, see Fabiani et al, 2007; McCallum, 1988; Rockstroh et al., 1989). Potential differences in uncertainty during indications of adjective future self-reference were examined using the post-imperative negative variation (PINV) component following an imperative stimulus (for a review see McCallum, 1988; Rockstroh et al., 1989). Very few studies have used CNV or PINV to index affective processing biases in mood disorders, and existing research fails to find an effect of affective valence on these ERP components (Serfaty et al., 2002; Yee & Miller, 1988). Rather, individuals with major depression generally demonstrate non-valence-specific decreases in CNV amplitudes (less
anticipation and response preparation; Ashton et al., 1988; Giedke & Bolz, 1980; Timsit-Berthier, 1993), and increases in PINV amplitudes (more response uncertainty; Kessler et al., 1992; Knott et al., 1991; Serfaty et al., 2002; Thier et al., 1986), compared to healthy controls.

The present study addresses a need for further research on chronic forms of depression such as DYS, and is unique in its combined use behavioral measures and the CNV and PINV ERP components to examine future-oriented, self-referent affective biases. Consistent with evidence for a positive bias in non-depressed individuals (Abramson et al., 1978; Abramson et al., 1989), healthy controls were hypothesized to have increased anticipation and response certainty for positive events (i.e., more indications of adjective future self-reference, larger CNV, shorter response times, smaller PINV), and decreased anticipation and response certainty for negative events (i.e., fewer indications of adjective future self-reference, smaller CNV, longer response times, larger PINV), compared to neutral events. Consistent with evidence for a negative bias in depressed individuals (Abramson et al., 1978, 1989; Beck, 1967, 1987), participants with DYS were expected to have increased anticipation and response certainty for negative events, and decreased anticipation and response certainty for positive events, compared to neutral events. Furthermore, these mood-congruent anticipation biases were expected to differentiate individuals with DYS from healthy controls.

Method

Participants
Participants included 15 healthy controls and 12 individuals with current DYS between 18 and 65 years of age. Participants were recruited through newspaper advertisements and fliers placed in outpatient psychiatric clinics within the greater Boston area. Diagnoses were determined using the Structured Clinical Interview for the DSM-IV (SCID; First et al., 1995) administered by a doctoral level clinician (PJD) or research assistants trained in SCID administration. Twenty-five percent of the SCID interview tapes were reviewed by a second rater to confirm diagnoses. Five DYS participants had comorbid major depressive disorder. Groups were balanced for sex, handedness (Edinburgh Handedness Questionnaire; Oldfield, 1971), age, and education, and differed predictably on measures of depression (Beck Depression Inventory; BDI; Beck et al., 1961; Beck Hopelessness Scale; BHS; Beck et al., 1974) and anxiety (State/Trait Anxiety Inventory; STAIS/STAIT; Spielberger et al., 1970; see Table 2-1). Individuals taking psychiatric medications and those with a history of cognitive impairment, major medical illness, substance abuse or dependence, head injury with loss of consciousness over 10 min, or seizure disorder were excluded from the study. All participants provided written informed consent and were paid $10/hr.

Materials

Emotional adjectives were selected from a list of 310 adjectives rated by 146 undergraduates for valence and arousal using two 5-point Likert scales ranging from very positive (1) to very negative (5), and very arousing (1) to very calm (5), respectively. Adjectives were then ranked according to mean valence
ratings, and the 40 most positive (e.g., “vivacious”, “thrilled”, “creative”, “loved”), neutral (e.g., “acceptable”, “silent”, “tolerable”, “unchanging”), and negative (e.g., “miserable”, “humiliated”, “wretched”, “guilty”) adjectives were selected for use in the present study. Adjectives in each valence condition were balanced for word length, \( F(2, 117) = .34, p > .1 \), and frequency of use, \( F(2, 117) = .12, p > .01 \), and varied in valence, \( F(2, 117) = 1601.45, p < .001 \), and arousal, \( F(2, 117) = 66.53, p < .001 \). Average valence ratings were 1.67 for positive words, 2.92 for neutral words, and 4.29 for negative words, and all paired comparisons were significant \( (p < .001 \) for all). Average arousal ratings were 2.16 for positive words, 3.41 for neutral words, and 2.52 for negative words, and all paired comparisons were significant \( (p < .01 \) for all).

**Procedure**

Participants toured the lab, provided informed consent, and completed the diagnostic assessment at least one day prior to completing the self-report questionnaires and physiological recording. Participants were seated in a comfortable chair approximately 115 cm from a computer monitor within a darkened experimental room during physiological recording. Participants were presented with one of four visual symbols (“+”, “=”, “-”, “?”; S1) for 250 ms, followed 3 s later by the presentation of an emotionally-valenced adjective (positive, neutral, or negative; S2) for 500 ms. Plus signs signaled positive adjectives, equal signs signaled neutral adjectives, minus signs signaled negative adjectives, and question marks signaled the pseudorandom presentation of either a positive, neutral, or negative adjective. Symbols were
3.8 cm in height, adjectives were 1.3 cm in height, and all stimuli were white with black background. After adjective presentation, participants had 4 s to indicate whether or not each adjective would likely describe their general feeling about themselves over the next two weeks by pressing one of two buttons on a response box. Response hand was counterbalanced across participants. Participants completed two blocks of 60 trials, with an optional break between blocks, for a total of 120 7 s trials (30 in each valence condition).

**Behavioral Analysis**

Mean adjective future self-reference, reaction time, and non-response rate were calculated for each participant and valence condition. Adjective future self-reference and reaction time were based on the total number of completed responses, rather than the number of trials. Adjective future self-reference, reaction time, and non-response rate were then analyzed using three separate Valence (positive, neutral, negative) x Group (CTL, DYS) ANOVAs. As a conservative test of interaction effects, higher order effects were required to be significant at each stage of post-hoc testing (e.g., if a 2-way interaction of Valence x Group was obtained, a main effect of valence within each group was required before paired valence comparisons were interpreted). Huynh-Feldt corrections were applied when data failed to meet the sphericity assumption. Pearson correlations were computed within each diagnostic group to assess associations between self-report measures of symptom severity and behavioral responses. Due to equipment malfunctions, behavioral data were not available for two participants with DYS.
Physiological Recording, Data Reduction, and Analysis

EEG was collected, filtered, and amplified using an S.A. Instruments Company (Encinitas, CA) polygraph. Signals were recorded from 32 sites using a conductive electrogel and tin electrodes mounted in an electrode cap (Electro Cap International, Inc., Easton, OH) according to the International 10-20 System. Electrooculography (EOG) was recorded for both horizontal and vertical eye movements using tin electrodes placed on the outer canthi, left suborbital, and right supraorbital positions. EEG was referenced to the left earlobe and then re-referenced offline to the average of both earlobes (Miller et al., 1991).

Impedances for all electrodes were kept below 10 KΩ. Data were digitally sampled at 512 Hz and filtered online with a high pass analog filter set to .01 Hz and a low pass filter set to 30 Hz. A 7 Hz low-pass digital filter was applied to the data offline.

Eye movement artifact was corrected by applying linear transformation based on computed regression weights for the propagation factors of vertical and horizontal EOG in each EEG channel (James Long Company, Caroga Lake, New York). Eye movement correction was then visually confirmed, and trials containing residual eye and muscle movement artifacts were excluded from analysis. Data from leads with remaining artifact (< 4%) were substituted with averages from all surrounding leads that did not require substitutions for each participant and valence condition.

Of the original 32 scalp sites, only midline sites Fz, Cz, and Pz were included in the analyses. This allowed the inclusion of left handed participants.
and participants with uncorrectable artifact at other sites. ERPs were averaged separately for each participant, valence condition, and site using a 500 ms pre-S1 baseline for CNV, and a 500 ms pre-S2 baseline for PINV. Principle component analysis, grand average inspection, and literature review (e.g., Ashton et al., 1988; Bolz & Giedke, 1981; Klein et al., 1998; Knott et al., 1991; Serfaty et al., 2002; Thier et al., 1986) were used to define time windows for CNV (800-3000 ms post-S1) and PINV (4000-5000 ms post-S1), and mean amplitudes for each component time window were calculated for analysis. Both CNV and PINV are negative components, where more negative amplitudes indicate greater component-related processing.

CNV and PINV were analyzed using two separate Valence (positive, neutral, negative) x Group (CTL, DYS) x Lead (Fz, Cz, Pz) repeated measures ANOVAs. Data for one participant with DYS were excluded from PINV analyses due to unresolvable artifact in the physiology data following S2. The inclusion of ERP data in the analyses was not contingent on behavioral responses, as per standard practice. Higher order effects were required to be significant at each stage of post-hoc testing, and Huynh-Feldt corrections were applied when data failed to meet the sphericity assumption. Pearson correlations were computed within each diagnostic group to assess associations between self-report measures of symptom severity and ERP components, averaging across leads.

Results

Behavioral Data
Mean self-reference ratings are presented in Table 2-2 and Figure 2-1. Analyses of adjective future self-reference revealed a significant Valence x Group interaction, $F(2, 46) = 52.92, p < .001$. Valence comparisons indicated that fewer negative than positive ($p < .001$) or neutral ($p < .001$) adjectives were expected to be self-referent by healthy controls. In contrast, fewer positive than neutral ($p < .01$) or negative ($p < .001$) adjectives were expected to be self-referent by individuals with DYS. Group comparisons indicated that more positive and fewer negative adjectives were expected by healthy controls than individuals with DYS ($p < .001$ for both). There was also a trend for healthy controls to expect more neutral adjectives than individuals with DYS ($p < .10$). No further significant effects were observed for adjective self-reference.

Mean response times (RT) are presented in Table 2-2. RT analyses revealed a significant main effects of Valence, $F(2, 46) = 32.72, p < .001$, where participants took longer to respond to neutral adjectives than to either positive ($p < .001$) or negative ($p < .001$) adjectives. No further significant effects were observed for RT.

The mean (and standard deviation) non-response rate was 4.61% (6.19) for healthy controls and 8.33% (11.97) for individuals with DYS. Analyses of non-response rate revealed a significant main effect of Valence, $F(2, 46) = 8.85, p < .01$, where participants failed to respond more often to neutral than positive ($p < .01$) or negative ($p < .01$) adjectives. No further significant effects were observed for non-response rate.
Correlational analyses indicated a negative relationship between the self-reference of positive adjectives and BDI score in healthy controls, \( r(13) = -.62, p < .05 \), and BHS score in individuals with DYS, \( r(8) = -.86, p < .01 \). Furthermore, the self-reference of negative adjectives was positively correlated with scores on the BDI, \( r(13) = .57, p < .05 \), STAIT, \( r(13) = .78, p < .001 \), and STAIS, \( r(13) = .74, p < .01 \), in healthy controls, and with scores on the STAIT, \( r(8) = .67, p < .05 \), and STAIS, \( r(8) = .68, p < .05 \), in individuals with DYS. There were no other significant correlations between behavioral responses and self-report measures of symptom severity.

**ERP Data**

Grand average ERP waveforms following S1 are presented in Figure 2-2, and average CNV amplitudes for each group at each valence condition are presented in Table 2-2 and Figure 2-3. CNV analyses revealed a significant Valence x Group interaction, \( F(2, 50) = 4.93, p < .05 \). Valence comparisons indicated that healthy controls had larger CNV amplitudes when positive adjectives were forecasted than when either neutral \((p < .05)\) or negative \((p < .05)\) adjectives were forecasted. The effect of valence was marginally significant for individuals with DYS \((p < .10)\), where pairwise comparisons indicated larger CNV amplitudes when negative compared to neutral adjectives were forecasted \((p < .05)\). Group comparisons of CNV amplitudes indicated that healthy controls had larger CNV amplitudes than individuals with DYS when neutral adjectives were forecasted \((p < .05)\), and CNV prior to positive and negative adjectives did not vary by group \((p > .10)\). Finally, across groups there was a main effect for
lead, $F(2, 50) = 5.55, p < .01$, where CNV amplitudes at Fz were smaller than those at Cz ($p < .01$), and marginally smaller than those at Pz ($p < .10$). No further significant effects were observed for CNV.

Grand average ERP waveforms following S2 are presented in Figure 2-4, and average PINV amplitudes for each group at each valence condition are presented in Table 2-2. PINV analyses revealed a main effect of Valence, $F(2, 48) = 3.32, p < .05$, where PINV amplitudes were larger in response to neutral compared to positive adjectives ($p < .05$). There was also a main effect of Group, $F(1, 24) = 6.66, p < .05$, where individuals with DYS had larger PINV amplitudes than healthy controls ($p < .05$). Finally, there was a marginally significant Valence x Lead interaction, $F(4, 96) = 3.84, p < .10$, where PINV at Pz was larger in response to neutral compared to positive adjectives ($p < .05$). No further significant effects were observed for PINV.

There were no significant correlations between CNV or PINV and self-report measures of symptom severity.

Discussion

The purpose of this study was to determine whether healthy controls and individuals with DYS demonstrate biased anticipation for future affective events at a behavioral and neurophysiological level. Behavioral data indicate that healthy controls expect fewer negative adjectives to apply to them in the future than either neutral or positive adjectives, and individuals with DYS expect fewer positive adjectives to apply to them in the future than either neutral or negative adjectives. Furthermore, these behavioral anticipation biases distinguished
healthy controls from individuals with DYS, and they were correlated with measures of depression and anxiety. ERP data indicate that healthy controls have greater anticipation (larger CNV amplitudes) for positive compared to neutral or negative events, and more anticipation for neutral events than individuals with DYS. However, neurophysiological anticipation was not correlated with measures of depression or anxiety.

These results are generally consistent with cognitive models of depression (Abramson et al., 1978, 1989; Beck, 1967, 1987). In particular, Abramson et al. (1978, 1989) posit that depression is associated with frequent exposure to negative events and infrequent exposure to positive events, which result in more anticipation for negative compared to positive events in the future. The present study indicates that individuals with DYS expected more negative than positive adjectives to describe them in the future, and these data are consistent with earlier behavioral studies of cognitive bias in individuals with major depressive disorder (e.g., Andersen et al., 1992; Serfaty et al., 2002). Furthermore, because we used self-reference ratings for neutral adjectives as a comparison condition, this study demonstrates that behavioral anticipation of negative adjectives is reduced in healthy controls (rather than being enhanced for positive stimuli), while behavioral anticipation of positive adjectives is reduced in individuals with DYS (rather than being enhanced for negative stimuli).

The direction of behavioral anticipation biases differed from the direction of neurophysiological anticipation biases, indexed by CNV. While healthy controls showed reduced behavioral anticipation for negative affect, they
demonstrated larger CNV amplitudes prior to positive versus neutral or negative adjectives. Furthermore, while individuals with DYS had reduced behavioral anticipation of positive affect, there was a non-significant trend for them to have larger CNV amplitudes prior to negative versus neutral adjectives. Thus, healthy individuals exhibit reduced anticipation of naturalistic negative events, but enhanced anticipatory processing of immediately oncoming positive information in laboratory conditions. Individuals with DYS exhibit reduced anticipation of naturalistic positive events, but tend to have enhanced anticipatory processing of immediately oncoming negative information in laboratory conditions. Despite within-group differences, there were no differences between groups in CNV amplitude prior to positive or negative stimuli. However, controls demonstrated more anticipatory processing of neutral stimuli than individuals with DYS. These data are consistent with general reductions in CNV amplitude prior to non-affective, non-self-relevant, stimuli in individuals with major depression compared to healthy controls (Ashton et al., 1988; Giedke & Bolz, 1980; Timsit-Berthier, 1993), and may reflect a selective reduction in anticipation for stimuli without hedonic value.

Participants did not exhibit the predicted interaction between affective valence and group on measures of response uncertainty (response time, PINV). Rather, ratings of adjective self-reference took longer for neutral compared to positive or negative adjectives across groups, and PINV amplitudes were larger overall for individuals with DYS than healthy controls. Larger response times and non-response rates observed for neutral stimuli reflect difficulty anticipating the
future self-reference of these adjectives. Furthermore, our PINV data indicate reduced response certainty in DYS, and these results are consistent with literature demonstrating larger PINV amplitudes in participants with major depression compared to healthy controls (Kessler et al., 1992; Knott et al., 1991; Thier et al., 1986). Enhanced PINV amplitudes in individuals with DYS compared to controls could reflect indecisiveness, which is a feature of both DYS and major depression. However, this neurophysiological index of decreased response certainty was not reflected by concurrent increases in response time.

The functional significance of CNV and PINV is not unanimously agreed upon. While CNV is probably most well-known as a measure of stimulus anticipation, it has also been interpreted as an index of motivation, excitability, and motor preparation independent of cognitive anticipation (for reviews see Fabiani et al., 2007; McCallum, 1988; Rockstroh et al., 1989). Likewise, PINV has been interpreted variously as an index of response uncertainty, stimulus ambiguity, and stimulus uncontrollability (for reviews see McCallum, 1988; Rockstroh et al., 1989). It is unclear whether alternate interpretations of CNV or PINV would change the significance of these ERP results: biased anticipation/motivation/excitement (larger CNV) for future positive adjectives characterized healthy controls, individuals with DYS had reduced anticipation/motivation/excitement (smaller CNV) for future neutral stimuli compared to controls, participants demonstrated less certainty/clarity/control (larger PINV) during decisions about neutral adjective future self-reference, and
individuals with DYS had less certainty/clarity/control (larger PINV) overall than healthy controls.

Changes in the characteristics of CNV and PINV are observed in many forms of pathology, including major depression, schizophrenia, anxiety disorders, epilepsy, and Parkinson’s disease (for review see McCallum, 1988). Rather than specifying particular forms of pathology, these components reflect synchronous activity in the frontal cortex, anterior cingulate, and thalamus during stimulus anticipation and response monitoring (Fan et al., 2007; Nagai et al., 2004; Zappoli, 2003). Though the timing, amplitude, and distribution of ERP components can vary widely across populations and experimental tasks (McCallum, 1988), the definitions and distributions reported here for CNV and PINV are within the usual ranges. The utility of this research is in the use of these ERP components as indices of cognitive processes that pertain to models of depression.

This study addresses a need for research on future-oriented biases in depressive disorders such as DYS, and it is unique in its combined use of behavior and the CNV and PINV ERP components as measures of affect anticipation and response uncertainty. Furthermore, because few differences have been found between individuals with DYS and those with other chronic forms of depression (McCullough et al., 2003), the implications of these data may extend to other populations of depressed patients. This study also has several limitations. Unfortunately, small sample size prevented us from analyzing ERP data across all leads, though graphs of CNV and PINV across all leads in right-
handed participants with resolvable artifact produced remarkably similar results. Another limitation is that we did not control for stimulus arousal, and we used undergraduates rather than study participants to rate stimulus valence and arousal. A final limitation, and hopefully one that will stimulate further research, is that we did not employ a control task to distinguish the effects of future-orientation from mood-congruent biases observed in past- or present-oriented tasks. Participants' ratings of which adjectives will describe them over the next two weeks may reflect their current mood as much, if not more than, their anticipated mood.

In summary, anticipation biases characterized healthy controls and individuals with DYS. Affective biases are important to understand because mood disorders are a leading cause of worldwide disease burden (Murray & Lopez, 1996). Furthermore, characteristic symptoms of mood disorders (e.g., low mood, anhedonia, decision making difficulties, suicidality) may result from unrealistic or unhelpful predictions about future affective events. Insights into the behavioral and neurophysiological mechanisms of affective anticipation biases may eventually improve the effectiveness of cognitive-behavioral therapy and similar mood-disorder treatments. Future research may benefit from explicit tests of illness severity and chronicity on affective anticipation biases in mood disorders as it is likely that illness chronicity is positively correlated with degree of anticipation for negative stimuli, and negatively correlated with degree of anticipation for positive stimuli. Furthermore, ERPs can be used to identify additional components of cognitive processing that underlie behavioral
indications of adjective future self-reference. Finally, manipulations of stimulus self-reference and arousal may determine whether these constructs are important to the phenomenology of unipolar mood disorders.
Table 2-1

*Group Demographics and Self-Report Questionnaire Scores*

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>CTL ($n = 15$)</th>
<th>DYS ($n = 12$)</th>
<th>$\chi^2$/$F$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>$10♀, 5♂$</td>
<td>$6♀, 6♂$</td>
<td>$\chi^2 (1) = 0.8$</td>
<td>$p &gt; .10$</td>
</tr>
<tr>
<td>Handedness</td>
<td>13 R, 2 L</td>
<td>9 R, 2 L, 1 A</td>
<td>$\chi^2 (2) = 1.4$</td>
<td>$p &gt; .10$</td>
</tr>
<tr>
<td>Age</td>
<td>31.6 (11.7)</td>
<td>35.8 (15.2)</td>
<td>$F(1, 25) = 0.9$</td>
<td>$p &gt; .10$</td>
</tr>
<tr>
<td>Education</td>
<td>16.3 (1.3)</td>
<td>15.3 (2.0)</td>
<td>$F(1, 23) = 4.3$</td>
<td>$p &gt; .10$</td>
</tr>
<tr>
<td>BDI</td>
<td>2.6 (3.5)</td>
<td>22.6 (9.9)</td>
<td>$F(1, 25) = 53.2$</td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>BHS</td>
<td>1.6 (1.2)</td>
<td>12.4 (4.7)</td>
<td>$F(1, 25) = 73.7$</td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>STAIS</td>
<td>26.3 (5.4)</td>
<td>38.1 (12.5)</td>
<td>$F(1, 25) = 10.8$</td>
<td>$p &lt; .01$</td>
</tr>
<tr>
<td>STAIT</td>
<td>30.1 (5.4)</td>
<td>57.1 (10.0)</td>
<td>$F(1, 25) = 80.1$</td>
<td>$p &lt; .001$</td>
</tr>
</tbody>
</table>

*Note:* Handedness was assessed using the Edinburgh Handedness Questionnaire (Oldfield, 1971; R = right handed, L = left handed, A = ambidextrous). Means (and standard deviations) are provided for age, number of years of education, and self-report questionnaire scores (Beck Depression Inventory; BDI; Beck et al., 1961; Beck Hopelessness Scale; BHS; Beck et al., 1974; State/Trait Anxiety Inventory; STAIS/STAIT; Spielberger et al., 1970). Post-hoc testing for all self-report questionnaire scores indicates that healthy controls (CTL) differed significantly from individuals with DYS. Education was unavailable for two control participants and these data are therefore omitted from this select demographic analysis.
Table 2-2

*Mean (and Standard Deviation) Self-reference Ratings, Response Times, CNV Amplitudes, and PINV Amplitudes*

<table>
<thead>
<tr>
<th>Valence</th>
<th>CTL</th>
<th>DYS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-reference (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>80.2 (18.9)</td>
<td>22.6 (12.8)</td>
</tr>
<tr>
<td>Neutral</td>
<td>68.2 (16.3)</td>
<td>53.5 (25.0)</td>
</tr>
<tr>
<td>Negative</td>
<td>12.3 (16.1)</td>
<td>67.2 (19.6)</td>
</tr>
<tr>
<td><strong>Response time (ms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>426.2 (16.8)</td>
<td>439.6 (27.8)</td>
</tr>
<tr>
<td>Neutral</td>
<td>450.1 (18.0)</td>
<td>464.2 (27.9)</td>
</tr>
<tr>
<td>Negative</td>
<td>428.7 (24.7)</td>
<td>444.6 (22.9)</td>
</tr>
<tr>
<td><strong>CNV (μV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>-2.8 (5.0)</td>
<td>0.0 (3.63)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-0.6 (3.0)</td>
<td>1.6 (2.3)</td>
</tr>
<tr>
<td>Negative</td>
<td>0.8 (4.1)</td>
<td>-0.9 (3.6)</td>
</tr>
<tr>
<td><strong>PINV (μV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>4.4 (4.5)</td>
<td>1.0 (4.2)</td>
</tr>
<tr>
<td>Neutral</td>
<td>3.1 (4.1)</td>
<td>-1.2 (3.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>2.5 (4.3)</td>
<td>0.6 (4.3)</td>
</tr>
</tbody>
</table>
Figure 2-1. Average (and standard deviation) self-reference ratings for positive (pos), neutral (neu), and negative (neg) adjectives, separated by group. Significant differences are indicated for within-group valence comparisons (V; p < .01) and between-group comparisons (G; p < .001); self-reference ratings for marked valence conditions (V) were significantly less than self-reference ratings for the two alternative valence conditions in both groups.
**Figure 2-2.** Grand average ERP waveforms following positive, neutral, and negative warning symbols, separated by group and lead. Data from 800-3000 ms were characterized as CNV.
Figure 2-3. Average (and standard deviation) CNV amplitude for positive (pos), neutral (neu), and negative (neg) adjectives, separated by group. Significant differences are indicated for within-group valence comparisons (V; $p < .05$) and between-group comparisons (G; $p < .05$); CNV prior to positive adjectives was significantly larger than the two alternative valence conditions in control participants.
Figure 2-4. Grand average ERP waveforms following positive, neutral, and negative adjectives, separated by group and lead. Data from 4000-5000 ms were characterized as PINV.
Footnotes

1 The random valence condition was included to determine whether uncertainty about the affective valence of the to-be-presented adjective would alter neurophysiological anticipation. This condition was ultimately excluded from CNV analyses because data for the random and neutral conditions were comparable. The random condition was excluded from PINV analyses a priori because there were not enough trials to compare responses to positive, neutral, and negative adjectives within the random valence condition, and a composite measure of these responses was not relevant to the project aims. Responses to adjectives in the random valence condition were also excluded from behavioral analyses.

2 CNV subcomponents thought to represent orienting (early CNV, 800-1300 ms), sustained attention (late CNV, 1300-2500 ms), and motor response preparation (2500-3000 ms) for expected stimuli were examined individually. As data for each subcomponent were essentially identical, only the composite CNV index (800-3000 ms) was analyzed.
References


Giedke, H., Bolz, J., 1980. Pre- and postimperative negative variation (CNV and PINV) under different conditions of controllability in depressed patients and healthy controls. Progress in Brain Research, 54, 579-582.


Chapter 3
Decision Making is Related to Time of Day, Sex, and Sleep Duration

The ability to make advantageous decisions is a critical life skill, and deficits in this skill are associated with a variety of clinical disorders (e.g., ADHD, mood disorders, schizophrenia, substance use disorders; for review see Buelow & Suhr, 2009). Furthermore, the ability to make advantageous decisions can be dissociated from other important cognitive functions such as attention, memory, and general executive functioning (e.g., Bechara, H. Damasio, Tranel, & Anderson, 1998; Eslinger & A. Damasio, 1985; Shallice & Burgess, 1991). Incentive-based decision making is commonly assessed using the Iowa Gambling Task (IGT; Bechara, A. Damasio, H. Damasio, & Anderson, 1994). The IGT depends on learning, by trial and error, which choices are associated with the most reward and the least punishment. Thus, this task mimics the requirements of advantageous decision making in real life.

Performance on a variety of cognitive tasks is affected by an interaction between two biological drives: circadian rhythms and the sleep-wake homeostat (for review see Cajochen, Blatter, & Wallach, 2004). Circadian rhythms cause fluctuations in performance across the day, while the homeostatic system results in performance changes with increasing time awake. The interaction of circadian and homeostatic drives is generally referred to as the “two-process model of sleep regulation” (Borbély, 1982). The two-process model predicts performance
for tasks of attention, memory, and executive functioning (for reviews see Pilcher & Huffcutt, 1996; Schmidt, Collette, Cajochen, & Peigneux, 2007). These skills are necessary, though not sufficient, for advantageous decision making.

Most closely related to decision making are tasks of non-incentive based executive functioning. These tasks often focus on resolution of cognitive conflict. For example, Harrison et al. (2007) performed a particularly elegant test of the two-process model on response inhibition in a Go/No-go task. These authors demonstrated that errors of commission increase with increasing time awake, while time of day effects are more apparent following 1 or 16 hr time awake than at intermediate times. Studies of the two-process model and executive functioning also demonstrate that subtle differences between tasks and individuals may mediate the influence of circadian and homeostatic processes. For example, Bennett et al. (2008) examined the effects of time of day and individual circadian chronotype (preference for morning versus evening) on several widely-used neuropsychological tests. These authors identified an interaction between circadian chronotype and session time on the Wisconsin Card Sorting Task, where morning types were more efficient at shifting between card sorting strategies in the morning than in the afternoon. However, there was no effect of circadian chronotype or time of day on errors of commission during other executive functioning tasks. Furthermore, while Manly et al. (2002) demonstrated that errors of commission on a Go/No-go task were more frequent at 01:00 and 08:00 than at 13:00 or 20:00, Matchock and Mordkoff (2009) demonstrated that executive skill is reduced at 12:00 and 16:00 compared to
08:00 and 20:00 using the Attentional Network Task. The influence of the two-process model on executive functioning is not simple and additional research is needed to dissociate the effects of circadian and homeostatic drives on performance.

Few studies examine the relationship between the two-process model and incentive-based decision making (Harrison & Horne, 1999; Killgore, Balkin, & Wesensten, 2006). However, understanding the relationship between circadian-homeostatic processes and decision making could evince ways to maximize benefits and minimize negative consequences from choices in daily life. The present study compares IGT performance in the morning to performance in the evening as a preliminary examination of the two-process model in decision making. It also examines the relationship between IGT performance and naturalistic variance in amount of pre-session sleep. There is evidence that 49 hr of sleep deprivation impairs performance on the IGT (Killgore et al.). However, no one has demonstrated an effect of time of day or partial sleep restriction on incentive-based decision making.

Previous studies examining the effect of time of day on non-incentive-based tasks of executive functioning have produced variable results (Bennett et al., 2008; Harrison et al., 2007; Manly et al., 2002). Thus, no a priori hypothesis was generated for the effect of time of day on IGT performance. However, based on the Killgore et al. (2006) study showing that IGT performance is impaired following 49 hr of total sleep deprivation, IGT performance was expected to be
positively correlated with the amount of sleep on the night before task administration.

This study also examines the effect of sex on IGT performance, as previous research indicates that females do not perform as well on the IGT as males (e.g., Bolla et al., 2004; Overman et al., 2006; Reavis & Overman, 2001). Furthermore, there is evidence that circadian and homeostatic effects on performance are sexually dimorphic (e.g., Acheson, Richards, & de Wit, 2007; Blatter et al., 2006). The effect of sex on IGT performance was expected to correspond with previous data demonstrating that females make fewer advantageous choices on the task compared to males. Furthermore, based on data that sleep-deprivation decreases risk taking in women but not men (Acheson et al.), pre-session sleep duration was expected to correlate positively with IGT performance in females.

Method

Participants

Participants included 63 individuals (42 female) between 18 and 45 years of age. All participants had normal or corrected-to-normal vision and hearing, no reported history of psychiatric or neurological disorder, no reported history of head injury resulting in loss of consciousness greater than 2 min, and no reported alcohol or recreational drug use on the day before or the day of the study. Individuals who reported consumption of more than six caffeinated beverages on the day of the study session were excluded from study participation. Individuals who obtained less than 5.5 hr sleep on the night prior to
study participation were excluded from study analyses. Participants received either one research credit toward introductory psychology course requirements, or $10, per hour of research participation. Participants were recruited through the introductory psychology subject pool, biopsychology subject pool, and paper fliers posted throughout the university campus and surrounding community. The study followed national and institutional ethical standards.

Procedure

Participants completed the IGT either in the morning (08:00-10:00) or in the evening (20:00-22:00). Session time was randomly assigned. Four decks of cards were simultaneously and continuously presented on the computer screen. Participants chose one card at a time, in any order, for 100 trials. Each card selection always resulted in either a $50 or $100 financial gain, but some selections in each deck also resulted in financial loss. The ratio of reward to punishment in the two decks of cards with $50 rewards made selections from these decks financially advantageous. Conversely, the ratio of reward to punishment in the two decks of cards with $100 rewards made selections from these decks financially disadvantageous. The frequency of punishment was balanced across good and bad decks, where one good deck and one bad deck delivered punishment 50% of the time, and the remaining two decks delivered punishment 10% of the time. Participants were told that the object of the game was to win as much money as possible and avoid losing as much money as possible, that there were some good decks and some bad decks, and that to win the game they should avoid the worst decks. Participants provided estimates of
pre-session sleep on a brief questionnaire administered at the beginning of the session.

Analysis

Chi-square analysis was performed to determine whether participant sex was balanced between session times. A t-test was performed to determine whether age and pre-session sleep duration were balanced between session times. Effects with \( p < .10 \) were considered significant for analyses of \textit{a priori} group equivalence.

Performance on the IGT was measured as number of card selections from good decks, minus the number of card selections from bad decks, across 100 trials. The effects of session time (AM, PM) and sex (female, male) on IGT performance were analyzed using a 2 x 2 ANOVA. Pearson’s correlational analyses were performed to assess the relationship between IGT performance and amount of pre-session sleep. Correlations were split by time of day and sex. Effects with \( p < .05 \) were considered significant.

Results

Participant sex and age were balanced across time of day (see Table 3-1). Pre-session sleep was not balanced across time of day: participants who completed sessions in the morning had less sleep than participants who completed sessions in the evening (see Table 3-1). Thus, the effect of time of day on IGT performance should be interpreted with caution.\(^2\)

Average IGT performance in blocks of 20 cards is presented in Figure 3-1, and average IGT performance across the session is presented in Figure 3-2.
ANOVA results are presented in Table 3-2. There was a significant interaction between time of day and sex where males performed better on the IGT in the morning \((M = 8.20, SD = 4.08)\) than in the evening \((M = 2.8, SD = 5.34)\), \(t(19) = 2.43, p = .03\). Females had comparable IGT performance in the morning \((M = 5.38, SD = 4.99)\) and evening \((M = 5.38, SD = 4.21)\), \(t(40) = 0.00, p = .99\). Sex differences were not observed in either morning or evening sessions. There was also a main effect of time of day on IGT performance, where IGT performance was better during AM sessions \((M = 6.19, SD = 4.85)\) than PM sessions \((M = 4.43, SD = 4.75)\). The main effect of sex did not reach statistical significance.

Correlation analysis indicated that hours of pre-session sleep predicted IGT performance for females with AM sessions, \(c(20) = .60, p = .005\) (see Figure 3-2). Hours of pre-session sleep did not predict IGT performance for females with PM sessions, \(c(22) = .06, p = .81\), males with AM sessions, \(c(8) = -.13, p = .77\), or males with PM sessions, \(c(13) = -.14, p = .66\).

**Discussion**

This study tested the effects of time of day and sex on IGT performance, and examined the association between IGT performance and pre-session sleep. Results indicate that males make more advantageous decisions in the morning than in the evening. Furthermore, amount of pre-session sleep was positively correlated with decision making skill in the morning in females, but not males, and was not associated with decision making skill in the evening. These data provide preliminary evidence that the two-process model predicts decision making, but does so differently for females compared to males.
This is the first study we are aware of to demonstrate an effect of time of session, and an interaction between session time and participant sex, on incentive-based decision making. These results suggest that healthy young adults, and males in particular, have more capacity to learn from mistakes in the morning compared to the evening. Time of day has variable effects on performance for other executive functioning tasks, but sex differences are not widely examined or reported (Bennett et al., 2008; Lawrence & Stanford, 1999; Manly et al., 2002; Matchock & Mordkoff, 2009).

This is also the first study to demonstrate a correlation between natural variation in pre-session sleep and IGT performance, which was present in females but not males. Killgore et al. (2006) demonstrated that 49 hr of total sleep deprivation impairs performance on the IGT, but did not report sex differences. The present study indicates that much more modest sleep decrements are associated with reductions in IGT performance, but only in females who completed the task in the morning. Notably, females demonstrate a larger rebound in delta-frequency activity than males following a night of sleep deprivation, suggesting that females are more sensitive to the effects of sleep loss than males (Armitage, Smith, Thompson, & Hoffmann, 2001). The correlation between pre-session sleep and IGT performance in females, but not males, is not due to sex differences in amount of pre-session sleep; a post-hoc t-test indicated that females and males had comparable amounts of pre-session sleep prior to morning sessions ($p > .10$). Future research, particularly partial
sleep restriction studies with experimental designs, may further elucidate the impact of sleep-restriction and sex on IGT performance.

Improved performance in the morning compared to the evening in males, and correlations between performance and amount of pre-session sleep in females, may reflect circadian rhythms and/or the sleep-wake homeostat. Young adults generally have a delayed circadian phase compared to older adults (May, Hasher, & Stoltzfus, 1993), and males generally have a small but significant evening preference compared to females (Adan & Natale, 2002; Randler, 2007). Furthermore, at least one study indicates that executive functioning is better when session time is matched to circadian chronotype (Bennett et al., 2008). Based on these data, one might expect young males to make better decisions in the evening than in the morning. Instead, the opposite was true. However, decreased performance in the evening compared to the morning fits the homeostatic model of sleep-wake regulation. Decision making in males may be impaired in the evening compared to the morning because there is an increase in sleep pressure, and decrease in performance, with increasing time awake. The homeostatic model also predicts the correlation between pre-session sleep duration and task performance, where cumulative sleep pressure is greater following reductions in sleep duration and should be associated with performance impairment. However, sleep duration only predicted performance in females, and only during morning sessions. Differences between males and females in the effect of time of day on decision making deserve further inquiry, and may delineate the relative influence of circadian and homeostatic drives.
In contrast to previous research, this study failed to demonstrate a main effect of sex on IGT performance. These data are inconsistent with evidence that females make less advantageous choices on the IGT than males (e.g., Bolla et al., 2004; Overman et al., 2006; Reavis & Overman, 2001). Sex differences in IGT performance are not always present (e.g., Overman, 2004; Preston, Buchanan, Stansfield, & Bechara, 2007; Stoltenberg & Vandever, 2010), but differences in sample size, sample characteristics, performance incentives, and punishment schedule do not obviously account for differences between studies. Notably, there is no indication that previous studies controlled for the effect of time of day or pre-session sleep duration on performance.

This study has a number of strengths. As noted above, it is the first study to examine the effect of time of day on incentive-based decision making. Prior research indicates that the two-process model predicts performance on non-incentive-based executive functioning tasks. However, the ability to make advantageous decisions is a distinct neurocognitive process with clear functional implications. Furthermore, the IGT is a common measure of decision making in both healthy and clinical populations, and the results from this study suggest that researchers and clinicians who use the IGT should consider the effects of time of day and sex on task performance. The analysis of pre-sleep duration and IGT performance is another strength of this research. Partial sleep restriction is a common social problem with serious socioeconomic implications (Hublin, Kaprio, Partinen, & Koskenvuo, 2001), and it may have more profound effects on cognitive performance than total sleep deprivation (Pilcher & Huffcutt, 1996).
Additional experimental and naturalistic studies would clarify the impact of partial sleep restriction and sex differences on decision making skill.

The novelty of the results presented here is tempered by limitations in the study design. An ideal test of the two-process model would independently manipulate circadian and homeostatic influences on performance using a forced desynchrony or constant routine protocol (for review see Carrier & Monk, 2000; e.g., Harrison et al., 2007). These approaches would also dissociate biologically-based circadian rhythms from external cues, or zeitgebers, that entrain behavior to a 24 hr cycle. Unfortunately, simply varying session time cannot dissociate circadian from homeostatic and entrainment effects on performance. Moreover, the present study cannot disentangle the effects of time of day and pre-session sleep duration because individuals who completed sessions in the morning had less pre-sleep than those who completed sessions in the evening. Another limitation of this study is the use of subjective rather than objective reports of pre-session sleep duration. Physiological measures of pre-session sleep duration would supplement the data presented here and be less prone to observer expectancy effects. We hope that the results presented here will stimulate additional research that has better controls for circadian and homeostatic effects, and uses additional measures of circadian rhythms and cognitive performance (e.g., self-report measures of circadian chronotype, body temperature as an endogenous physiological indicator of circadian rhythm, neuroimaging of brain activation during task performance).
In summary, this study demonstrates that participant sex mediates the relationships between time of day, pre-sleep duration, and IGT performance. Learning to make advantageous decisions is best accomplished in the morning compared to the evening for males, while females are as good at making decisions in the morning as in the evening. Furthermore, females show a robust effect of previous night's sleep duration on performance in the morning. This suggests that while males may want to skew decision making to earlier in the day, females can expect to perform well all day and they may find a good night's sleep particularly beneficial. Future research should attempt to dissociate the role of circadian and homeostatic processes on decision making skill. In the immediate term, researchers and clinicians should control for time of day when assessing executive functioning, and sex differences should be examined in research on performance and the two-process model of sleep-wake regulation.
Table 3-1

*Participant Demographic Characteristics by Session Time*

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>AM</th>
<th>PM</th>
<th>$\chi^2$ / $t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F:M)</td>
<td>20:8</td>
<td>22:13</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean age</td>
<td>20.8 (4.9)</td>
<td>20.2 (2.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>Mean pre-session sleep</td>
<td>6.8 (0.8)</td>
<td>7.3 (1.1)</td>
<td>-2.12*</td>
</tr>
</tbody>
</table>

Note. * $p < .05$. *t*-test $df = 61$. Numbers in parentheses indicate standard deviation.
Table 3-2

*Results from Time of Day x Sex ANOVA*

<table>
<thead>
<tr>
<th>Effect</th>
<th>$F$</th>
<th>Partial $\eta^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of day</td>
<td>4.38*</td>
<td>.07</td>
</tr>
<tr>
<td>Sex</td>
<td>0.01</td>
<td>.00</td>
</tr>
<tr>
<td>Time of Day x Sex</td>
<td>4.38*</td>
<td>.07</td>
</tr>
</tbody>
</table>

Note. * $p < .05$. $df = 1, 59$ for all effects
Figure 3-1. Mean IGT performance by block of cards, time of day (AM, grey; PM, black), and participant sex (female, circles; male, triangles).
Figure 3-2. Mean IGT performance by time of day and participant sex (female, •; male, ∆). Error bars represent standard deviation.
Figure 3-3. Hours of pre-session sleep by number good-bad card selections for females with AM sessions, $c(20) = .60, p = .005$. 

$y = 6x + 38$
Footnotes

1 Time of day effects may also reflect external zeitgebers (time-givers) that entrain behavior to a 24 hr cycle. For example, light-dark cycles entrain wake-sleep cycles to a 24 hr rhythm.

2 The effects of session time (AM, PM) and sex (female, male) on IGT performance were also analyzed using a 2 x 2 ANCOVA with amount of pre-session sleep as a covariate. The results of this analysis were comparable to the ANOVA results, with significant effects observed for time of day and time of day x sex ($p < .05$ for both analyses).
References


Chapter 4

Effects of Depression and Sex on Ultradian Sleep Rhythms

Sleep abnormalities are key features of mood disorders, and are included in most diagnostic and symptom-severity classification instruments. Most individuals with major depressive disorder (MDD) report sleep complaints such as insomnia and hypersomnia (for review see Reynolds & Kupfer, 1987). Furthermore, sleep disturbances that persist beyond clinical remission of depressive symptoms increase the risk of suicide and of relapse and recurrence of depression (Fawcett et al., 1990; Ford & Kamerow, 1989; Wingard & Berkman, 1983). Reciprocally, individuals with clinical insomnia are 9 times more likely to have mood disorders compared to healthy individuals (for review see Peterson & Benca, 2006), and insomnia of at least 2 weeks duration increases the lifetime risk of developing depression (Ohayon, Caulet, & Lemoine, 1998).

Reports of subjective sleep disturbance in mood disorders are substantiated by laboratory sleep studies. Studies that use visual stage scoring to examine sleep macro-architecture in MDD commonly find abnormalities in: (1) sleep efficiency, including increased sleep latency (sleep onset insomnia), nighttime awakening (middle insomnia), and early awakening (terminal insomnia); (2) non-rapid eye movement (NREM) sleep, including increased stage 1 sleep and decreased slow wave sleep (SWS); and, (3) rapid eye movement (REM) sleep, including decreased REM latency, and increased REM duration,
amount and activity (for reviews see Armitage, 2007; Benca, Obermeyer, Thisted, & Gillin, 1992; Perlis et al., 1997; Peterson & Benca, 2006; Tsuno, Besset, & Ritchie, 2005). Studies using quantitative analysis to examine sleep micro-architecture in MDD demonstrate: (1) increased fast-frequency beta (16 – 32 Hz) activity (Tekell et al., 2005); (2) decreased slow-frequency delta (0.5 – 4 Hz) activity, especially in males (Armitage, Hoffmann, Trivedi, & Rush, 2000; Reynolds, Kupfer, Thase, & Frank, 1990); (3) reduced synchrony of activity between brain hemispheres (inter-hemispheric coherence; Armitage, Hoffmann, & Rush, 1999); and, (4) reduced synchrony between fast- and slow-frequency activity (inter-frequency coherence), especially in females (Armitage et al., 1992; Armitage et al., 1999). Quantitative analyses of sleep micro-architecture are particularly well suited to detecting patterns within complex activity, and they often differentiate patients from healthy controls when visual stage scoring does not.

The present study builds on previous studies of sleep micro-architecture to determine how bursts of beta- and delta-frequency activity are organized across the night. This is important because organization of brain activity across the night appears to predict clinical and cognitive functioning. Both subjective reports and laboratory measures indicate that depression is associated with sleep disorganization, and there is a long-standing notion that biological rhythm disruption may be involved in the pathogenesis of mood disorders (e.g., Healy, 1987). Furthermore, organization of brain activity during sleep may be important
to cognitive functions such as learning and memory (e.g., Sejnowski & Destexhe, 2000; Steriade, McCormick, & Sejnowski, 1993).

This paper is likely the first to quantify the strength of rhythms in the percent time in beta- and delta-frequency activity during sleep in MDD. Armitage et al. (1992) used a similar analytic method to describe maximal power in the percent time in frequency in MDD and CTL participants. The paper reported that there is a dominant 90 min periodicity to ultradian sleep rhythms. It did not quantify the strength of this rhythm, nor did it examine the strength of ultradian rhythms with shorter period lengths. The present study fills these gaps. Specifically, it examines the strength of ultradian rhythms in beta- and delta-frequency activity across 1-210 min period lengths. Beta- and delta-frequency activity were selected for analysis *a priori* because activity within these frequency ranges is generally disrupted in MDD. Sex effects were tested because previous studies indicate that there are differences in sleep micro-architecture between males and females. Because the coherence of EEG activity is reduced in MDD, suggesting that brain activity is disorganized in depression, individuals with MDD were expected to have reduced rhythmicity in periods of beta- and delta-frequency activity across the night compared to healthy controls. Furthermore, because females with MDD tend to have greater reductions in coherence than depressed males, females with MDD were expected to have less rhythmicity in periods of beta- and delta-frequency activity compared to males with MDD and controls.
In addition to testing the primary study hypotheses described above, this paper includes traditional analyses of sleep macro- and micro-architecture for comparison with previous literature. Based on previous studies of sleep macro-architecture, individuals with MDD were expected to have decreased sleep efficiency, decreased slow wave sleep, and increased REM sleep compared to controls. Based on studies of sleep micro-architecture, individuals with MDD were expected to have increased beta-frequency activity compared to controls, and males with MDD were expected to have decreased delta-frequency activity compared to females with MDD and controls.

Method

Participants

Participants were 86 individuals (37 females) between 18 and 40 years of age whose data were archived and made available for secondary analysis. Fifty-nine of these participants were healthy controls (CTL) who scored below 2 on the 17-item Hamilton Rating Scale for Depression (HRS-D_{17}; Hamilton, 1967). Twenty-seven of these participants were clinician-diagnosed with MDD and scored above 18 on the HRS-D_{17}. Individuals were excluded from study participation for the following: use of medications other than non-steroidal anti-inflammatories or birth-control within the two weeks of the study, independent sleep disorders (e.g., bruxism, sleep apnea, restless leg syndrome), history of head injury resulting in greater than 2 min loss of consciousness, and neurological illness (e.g., seizure disorder). Participants were also excluded for lifetime histories of substance dependence, bipolar disorder, psychotic
depression, and anorexia or bulimia. Participants received $150 for two nights of research participation. The study followed national and institutional ethical standards.

**Procedure**

Participants were required to maintain a regular 11 pm to 6 am sleep schedule for five days prior to study participation. Sleep schedule compliance was monitored by light and motion actigraph recording and sleep diary. Greater than 0.5 hr deviation from this schedule during the five pre-study days was grounds for study exclusion. Participants were also asked to restrict caffeine intake to 1 cup before noon and abstain from drug or alcohol use.

Following the pre-study period, participants spent two contiguous nights in the sleep laboratory, maintaining the same 11 pm to 6 am sleep schedule. The first night served to adapt participants to the sleep laboratory and screen for independent sleep disorders. All analyses are based on the second study night.

Polysomnographic recording included eight scalp electrodes (EEG; F3, F4, C3, C4, P3, P4, O1, O2) placed according to the International 10-20 system, electro-oculogram (EOG) from the left suborbital and right supraorbital ridges, and bipolar chin-cheek electromyogram (EMG). Scalp and face electrode impedances were kept below 2 KOhms and 5 KOhms, respectively. EEG was referenced to linked signal from the left and right earlobes passed through a 10 KOhm resistor. Data were collected with a GRASS™ Model P511 AC system (Grass Instruments, Quincy, MA). EEG data were amplified by 50,000, and digitized at 250 Hz using a 64-channel MICROSTAR 16-bit analog to digital
converter housed in a 586 MHz microcomputer. Filters were set from 0.3 Hz to 30 Hz for EEG data, 1 Hz to 35 Hz for EOG data, and 1 Hz to 30 Hz for EMG data. A 60 Hz notch filter was applied to reduce electrical noise.

Analysis

Demographic analysis. Pearson’s chi-square analysis was performed to assess the distribution of sex across diagnosis. A univariate ANOVA was performed to assess the distribution of age across the four study groups (CLT females, CTL males, MDD females, MDD males). A 2 (CTL, MDD) x 2 (female, male) ANOVA was performed to assess the distribution of HRS-D scores across diagnosis and sex.

Macro-architectural analysis. Sleep data were stage scored according to standard criteria (Rechtschaffen & Kales, 1968) by raters trained to at least 90% reliability. Epochs dominated by movement or recording artifact were excluded from analysis. Effects of diagnosis and sex on macro-architectural sleep variables were analyzed using a 2 (CTL, MDD) x 2 (female, male) MANOVA.

Micro-architectural analysis. Quantitative sleep analyses examined beta and delta frequency activity from two central electrode sites (C3, C4). Period amplitude analysis (PAA) was performed to determine the percentage of time spent in beta- and delta-frequency activity during sleep. PAA calculates the percentage of time in a given frequency by counting the number of sampled events between signal polarity changes, using the time between signal polarity changes to determine the frequency of activity, and then calculating the percentage of the 30 s sampling epoch occupied by events in a given frequency.
band. Full-wave first derivative PAA, which is sensitive to fast-frequency oscillations, was used to quantify beta activity. First derivative analysis computes the time between successive negative voltage inflections in each second. Full-wave zero cross PAA, which is sensitive to slow frequency oscillations, was used to quantify delta activity. Zero cross analysis computes the time between successive zero voltage crossings in each second. Average percent time in frequency was calculated across approximately 840, 30 s epochs (420 min) of sleep.

Power spectral analysis (PSA) was then applied to PAA results to determine the rhythmicity of periods of beta- and delta-frequency activity across the night (power in percent time in frequency; see Figure 4-1). PSA, also known as fast-Fourier transform analysis, examines the goodness-of-fit of a set of sine and cosine functions applied to an oscillating signal. Thus, the application of PSA to PAA results indicates the reliability of the percentage of time spent in a given frequency of activity. Average spectral power in beta and delta periods was calculated across period lengths of 1 to 210 min for each participant. Thus, an increase in power at a 210 min period length represents two rhythmic bursts of activity within the 420 min sleep period. Likewise, an increase in power at a 1 min period length represents rhythmic bursts of activity every minute across the 420 min sleep period.

Effects of diagnosis, sex, and electrode location on average percent time in frequency, and average power in percent time in frequency, were analyzed using 2 (CTL, MDD) x 2 (female, male) x 2 (left central lobe, C3; right central
lobe, C4) mixed measures ANOVAs. Analyses were performed separately for beta and delta periods.

Results

Demographic Characteristics

Participant sex was balanced across diagnosis, \( \chi^2(86) = 0.03, p = .85 \). Participant age was balanced across the four study groups (CTL females, CTL males, MDD females, MDD males), \( F(3, 82) = 0.46, p = .71 \). The average age of participants was 28.88 (SD = 5.56). There was a significant main effect of diagnosis on HRS-D\textsubscript{17} scores, where depression symptom severity was greater in participants with MDD compared to CTL participants, \( F(1,82) = 1025.39, p = .00 \). Average HRS-D\textsubscript{17} scores were 0.68 (SD = 1.17) in CTL participants, and 22.56 (SD = 4.95) in participants with MDD. Neither the main effect of sex, nor the interaction effect of diagnosis x sex, reached statistical significance in HRS-D\textsubscript{17} score comparisons.

Sleep Macro-architecture

Average sleep stage-score characteristics, separated by diagnosis and sex, are presented in Table 4-1. Results from the 2 (CTL, MDD) x 2 (female, male) MANOVA are presented in Table 4-2. There was a significant main effect of diagnosis on REM density, where participants with MDD had greater REM density (more rapid eye movements) than CTL participants. There was a significant interaction effect of diagnosis x sex on sleep latency, where females with MDD took longer to fall asleep than either CTL females (\( p = .01 \)) or males with MDD (\( p = .03 \)) and marginally longer than CTL males (\( p = .06 \)). Remaining
main effects and interaction effects did not reach statistical significance.

Sleep Micro-architecture

**PAA results.** The average percentages of time spent in beta- and delta-frequency activity, separated by diagnosis and sex, are presented in Table 4-3. Results from the 2 (CTL, MDD) x 2 (female, male) x 2 (C3, C4) mixed measures ANOVAs examining the percentage of time in beta- and delta-frequency activity are presented in Table 4-4. There was a significant main effect of diagnosis on percent time in beta-frequency activity, with higher percent time in beta in participants with MDD compared to CTL participants. There was also a significant main effect of lead on percent time in beta-frequency activity, with higher percent time in beta at the right central lead than the left central lead. Remaining main effects, and all interaction effects, did not reach statistical significance.

**PSA results.** The average power in the percent time in beta- and delta-frequency activity, separated by diagnosis and sex, is presented in Table 4-3, Figure 4-2, and Figure 4-3. Results from the 2 (CTL, MDD) x 2 (female, male) x 2 (C3, C4) mixed measures ANOVAs examining power in the percent time in beta- and delta-frequency activity are presented in Table 4-4. There was a significant main effect of sex on power in percent time in beta-frequency activity, where males had greater average power than females. There was also a marginally significant main effect of sex on power in percent time in delta-frequency activity ($p = .052$), where males again had greater power than females. Remaining main effects, and all interaction effects, did not reach statistical significance.
Discussion

This study was designed to assess the rhythmicity of periods of beta- and delta-frequency activity across a night of sleep in depressed and healthy participants. In addition, traditional sleep macro- and micro-architectural analyses are presented for comparison with previous literature. The results from the PSA, PAA, and sleep macro-architectural analyses are discussed in order below.

The PSA results indicate that the percentages of time spent in beta-frequency activity, which is characteristic of arousal, and delta-frequency activity, which is characteristic of deep sleep, are less predictably organized in females compared to males. Female participants had less power in the percent time in beta-frequency activity than males, across diagnostic group. There was also a marginally significant trend for females to have less power in the percent time in delta-frequency activity compared to males. These data underscore the significance of sex of participants in studies of sleep (also see Armitage et al., 1999; Reynolds et al., 1990). Furthermore, by examining the rhythmicity of bursts in beta- and delta-frequency during sleep, these data make a novel contribution to previous literature on sex differences in circadian rhythms (for further discussion see T. M. Lee, Hummer, Jechura, & Mahoney, 2004). Future research might examine the functional significance of rhythms in beta- and delta-frequency periods, for example, using measures of cognitive ability.

Notably, the PSA results presented here indicate that rhythms in the incidence of beta- and delta-frequency activity do not differ between individuals with MDD and controls. Rhythmicity may be reflected by either the incidence or
amplitude of activity, and both have been implicated in the pathogenesis of mood disorders (for further discussion see Rosenwasser & Wirz-Justice, 1997). The results presented here belie the notion that the incidence of beta- or delta-frequency activity is disrupted in MDD. Rather, depression may be associated with weakness in the amplitude of ultradian rhythms. Future research could test this hypothesis using PSA (which is a composite index of both the incidence and amplitude of activity) to quantify EEG activity in place of the PAA analysis used in this study. Furthermore, animal models of circadian rhythms and depression may complement these results by describing the incidence and synchrony of activity in circadian pacemakers such as the locus coeruleus and suprachiasmatic nucleus (for further discussion see Siever & Davis, 1985).

The PAA results in this study are consistent with previous research that demonstrates increased beta-frequency activity in participants with MDD compared to healthy controls (Armitage et al., 1992; Tekell et al., 2005). Beta-frequency activity is characteristic of arousal. Thus, these data indicate that individuals with depression have more arousal during sleep than CTL participants. However, we did not find a difference between MDD and CTL participants in the percentage of delta-frequency activity during sleep. Delta-frequency activity is indicative of deep sleep. Thus, while participants with MDD may have more arousal during sleep than CTL participants, they do not spend a smaller percentage of time in deep sleep. This argues against the notion that depression is characterized by general hyperarousal (e.g., Armitage, Hudson, Trivedi, & Rush, 1995).
Studies of sleep micro-architecture often demonstrate decreased delta-frequency activity in MDD compared to CTL participants (Borbély et al., 1984; Kupfer, Ulrich, et al., 1984), but this is not always the case (Kupfer, Reynolds III, & Ehlers, 1989). Differences between studies may be accounted for by depression severity or analytic method. Participant depression severity was greater in studies by Borbély et al. and Kupfer, Ulrich, et al. (MDD HRS-D$_{17}$ scores ≥ 30) compared to the present study (average HRS-D$_{17}$ score = 22) and that of Kupfer, Reynolds, et al. (average HRS-D$_{17}$ score = 23 for non-delusional depressives, 30 for delusional depressives). The age range and average age of participants in the present study is comparable to other studies (Borbély et al.; Kupfer, Ulrich, et al.), and the sample size is generally larger. Methodological differences may also account for differences between studies: reductions in delta-frequency activity are often restricted to the first half of the night (Borbély et al.; Kupfer, Ulrich, et al.), and the present study quantifies delta-frequency activity over the entire night. A comparison of first- versus second-half of the night effects was beyond the aim of the present study, as we were primarily interested in the rhythmicity of periods of beta- and delta-frequency activity across the night.

Results for studies of sleep macro-architecture in MDD are generally more variable than studies of sleep micro-architecture, but REM abnormalities are probably the most commonly observed form of sleep disturbance in depression (Benca et al., 1992). In the present study, individuals with MDD had increased REM density (more rapid eye movements) compared to CTL participants, though there were no significant differences between MDD and CTL participants in REM
latency and percentage. Furthermore, females with MDD took longer to fall asleep than males with MDD or CTL participants, but there were no differences between MDD and CTL participants in the percentage of time in slow-wave sleep (stages 3 & 4). As noted earlier, quantitative analyses of sleep micro-architecture may be better-suited than visual stage scoring to detect patterns in sleep activity, particularly in clinical populations.

This study has several limitations. First, though this study demonstrated reduced rhythmicity in periods of beta-frequency activity in females compared to males, the functional significance of this result is unclear. Biological rhythm disruption may be involved in the pathogenesis of mood disorders (e.g., Healy, 1987), and organization of brain activity during sleep may be important to cognitive functions such as learning and memory (e.g., Sejnowski & Destexhe, 2000; Steriade et al., 1993). However, neither pre-morbid sleep nor cognition were available for examination in the present study. Second, the study does not examine the effect of age on sleep architecture due to the limited age range in our sample. Aging is associated with an increase in beta-frequency activity and a decrease in delta-frequency activity during sleep (Carrier, Land, Buysse, Kupfer, & Monk, 2001). Third, the study design did not control for the menstrual phase of the female participants though there is research indicating that sleep macro-architecture differs during follicular and luteal phases (K. A. Lee, Shaver, Giblin, & Woods, 1990; Parry, Mendelson, Duncan, Sack, & Wehr, 1989).

Despite these limitations, this study demonstrates that periods of beta-frequency activity are more predictable in males than females, indicating a sex
difference in the overall organization of beta-frequency activity during sleep. Organization of brain activity during sleep has been implicated in clinical and cognitive functioning, and further research may delineate the functional consequences of rhythmic bursts of beta- and delta-frequency activity. Furthermore, these data indicate that the rhythmicity of bursts in beta- and delta-frequency activity do not distinguish individuals with MDD from controls. This suggests that the amplitude of ultradian rhythms may play a greater role in the pathogenesis of MDD than the incidence of activity. Finally, comparisons between the data from this study and others demonstrate variability between studies of sleep macro- and micro-architecture in MDD. Examining individual differences in sleep may help predict participant variance within studies. In addition, systematic reviews and/or meta-analyses of existing sleep micro-architectural data may help explain variance between studies and identify the most robust effects in depressed individuals compared to healthy controls, and in females compared to males.
### Table 4-1

*Mean (Standard Deviation) Sleep Stage Score Characteristics by Diagnosis and Sex*

<table>
<thead>
<tr>
<th>Variable</th>
<th>CTL</th>
<th>MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Time in bed</td>
<td>416.6 (6.1)</td>
<td>415.7 (9.2)</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>405.6 (13.5)</td>
<td>405.9 (13.1)</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>97.4 (3.2)</td>
<td>97.7 (2.5)</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>6.9 (5.4)</td>
<td>8.6 (7.4)</td>
</tr>
<tr>
<td>REM latency</td>
<td>69.1 (24.0)</td>
<td>75.5 (26.3)</td>
</tr>
<tr>
<td>Stage 1 %</td>
<td>5.7 (3.9)</td>
<td>7.1 (6.5)</td>
</tr>
<tr>
<td>Stage 2 %</td>
<td>54.6 (8.3)</td>
<td>56.7 (8.0)</td>
</tr>
<tr>
<td>Stages 3 &amp; 4 %</td>
<td>13.0 (9.4)</td>
<td>7.6 (7.5)</td>
</tr>
<tr>
<td>REM %</td>
<td>24.0 (5.1)</td>
<td>24.6 (5.4)</td>
</tr>
<tr>
<td>Awake/Movement %</td>
<td>2.7 (1.9)</td>
<td>4.0 (3.8)</td>
</tr>
<tr>
<td>REM density</td>
<td>3.1 (1.2)</td>
<td>3.0 (0.9)</td>
</tr>
</tbody>
</table>

*Note.* CTL = healthy control, MDD = major depressive disorder.
Table 4-2

*Results from 2 (Diagnosis) x 2 (Sex) MANOVA of Sleep Stage Score Characteristics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dx</th>
<th></th>
<th>Sex</th>
<th></th>
<th></th>
<th>Dx x Sex</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$F$</td>
<td>Partial $\eta^2$</td>
<td>$F$</td>
<td>Partial $\eta^2$</td>
<td>$F$</td>
<td>Partial $\eta^2$</td>
<td></td>
</tr>
<tr>
<td>Time in bed</td>
<td>1.77</td>
<td>.02</td>
<td>0.00</td>
<td>.00</td>
<td>0.21</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td>Total sleep time</td>
<td>0.18</td>
<td>.00</td>
<td>0.42</td>
<td>.01</td>
<td>0.29</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>0.11</td>
<td>.00</td>
<td>0.64</td>
<td>.01</td>
<td>0.13</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td>Sleep latency</td>
<td>2.06</td>
<td>.03</td>
<td>1.68</td>
<td>.02</td>
<td>5.52*</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>REM latency</td>
<td>1.69</td>
<td>.02</td>
<td>0.01</td>
<td>.00</td>
<td>0.97</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Stage 1 %</td>
<td>0.42</td>
<td>.01</td>
<td>1.75</td>
<td>.02</td>
<td>0.05</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td>Stage 2 %</td>
<td>2.11</td>
<td>.03</td>
<td>0.44</td>
<td>.01</td>
<td>0.17</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td>Stages 3 &amp; 4 %</td>
<td>0.85</td>
<td>.01</td>
<td>3.39†</td>
<td>.04</td>
<td>0.80</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>REM %</td>
<td>2.72</td>
<td>.03</td>
<td>0.04</td>
<td>.00</td>
<td>0.41</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Awake/Movement %</td>
<td>0.25</td>
<td>.00</td>
<td>1.39</td>
<td>.02</td>
<td>0.33</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td>REM density</td>
<td>4.11*</td>
<td>.05</td>
<td>0.09</td>
<td>.00</td>
<td>0.03</td>
<td>.00</td>
<td></td>
</tr>
</tbody>
</table>

Note. Dx = diagnosis. df = 1, 82 for all effects.
* $p < .05$; † $p < .10$
Table 4-3

*Mean (Standard Deviation) Percent Time in Frequency and Power in Percent Time in Frequency by Diagnosis, Sex, and Lead*

<table>
<thead>
<tr>
<th>Lead</th>
<th>CTL</th>
<th></th>
<th>MDD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td></td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Percent Time in Beta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>17.7 (3.4)</td>
<td>18.5 (6.1)</td>
<td>20.3 (4.0)</td>
<td>22.1 (8.2)</td>
</tr>
<tr>
<td>C4</td>
<td>18.6 (4.2)</td>
<td>19.1 (6.4)</td>
<td>20.8 (4.8)</td>
<td>23.6 (8.4)</td>
</tr>
<tr>
<td></td>
<td>Percent Time in Delta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>58.7 (3.9)</td>
<td>57.8 (5.3)</td>
<td>59.1 (5.1)</td>
<td>60.0 (3.6)</td>
</tr>
<tr>
<td>C4</td>
<td>59.6 (4.7)</td>
<td>57.9 (5.1)</td>
<td>59.6 (5.1)</td>
<td>60.3 (4.1)</td>
</tr>
<tr>
<td></td>
<td>Power in Percent Time in Beta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>270.3 (118.8)</td>
<td>342.5 (205.7)</td>
<td>287.2 (117.1)</td>
<td>338.0 (108.5)</td>
</tr>
<tr>
<td>C4</td>
<td>265.9 (120.5)</td>
<td>335.1 (185.2)</td>
<td>260.1 (106.2)</td>
<td>371.3 (158.1)</td>
</tr>
<tr>
<td></td>
<td>Power in Percent Time in Delta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>394.4 (127.1)</td>
<td>420.6 (132.6)</td>
<td>353.6 (109.5)</td>
<td>438.9 (187.4)</td>
</tr>
<tr>
<td>C4</td>
<td>380.7 (131.8)</td>
<td>420.9 (132.8)</td>
<td>354.7 (95.0)</td>
<td>463.0 (221.8)</td>
</tr>
</tbody>
</table>

*Note.* CTL = healthy control, MDD = major depressive disorder.
### Table 4-4

**Results from 2 (Diagnosis) x 2 (Sex) x 2 (Lead) ANOVAs of Percent Time in Frequency and Power in Percent Time in Frequency**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Beta</th>
<th></th>
<th>Delta</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Percent Time in Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dx</td>
<td>5.93*</td>
<td>.07</td>
<td>1.28</td>
<td>.02</td>
</tr>
<tr>
<td>Sex</td>
<td>1.19</td>
<td>.01</td>
<td>0.05</td>
<td>.00</td>
</tr>
<tr>
<td>Lead</td>
<td>5.44*</td>
<td>.06</td>
<td>3.30†</td>
<td>.04</td>
</tr>
<tr>
<td>Dx x Sex</td>
<td>0.42</td>
<td>.00</td>
<td>0.94</td>
<td>.01</td>
</tr>
<tr>
<td>Dx x Lead</td>
<td>0.14</td>
<td>.00</td>
<td>0.09</td>
<td>.00</td>
</tr>
<tr>
<td>Sex x Lead</td>
<td>1.25</td>
<td>.00</td>
<td>3.11</td>
<td>.02</td>
</tr>
<tr>
<td>Dx x Sex x Lead</td>
<td>4.65</td>
<td>.01</td>
<td>0.48</td>
<td>.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Power in Percent Time in Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dx</td>
<td>0.09</td>
<td>.00</td>
<td>0.00</td>
<td>.00</td>
</tr>
<tr>
<td>Sex</td>
<td>4.58*</td>
<td>.05</td>
<td>3.89†</td>
<td>.05</td>
</tr>
<tr>
<td>Lead</td>
<td>0.03</td>
<td>.00</td>
<td>0.19</td>
<td>.00</td>
</tr>
<tr>
<td>Dx x Sex</td>
<td>0.02</td>
<td>.00</td>
<td>0.93</td>
<td>.01</td>
</tr>
<tr>
<td>Dx x Lead</td>
<td>0.24</td>
<td>.00</td>
<td>2.07</td>
<td>.03</td>
</tr>
<tr>
<td>Sex x Lead</td>
<td>2.45</td>
<td>.03</td>
<td>1.92</td>
<td>.02</td>
</tr>
<tr>
<td>Dx x Sex x Lead</td>
<td>2.98†</td>
<td>.04</td>
<td>0.11</td>
<td>.00</td>
</tr>
</tbody>
</table>

*Note.* Dx = diagnosis. df = 1, 82 for all effects.

* * < .05; † * p < .10
Figure 4-1. PAA (top) and PSA (bottom) data for a single subject, a female CTL, presented to illustrate the method of analysis. Note that the time-course of oscillations in PAA data are represented by PSA peak spectral power at an 105 min period for beta-frequency activity and 84 min period for delta-frequency activity.
Figure 4-2. Average PSA power in percent time in beta-frequency activity (top) and delta-frequency activity (bottom) at 1-210 min period lengths, separated by diagnosis (CTL in solid lines; MDD in dashed lines) and sex (female, F, in grey; male, M, in black). “Power in the percent time in beta/delta” indicates the rhythmicity of bursts in beta- and delta-frequency activity.
Figure 4-3. Average PSA power in the percent time in beta- (●) and delta- (△) frequency activity, collapsed across 1-210 min period lengths, separated by diagnosis (CTL, MDD) and sex (female, F; male, M). “Power in the percent time in frequency” indicates the rhythmicity of bursts in beta- and delta-frequency activity. Error bars represent standard deviation. Males have more beta-period rhythmicity, and marginally more delta-period rhythmicity, than females.


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Chapter 5

Conclusion

This dissertation addresses critical gaps in the literature on affective bias in depression, the effects of circadian rhythms and sleep on affective processing, and organization of brain activity during sleep in depression. First, previous literature demonstrated that depression is associated with decreased attention and memory for positive events, and increased attention and memory for negative events. However, mood-congruent biases in expectations for future affective events were largely unexamined. Thus, the first study in this dissertation measured behavioral and physiological indicators of anticipation for future affective events in individuals with dysthymia (DYS) and healthy controls. Second, depression is associated with chronophysiological disruption and difficulty making decisions, but the relationship between circadian-homeostatic processes and decision making is not well understood. Thus, the second study in this dissertation examined the impact of time of day and sleep duration on decision making skill. Third, while affective processing may be influenced by rhythmic oscillations in brain activity during sleep, and disruptions in chronophysiology may contribute to the onset and maintenance of depression, ultradian sleep rhythms in depression have not been fully characterized. Thus, the third study in this dissertation examined the rhythmicity of bursts of fast- and slow-frequency activity during sleep in individuals with major depressive disorder.
(MDD) and healthy controls. Together, these studies provide a foundation for integrative research on affective processing, chronophysiology, and mood disorders. The discussion that follows is an integrative analysis with suggestions for future research.

The first study in this dissertation demonstrated that expectations for future affect are biased in healthy individuals and those with DYS. Controls expected fewer negative, and individuals with DYS expected fewer positive, adjectives to apply to them in the future. Event-related potentials (ERP) indicated increased physiological anticipation in controls prior to positive versus other adjectives. Thus, this study lends experimental support to leading cognitive models of depression that emphasize the role of future-oriented affective biases (e.g., Abramson, Metalsky, & Alloy, 1989; Abramson, Seligman, & Teasdale, 1978; Beck, 1967). Furthermore, anticipation of future affect may have significant functional consequences. For example, hopelessness about the future is one of the greatest long-term risk factors for suicide (Joiner, Brown, & Wingate, 2005).

Expectations for the future can also impact decisions that are less dire. For example, if healthy individuals under-predict negative outcomes, as they did in the anticipation task, they may be more likely to disregard risks of future punishment during the Iowa Gambling Task (IGT). Conversely, if individuals with dysthymia accurately fail to suppress expectations of negative outcomes, they should make less risky decisions on the IGT than controls. However, healthy individuals have better performance on the IGT than those with depression (Must et al., 2006). This suggests that though healthy individuals under-predict negative
events, they have a greater ability to adaptively change behavior in response to prior reinforcement than individuals with depression. The ability to do so helps explain why people who inaccurately predict negative outcomes (i.e., those without depression) can still make functional decisions in the long-run.

What is the mechanism of adaptive response to reinforcement?
Successful behavior change may depend on efficient executive functioning. Learning from mistakes requires negotiation of cognitive dissonance between the expected and achieved outcome, as well as a summation of the likely cost-benefit ratio of future choices. Furthermore, taking appropriate action toward long-term goals requires inhibition of actions that result in short-term rewards but are ultimately disadvantageous. All three operations rely on executive control.

There is converging evidence that executive skills are impaired in MDD. Individuals with depression have difficulty removing negative information from memory (Berman et al., 2010; Joormann & Gotlib, 2008), but can learn to forget negative information when instructed to substitute it with positive information (Joormann, Hertel, LeMoult, & Gotlib, 2009). Thus, when given an explicit strategy for executive control, individuals with depression can appropriately disengage from negative stimuli and maintain attention and memory for positive stimuli. Furthermore, individuals with depression demonstrate blunted or less efficient activation of brain regions that support executive functioning: prefrontal cortex activation is reduced in response to punishment (Elliott, Sahakian, Michael, Paykel, & Dolan, 1998), and there is more spatial variance in activation of the left inferior frontal gyrus during affective processing (Berman et al., 2010),
in individuals with MDD compared to controls. Moreover, performance on the Iowa Gambling Task (IGT) is impaired in MDD (Must et al., 2006), and performance on this task depends on the ventral and medial prefrontal cortex, among other regions (Bechara, H. Damasio, A. R. Damasio, & Lee, 1999; Lawrence, Jollant, O'Daly, Zelaya, & Phillips, 2009; Lin, Chiu, Cheng, & Hsieh, 2008). Collectively, these data support the idea that depression is associated with impaired executive functioning. Future research could determine how executive control of attention and memory impacts behavior. Furthermore, the cognitive and neurophysiological mechanisms of executive control could be further delineated through event-related potential or functional magnetic resonance imaging studies that measure immediate responses to reinforcement and anticipatory responses to future choice.

The second study in this dissertation demonstrated that time of day and sleep duration predict decision making skill, but do so differently for males compared to females. Males had better IGT performance in the morning than the evening. Pre-session sleep duration was positively correlated with morning IGT performance in females, but not males. These results suggest that sex differences in chronophysiology should be carefully considered when testing the effects of sex on decision making (e.g., Bolla, Eldreth, Matochik, & Cadet, 2004; Overman et al., 2006; Reavis & Overman, 2001). They also highlight the importance of chronophysiology in studies of incentive-based decision making (also see Killgore, Balkin, & Wesensten, 2006), and add to evidence that circadian rhythms and sleep influence performance on executive functioning.
tasks (for reviews see Pilcher & Huffcutt, 1996; Schmidt, Collette, Cajochen, & Peigneux, 2007).

Affective processing biases may underlie the relationship between sleep duration and sex as predictors of decision making. Sleep deprivation impacts identification of emotion, where relatively neutral stimuli are rated more negatively following sleep deprivation than after a night of sleep (Daniela et al., 2010). Furthermore, sleep deprivation impairs identification of human emotion in females more than males, particularly when facial expressions are ambiguous (Van der Helm, Gujar, & Walker, 2010). Moreover, studies that examine the effect of participant sex on affective processing indicate that electrophysiological responses to emotional stimuli, particularly negative emotional stimuli, are enhanced in females compared to males (Gasbarri et al., 2006, 2007; Kemp, Silberstein, Armstrong, & Nathan, 2004; Lithari et al., 2010). Thus, the association between partial sleep restriction and impaired IGT performance during the morning in females may be due to impaired perception of relatively ambiguous choices combined with increased reactivity to reinforcement. Future research might test this hypothesis using behavioral and physiological measures of incentive response during decisions where the ambiguity of the outcome is varied.

In addition, the relative influence of circadian rhythms and homeostatic sleep drive on sex differences in affective processing could be delineated by studies that experimentally manipulate circadian and homeostatic processes. Improved performance in the morning compared to the evening in males, and
correlations between performance and amount of pre-session sleep in females, may reflect circadian rhythms and/or the sleep-wake homeostat. Ideally, the influence of circadian rhythms on performance would be examined using a forced desynchrony protocol. This technique dissociates the influence of the endogenous circadian rhythms from homeostatic sleep pressure by imposing a sleep-wake schedule that is either shorter or longer than the body’s endogenous, roughly 24 hr, circadian cycle. Furthermore, the effects of homeostatic sleep pressure on performance could be assessed using experimentally controlled partial sleep restriction to increase sleep pressure, and/or scheduled naps to decrease sleep pressure.

The influence of chronophysiology and sex on affective processing is especially relevant to depression. Depression is associated with disruptions in sleep and circadian rhythms (for reviews see Armitage, 2007; Germain & Kupfer, 2008; McClung, 2007; Wirz-Justice, 2006), and biases in affective processing (for reviews see Matt, Vázquez, & Campbell, 1992; Shestyk & Deldin). Furthermore, sleep deprivation has a greater effect on mood than either cognitive or motor functioning (Pilcher & Huffcutt, 1996). Moreover, depression disproportionately affects women compared to men by a ratio of 2:1 (Kessler et al., 2003). Studies that examine sex differences in chronophysiology and affective processing may elucidate the etiology of sex differences in depression prevalence.

The importance of sex differences in chronophysiology is also highlighted by the third study in this dissertation. Males had more rhythmic bursts in beta- and delta-frequency activity than females during a night of sleep. Notably, the
rhythmicity of bursts in beta- and delta-frequency activity did not distinguish individuals with MDD from healthy controls; those with MDD spent more time than controls in beta-frequency activity during sleep, but the organization of beta-frequency activity across the night did not differ between groups. This suggests that the amount of beta-frequency activity, rather than the organization of this activity across the night, is pathological in MDD. Biological rhythm disruption has long been implicated in the pathogenesis of mood disorders (for reviews see Germain & Kupfer, 2008; McClung, 2007; Wirz-Justice, 2006). Furthermore, participant sex moderates the relationship between circadian-homeostatic influences and depression in some studies (for review see Armitage, 2007). Further research on sex differences in chronobiology may elucidate the comparative value of organized rhythms in activity versus the amount and/or duration of activity.

The results of this research have implications for the hypothesis that disruptions in chronophysiology may contribute to affective processing biases in depression. Rhythmic oscillations in brain activity may promote new learning (for reviews see Diekelmann & Born, 2010; Giuditta et al., 1995). More specifically, memories may be re-activated and strengthened by rhythmic oscillations in fast- and slow-frequency brain activity (Diekelmann & Born; Sejnowski & Destexhe, 2000; Steriade, 2003). However, the third study in this dissertation indicates that the rhythmicity of bursts in beta- and delta-frequency during sleep is comparable between individuals with MDD and healthy controls. This suggests that affective processing biases in depression may not be attributable to differences in beta-
and delta-frequency rhythmicity. An alternative hypothesis is that the synchrony of activity between brain hemispheres (inter-hemispheric coherence), or between fast- and slow-frequency activity (inter-frequency coherence), may moderate affective biases in depression. Thus, the rhythmicity of bursts in a single frequency of activity across the night may not be as relevant to affective processing as the coordination of activity between brain hemispheres or frequencies. Individuals with depression demonstrate reduced inter-hemispheric coherence (Armitage, Hoffmann, & Rush, 1999). They also have reduced inter-frequency coherence that is especially pronounced in females (Armitage et al., 1992; Armitage et al., 1999). The relationship between the coherence of activity and affective processing in depression has not been examined. Therefore, future research could combine quantitative sleep analyses with cognitive measures to elucidate the relationship between activity coherence, affective processing, and sex in depression.

Literature on affective bias, chronophysiology, and depression is gradually converging. This dissertation indicates that: (1) anticipation for future affective events is biased in depression, (2) interactions between chronophysiology and sex influence incentive-based decision making, and (3) the rhythmicity of bursts in brain activity during sleep differs between males and females but does not distinguish individuals with depression from controls. Several questions remain unanswered. First, while individuals with depression have affective processing biases, the impact of these biases on behavior is unknown. Second, this dissertation provides preliminary evidence that incentive-based decision making
is impacted by time of day, sleep, and sex, but replication of these results with better experimental control for sleep and circadian rhythms is necessary. Third, the impact of chronophysiological organization on cognition, both between sexes and as a predictor of depression, is relatively unexplored. Each of these steps will further define the relationship between affective processing and chronophysiology in depression.

I am involved in an ongoing study that will accomplish several of these goals. Individuals with MDD and healthy controls are currently being recruited to participate in a 4 day laboratory-based study of sleep and affective processing. The sample will eventually be large enough to examine main and interaction effects of diagnosis and participant sex. To control for potential influences of sleep duration on performance, participants are required to maintain a standard sleep schedule for 5 days prior to their first overnight visit, and continue this schedule throughout study participation. Affective processing is examined using measures of interference resolution, memory, and decision making. Furthermore, behavioral indices of affective memory bias are complemented by measurement of event-related potentials during word encoding and recognition. In combination, these behavioral and physiological indices will clarify the relationship between interference resolution and memory in incentive-based decision making. Furthermore, electroencephalographic (EEG) recording is conducted during the 4 overnight visits to assess the relationship between affective processing and the amount and organization of brain activity during sleep. The study also includes experimental manipulation of slow-wave activity during sleep to determine how
disrupting the sleep-wake homeostat will affect affective processing. Finally, affective memory tasks are administered in both the mornings and evenings. The measurement of performance at two different times of day, combined with experimental manipulation of the sleep-wake homeostat, will help dissociate the relative influences of circadian rhythms and the sleep-wake homeostat on emotional processing. In effect, this ongoing project will partially replicate the studies in this dissertation and significantly extend the literature on affective processing, chronophysiology, and depression.

Ultimately, the value of these projects rest on their ability to improve prevention and treatment of depression and other disorders. Chronotherapies, which organize circadian rhythms and adjust the sleep-wake homeostat, may benefit affective processing and/or goal-directed behavior. Consequently, cognitive therapy for depression may be maximally effective when it both targets specific processing biases (e.g., affective memory) and capitalizes on the benefits of circadian rhythms and sleep. Thus, integrative research on depression-related cognition and chronophysiology may benefit existing therapies for depression and ultimately reduce the profound personal and socioeconomic repercussions of this pernicious illness.
References


