PSYCHOLOGY

ANTICIPATORY AFFECTIVE STARTLE MODULATION IN UNIPOLAR DEPRESSION

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Dissertation under the direction of Professor Andrew J. Tomarken

Affective startle eyeblink modulation by unipolar depressed and nondepressed participants was assessed during the anticipation and viewing of emotional pictures. Anticipatory startle probes were presented at 2000 ms and 750 ms before picture onset. Startle probes during picture viewing were presented at 300 ms and 3500-4500 ms after picture onset. Nondepressed participants exhibited the expected arousal-dependent startle modulation to probes presented 2000 ms before picture onset, a trend towards linear valence-dependent startle modulation to probes presented 750 ms before picture onset, no relation between startle modulation and picture category to probes presented 300 ms after picture onset, and the expected linear valence-dependent startle modulation to probes presented 3500-4500 ms after picture onset. In contrast, startle modulation of depressed participants was unrelated to picture valence category at all probe intervals. Depressed participants differed from nondepressed participants in startle potentiation to pleasant pictures at the 2000 ms anticipatory interval and in linear startle modulation to probes presented 3500-4500 ms after picture onset. There were no between-group differences with respect to the other two probe conditions, self-report ratings of picture valence, or

voluntary viewing time. These results replicate prior findings that late-probe blink magnitudes of depressed participants are unrelated to picture valence and demonstrate attenuated anticipation of pleasant stimuli by depressed participants. Diminished startle modulation during the anticipation of pleasant pictures in individuals with unipolar depression may represent a novel method to assess anhedonia.

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CHAPTER I

INTRODUCTION

Anhedonia and the Diagnosis of Major Depressive Disorder

Anhedonia, the diminished capacity to experience pleasure in response to putatively pleasurable stimuli, is a defining symptom of depression. The Diagnostic and Statistical Manual for Psychiatric Disorders (DSM-IV) stipulates that a major depressive episode is defined by the presence of depressed mood or anhedonia, plus four other symptoms. The DSM-IV melancholic subtype of depression is contingent upon a depressive episode characterized by anhedonia, whereas mood reactivity is the central feature of the DSM-IV atypical subtype of depression (American Psychiatric Association, 1994). Similarly, the International Classification of Diseases (ICD-10) specifies that the diagnosis of depression is contingent upon two of three essential symptoms, depressed mood, marked loss of interest or pleasure, and decreased energy and fatigability, and the ICD-10 somatic depressive syndrome is characterized by a subset of symptoms with a particular emphasis on anhedonia (i.e., loss of interest, lack of emotional reactions, and loss of libido, World Health Organization, 1992). Notably, both classification systems permit the diagnosis of depression in the absence of depressed mood when anhedonia is present. Moreover, both classification systems emphasize that anhedonia is a central symptom of depression and is the symptom that differentiates depressive subtypes.

Experimental Evidence of Anhedonia in Depression

Although several theories of depression postulate that anhedonia and related constructs are core features of the disorder (e.g., Costello, 1972; Davidson, 1992; Meehl, 1975), there is relatively little experimental evidence that addresses how depressed individuals respond to pleasant stimuli. For the most part, however, the available experimental evidence indicates that depressed individuals demonstrate attenuated responses to pleasant stimuli. The majority of research that has addressed how depressed individuals respond to pleasant stimuli has investigated subjective ratings of putatively pleasant stimuli. Sloan and colleagues (1997; 2001) reported that depressed women rated positive pictures to be both less pleasant and less arousing than did nondepressed women, and Allen and colleagues (1999) found that depressed participants rated pleasant pictures to be marginally less pleasant than did nondepressed participants. However, other researchers (Berenbaum & Oltmanns, 1992; Dichter, Tomarken, Shelton, & Sutton, 2004), perhaps due to the different methods used to collect subjective rating data, have found no diagnostic group differences with respect to subjective ratings of pleasant stimuli.

A few research groups have examined facial electromyographic (EMG) responses to pleasant stimuli in depressed individuals. Schwartz and colleagues (Schwartz, Fair, Salt, Mandel, & Klerman, 1976a, 1976b) demonstrated an attenuated zygomatic EMG pattern during happy imagery in depressed outpatients that was attenuated after successful antidepressant treatment. Gehricke & Shapiro (2000) and Greden and colleagues (1986) have also demonstrated zygomatic EMG differences between

depressed and control participants during pleasant imagery, and Sloan and colleagues (2002) have extended such findings to include dysphoric women.

Analyses of depressed individuals' mood ratings also constitute a compelling source of non-experimental and indirect evidence linking anhedonia and depression. When the mood ratings of individuals with anxious and depressive disorders are factor analyzed, ratings of anhedonia are specific to depression, whereas ratings of physiological arousal are specific to anxiety disorders and ratings of general distress are common to individuals with both anxious and depressive disorders (e.g., Brown, Chorpita, & Barlow, 1998; Clark & Watson, 1991; Watson, Clark et al., 1995; Watson, Weber et al., 1995). Although such findings shed light on the subjective mood states of depressed individuals rather than on their actual responses to pleasant stimuli, they are nevertheless consistent with the notion that depression is characterized by anhedonia.

Finally, there is a substantial literature that has demonstrated that depression is associated with decreased neuronal activity in the left anterior regions of the cerebral cortex (for reviews, see Davidson, 1995, 1998; Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Tomarken & Keener, 1998b). These brain activity findings suggest decreased sensitivity to cues of reward and a decreased approach-related disposition in depressed individuals. Once again, however, although this body of research indirectly supports the conclusion that depression is characterized by anhedonia, these studies did not directly assess how depressed individuals respond to pleasant stimuli. Thus, although the available evidence is generally supportive of the conclusion that depression is characterized by anhedonia, relatively few studies have directly assessed how individuals with depression respond to pleasant stimuli.

Contributions of Animal Models of Anhedonia

Animal models of anhedonia have focused on the mesolimbic dopamine (DA) tract that projects from A10 cells in the ventral tegmental area to limbic areas, such as the nucleus accumbens, the amygdala, the olfactory tubercle, and the septum. This tract has been linked to primary rewards, secondary rewards, emotional processes, and is part of the limbic-striatal-pallidal circuit that is involved in motivated behavior. Dysregulation of this tract is implicated in schizophrenia, affective disorders, and substance abuse disorders (for reviews, see, e.g., Heinz, Schmidt, & Reischies, 1994; Kapur & Mann, 1992; Swerdlow & Koob, 1987).

Investigations of the behavioral and neurobiological sequelae of mesolimbic DA manipulation in animal studies have elucidated important temporal factors relevant to investigations of anhedonia in humans. Whereas initially it was believed that mesolimbic DA subserves all appetitive behaviors (Wise, 1982), recently it has been demonstrated that animals with extensive DA depletion do not differ from control animals with respect to taste reactivity to sucrose (i.e., "liking"). Rather, DA depletion seems to cause a selective decrement in reward "wanting" (Berridge & Robinson, 1998). For example, Schultz, Apicella, and Ljungberg (1993) demonstrated that mesolimbic DA neurons showed greater responses to a conditioned incentive stimulus predicting reward than to the reward stimulus itself, and Aberman, Ward, and Salamone (1998) demonstrated that the greatest behavioral differences between control and lesioned animals were evident when cumulative operant responses over time were measured in unpredictable reward contingency paradigms.

Additionally, in a series of animal studies examining the involvement of dopaminergic systems in appetitive and ingestive feeding behaviors, Blackburn and colleagues demonstrated that: (a) dopamine receptor antagonists attenuated preparatory responses to conditioned stimuli signaling the delivery of food but not responses to the delivery of food itself (Blackburn, Phillips, & Fibiger, 1987, 1989); and (b) animals sacrificed after exposure to a conditioned stimulus, but not after simple feeding, contained more dopamine metabolites in the nucleus accumbens than did control animals (Blackburn, Phillips, Jakubovic, & Fibiger, 1989). Together, these investigations suggest that the effects of mesolimbic DA depletion appear to be more pronounced during the anticipatory phase of an appetitive response than during the consummatory phase. The broad implication of these animal findings for human anhedonia research is that in order to elucidate pleasure responding comprehensively, hedonic responses should be systematically assessed during both anticipatory and consummatory phases.

The idea that anhedonia may be separable into anticipatory and consummatory components in individuals with depression is not a novel concept. Based on his observations of depressed patients, Klein (1974; 1987) proposed that the experience of pleasure is divisible into the two functional pleasure systems of appetitive pleasure ('wanting') and consummatory pleasure ('liking'). Klein (1987) illustrated that states of appetitive pleasure produce the motivation to approach rewarding stimuli and are primarily linked to processes of pursuit and interest. He further proposed that some depressed patients who reported anhedonia were capable of subjective pleasurable states when placed in enjoyable situations with readily available pleasurable stimuli. Although this observation was anecdotal, the possibility of an appetitive pleasure deficit in the

absence of a concomitant consummatory pleasure deficit suggests that anhedonia may be parsed into these two more elemental units, and that depression may be characterized by deficits in one or both types of pleasure systems.

Affective Startle Blink Reflex Modulation

The present study assessed whether depressed and nondepressed individuals differed in affective modulation of the startle eyeblink reflex during both anticipatory and processing phases of an affective response. Startle modulation induced by emotional stimuli is a well-established phenomenon among predominantly nondepressed samples. When nondepressed individuals view affective pictures and the latency between picture onset and startle probe onset is relatively long (e.g., 3500-4500 ms), response magnitude is modulated by the valence (i.e., pleasantness) of the picture. Unpleasant pictures potentiate and pleasant pictures attenuate the magnitude of the startle blink relative to neutral pictures (e.g., Bradley, Cuthbert, & Lang, 1993). This linear pattern of valence-dependent startle modulation is thought to reflect the priming of neurobiologically-based defensive and appetitive systems by unpleasant and pleasant foreground stimuli, respectively (e.g., Lang, Bradley, & Cuthbert, 1998). This valence modulation phenomenon is clearly robust, occurring with a range of affective manipulations, including picture viewing (Vrana, Spence, & Lang, 1988), olfaction (Miltner, Matjak, Braun, Diekmann, & Brody, 1994), and imagery (Cook, Hawk, Davis, & Stevenson, 1991). Additionally, affective startle modulation has been demonstrated with auditory (Vrana et al., 1988), visual (Bradley, Cuthbert, & Lang, 1990), and tactile (Hawk & Cook, 1997) startle probes.

In other contexts, the magnitude of the startle reflex is modulated by the arousal, rather than valence, dimension of affective stimuli. Using predominantly non-clinical college student participants, Bradley, Cuthbert, and Lang (1993) found that both unpleasant and pleasant foreground stimuli attenuated blink magnitudes relative to neutral stimuli when startle probes were presented soon after the onset of the foreground stimulus (e.g., 300 ms). This research group suggested that this pattern of startle modulation reflects differential allocation of attentional resources, with heightened allocation to those pictures that elicit high levels of arousal. Thus, by manipulating probe latency, startle modulation to both the arousal (300 ms) and valence (3500-4500 ms) dimensions of the pictorial foreground stimuli may be assessed.

Recently, startle modulation during the anticipation of affective stimuli has been demonstrated. Similar to startle modulation during picture viewing, the form of anticipatory startle modulation is dependent on the latency between the startle probe and the onset of the emotional stimulus. In an anticipatory affective startle modulation paradigm, a neutral cue that signals the valence of the forthcoming emotional stimulus precedes the presentation of that emotional stimulus. Startle responses are recorded during the anticipatory interval that occurs after cue onset and before emotional stimulus onset. When the latency between the startle probe and the onset of the emotional stimulus is relatively long (i.e., 2000 ms), blink magnitudes to both unpleasant and pleasant stimuli are potentiated, relative to responses during the anticipation of neutral stimuli (Dichter, Tomarken, & Baucom, 2002). This pattern is essentially the inverse of what is observed during the 300 ms viewing interval and is consistent with modulation of

the startle eyeblink response by the arousal, rather than valence, dimension of affective stimuli.

One proposed psychological mechanisms underlying anticipatory startle modulation is that soon after the presentation of an informative cue indicating the imminent onset of a future stimulus, the organism acts conservatively to withdraw attentional resources from the immediate external environment (Dichter et al., 2002). Such withdrawal may reflect an adaptive attempt to go "off-line" temporarily to conserve resources for later use, and such preservation of resources may be greater when the organism anticipates an arousing (i.e., pleasant or unpleasant) stimulus that will require more attentional resources.

Whereas there is evidence, reviewed above, of a quadratic valence-startle magnitude relation at longer (i.e., 2000 ms) anticipatory intervals, one unpublished study to date has employed a shorter (i.e., 750 ms) anticipatory interval. Although systematic statistical tests of quadratic and linear startle modulation were not presented in this study, Erickson (1996) reported what appears to be linear valence modulation of the startle response to 750 ms anticipatory probes isomorphic to that which is typically observed during late-probe picture perception (i.e., potentiated and attenuated startle responses in the unpleasant and pleasant conditions, respectively, relative to the neutral condition). This study also demonstrated what appears to be quadratic startle modulation to 2750 ms anticipatory probes and modulation that appears to be both linear and quadratic at an intermediate anticipatory interval (i.e., 1750 ms). This pattern of results suggests that anticipatory startle modulation is quadratic at longer lead intervals and becomes progressively more linear at shorter lead intervals. In essence, during an anticipatory

interval there appears to be a transition from arousal-dependent startle modulation to valence-dependent startle modulation as the affective stimulus approaches.

It is interesting to note that one published study that employed another intermediate anticipatory interval, 1000 ms, demonstrated both a quadratic and linear pattern of affective startle modulation (i.e., both potentiated and attenuated startle responses in the unpleasant and pleasant conditions, respectively, as well as potentiated responses in the unpleasant condition, relative to the pleasant condition). Such a pattern of results lends further credence to the notion that anticipatory startle modulation is quadratic at longer lead intervals and becomes more linear at shorter lead intervals (Nitschke et al., 2002).[1]

The complex pattern of relations between startle modulation and startle probe onset latency is summarized in Figure 1. Negative probe delays (the left side Figure 1) depict startle magnitudes during affective picture anticipation. Positive probe delays (the right side of Figure 1) depict startle magnitudes during affective picture viewing. Note that the patterns of affective startle modulation at the -2000 ms and +300 ms probe delays are: (1) essentially the inverse of one another; (2) consistent with modulation of startle magnitude by the arousal dimension of emotional pictures; and (3) quadratic in shape (i.e., startle magnitudes in the neutral condition differ from those to the other two picture categories). The patterns of startle modulation at the -750 ms and +4000 ms probe delays are: (1) consistent with modulation of startle magnitude by the valence dimension of

[1] Sabatinelli, Bradley, and Lang (2001) presented probes at both 2000 ms and 500 ms before picture onset but did not differentiate between these two anticipatory probe latencies in their analyses. Although these researchers found a quadratic pattern of affective startle modulation during the anticipatory phase, it is impossible to determine from their analyses the form of startle modulation uniquely to the 500 ms anticipatory probes.

emotional pictures; and (2) linear in shape (i.e., greatest to unpleasant pictures and least to pleasant pictures, relative to neutral pictures).

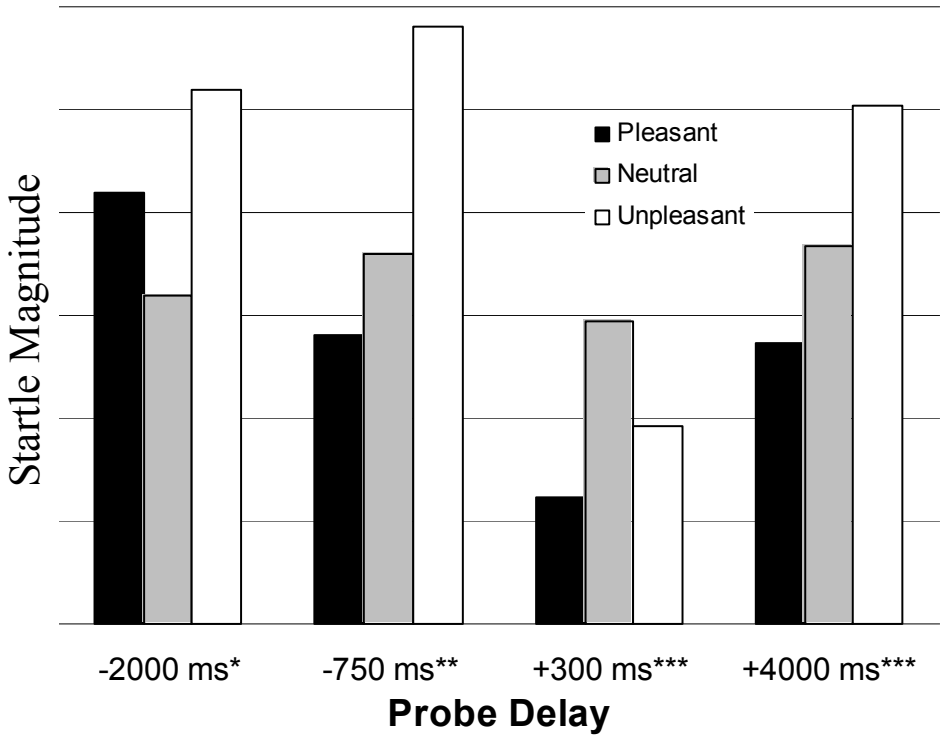

Figure 1: Summary of the relation between probe delay and affective startle modulation by affective pictures in nondepressed participants. Negative and positive probe delays indicate probes presented while participants anticipate and view, respectively, emotional pictures. Magnitudes are in arbitrary units. *Data are reproduced from Dichter et al. (2002). ** Data are reproduced from Erickson (1996). *** Data are reproduced from Dichter et al. (2004). The category label "+4000 ms" indicates results from probes presented 3500-4500 ms after probe onset.

Affective Startle Blink Reflex Modulation in Unipolar Depression

As the preceding discussion would suggest, the startle blink paradigm may be an ideal way to assess the time course of affective responding during both an anticipatory phase before a stimulus appears and a processing phase after stimulus onset. Furthermore, on theoretical grounds the startle-blink paradigm would appear ideally suited to assess the

affective response deficits hypothesized to be characteristic of depression. Many theorists have argued that deficits in emotional and motivational responses to stimuli are core feature of unipolar depression (e.g., American Psychiatric Association, 1994; Fowles, 1988; Tomarken & Keener, 1998a). Correspondingly, several theorists have posited that: (a) core features of unipolar depression are exaggerated responses to stressful or other aversive stimuli and/or deficient responses to positive hedonic stimuli; and, (b) such responses are attributable to dysfunction in neurobiologically-based defensive and appetitive systems that organize responses to motivationally significant stimuli (e.g., Fowles, 1988; Klein, 1974; Tomarken & Keener, 1998a). Finally, as discussed earlier, theoretical accounts of affective startle modulation highlight the priming of defensive and appetitive systems by affectively meaningful foreground stimuli. Thus, theoretical accounts of both the motivational dysfunction characteristic of depression and models of affective startle modulation highlight the critical role of higher-order appetitive and defensive motivational systems. If depression were characterized by deficits in the mobilization and/or operation of such systems, one would expect a pattern of startle-modulation among depressed individuals that deviates from the pattern commonly observed among nondepressed samples.

Two published studies to date have examined affective startle modulation in depressed individuals during picture perception. Allen and colleagues (1999) evaluated affective startle modulation in depressed individuals to probes presented 4000-6000 ms after picture onset and failed to find the linear pattern commonly observed among nondepressed participants. If anything, startle blinks elicited while viewing both pleasant and unpleasant pictures appeared potentiated relative to neutral pictures, although this

trend was not significant. Dichter and colleagues (2004) examined startle modulation to probes presented at both 300 ms and 3500-4500 ms after picture onset. Consistent with the findings of Allen and colleagues (1999), depressed and nondepressed individuals differed significantly during the later probe condition; however, diagnostic groups did not differ during the earlier probe condition, suggesting that diagnostic groups may differ in startle responses to the valence, but not arousal, dimension of affective pictures. Anomalous responses to the valence dimension of pictures are consistent with prior empirical studies on the subjective responses of depressed individuals to pleasant stimuli (e.g., Sloan et al., 1997; Sloan et al., 2001) and the broader evidence that depression is characterized by dysfunction in systems that mediate responses to pleasant stimuli (e.g., Brown et al., 1998).

As reviewed earlier, animal literature on anhedonia suggests that a comprehensive investigation of responses to hedonic stimuli should assess both anticipatory and consummatory components of a response system. No published study to date has assessed startle modulation during the anticipation of affective stimuli in depressed individuals. In the current investigation, startle eyeblink modulation was examined during both anticipatory and viewing phases by presenting startle probes at four latencies. Two latencies occurred during an anticipatory interval (i.e., 2000 ms and 750 ms before picture onset), and two during a viewing interval (i.e., 300 ms and 3500-4500 ms after picture onset).

Hypotheses concerning responses to startle probes presented during picture viewing were based on the results of Dichter et al. (2004): at the 300 ms viewing condition, it was hypothesized that startle responses would be moderated by picture

arousal (i.e., a quadratic relation to picture valence) and that this effect would not be moderated by diagnostic group; at the 3500-4500 ms viewing condition, it was hypothesized that nondepressed individuals would demonstrate a valence-based linear pattern of startle responses and that diagnostic group status would moderate this pattern.

Although affective startle modulation differences between diagnostic groups during the anticipatory conditions were also hypothesized, such predictions were more cautious for two reasons. First, only one, unpublished study has examined affective startle modulation in a nondepressed sample to 750 ms anticipatory probes, and thus the replicability of startle modulation to 750 ms anticipatory probes in nondepressed participants has not yet been established. Second, anticipatory affective startle modulation in depressed individuals is unexplored.

Nevertheless, group differences in affective startle modulation were hypothesized during both anticipatory conditions for four reasons. First, as reviewed above, anhedonia is a prominent feature of depression (American Psychiatric Association, 1994; World Health Organization, 1992) and an animal model of anhedonia has demonstrated pronounced deficits during the anticipation of pleasant stimuli (e.g., Blackburn et al., 1987; Blackburn, Phillips, & Fibiger, 1989; Blackburn, Phillips, Jakubovic et al., 1989). Second, a number of theories conceptualize depression to be a disruption of appetitive motivational systems (e.g., Eastman, 1976; Fowles, 1988). According to such theories, both depressed mood and anhedonia imply a reduction not only in the experience of reward but also in responding to cues of reward. Third, cognitive theories of depression highlight the effects of the (false) expectation that reward-seeking will be ineffective (e.g., Abramson, Seligman, & Teasdale, 1978; Beck, 1974). Finally, as reviewed above,

because the anticipatory startle modulation paradigm appears to be capable of indexing both motivational priming and valence-based anticipation, it seems to be an ideal paradigm to evaluate attenuated affective stimulus anticipation in depressed individuals. Although groups were hypothesized to differ at both anticipatory latencies, group differences were hypothesized to be more pronounced at the 750 ms anticipatory latency. This hypothesis was based on the finding that startle responses in nondepressed samples at the 750 ms anticipatory latency may be modulated by the valence of foreground stimuli (Erickson, 1996), and depressed samples have been shown to demonstrate anomalous startle responses to the valence dimension of foreground stimuli (Dichter et al., 2004).

CHAPTER II

METHOD

Participants

Participants provided written informed consent after all procedures were explained. Twenty-seven depressed adults participated in the startle session. Outpatient depressed participants (14 women, age range: 22.9-59.0 years, mean = 41.8, SD = 10.6) were recruited from depression treatment studies conducted in the Vanderbilt Medical Center Department of Adult Psychiatry. Nine depressed individuals declined to participate in the startle session. The clear majority of individual in the depressed group participated in the startle session before they had begun antidepressant medication. However, because the depression treatment studies from which depressed participants were recruited did not require an antidepressant washout period, five depressed participants were taking venlafaxine at the time of their startle session (four of them for seven or less days, one for 28 days)[2].

Depressed participants qualified for the study if they: (1) were at least 18 years of age; (2) met criteria for DSM-IV unipolar major depression assessed by semi-structured clinical interview (Frist, Spitzer, Gibbon, & Williams, 1996) performed at Vanderbilt University Medical Center by experienced interviewers; (3) had scores on the 17-item

[2] Beck Depression Inventory scores did not differ significantly between these five participants (M=31.6, SD=4.2) and the depressed participants who were medication-free (M=34.5, SD=11.5), $p > .50$. Additionally, the patterns of startle modulation of these five participants are nearly isomorphic to those of the other depressed participants. Finally, a recent study found that 12 weeks of antidepressant medication treatment did not moderate affective startle modulation to probes presented 300 ms or 3500-4500 ms after picture onset (Dichter et al., 2004).

version of the Hamilton Rating Scale for Depression (HRSD-17, Hamilton, 1960) that were greater than 18; (4) did not meet criteria for current or past bipolar disorder or any psychotic disorder; (5) did not meet criteria for a current diagnosis of delirium or dementia; (6) did not have current psychotic symptoms; and (7) did not meet criteria for alcohol or drug abuse or dependence in the previous six months. Of the final sample, five participants met criteria for melancholic depression and four met criteria for atypical depression. In addition to meeting criteria for a unipolar major depression, five participants met criteria for current or past PTSD, five met criteria for a past alcohol use disorder, and eight met criteria for a current anxiety disorder (three for phobia, three for obsessive-compulsive disorder, one for generalized anxiety disorder, and one for panic disorder).

Nondepressed participants were recruited through announcements placed in local newspapers and by telephone from control participant lists maintained through Vanderbilt University. Nondepressed participants were lifetime-free of major depressive disorder and dysthymia and did not meet criteria for any current axis I disorder, as assessed by semi-structured clinical interview (Frist et al., 1996) performed at Vanderbilt University Medical Center by a Masters-level clinical psychology doctoral candidate. One hundred and one adults were contacted to participate. Seven declined the diagnostic interview. Of those interviewed, six were excluded because they were taking an anti-depressant medication, fourteen were excluded because they met criteria for a past or current depressive episode, six were excluded because they met criteria for past or current dysthymia, two were excluded because they met criteria for a current drug use disorder, and two were excluded because they met criteria for a current anxiety disorder. Of the

individuals who met inclusion criteria for the current study, four declined to participate in the startle session. The final nondepressed sample consisted of 60 participants (31 women; age range: 30.0-69.1 years, mean = 46.5, SD = 8.3). Participant groups did not differ with respect to age, $t(85)=1.11$, $p>.25$ or gender distribution, $\chi^2 (1) = 0.0003$, $p >0.98$.

Questionnaires

During the startle session, participants completed the Beck Depression Inventory, 2nd version (BDI, Beck, Steer, & Brown, 1996), one of the most common self-report continuous rating scales of depressive symptoms (Piotrowski & Keller, 1992), and the Mood and Symptom Questionnaire (MASQ, Watson, Clark et al., 1995; Watson, Weber et al., 1995). The MASQ assesses the dimensions of mood derived from the tripartite model of emotion and has five subscales: General Distress: Mixed, General Distress: Anxiety, General Distress: Depression, Anxious Arousal, and Anhedonic Depression[3].

Experimental Design

In addition to the between-subjects variable of depression status (Depressed/Nondepressed), two within-subjects variables were varied: Picture Valence (Unpleasant/Pleasant/Neutral) and Probe Onset Time (2000 ms Anticipatory/750 ms Anticipatory/300 ms Viewing/3500-4500 ms Viewing).

[3] The MASQ Anhedonic Depression scales consists of items that reflect both the low pole of anhedonia (e.g., "slowed down") and the high pole of positive affect (e.g., "energetic"), the latter of which is reverse-keyed. In addition to examining the total scale, both end-points of the anhedonia-positive affect continuum were analyzed separately in the current investigation because of prior evidence of unique relations to each pole (Tomarken, Dichter, Freid, Addington, & Shelton, 2004).

Stimulus Materials

Each participant viewed two sets of color pictures (one habituation set and one experimental set) chosen from the International Affective Picture System (IAPS, "Center for the Study of Emotion and Attention," 1999) on the basis of their published affective valence and arousal ratings. Pleasant and unpleasant pictures were selected on the basis of extreme normative ratings of both valence and arousal. The habituation set consisted of three neutral pictures and was included to allow the startle blink reflex to habituate. The experimental set consisted of 54 pictures (18 pleasant, 18 neutral, and 18 unpleasant) presented in nine blocks of six pictures. Each block contained two pictures of each of the three picture categories. Pictures were displayed on a 17 in color monitor approximately 1.3 m in front of the participant.

Procedure

Nondepressed participants first took part in the diagnostic interview session performed at Vanderbilt University Medical Center during which the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID, Frist et al., 1996) was administered. If the inclusion criteria for the present study were met, nondepressed participants were then scheduled for the startle session that took place within one week of the diagnostic interview. Depressed participants were recruited by telephone on the day they entered their treatment study and scheduled for the startle session that took place within one week of their enrollment in their treatment study. All participants were given monetary compensation for their participation.

During the startle session, participants first completed the questionnaires. Next, participants viewed the habituation pictures and then the experimental pictures while electromyography (EMG) was recorded. Each trial consisted of a 2 s cue arrow indicating forthcoming picture valence, 4 s of no visual stimulation ("anticipatory phase"), and 6 s of picture presentation ("viewing phase"). The inter-trial interval (i.e., the interval between picture offset and the onset of the subsequent trial's warning cue) was 7-9 s (mean = 8 s)[4]. The cue arrow was either an "up-arrow" indicating a pleasant picture, a "down-arrow" indicating unpleasant picture, or a "sideways-arrow" indicating a neutral picture. Arrows were large, black block figures on a white background.

Acoustic startle probes of 50 ms, 100 dB white-noise bursts with instantaneous rise times were binaurally-presented. During each trial, startle probes were presented at one of four intervals: 2000 ms or 750 ms before the onset of the picture ("anticipatory probes"), or 300 ms or 3500 – 4500 ms (mean = 4000 ms) after the onset of the picture ("viewing probes"). Participants received an anticipatory probe or a viewing probe during each trail. Figure 2 shows the timing of the informational cue, picture presentation, startle probes, and ITI. Picture and probe presentation were controlled by the STIM software package from the James Long Company (Caroga Lake, N.Y.).

[4] An inter-trial interval of 7 s - 9 s is briefer than is generally employed in other startle investigations (e.g., Dichter et al., 2004; Vrana et al., 1988). However, published studies have failed to demonstrate affective startle modulation at 2000 ms after picture offset (Dichter et al., 2002) and 3800 ms after picture offset (Bradley et al., 1993). Thus, the affective effects of the IAPS images appear to subside well before the end of the 7 s - 9 s inter-trial interval used in the current study. Thus, this shorter inter-trial interval was used to minimize participant fatigue.

← 2 s →	← 4 s →	← 6 s →	← 7-9 s →
Informational cue	Anticipatory probes: either 750 ms or 2000 ms before picture onset	Viewing probes: either 300 ms or 3500 – 4500 ms after picture onset	Inter-trial interval

Figure 2. Timing of the informational cue, picture presentation, startle probe, and ITI. Participants received an anticipatory probe or a viewing probe during each trail.

To diminish the predictability of the procedure, three probes, equally spaced throughout the trials, were presented during ITI's and six of the 54 trials did not contain startle probes. Of the 48 probed trials, 16 trials each contained pictures of each of the three valences. Within each valence category, four trials each contained probes of each of the four probe conditions. In other words, there were four trials in each of the 12 cells produced by the crossing of Valence (three levels) X Probe (four levels) categories. Male and female sets were invariant with respect to valence and probe order and were matched, picture-by-picture, with respect to published gender-specific IAPS ratings of valence and arousal. Pictures were presented in one of two counter-balanced orders to diminish the probability that startle modulation would be affected by the particular order of picture presentation.

The picture stimuli were presented twice to each participant. During the first presentation, startle blinks were recorded. During the second presentation (without startle probes), participants controlled picture exposure duration and rated each picture

with respect to emotional pleasure (i.e., extremely unpleasant - extremely pleasant) and arousal (i.e., not at all aroused - extremely aroused) using 9-point Likert scales.

Physiological Recording and Data Reduction

The eyeblink component of the startle reflex was measured by bipolar recording of the EMG activity below the left eye with two miniature Ag-AgCl electrodes filled with electrolyte paste. A ground electrode was placed on the forehead. All electrode impedances were below 20 kΩ. Custom-built isolated bioelectric amplifiers sold by James Long Company were used for recording. The input impedance of the amplifiers was > 1 gigaohm. The raw EMG signal was bandpass-filtered (high-pass filter set at 10 Hz, low-pass filter set at 500 Hz), amplified (gain = 5K), and sampled at 1,024 Hz by an Analogue Devices RTI-815A analogue to digital converter interfaced to Snapstream (HEM Inc.), a commercially available signal acquisition program.

The digitized EMG was digitally filtered off-line to highlight signals between 80 and 240 Hz. A truncated convolution filter was used with weights yielded by an inverse Fourier transformation of a rectangle function with values of unity in the 80-240 Hz range and values of 0 outside this range. This filter provided a very sharp cut-off (i.e., in excess of 40 dB down immediately outside the band of interest). The data were then digitally rectified and low-pass filtered by integrating values in 32 ms time windows. Consistent with other research groups (e.g., Bradley et al., 1993), peak EMG magnitudes were computed in search windows between 10 and 250 ms after the onset of the startle probes. Trials with artifact were detected by EMGART software from the James Long Company (Caroga Lake, N.Y.). This software computes the standard deviation and mean

of each trial's baseline (defined as the 50 ms prior to probe onset) and rejects trials with baselines that exceed at any time either the baseline mean plus two standard deviations of that mean or four times the mean.

After deletion of trials with artifact (less than 1.0 % of the trials), magnitude measures were averaged across each of the 12 levels formed by the crossing of the Valence (Unpleasant/Pleasant/Neutral) X Probe Onset Time (2000 ms Anticipatory/750 ms Anticipatory/300 ms Viewing/3500-4500 ms Viewing) within-subjects factors for each participant [5,6].

Data Analysis

The habituation trials were not included in analyses. Omnibus repeated measures effects were evaluated using multivariate test criteria that do not require the assumption of sphericity (Vasey & Thayer, 1987). In order to verify that the nondepressed group demonstrated the expected patterns of startle modulation and to evaluate startle modulation in the depressed group alone, initial analyses were repeated measures ANOVAs testing for the effect of Valence (pleasant, neutral, unpleasant) performed on startle magnitude during each of the four probe conditions separately for nondepressed

[5] Although results are presented based on raw startle magnitudes, analyses using z-transformed startle magnitudes did not in any way alter the primary findings or conclusions. Other researchers have noted highly similar results obtained with both raw and standardized scores (e.g., Grillon & Ameli, 2001). Raw startle magnitudes are reported to be consistent with studies in the startle literature addressed (e.g., Bradley et al., 1993; Dichter et al., 2004) and the core diagnostic analysis of Allen et al. (1999).

[6] Consistent with the suggestion of Berg & Balaban (1999) regarding proper terminology, startle "magnitudes" are reported because trials with no discernable startle responses were included in averaging. These authors have suggested that a peak startle average that includes trials with no startle blink should be termed startle "magnitude" whereas a peak startle average that does not include such trials should be termed startle "amplitude." Startle magnitudes are commonly reported in the startle literature.

and depressed participants. Next, to assess whether diagnostic groups differed with respect to startle modulation, the omnibus analyses of interest were Group (depressed, control) X Valence (pleasant, neutral, unpleasant) repeated measures ANOVAs performed separately on startle magnitude during each of the four probe conditions.

In the 2000 ms anticipatory condition, the primary analyses of interest were tests for a quadratic pattern of startle modulation across the unpleasant, neutral, and pleasant pictures (trend coefficients = +1, -2, and +1, respectively). Therefore, in addition to the omnibus analyses, a planned Group X Quadratic Contrast ANOVA was conducted on startle magnitudes. Because it was unclear whether diagnostic groups would manifest differential startle responses during anticipation of both pleasant and unpleasant pictures or pictures of only one valence category, exploratory follow-up analyses tested for group differences with respect to startle potentiation to pleasant and unpleasant pictures separately.

In the 750 ms anticipatory condition, the primary analyses of interest were tests for a linear pattern of startle modulation across the unpleasant, neutral, and pleasant pictures (trend coefficients = +1, 0, and -1, respectively). Therefore, in addition to the omnibus analyses, a planned Group X Linear Contrast ANOVA on startle magnitudes was conducted. Exploratory follow-up analyses tested for group differences with respect to startle potentiation and inhibition in response to unpleasant and pleasant pictures, respectively.

In the 300 ms viewing condition, the primary analyses of interest were tests for a quadratic pattern of startle modulation across the unpleasant, neutral, and pleasant pictures (trend coefficients = -1, +2, and -1, respectively). A planned Group X Quadratic

Contrast ANOVA was conducted on startle magnitudes, and exploratory follow-up analyses tested for group differences with respect to startle attenuation in response to pleasant and unpleasant pictures separately.

Similar to the 750 ms anticipatory condition, in the 3500-4500 ms viewing condition, the primary analyses of interest were tests for a linear pattern of startle modulation across the unpleasant, neutral, and pleasant picture (trend coefficients = +1, 0, and -1, respectively). A planned Group X Linear Contrast ANOVA was conducted on startle magnitudes, and exploratory follow-up analyses tested for group differences with respect to startle potentiation and inhibition in response to unpleasant and pleasant pictures, respectively.

CHAPTER III

RESULTS

Symptom Measures

Table 1 indicates depressed and nondepressed participants' responses on the self-report questionnaires. Overall, diagnostic groups differed significantly in the predicted direction on all measures.

Table 1: Questionnaire scores for depressed and nondepressed participants. Possible scores on the BDI ranged from 0 to 63. Possible scores on the MASQ subscales ranged from 1 to 5. All tests were two-tailed. Standard Deviations are in parentheses. MASQ Anhedonic Depression (low pole) and Anhedonic Depression (high pole) represent scores from only negative and (reverse-keyed) positive items, respectively, from the MASQ Anhedonic Depression subscale.

	Mean Scores (SD)		
	Depressed Participants (N=27)	Nondepressed Participants (N=60)	t(85)
Beck Depression Inventory	33.96 (10.55)	1.73 (2.81)	22.12*
MASQ subscales			
General Distress Mixed	3.68 (0.73)	1.61 (0.60)	13.91*
General Distress: Anxiety	2.66 (0.78)	1.36 (0.48)	9.57*
General Distress: Depression	3.71 (0.85)	1.33 (0.47)	16.88*
Anxious Arousal	2.03 (0.73)	1.13 (0.21)	8.85*
Anhedonic Depression (low pole)	3.46 (0.74)	1.33 (0.40)	17.35*
Anhedonic Depression (high pole)	4.56 (0.47)	2.53 (0.58)	15.94*
Anhedonic Depression (total scale)	4.16 (0.48)	2.09 (0.45)	19.62*

* Bonferroni-corrected $p < .001$

Startle Modulation

When gender, age, and picture set were entered into analyses of affective startle modulation as covariates, there were no main effects or interactions involving these

factors on the primary dependent measures. Thus, they were excluded from all the analyses reported below.

Startle Probes 2000 ms Before Picture Onset

The top left panel of Figure 3 shows mean blink magnitudes in response to probes presented 2000 ms before picture onset for the depressed and nondepressed groups. This figure illustrates that the nondepressed group demonstrated the hypothesized quadratic pattern of startle modulation with startle responses during the anticipation of pleasant and unpleasant picture potentiated relative to neutral pictures and that the depressed group did not. An examination of startle modulation within the nondepressed group revealed that there was a significant main effect of Valence, $F[2,58] = 3.80$, $p < .05$ and a significant Quadratic Trend, $F[1,59] = 4.76$, $p < .05$. Within the depressed group, there were no significant effects of Valence or Quadratic Trend, p's $> .25$. A Valence X Group ANOVA revealed no main effect of Valence, $F[2,84] = 0.63$, $p > .50$, or Group, $F[1,85] = 0.10$, $p > .75$, and only trends towards a Group X Valence interaction, $F[2,84] = 2.63$, $p < .08$, a Quadratic Trend, $F[1,85] = 3.52$, $p < .07$, and a Group X Quadratic Trend interaction, $F[1,85] = 3.52$, $p < .07$. Exploratory follow-up analyses revealed that although groups did not differ with respect to startle potentiation to unpleasant, relative to neutral, pictures, $F[1,85] = 1.75$, $p > .15$, groups did differ with respect to startle potentiation to pleasant pictures, $F[1,86] = 4.91$, $p < .03$. This difference reflects the fact that nondepressed participants demonstrated startle potentiation in anticipation of pleasant pictures while depressed participants did not.

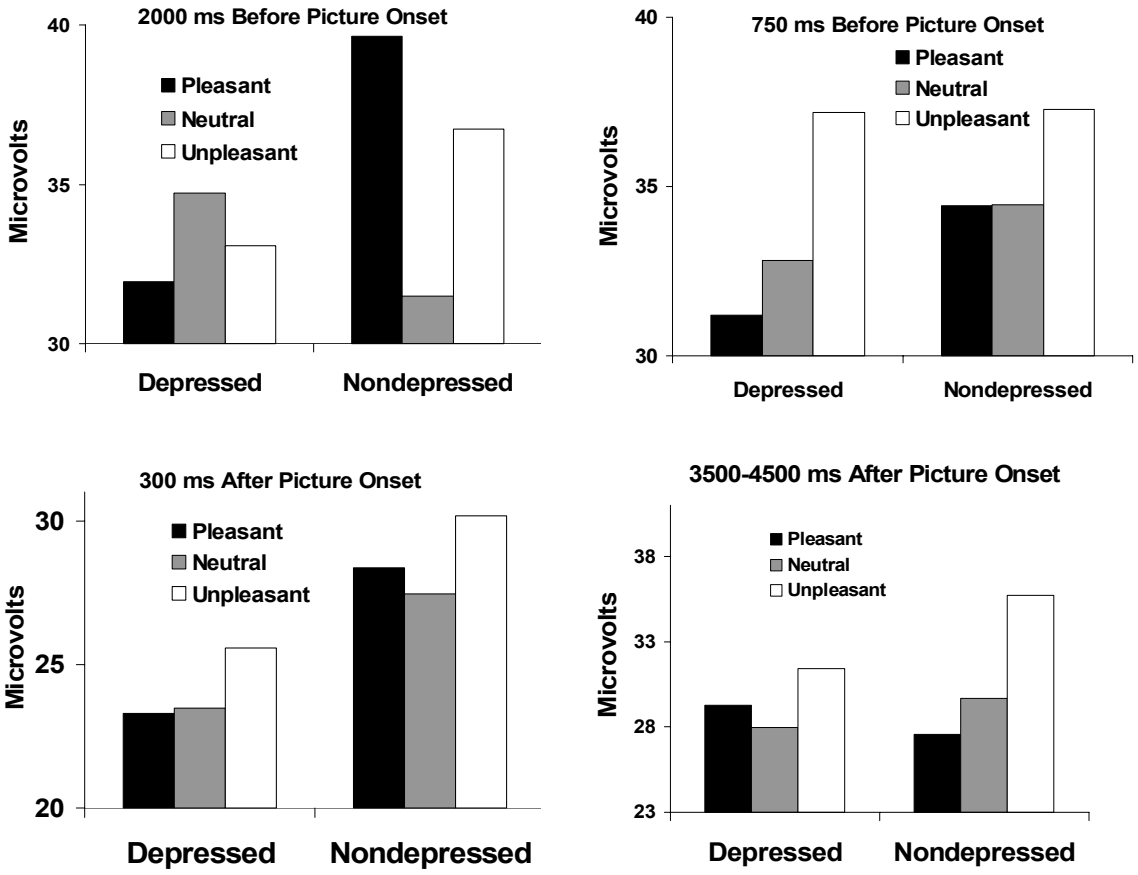

Figure 3: Startle responding to pleasant, neutral, and unpleasant pictures by depressed and nondepressed participants to probes presented 2000 ms before (top left), 750 ms before (top right), 300 ms after (bottom left), and 3500-4500 ms after (bottom right) picture onset.

Startle Probes 750 ms Before Picture Onset

The top right panel of Figure 3 shows mean blink magnitudes in response to probes presented 750 ms before picture onset for the depressed and nondepressed groups. This figure illustrates that both groups appeared to demonstrate a linear pattern of startle modulation with startle responses during the anticipation of unpleasant and pleasant pictures potentiated and attenuated, respectively, relative to neutral pictures, although,

unexpectedly, this linear patter appears to be more pronounced in the depressed group. An examination of startle modulation within the nondepressed group revealed no significant main effect of Valence, F[2,58] = 1.83, $p > .15$ and a trend towards a significant Linear Trend, F[1,59] = 3.27, p<.08. Within the depressed group, there was no significant effect of Valence, F[2,25] = 1.76, p>.15 and a trend towards a significant Linear Trend, F[1,26] = 3.56, p<.08. A Valence X Group ANOVA revealed no significant main effect of Group, F[1,85] = 0.04, p > .80, a main effect of Valence, F[2,84] = 4.04, $p < .05$, a significant Linear Trend, F[1, 85] = 7.81, p<.006, but no Group X Valence interaction, F[2,84] = .50, p > .60 or Group X Linear Trend interaction, F[1,85] = 0.00, $p > .99$. Groups did not differ with respect to differences between pictures of any valence category, *p*'s > .32.

Startle Probes 300 ms After Picture Onset

The bottom left of Figure 3 shows mean blink magnitudes in response to probes presented 300 ms after picture onset for the depressed and nondepressed groups. This figure illustrates that startle modulation by the nondepressed group appears to be quadratic in the direction opposite to predictions, with startle responses augmented to unpleasant and pleasant pictures, relative to neutral pictures. For both groups, there were no significant main effects of Valence or significant Quadratic trends, *p*'s > .25. A Valence X Group ANOVA revealed no main effects of Valence or Group, no Quadratic Trend, no Group X Valence interaction, and no Group X Quadratic Trend interaction, *p*'s > .45. Additionally, differences between pairs of picture categories did not differ between diagnostic groups, *p*'s > .65.

Startle Probes 3500-4500 ms After Picture Onset

The bottom right panel of Figure 3 shows mean blink magnitudes in response to probes presented 3500-4500 ms after picture onset for the depressed and nondepressed groups. This figure illustrates that startle modulation by the nondepressed group appears linear, with startle responses to unpleasant and pleasant pictures potentiated and attenuated, respectively, relative to neutral pictures. This linear relation appears to be weaker in the depressed group. Within the nondepressed group, there was a significant main effect of Valence, $F[2,58] = 10.48$, $p < .0001$, and a significant Linear trend, $F[1,59] = 19.62$, $p < .0001$. Within the depressed group, there was no significant effect of Valence, $F[2,25] = 1.39$, $p > .25$ and no significant Linear trend, $F[1,26] = 1.59$, $p > 20$. A Valence X Group ANOVA revealed a main effect of Valence, $F[2,84] = 7.19$, $p < .0013$, no main effect of Group, $F[1,85] = 0.10$, $p > .75$, no Group X Valence interaction, $F[2,84] = 2.05$, $p > .10$, a significant Linear Trend, $F[1, 85] = 11.97$, $p<.0008$, and a significant Group X Linear Trend interaction, $F[1,85] = 4.09$, $p < .05$. The diagnostic groups did not differ with respect to unpleasant/neutral and pleasant/neutral differences, *p*'s > .20.

Relations Between Probe Conditions

Because diagnostic groups differed with respect to startle potentiation to pleasant pictures at the 2000 ms anticipatory condition and linear valence startle modulation at the 3500-4500 ms viewing condition, supplementary correlational analyses were conducted to evaluate whether these two effects were related. An "anticipatory pleasant potentiation" metric was computed by subtracting startle magnitudes in response to

neutral pictures from those in response to pleasant pictures at the 2000 ms anticipatory condition. A "viewing linear modulation" metric was computed by subtracting startle magnitudes in response to pleasant pictures from those in response to unpleasant pictures at the 3500-4500 ms viewing condition. These metrics were significantly correlated in nondepressed participants, $r = .53$, $p < .0001$ but not in depressed participants, $r = .310$, $p > .10$. The magnitudes of these correlations did not differ significantly, $p > .25$.

Self-report Responses to Pictures

Ratings data were not available for one nondepressed female participant. Table 2 shows the mean picture ratings for each diagnostic group. For both groups, pleasure ratings appear follow the pattern of the a priori valence categories (i.e., pleasant and unpleasant pictures rated more and less pleasant, respectively, than neutral picture). As expected, the Group (depressed, nondepressed) X Valence (pleasant, neutral, unpleasant) ANOVA on pleasure ratings revealed a significant main effect of Valence, $F[2,84] = 389.66$, $p < .0001$, and a significant Linear valence contrast, $F[1,85]= 767.00$, $p<.0001$. There was no significant effect of Group, $F[1,85] = 0.77$, $p > 0.40$, and no interactions with Group, p's>.20. The diagnostic groups did not differ with respect to unpleasant/neutral and pleasant/neutral differences, p's > .25.

Table 2 illustrates that both groups judged pleasant and unpleasant pictures to be more arousing than neutral pictures. Analyses of arousal ratings indicated a significant main effect for Valence, $F[2,84] = 208.66$ $p < .0001$ and a significant Quadratic Trend, $F[1,85]= 413.04$, $p<.0001$, and no significant effect of Group, $F[1,85] = 0.05$, $p > 0.80$, or Valence X Group interaction, $F[2,84] = 2.29$, $p > 0.11$. However, the Group X Quadratic

trend interaction was significant, F[1,85]= 4.37, $p < .05$. An examination of this interaction revealed that depressed participants rated unpleasant pictures to be less arousing, relative to neutral pictures, than did nondepressed participants, $p < .05$. The diagnostic groups did not differ with respect to unpleasant/pleasant and pleasant/neutral differences, p's > .10.

Table 2 indicates that both groups spent more time rating pleasant and unpleasant pictures than neutral pictures. The Group (depressed, nondepressed) X Valence (pleasant, neutral, unpleasant) ANOVA on the time spent rating the pictures revealed a main effect of Valence, F[2,84] = 33.98, $p < .0001$, a significant Quadratic trend, F[1,85] = 9.04, $p < .001$, but no significant effect of Group, F[1,85] = 2.55, $p > 0.10$ or interactions with Group, p's > .15. The diagnostic groups did not differ with respect to unpleasant/pleasant and pleasant/neutral differences, p's > .20.

Table 2: Mean ratings of pleasure-displeasure, arousal, and voluntary viewing time (in seconds) of pleasant, neutral, and unpleasant pictures by depressed and nondepressed participants. The range and direction of the ratings are as follows: pleasure = -4 (extremely unpleasant) to +4 (extremely pleasant), arousal = 0 (not at all aroused) to +8 (extremely aroused). Standard deviations are in parentheses.

	Nondepressed	Depressed
Pleasure-displeasure rating		
Pleasant	1.90 (0.60)	1.74 (0.94)
Neutral	0.09 (0.25)	0.12 (0.35)
Unpleasant	-2.83 (0.80)	-2.58 (0.95)
Arousal rating		
Pleasant	4.31 (1.39)	4.19 (1.84)
Neutral	0.78 (0.84)	1.20 (1.44)
Unpleasant	4.93 (1.69)	4.44 (1.92)
Viewing Time		
Pleasant	9.78 (2.61)	10.34 (4.14)
Neutral	7.58 (2.11)	8.79 (3.66)
Unpleasant	10.25 (3.81)	11.83 (5.31)

Associations between Questionnaire Responses and Startle Modulation

Exploratory analyses examined the relations between startle modulation and BDI scores and the seven MASQ subscale scores during each probe condition using hierarchical multiple regression (Cohen & Cohen, 1983). In these analyses, the dependent variables were the relevant startle polynomial trends (i.e., quadratic trends for the 2000 ms anticipatory and 300 ms viewing conditions and linear trends for the 750 ms anticipatory and 3500-4500 ms viewing conditions) and the predictors were group and questionnaire scores. Subsequent models included interactions between group and questionnaire scores. Because eight sets of multiple regressions were examined, a step-down Bonferroni procedure was used to control for multiple significance tests where the initial significance cutoff was $\alpha = .05/8 = .00625$ (e.g., Westfall & Young, 1992). In all models analyzed, neither group (p's > .04), questionnaire scores (p's > .03), nor their interaction (p's > .03) contributed significant unique variance to the prediction of the relevant startle polynomial trends.

CHAPTER IV

DISCUSSION

2000 ms Anticipatory Probes

In the current study, startle modulation in response to auditory probes presented both before and during affective picture presentation was assessed in depressed and nondepressed participants. The most novel and provocative finding was the diagnostic group difference in affective startle modulation at the 2000 ms anticipatory interval. At this probe interval, consistent with prior findings (Dichter et al., 2002; Nitschke et al., 2002; Sabatinelli et al., 2001), nondepressed participants demonstrated quadratic valence startle modulation characterized by potentiated startle responses in anticipation of both pleasant and unpleasant pictures relative to neutral pictures. Although diagnostic groups did not differ with respect to quadratic valence startle modulation at this probe interval, analyses of group differences in startle potentiation to pleasant and unpleasant pictures indicated that groups differed with respect to startle potentiation only to the pleasant pictures. Because this group difference is specific to the anticipation of pleasant pictures, this anticipatory startle finding may represent a novel method to assess anhedonia in depression.

The current study is the first investigation to demonstrate attenuated anticipation of pleasant stimuli in individuals with depression. Although diagnostic groups differed with respect to linear startle modulation to the 3500-4500 ms viewing probes, this viewing probe effect is not specific to responses to pleasant pictures because of how the linear metric is calculated (i.e., responses to unpleasant pictures minus responses to

pleasant pictures). In other words, at the 3500-4500 ms viewing probe condition, diagnostic group differences may be due to attenuated responses by depressed participants to pleasant pictures, to unpleasant pictures, or to both. At the 2000 ms anticipatory interval, however, group differences were specific to responses to pleasant stimuli, and thereby represent a demonstration of a form of anhedonia that is not evidenced at any of the other probe conditions.[7]

The proposed psychological mechanisms underlying startle modulation at the 2000 ms anticipatory condition is that the organism may adaptively go "off-line" temporarily to conserve resources for later use (Dichter et al., 2002). The current results suggest an attenuated capacity to go "off-line" by depressed individuals during the anticipation of pleasant stimuli. This finding may be linked to a diminished ability to visualize or imagine emotional scenes demonstrated by Schwartz and colleagues (1976a). The possible relation between emotional anticipation and imagery is born out in part by similarities with respect to the shape of affective startle modulation by non-clinical samples during the anticipation and imagery of emotional stimuli: startle reflexes elicited during emotional imagery may be modulated by the arousal dimension of the imagined scenes under certain conditions in a manner that is analogous to startle modulation during emotional anticipation. Witvliet and Vrana (1995) demonstrated potentiated startle during imagery of unpleasant scenes as well as during imagery of high-arousal pleasant scenes (e.g., joy). This pattern is analogous to the quadratic valence startle modulation pattern in nondepressed participants at the 2000 ms anticipatory probe condition. However, startle blinks were attenuated to low-arousal pleasant scripts (e.g., pleasant

[7] The reader will recall that groups did not differ with respect to responses specifically to pleasant pictures, relative to neutral pictures, at the 3500-4500 ms viewing condition.

relaxation).[8] Because the pleasant pictures used in the current study were pre-selected to be high-arousal images, startle potentiation during the anticipation of pleasant pictures by nondepressed participants may be due, at least in part, to imagery of high-arousing pleasant scenes. Therefore, attenuated startle potentiation during the anticipation of the same pleasant stimuli by depressed participants may be due to a diminished predisposition or ability to imagine pleasant stimuli. A diminished tendency or capacity to anticipate pleasant stimuli may have a profound effect on the perception of the pleasantness of future events and result in the sense of amotivation that is characteristic of individuals with depression (American Psychiatric Association, 1994).

Because pleasant pictures in the current investigation did not vary across the arousal continuum, it is not possible to determine from the present study design whether diagnostic group differences during the anticipation of pleasant pictures is specific only to high-arousal pleasant pictures. Future studies that systematically vary picture arousal within each valence category would be necessary to assess whether attenuated anticipation of pleasant pictures by depressed individuals is contingent on picture valence, picture arousal, or both.

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[8] Although the precise reasons for different responses to high-arousal and low-arousal pleasant imagery are unclear, one possibility is that they are due to the differential cognitive demands of high-arousal imagery scenes. Because there is evidence that increased cognitive processing results in enhanced startle responses (Panayiotou & Vrana, 1998), the increased attentional demands towards internal, cognitive processes in high-arousal imagery may lead to augmentation of the startle reflex. Thus, although viewing pleasant pictures and imaging pleasant scenes may both activate appetitive motivational systems that are believed to inhibit the startle reflex, the recruiting of relatively greater cognitive resources in high-arousal imagery may compete to augment the startle response. Consistent with this explanation is the fact that both linear and quadratic trends typically are evident in imagery data: unpleasant and pleasant conditions are typically augmented relative to neutral, and unpleasant is augmented relative to pleasant conditions (Miller, Patrick, & Levenston, 2002).

750 ms Anticipatory Probes

Both diagnostic groups demonstrated a trend towards linear valence-dependent startle modulation at the 750 ms anticipatory condition, and such a pattern of startle modulation supports the unpublished findings of Erickson (1996). Diagnostic groups did not differ in linear startle modulation at this probe interval. This failure to find group differences in response to the valence dimension of pictures at this probe condition is surprising given the evidence that depressed individuals demonstrate anomalous startle responding to the valence dimension during picture viewing. One possible explanation for the failure to find group differences at this probe interval is that diagnostic group differences in responding to the valence dimension of pictures may be constrained to stimulus perception. Brunia and colleagues (e.g., Bocker, Forget, & Brunia, 1993; Brunia, 1993) have argued that anticipatory or preparatory motor responses involve the gating of sensory information and are modulated predominantly by attentional mechanisms, and thus variations in anticipatory startle modulation may be more pronounced at a probe interval sensitive to the arousal, rather than valence, dimension of foreground stimuli.

300 ms Viewing Probes

Startle responses to 300 ms viewing probes did not replicate the arousal-modulated startle findings of Bradley et al. (1993) and Dichter et al. (2004) for both diagnostic groups. Additionally, diagnostic groups did not differ with respect to startle modulation at this probe interval. Bradley et al. (1993) suggested that the 300 ms probe

effect is an example of prepulse inhibition (e.g., Graham & Hackley, 1991). Prepulse inhibition is observed when startle probe onset occurs soon after the onset of a non-startle eliciting stimulus (i.e., the prepulse picture) and the attenuation of startle responses that occurs under these circumstances has been attributed to attentional processes that serve to protect the processing of the prepulse stimulus from disruption.

The failure to replicate startle modulation at the 300 ms viewing interval in the present study may be due, at least in part, to the effects of the anticipatory cues on the differential allocation of attentional resources to the prepulse pictures. Sokolov and colleagues have proposed that the orienting response reflects a comparison of the properties of an external stimulus with a trace or neuronal model (e.g., Barry & Sokolov, 1993; Voronin & Sokolov, 1960). Once the neuronal model is established, each new incoming stimulus is compared with it and an orienting response is elicited when there is a discrepancy, and the strength of the orienting response depends on the degree of discrepancy or novelty. Of particular relevance in the present context is Sokolov's proposition that attentional resources are directed at an external stimulus in proportion to the relative degree of stimulus novelty (Sokolov, Nezlina, Polyanskii, & Evtikhin, 2002). In the present context, orientation initially may occur in response to the informational cues that are presented before the onset of the pictures. Because picture valence has already been established by the informational cue, the picture itself may afford less novelty when it is presented than in a paradigm without an informational cue. Such decreased novelty may lessen the attentional resources directed at the prepulse picture, thereby decreasing the impact of picture valence on the protection of probe processing, resulting in attenuated attention-dependent affective startle modulation. In fact, because

the startle probe in the 300 ms viewing probe condition is presented 6.3 seconds after the onset of the informational cue, this probe may be processed similarly to probes in the 3500-4500 ms viewing condition. This supposition is partially borne out by the (nonsignificant) linear shape of startle modulation by both diagnostic groups in this probe condition.

3500-4500 ms Viewing Probes

During the 3500-4500 ms viewing probe condition, nondepressed participants exhibited the well-established linear increase in startle magnitude across the pleasant, neutral, and unpleasant picture categories, whereas depressed participants failed to show evidence of valence modulation. These results replicate with a larger sample size the findings of Dichter and colleagues (2004) that unipolar major depressive disorder may be associated with anomalies in later-onset processes that subserve responses to the valence properties of affective and motivational stimuli. Supplementary analyses revealed that the magnitude of potentiation to pleasant pictures at the 2000 ms anticipatory condition and the magnitude of linear valence startle modulation at the 3500-4500 ms viewing condition were significantly correlated in nondepressed participants but not in depressed participants. Although these correlations did not differ statistically, this disparity between diagnostic groups may imply a "temporal continuity" in emotional responding during the full temporal course of a response in nondepressed participants and more variable responding during the course of a response in depressed participants.

Picture Ratings and Questionnaires

For both groups, pleasure ratings followed the pattern of the a priori valence categories. The absence of between-group differences in self-report ratings of valence corroborates previous findings from our research group (Dichter et al., 2004) and contrasts evidence from previous studies that depressed individuals rate IAPS pictures to be less pleasant than do nondepressed controls (Allen et al., 1999; Sloan et al., 1997; Sloan et al., 2001). Discrepancies in the procedures used to assess self-reports might have been one factor that contributed to the disparity between our results and those of prior investigations: studies that have demonstrated group differences in picture ratings have employed a computerized version of the Self-Assessment Manikin rating scale (Hodes, Cook, & Lang, 1985) to rate pictures, a procedure that involves pictorial representations of mood states. Such a procedure may be a more sensitive index of subjective reactions to emotional stimuli than the lexical scales used in the present study.

Whatever the reasons for our failure to find group differences in self-reported valence, there is a notable contrast between the present null findings in this domain and the significant differences between depressed and nondepressed groups in startle modulation at the 2000 ms anticipatory and 3500-4500 ms viewing probe conditions. These disparities suggest that variations in startle modulation may be a more sensitive index of the affective response deficits linked to depression than self-report measures.

Participants judged pleasant and unpleasant pictures to be more arousing than neutral pictures. This pattern of arousal ratings is presumed to reflect that pleasant and unpleasant stimuli are more interesting and thus draw greater attentional resources than neutral stimuli. The only difference observed between diagnostic groups with respect to

arousal ratings was the finding that depressed participants rated unpleasant pictures to be less arousing, relative to neutral pictures, than did nondepressed participants. Because this finding was unexpected, differs from the results of Dichter et al. (2004), and contradicts the theory that depression is characterized by exaggerated responses to aversive stimuli (e.g., Fowles, 1994), its meaningfulness is unclear without replication.

Participants spent more time rating pleasant and unpleasant pictures than neutral pictures, a behavioral validation of the idea that pleasant and unpleasant pictures were more interesting than neutral pictures. It is interesting to note that depressed participant appeared to take more time overall to rate pictures, although this difference was not statistically significant. A slower behavioral response is consistent with the notion that psychomotor retardation is a symptom of major depressive disorder (American Psychiatric Association, 1994).

Finally, depressed participants demonstrated higher BDI and MASQ scores than their nondepressed counterparts. Exploratory hierarchical multiple regression analyses examined the relations between startle modulation and BDI and MASQ subscale scores during each probe condition. These analyses demonstrated no significant relations to questionnaire scores and indicate that scores on these questionnaires did not contribute significant unique variance to the prediction of startle modulation at these probe intervals.

Conclusions and Future Directions

Nondepressed participants exhibited the expected arousal-dependent startle modulation to probes presented 2000 ms before picture onset, a trend towards linear valence-dependent startle modulation to probes presented 750 ms before picture onset, no

relation between startle modulation and picture category to probes presented 300 ms after picture onset, and the expected linear valence-dependent startle modulation to probes presented 3500-4500 ms after picture onset. In contrast, startle modulation of depressed participants was unrelated to picture valence category at all probe intervals. Depressed participants differed from nondepressed participants in startle potentiation to pleasant pictures at the 2000 ms anticipatory interval and in linear startle modulation to probes presented 3500-4500 ms after picture onset. These dissociations indicate that major depressive disorder may be associated with anomalies in the mobilization of neurobiological systems that mediate both anticipation of pleasant stimuli and responses to affective stimuli. Results of the current study suggest that although diagnostic group differences with respect to responses to affective pictures are apparent during late-probe picture viewing, differences in responses specifically to pleasant pictures occur only during the earlier anticipatory condition.

The finding that depressed individuals demonstrated diminished anticipatory startle responding to pleasant stimuli suggests a novel methodology to assess anticipatory anhedonia in depressed individuals. A more thorough evaluation of the association between anticipatory anhedonia and depression would include a number of other design features. For example, future research should examine the sensitivity and specificity of anticipatory anhedonia to depression by including comparisons between depressed individuals, individuals with other forms of psychopathology characterized by anhedonia (e.g., schizophrenia and post traumatic stress disorder), and individuals who are lifetime-free of psychopathology.

The current investigation suggests a number of other possible anticipatory affective startle modulation studies. For example, a longitudinal high-risk design study that assesses anticipatory affective startle modulation and depressive symptomatology over time would be appropriate to assess whether anticipatory anhedonia is related to vulnerability to depression (e.g., Alloy, Ambramson, Raniere, & Dyller, 1999). Such a study design could demonstrate whether the currently observed anticipatory affective response deficits are trait or state markers of depression. Of note, one provocative study has found evidence that individuals at risk for depression may be more vulnerable to the effects of stress on anhedonia (Berenbaum & Connelly, 1993), suggesting a possible link between vulnerability to depression and variations in pleasure response systems.

The findings of the current investigation are theoretically consistent with studies of animal models of anhedonia that suggest that the effects of certain pharmacologic manipulations on hedonic responses are more pronounced during the anticipatory phase of an appetitive response. Furthermore, the current study indicates that future animal and human anhedonia research should systematically assess hedonic responding during both anticipatory and consummatory phases because an organism may demonstrate attenuated responding during one phase while responding during another phase is attenuated to a lesser degree or remains intact.

Given the extensive animal evidence reviewed earlier concerning links between the mesolimbic dopamine projection system and animal models of anhedonia, future studies should investigate whether anticipatory affective startle modulation is dopaminergically mediated. Although many current methodologies for the measurement of dopaminergic activity in humans are far less precise than in animals (see Depue,

Luciana, Arbisi, Collins, & Leon, 1994 for a review), recent advances in brain imaging techniques allow for measurement of synaptic concentrations of dopamine in humans (e.g., Zald et al., 2004). A demonstration of a link between decreased synaptic dopamine concentrations and diminished anticipatory affective startle modulation would help to bridge the gap between animal and human anhedonia research.

In conclusion, the findings of the present investigation suggest that individuals with unipolar major depressive disorder demonstrate attenuated responding both during the anticipation of pleasant stimuli and while viewing affective stimuli. These results add to the growing body of literature indicating that various forms of psychopathology may be linked to unique patterns of startle responding to emotional stimuli (e.g., Grillon & Morgan, 1999; Patrick, Bradley, & Lang, 1993; Sabatinelli, Bradley, Cuthbert, & Lang, 1996). The current study represents a validation and refinement of one DSM-IV Major Depressive Disorder criterion (American Psychiatric Association, 1994) and suggests a novel method to assess anhedonia in depression.

APPENDIX: IAPS PICTURES USED IN THIS STUDY

Pictures are presented grouped by Valence condition (Pleasant, Neutral, Unpleasant) and Probe condition (2000 ms Anticipatory, 750 ms Anticipatory, 300 ms Viewing, 3500-4500 ms Viewing).

Male Picture Set[9]:

Pleasant, 2000 ms Anticipatory: 5629, 8170, 4660, 4240.

Pleasant, 750 ms Anticipatory: 4689, 4320, 8380, 4653.

Pleasant, 300 ms Viewing: 8501, 8470, 1650, 8080.

Pleasant, 3500-4500 ms Viewing: 8180, 8260, 7501, 8300.

Neutral, 2000 ms Anticipatory: 2630, 5130, 5534, 7950.

Neutral, 750 ms Anticipatory: 2580, 7006, 7025, 7009.

Neutral, 300 ms Viewing: 7491, 7217, 7030, 7150.

Neutral, 3500-4500 ms Viewing: 7224, 2570, 7187, 7175.

Unpleasant, 2000 ms Anticipatory: 3150, 9810, 3110, 3130.

Unpleasant, 750 ms Anticipatory: 6570, 9570, 3053, 9410.

Unpleasant, 300 ms Viewing: 3530, 3080, 6313, 3015.

[9]After one control and three depressed male participants had completed the startle session, three pleasant pictures from the set presented to male participants were replaced: 4210 was replaced with 4660, 4659 was replaced with 4689, and 4652 was replaced with 4653.

Unpleasant, 3500-4500 ms Viewing: 6260, 3060, 3071, 3170.

Female Picture Set:

Pleasant, 2000 ms Anticipatory: 4572, 4690, 8370, 7270.

Pleasant, 750 ms Anticipatory: 8200, 4660, 8034, 7502.

Pleasant, 300 ms Viewing: 8080, 5910, 5460, 8210.

Pleasant, 3500-4500 ms Viewing: 8180, 8400, 8030, 8185.

Neutral, 2000 ms Anticipatory: 7150, 5130, 7110, 7187.

Neutral, 750 ms Anticipatory: 7010, 7491, 7185, 6150.

Neutral, 300 ms Viewing: 5740, 2840, 7040, 9360.

Neutral, 3500-4500 ms Viewing: 5530, 7035, 7031, 7004.

Unpleasant, 2000 ms Anticipatory: 3500, 3030, 9600, 6350.

Unpleasant, 750 ms Anticipatory: 9433, 9050, 3100, 3010.

Unpleasant, 300 ms Viewing: 3120, 3015, 9571, 2730.

Unpleasant, 3500-4500 ms Viewing: 3053, 6312, 9921, 3060.

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