June 2018

An Experimental Examination of Automatic Interpretation Biases in Major Depression

Alexandra H. Cowden Hindash
University of South Florida, cowdenhi@gmail.com

An Experimental Examination of Automatic Interpretation Biases in Major Depression

by

Alexandra H. Cowden Hindash

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
Department of Psychology
College of Arts and Sciences
University of South Florida

Major Professor: Jonathan Rottenberg, Ph.D.
Mark Goldman, Ph.D.
Edelyn Verona, Ph.D
Kristen Salomon, Ph.D.
Geoffrey Potts, Ph.D.

Date of Approval:
May 18, 2018

Keywords: cognitive biases, pupillary reactivity, hedonic deficits, psychophysiological correlates

Dedication

Thoughts are the shadows of our feelings – always darker, emptier, simpler. -Friedrich Nietzche, *Die fröhliche Wissenschaft* (1882) *Sec* 179

I dedicate this work to my loving mother and stepfather. I grew up with a great deal of acceptance, love, and care which I can only hope to pay forward to others – the sense of humor helps. I further dedicate this to my deceased father, whom I've been assured would be very proud of me by those who knew him and by my Hindash family tribe. I also dedicate this to my loving life partner who has born the brunt of my stress induced irritable and sometimes unreasonable tendencies. Thank you for patiently bringing me snacks and reminding me to take care of myself when I forget.

Acknowledgments

I would like to thank my mentor Dr. Jonathan Rottenberg for all his support. Not only did you provide great academic and career advice to me on weekly basis for four years, but you empowered me, advocated for my future, and respected my decisions once they were made. I hope to be half as caring and giving a mentor as you have been to me.

I would like to thank my project managers Rachel Christopher, Ashley Kelly, and Jared McLean for all of their hard work coordinating and running this ambitious project while I worked 3000 miles away on internship. Finally, I want to thank and acknowledge the hard and often confused/troubleshooting work completed by my team of research assistants: Brittney Ankrom, Maha Balouch, Anthony Colontonio, Anne Eible, Ashley Frank, Emma Frank, Teresa Goff, Danyelle Guido, Skylar Guilder, Marina Kleinschmidt Leal Santos, Emily Macias, Giovanni Mercado, Mownika Mantripragada, Ruba Rum, and Quynh Tran. This project simply could not have been completed without the hard work of these people.

Table of Contents

List of Tables

List of Figures

Abstract

Cognitive theories of depression have long posited automatic interpretation biases (AIB) as a central contributor to depressed mood. The current study was first to examine AIB in a clinically defined depressed sample. While assessing AIB using a semantic association paradigm, pupillary reactivity was simultaneously recorded to build insight into the AIB process. A total of 53 individuals (25 depressed and 28 healthy control) completed the Word Sentence Association Paradigm for Depression (WSAP-D) while pupillary reactivity was recorded. Results revealed the depressed group was significantly more likely to endorse negative AIB and less likely to endorse benign AIB compared to healthy controls. The depressed group demonstrated a modest effect size difference indicating they were faster to endorse negative AIB compared to the healthy controls, but did not differ in endorsing benign AIB or in rejecting either valence. Pupillary reactivity was found to differentiate behaviorally defined AIB type from a natural processing condition when counter to theorized, group relevant AIB. The depressed group demonstrated greater initial pupillary constriction during initial presentation of ambiguous information and comparatively less pupillary dilation during and after endorsing a benign AIB. Taken together, the results suggest that theorized negative AIB and lack of benign AIB are characteristic of depression, that greater cognitive effort is required to reject interpretations consistent with theorized biases consistent with reinterpretation processes, and that depressed individuals are less engaged with benign AIB compared to healthy controls, possibly associated with hedonic deficits. Theoretical implications and future directions are discussed.

Chapter One:

Introduction

Cognitive theories of psychopathology highlight the central role that automatic negative thoughts play in the etiology and maintenance of depression. Interpretation can feed automatic thoughts via slow and effortful elaborations or via more automatic processes. Automatic interpretation biases have been understudied, largely due to difficulty matching the timescale of experimental procedures to the timescale of the automatic interpretation biases. The present study reviews evidence of interpretation biases in depression and uses pupillary reactivity measures to better understand the emotional information processing involved in automatic interpretation biases.

Cognitive Theory of Depression

Cognition has been central to the conceptualization of depression for over half a century (Beck, 1963; 1979). Aaron Beck's influential cognitive theory of depression focused on schemas, or beliefs, as the organizing subcomponents of thoughts (Beck, 1967; 1979). A schema is an informational shortcut; rather than processing every detail of the situation, the schema fills in meaning based on a subset of environmental cues. More recent cognitive theories have focused on information processing, or the processes by which stimuli from the environment are noticed (attention), appraised or judged (interpretation), and referenced for comparison (memory; Mathews & MacLeod, 2005).

Cognitive theories of depression have focused largely on three information processing components that may contribute to the onset and maintenance of depression: attention, interpretation, and memory (Beck, 1987; Williams, Watts, MacLeod, & Mathews, 1988). Theorized negative biases or distortions in these processes are hypothesized to increase vulnerability to and then maintain depression and other emotional disorders (Beck, 1987; Beevers, 2005; Mathews & MacLeod, 2005; Williams, Watts, MacLeod, & Mathews, 1988). Information processing loops are implicated in a potentially vicious cycle that maintains depression: Negative mood produces a tendency to attend to negative information, to assign negative meaning (i.e., negatively interpret) to ambiguous information, and to recall negative information, all of which are, in turn, presumed to help maintain the negative mood (Beck, 1987; Clark, Beck, & Alford, 1999). Although depicted as circular, it is not possible to specify an exact sequence of events because the components likely interact (Beevers, 2005; Williams, Watts, MacLeod, & Mathews, 1988).

Cognitive theories of depression integrate negative affect into the cognitive vicious cycle (Beck, 1987; Williams, Watts, MacLeod, & Mathews, 1988) with particular focus on "hot" emotion-laden cognitions (Ellis, 1994). One issue when studying fast, automatic information processing is that it is difficult to make a sharp distinction between cognition and emotion. In cognitive neuroscience, examinations of appraisal (i.e., meaning taken from stimuli perception) and reappraisal (i.e., changing the initial meaning taken from stimuli perception) processes - representing interactions between cognition and emotion - overlap in neural circuitry, particularly in cortico-limbic neurocircuits (Otto, Misra, Prasad, & McRae, 2014; Wilson-Mendenhall, Barrett, & Barsalou, 2015).

The overlap and interconnectivity between cognitive and emotional processing neurologically and phenomenologically speak to the value of examining automatic interpretation biases in depression. Examining these automatic biases using measures which can capture elements of this interaction, such as pupillary reactivity, during participant responses to emotionally salient and ambiguous information, can aid understanding of these biases. An improved understanding of the interaction between cognitive and emotional elements in information processing will help better characterize depression and, potentially, facilitate the development of treatments that directly target the cognitive components maintaining this disorder.

Interpretation Processes

Interpretation processes are a central aspect of information processing because they function to integrate the information provided by attention, emotion, and memory (Beevers, 2005; Mathews & MacLeod, 2005; Williams, Watts, MacLeod, & Mathews, 1988). In essence, interpretations function as the theoretical schemas discussed by cognitive theorists, in that interpretations are the information processing component that functions to yield meaning, based on current context and past experience, for the current situation (Beck, 1987; Beck & Haigh, 2014; Beevers, 2005; Mathews & MacLeod, 2005; Williams, Watts, MacLeod, & Mathews, 1988). Beck and Haigh (2014) discuss automatic interpretations (i.e., protoschemas) as the primary activation of schemas that monitor, detect, and abstract data from the environment for survival-based needs.

When the interpretation fits the true environmental context, it is accurate and would not be considered biased. When inaccurate interpretations are successfully challenged by further information in the environment, or from the individual's explicit effort, then again the individual

can be successful in the environmental context, even if at a slower pace. Unfortunately, outside of laboratory contexts, it is difficult to know the "true" environmental context, and it is therefore difficult to evaluate bias in an absolute sense. It is often easier to examine relative biases in terms of comparison of interpretation patterns between psychologically healthy versus unhealthy individuals. Psychologically healthy individuals have consistently demonstrated a positive interpretation bias in which they interpret standardized ambiguous information as positive (Mathews & MacLeod, 2005). By contrast, negative interpretations which are not accurate in the environmental context (e.g., interpreting others' smiles as derisive) and which go unchallenged are likely to decrease effective reactions to the environment (e.g., withdrawing because you believe others are making fun of you). It is these negatively biased interpretations which are theorized to drive depressive and other emotional disorders.

Interpretation occurs on a continuum of speed and automaticity. More automatic interpretations function to quickly determine if a stimulus is good or bad and then activate the appropriate affective and behavioral systems based on the initial evaluation. More reflective, elaborative interpretations then reevaluate the initial conclusions, correcting the judgments as more information is integrated from either attention to the environment or memories of similar experiences (Mathews, 2012; Mathews & MacLeod, 2005; Ouimet, Gawronski, & Dozois, 2009, Wisco, 2009). Although the automaticity of interpretation biases reside on a continuum, researchers often focus on the extremes of this continuum, and discuss automatic and reflective/elaborative processing as separate systems that interact to assign meaning. Clinically, automatic interpretations may reflect the automatic thought while elaborative/reflective interpretations may reflect reappraisal processes. Despite a central role in the cognitive

conceptualization of depression, the process of interpretation and interpretation biases, especially automatic interpretation biases, remain poorly understood.

Automatic and Elaborative Interpretation Biases

Recent iterations of the cognitive theory of depression emphasize distinction between automatic and reflective systems of cognition (Beck & Haigh, 2014). The automatic system processes information rapidly (< 1500ms), uses few cognitive resources, and is triggered by or vigilant for events signaling loss, threat, or gain. The reflective system processes information slowly (> 5000ms), is resource demanding, and is controlled and deliberate. These systems work in tandem, the automatic making quick, primary judgments and the reflective working to correct or modify those judgments. In essence, the automatic system decides whether something is good or bad and should be approached or avoided, whereas the reflective system reevaluates the accuracy of the automatic system's initial appraisal if given time and resources (Beck & Haigh, 2014).

From a neuroscience perspective, automatic and reflective processes do not appear completely separate. Interpretation processes likely correlate with cortico-limbic neurocircuitry in the dorsolateral prefontrol cortext (DLPFC) and rostral anterior cingulate cortex (rACC; Disner, Beevers, Haigh, & Beck, 2011). The DLPFC is a component of the cognitive control network, which is associated with making controlled, effortful cognition (Breakelaar, et al., 2017). The rACC is a component of the salience network which makes rapid estimates of valence and personal investment (Mennon, 2015). However, both the DLPFC and ACC are part of the default mode network, which is thought to represent resting state "thinking activity" and is abnormally active in depression (Korgaonkar, Fornito, Williams, & Grieve, 2014). Taken together, it appears key neurological structures lie within different and the same neurocircuits

depending on the type of cognition being studied. Although we cannot expect to tease apart the automatic and reflective components of interpretation biases given likely neurological overlap in activity, assessing ongoing and active processing of standardized stimuli may help us better understand the process of interpretation biases.

Importantly, cognitive theories emphasize dysfunction at the automatic processing level in depression (i.e., automatic thoughts drive the disorder; Beck, 1979; Beck &Haigh, 2014; Beevers, 2005). Biases in automatic processes are postulated to create vulnerabilities to emotional disorders (Beevers, 2005; Mathews & MacLeod, 2005). Theoretically, such automatic biases can be corrected only if the individual becomes aware of their automatic thoughts and consciously devotes cognitive resources to challenge the thoughts (Beevers, 2005; however see Jones & Sharpe, 2017 and Koster, Hoorelbeke, Onradt, Owens, & Derakshan, 2017 for studies which modify cognitive biases without conscious awareness in anxiety and depression). Thought challenging is a technique in cognitive therapy designed to increase the interaction between the two levels of processing (Beck, 1979, 1987) and which is associated with neurological changes, including strengthened connectivity between the amygdala and both the ACC and prefrontal cortices (Fischer, Keller, & Etkin, 2016; Goldapple, et al., 2004).

Despite the theorized importance of automatic processing biases in depression, it has proven difficult to document their presence. As the primary interpretation of an ambiguous stimulus, automatic interpretations may be difficult to observe because of their rapidity: Generally, they occur within 1500ms of stimulus presentation. By contrast, reflective level, or elaborative, interpretation biases have been demonstrated for decades (see Gotlib & Joorman, 2010; MacLeod & Mathews, 2005; Wisco, 2009 for reviews), possibly because the slower timescale (>5000ms) is easier to study. There is consistent evidence of elaborative interpretation

biases in depression (Wisco, 2009). However, in part because elaborative interpretations assess past and current experience while integrating new information, it is difficult to pinpoint where and when in the information processing stream negative interpretation originates. For instance, it is unclear what portion of the elaborative bias is based on automatic interpretations, response tendencies, or comparative processing. We cannot assume that elaborative biases reflect automatic biases because of the interconnected nature of elaborative processing, especially over extended time. This has led to calls for empirical research to strive to observe and understand automatic cognitive processes generally, and automatic interpretation biases specifically (Beck & Haigh, 2014).

Empirical Evidence for Elaborative Interpretation Biases in Depression

Further evidence of elaborative interpretation biases comes from Emily Holmes and her colleagues using an imagery based interpretation bias paradigm that presents scenarios which remain ambiguous until the final word, presented as a fragment (e.g. e _ j _ y = enjoy), resolves the ambiguity in either a positive or negative manner (Holmes et al, 2006). Scenario-based paradigms with word fragments have reliably demonstrated reflective negative interpretation biases in dysphoric and depressed samples (Blackwell & Holmes, 2010; Blackwell et al., 2015; Holmes et al., 2008, 2009; Joormann, Waugh, & Gotlib, 2015; Lang et al., 2012), as well as at risk samples (Dearing & Gotlib, 2009). Compared to healthy controls, generally depressotypic individuals resolve the scenarios negatively more often and positively less often, reflecting a lack of positive biases (Dearing & Gotlib, 2009) as well as the presence of a negative bias (Holmes et al., 2008, 2009).

Unfortunately, elaborative interpretation biases are limited by confounding processes. First, elaborative interpretation biases are difficult to distinguish from response styles (e.g.,

generally choosing the most negative option) and expectancy biases (i.e., choosing options believed to be expected by others). Second, elaborative interpretation biases are highly intercorrelated with both attention and memory biases (Everaert, Duyck, Eouter, & Koster, 2014; Everaert, Koster, & Derakshan, 2012; Everaert, Tierens, Uzieblo, & Koster, 2013; Joormann, Waugh, & Gotlib, 2015). These intercorrelations are especially troubling given evidence that depressed persons tend to attend to negative environmental information for longer periods of time (Kellough et al., 2008; for reviews see Gotlib & Joormann, 2010; Teachman, Jorrmann, Steinman, & Gotlib, 2012) and tend to recall negative information more easily than neutral or positive information (for reviews see Gotlib & Joormann, 2010; Matthews & MacLeod, 2005). This makes it difficult to disentangle elaborative interpretation biases from other aspects of biased cognition.

Indeed, in some paradigms, interpretation biases are taken from participant's memory of scenarios. In these paradigms, ratings of how associated comprehension statements are with ambiguous scenarios are recorded after all scenarios have been viewed – requiring participants to use their memory of the scenarios to make their interpretations minutes after seeing all scenarios (Bowler et al., 2017; Pictet, Jermann, Ceschi, 2016). Given that time allows for other information to be incorporated into (or elaborated on) the meaning assigned to the ambiguous stimuli, it is unsurprising that attention and memory biases are associated with elaborative interpretation biases (Everaert, Koster, & Derakshan, 2012; Everaert, Tierens, Uzieblo, & Koster, 2013; Joormann, Waugh, & Gotlib, 2015).

Further, combined methods studies which integrate attention bias assessment during an interpretation bias task – the Scrambled Sentences Task (Romero et al., 2014; Rude et al., 2002; Wenzlaff & Bates, 1998), have found not only a strong relationship between attentional

preference for unambiguous negative information and negative interpretation biases (De Raedt & Koster, 2010; Everaert, Koster, & Derakshan, 2012), but has repeatedly demonstrated the centrality of interpretation biases in forming negative memories (Everaert, Duyck, Eouter, & Koster, 2014; Everaert, Tierens, Uzieblo, & Koster, 2013). Within the combined cognitive bias hypothesis (Everaert, Koster, Derakshan, 2012), the interplay between cognitive biases has repeatedly demonstrated depressive preference for negative interpretations in the simultaneous presence of both a positive and negative option. Pathway analyses testing the combined cognitive bias hypothesis found that negative interpretation bias was central to forming memory biases with no direct effect of attention biases on memory. Further, this study demonstrated that interpretation bias accounted for the majority of variance in depressive symptoms with no significant contributions of either memory or attention biases (Sanchez, Duque, Romero, & Vazquez, 2017).

These studies highlight two important principles. First, that these cognitive biases are interconnected and follow the path of attention -> interpretation -> memory (Evereart et al., 2017; Sanchez et al., 2017). Second, these studies show that when given unambiguous information for a positive meaning (e.g., "winner") simultaneously with a negative meaning (e.g., "loser"), depressive individuals will choose the negative to describe themselves. While these studies provide some insight into how various cognitive biases interact in depression, they do not tell us about automatic interpretation biases specifically. Across these studies, participants are given as much time as they prefer (with an 8 second limit) to process the information before providing their responses – ample time to compare possibilities, reinterpret the information presented, or guess as to what the experimenter is hoping to discover. Thus, although this area of

research provides insight into the importance of interpretation biases in depression, these studies do not necessarily capture automatic interpretation biases.

Obstacles to Observing Automatic Interpretation Biases

One impediment to studying automatic emotional information processing biases, such as automatic interpretation biases, is that, by definition, automatic biases occur quickly (<1500ms). The few studies which have examined automatic biases (including three of our own) suggest biased processing can be detected within one second of stimulus presentation, as indexed by behavioral responses occurring at 1200ms on average (Cowden Hindash & Amir, 2012; Cowden Hindash & Rottenberg, 2015; 2017; Mobius et al., 2015; Sears, Bisson, & Nielson, 2011; Siegle et al., 2001, 2003). Despite consistency across laboratories, we do not know when the bias forms in response to an ambiguous cue. Few indices of emotional information processing in depression, outside of gaze-tracking attention paradigms and experimental semantic association interpretation tasks such as our own, are suited to studying automatic processes at this brief timescale.

A second, related, obstacle is that as observed clinically, automatic thoughts are difficult for individuals to identify and report accurately. However, an individual's automatic thoughts could only be accessed via self-report methodology, which by definition allows time to reconsider or weigh options. An extensive literature using self-report measures reports negative interpretation biases in depression (for reviews, see Matthews & MacLeod, 2005; Wisco, 2009). Increasingly, researchers are aware of the ways in which self-reports of automatic thinking are prone to error and bias, especially with depressed individuals (Mathews & MacLeod, 2005; Wisco, 2009) who have a demonstrated negative memory bias (see Gotlib & Joorman, 2010 for

review) and difficulty identifying their automatic thoughts generally (Kircanski, Joormann, & Gotlib, 2012).

In the study of anxiety disorders, these methodological difficulties have been addressed by use of computerized cognitive bias assessment paradigms to evaluate interpretation biases. Such computer tasks have included priming paradigms (e.g., an unambiguous word or image is presented prior to an ambiguous stimulus with participants asked to interpret the ambiguity) including the Word Sentence Association Paradigm (Beard & Amir, 2009; Teachman et al., 2012). Priming paradigms have detected and modified automatic interpretation biases in anxiety disorders. However, the same paradigms have not been able to detect automatic interpretation biases in depressed samples (Bison & Sears, 2007; Lawson & MacLeod, 1999; Mogg, Bradbury, & Bradley, 2006).

The negative results in studies of depression may stem from methodological factors related to the types of stimuli used in these paradigms. Generally, stimuli used in these studies were created for a specific anxiety disorder (e.g., social anxiety or obsessive-compulsive disorder) or referred to unknown other people, and the unambiguous stimulus was presented prior to the ambiguous stimulus to prime interpretation in a specific direction. These characteristics fit with the cognitive conceptualization of anxiety disorders involving an oversensitive vigilance system to threatening environmental information – thereby reacting to the negative priming. It was assumed depressed samples would react to the same stimuli simply because the stimuli were negative in nature. However, depression is cognitively conceptualized as negative mood affecting the perception of the external world, such that everything appears worse for the depressed person and better for everyone else. This suggests that utilizing stimuli which reflect characteristics specific to depression – self-focused and emotionally salient (i.e.,

content with emotional relevancy and individual value) – may be key to experimentally observing automatic interpretation biases in depression. In line with this idea, our work found that automatic interpretation biases in dysphoric individuals hinged on the use of self-relevant stimuli (Cowden Hindash & Rottenberg, 2015; see also Wisco, 2009 for a review in elaborative biases). Similarly, self-relevance may be an important driver of emotional reactivity in depression, especially in a laboratory setting, as depressed individuals demonstrate modest reactivity to generic sad stimuli (Rottenberg, Gross, & Gotlib, 2005, Salomon et al., 2013).

Burgeoning Evidence of Automatic Interpretation Biases

Automatic interpretation biases have proven difficult to demonstrate empirically in depression until recently. Early attempts to assess automatic interpretation biases in depression used semantic priming paradigms which were successful in anxiety based samples. Early semantic priming paradigms presented an unambiguous valenced (i.e., negative, positive, or neutral) word prior to an ambiguous sentence or scenario to prime a specific interpretation and did not find behavioral evidence of interpretation biases in depression (Bison & Sears, 2007; Lawson & MacLeod, 1999; Mogg, Bradbury, & Bradley, 2006). These null effects were puzzling since these paradigms detected effects among anxious individuals (Beard & Amir, 2009; Teachman et al., 2012), and because automatic negative interpretation biases were found in other studies that used non-reaction time indices such as eye-blink startle responses during imaginal interpretations (Lawson, MacLeod, & Hammond, 2002), number of homophones assigned negative meaning (e.g., writing “die” rather than “dye”; Mogg, Bradbury, & Bradley, 2006), and word valence identification tasks (Siegle et al., 2001; 2003). The lack of behavioral response time evidence of automatic interpretation biases led to suggestions that depression slowed

reaction times generally (Lawson & MacLeod, 1999) or even that automatic interpretation biases are non-existent in depression (Wisco, 2009).

Importantly, other work reveals patterns consistent with the existence of automatic negative interpretation biases, even though these were not interpreted as such. For instance, Siegle and colleagues made no substantive interpretation of depressed individuals rating nearly 15% of neutral word stimuli as negative, compared to 1% in controls, in a valence identification task which presented words for 150ms before being masked by a series of X's (Siegle et al., 2001; 2003).

Our work has found more direct behavioral evidence of depressive automatic interpretation biases (Cowden Hindash & Amir, 2012; Cowden Hindash & Rottenberg, 2015; 2017). This work is distinguished by our use of a semantic association paradigm and incorporation of self-relevant ambiguous stimuli. In contrast to semantic priming paradigms, the semantic association paradigm presents the ambiguous stimulus without cues as to the possible meaning of the information. Individuals are then asked if an unambiguous stimulus –a single word presented immediately *after* the ambiguous stimulus is removed – is related to the ambiguous stimulus. Importantly, semantic association paradigms provide two distinct indices of automatic interpretation biases from a single behavioral response: reaction times and endorsement rates. In this paradigm, the Word Sentence Association Paradigm for Depression (WSAP-D; Cowden Hindash & Amir, 2012), reaction times assessed how quickly the individual indicated whether an association between an ambiguous sentence and an unambiguous word existed. A faster endorsement decision (i.e., indicating the sentence and word are related) indicates bias because a faster association means the unambiguous word fit the semantic model (i.e., semantic expectation) already formed by the individual. Endorsement rates reflect the

proportion of trials in which an individual indicated a word type was related to the ambiguous sentence, with a higher endorsement rate reflecting a greater likelihood of making a negative interpretation of ambiguous material. In our past work, we have argued that since both indices come from a single speeded response, which is generally provided in less than 1200ms, we can view both indices as relatively automatic, with reaction times higher on the automaticity continuum of than endorsement rates (Cowden Hindash & Rottenberg, 2015; 2017).

Importantly, automatic interpretation biases using the WSAP-D were found in three distinct dysphoric samples (Cowden Hindash & Amir, 2012; Cowden Hindash & Rottenberg, 2015; 2017). Dysphoric individuals were both faster and more likely to endorse negative interpretations of ambiguous sentences compared to non-dysphoric controls (Cowden Hindash & Amir, 2012). We replicated these results in an independent sample while also directly demonstrating that negative automatic interpretation biases were only observable when the ambiguous stimulus was self-referent (Cowden Hindash & Rottenberg, 2015). We further replicated this finding in a third sample, while demonstrating that automatic negative interpretation biases can be reduced after a single session of modification training (Cowden Hindash & Rottenberg, 2017). Dysphoric individuals also demonstrated a greater likelihood to endorse negative words as related to ambiguous sentences when sentences were presented aurally, although reaction times did not differ from non-dysphoric individuals (Sears, Bisson, & Nielsen, 2011). These studies provided relatively consistent evidence of semantic automatic interpretation biases in currently dysphoric persons. However, these biases have yet to be reported in a clinically depressed sample, and it remains important to confirm that negative automatic interpretation biases are characteristic of well-defined depression.

Delving into the Origins of Automatic Interpretation Biases

As we amass evidence of automatic interpretation biases in depression-prone individuals, a critical next step is to clarify the processes by which these biases operate. For example, it is unclear if biases observed in semantic association paradigms are driven by the emotional content of the words, the ambiguity of the sentences, or by mood congruency effects because a single behavioral response is recorded after the word is presented. All three possibilities could explain the observed behavioral differences between groups but could have different implications for the characterization and treatment of depression. For example, theoretically, ambiguity triggers negative schemas which lead to negative interpretations. These interpretations then feed a negative mood. This conceptualization suggests that treatment should focus on eliminating the negative interpretation bias. However, response biases or mood congruency effects suggest that depression is better characterized by relating and reacting more strongly to unambiguous negative material. With negative mood driving effects, treatments should focus on alleviating the depressed mood with natural resolution of cognitive biases following uplifted affect. Illuminating the process of interpretation biases may serve to also illuminate what accounts for the behavioral observations as well as provide clues for potential best targets for treatment.

From a process perspective, it is important to differentiate when the bias begins from when it is further altered or challenged. For example, reacting to the ambiguity of the sentence may reflect a projection from mood onto the ambiguous information, which is consistent with cognitive theory, but reacting emotionally to words alone could reflect mood congruency rather than extant schematic biases. Although semantic association paradigms provide evidence of automatic interpretation biases, functioning from a single behavioral response after presentation of both ambiguous and unambiguous stimuli limits our ability to reveal the underlying process.

Understanding the formation of automatic interpretation biases by examining when and in reaction to what biases are taking place could provide a target for direct intervention to deter bias formation, thereby cutting off the depressive "vicious cycle" (Beck, 1987; Matthews & MacLeod, 2005; Williams, Watts, MacLeod, & Mathews, 1988). As such, an understanding of cognitive biases and their role in depression may come from use of methodological tools associated with neurological correlates of cognition and depression.

Neural Correlates of Cognitive Biases in Depression

Generally, it is postulated that information-processing biases reflect cortico-limbic circuity dysregulation in which prefrontal circuits do not effectively downregulate limbic – particularly amygdala – reactivity (Disner, Beevers, Haigh, & Beck, 2011). The cortico-limbic circuits function to inhibit limbic reactivity to environmental stimuli (Brown, Manuck, Flory, & Hariri, 2006; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Klauser, et al., 2015). Individuals with depression have been observed to demonstrate decreased activation of the DLPFC (Holmes & Pizzagalli, 2008), particularly during activities which increase limbic reactivity (Dannlowski et al., 2009; Hooley et al, 2009; Siegle, Thompson, Carter, Sheinhauer, & Thase, 2007; Johnstone et al., 2007; Klauser, et al., 2015). Tasks assessing cognitive control in depression also demonstrate hypoactivation of the rACC, which may reflect attempts to control increased amygdala reactivity (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Gianaros et al., 2008; Yoshimura et al., 2014). Both the DLPFC and rACC are connection points between the limbic and cortical structures of the brain. That is, these sub-cortex neural circuits are likely where cortical semantic meaning is attached to limbic perceptual and emotional information, conceptually akin to interpretation processes. It is thus practical to utilize a psychophysiological

method associated with activity in these subcortical areas to gain a better understanding of interpretation biases.

Pupillary Reactivity as a Measure of Cognitive Processes

Physiological measures collected during interpretation bias assessment might reveal additional insight into the processes taking place, including the processes taking place prior to, during, and after the formation of interpretation biases. One candidate measure is pupil dilation. Pupil dilation reflects innervation by both sympathetic and parasympathetic nervous system connections. When activated by the sympathetic connection, the pupil dilator muscle increases pupil size via neural connections to the posterior hypothalamic nuclei. When activated by the parasympathetic system, the iris sphincter muscle loosens via central inhibition of the midbrain Edinger-Westphal complex resulting in increased pupil size (Steinhauer, Siegle, Condray, & Pless, 2004). The pupil constricts during the basic light reflex and the accommodation reflex, which occurs when the eye lens must refocus on near visual stimuli. For the present study, we are interested in the psychosensory reflex —small changes in dilation due to emotional and/or cognitive processes (Beatty &Lucero-Wagoner, 2000). Interestingly, although an autonomic reflex, the pupillary reflexes – including the light reflex – have been found to be cortically mediated in both high and low light environments (Wilhelm & Kardon, 1997). Importantly, psychosensory dilations can occur in response to both sympathetic and parasympathetic nervous system activation (Beatty & Lucero-Wagoner, 2000), but dilation purely in response to increased cognitive effort (i.e., greater cognitive load due to increased task difficulty) appears uniquely related to parasympathetic activation (Steinhauer, Siegle, Condray, & Pless, 2004). Although it is difficult to tease apart pupillary reactivity which is related to emotional arousal (Bradley, Miccoli, Escrig, & Lang, 2008) from that which is related to task difficulty (Steinhauer, Siegle,

Condray, & Pless, 2004) when paradigms use elements of both (Siegle et al., 2001, 2003), there is a consistent pattern of greater dilation in depression when emotionally salient information takes greater effort to process (Burkhouse, Siegle, & Gibb, 2014; Siegle et al., 2003)

Given that functional neuroimaging suggests corticolimbic circuit deficiencies are most likely at play in major depressive disorders (Korgaonkar, Fornito, Williams, & Grieve, 2014) and that interpretation processes are likely related to sub-cortical neurocircuits, use of a neurophysiological measure associated with activity in both the DLPFC and rACC is ideal for increasing our understanding of automatic interpretation biases in depression. Neurological correlates of pupillary changes include brain regions associated with both emotional information processing and depressive psychopathology such as the DLPFC (Siegle, Steinhouer, Stenger, Konecky, & Carter, 2003), amygdala (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002), and the rACC (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005). These associations suggest that pupillary reactivity may be indicative of both emotional reactivity and cognitive effort during emotional information processing, in neural structures associated with depressive disorders (Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011; Rive et al., 2013) that are aligned with initial information processing circuitry (Kohn, et al., 2014), as well as circuitry specifically associated with reinterpretation (i.e., reappraisal) based emotion regulation strategies (Dörfel et al., 2014).

As such, simultaneous collection of pupillometry (i.e., pupil dilation responses) may be a reasonable place to begin examining the process of automatic interpretation biases. Pupillary reactivity has already proven useful in illuminating the points at which ruminative processes begin to take place as late cognitive effort during valenced decision tasks in depressed groups (Siegle et al., 2001, 2003; Siegle, Steinhauer, & Thase, 2004). In the context of automatic

interpretation biases, pupillary responses can be recorded during each stage of an experimental trial. Thus, reactivity to ambiguous information, unambiguous information, and behavioral response can all be assessed with interpretable measures during each portion of the trial. Further, pupillary waveforms can be compared across trial types, providing another avenue in which biases may be examined for the point of greatest cognitive effort and emotional salience. Finally, pupillary reactivity takes place within milliseconds of stimulus presentation (Fountoulakis, et al., 1999).

Assessing pupillary reactivity during a semantic association paradigm could also illuminate *when* during automatic emotional information processing the interpretation bias is being formed and expressed. Pupillary reactivity is evident on the time scale (<1500ms) implied by the reaction time based behavioral index of the automatic bias. Siegle et al. (2001, 2003) report evidence of initial pupillary response to emotional information beginning at 250ms post stimulus presentation in a depressed sample. Further, the level of pupil dilation was related to emotional information processing, as depressed individuals evidenced no change in pupil response to a purely cognitive working memory task (Siegle et al., 2001, 2003; Siegle, Steinhauer, & Thase, 2004). Of note, although Siegle and his colleagues were focused on examining ruminative processes, they reported differences between depressed and non-depressed groups at early (< 1000ms) stages of processing in all studies. This indicates that pupillary dilation occurs in the presence of emotionally evocative information with greater dilation change associated with the level of cognitive effort over time. These aspects of pupillary reactivity make this index a useful measure of emotional information processing to elucidate the process of interpretation bias formation throughout trials, as well as when comparing separate trial types.

Pupillary reactivity is also an attractive point of departure because alternative methods to tap the process of interpretation biases, including functional neuroimaging and event related potentials(ERPs) components have significant potential drawbacks. Functional neuroimaging is prohibitively costly and struggles with rapid timescales (Laumann, et al., 2017). ERP measures could be of use when points of comparison during interpretation are already known, particularly with complex multi-stimulus paradigms. For example, different ERP components reflect orienting attentional processes (N2; Loveless, 1983; Ritter, Simson, Vaughan, 1983; Satterfield, Schell, Nicholas, Satterfield, & Freese, 1990), emotion content and mood congruence (N400;Chung, et al., 1996; Kutas & Hillyard, 1980a; 1980b;), and sustained attention to emotionally salient information (late positive potential (LPP); Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Foti, Hajcak, & Dien, 2009; Hajcak, MacNamara, & Olvet, 2010). Additionally, some ERP components are associated with prefrontal cortex activation (MacNamara, Ferri, & Hajcak, 2011). However, each stimulus in the WSAP-D trial would potentially illicit each of these ERP components. It would be difficult to interpret ERP measures from the unambiguous word if interpretation first takes place during the presentation of the sentence because the LPP from the sentence would overlap with the N2 and N400 from the word. Thus, use of a physiological measure which allows for assessment of neurophysiological reactivity across the entire trial, such as pupillary reactivity, may provide guidance for future use of ERPs and fMRI to further tease apart the formation of interpretation biases.

Current Study

The present study had two main aims. First, to replicate the previously observed negative automatic interpretation biases in symptomatic samples within a clinically defined depressed

sample. Secondly, to illuminate the process of automatic interpretation biases using pupillary reactivity indices.

Gaining an understanding of the process involved in the formation of interpretation biases may help to model how emotional information is processed or distorted as well as pinpoint intervention targets before the bias is formed. Unfortunately, individuals generally, and especially those suffering from depression, are unaware of what aspects of the information to which they are reacting to actually activated their schemas and automatic biases. Integrating objective indices of cognitive and emotional reactivity into cognitive bias assessment paradigms may shed light on the process of interpretation bias formation, and particularly on what aspects of ambiguous information (e.g., self-relevancy, emotional salience, cognitive effort) may play a role in bias formation.

To better characterize the process of forming an automatic interpretation bias, we used pupillometry during a semantic association task, the word-sentence association paradigm for depression (WSAP-D; see detail below). The WASP-D, an experimental semantic association paradigm has previously demonstrated automatic interpretation biases in dysphoric individuals (Cowden Hindash & Amir, 2012; Cowden Hindash & Rottenberg, 2015; 2017). We administered the WSAP-D to individuals diagnosed with major depressive disorder and never-depressed controls. Four hypotheses were tested, see Table 1 for an overview of our hypotheses. Our predictions were guided by a cognitive effort perspective on pupillary dilation. We are using cognitive effort as the driver of pupillary dilation in two of the three hypotheses (hypothesis 3 predicts greater emotional saliency of ambiguous information in MDD) because of evidence that psychosensory reflexes in depression have been observed when emotional information requires greater cognitive effort to resolve (Burkhouse, Siegle, & Gibb, 2014; Siegle et al., 2003). Our

Table 1: Study Hypotheses and Expected Effects

Hypotheses	Expected Results
1. Groups Will Differ Behaviorally in Observed Interpretation Biases	- Interaction of Group X Interpretation Bias - MDD endorse negative interpretations faster and more often - HC endorse benign interpretations faster and more often
2. Pupillary Responses Indicate Presence of Interpretation Biases	- Theory-based Specified Contrasts - MDD group will demonstrate greater pupillary dilation for benign bias trials (reject negative and endorse benign) compared to sentence only control condition - HC group will demonstrate greater pupillary dilation for negative bias trials (endorse negative and reject benign) compared to sentence only control
3*:* Pupillary Responses Indicate Ambiguity is Differentially Salient for Depressed Persons	- MDD group demonstrates greater dilation during ambiguous sentence presentation compared to HC group
4. Group pupillary reactivity will differ based on semantic incongruence	- Interaction of Group X Valence X Response - MDD group demonstrate greater pupillary dilation on benign trials - HC group will demonstrate greater pupillary dilation on negative trials

predictions thus assume (except hypothesis 3 where we specifically test this assumption) that the ambiguous stimuli are generally emotionally salient and changes from this baseline reflect greater difficulty in evaluating an interpretation.

Hypothesis 1: Groups Will Differ Behaviorally in Observed Interpretation Biases. We hypothesize that compared to a never depressed control group, depressed individuals will evidence automatic negative interpretation biases on the WASP-D, as indicated behaviorally by faster reaction times and higher endorsement rates for negative interpretations in the MDD group. In contrast, we expect that the HC group will evidence the same pattern with benign interpretations. If confirmed, this study will provide the first evidence that automatic interpretation biases take place in individuals suffering with major depressive disorder.

Hypothesis 2: Pupillary Responses Indicate Presence of Interpretation Biases. In order to be able to interpret pupillary reactivity in relationship to behavioral indicators of interpretation biases, it is important to establish that reactivity differentiates natural interpretation processing from biased processing. This is difficult given that theoretically, natural processing is biased in an absolute sense and therefore must be examined relative to theorized group differences. However, natural processing is likely to be different based on group membership, in that we expect negative interpretation biases in the MDD group and benign interpretation biases in the HC group (hypothesis 1). One way of establishing if pupillary reactivity is associated with differential interpretations is to examine if dilation differs from a condition in which there is no further stimulus to illicit a response after the ambiguous information. This sentence only condition serves as a control condition in which natural processing of the ambiguous stimulus is not challenged by a need to evaluate potential associations with an unambiguous word. We thus expect consistent cognitive effort will be deployed during the processing of the sentence and therefore that pupillary waveforms will reflect attentive processing of the information. We predict that compared to unchallenged interpretations of the ambiguous sentence (i.e., the sentence only condition), groups will differ on which trial types produce differing pupillary reactivity based on theorized interpretation response patterns associated with depression (Beck, 1976; Beck & Haigh, 2014). As such, we specifically expect that the MDD group will require greater cognitive effort to process the interpretation and hence greater dilation on trials consistent with a benign bias (i.e., benign endorsement and negative rejection trials) compared with a sentence only control condition.. Likewise, we specifically expect that the HC group will require greater cognitive effort to process the interpretation and hence greater dilation on trials consistent with a negative bias (i.e., negative endorsement and benign rejection) when compared to a

sentence only control condition. We examined these specific contrasts in part due to recognition that when all trial type conditions are included together, we expect to observe no difference between at least three of the five conditions within groups. Further, because groups should not overlap in which conditions differ from the sentence only control, it is possible that interaction effects would be washed out by opposing directions in the group effect.

Hypothesis 3: Pupillary Responses Indicate Ambiguity is Differentially Salient for Depressed Persons. Regarding the process of bias formation, we hypothesize that depressed individuals will demonstrate initial pupillary reactivity during the WSAP-D in response to the ambiguous sentence as an index of emotional salience of the ambiguous sentence. Specifically, we expect dilation in response to the sentence to be greater in the MDD group than in the HC group due to greater likelihood of viewing the stimulus as negative and therefore more emotionally activating. We are thus specifically testing the emotional saliency of the ambiguous stimulus in depression rather than taking this for granted as in our other hypotheses. We expect greater dilation in the MDD group relative to HC due to increased likelihood of depressed individuals making negative interpretations and experiencing a negative emotional response to the sentence. Although there are no previous data that directly bear on this prediction, previous work has shown greater MDD-related pupillary reactivity during emotion relevant decision-making tasks such as identifying the valence of masked words (Siegle et al., 2003), emotion expression identification tasks (Laeng et al., 2013), and responding to emotionally arousing pictures (Bradley, Miccoli, Escrig, & Lang, 2008). Together, this suggests that pupillary reactivity may be used both as a measure of emotional decision making and cognitive control simultaneously.

Hypothesis 4: Group Pupillary Reactivity Will Differ Based on Semantic Incongruence. We hypothesize that groups will differentially demonstrate pupillary reactivity based on interpretation biases. Across the groups, we expect that pupillary reactivity will continue to increase with the presentation of the unambiguous word such that greater dilation will be observed when the word is incongruent with the interpretation (i.e., semantic expectation) made by the participant regarding the meaning of the ambiguous sentence. We expect greater dilation because of increased cognitive effort (i.e., greater task difficulty) when needing to evaluate a potential relationship with the ambiguous stimulus when the unambiguous word does not fit the participant's natural bias. Although no previous data directly bear on this prediction, it is plausible since previous work has demonstrated greater pupillary reactivity during tasks requiring increased cognitive effort for decision making (Siegle et al., 2001) and valence identification (Lang et al., 2013; Siegle et al., 2001). Pupillary reactivity has also been demonstrated as sensitive to cognitive control tasks (Jones, Siegle, & Mandell, 2015). Further, we hypothesize groups will differ on which trial types trigger extended cognitive processing as indicated by increased dilation in response to the unambiguous words. Specifically, we expect that compared with non-depressed individuals, depressed individuals will demonstrate continued pupillary reactivity in response to unambiguous benign words during WSAP-D trials, possibly due to greater cognitive effort in resolving the association. By contrast, we expect non-depressed individuals will demonstrate the opposite pattern, with continued reactivity in response to unambiguous negative words.

Chapter Two:

Method

Participant Recruitment and Eligibility

Participants were recruited from the Tampa Bay area through fliers, online advertisements, the Psychological Services Center, and University of South Florida Counseling Center. Eligibility for the study consisted of either a primary current MDD diagnosis (i.e., depression that is not secondary to another disorder such as obsessive-compulsive disorder or post-traumatic stress disorder) or having no history of a major depressive episode (although anxiety disorders were not specifically an exclusion criteria for the healthy control group, we did not have any individuals who met criteria for anxiety disorders who did not also experience at least a past depressive episode). A primary MDD diagnosis was required to reduce sample heterogeneity and increase the chances that our depressotypic stimuli were perceived as self-relevant (see stimuli set section and appendix E; Gotlib & Joormann, 2010; Matthews & MacLeod, 2005). Individuals with current or history of serious brain injury or other neurological illness, moderate to severe alcohol or substance use disorder (i.e., formally substance abuse or dependence according to DSM-IV criteria) within the past six months, or a lifetime or current diagnosis of bipolar or psychotic disorder were excluded. Treatment use and participation information was collected for potential covariate analyses, but was not part of exclusion criteria.

Of 242 individuals who initially responded to advertisements, 148 completed a phone screen with a research assistant. Of these, 94 were invited to the laboratory to complete the

diagnostic interview to determine final eligibility for the study. Individuals were most commonly excluded from the study after phone screen if they endorsed a lifetime history of manic or psychotic symptoms (n=23), were not fluent English language speakers (n=12), endorsed past but not current symptoms of depression (n=7), or reported high current substance use (n=7). A total of 75 participants completed the diagnostic interview. Of these participants, 12 were excluded according to our exclusion criteria (5 for past but not current depressive episode, 2 for bipolar disorder diagnosis, 3 for current substance use disorder, 2 for lack of English fluency). Of the 63 participants invited to complete the experimental session, 54 completed the full session (see chart 1), with one individual excluded from analysis due to changes to the paradigm after individuals in the HC group for the WSAP-D endorsement rate and reaction time analyses. Pupillary data from four individuals in the HC group was lost due to equipment failure or experimenter error. Thus a final sample of 25 MDD and 24 HC individuals were included in the pupillary reactivity analyses.

Power Analyses

Our recruiting did not reach our originally proposed sample size of 35 individuals per group (70 total). This earlier power estimate was based on our prior studies using the WSAP-D with sub-clinical depression samples and medium to large Cohen's d (Cohen, 1988) and partial eta squared effect sizes (Cowden Hindash & Amir, 2012; Cowden Hindash & Rottenberg, 2015; 2017; Sears, Bisson, & Nielson, 2011). Our original power analyses were conducted using G*Power version 3.1.9.2 (Faul, Erdfelder, Buchner, Lang, 2009) with .80 power. These power analyses were likely conservative. First, there is evidence from other cognitive bias research that effect sizes are similar or larger in clinically diagnosed samples relative to subclinical dysphoric samples (Cristea, Kok, & Cuijpers, 2015; Hallion, et al., 2009). Second, studies have found

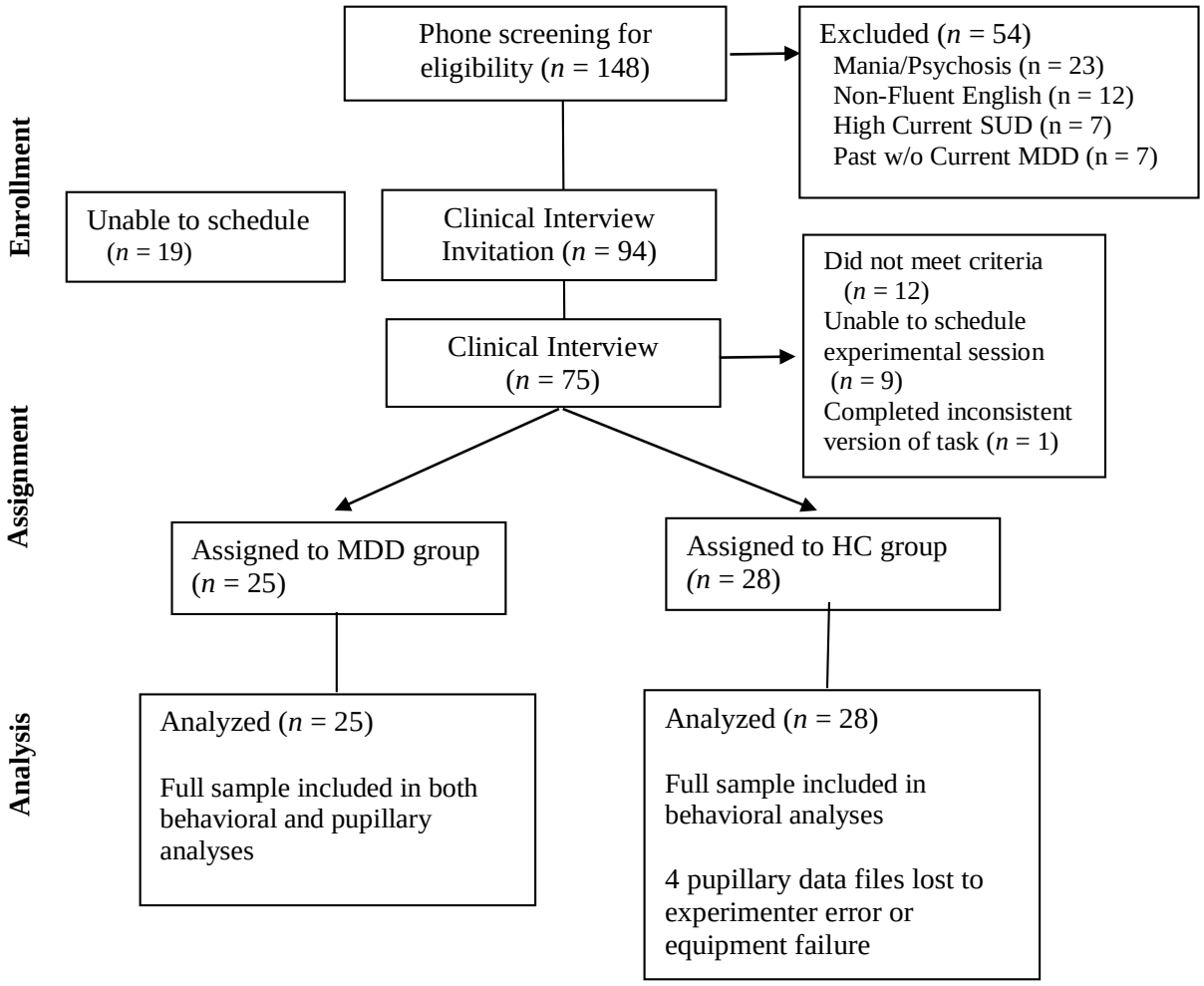

Chart 1: Participant Recruitment Flow Chart

effects on pupillary reactivity measures in depressed samples with samples ranging from 14 (Siegle et al., 2001; 2003) to 25 (Siegle, Steinhauer, & Thase, 2004; Steidtmann, Ingram, & Siegle 2010) for analyses. Examination of previous studies and observed effect sizes suggests our recruited sample was adequate to examine medium to large effects in both the behavioral and pupillary reactivity analyses. Nevertheless, we utilized a conservative analysis approach, particularly in the pupillary reactivity data including use of restricted maximum likelihood while running multilevel models and testing specified contrasts to reduce the overall number of models

run. Further, to better understand the potential role that sample size may play in detecting effects, effect size information was reported for all comparisons.

Study Design and Procedure

The current study used a mixed within- and between-subjects design. Participants were screened via phone interview to make a preliminary determination of eligibility. If potentially eligible to participate, participants were invited to complete a longer in-person clinical interview for final determination of eligibility. Eligible participants were then scheduled to complete the experimental session on a different date. During the experimental session, they had their Smart Eye Pro gaze calibration profile created (see SmartEye Tracker procedure below), completed self-report questionnaires, a baseline pupillary reactivity measure, a practice version of the WSAP-D task, and the WSAP-D task. Participants also completed paper and pencil tasks and a delayed word recognition task for future, secondary analyses by the primary investigator (not reported here).

Diagnostic Evaluation and Procedure

Immediately after providing written informed consent, participants completed a diagnostic interview. Diagnostic evaluations were conducted by the primary investigator and three trained upper-level research assistants based on DSM-5 (APA, 2013) diagnostic criteria. The interviews consisted of the mood module (major depressive disorder, past depressive episodes, and mania/hypomania) of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I, First, Spitzer, Gibbon, et al., 2002) and all but the mood modules of the Mini International Neuropsychiatric Interview (MINI; Sheehan et al, 1998) Version 7 for DSM-5, which has been used in clinical trials (Balestri et al., 2016; Castro eta l., 2015; Day et al., 2015; de Ornelas, et al., 2015; Linden & Rath; 2014; Shvartzman, et al., 2005). The combination of the

SCID and MINI for diagnostic assessment was chosen to ensure thorough standardized assessment of mood disorder symptoms (SCID) while mitigating participant burden through faster assessment of other potential psychopathology (e.g., anxiety disorders, PTSD, psychotic disorders). Per our experience, the average full SCID with a depressed individual with few comorbidities is between 60-90 minutes while the average MINI is just 20-30 minutes. In the present study, the average diagnostic interview lasted between 20-30 minutes for healthy control participants and 30-45 minutes for depressed participants.

The primary investigator in the study had completed training to use both the SCID and the MINI to determine individual diagnoses as well as primary diagnoses. The primary investigator trained upper-level research assistants to complete the interviews through training time, role playing, and listening to tapes of interviews and comparing diagnostic outcomes. After training and during data collection, a subset of 15 interviews were submitted to a reliability analysis by three separate individuals conducting the interviews. The primary investigator was always either the primary interviewer or one of the interview reliability raters. Interrater agreement on group assignment – MDD versus never depressed HC - was excellent ICC = .97 [95% CI: .93, .99].

Measures

Demographic and health questionnaire. General demographic (e.g., age, gender, ethnicity) and health information (e.g., medication treatments, brain trauma history) was acquired through a self-report questionnaire (appendix A). Demographics were used for sample description and to examine whether MDD and HC groups differed on confounding factors. This measure will also allow secondary analyses on the dataset relevant to physical health.

Beck Depression Inventory – Second Edition (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II is a well-validated 21-item scale assessing depressive symptom severity during the previous two weeks via self-report. Scores range from 0 to 63 with higher scores representing greater symptom severity. The BDI-II (appendix B) has well established psychometric properties including high measure (α=.91) and test-retest (r=.93) reliability (Beck, Steer, & Brown, 1996). The BDI-II was used as a continuous measure of depressive symptoms to potentially examine depression severity effects and to further substantiate distress differences between the MDD and HC groups. The reliability of the BDI-II in the current sample was excellent (α=.97).

Spielberger State/Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Luschene, Vagg & Jacobs, 1983). The STAI is a 40-item scale assessing state and trait anxiety symptoms. Scores range from 40 to 120, with higher scores indicating greater levels of anxiety. The STAI (appendix C) has been shown to have adequate psychometric properties (Ramanaiah, Franzen, & Schill, 1983). The STAI was used to assess anxiety levels and to further substantiate distress differences between the MDD and HC groups. The STAI may also be used in secondary analyses. The reliability of both the state (α=.96) and trait (α=.98) version of the STAI was excellent in the current sample.

Positive and Negative Affect Schedule – State/Trait (PANAS; Watson, Clark, & Tellegen, 1988). The PANAS (appendix D) is a 22-item scale assessing positive and negative affect. Participants rate their general (trait) and current (state) experience of single word "feeling" descriptors (e.g., interested, distressed, anxious) on a 5-point Likert scale ranging 1 to 5, with 1 "representing very slightly or not at all" and 5 representing "extremely." The PANAS has scores for positive affect and for negative affect with high internal consistency. The PANAS has been found to be a valid, reliable assessment of affective experience (Crawford & Henry, 2004). The

PANAS provided further affective characterization of the sample. There was good reliability for both the positive (α=.95) and negative (α=.91) subscales of the PANAS within the sample.

Word-Sentence Association Paradigm for Depression (WSAP-D)

The WSAP-D is an experimental task based on semantic association processing measures from cognitive psychology. The WSAP-D is presented through E-Prime 2.0 professional. Participants were seated approximately 52cm from the monitor. Stimuli were presented in black Times New Roman 14pt font on a grey background to control for luminosity and pupillary light reflexes. In our previous studies, WSAP-D trials began with a fixation cross in the middle of the screen. This fixation point was then replaced by a single ambiguous sentence (e.g., "You begin a new job.") for 1000ms. After 1000ms, the sentence disappeared and was replaced by a single word, which was either negative (e.g., "unqualified") or benign (e.g., "qualified"). The word remained on the screen until the participant indicated whether or not the word is related to the sentence. Participants were instructed to make their response as quickly as possible. Participants indicated the word was related to the sentence by pressing the left mouse button or that the word was not related to the sentence by pressing the right mouse button. The next trial began immediately after the participant responded to the word with a fixation cross in the center of the screen. The WSAP-D was used to demonstrate evidence of automatic interpretation biases in two separate studies completed by the primary investigator comparing dysphoric and non-dysphoric groups (Cowden Hindash & Amir, 2012; Cowden Hindash & Rottenberg, 2015). Further, a modification of this paradigm was successful in reducing negative interpretation biases in a sample of dysphoric individuals (Cowden Hindash & Rottenberg, 2017).

The WSAP-D used a stimuli set of 170 unique ambiguous sentences, each paired with a negative and a benign word. Participants saw each sentence only once and paired with only one

of the two possible words. The sentence order and word pairing was randomized for each participant. Thus, two participants might have no overlap in the sentence-word stimulus pair that as presented, although all participants saw the same 170 sentences. For the purposes of this study, the WSAP-D was modified for assessment of pupillary reactivity per suggestions made by a pupillary reactivity in depression expert and consultant, Greg Siegle, PhD. The goal of these modifications was to isolate the different components of a WSAP-D trial (fixation, sentence, word, and response) to differentiate pupillary responses while working as best as possible to avoid light reflex reactions. In general, all stimuli were matched in length across trials using a series of XX's on either side of the words/sentence. Further, an inter-stimulus interval (ISI) was added to all trials to assess for pupillary reactivity to the response in order to allow the pupil to return to a baseline diameter before beginning the next trial. For 75 trials, the previously used WSAP-D trial (as described above) was presented with the addition of a 4000ms ISI slide consisting of a series of XXs across the screen. To assess reactivity to the ambiguous sentence alone, 15 trials consisted of fixation, sentence, and a 5000ms ISI. These trials serve as a baseline comparison for reactivity to the sentence without exposure to an associated word and without requiring a response (i.e., natural processing of the ambiguous sentence). Because these trials do not display a word stimulus, the ISI was extended by 1000ms to keep trial length as consistent as possible with other trials in which participants provided responses. To assess reactivity effects to the word and to eliminate possible effects of the word disappearing or of attempts to remember the word, a second control condition consisting of 80 trials was added in which the word remained on the screen for an additional 3000ms after the participant responded, followed by a 1000ms ISI consisting only of a series of XXs. The participant was able to see that their behavioral response was recorded by the appearance of an asterisk under the word, indicating

that no further response was necessary. This combination of trials allowed us to isolate the pupillary reactivity to the sentence, to the word, and to possible continuing thoughts related to the response made. Trial conditions were programmed with different sentences at random and changed every eight participants to control for possible stimuli effects.

Before completing the WSAP-D task, experimenters read instructions aloud while participants read along on the computer screen. After participants indicated they understood the instructions, they completed a practice version of the WSAP-D. The practice version was a short block of trials where sentences and words were neutral in content, were not self-referent, and it was clear whether or not the word related to the sentence (e.g., sentence: The bird flapped its wings. Word: Pickle). These trials consisted of the fixation, the sentence, the word, and the 4000ms ISI. The experimenter remained in the room during practice to answer participants' questions and to ensure participants understood the instructions (i.e., participants were using the mouse buttons correctly). After it was clear the participant understood the task from the practice block, the experimenter began the experimental version of the WSAP-D and left the room. Upon completion of the task, participants completed paper and pencil tasks followed by a delayed word recognition task. These tasks will be used in secondary analyses and are not discussed further for this project.

Stimuli Set. The WSAP-D stimuli set (appendix E) was composed of ambiguous sentences paired with unambiguous and abstractly related words. Each sentence was paired with a negative word and a benign word. All paired words were abstractly related to the sentence. A total of 414 self-referent ambiguous sentences were created and tested by the primary investigator while obtaining her Master's degree at San Diego State University. Items were created to relate either to symptoms of depression (e.g., You do not want to get out of bed;

negative word: sad; benign word: comfortable) or based on theories of depression (e.g., People always tell you to smile; negative word: defective; benign word: loved). The convergent and divergent validity of each sentence was tested by correlating the word relatedness rating difference score between the associated words (negative – benign) for the sentence with standardized self-report measures of depression and anxiety.

At San Diego State University, 248 undergraduate students completed a short consent form, demographics information, BDI-II, STAI, Leibowitz Social Anxiety Scale (Fresco, et al., 2001) and Penn State Worry Questionnaire (Molina & Borkovec, 1994), and rated "how well each word relates to the sentence" on a 4-point scale ranging from "not at all" to "very much". Difference scores were calculated for each sentence such that the rating for the benign word was subtracted from the rating for the negative word. A positive difference score reflected a negative bias because participants indicated that the negative word was more related to the sentence than the benign word.

The WSAP-D stimuli set was composed of sentences for which the difference score correlated with the BDI-II above a cutoff (r=.2) or if the correlation was greater with the BDI-II than with any anxiety measure by at least .05. This second cutoff was implemented because it was apparent that many sentences were highly correlated with both anxiety and depressive symptoms. A pool of 170 sentences was created based on these cutoffs to be used as stimuli in the WSAP-D. For the full stimuli set, see appendix E.

Interpretation Bias Scores. The WSAP-D assessed automatic interpretation biases via two distinct bias indices (endorsement rates and reaction times) based on a single behavioral response (i.e., the participant's decision indicated by mouse click). This response generally

occurred within 1500ms of the presentation of the unambiguous word, indicating that the information was processed quickly.

Endorsement rates. Endorsement rates were the proportion of each word type that the participant endorsed as related to the sentence, out of the total number of trials in which the word type was presented. For example, the negative endorsement rate would be the number of trials where the person endorsed the negative word as related to the ambiguous sentence divided by the total number of trials in which a negative word was presented. A negative endorsement rate of 0 would indicate that the participant never endorsed a negative word as related to the sentence, while an endorsement rate of 1 would indicate that the participant always endorsed the negative word as related to the sentence. A tendency to endorse negative words as related to the sentence more often than benign words would be indicative of a negative interpretation bias within individuals. Similarly, group differences in which participants suffering from MDD demonstrate higher endorsement rates for negative words than healthy controls would be indicative of a negative interpretation bias in depression.

Reaction times. Prior to analysis, reaction times less than 200ms, greater than 5000ms, or greater than ± 2.5 standard deviations from the mean reaction time for each participant were defined as outliers and excluded from analyses (Cowden Hindash & Rottenberg, 2015, 2017). This data cleaning removes trials indicative of impulsive responding (< 200ms), inattention (>5000ms) or that differ markedly from an individual's general reaction time tendency. We did not restrict reaction times to a specific cut-off in order to allow for individual differences in processing speed. One participant endorsed only one negative word as related to the sentence and therefore this value was preserved despite it being outside the participant's individual reaction time tendency.

Reaction time indices were separated into four different types of trials: (1) time to endorse a negative word, (2) time to reject a negative word, (3) time to endorse a benign word, and (4) time to reject a benign word. Generally, faster times to endorse negative words or reject benign words as related to the sentence are indicative of a negative interpretation bias. Further, slower times to reject negative words or endorse benign words as related to the sentence are also interpreted as being indicative of a negative interpretation bias. Faster reaction times indicate that the person had already resolved the ambiguity of the sentence in line with the semantic association represented by the word. Thus, a faster reaction to endorse negative words indicates that the individual had already resolved the ambiguity as negative, and therefore represents a negative bias. Conversely, a faster reaction time to reject a negative word would indicate the ambiguity had already been resolved as benign, and thus the negative word did not fit the semantic association made by the individual.

Within individuals, a faster reaction time to endorse than to reject the relationship between a negative word and the ambiguous sentence is indicative of a negative interpretation bias. Similarly, a faster reaction time to reject than to endorse the relationship between a benign word and the ambiguous sentence is indicative of a negative interpretation bias. Between groups, endorsing negative words as related more quickly in the MDD group compared to the healthy controls would be indicative of a negative interpretation bias in the MDD group. Conversely, endorsing benign words as related more slowly in the MDD group compared to the healthy controls would be indicative of a negative interpretation bias in the MDD group, or possibly a benign interpretation bias in the healthy control group.

Pupillary Reactivity: Equipment and Procedure

Smart Eye Pro Eye Tracker. Pupillary reactivity was recorded via Smart Eye Pro 6.0 on a SmartEye DR-120 system, located in the EEG laboratory at the University of South Florida. The Smart Eye Pro DR-120 system is capable of tracking both gaze and pupil diameter at a rate of 120Hz or every 8.3ms. Raw and processed pupil size was recorded through the system and time locked with a computer system running E-prime software with the Smart Eye Pro E-prime extensions installed. The E-prime extensions route the Smart Eye Pro and gaze data through E-prime into a single data file with the WSAP-D experimental data. Real time pupil diameter was recorded and time stamped by the Smart Eye Pro 6.0 software and matched to the E-prime stimulus through the gaze data file produced by E-prime. These files were then merged so that files contain pupil diameter, gaze point, stimulus, and accurate stimulus/response pairing.

Participants sat as comfortable as possible in a chair in front of a computer monitor. Prior to completing the experimental tasks, each participant had an eye-tracking profile created and baseline of their natural pupil diameter measured for an extended period of time. The Smart Eye DR120 was calibrated by positioning participants' chins on a stable block while they look at five different points on the screen and a profile of the participant's gaze was created. The Smart Eye Pro marked the participant's facial features at the pupils, corners of the eyes, and upper lip to increase eye tracking sensitivity. The profile allowed participants to complete all tasks without recalibrating their gaze before each task and without the use of a chinstrap to restrict head movement (Klingner, 2010). Smart Eye profiles also allowed experimenters to restart a task without repeating the full setup when technical errors occurred.

Data processing: Data was processed using Dr. Greg Siegle's pupil toolkit (Siegle, Ichikawa, & Steinhauer, 2008) which uses the procedures reported by Siegle et al. (2001; 2003), derived from Granholm, Asarnow, Sarkin, and Dykes (1996). MatLab R2016B (MathWorks, 2016) was used to process the raw pupillary data with scripts modified with Dr. Siegle. Base scripts are well validated and available from Dr. Siegle upon request, modifications were made for the specific experimental needs of the study with guidance from Dr. Siegle regarding reductions in type I error due to highly intercorrelated, closely recorded data sampling procedures. Processing considers the experimental task timing and the rate of data recording. Trials comprised of more than 50% blinks were removed from consideration. Trials with less than 50% blinks have linear interpolations replacing blink related pupil dilation changes to facilitate data smoothing with a 10-point weighted average filter. Because of how WSAP-D stimuli are presented (black ink on a grey background where stimuli are all the same length across the screen so that luminosity does not change throughout the experiment), we did not encounter light reflex related noise in the data outside of a general blink response at baseline (see pupillary dilation indices below).

Further, as suggested by Dr. Siegle due to the high level of autocorrelation in pupillary data collected continuously overtime, data was collapsed across 2 Hz, leaving one sample every 500ms. This procedure allows an inspection of the pupillary reactivity and motility beyond the high level of autocorrelation in the smoothed pupil waveform (Burkhouse, Siegle, & Gibb, 2014) As we are focused on group level differences in the present project, pupil dilation means for every 500ms throughout the trial were used for all analyses, consistent with use of mixed multilevel modeling statistical analyses. This procedure was suggested by Dr. Siegle due to the potential need to examine nine separate conditions based on condition type (sentence only

control, word disappears after response [classic WSAP], and word remains on screen after response [stimulus change control]), word valence, and participant response). Pupillary reactivity was calculated by subtracting the mean pupil dilation from trial baseline to each epoch in the trial (see figure 1). This procedure produced pupillary changes for each trial which can be examined as waveforms over the course of the trial. Waveforms were then averaged for group comparisons on specific trial types: endorse a negative association, endorse a benign association, reject a negative association, reject a benign association and analyzed both by comparing the waveform as a whole (Burkhouse, Siegle, & Gibb, 2014; Frazen, Buysee, Dahl, Thompson, & Siegle, 2009) as well as comparing peak dilation points across trials (Siegle, et al., 2003). Maintaining timestamped reactivity allows for an analysis of individual reactivity across time in each trial through mixed method modeling using an autoregressive structure. Dr. Siegle personally worked with the principal investigator examining her MatLab script to ensure that processing was completed as described and that resultant pupillary data is consistent with standard observations of pupillary reactivity data.

Pupillary dilation indices: We initially proposed to measure pupillary reactivity by subtracting each epoch post stimulus from the last epoch pre-stimulus at each portion of the trial. However, pupil dilation processing revealed that a number of participants began trials with a blink. Examination revealed significant group differences at timepoint 0ms (i.e., trial start; $t(403) = 2.35$, $p=.019$, $d = 1.79$), suggesting that the MDD group was more likely to open their eyes from a blink at the start of a trial. We therefore ran all pupillary analyses using reactivity as measured by subtracting baseline pupil dilation at the beginning of each trial from each epoch. Adjusting each epoch relative to the pre-trial baseline allowed us to examine effects within the trials associated with specific intra-trial differences. We then examined how dilation changes are

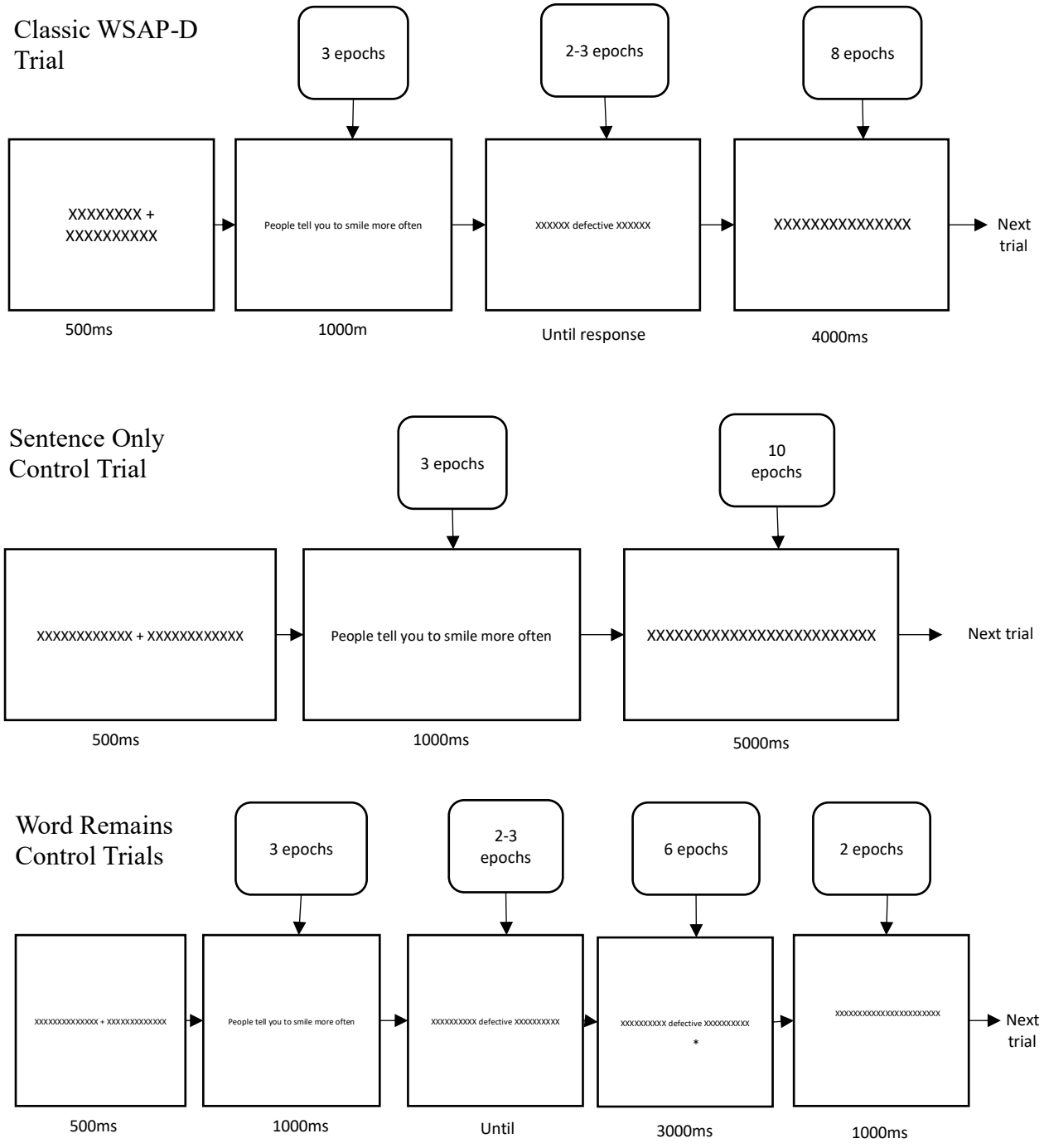

Figure 1: Example Pupillary WSAP-D Experimental Conditions.
*Classic WSAP-D Trial = previously published stimulus sequence in WSAP trial; Sentence Only Control Trial = control condition in which only the sentence is presented to assess sentence only pupillary responding; Word Remains Control Trial = control condition in which word remains on the screen after response to assess response to word presentation and potential effects of attempting to remember the word. *Note: Text size variation in figure due to page size, text was consistent across experimental trails for participants*

associated with different points in the interpretation process and identified both the peak of dilation during the entire trial (waveform analysis) as well as when the greatest change in dilation was observed (peak dilation analysis), providing insight into the process of interpretation bias formation and reinterpretation.

As such, reactivity to the ambiguous sentence was calculated by subtracting the pupil dilation from trial baseline (time point 0ms) from pupil dilation at each epoch (i.e., time points 500ms at sentence onset, 1000ms, and 1500ms at sentence offset) during sentence presentation (a total of 3 epochs). The reactivity for the word was calculated by subtracting the baseline pupil dilation from each epoch (i.e., time points 2000ms and 2500ms) during word presentation (an average of 2 epochs). The reactivity for the response was calculated by subtracting dilation from trial baseline from dilation during the first 1000ms of the interstimulus interval (i.e., time points 3000ms and 3500ms) epochs (a total of 2 epochs) because the slide switched to the interstimulus interval when the participant provided a response. The remainder of the interstimulus interval (i.e., time points 4000ms and 4500ms) was used to evaluate potential continued cognition regarding decision. Thus, each trial produced an average of 10 epochs through which to examine pupillary reactivity. A total of five seconds of each trial condition were compared due to participant response partially determining the total time of a trial. Five seconds is present for all conditions and includes fixation, sentence, word, response, and interstimulus interval from all interpretation trials. These epochs formed waveforms together which were then compared across trials both within participants and across groups.

Prior to hypothesis testing, standard WSAP trials in which the word disappeared after a response was recorded (previously used version of task, Cowden Hindash & Amir, 2012; Cowden Hindash & Rottenberg, 2015, 2017) were compared to pupillary reactivity control

condition trials in which the word remained on the screen after response. This control condition was added per Dr. Siegle's suggestion to be able to account for potential effects of changes in the visual stimulus associated with response. Waveform comparisons between standard and control WSAP presentations within trial types (i.e., endorse negative, endorse benign, reject negative, reject benign) revealed no significant differences between standard and control conditions of the WSAP (all *p*s > .5). As such, the standard and control conditions were collapsed into interpretation trial types to increase power to detect effects. This suggests that secondary analyses may be able to examine stimulus locked waveforms rather than time locked waveforms in the future.

Waveform analysis was completed by comparing whole waveforms from trial types for differences in amplitude and shape (Burkhouse, Gibb, & Siegle, 2014). On an individual level of analysis, waveform analyses compare the aggregate waveform for each trial type to examine differing pupillary responses within the individual. On a group level, individual mean waveforms are aggregated to form group mean waveforms which are then compared by trial type to examine differential group pupillary responses to different trial types and potentially identify different patterns of information processing and interpretation bias. Group level analyses are the focus of the current project, although future examination of individual differences in waveforms could be examined in a secondary analysis with the addition of a trial number factor.

In addition to whole waveform analysis, waveforms can be examined for a peak dilation point both across the entire waveform (i.e., greatest pupillary dilation change during the trial) and within each segment of the trials (i.e., greatest pupillary dilation change from pre-stimulus presentation to post-stimulus presentation). These statistical analyses can be run both with aggregate waveforms and trial by trial waveforms, allowing for the possibility of examining

greater individual differences and to account for learning effects as trials proceed. For the purposes of this study, we examined the aggregate waveforms, although we acknowledge the potential for secondary analyses examining individual differences through a trial by trial waveform analysis through use of a trial number factor.

Peak dilation analyses compare the amplitude of dilation changes during the waveform as a whole and during specific, stimulus bound segments of a trial. Amplitudes differ according to the amount of cognitive effort needed in a task. As such, we expected peak dilation to occur during and immediately after the response (i.e., time points 3000ms and 3500ms – after the word has disappeared in the classic WSAP-D trials), as this likely required the largest cognitive effort (i.e., the greatest amount of activity) due to organizing a decision and a button push action. We also expected that at the waveform level of analysis, peak dilation will differ in association with behavioral measures of interpretation biases such that when information is incongruent with biased expectations, it will take greater cognitive effort (thereby leading to greater pupillary reactivity amplitude) to evaluate and respond to the stimulus. At the trial segment level, comparing peak dilation within a segment (i.e., within fixation, sentence, word, response, and ISI segments) allows for examination of changes in pupillary dilation amplitude during the process of interpretation biases. Thus, examining changes between segments provides insight into the formation of a bias as well as comparison of greatest peak responding in association with behavioral indices of interpretation biases.

Statistical Analysis

WSAP-D data cleaning and analyses were completed using SPSS statistical software (IBM Corp., 2016). Pupil dilation was processed using the pupil Toolkit (Siegle, 2003) via Matlab R2016B statistical software (MathWorks, 2016). Multilevel mixed effect models were

run using the MIXED function in SPSS. Pupillary reactivity waveform graphs were created using the ggplot2 function (Wickham, 2009) in RStudio (R Core Team, 2018). Bivariate relationships between the WSAP-D indices and baseline relative pupillary reactivity are presented in Appendix G.

Multivariate assumptions testing: Multilevel mixed (MLM) effects models function with a number of assumptions. As outlined by Curran and Bauer (2014), it is important to test underlying assumptions to improve confidence in model results. Key MLM assumptions include mean level 1 and level 2 residuals are equal to 0, level 1 residuals and level 2 random effects are uncorrelated with each other and with predictors, level 1 residuals and level 2 random effects are homoscedastic and normally distributed, and finally effects are not misspecified nor are important predictors omitted. Using the procedures outlined by Curran and Bauer (2014), we empirically evaluated our model assumptions to the extent possible in the sample. As such, all models have been examined for level 1 residual and level 2 random effect homoscedasticity and normal distributions, important effects between predictors and criterions have been examined for misspecification, and potentially important predictors have been examined prior to choosing to omit them from a model. Of note, this procedure led us to include the quadratic time based random effect to account for the curvilinear random normalized level 1 residuals. Inclusion of this parameter also strengthened models across tests as well as fits with visual inspection of pupillary waveforms. All reported models meet accepted standards for MLM assumption adherence (Crawley, 2007; Curran & Bauer, 2014). Further, due to potentially small sample size, all models were run using Restricted Maximum Likelihood which corrects for potential bias related to small samples through use of an extra degree of freedom. While this may reduce power, it increases confidence in observed model estimation and fit.

Potential covariates: We did not expect antidepressant medication to influence our analyses of interpretation biases in depressed individuals who remain symptomatic despite indication that individuals treated with antidepressant medications demonstrate restored positive cognitive biases (Harmer et al., 2009). Prior to hypothesis testing, we compared the five individuals treated with antidepressant medications to the rest of the individuals in the MDD group who were not treated with antidepressant medication (no healthy controls endorsed current or past treatment with psychotropic drugs). There were no significant or observable differences between individuals on symptoms measures, on WSAP-D reaction time and endorsement rate indices, or on pupillary reactivity indices. We also tested medication as a statistical covariate in all repeated measures ANOVA and mixed effected MLM models which revealed no significant effects of medication use. Thus, medication use was not retained as a covariate during hypothesis testing and is not considered further.

Hypothesis 1: WSAP-D interpretation biases. We expected that depressed individuals would demonstrate a negative interpretation bias, as assessed by the reaction time and endorsement rate indices of the WSAP-D. Group comparisons on all indices of interpretation biases from the WSAP-D were examined through repeated measures ANOVAs. For the endorsement rate indices, a 2 (Group: depressed vs healthy) X 2 (valence: negative vs benign) ANOVA with repeated measures on the second factor was used to examine interaction effects. For the reaction time indices, a 2 (Group: depressed vs healthy) X 2 (valence: negative vs benign) X 2 (response: endorse vs reject) ANOVA with repeated measures on the last two factors was used to examine interaction effects. For both indices, simple effects follow-up analyses were conducted to decompose the specific effects driving the interaction.

Hypothesis 2: Pupillary Responses Indicate Presence of Interpretation Biases. We predicted that the greatest pupillary reactivity (increased dilation compared to baseline dilation level) compared to natural, unchallenged information processing during the sentence only control condition would occur during trials in which the behavioral response indicated a benign interpretation (i.e., the negative rejection and benign endorsements) in the MDD group. In contrast, for the HC group, we predicted the greatest increase in dilation to occur during trials in which the participant's behavior indicated a negative interpretation bias (i.e., benign rejection and negative endorsements. We hypothesized specific contrast models to avoid type I error inflation and account for our expectation that groups will not differ in reactivity during natural processing and trials consistent with natural processing styles (i.e., extant biases), which would decrease the likelihood of observing interaction effects generally.

Because we are making specific within group predictions of how interpretation biases will relate to a measure of natural information processing, we begin analyses with examination of models consistent with these predictions. First, we examine if groups differ on the sentence only condition by running a mixed effects model with pupillary dilation as the dependent measure, fixed effects of group, time, and quadratic time and random effects accounting for participant, time, and quadratic time using an autoregressive covariance structure to account for the high level of autocorrelation in pupillary reactivity data (Burkhouse, Siegle, & Gibb, 2014). With no group differences in natural processing, we then examined within group differences on trial types using a priori contrast comparison models examining the different trial types we would expect to differ from natural interpretation processes within each group. Follow up analyses were conducted in reverse order from usual interaction effects due to starting with specific contrasts in our hypotheses. As such, we examined between group differences

comparing natural processing to behaviorally indicated biased processing through the addition of a group fixed effect to each significant within group trial type comparison. For all models, 95% confidence intervals for each effect are reported in Appendix F.

Hypothesis 3: Pupillary Responses Indicate Ambiguity is Differentially Salient for Depressed Persons. We expected pupil dilation in response to the sentence to be greater in the depressed group compared to the healthy control group due to depressed individuals viewing the ambiguous sentences as more emotionally salient. To examine this, we compared the waveforms of the WSAP-D for group differences in peak dilation during sentence presentation.

To examine differences in dilation during sentence presentation, mixed effects multilevel models with reactivity during the sentence as the dependent measure, random effects accounting for participant, time, and quadratic time to account for observable curvilinear pupillary dilation in raw data, and trial type and group as fixed effects were run with an autoregressive covariance structure to account for the high level of autocorrelation in the pupillary reactivity data, similar to the analyses conducted by Burkhouse, Siegle, and Gibb (2014). Follow up analyses examined between group differences at each epoch during the sentence presentation. For all models, 95% confidence intervals for each effect are reported in Appendix F.

Hypothesis 4: Greater Pupillary Reactivity Will be Associated with Semantic Incongruence. Across the groups, we expected that pupillary reactivity would continue to increase with the presentation of the word such that greater dilation would be observed when the word is incongruent with the interpretation (i.e., semantic expectation) made by the participant regarding the meaning of the ambiguous sentence. We predicted a group by valence by response interaction (similar to reaction time analyses completed in hypothesis 1). Specifically, we expected the depressed group to show greater peak dilation on trials with benign words and

healthy controls to show greater peak dilation on trials with negative words. We compared groups on where they demonstrated peak dilation with the expectation that dilation will begin in response to processing the ambiguous sentence (hypothesis 3) with greater dilation related to the behavioral response during trials reflecting group differences in biased interpretations (hypothesis 1) consistent with observing greater dilation related to greater cognitive effort to resolve the incongruence.

To examine this hypothesis, mixed effects models with fixed effects of Group (MDD vs Healthy), Valence (negative vs benign), Response (endorse or reject), and Time (9 epochs across waveform) model with pupil dilation reactivity as the dependent measures and participant, time, and quadratic time as random effects was run with an autoregressive covariance structure. This analysis examined differences in trial type waveforms and allows for follow-up analyses based on interaction effects to identify specific points of difference along the waveform between groups (Burkhouse, Siegle, & Gibb, 2014). This hypothesis examined if behavioral responses reflect interpretation biases as assumed in our prior studies. Follow up analyses began with the highest order significant interaction effect to examine and understand observed effects. For all models, 95% confidence intervals for each effect are reported in Appendix F.

Chapter Three:

Results

Participant Demographics: A total of 53 (25 MDD and 28 HC) participants completed the experimental session. Groups did not differ on race (χ^2 (3, N=53) = 1.73, p = .63), Hispanic ethnicity (χ^2 (1, N=53) = 2.09, p = .15), gender (χ^2 (1, N=53) = .432, p = .51), age (t(51) = 0.07, p =.94) or education (t(51) = -0.08, p =.94). Groups did not differ in rates of taking hormonal birth control. Based on clinical interview, the MDD group was significantly more likely to report suicidality (χ^2 (1, N=53) = 21.31, p < .001) and at least one current anxiety disorder (MDD n=12, HC n=1; χ^2 (1, N=53) = 17.89, p < .001). The MDD group was specifically more likely to experience a lifetime history of panic disorder (χ^2 (1, N=53) = 13.81, p < .001), current panic disorder (χ^2 (1, N=52) = 9.03, p = .003), lifetime history of agoraphobia (χ^2 (1, N=53) = 4.85, p = .028), current social anxiety disorder (χ^2 (1, N=53) = 4.85, p = .028), and current generalized anxiety disorder (χ^2 (1, N=53) = 10.55, p < .001). The MDD group (n=11) was more likely to experience a traumatic event (χ^2 (1, N=53) = 4.28, p = .038) than the HC group (n=5), but did not experience PTSD more often (χ^2 (1, N=53) = 1.14, p = .285) despite reporting thinking about the event more often compared to the HC group (χ^2 (1, N=53) = 7.57, p = .006). Also as expected, the MDD group scored significantly higher on self-reported symptoms of depression (t(26.70) = 15.99, p <.001), trait anxiety (t(38.05) = 16.51, p <.001), and trait negative affect (t(32.59) = 12.265, p <.001) as well as lower trait positive affect (t(49.33) = -11.72, p <.001). Due to lack of

variability in the HC group on these measures, reported degrees of freedom are based on unequal variance assumptions. See Table 2 for group means and standard deviations for all demographic information.

Table 2: Participant Demographics

Demographic	**MDD Group (n=25)**	**HC Group (n=28)**
Age (Mean, SD, Range)	21.44 (6.93, 18-51)	21.32 (5.13, 18-45)
Gender (% Female, N Female)	76.0% (19)	67.9% (19)
Education (Mean, SD, Range)	13.36 (1.35, 12-18)	13.39 (1.60, 12-18)
Race/Ethnicity		
White (%, N)	80.0% (20)	75.0% (21)
Black (%, N)	12.0% (3)	7.1% (2)
Asian (%, N)	8.0% (2)	14.3% (4)
Hispanic (%, N)	24.0% (6)	42.9% (12)
Psychotropic Medications		
Current (%, N)	20.0% (5)	0.0% (0)
Past (%, N)	32.0% (8)	0.0% (0)
Symptom Measure (Mean, SD, Range)		
BDI-II	30.20 (8.70, 14-48)	1.61 (2.18, 0-7)
STAI Trait	62.60 (9.05, 41-77)	28.36 (5.36, 21-45)
STAI State	53.88 (9.90, 33-70)	27.86 (6.36, 20-47)
PANAS Trait Positive Affect	19.32 (5.28, 11-29)	39.43 (7.16, 23-55)
PANAS Trait Negative Affect	31.48 (6.63, 15-45)	13.79 (3.00, 10-22)

Groups do not differ on demographic factors. Groups differed on all symptom and affect measures, all ps < .01. BDI-II = Beck Depression Inventory – Second Edition; STAI = Speilberger State/Trait Anxiety Inventory; PANAS = Positive and Negative Affect Scale.

The MDD group was more likely to be taking psychiatric medications (χ^2 (1, N=53) = 6.183, $p < .013$). Five participants endorsed regularly taking psychotropic medications at the time of the study, with three individuals regularly taking SSRI medication (Zoloft n=2, Celexa n=1), one individual taking an SNRI (Effexor), and one individual taking Xanax as needed but not prior to the experimental session. We did not exclude participants for medication use initially due to expectation that medication use would not influence our results as medicated individuals

would still meet criteria for MDD. We tested medication as a statistical covariate and found no effect of medication use and therefore did not retain it as a covariate in subsequent analyses.

Hypothesis 1: Negative interpretation biases will be present in the MDD group. We hypothesized that compared to a never depressed control group, depressed individuals will evidence automatic negative interpretation biases on the WSAP-D, as indicated behaviorally by faster reaction times and higher endorsement rates of associations between negative words and ambiguous sentences. In contrast, the healthy control group will demonstrate benign interpretation biases on the WSAP-D as indicated behaviorally with faster reaction times and higher endorsement rates.

To examine endorsement rate indices of interpretation bias, we conducted a 2 (Group: MDD vs HC) x 2 (Valence: Negative vs Benign) ANOVA with repeated measurement on the second factor. This analysis revealed a significant main effect of valance [$F(1,51) = 39.69$, $p < .001$; observed power = 1.0] which was modified by a Group X Valence interaction [$F(1,51) = 16.80$, $p < .001$; observed power = .98] (Figure 2). Follow up independent samples t-tests to decompose this interaction revealed that the MDD group endorsed more associations between negative words and ambiguous sentences than the HC group [$t(51) = -3.67$, $p = .001$, $d = 1.01$; CI of difference: -0.31, -0.09]. By contrast, the MDD group endorsed fewer associations between benign words and ambiguous sentences than the HC Group [$t(51) = 2.63$, $p = .011$, $d = 0.72$; CI of difference: 0.26, 0.20]. Large effect sizes reflect group differences in both negative and benign endorsement rate interpretation biases, in directions consistent with expected group differences in interpretation biases.

To examine the reaction time indices, we conducted a 2 (Group: MDD vs HC) x 2 (Valence: Negative vs Benign) x 2 (Response: Endorse vs Reject) ANOVA with repeated

measures on the last two factors. This analysis revealed significant main effects of Valence [$F(1,51) = 5.82$, $p < .020$; observed power = .658] and Response [$F(1,51) = 11.34$, $p = .001$; observed power = .910]. These main effects were modified by a two-way Valence X Response interaction effect [$F(1,51) = 16.85$, $p < .001$; observed power = .981]. All lower level effects were modified by a significant Group X Valence X Response interaction effect [$F(1,51) = 5.99$, $p = .018$; observed power = .670].

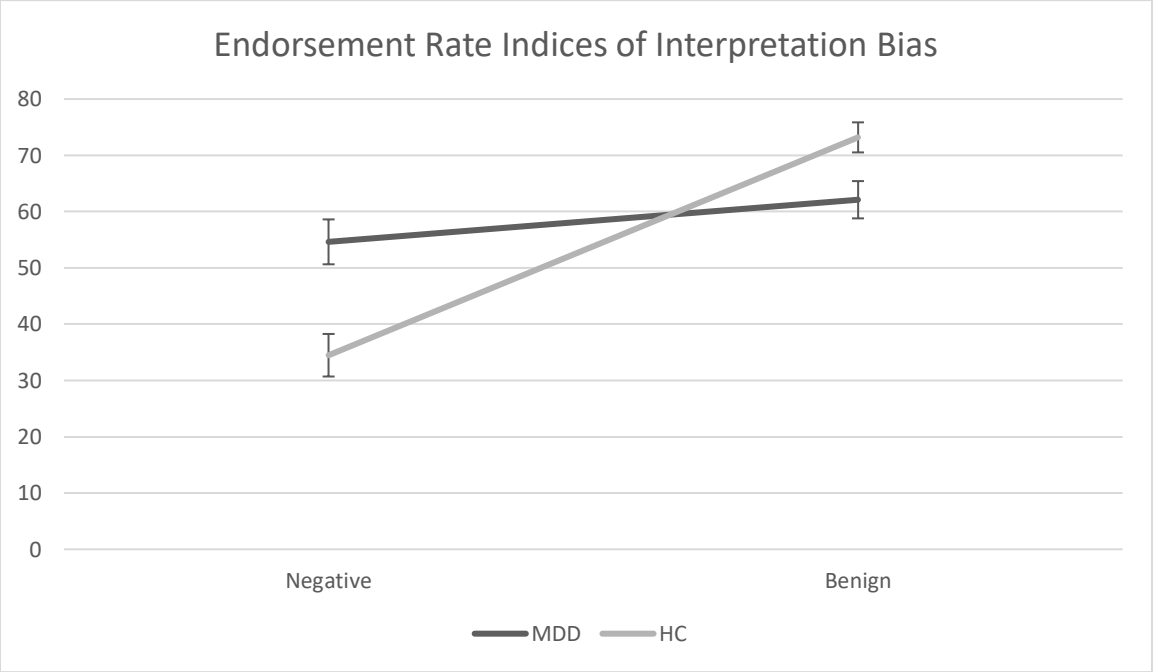

Figure 2: Endorsement rate indices of automatic interpretation biases between groups. MDD = Major Depression Disorder Group; HC = Healthy Control Group; error bars show standard error of the mean.

To better understand this three-way interaction and maintain consistency with our prior studies, we conducted separate analyses within each valence. Within the benign words, a 2 (Group: MDD vs HC) X 2 (Response: Endorse vs Reject) ANOVA with repeated measures on the second factor revealed a significant main effect of Response [$F(1,51) = 29.45$, $p < .001$; observed power = 1.0]. However there was not a significant group by response interaction effect

[$F(1,51) = 0.70$, p =.407; observed power = .13]. For negative words, a 2 (Group: MDD vs HC) X 2 (Response: Endorse vs Reject) ANOVA with repeated measures on the second factor revealed a Group X Response interaction [$F(1,51) = 7.09$, $p = .01$; observed power = .743]. Follow-up analyses examining group differences using independent t-tests revealed a moderately small effect size in which MDD persons were faster to endorse negative interpretations, although this effect was not significant at a conventional p value [$t(51) = 1.43$, $p = .160$, $d = 0.39$; CI of difference: -57.72, 341.57].

Because were we unable to statistically isolate the interaction effect to between group differences, as we have done in the past, we conducted secondary follow-up analyses to examine whether within-group differences were the source of the observed interaction effect. Follow-up analyses examining within-group differences in reaction time indices revealed that the groups exhibited the same reaction time pattern on the benign trials, but a different reaction time pattern on the negative trials. Specifically, on the negative trials, the HC group was significantly faster to reject negative interpretations than to endorse negative interpretations (mean difference = 80.96 [95% CI of difference: 40.07, -1.26]; $t(27) = 2.02$, $p = .053$, $d = -0.56$). By contrast, the MDD group tended to be faster to endorse negative interpretations than to reject negative interpretations (mean difference = -56.23 [95% CI of difference: 30.97, -120.14], $t(24) = -1.82$, $p = .082$, $d = -0.37$). Both groups were significantly faster to endorse benign interpretations than to reject benign interpretations with large effect size differences. The HC group demonstrated a mean difference of -152.43 (95% CI of difference: -231.18, -73.68; $t(27) = -3.97$, $p < .001$, $d = -0.76$). The MDD group demonstrated a mean difference of -111.33 (95% CI of difference: -171.58, -51.09; $t(24) = -3.81$, $p = .001$, $d = -0.84$). Within group reaction time index differences are shown in Figure 3. In sum, within group differences of interpretation bias patterns indicate

that both groups show the same reaction time mean difference in the benign trials, but the opposite pattern in the negative trials. This is consistent with our hypotheses regarding negative biases in the depressed group and benign biases in the healthy control group.

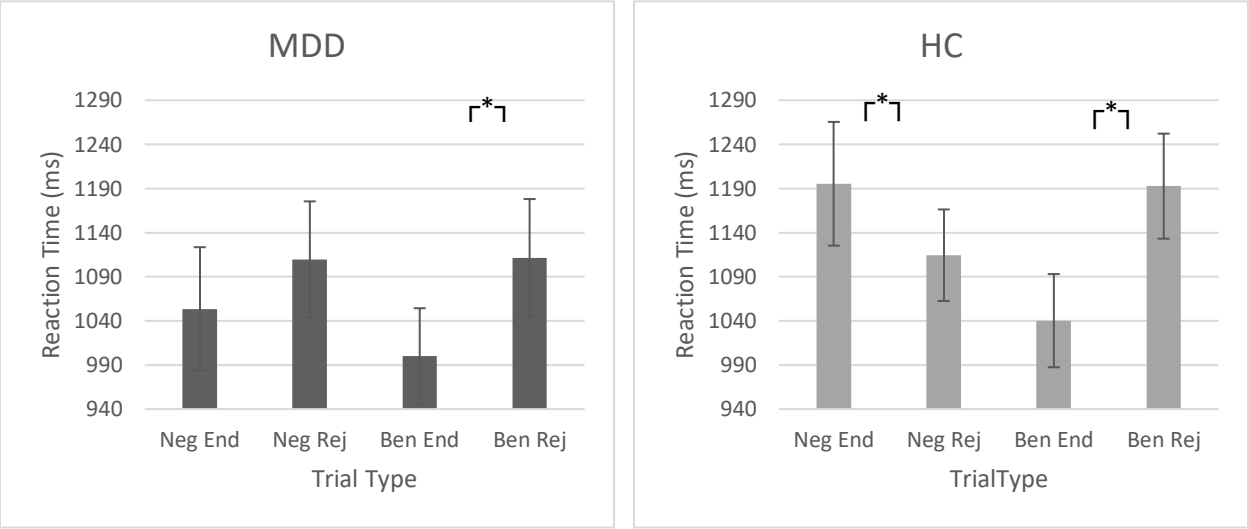

Figure 3: Reaction time indices of automatic interpretation biases within groups. MDD = Major Depression Disorder Group; HC = Healthy Control Group; error bars show standard error of the mean. * = statistical significance ≤ .05.

In summary, consistent with hypothesis, the MDD group was significantly more likely than the healthy controls to endorse negative interpretations and significantly less likely to endorse benign interpretations as indicated by the endorsement rate indices. Our hypothesis was supported overall in the reaction time bias indices in that there was a significant group by valence by response interaction which was driven by within group differences in reaction times to endorse versus reject interpretations in the two valence conditions. Although not statistically significant, there was moderate effect size group differences when endorsing negative interpretations, consistent with our hypothesis.

Hypothesis 2: Pupillary Responses Indicate Presence of Interpretation Biases. To establish the presence of differential pupillary reactivity based on interpretation biases, we

compared the average waveform from the sentence only control condition, in which participants were not asked to evaluate a relationship between the ambiguous sentence and a word (i.e., were allowed time to process the sentence naturally) with a priori specific contrasts based on extant interpretation biases within groups. As such, within group comparisons of WSAP-D interpretation trial types which differ from extant biases, that is – benign biases in the MDD group and negative biases in the HC group, were compared to the sentence only control condition.

Although we hypothesized specific within group contrasts for analysis based on interpretation bias differences to avoid running four separate large models examining each condition type (thereby increasing Type I error and chance of spurious results), we report the overall MLM model in line with standard reporting procedures. As such, we first conducted a mixed effects MLM model with 5 (condition: sentence only, benign endorse, benign reject, negative endorse, negative reject) X 2 (Group: MDD, HC) X 9 (time: sampled every 500ms) X 9 (quadratic time: sampled every 500ms) fixed effects with time, quadratic time, and participant as random effects and pupillary reactivity across the entire trial as the dependent variable. As presented in Table 1 of Appendix F, there were no significant interaction effects (all *ps* > 0.14). We next examined group differences on the sentence only control condition to establish no pupillary reactivity differences in natural information processing. We conducted a mixed effects MLM model with 2 (Group: MDD, HC) X 9 (time: sampled every 500ms) X 9 (quadratic time: sampled every 500ms) fixed effects with time, quadratic time, and participant as random effects and pupillary reactivity across the sentence only condition as the dependent variable. As expected, there were no group differences in pupillary reactivity when naturally processing information as demonstrated by non-significant Group*Time interaction ($F(1,121.61) = 0.13$,

p=.714) and Group effects (*F*(1,320.00) = 2.41, *p*=.122; full model presented in Table 2 of Appendix F). After establishing no group differences in pupillary reactivity during natural information processing, we continue to run our specific contrast models within groups.

To examine potential differences in pupillary reactivity waveforms within the MDD group, we conducted a mixed effects MLM model with 5 (condition: sentence only, benign endorse, benign reject, negative endorse, negative reject) X 9 (time: sampled every 500ms) X 9 (quadratic time: sampled every 500ms) fixed effects with time, quadratic time, and participant as random effects and pupillary reactivity across the entire trial as the dependent variable. As presented in Table 3 of Appendix F, this model indicated significant fixed effects of condition (*F*(1,1785.05) = 5.23, *p*=.022) and time (*F*(1,53.99) = 6.40, *p*=.014). Examination of a priori trial type comparisons revealed no significant difference between sentence only and benign endorsement conditions in the MDD group, indicating that the MDD group did not demonstrate significantly greater pupillary dilation when endorsing a benign sentence, compared to processing the sentence alone. However, consistent with our hypothesis, examination of a priori trial comparisons between the sentence only and the negative rejection conditions revealed a significant condition effect (*F*(1,560.11) = 9.96, *p*=.002; $\beta = 0.05$), indicating greater pupillary dilation during negative interpretation rejection trials. Thus reactivity differs significantly when the MDD group behaviorally rejects a negative association between an ambiguous sentence and an unambiguous word (Figure 4).

While rejecting a negative interpretation is consistent with our hypotheses, this may indicate that greater dilation reflects greater effort in overcoming the initial interpretation or that rejected negative interpretations are more emotionally engaging; it raises the possibility that we will observe greater pupil dilation when MDDs reject any association. To examine this, we ran a

comparison within the MDD group between the sentence only condition and the benign rejection condition. Easy rejection of benign interpretations is an MDD-related negative interpretation bias. As such, we would not expect to see greater cognitive effort, as indicated by pupillary

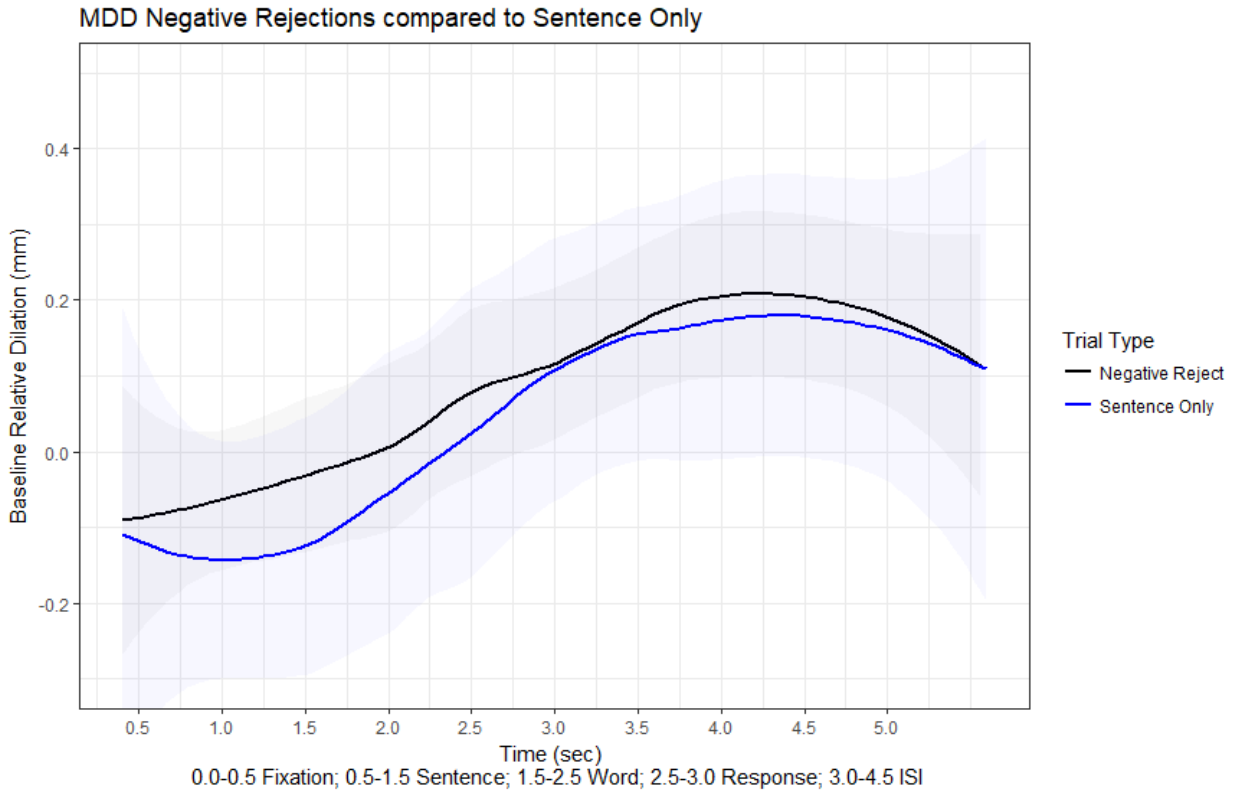

Figure 4: Depressed Group Comparison of Negative Rejection Trials and Sentence Only Control Condition. 95% Confidence interval bands surround predicted lines. Baseline Relative Dilation = Pupil dilation at each time point during trial – Pupil dilation at trial baseline. Whole trials are presented and compared for each condition.

dilation, during such trials due to consistency with extant processing biases. The comparison model revealed that condition is not a significant effect ($F(1,558.24) = 0.49$, $p=.484$) and that there is no difference between ambiguous sentence processing alone and rejecting a benign interpretation of an ambiguous sentence. See Table 3 of Appendix F for full model statistics for each comparison model run within the MDD group.

We repeated these analyses within the HC group substituting trial types which are inconsistent with extant benign biases in these analyses. As presented in Table 4 of Appendix F, there was no significant condition fixed effect ($F(1,1709.95) = 1.02$, $p=.314$) in the HC group. Similar non-significant effects were found in the specific comparison between the sentence only condition and the negative endorsement condition ($F(1,524.22) = 1.29$, $p=.256$). However, the specific comparison between the sentence only condition and the benign rejection condition revealed a significant effect of condition ($F(1,534.89) = 8.53$, $p=.004$; Figure 5) in which there was significantly less dilation in response to the benign rejection compared to the sentence only control. As with the analyses within the MDD group, we examined potential condition

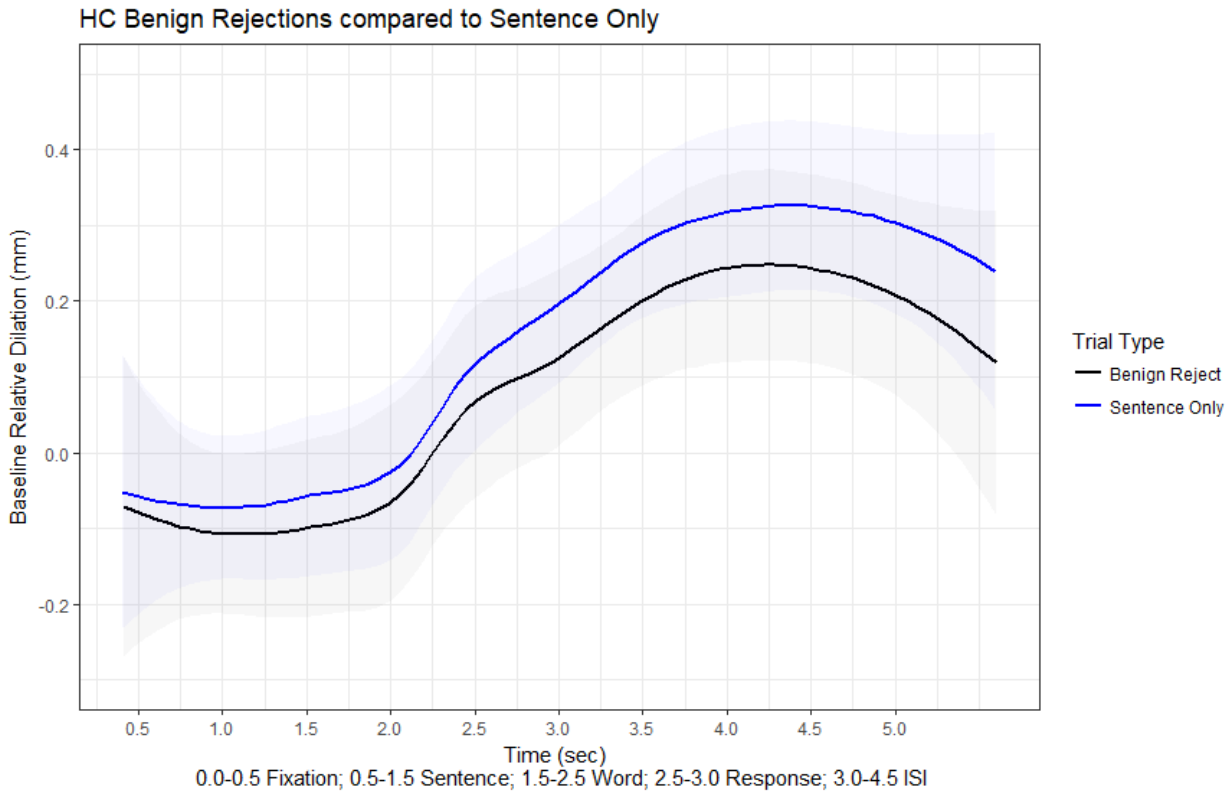

Figure 5: Healthy Control Group Comparison of Benign Rejection Trials and Sentence Only Control Condition. 95% Confidence interval bands surround predicted lines. Baseline Relative Dilation = Pupil dilation at each time point during trial – Pupil dilation at trial baseline.

differences between the sentence only condition and the negative rejection condition to address potential effects related to rejecting an association in general. Similar to the pattern found within the MDD group, there was not a significant effect of condition ($F(1,536.07) = 1.18$, $p=.279$), suggesting no difference in pupillary reactivity when comparing a sentence only condition and a benign interpretation consistent with extant interpretation biases.

Based on these findings, we conducted follow-up analyses comparing the sentence only control with benign rejection and negative rejection conditions, respectively, between groups through the addition of a group effect to each model.. Because these follow-up comparisons were post-hoc, to reduce the chance of Type I error we only considered effects with *p*-values at or less than .01 as significant. For the follow-up negative rejection compared to sentence only control model, results demonstrate a significant group*condition interaction effect ($F(1,1097.44) = 9.016$, $p=.003$) which moderates significant group ($F(1,11.92.26) = 5.988$, $p=.015$), condition ($F(1,1097.44) = 11.138$, $p=.001$), and time ($F(1,191.47) = 10.13$, $p=.002$) main effects (Table 5 in Appendix F). This suggests that group pupillary reactivity when rejecting a negative interpretation differs significantly from natural processing, with greater differences in waveform found in the MDD group, potentially suggesting a departure from extant information processing biases. The HC group demonstrated no difference in pupillary reactivity when rejecting a negative interpretation, suggesting consistency with extant information processing biases.

Examination of potential group differences in benign rejection trials revealed a trending Group*Condition interaction effect ($F(1,1093.70) = 2.82$, $p=.093$) and a traditionally significant (but not after post-hoc correction) main effect of time ($F(1,162.42) = 4.88$, $p=.029$; Table 6 of Appendix F). This suggests that the HC and MDD groups do not differ overall in pupillary reactivity when rejecting a benign interpretation in comparison to natural information processing.

Although the HC group demonstrated a significant difference in this comparison as specifically hypothesized.

In summary, our examination of pupillary reactivity as a measure of differential information processing revealed that compared to natural information processing via a sentence only control condition, groups demonstrated differing pupillary reactivity when interpretations were incongruent with natural processing. In line with our specific contrast hypotheses, the MDD group demonstrated this departure when rejecting a negative interpretation but did not demonstrate a difference when endorsing a benign interpretation. Within the HC group, reactivity was differential when rejecting a benign interpretation but not when endorsing a negative interpretation. Follow-up models examining group differences in the comparison of natural processing to each rejection based trial type revealed significant group effects when rejecting a negative interpretation, with only a trending difference when rejecting a benign interpretation. Taken together, this suggests pupillary reactivity may be able differentiate biased interpretation processing within groups based on behaviorally defined interpretation conditions with some indication of group differences from follow up models.

Hypothesis 3: Pupillary Responses Indicate Ambiguity is Differentially Salient for Depressed Persons. We hypothesized that dilation in response to the sentence would be greater in the MDD group compared to the HC group, reasoning that depressed individuals would view ambiguous sentences as more emotionally salient. First, we conducted a mixed effects MLM model with 5 (condition: sentence only, benign endorse, benign reject, negative endorse, negative reject) X 2 (Group: MDD, HC) X 3 (time: sampled every 500ms) X 3 (quadratic time: sampled every 500ms) as fixed effects and time, quadratic time, and participant as random effects with pupillary reactivity to the sentence as the dependent variable. Full model results are

presented in Table 7 of Appendix F. The interaction effect was non-significant, leading us to drop the effect and rerun the model. After dropping this parameter, we observed fixed effects of group (F(1,88.186) = 4.00, p=.049) and time (F(1,1201.566) = 7.17, p=.008), and a marginally significant effect of quadratic time (F(1,197.31) = 3.67, p=.057). Condition did not affect model fit (p=.414), suggesting that pupillary reactivity to the ambiguous sentence differed by group but was not affected by which stimuli or response followed the ambiguous sentence.

Post-hoc comparisons to follow up on the group effect revealed unexpectedly that the MDD group's pupils constricted by .05mm more than the HC group's pupils when the sentence initially appeared on the screen (t(369.31) = -2.73, p=.007, d=.27) (Figure 6). Groups did not differ and effect sizes were smaller for the middle (d=.12) and end (d=.03) of sentence presentation. This raises the possibility that initial group differences reflect differential reactivity to changing stimuli rather than a specific reaction to the sentence. However, if this were the case,

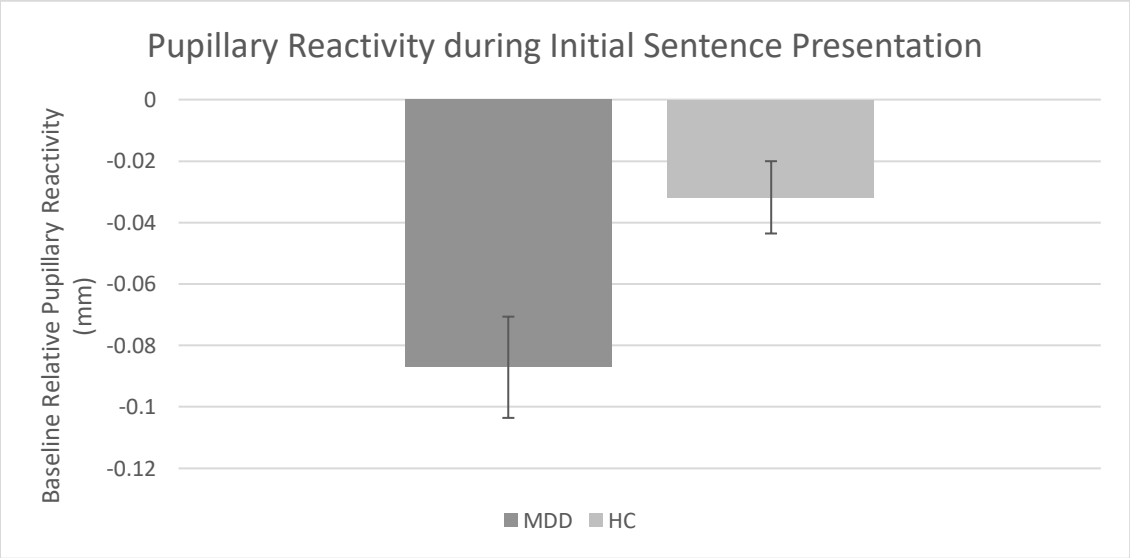

Figure 6: Mean pupillary reactivity to sentence appearance on the screen between groups. MDD = Major Depression Disorder Group; HC = Healthy Control Group.

we would expect to see a difference at the end of the sentence presentation, when the sentence stimulus is replaced by the word stimulus, which is the smallest effect.

In summary, our examination of pupillary reactivity related to the ambiguous sentence revealed group differences in pupillary reactivity to the sentence during initial processing. Counter to our hypothesis, the MDD group displayed greater pupillary constriction in response to the sentence than the HC group.

Hypothesis 4: Greater Pupillary Reactivity Will be Associated with Semantic Incongruence. We hypothesized that pupillary dilation would be greatest when the word was incongruent with the interpretation (i.e., semantic expectation) made by the participant regarding the meaning of the ambiguous sentence. Specifically, we hypothesized that the groups would differ on which trials they showed the greatest pupillary reactivity consistent with WSAP-D indices of interpretation biases such that the depressed group would show greater peak dilation on trials with benign words and healthy controls would show greater peak dilation on trials with negative words. First, we conducted a mixed effects MLM model with 2 (Group: MDD vs Healthy) X 2 (Valence: negative vs benign) X 2 (Response: endorse or reject) X 9 (Time: sampled every 500ms) X 9 (Time squared: sampled every 500ms) as fixed effects and participant, time, and quadratic time as random effects with pupil dilation reactivity as the dependent measure. There was no significant three-way interaction between Group*Response*Valence ($F(1,3091.70) = 0.85$, $p=.357$; $\beta=0.026$, 95% CI[-0.0298, 0.0826]). This parameter was removed and the model rerun. A likelihood ratio test (LRT) revealed significantly better model fit ($\chi^2(1) = 4.42$, $p=.036$) following removal of the three-way interaction effect. Further model refinement led to exclusion of the non-significant Group*Response ($F(1,3092.70) = 1.12$, $p=.289$; $\beta=-0.015$, 95% CI[-0.0433, 0.0129]) interaction

effect with a LRT supporting increased model fit after exclusion of this parameter ($\chi^2(1) = 5.53$, $p<.019$). Our final model resulted in significant Group*Valence ($F(1,3093.70) = 6.91$, $p=.009$) and Valence*Response ($F(1,3093.70) = 5.12$, $p=.024$) interaction effects moderating significant Response ($F(1,3093.70) = 9.29$, $p=.002$), Group ($F(1,416.09) = 6.95$, $p=.009$), and Time ($F(1,117.25) = 10.76$, $p=.001$) main effects. See Table 8 in Appendix F for the full model guiding follow-up comparisons.

Proceeding from the best fitting model, follow-up analyses examined the significant Group*Valence interaction effect ($F(1,3093.70) = 6.91$, $p=.009$; $\beta=-0.038$, 95% CI[-0.0657, 0.0096]) within each Response type (endorse or reject) separately. As shown in Table 9 of Appendix F, all model effects were significant within the endorsement trials, including the Group*Valence interaction effect ($F(1,1478.30) = 11.09$, $p=.001$; $\beta= -0.051$, 95% CI[-0.0808, 0.0209]). We further decomposed this interaction by examining the effect of Group within each Valence, where group remained a significant effect in benign endorsement trials ($F(1,247.15) = 4.87$, $p=.028$; $\beta= 0.100$, 95% CI [0.0107, 0.1889]) but not the negative endorsement trials ($F(1,240.92) = 1.86$, $p=.174$; $\beta= 0.054$, 95% CI [-0.0238, 0.1311]). Follow-up examination of group differences in pupillary reactivity on benign endorsement trials (Figure 7) using independent sample t-tests revealed a trend towards significant differences between groups at four timepoints along the wavelength: initial sentence presentation (graph timepoint 0.5; $t(64.70) = -1.83$, $p=.071$, $d=.39$), response (graph timepoint 3.5; $t(66.47) = -1.39$, $p=.170$, $d=.29$), 500ms after the response (graph timepoint 4.0; $t(68.345) = -1.43$, $p=.157$, $d=.29$), and 1000ms after the response (graph timepoint 4.5; $t(67.31) = -1.55$, $p=.126$, $d=.32$). Although small, consistent effect sizes suggest that the groups differ in pupillary reactivity during and after their endorsement of a

benign interpretation with the HC group showing greater dilation in relationship to their response compared to the MDD group.

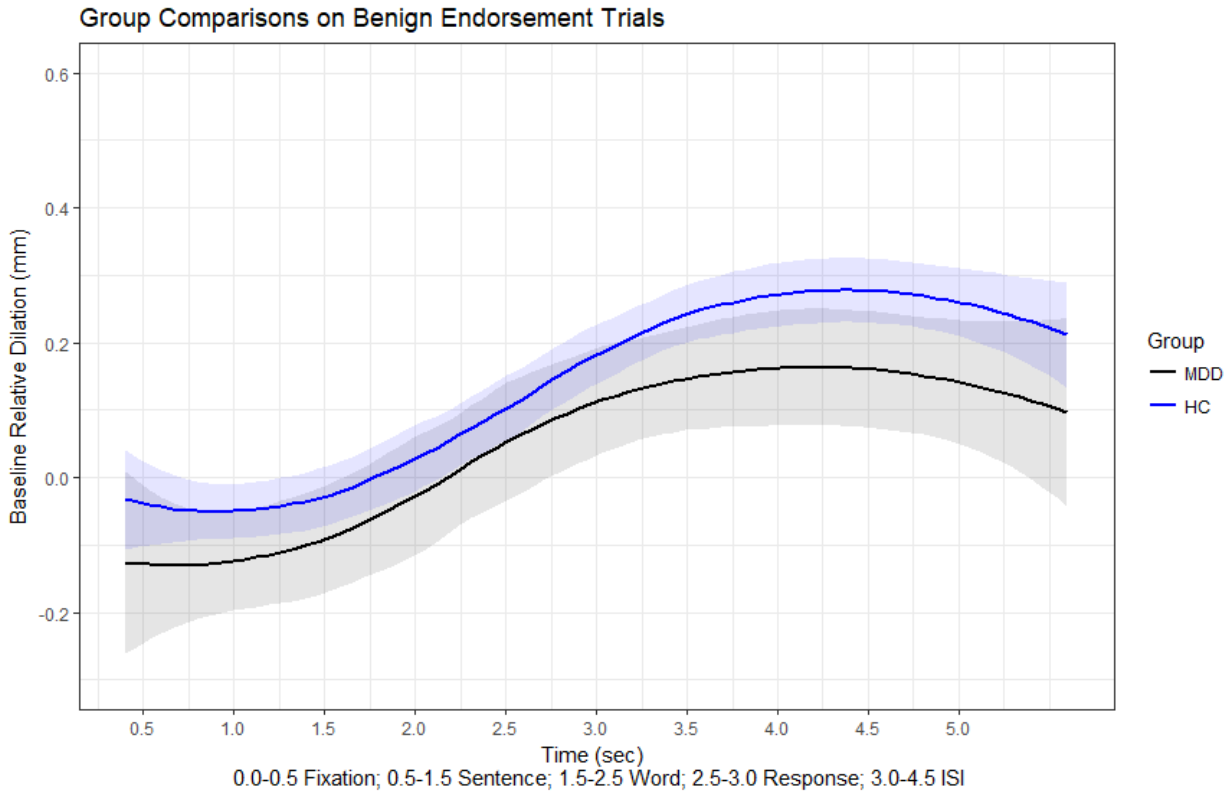

Figure 7: Group Comparisons on Benign Endorsement Trials. 95% Confidence interval bands surround predicted lines. MDD = Major Depression Disorder Group; HC = Healthy Control Group. Baseline Relative Dilation = Pupil dilation at each time point during trial – Pupil dilation at trial baseline

Analyses within the rejection response type followed a different pattern in that the Group*Valence interaction effect was not significant ($F(1,1501.25) = 1.08$, $p=.298$; $\beta= -0.024$, 95% CI [-0.0706, 0.0216]). See Table 10 of Appendix F for model effects. Further examination of group effects within separate valence conditions revealed no significant effects of group on either negative rejection ($F(1,234.21) = 0.04$, $p=.836$; $\beta= 0.009$, 95% CI [-0.0749, 0.0926]) or benign rejection ($F(1,221.26) = 0.28$, $p=.597$; $\beta= 0.031$, 95% CI [-0.0856, 0.1486]) trials. This suggests that valence is the driving effect of differences in pupillary reactivity in trials in which

the association between the word and the sentence were rejected, and that the pupillary reactivity pattern is not due to group differences in interpretation biases when rejecting an association.

In summary, we were able to specify a model which fit the pupillary reactivity waveforms observed in our sample while they completed an automatic interpretation bias assessment task. Group differences were observed in this model, with follow-up analyses suggesting that the MDD group displayed less pupillary reactivity during benign endorsement (i.e., benign interpretation) trials compared to the HC group. Notably, there was no difference found between groups on the rejection based trials.

Chapter Four:

Discussion

The present study sought to examine automatic interpretation biases in depression. We expanded upon previous work by assessing interpretation biases in a clinically defined sample of depressed individuals, who were compared with never depressed healthy controls. We further attempted to gain insight into the process of interpretation biases through the simultaneous assessment of pupillary reactivity during interpretation bias assessment.

We found evidence of automatic negative interpretation biases in the MDD group such that they were both more likely and faster to endorse negative interpretations compared to the HC group. The MDD group was also significantly less likely to endorse benign interpretations compared with the HC group. We were able to demonstrate significant reaction time differences within groups when comparing responses to both negative and benign interpretations in the HC group. In contrast, the MDD group differed significantly within the benign valence but did not reach statistical difference in the negative trials, although there was a moderate effect size difference between endorsing and rejecting negative interpretations (d = 0.37). Although low power may have constrained our ability to detect between group reaction time differences, examination of effect sizes revealed a moderate effect size (d=.39) mean difference between the MDD and HC group when comparing negative endorsement trials. Notably, this effect size is consistent with our previously reported effect sizes examining automatic negative interpretation

biases in dysphoric undergraduate samples (Cowden Hindash & Amir, 2012; Cowden Hindash & Rottenberg, 2015). The congruent effect sizes across multiple studies suggests a consistent difference in interpretation biases across three distinct depressive samples, with the largest differences demonstrated in the clinically depressed group overall, although not statistically significant at the reaction time group difference level. We thus demonstrated differences both between and within groups in rates of negative and benign biases and speed at which biases are indicated. This is the first study to report automatic interpretation biases in a clinically defined depressed sample through two indices of automatic interpretation biases.

The second hypothesis concerning differential waveforms between a sentence only control condition and responses which reflect a challenge to extant automatic interpretation biases was not fully confirmed. This analysis acted both as a validity check that pupillary reactivity can assess online cognitive processing while differentiating between conditions and provides an initial examination of within group pupillary differences based on behaviorally defined interpretation bias conditions. The results suggest that on trials in which a response rejected theory consistent automatic bias, there was greater dilation in the MDD group but decreased dilation in the HC group. Specifically, in the MDD group, greater dilation was observed when negative associations were rejected, while in the HC group decreased dilation was observed when benign associations were rejected. In both groups, trials in which rejection was consistent with theorized extant interpretation biases (i.e., rejecting benign interpretations in the MDD group and rejecting negative interpretations in the HC group) did not differ significantly from the sentence only control condition. This would suggest that pupillary reactivity can differentiate interpretation bias conditions from a natural processing control condition. Greater effort to reject extant biases may be preliminary evidence of reinterpretation

in the MDD group, although this effect is more difficult to interpret in the HC group, as it is in the opposite direction. Lack of pupillary reactivity differences between endorsing an interpretation and natural processing would suggest that endorsed biases are in line with natural processing – thereby not requiring increased effort to evaluate and decide on a relationship. However increased pupillary dilation during natural processing may suggest the HC group was less engaged with benign interpretations which were rejected than when naturally processing information. As such, this suggests that when pairing our behavioral data and the pupillary reactivity, we may be able to examine differences in biased processing. The pattern suggested from these analyses is that greater dilation may reflect cognitive effort or emotional engagement at the same time, depending on the comparison at play. Greater cognitive effort relative to natural information processing when rejecting an interpretation which fits theory consistent, extant automatic interpretation biases would increase pupillary dilation. Decreased engagement with benign material which does not fit an expectation may be evidence of lack of self-relevant fit or could reflect lack of emotional engagement with the stimuli. Regardless, this implies that automatic biases occur rapidly and pupillary reactivity may be able to provide signs of processing during bias formation and differentiate responses which reflect reinterpretation – via evidence of greater cognitive effort after response from trials which may reflect lack of engagement during stimulus processing.

It is important to note that trials which were consistent with interpretation biases did not differ from a sentence only control condition which did not require participants to consider alternative interpretations or associations or provide any behavioral response. Similarity between the sentence only control condition and specific, response defined trials indicates that trials in which responding was consistent with automatic biases did not induce greater pupillary

reactivity, because both cognitive effort and emotional saliency were consistent between unchallenged interpretations of ambiguous material and semantically congruent interpretations. As such, it appears that pupillary reactivity is able to map cognitive effort and saliency over the course of interpretation processes, including examining different points of processing over the course of an assessment trial. However, pupillary reactivity may not be able to specifically differentiate automatic biases from natural processing – at least at the group level. This is consistent with the behavioral data which observed that regardless of psychiatric status, individuals demonstrate both negative and benign biases – differing in gradients of frequency and speed rather than lacking one type of bias completely. As we cannot observe unbiased interpretations in an absolute sense, comparative processing can provide insight into automatic processes. This is consistent with cognitive theories of depression, which posit rapid, automatic and negatively biased interpretations are more easily accessed than alternatives during depressive episodes and thereby have greater influence on the individual's perception of themselves, the world, and the future (Beck, 1979, Beevers, 2005).

Our third hypothesis was not supported in that we observed differential pupillary responses to the ambiguous sentence in the direction opposite to what we predicted during group comparisons. We expected to observe greater pupillary reactivity (i.e., increased pupil dilation) in the MDD group indicative of greater salience of ambiguous material indirectly due to greater likelihood of negative interpretation and consistent with negative emotionality. However, counter to our predicted direction, there was greater pupillary constriction in response to the ambiguous sentence. This may suggest that the MDD group was less emotionally engaged with the ambiguous information, potentially due to less disposition to see the information as ambiguous – regardless of later interpretations made. This could reflect a comparatively general decreased

level of engagement overall in the task consistent with hedonic deficits (Berenbaum & Oltmanns, 1992). Conversely, there is evidence of generally increased resting state neural activity in depression (Korgaonkar, Fornito, Williams, & Grieve, 2014) which we would expect to be associated with greater pupillary dilation (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005; Siegle, Steinhouer, Stenger, Konecky, & Carter, 2003; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002). Thus, it is possible that the observed pupillary constriction reflects the MDD group having greater difficulty focusing their attention on the sentence relative to ongoing background cognition. Constriction would also be consistent with an accommodation reflex which occurs during visual refocusing on new stimuli (Beatty & Lucero-Wagoner, 2000). Further study with replication will be necessary to fully understand this effect, perhaps with longer inter-stimulus intervals between trials to allow for a greater comparison between potential ongoing cognition (Siegle et al., 2015) and reorienting processes.

Finally, our fourth hypothesis that pupillary reactivity would differ between groups based on interpretation bias was largely supported. Hypothesis four examined trial type waveform differences between groups with an expectation that group waveforms would differ based on interpretation type. These models, constructed in a manner similar to the repeated measures ANOVAs run in the behavioral reaction time data, supported differential pupillary reactivity based on trial type. While we did not observe group differences in the rejection based trials, we found that groups differed significantly in their pupillary activity while endorsing benign associations. In particular, the MDD group demonstrated less pupillary reactivity when endorsing benign interpretations than the HC group. Given that in both groups, benign endorsement trials did not differ from the sentence only condition (as tested in hypothesis two) and therefore did not require greater cognitive effort on the part of either group to resolve, the

observed group difference may be indicative of differential emotional saliency of the benign interpretations. Specifically, the HC group may have found the benign trials more emotionally salient than the MDD group, consistent with theories of automatic interpretation biases. Importantly, our use of pupillary reactivity as the outcome measure controls for potential baseline differences in pupillary dilation between groups. Our analyses compared changes from baseline across the entirety of the trials and thus reflect changes relative to stimuli and response while accounting for potential baseline differences in dilation. As such, this may further provide evidence of hedonic deficits in depression (Berenbaum & Oltmanns, 1992) consistent with anhedonia symptomatology and perhaps reflecting a reduced likelihood of benefitting from positive information (Fletcher et al., 2015; Pizzagalli et al., 2008).

When we consider our hypotheses together, we find a pattern of pupillary reactivity suggestive of both automatic interpretation biases and reinterpretation processes. First, our observations relative to our third hypothesis suggest differential engagement initially with ambiguous information between the MDD and HC groups, with the MDD group demonstrating greater initial pupillary constriction, perhaps indicating decreased engagement or saliency of the ambiguous sentence or a shift in focus towards the sentence and away from internal thoughts. While our observations relative to our fourth hypothesis suggest differential engagement during and after responses indicative of a benign interpretation bias, such that the MDD group demonstrated less pupil dilation than the HC group – reflecting a lower level of engagement. Pupillary reflexes have been found to indicate attentional processes (Kang, Huffer, & Wheatley, 2014; Wahn, Ferris, Hairston, & König, 2016), suggesting that in general, the MDD group may have been less engaged with benign interpretations. Decreased engagement may also account for a tendency to benefit less from making benign interpretations, consistent with hedonic deficits

previously observed in depressed samples (Fletcher et al., 2015; Pizzagalli et al., 2008) and associated with a worse course of depression overall (Rottenberg, Kasch, Gross, & Gotlib, 2002). This is consistent with clinical observations in which individuals with MDD often can make benign or even positive interpretations of events, but are unlikely to emotionally engage with (or believe) these interpretations.

Notably, group differences in rates of benign endorsement rates suggest the MDD group makes fewer benign interpretations, while reaction time indices suggest that the MDD group is comparable with the HC group in terms of how quickly they make benign interpretations. Thus, the driving difference between the groups behaviorally is how often they make benign interpretations. Simultaneously, pupillary reactivity suggests that during automatic benign interpretations, both groups demonstrate comparable reactivity as to when ambiguity is unchallenged (i.e., there is no need to assess if an unambiguous word relates to the sentence). Yet, reactivity in the MDD group was smaller overall when compared with the HC group. This implies that while the MDD group can and does make benign interpretations of ambiguous information, the emotional appeal of these interpretations may be weaker than that experienced in the HC group, even when fitting with the expectations of the MDD group.

In summary, this was the first study which examined automatic interpretation biases in major depression using an experimental paradigm while simultaneously collecting pupillary reactivity during bias assessment. As such, there was some question as to how pupillary reactivity would map onto the process of interpretation biases. Our initial hope was that we would be able to map the process of automatic interpretation bias formation. We found behavioral evidence of automatic negative interpretation biases in depression, which differed in rate and speed of response compared to healthy controls whom favored benign biases. We

further found that while pupillary reactivity did not provide direct evidence of automatic interpretation biases, there is potential evidence of reinterpretation processes as indexed by pupillary reactivity differences from a natural, unchallenged processing condition. Greater pupillary constriction in response to the initial presentation of the ambiguous sentence could reflect a shift in focus or decreased engagement with the standardized stimuli presented in the WSAP-D. We further found potential evidence of hedonic deficits in depression through decreased engagement with benign interpretations. As this is the first study to examine interpretation biases in conjunction with pupillary reactivity, replication is necessary to increase certainty in results and their implications. Nonetheless, there are a number of theoretical implications based on the results of the study.

Theoretical Implications

There are a few possible implications of the relationship between the behavioral indicators of interpretation biases and the neurophysiological indices. First, within group trial type comparisons provide further evidence for cognitive theories of depression, particularly in terms of automatic interpretation biases. Specifically, cognitive theories of depression indicate that negative biases are automatic, low effort cognitive processes. This is consistent with the results from sentence only control condition comparisons where waveform differences were only found when usual response styles were rejected. This difference suggests that greater effort is required to reject an extant bias, implying the presence of the bias initially.

Second, we did not see evidence of either mood congruency or response bias effects despite significant baseline group differences in depression, anxiety, and both positive and negative affect. Were mood congruency at play, we would expect to see a pattern of greater dilation in response to benign words in the HC group and negative words in the MDD group

regardless of interpretation response. However, there were no group differences apparent during the word presentation prior to participant response and no Valence*Group effect present when comparing trials with behavioral markers of interpretation to the sentence only, natural processing control condition. Were response biases at play, we would expect to see little to no variability in the types of interpretations observed behaviorally with pupillary reactivity apparent only during the word presentation and specific types of responses. As part of testing hypothesis two, we found no rejection based pupillary effects, instead demonstrating theory consistent greater effort to reject extant biases. The greatest group differences in the pupillary waveform occurred at the beginning of sentence presentation and during and after providing a response indicative of a benign interpretation. This pattern in the pupillary data is consistent with previously reported pupillary response data in which reactivity reflects continued cognitive processing of emotionally relevant information after making a decision regarding a stimulus rather than based on valence alone (Burkhouse, Siegle, & Gibb, 2014; Siegle, et al., 2003; van der Wel & van Steenbergen, 2018). Further, lack of reactivity related to specific word valence or response type both within the groups compared to a control condition and between groups suggests that rather than generalized emotional reactivity to negative or benign stimuli or generalized responding, responses may be more individually relevant based on pre-existing interpretation biases driven by schemas rather than specifically driven by stimuli characteristics alone. This is consistent with numerous studies which find that self-relevance is central to the expression of depressive biases (Cowden Hindash & Rottenberg, 2015; Wisco, 2009) and that a variety of interpretations are observable regardless of psychological status (Cowden Hindash & Amir, 2012; Cowden Hindash & Rottenberg, 2015).

Third, the pattern of group differences in reactivity to benign interpretations is consistent with hedonic deficits in depression. Across studies of interpretation bias, individuals with MDD or subthreshold depression have demonstrated a consistent lack of positive bias (Cowden Hindash & Amir, 2012; Cowden Hindash & Rottenberg, 2015; Sears, Bisson, & Neilsen, 2011; see Mathews & MacLeod, 2005, & Wisco, 2009 for reviews). Our behavioral data adds to this pattern in the literature in that the MDD group endorsed significantly fewer benign interpretations compared to the HC group. Further, pupillary reactivity differences were most prominent in the benign interpretation endorsement condition, with a pattern indicative of less engagement with the benign stimulus in the depressed group – even while endorsing a relationship. This could be indicative of less emotional engagement with the benign interpretation and therefore less benefit from making the benign interpretation.

Interestingly, the reaction time indices of the WSAP-D demonstrate a difference in speed to endorse negative interpretations in which the MDD group is nearly 200ms faster to endorse a negative interpretation than the HC group. This group difference has been consistently found across samples (Cowden Hindash & Amir, 2012, Cowden Hindash & Rottenberg, 2015), however there were no significant pupillary reactivity differences consistent with this behavioral finding, indeed pupillary reactivity was correlated with endorsement rates rather than reaction times (see Appendix G). One potential issue which may influence our results is that the HC group made significantly fewer (> 25%) negative interpretations compared with the MDD group. Notably, one HC participant endorsed only one negative interpretation – meaning this individual's negative endorsement rate was 1%, and their reaction time and pupillary reactivity waveform consisted of a single trial rather than an average of many trials. As the pupillary reactivity indices have smaller effects inside of larger models, it is possible that group

differences consistent with negative interpretation biases observed in the behavioral data were underpowered in the pupillary data.

Mapping Interpretation Biases

It was our prediction that pupillary reactivity would map onto the process of interpretation bias formation. This prediction stemmed from previous work which found evidence of differential reactivity during early stages of decision making, including masked valence identification tasks (Siegle et al., 2003). Further, evidence which suggested emotional saliency was integral to observing pupillary reactivity (Siegle et al., 2004; Siegle et al., 2015) suggested that reactivity would be greatest when information was emotionally relevant and a decision needed to be made quickly. This fit our conceptualization of automatic interpretation biases as self-relevant and negative when the individual is experiencing depression. However as this was the first study to examine these indices together, this was not a certainty. It is possible that pupillary reactivity may not be able to directly detect differential automatic interpretation biases precisely because automatic biases are the natural course of information processing. Rather, pupillary reactivity was more indicative of reinterpretation processes (which greater effort was needed to make an interpretation) or emotional engagement with the stimuli. Our waveform difference analyses in both the within group trial type comparisons with a sentence only control condition and the between group trial type comparisons suggest pupillary reactivity did not differentiate trial types during early stages of ambiguous stimulus processing, although overall groups differed in their reactivity to the initial presentation of the ambiguous sentence. Examination of where waveforms differed during trials indicated that pupillary reactivity was greatest when responses were counter to theorized automatic biases. Therefore, pupillary reactivity may be a better measure of continued information processing - as previously

demonstrated in studies of rumination (Siegle et al, 2003, 2004) – or of semantic incongruence effects than a direct index of immediate biases. As a measure of semantic incongruence effects, we would expect pupillary reactivity to correlate with the late positive potential (LPP) in event-related potential studies (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Foti, Hajcak, & Dien, 2009; Hajcak, MacNamara, & Olvet, 2010). As such, use of pupillary reactivity during the WSAP-D may reflect neurological activity consistent with cognitive control (Breakelaar, et al., 2017) and default node (Korgaonkar, Fornito, Williams, & Grieve, 2014) networks rather than associated with the saliency network (Mennon, 2015). This is consistent with fMRI research which has consistently demonstrated depression linked activity differences in both the cognitive control and default node networks when compared to healthy, non-depressed individuals (Breakelaar, et al., 2017).

Future Directions

The benefit of identifying trials indicative of reinterpretation should not be overlooked, as reinterpretation is one of the foundations of cognitive therapies. Specifically, cognitive therapies focus on evaluating automatic thoughts for biases which feed the vicious cycle of depression (Beck, 1976) and then teach depressed individuals to reinterpret situations in a more benign manner. Cognitive therapies work to increase the interaction between elaborative and automatic processing to increase access to less negative alternatives (Beevers, 2005). A measure of real time reinterpretation processes may be clinically useful as an assessment tool in clinical and process oriented research practices. For example, use of the WSAP-D with simultaneous pupillary reactivity recorded may help identify negative interpretation bias themes (e.g., accomplishment, symptom, or socially relevant) which can become the focus of therapy. Specifically, unhelpful automatic interpretation biases could be assessed via WSAP-D behavioral

indices and provide a clinician with area themes to focus thought challenging exercises as well as potential insight into pathological core beliefs. Further, extant reinterpretation processes may be observed via pupillary reactivity indices suggesting areas in which reinterpretation occurs but was initially biased. Finally, repeated measurement during and after therapeutic treatment may provide evidence of strengthened reinterpretation abilities or potentially evidence of changes to automatic biases in line with those observed in healthy, never depressed individuals.

An avenue in which a physiological indicator of reinterpretation may be of use in characterizing depression would be in understanding the hedonic benefit of benign interpretations in and after a major depressive episode. Our study found that although the MDD group made benign interpretations, they displayed less pupillary reactivity compared to the HC group. This suggests the benign interpretations were less salient to the MDD group and that they may not "believe" them to the same extent as negative interpretations. If replicable, this effect could be used to assess whether benign interpretations benefit formally depressed individuals. Evidence of similar responses to benign interpretations in a formally depressed group of individuals would suggest that decreased reactivity is depression state dependent. However, if decreased reactivity remained in a remitted depressed group, it would indicate that low hedonic benefit from benign interpretations is an individual trait – and therefore a potential risk factor for developing major depression. Given evidence that high-risk, never-depressed individuals demonstrate similar rates of positive interpretation bias compared to low-risk, never-depressed individuals with increased negative interpretation bias (Dearing & Gotlib, 2009), it is possible that evidence of decreased engagement with positive information is an early indicator of vulnerability.

Limitations

The results of this study should be considered in light of a few limitations. First, given that modest effect sizes (d=.29-.31) characterized the observed group differences in pupillary reactivity, it is possible that we were underpowered to observe differences in the negative interpretation indices due to fewer overall trials indicative of negative interpretation within the HC sample. Future studies should address this limitation through use of a larger sample size. Second, the WSAP-D defines trial types based on participant responses, which can lead to inconsistent cell sizes in comparison analyses. While our sample was sufficiently powered to observe medium to large effects, small effects in both the reaction time indices and the pupillary reactivity data were potentially underpowered. Future studies should address this design issue through use of either a greater number of trials to increase the likelihood of varied responses from each participant or through inclusion of stimuli which never depressed healthy control individuals would be more likely to interpret negatively. A further limitation is that our pupillary data was processed so that waveforms were time locked rather than stimulus locked. The pupil dilation data was processed in this manner due to the large number of initial conditions in the task, which led to 90 data points (9 conditions by 10 time points) per person. While this is an excellent starting point in terms of examining standardized waveforms across conditions and between groups, it limits some analyses of interest – particularly reaction time locked comparisons examining potential group by condition interactions or specific waveform differences where response times were smoothed in a general time span. Future studies, or secondary analyses led by specific hypotheses, should process pupillary data in multiple manners to further increase interpretability of pupillary reactivity data.

Contributions

Despite these limitations, the present study makes a number of scientific contributions. Primarily, this is the first study to report automatic interpretation biases, based on both response and reaction time indices, in a clinically depressed sample of individuals. This finding builds upon previous work using subthreshold or self-reported samples and indicates that the WSAP-D may be a consistent measure of automatic interpretation biases in depression. Second, this study is the first to assess physiological reactivity, through pupillary dilation, during an automatic interpretation bias task. The pupillary reactivity data suggests that cognitive processing differs between groups relative to both unchallenged information processing (sentence only comparisons) and specific interpretation biases (benign endorsement trials). These findings suggest that individuals with depression differentially process ambiguous information in a way consistent with cognitive theories of depression and may benefit less from processing biases which are consistent with healthy patterned responding. As such, this study contributes evidence to the cognitive theoretical framework of major depression as well as provides a starting point for future studies assessing changes in interpretation biases in the course of treatment and whether such biases are a risk factor for depression, an indicator of current depression, or both.

References

Balestri, M., Calati, R., Souery, D., Kautzky, A., Kasper, S., Montgomery, S., . . . Serretti, A. (2016). Socio-demographic and clinical predictors of treatment resistant depression: A prospective european multicenter study. *Journal of Affective Disorders, 189*, 224-232. doi:10.1016/j.jad.2015.09.033

Beard, C., & Amir, N. (2009). Interpretation in social anxiety: When meaning precedes ambiguity. *Cognitive Therapy and Research, 33*(4), 406-415. doi:10.1007/s10608-009-9235-0

Beatty, J., & Lucero-Wagoner, B. (2000). The pupillary system. In J. T. Cacioppo, L. G. Tassinary, & G. G. Berntson (Eds.), *Handbook of psychophysiology* (pp. 142-162). New York, NY, US: Cambridge University Press.

Beck, A. T. (1979). *Cognitive therapy and the emotional disorders*. New York: Meridian Books.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the beck depression inventory-II*. New York, NY: Harper and Row.

Beck, A. T. (1963). Thinking and depression: I. idiosyncratic content and cognitive distortions. *Archives of General Psychiatry, 9*(4), 324-333.

Beck, A. T. (1987). Cognitive models of depression. *Journal of Cognitive Psychotherapy, 1*(1), 5-37.

Beck, A. T., & Haigh, E. A. P. (2014). Advances in cognitive theory and therapy: The generic cognitive model. *Annual Review of Clinical Psychology, 10*, 1-24.

Beevers, C. G. (2005). Cognitive vulnerability to depression: A dual process model. *Clinical Psychology Review, 25*(7), 975-1002. doi:http://dx.doi.org/10.1016/j.cpr.2005.03.003

Berenbaum, H. & Oltmanns, T. F. (1992). Emotional experience and expression in schizophrenia and depression. *Journal of Abnormal Psychology, 101*, 37-44. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4370316/pdf/nihms672624.pdf

Blackwell, S. E., Browning, M., Mathews, A., Pictet, A., Welch, J., Davies, J., . . . Holmes, E. A. (2015). Positive imagery-based cognitive bias modification as a web-based treatment tool for depressed adults: A randomized controlled trial. *Clinical Psychological Science, 3*(1), 91-111.

Blackwell, S. E., & Holmes, E. A. (2010). Modifying interpretation and imagination in clinical depression: A single case series using cognitive bias modification. *Applied Cognitive Psychology, 24*(3), 338-350.

Bowler, J.O., Hoppitt, L., Illingworth, J., Dalgleish, T., Ononaiye, M., Perez-Olivas, G., & Mackintosh, B. (2017). Asymmetrical transfer effects of cognitive bias modification: Modifying attention to threat influences interpretation of emotional ambiguity, but not vice versa. *Journal of Behavior Therapy and Experimental Psychiatry, 54*, 239-246. DOI: https://doi.org/10.1016/j.jbtep.2016.08.011

Bradley, M. M., Miccoli, L., Escrig, M. A., & Lang, P. J. (2008). The pupil as a measure of emotional arousal and autonomic activation. *Psychophysiology, 45,* 602-607. DOI: 10.1111/j.1469-8986.2008.00654.x

Breukelaar, I.A., Antees, C., Grieve, S.M., Foster, S.L., Gomes, L., Williams, L.M., & Korgonkar, M.S. (2017). Cognitive control network anatomy correlates with neurocognitive behavior: A longitudinal study. *Human Brain Mapping, 38,* 631-643. DOI: 10.1002/hbm.23401

Brown, S.M., Manuk, S.B., Flory, J.D., & Hariri, A.R. (2006). Neural basis of individual differences in impulsivity: Contribution of corticolimbic circuits for behavioral arousal and control. *Emotion, 6(2),* 239-245. DOI: https://doi.org/10.1037/1528-3542.6.2.239

Burkhouse, K. L., Siegle, G. J., & Gibb, B. E. (2014). Pupillary reactivity to emotional stimuli in children of depressed and anxious mothers. *Journal of Child Psychology and Psychiatry*, *55*(9), 1009-1016.

Castro, A., García-Palacios, A., García-Campayo, J., Mayoral, F., Botella, C., García-Herrera, J. M., . . . Gili, M. (2015). Efficacy of low-intensity psychological intervention applied by ICTs for the treatment of depression in primary care: A controlled trial. *BMC Psychiatry*, *15*(1), 1-10. doi:10.1186/s12888-015-0475-0

Chung, G., Tucker, D. M., West, P., Potts, G. F., Liotti, M., Luu, P., & Hartry, A. L. (1996). Emotional expectancy: Brain electrical activity associated with an emotional bias in interpreting life events. *Psychophysiology, 33(3),* 218-233. https://doi.org/10.1111/j.1469-8986.1996.tb00419.x

Clark, D. A., Beck, A. T., & Alford, B. A. (1999). *Scientific foundations of cognitive theory and therapy of depression*. Hoboken, NJ, US: John Wiley & Sons Inc.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Erlbaum: Hillsdale, NJ.

Cowden Hindash, A. H., & Amir, N. (2012). Negative interpretation bias in individuals with depressive symptoms. *Cognitive Therapy and Research, 36*(5), 502-511.

Cowden Hindash, A. H., & Rottenberg, J. (2015). Turning quickly on myself: Automatic interpretation biases in dysphoria are self-referent. Cognition and Emotion, 31, 1-8. http://dx.doi.org/10.1080/02699931.2015.1105792

Cowden Hindash, A. & Rottenberg, J. (2017). Moving towards the benign: Automatic interpretation bias modification in dysphoria. Behaviour Research and Therapy, 99, 98-107. https://doi.org/10.1016/j.brat.2017.09.005

Crawford, J. R., & Henry, J. D. (2004). The positive and negative affect schedule (PANAS): Construct validity, measurement properties and normative data in a large non-clinical sample. *British Journal of Clinical Psychology, 43*, 245-265.

Crawley, M.J. (2007). *The R Book*. Retrieved from https://onlinelibrary.wiley.com/doi/pdf/10.1002/9780470515075

Cristea, I., Kok, R. N., & Cuijpers, P. (2015). The efficacy of cognitive bias modification interventions for mental health problems: A meta-analysis. *European Psychiatry,* doi:10.1016/S0924-9338(15)30663-5

Critchley, H.D., Tang, J., Glaser, D., Butterworth, B., Dolan, R.J. (2005). Anterior cingulate activity during error and autonomic response. *Neuroimage, 27*(4), 885-895.

Curran, P. & Bauer, M. (2014, June). Model assumptions and model evaluation. In *Introduction to multilevel modeling.* Statistics workshop conducted by Curran & Bauer Analytics, Chapel Hill, North Carolina.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology, 52, 95–111.* https://doi.org/10.1016/S0301-0511(99)00044-7

D'Esposito, M., Zarahn, E., & Aguirre, G. K. (1999). Event-related functional MRI: Implications for cognitive psychology. *Psychological Bulletin, 125*(1), 155-164. http://dx.doi.org/10.1037/0033-2909.125.1.155

Day, C. V., Gatt, J. M., Etkin, A., DeBattista, C., Schatzberg, A. F., & Williams, L. M. (2015). Cognitive and emotional biomarkers of melancholic depression: An iSPOT-D report. *Journal of Affective Disorders, 176,* 141-150. doi:10.1016/j.jad.2015.01.061

De Raedt, R. & Koster, E.H. (2010). Understanding vulnerability for depression from a cognitive neuroscience perspective: A reappraisal of attentional factors and a new conceptual framework. *Cognitive, Affective, and Behavioral Neuroscience, 10(1)*,50-70. DOI: https://doi.org/10.3758/CABN.10.1.50

Dearing, K. F., & Gotlib, I. H. (2009). Interpretation of ambiguous information in girls at risk for depression. *Journal of Abnormal Child Psychology, 37*(1), 79-91. doi:10.1007/s10802-008-9259-z

Disner, S.G., Beevers, C.G., Haigh, E.A., & Beck, A.T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews, Neuroscience, 12(8)*, 467-477. DOI: https://doi.org/10.1038/nrn3027

Dörfel, D., Lamke, JP., Hummel, F., Wagner, U., Erk, S., & Walter, H. (2014). Common and differential neural networks of emotion regulation by detachment, reinterpretation, distraction, and expressive suppression: A comparative fMRI investigation. *Neuroimage, 101,* 298-309. DOI: https://doi.org/10.1016/j.neuroimage.2014.06.051

Ellis, A. (1994). *Reason and emotion in psychotherapy*. Secaucus, NJ: Birch Lane.

Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., & Hirsch, J. (2006). Resolving emotional conflict: A role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron, 51(6),* 871-82. DOI: https://doi.org/10.1016/j.neuron.2006.07.029

Everaert, J., Duyck, W., & Koster, E. H. W. (2014). Attention, interpretation, and memory biases in subclinical depression: A proof-of-principle test of the combined cognitive biases hypothesis. *Emotion, 14*(2), 331-340.

Everaert, J., Koster, E. H. W., & Derakshan, N. (2012). The combined cognitive bias hypothesis in depression. *Clinical Psychology Review, 32,* 413-424. doi:10.1016/j.cpr.2012.04.003

Everaert, J., Tierens, M., Uzieblo, K., & Koster, E. H. W. (2013). The indirect effect of attention bias on memory via interpretation bias: Evidence for the combined cognitive bias hypothesis in subclinical depression. *Cognition and Emotion, 27*(8), 1450-1459.

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods, 41(4),* 1149-1160. DOI: https://doi.org/10.3758/BRM.41.4.1149

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders, research version, non-patient edition (SCID-I/NP)*. New York: Biometrics Research, New York State Psychiatric Institute.

Fischer, A. S., Keller, C. J., & Etkin, A. (2016). The clinical applicability of functional connectivity in depression: Pathways toward more targeted intervention. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 1(3)*, 262-270. DOI: https://doi.org/10.1016/j.bpsc.2016.02.004

Fletcher, K., Parker, G., Paterson, A., Fava, M., Iosifescu, D., & Pizzagalli, D.A. (2015). Anhedonia in melancholic and non-melancholic depressive disorders. *Journal of Affective Disorders, 184,* 81-88. DOI: https://doi.org/10.1016/j.jad.2015.05.028

Formisano, E. & Goebel, R. (2003). Tracking cognitive processes with functional MRI mental chronometry. *Current Opinion in Neurobiology, 13(2),* 174-181. DOI: https://doi.org/10.1016/S0959-4388(03)00044-8

Foti, D., Hajcak, G., & Dien, J. (2009). Differentiating neural responses to emotional pictures: Evidence from temporal-spatial PCA. *Psychophysiology, 46,* 521–530. DOI: 10.1111/j.1469-8986.2009.00796.x

Fountoulakis, K., Fotiou, F., Iacovides, A., Tsiptsios, J., Goulas, A., Tsolaki, M., & Ierodiakonou, C. (1999). Changes in pupil reaction to light in melancholic patients. *International Journal of Psychophysiology, 31*(2), 121-128.

Fresco, D. M., Coles, M. E., Heimberg, R. G., Liebowitz, M. R., Hami, S., . . . Goetz, D. (2001). The liebowitz social anxiety scale: A comparison of the psychometric properties of self-report and clinician-administered formats. *Psychological Medicine, 31*(6), 1025.

Gianaros, P.J., Horenstein, J.A., Hariri, Sheu, L.K., Manuk, SB., Matthews, K.A., Cohen, S. (2008). Potential neural embedding of parental social standing. *Social Cognitive and Affective Neuroscience, 3(2),* 91-96. DOI: https://dx.doi.org/10.1093%2Fscan%2Fnsn003

Goldapple, K., Segal, Z., Garson, C., Lau, M., Bieling, P., Kennedy, S., & Mayberg, H. (2004). Modulation of cortical-limbic pathways in major depression: Treatment-specific effects of cognitive behavior therapy. *Archives of General Psychiatry, 61,* 34-41. doi:10.1001/archpsyc.61.1.34

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: Current status and future directions. *Annual Review of Clinical Psychology, 6*, 285-312.

Granholm, E., Asarnow, R. F., Sarkin, A. J., & Dykes, K. L. (1996). Pupillary responses index cognitive resource limitations. *Psychophysiology*, *33*(4), 457-461.

Hajcak, G., MacNamara, A., & Olvet, D. M. (2010). Event-related potentials, emotion, and emotion regulation: An integrative review. *Developmental Neuropsychology, 35,* 129–155. DOI: 10.1080/87565640903526504

Hallion, L. S., Ruscio, A. M., Faul, F., Erdfelder, E., Lang, A. G., Buchner, A., . . . Lang, A. G. (2009). *A meta-analysis of the effect of cognitive bias modification on anxiety and depression* American Psychological Association, Inc. doi:10.1037/a0024355

Harmer, C.J., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., Goodwin, G.M. & Cowen, P.J. (2009). Effect of acute antidepressant administration on negative affective bias in depressed patients. *American Journal of Psychiatry, 166(10),* 1178-1184.

Holmes, A. J. & Pizzagalli, D.A. (2008). Response conflict and frontocingulate dysfunction in unmedicated participants with major depression. *Neuropsychologia, 46(12),* 2904-2913. DOI: https://dx.doi.org/10.1016%2Fj.neuropsychologia.2008.05.028

Holmes, E. A., Lang, T. J., Moulds, M. L., & Steele, A. M. (2008). Prospective and positive mental imagery deficits in dysphoria. *Behaviour Research and Therapy, 46*(8), 976-981.

Holmes, E. A., Lang, T. J., & Shah, D. M. (2009). Developing interpretation bias modification as a 'cognitive vaccine' for depressed mood: Imagining positive events makes you feel better than thinking about them verbally. *Journal of Abnormal Psychology, 118*(1), 76-88.

Holmes, E. A., Mathews, A., Dalgleish, T., & Mackintosh, B. (2006). Positive interpretation training: Effects of mental imagery versus verbal training on positive mood. *Behavior Therapy, 37*(3), 237-247.

IBM Corp. (2016). IBM SPSS Statistics for Windows (Version 24.0). Armonk, NY: IBM Corp.
Johnstone, T., van Reekum, C.M., Urry, H.L., Kalin, N.H., & Davidson, R.J. (2007). Failure to regulate: Counterproductive recruitment of top-down prefrontal-subcortical circuity in major depression. *The Journal of Neuroscience, 27(33),* 8877-8884. DOI: https://doi.org/10.1523/JNEUROSCI.2063-07.2007
Jones, E. B. & Sharpe, L. (2017). Cognitive bias modification: A review of meta analyses. *Journal of Affective Disorders, 223,* 175-183. https://doi.org/10.1016/j.jad.2017.07.034
Jones, N.P., Siegle, G.J., & Mandell, D. (2015). Motivational and emotional influences on cognitive control in depression: A pupillometry study. *Cognitive Affective and Behavioral Neuroscience, 15(2),* 263-275. DOI: https://dx.doi.org/10.3758%2Fs13415-014-0323-6
Joormann, J., Waugh, C. E., & Gotlib, I. H. (2015). Cognitive bias modification for interpretation in major depression: Effects on memory and stress reactivity. *Clinical Psychological Science, 3*(1), 126-139.
Kang, O.E., Huffer, K.E., & Wheatley, T.P. (2014). Pupil dilation dynamics track attention to high-level information. *PLoS One, 9(8),* e102463. DOI: https://dx.doi.org/10.1371%2Fjournal.pone.0102463
Kellough, J. L., Beevers, C. G., Ellis, A. J., & Wells, T. T. (2008). Time course of selective attention in clinically depressed young adults: An eye tracking study. *Behaviour Research and Therapy, 46*(11), 1238-1243.
Kircanski, K., Joormann, J., & Gotlib, I. H. (2012). Cognitive aspects of depression. *Wiley Interdisciplinary Reviews – Cognitive Science, 3,* 301-313.
Klingner, J. (2010). *Measuring cognitive load during visual tasks by combining pupillometry and eye tracking.* (Doctoral dissertation, Stanford University). Retrieved from http://smarteye.se/wp-content/uploads/2015/01/Klingner-Jeff.pdf.
Klauser, P., Fornito, A., Lorenzetti, V., Davey, C.G., Dwyer, D.B., Allen, N.B., & Yücel, M. (2015). Cortico-limbic network abnormalities in individuals with current and past major depressive disorder. *Journal of Affective Disorders, 173,* 45-52. DOI: https://doi.org/10.1016/j.jad.2014.10.041
Kohn, N. Eickhoff, S.B., Scheller, M., Laird, A.R., Fox, P.T., & Habel, U. (2014). Neural network of cognitive emotion regulation – an ALE meta-analysis and MACM analysis. *Neuorimage, 87,* 345-355. DOI: https://doi.org/10.1016/j.neuroimage.2013.11.001
Korgaonkar, M.S., Fornito, A., Williams L.M., & Grieve, S.M. (2014) Abnormal structural networks characterize major depressive disorder: A connectome analysis. *Biological Psychiatry, 76m* 567-574. http://dx.doi.org/10.1016/j.biopsych.2014.02.018
Koster, E.H.W., Hoorelbeke, K., Onradt, T., Owens, M., & Derakshan, N. (2017). Cognitive control interventions for depression: A systematic review of findings from training studies. *Clinical Psychology Review, 53,* 79-92. https://doi.org/10.1016/j.cpr.2017.02.002
Kutas, M., & Hillyard, S. A. (1980a). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science, 207(4427),* 203-205
Kutas, M., & Hillyard, S. A. (1980b). Reading between the lines: Event-related brain potentials during natural sentence processing. *Brain and Language, 11(2),* 354-373.
Laeng, B., Sæther, L., Holmlund, T., Wang, C. E. A., Waterloo, K., Eisemann, M., & Halvorsen, M. (2013). Invisible emotional expressions influence social judgments and pupillary responses of both depressed and non-depressed individuals. *Frontiers in Psychology, 4.* DOI: 10.3389/fpsyg.2013.00291

Lang, T. J., Blackwell, S. E., Harmer, C. J., Davison, P., & Holmes, E. A. (2012). Cognitive bias modification using mental imagery for depression: Developing a novel computerized intervention to change negative thinking styles. *European Journal of Personality, 26*(2), 145-157.

Laumann, T.O., Snyder, A.Z., Mitra, A., Gordon, E.M., Gratton, C., Adeyemo, B…Petersen, S.E. (2017). On the stability of BOLD fMRI correlations. *Cerebral Cortex, 27(10),* 4719-4732. DOI: https://doi.org/10.1093/cercor/bhw265

Lawson, C., & MacLeod, C. (1999). Depression and the interpretation of ambiguity. *Behaviour Research and Therapy, 37*(5), 463-474.

Linden, M., & Rath, K. (2014). The impact of the intensity of single symptoms on the diagnosis and prevalence of major depression. *Comprehensive Psychiatry, 55*, 1567-1571. doi:10.1016/j.comppsych.2014.06.005

Loveless, N.E. (1983). Event-related brain potentials and human performance. In A. Gale & J. Edwards (Eds.), *Physiological correlates of human behavior* (Vol 2, pp 79-97). New York: Academic Press.

MacNamara, A., Ferri, J., & Hajcak, G. (2011) Working memory load reduces the late positive potential and this effect is attenuated with increasing anxiety. *Cognitive, Affective, and Behavioral Neuroscience, 11*, 321–331. DOI 10.3758/s13415-011-0036-z

Mathews, A. (2012). Effects of modifying the interpretation of emotional ambiguity. *Journal of Cognitive Psychology, 24*(1), 92-105. doi:10.1080/20445911.2011.584527

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology, 1*(1), 167-195.

MathWorks (2016). MATLAB and Statistics Toolbox (R2016b). Natick, Massachusetts, United States: The MathWorks, Inc.

Menon V. (2015) Salience Network. In: Arthur W. Toga, editor. Brain Mapping: An Encyclopedic Reference, vol. 2, pp. 597-611. Academic Press: Elsevier.

Mobius, M., Tendolkar, I., Lohner, V., Baltussen, M., & Becker, E. S. (2015). *Refilling the half-empty glass - investigating the potential role of the interpretation modification paradigm for depression (IMP-D)* Elsevier B.V. doi:10.1016/j.jbtep.2015.03.002

Mogg, K., Bradbury, K. E., & Bradley, B. P. (2006). Interpretation of ambiguous information in clinical depression. *Behaviour Research and Therapy, 44*(10), 1411-1419.

Molina, S., & Borkovec, T. D. (1994). The penn state worry questionnaire: Psychometric properties and associated characteristics. In G. C. L. Davey, F. Tallis, G. C. L. (Eds.), 265-283. Oxford, England: John Wiley & Sons.

Otto, B., Misra, S., Prasad, A., & McRae, K. (2014). Functional overlap of top-down emotion regulation and generation: An fMRI study identifying common neural substrates between cognitive reappraisal and cognitively generated emotions. *Cognitive, Affective & Behavioral Neuroscience, 14*(3), 923-938. doi:10.3758/s13415-013-0240-0

Ouimet, A. J., Gawronski, B., & Dozois, D. J. A. (2009). Cognitive vulnerability to anxiety: A review and an integrative model. *Clinical Psychology Review, 29*(6), 459-470.

Pictet, A., Jermann, F., & Ceschi, G. (2016). When less could be more: Investigating the effects of a brief internet-based imagery cognitive bias modification intervention in depression. *Behavior Research and Therapy, 84*, 45-51. DOI: https://doi.org/10.1016/j.brat.2016.07.008

Pizzagalli, D.A., Iosifescu, D., Hallett, L.A., Ratner, K.G., & Fava, M. (2008). Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. *Journal of Psychiatric Research, 43*, 76-87. DOI: https://doi.org/10.1016/j.jpsychires.2008.03.001

R Core Team (2018). R: A language and environment for statistical computing (Version 3.4.4). Vienna, Austria: R Foundation for Statistical Computing. Retrieved from http://www.R-project.org/

Ramanaiah, N. V., Franzen, M., & Schill, T. (1983). A psychometric study of the state-trait anxiety inventory. *Journal of Personality Assessment, 47*(5), 531.

Ritchey, M., Dolcos, F., Eddington, K.M., Strauman, T.J., & Cabeza, R. (2011). Neural correlates of emotional processing in depression: Changes with cognitive behavioral therapy and predictors of treatment response. *Journal of Psychiatric Research, 45(5),* 577-587. DOI: https://doi.org/10.1016/j.jpsychires.2010.09.007

Ritter, W., Simson, R., & Vaughan, H. G. (1983). Event-related potential correlates of two stages of information processing in physical and semantic discrimination trials. *Psychophysiology, 20(2),* 168-179

Rive, M.N., van Rooijen, G., Veltman, D.J., Phillips, M.L., Schene, A.H., Ruhé, H.G. (2013). Neural correlates of dysfunctional emotion regulation in major depressive disorder: A systematic review of neuroimaging studies. *Neuroscience and Biobehavioral Reviews, 37(10),* 2529-2553. DOI: https://doi.org/10.1016/j.neubiorev.2013.07.018

Rottenberg, J., Gross, J. J., & Gotlib, I. H. (2005). Emotion context insensitivity in major depressive disorder. *Journal of Abnormal Psychology, 114*(4), 627-639.

Rottenberg, J., Kasch K.L., Gross, J.J., & Gotlib, I.H. (2002). Sadness and amusement reactivity differentially predict concurrent and prospective functioning in major depressive disorder. *Emotion, 2,* 135-146. DOI: 10.1037//1528-3542.2.2.135

Salomon, K., Bylsma, L. M., White, K. E., Panaite, V., & Rottenberg, J. (2013). Is blunted cardiovascular reactivity in depression mood-state dependent? A comparison of major depressive disorder remitted depression and healthy controls. *International Journal of Psychophysiology, 90*(1), 50-57.

Satterfield, J. H., Schell, A. M., Nicholas, T. W., Satterfield, B. T., & Freese, T. E. (1990). Ontogeny of selective attention effects on event-related potentials in attention-deficit hyperactivity disorder and normal boys. *Biological Psychiatry, 28(10),* 879-903.

Sears, C. R., Bisson, S, & Nielsen, K. E. (2011). Dysphoria and the immediate interpretation of ambiguity: Evidence for a negative interpretive bias in error rates but not response latencies. *Cognitive Therapy and Research, 35*(5), 469-476.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The mini-international neuropsychiatric interview (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59,* 22-33.

Shvartzman, P., Weiner, Z., Vardy, D., Friger, M., Sherf, M., & Biderman, A. (2005). Health services utilization by depressive patients identified by the MINI questionnaire in a primary care setting. *Scandinavian Journal of Primary Health Care, 23*(1), 18-25. doi:10.1080/02813430510018383

Siegle, G.J., D'Andrea, W., Jones, N., Hallquist, M.N., Stepp, S.D., Fortunato, A., Morse, J.Q., & Pilkonis, P.A. (2015). Prolonged physiological reactivity and loss: Association of pupillary reactivity with negative thinking and feelings. *International Journal of Psychophysiology, 98,* 310-320. DOI: https://doi.org/10.1016/j.ijpsycho.2015.05.009

Siegle, G. J., Granholm, E., Ingram, R. E., & Matt, G. E. (2001). Pupillary and reaction time measures of sustained processing of negative information in depression. *Biological Psychiatry, 49*(7), 624-636.

Siegle, G.J., Ichikawa, N., & Steinhauer, S. R. (2008). Blink before and after you think: Blinks occur prior to and following cognitive load indexed by pupillary responses. *Psychophysiology, 45,* 679-687.

Siegle, G. J., Steinhauer, S. R., Stenger, V. A., Konecky, R., & Carter, C. S. (2003). Use of concurrent pupil dilation assessment to inform interpretation and analysis of fMRI data. *Neuroimage, 20,* 114-124.

Siegle, G. J., Price, R. B., Jones, N. P., Ghinassi, F., Painter, T., & Thase, M. E. (2014). You gotta work at it: Pupillary indices of task focus are prognostic for response to a neurocognitive intervention for rumination in depression. *Clinical Psychological Science, 2*(4), 455-471.

Siegle, G. J., Steinhauer, S. R., Carter, C. S., Ramel, W., & Thase, M. E. (2003). Do the seconds turn into hours? Relationships between sustained pupil dilation in response to emotional information and self-reported rumination. *Cognitive Therapy and Research, 27*(3), 365-382.

Siegle, G. J., Steinhauer, S. R., & Thase, M. E. (2004). Pupillary assessment and computational modeling of the stroop task in depression. *International Journal of Psychophysiology, 52*(1), 63-76.

Siegle, G. J., Steinhauer, S. R., Thase, M. E., Stenger, V. A., & Carter, C. S. (2002). Can't shake that feeling: Event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biological Psychiatry, 51,* 693-707. doi:10.1016/S0006-3223(02)01314-8

Siegle, G.J., Thompson, W., Carter, C.S., Steinhauer, S.R., & Thase, M.E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biological Psychiatry, 61(2),*198-209. DOI: https://doi.org/10.1016/j.biopsych.2006.05.048

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologist Press.

Steidtmann, D., Ingram, R. E., & Siegle, G. J. (2010). Pupil response to negative emotional information in individuals at risk for depression. *Cognition and Emotion, 24*(3), 480-496.

Steinhauer, S. R., Siegle, G. J., Condray, R., & Pless, M. (2004). Sympathetic and parasympathetic innervation of pupillary dilation during sustained processing. *International Journal of Psychophysiology, 52,* 77-86. DOI: 10.1016/j.ijpsycho.2003.12.005

Teachman, B. A., Joormann, J., Steinman, S. A., & Gotlib, I. H. (2012). Automaticity in anxiety disorders and major depressive disorder. *Clinical Psychology Review, 32,* 575-603. doi:10.1016/j.cpr.2012.06.004

van der Wel, P. & van Steenbergen (2018). Pupil dilation as an index of effort in cognitive control tasks: A review. *Psychonomic Bulletin & Review.* (Published online: February 12, 2018) https://doi.org/10.3758/s13423-018-1432-y

Wahn, B. Ferris, D. P., Hairston, W.D., & König, P. (2016). Pupil sizes scale with attentional load and task experience in a multiple object tracking task. *PLoS One, 11,* e0168087. DOI: https://dx.doi.org/10.1371%2Fjournal.pone.0168087

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology, 54*(6), 1063-1070. doi:10.1037/0022-3514.54.6.1063

Wickham, H. (2009). ggplot2: Elegant Graphics for Data Analysis. New York: United States of America: Springer Verlag.

Wilhelm, H. & Kardon, R. H. (1997). The pupillary light reflex pathway. *Neuro-Opthalmology, 17,* 59-62. DOI: 10.3109/01658109709044647

Williams, J. M., Watts, F. N., MacLeod, C., & Mathews, A. (1988). *Cognitive psychology and emotional disorders*. Oxford, England: John Wiley & Sons.

Wilson-Mendenhall, C., Barrett, L. F., & Barsalou, L. W. (2015). Variety in emotional life: Within-category typicality of emotional experiences is associated with neural activity in large-scale brain networks. *Social Cognitive and Affective Neuroscience, 10*(1), 62-71. doi:10.1093/scan/nsu037

Wisco, B. E. (2009). Depressive cognition: Self-reference and depth of processing. *Clinical Psychology Review, 29*(4), 382-392. doi: http://dx.doi.org/10.1016/j.cpr.2009.03.003

Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Okada, G., Kunisato., Y…Yamawaki, S. (2014). Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. *Social Cognitive and Affective Neuroscience, 9(4),* 487-493. DOI: https://doi.org/10.1093/scan/nst009

Appendices

Appendix A: Demographics, Health, and Family History Questionnaire

Demographics

Age: _____ years
Gender: _____ Male _____ Female
Marital Status: Please check your current marital status.
_____ Single _____ Married _____ Domestic partner (living together)
_____ Separated _____ Divorced _____ Widowed
Children: If applicable, please provide the following information about your children.
Number of children: _____
Age and sex of each child: _____ _____ _____ _____
Education: Please check the highest level of schooling that you completed.
_____ Elementary school _____ Junior high school _____ High school
_____ Some college _____ Technical school _____ Junior college
_____ Four-year college _____ Graduate or professional degree

Occupation: _____
Please indicate which of the following categories best describes your occupation. Select only one category.
1. Higher executive of large company, proprietor, or major professional
2. Business manager, proprietor of medium-sized business, or lesser professional
3. Administrative personnel, owner of small business, or minor professional
4. Clerical and sales worker, technician, or owner of very small business
5. Skilled manual employee
6. Machine operator or semiskilled employee
7. Unskilled employee
8. Unemployed and receiving public assistance
9. Unemployed and not receiving public assistance

Income (optional): Please check your annual household income. (Include **all sources** of income – wages of **everyone** contributing to your home, any alimony, child support, welfare, or any other source of income.)

_____0$ - $4,999	_____$20,000 - $24,999	_____$55,000 - $64,999
_____$5,000 - $9,999	_____$25,000 - $34,999	_____$65,000 - $74,999
_____$10,000 - $14,999	_____$35,000 - $44,999	_____$75,000 - $100,000.
_____$15,000 - $19,999	_____$45,000 - $54,999	_____More than $100,000

Health Questionnaire

INSTRUCTIONS: If you can answer YES to the question asked, put a circle around the Yes. If you have to answer NO to the question asked, put a circle around the No. Answer all questions. If you are not sure, guess.

1.	Do you often catch severe colds?	YES	NO
2.	When you catch a cold, do you always have to go to bed?	YES	NO
3.	Do you sometimes have severe soaking sweats at night?	YES	NO
4.	Does heart trouble run in your family?	YES	NO
5.	Do you often suffer from an upset stomach?	YES	NO
6.	Do you suffer from indigestion?	YES	NO
7.	Do you suffer from frequently loose bowel movements?	YES	NO
8.	Do you constantly suffer from bad constipation?	YES	NO
9.	Are your joints often painfully swollen?	YES	NO
10.	Do your muscles and joints constantly feel stiff?	YES	NO
11.	Do pains in the back make it hard for you to keep up with your work?	YES	NO
12.	Do you suffer badly from frequent severe headaches?	YES	NO
13.	Do you often have spells of severe dizziness?	YES	NO
14.	Do you frequently feel faint?	YES	NO
15.	Have you fainted more than twice in your life?	YES	NO
16.	Do you have constant numbness or tingling in any part of your body?	YES	NO
17.	Do you often get spells of complete exhaustion or fatigue?	YES	NO
18.	Does working tire you out completely?	YES	NO
19.	Do you usually get up tired and exhausted in the morning?	YES	NO
20.	Does every little effort wear you out?	YES	NO
21.	Are you frequently ill?	YES	NO
22.	Are you frequently confined to bed by illness?	YES	NO
23.	Do severe pains and aches make it impossible for you to do your work?	YES	NO
24.	Are you definitely under weight?	YES	NO
25.	Are you definitely over weight?	YES	NO

FEMALES ONLY

26.	Have your menstrual periods usually been painful?	YES	NO
27.	Have you often felt weak or sick with your periods?	YES	NO
28.	Have you often had to lie down when your periods came on?	YES	NO
29.	Have you usually been tense or jumpy with your periods?	YES	NO
30.	Have you ever had constant severe hot flashes and sweats?	YES	NO

Medical History Checklist

Please check **ALL PAST and CURRENT** illnesses or conditions diagnosed by a physician. **DO NOT** check items that you have self-diagnosed, or that you believe you may have experienced.

- ☐ Abnormal EEG
- ☐ Acute Sinusitis
- ☐ ADHD
- ☐ Attention Deficit Disorder
- ☐ Alcoholism
- ☐ Allergies
- ☐ Alzheimer's
- ☐ AIDS/HIV
- ☐ Anemia
- ☐ Angina
- ☐ Anorexia
- ☐ Appendicitis
- ☐ Arthritis
- ☐ Asthma
- ☐ Bipolar
- ☐ Bipolar 2
- ☐ Bipolar Manic Depressive
- ☐ Birth Control
- ☐ Bleeding Disorders
- ☐ Bronchitis
- ☐ Bulimia
- ☐ Cancer
- ☐ Cardiac Arrhythmia
- ☐ Cataracts
- ☐ Chemical Dependency
- ☐ Cholecystectomy
- ☐ Chronic Back Pain
- ☐ Chronic Lower Back Pain
- ☐ Chronic Obstructive Pulmonary Disease
- ☐ Chronic Pain
- ☐ Chronic Sinusitis
- ☐ Congestive Heart Failure
- ☐ Constipation
- ☐ Crohn's Disease
- ☐ Depression
- ☐ Depression with Psychosis
- ☐ Diabetes Mellitis
- ☐ Diabetes Type 1
- ☐ Diabetes Type 2
- ☐ Diabetic Neuropathy
- ☐ Diverticuli Disease
- ☐ Drug Sensitive
- ☐ Drug Allergy
- ☐ Eczema
- ☐ Elevated Liver Enzymes
- ☐ Emphysema
- ☐ Endometriosis
- ☐ Epilepsy
- ☐ Fatigue
- ☐ Fibrocystic Breast Disease
- ☐ Fibromyalgia
- ☐ Gallbladder disease
- ☐ Gastric Ulcer
- ☐ Gastrointestinal Ulcers
- ☐ General Anxiety Disorder
- ☐ GERD
- ☐ Glaucoma
- ☐ Gonorrhea or Chlamydia
- ☐ Gout
- ☐ Headache
- ☐ Hepatitis A
- ☐ Hepatitis B
- ☐ Hepatitis C
- ☐ Herpes
- ☐ High Cholesterol
- ☐ High Blood Pressure
- ☐ Hip Surgery
- ☐ Hormone Therapy
- ☐ Hot Flashes
- ☐ Hypoactive Sexual Desire
- ☐ Hysterectomy
- ☐ Insomnia
- ☐ Irritable Bowel Syndrome
- ☐ Joint Pain
- ☐ Kidney Disease
- ☐ Kidney Stones
- ☐ Knee Surgery
- ☐ Liver Disease
- ☐ Lupus
- ☐ Major Depression
- ☐ Malignant Melanoma
- ☐ Memory Loss
- ☐ Migraine
- ☐ Mild Cognitive Impairment
- ☐ Multiple Sclerosis
- ☐ Myocardial Infarction
- ☐ Nausea
- ☐ NSAID Medication
- ☐ Obesity
- ☐ Obsessive Compulsive Disorder
- ☐ Oral Contraceptives
- ☐ Osteoarthritis
- ☐ Osteoarthritis of the hip
- ☐ Osteoarthritis of the knee
- ☐ Osteopenia
- ☐ Osteoporosis
- ☐ Overactive Bladder
- ☐ Pacemaker
- ☐ Panic Disorder
- ☐ Peripheral Neuropathy
- ☐ Peripheral Vascular Disease
- ☐ Pneumonia
- ☐ Polio
- ☐ Postmenopausal
- ☐ Postmenopausal Depression
- ☐ Post Traumatic Stress Disorder

- ☐ Prostatitis
- ☐ Psoriasis and similar
- ☐ Rheumatic Fever
- ☐ Rheumatoid Arthritis
- ☐ Rosacea
- ☐ Schizophrenic Disorders
- ☐ Scoliosis
- ☐ Shingles
- ☐ Sleep Apnea
- ☐ Smoker
- ☐ Spinal Meningitis
- ☐ Stroke/TIA
- ☐ Substance Abuse
- ☐ Suicide Attempt
- ☐ Thyroid Problems
- ☐ Tubal Ligation
- ☐ Tuberculosis
- ☐ Ulcerative Proctitis
- ☐ Urinary Incontinence
- ☐ Uterine Fibroids
- ☐ Vascular Dementia
- ☐ Atopic Dermatitis
- ☐ Cocaine Abuse

Appendix B: Beck Depression Inventory Second-Edition

BDI-II

This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the ONE STATEMENT in each group that bests describes the way you have been feeling during the **PAST TWO WEEKS, INCLUDING TODAY.** Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in sleeping pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel that my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry any more than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I don't feel I am worthless.
1 I do not consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.
2b I sleep a lot less than usual.

3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.
2b My appetite is much greater than usual.

3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

Appendix C: Spielberger State-Trait Anxiety Inventory

SELF-EVALUATION QUESTIONNAIRE
STAI Y-1

DIRECTIONS: A number of statements which people used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel RIGHT NOW, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

		Not at all	Some-what so	Moder-ately	Very much so
1.	I feel calm	(1)	(2)	(3)	(4)
2.	I feel secure	(1)	(2)	(3)	(4)
3.	I feel tense	(1)	(2)	(3)	(4)
4.	I feel strained	(1)	(2)	(3)	(4)
5.	I feel at ease	(1)	(2)	(3)	(4)
6.	I feel upset	(1)	(2)	(3)	(4)
7.	I am presently worrying over possible misfortunes	(1)	(2)	(3)	(4)
8.	I feel satisfied	(1)	(2)	(3)	(4)
9.	I feel frightened	(1)	(2)	(3)	(4)
10.	I feel comfortable	(1)	(2)	(3)	(4)
11.	I feel self-confident	(1)	(2)	(3)	(4)
12.	I feel nervous	(1)	(2)	(3)	(4)
13.	I feel jittery	(1)	(2)	(3)	(4)
14.	I feel indecisive	(1)	(2)	(3)	(4)
15.	I feel relaxed	(1)	(2)	(3)	(4)
16.	I feel content	(1)	(2)	(3)	(4)
17.	I am worried	(1)	(2)	(3)	(4)
18.	I feel confused	(1)	(2)	(3)	(4)
19.	I feel steady	(1)	(2)	(3)	(4)
20.	I feel pleasant	(1)	(2)	(3)	(4)

SELF-EVALUATION QUESTIONNAIRE
STAI Y-2

DIRECTIONS: A number of statements which people used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you GENERALLY feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

		Not at all	Some-what so	Moder-ately	Very much so
21.	I feel pleasant	(1)	(2)	(3)	(4)
22.	I feel nervous and restless	(1)	(2)	(3)	(4)
23.	I feel satisfied with myself	(1)	(2)	(3)	(4)
24.	I wish I could be as happy as others seem to be	(1)	(2)	(3)	(4)
25.	I feel like a failure	(1)	(2)	(3)	(4)
26.	I feel rested	(1)	(2)	(3)	(4)
27.	I am calm, cool, and collected	(1)	(2)	(3)	(4)
28.	I feel that difficulties are piling up so that I cannot overcome them	(1)	(2)	(3)	(4)
29.	I worry too much over something that really doesn't matter	(1)	(2)	(3)	(4)
30.	I am happy	(1)	(2)	(3)	(4)
31.	I have disturbing thoughts	(1)	(2)	(3)	(4)
32.	I lack self-confidence	(1)	(2)	(3)	(4)
33.	I feel secure	(1)	(2)	(3)	(4)
34.	I make decisions easily	(1)	(2)	(3)	(4)
35.	I feel inadequate	(1)	(2)	(3)	(4)
36.	I am content	(1)	(2)	(3)	(4)
37.	Some unimportant thought runs through my mind and bothers me	(1)	(2)	(3)	(4)
38.	I take disappointments so keenly that I can't put them out of my mind	(1)	(2)	(3)	(4)
39.	I am a steady person	(1)	(2)	(3)	(4)
40.	I get in a state of tension or turmoil as I think over my recent concerns and interests	(1)	(2)	(3)	(4)

Appendix D: Positive and Negative Affect Scale

PANAS

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you have these feelings **RIGHT NOW**. Use the following scale to record your answers:

1	**2**	**3**	**4**	**5**
very slightly or not at all	**a little**	**moderately**	**quite a bit**	**extremely**

1. Guilty_____
2. Scared_____
3. Hostile_____
4. Enthusiastic_____
5. Interested_____
6. Distressed_____
7. Excited_____
8. Upset_____
9. Strong_____
10. Nervous_____
11. Depressed_____
12. Determined_____
13. Attentive_____
14. Jittery_____
15. Active_____
16. Irritable_____
17. Alert_____
18. Ashamed_____
19. Happy_____
20. Proud_____
21. Afraid_____
22. Inspired_____

Appendix E: Word Sentence Association Paradigm for Depression - Stimuli Set

Self-relevant sentence	negative word	benign word
A warm feeling spreads from your stomach to your chest.	Illness	Soup
A friend does not respond when you wave hello.	Mad	Distracted
A friend sets you up on a blind date.	Uncomfortable	Comfortable
You hear a loud noise at night.	Robber	Fireworks
An old friend comments on how you look different now.	Ugly	Attractive
Colleagues found your views unusual.	Weird	Cool
Everyone stops talking when you enter the room.	Mocked	Respected
For a moment you forget where you are.	Going Crazy	Dreamy
People believe you have to think about stuff for a long time.	Stupid	Smart
People judge the speech you just gave.	Dumb	Intelligent
People laugh after something you said.	Embarrassing	Funny
Someone comments on your new outfit at a party.	Hideous	Good-Looking
Someone looks at you as you walk by.	Weird	Cool
Someone you like says hello to you.	Pity	Admire
Sometimes your limbs go numb unexpectedly.	Disordered	Asleep
Suddenly time seems to slow down and everything seems strange to you.	Emergency	Dozing
The air is not clear and you find it hard to see.	Pollution	Fog
The plumber sends you the bill.	Unaffordable	Reasonable
You see no quick exit from this room.	Urgent	Unnecessary
While running errands you feel a hot flash.	Disabled	Summer
You and a classmate accidentally bump into each other.	Embarrassing	Funny
You are at a party with a friend.	Stay close	Venture out
You are far away from your local hospital.	Unprotected	Vacation
You are interviewing for a job.	Boring	Captivating
You are invited to a party.	Avoid	Fun
You are on a first date.	Good-looking	Hideous
You are playing at the beach.	Ugly	Attractive
You are standing next to an attractive person.	Look away	Smile
You are unsure of your test score.	Drop class	Think positive
You begin to tremble when you walk outside.	Faint	Chilly
You cannot fall asleep.	Pills	Relaxation
You cannot find your favorite shirt.	Stolen	Borrowed
You experience a sense of unreality.	Crazy	Daydream
You feel detached from your body.	Death	Meditative
You feel distracted then find that your thoughts are random.	Helpless	Imagination
You feel nauseous.	Get Help	Indigestion
You feel weak.	Breakdown	Tired
You have a change in salary.	Pay cut	Raise
You have several options for places to live.	Stressful	Exciting

You have to throw a party for the office.	Disliked	Well-liked
You have to write an essay about achievements in your life.	Disaster	Success
You hear your name mentioned in a nearby conversation.	Mocked	Respected
You just finished taking an oral exam.	Stupid	Smart
You just got your yearbook pictures back.	Ugly	Attractive
You laugh differently than other people.	Weird	Cool
You notice someone pointing in your direction.	Hideous	Beautiful
You notice your breath is uneven and uncontrollable.	Threat	Laughing
You receive a call from a company you interviewed with.	Rejection	Acceptance
You receive a call from a loan officer.	Declined	Approved
You receive a letter from the IRS.	Owe	Refund
You receive an unexpected grade on your test.	Dumb	Intelligent
You see a big flash of light.	Bomb	Camera
You see a group of people approaching.	Walk away	Greet
You spent too much money.	Worry	Save
You stand up to introduce yourself at a meeting.	Uncomfortable	Comfortable
You take a long time to make decisions about the future.	Confused	Careful
Your advisor examines your schedule for next year.	Worried	Calm
Your bank statement is surprising.	Broke	Wealthy
Your body feels sweaty.	Unwell	Sunny
Your boss calls you into his office.	Avoid	Enter
Your boss wants to meet with you.	Criticize	Praise
Your child does not sleep at home tonight.	Kidnapped	Sleepover
Your Christmas party turns out different than last year.	Disaster	Better
Your classmates are surprised by your project.	Disaster	Success
Your competition is good.	Quit	Try hard
Your face feels moist with sweat.	Frail	Exercise
Your friend asks you to go to a party.	Stay Home	Dance
Your friend comments on your new haircut.	Pity	Admire
Your friend does not call you back.	Upset	Try Later
Your friend does not return your call.	Missing	Vacation
Your friend opens your present and makes a face.	Disappointed	Happy
Your friends are surprised at your painting.	Disliked	Well-liked
Your friends think of you differently after a long road trip.	Boring	Captivating
Your front door is open.	Call police	Close
You notice your money is not here.	Stolen	Bank
Your picture is going to be in the newspaper.	Panicky	Excited
Your stomach has been bothering you today.	Horrible	Manageable
Your taxes are due.	Procrastinate	Get Refund
Your teacher calls on you to answer.	Uncomfortable	Capable
Your teacher wrote many comments on your essay.	Criticize	Praise
Your test will be difficult.	Stress	Study
You are confused because you are thinking about so many things at once.	Hysterical	Make a List

You cannot recall if you locked your car door.	Unsafe	Safe
You cannot remember if you correctly addressed a letter.	Disaster	Deliver
You suddenly think about someone dying.	Responsible	Meaningless
An insect is on your window.	Germs	Small
It is a very hot day and you are on a crowded subway.	Exit	Fan
You get a new coworker in the cubicle next to you.	Avoid	Befriend
You go past a power plant and think you were exposed to radiation.	Panic	Irrational
Several of your friends came to visit you at your house.	Contaminated	Fun
The doctor examined your growth.	Cancer	Weight
You leave the door unlocked.	Break in	Expecting Company
You watch the television news program.	Homicide	Weather
You open the window in your bedroom.	Burglary	Cold
You come home and find a letter in your mailbox.	Collections	Card
The doorman at your apartment building has a package for you.	Eviction	Free Rent
The mailroom at work notifies you that they have a package for you.	Collection Notice	Cookies
When you turn on your computer the screen flashes.	Crashing	Startup
Today is marked on your calendar.	Deadline	Celebration
You cannot roll your car window up.	Broken	Tray
There is a delivery waiting for you when you get to work.	Severance	Flowers
The floor you are walking on is wet.	Flooded	Cleaned
A policeman comes to your door.	Car Accident	Fund-Raising
You are in bed until noon.	Upset	Newspaper
You do not want to get out of bed.	Sad	Comfortable
You do not want lunch.	Nauseous	Big Breakfast
You do not want dinner.	Upset	Big Lunch
Your boss is not happy with your report.	Angry	Bad News
You do poorly on an exam.	Stupid	Bad Luck
You get a bad paper grade.	Dumb	Hard Grader
Your favorite newspaper comic is cancelled.	Weird	New Comics
You want to continue sleeping.	Exhausted	Late Night
You want to take a nap.	Unhappy	Good Game
You go to a bar.	Alone	New People
You go to dinner with friends.	Outcaste	Fun
You are home alone.	Unwanted	Relaxing
You go to a coffee shop alone.	Outcast	Delicious
You watch television.	Sad	Funny
You turn down a party invitation.	Guilty	Busy
You refuse a dinner invite.	Ashamed	Engaged
You get a promotion.	Undeserved	Excited
You listen to an emotional song.	Sob	Smirk
Your boss ignores your input.	Worthless	Distracted

Your friend ignores your advice.	Useless	Stubborn
Someone is talking a cell phone next to you.	Annoyed	Day-Dreaming
You lie awake in bed.	Distressed	Excited
You cannot sleep.	Angry	Delighted
You miss your bus.	Punished	Walk
Your car will not start.	Punitive	Bus
You go out with friends.	Bored	Happy
You visit your family.	Tiresome	Joyful
You have trouble with an assignment.	Helpless	Capable
You are stuck at home by yourself for a week after a surgery.	Incapacitated	Self-Sufficient
You have been asked to take on a new responsibility at work.	Inadequate	Adequate
Someone asks you to help them move to a new house.	Powerless	Powerful
Your parents expect you to vacation with them at home.	Trapped	Free
People are confused by your opinions.	Inferior	Superior
You try to break up an argument.	Ineffective	Effective
Your boss says your report is not what he expected.	Incompetent	Competent
You get a new job.	Unqualified	Qualified
Your car breaks down and you have to ride a bike to work.	Debilitated	Strong
You get only one follow up job interview.	Failure	Successful
You go for a run and stop after one mile.	Defective	Great
You stay home with a loved one instead of going out with friends.	Needy	Independent
You go for a ride on a horse and he starts to gallop.	Out of control	In control
People stare at you while you shop.	Unattractive	Beautiful
Everybody calls to tell you what they are doing.	Alone	Popular
Your friends take you out after your significant other leaves you.	Uncared for	Cared For
People always tell you to smile.	Defective	Loved
You see an attractive person looking at you from across the room.	Loser	Loved
You need help with a report.	Helpless	Capable
You are stuck at home alone with the flu.	Incapacitated	Self-Sufficient
You are asked to start a new project at work.	Inadequate	Adequate
You supervisor is surprised by your report.	Incompetent	Competent
You get a promotion.	Unqualified	Qualified
You want to move your bed but are alone.	Weak	Strong
You sing along to a song.	Vulnerable	Invulnerable
You have only one job interview.	Failure	Successful
You go the gym for a half hour.	Defective	Great
You get an B+ on your exam.	Not good enough	Superb
You are paddling and your canoe starts to tip.	Out of control	In control
People stare at you at a restaurant.	Unattractive	Beautiful

You hear a friend make a joke about you.	Rejected	Accepted
Your friends tell you about a movie they saw together.	Alone	Popular
You are told by your parents about your sister getting married.	Unwanted	Wanted
The project you want is given to a co-worker.	Worthless	Worthy
You hear someone whispering about you.	Different	Special
People tell you to laugh more often.	Defective	Loved
Your parents watch you closely.	Not good enough	Adored
You see an attractive person looking at you in the store.	Loser	Loved

Appendix F: Mixed Effects Multilevel Model Results Tables

Table F1: Mixed Effects Multilevel Model of Pupillary Reactivity Comparing Sentence Only Condition to WSAP-D Conditions

Fixed effect	**Coefficient**		**95% CI**	***p***
Value				
Condition*Group*Time	0.0008	-0.0004, 0.0020	.199	
Condition*Group	-0.0088	-0.0205, 0.0030	.143	
Group*Time	-0.0246	-0.0844, 0.0351	.415	
Condition	0.0131	-0.0026, 0.0288	.102	
Group	0.0894	0.0078, 0.1710	.032	
Time	0.0821	-0.0117, 0.1759	.086	
$Time^2$	-0.0006	-0.0286, 0.0275	.968	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + $Time^2$				
AR1 Diagonal	0.0089	0.0065, 0.0122	<.001	
AR1 Rho	0.2067	-0.031, 0.4229	.086	
Residual	0.0409	0.0391, 0.0430	<.001	
Model Fit				
X^2	-582.99			
AIC	-576.99			
BIC	-558.39			

Table F2: Mixed Effects Multilevel Model of Pupillary Reactivity Comparing Groups on Sentence Only Condtion

Fixed effect	**Coefficient**		**95% CI**	***p***
Value				
Group*Time	-0.0137	-0.0874, 0.0601	.713	
Group	0.0817	-0.0218, 0.1851	.121	
Time	0.0721	-0.0443, 0.1885	.223	
$Time^2$	-0.0003	-0.0347, 0.0342	.988	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + $Time^2$				
AR1 Diagonal	0.0134	0.0096, 0.0186	<.001	
AR1 Rho	0.3738	0.1387, 0.5689	.001	
Residual	0.0113	0.0095, 0.0133	<.001	
Model Fit				
X^2	-38.01			
AIC	-32.01			
BIC	-20.04			

Table F3: MDD Group Mixed Effects Multilevel Models Comparing of Pupillary Reactivity Between Sentence Only Condition and WSAP-D Benign Interpretation Conditions

Model Including All Conditions within MDD Group

Fixed effect	**Coefficient**		**95% CI**	***p***
Value				
Condition	0.0083	0.0012, 0.0155	.022	
Time	0.0594	0.0123, 0.1065	.014	
$Time^2$	-0.0021	-0.0464, 0.0423	.925	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + $Time^2$				
AR1 Diagonal	0.0111	0.0072, 0.0171	<.001	
AR1 Rho	0.1694	-0.1620, 0.4665	.307	
Residual	0.0429	0.0401, 0.0458	<.001	
Model Fit				
X^2	-209.27			
AIC	-203.27			
BIC	-186.69			

Model Comparing Sentence Only and Benign Endorsement Conditions

Fixed effect	**Coefficient**		**95% CI**	***p***
Value				
Condition	0.0026	-0.0102, 0.0492	.501	
Time	0.0693	0.0119, 0.1267	.019	
$Time^2$	-0.0028	-0.0549, 0.0492	.913	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + $Time^2$				
AR1 Diagonal	0.0151	0.0095, 0.0241	<.001	
AR1 Rho	0.4032	0.0690, 0.6560	.008	
Residual	0.0333	0.0296, 0.0375	<.001	
Model Fit				
X^2	-11.87			
AIC	-5.87			
BIC	-7.40			

Table F3 Continued:

Model Comparing Sentence Only and Negative Rejection Conditions

Fixed effect	**Coefficient**		**95% CI**	***p***
Value				
Condition	-0.0507	-0.0822, -0.0191	.002	
Time	0.0557	0.0073, 0.1041	.025	
Time^2	-0.0016	-0.0429, 0.0396	.938	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + Time^2				
AR1 Diagonal	0.0096	0.0062, 0.0147	<.001	
AR1 Rho	0.1773	-0.1644, 0.4810	.299	
Residual	0.0356	0.0316, 0.0400	<.001	
Model Fit				
X^2	1.72			
AIC	7.72			
BIC	20.99			

Model Comparing Sentence Only and Benign Rejection Conditions

Fixed effect	**Coefficient**		**95% CI**	***p***
Value				
Condition	-0.0041	-0.0074, 0.0156	.484	
Time	0.0515	-0.0016, 0.1046	.057	
Time^2	-0.0014	-0.0468, 0.0439	.949	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + Time^2				
AR1 Diagonal	0.0115	0.0074, 0.0180	<.001	
AR1 Rho	0.2955	-0.0506, 0.5783	.074	
Residual	0.0426	0.0379, 0.0479	<.001	
Model Fit				
X^2	114.67			
AIC	120.67			
BIC	133.95			

Table F4: HC Group Mixed Effects Multilevel Models Comparing of Pupillary Reactivity Between Sentence Only Condition and WSAP-D Negative Interpretation Conditions

Model Including All Conditions within HC Group

Fixed effect	**Coefficient**		**95% CI**	***p***
Value				
Condition	0.0036	-0.0034, 0.0106	.314	
Time	0.0376	-0.0016, 0.0768	.060	
$Time^2$	0.0010	-0.0350, 0.0370	.955	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + $Time^2$				
AR1 Diagonal	0.0069	0.0044, 0.0110	<.001	
AR1 Rho	0.2520	-0.1031, 0.5501	.144	
Residual	0.0390	0.0365, 0.0417	<.001	
Model Fit				
X^2	-386.06			
AIC	-380.06			
BIC	-363.61			

Model Comparing Sentence Only and Negative Endorsement Conditions

Fixed effect	**Coefficient**		**95%CI**	***p***
Value				
Condition	0.0060	-0.0044, 0.0164	.256	
Time	0.0342	-0.0048, 0.0731	.084	
$Time^2$	0.0015	-0.0338, 0.0367	.933	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + $Time^2$				
AR1 Diagonal	0.0066	0.0042, 0.0105	<.001	
AR1 Rho	0.1641	-0.1962, 0.4773	.350	
Residual	0.0148	0.0131, 0.0167	<.001	
Model Fit				
X^2	-489.66			
AIC	-483.66			
BIC	-470.52			

Table F4 Continued

Model Comparing Sentence Only and Benign Rejection Conditions

Fixed effect	**Coefficient**		**95% CI**	***p***
Value				
Condition	0.0186	0.0061, 0.0311	.004	
Time	0.0316	-0.0224, 0.0857	.248	
$Time^2$	0.0018	-0.0431, 0.0468	.935	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + $Time^2$				
AR1 Diagonal	0.0107	0.0067, 0.0172	<.001	
AR1 Rho	0.3544	0.0060, 0.6260	.029	
Residual	0.0482	0.0427, 0.0543	<.001	
Model Fit				
X^2	174.16			
AIC	180.16			
BIC	193.30			

Model Comparing Sentence Only and Negative Rejection Conditions

Fixed effect	**Coefficient**		**95% CI**	***p***
Value				
Condition	0.0173	-0.0140, 0.0486	.279	
Time	0.0424	0.0047, 0.0802	.028	
$Time^2$	0.0008	-0.0273, 0.0289	.954	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + $Time^2$				
AR1 Diagonal	0.0042	0.0026, 0.0068	<.001	
AR1 Rho	0.2998	-0.1380, 0.5419	.202	
Residual	0.0335	0.0298, 0.0378	<.001	
Model Fit				
X^2	-66.42			
AIC	-60.42			
BIC	-47.28			

Table F5: Mixed Effects Multilevel Model of Pupillary Reactivity Comparing Sentence Only Condition to Negative Rejection Condition Between Groups

Fixed effect	**Coefficient**		**95% CI**	***p***
Value				
Condition*Group	0.0680	0.0236, 0.1124	.003	
Condition	-0.1186	-0.1884, -0.0489	.001	
Group	-0.2626	-0.4731, -0.0521	.015	
Time	0.0492	0.0187, 0.0797	.002	
$Time^2$	-0.0004	-0.0250, 0.0241	.973	
Random effect	**Variance Component**	**95% CI**	***p* Value**	
Intercept + time + $Time^2$				
AR1 Diagonal	0.0068	0.0050, 0.0093	<.001	
AR1 Rho	0.2048	-0.0439, 0.4295	.096	
Residual	0.0346	0.0318, 0.0376	<.001	
Model Fit				
X^2	-68.28			
AIC	-62.28			
BIC	-46.98			

Table F6: Mixed Effects Multilevel Model of Pupillary Reactivity Comparing Sentence Only Condition to Benign Rejection Condition Between Groups

Fixed effect	**Coefficient**	**95% CI**	***p* Value**
Condition*Group	0.0145	-0.0024, 0.0314	.093
Condition	-0.0104	-0.0370, 0.0162	.443
Group	0.0088	-0.1062, 0.1238	.880
Time	0.0418	0.0049, 0.0787	.027
$Time^2$	0.0002	-0.0304, 0.0307	.992
Random effect	**Variance Component**	**95% CI**	***p* Value**
Intercept + time + $Time^2$			
AR1 Diagonal	0.0106	0.0077, 0.0145	<.001
AR1 Rho	0.3243	0.0870, 0.5268	.004
Residual	0.0452	0.0416, 0.0491	<.001
Model Fit			
X^2	242.65		
AIC	260.65		
BIC	306.57		

Table F7: Mixed Effects Multilevel Model of Pupillary Reactivity to Sentence Across All Trials

MLM with Interaction Effect

Fixed effect	**Coefficient**	**95% CI**	***p* Value**
Condition*Group	-0.0084	-0.0237, 0.0069	.281
Condition	0.0157	-0.0083, 0.0397	.200
Group	0.0879	0.0112, 0.1646	.025
Time	-0.1202	-0.2083, -0.0321	.008
$Time^2$	0.0277	-0.0008, 0.0561	.057
Random effect	**Variance Component**	**95% CI**	***p* Value**
Intercept + time + $Time^2$			
AR1 Diagonal	0.0041	0.0026, 0.0064	<.001
AR1 Rho	0.4092	0.1121, 0.6392	.003
Residual	0.0318	0.0292, 0.0346	<.001
Model Fit			
X^2	-427.13		
AIC	-421.13		
BIC	-405.84		

MLM with Main Effects Only

Fixed effect	**Coefficient**	**95% CI**	***p* Value**
Condition	0.0032	-0.0044, 0.0108	.414
Group	0.0646	0.0004, 0.1288	.049
Time	-0.1202	-0.2083, -0.0321	.008
$Time^2$	0.0277	-0.0008, 0.0561	.057
Random effect	**Variance Component**	**95% CI**	***p* Value**
Intercept + time + $Time^2$			
AR1 Diagonal	0.0041	0.0026, 0.0064	<.001
AR1 Rho	0.4092	0.1121, 0.6392	.003
Residual	0.0318	0.0293, 0.0346	<.001
Model Fit			
X^2	-433.84		
AIC	-427.84		
BIC	-412.54		

Table F8: Mixed Effects Multilevel Model of Pupillary Reactivity Between Groups Across WSAP-D Conditions

Fixed effect	**Coefficient**	**95% CI**	***p* Value**
Group*Valence	-0.0377	-0.0657, -0.0096	.009
Response*Valence	0.0324	0.0043, 0.0605	.024
Valence	0.0423	-0.0187, 0.1033	.174
Response	-0.0690	-0.1134, -0.0246	.002
Group	0.1143	0.0290, 0.1995	.009
Time	0.0484	0.0192, 0.0776	.001
$Time^2$	-0.0006	-0.0272, 0.0260	.964
Random effect	**Variance Component**	**95% CI**	***p* Value**
Intercept + time + $Time^2$			
AR1 Diagonal	0.0080	0.0059, 0.0110	<.001
AR1 Rho	0.1982	-0.0430, 0.4175	.097
Residual	0.0415	0.0395, 0.0437	<.001
Model Fit			
X^2	-427.34		
AIC	-421.34		
BIC	-403.10		

Table F9: Mixed Effects Multilevel Model of Pupillary Reactivity Between Groups Within Endorsement Trials

Fixed effect	**Coefficient**	**95% CI**	***p* Value**
Group*Valence	-0.0508	-0.0808, -0.0209	.001
Valence	0.0943	0.0473, 0.1413	<.001
Group	0.1582	0.0705, 0.2458	<.001
Time	0.0544	0.0255, 0.0833	<.001
$Time^2$	-0.0011	-0.0270, 0.0247	.930
Random effect	**Variance Component**	**95% CI**	***p* Value**
Intercept + time + $Time^2$			
AR1 Diagonal	0.0076	0.0055, 0.0104	<.001
AR1 Rho	0.2553	0.0100, 0.4717	.033
Residual	0.0236	0.0219, 0.0253	<.001
Model Fit			
X^2	-822.21		
AIC	-816.21		
BIC	-800.05		

Table F10: Mixed Effects Multilevel Model of Pupillary Reactivity Between Groups Within Rejection Trials

Fixed effect	**Coefficient**	**95% CI**	***p* Value**
Group*Valence	-0.0245	-0.0706, 0.0216	.298
Valence	0.0874	0.0150, 0.1598	.018
Group	0.0600	-0.0541, 0.1743	.302
Time	0.0424	0.0102, 0.0745	.010
$Time^2$	<-0.0000	-0.0253, 0.0252	.995
Random effect	**Variance Component**	**95% CI**	***p* Value**
Intercept + time + $Time^2$			
AR1 Diagonal	0.0072	0.0052, 0.0099	<.001
AR1 Rho	0.2088	-0.0436, 0.4362	.094
Residual	0.0559	0.0520, 0.0600	<.001
Model Fit			
X^2	482.74		
AIC	488.74		
BIC	504.90		

Appendix G: Correlations Between Behavioral Data and Pupillary Reactivity

Table G1: Bivariate Correlations between WSAP-D Indices and Pupillary Reactivity

	Baseline Relative Pupillary reactivity time point (ms from trial start)								
WSAP-D Index	500	1000	1500	2000	2500	3000	3500	4000	4500
Neg End Rate	-.286	-.232	-.184	-.211	-.235	-.254	**-.317***	**-.343***	**-.354***
Ben End Rate	.162	.104	.118	.181	.232	.251	.217	.221	.237
Neg End RT	.184	.102	.030	-.002	.016	.017	.009	.077	.093
Neg Rej RT	.148	.081	.042	.013	.043	.030	-.010	.054	.065
Ben End RT	.103	.032	-.036	-.062	-.011	.012	.002	.080	.078
Ben Rej RT	.163	.108	.060	.039	.065	.064	.042	.105	.106

Bivariate correlations between Word Sentence Association Paradigm for Depression (WSAP-D) interpretation bias indices and pupillary reactivity outcome measure. * indicates statistical significance of < .05. Neg End Rate = Negative Endorsement Rate; Ben End Rate = Benign Endorsement Rate; Neg End RT = Negative Endorsement Reaction Time; Neg Rej RT = Negative Rejection Reaction Time; Ben End RT = Benign Endorsement Reaction Time; Ben Rej RT = Benign Rejection Reaction Time.