THE IMPORTANCE OF PSYCHIATRIC MEDICATION HISTORY: THE ROLE OF TRAIT WORRY IN THE STARTLE REFLEX TO THREAT

by
BAHIRE BÜŞRA TEMUR

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Approved by:

Assoc. Prof. ROBERT W. BOOTH .....
(Thesis Supervisor)

Prof. FEYZA ÇORAPÇI .....

Assoc. Prof. AYŞE ALTAN ATALAY .....

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ABSTRACT

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BAHIRE BÜŞRA TEMUR

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Thesis Supervisor: Assoc. Prof. Robert W. Booth

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Worry is an uncontrollable, persistent thinking pattern involving negatively loaded "what if" scenarios. Worry is conceptualized as heightened anticipation of future events. However, psychophysiological studies of worry regarding its function in the face of threat anticipation and uncertainty have indicated inconsistent findings, raising the importance of studying additional variables that might explain the results. This study investigated the role of psychiatric medication history in the association between trait worry and startle reflexes to different degrees of threats. In the current study, university students (n = 65) completed the Threat Probability Task (TPT), which manipulates the occurrence of probability while featuring certain threats (100% chance of electric shock), uncertain threats (20% chance of electric shock), safety conditions, and startle reflexes measured with auditory probes. Self-reported worry tendency was measured using the Penn State Worry Questionnaire (PSWQ), and we collected psychiatric medication history via self-report. Multi-level analysis showed the main effect of threat conditions, a two-way interaction between psychiatric medication history and threat conditions, and a three-way interaction between trait worry, threat conditions, and psychiatric mediation history. Higher worry scores are associated with a blunted startle reflex to uncertain threats, particularly among individuals with a history of psychiatric medication, so that high-worry participants with a history of psychiatric medication did not startle more to uncertain threats than certain threats anymore. Our findings are in line with previous studies indicating that individuals who worry have difficulty coping with uncertainty. This study expanded our knowledge regarding the function of worry in uncertain threat anticipation, considering the clinically relevant participant characteristics.

ÖZET

TEHDİDE KARŞI İRKİLME REFLEKSİ ÜZERİNDE SÜREKLİ ENDİŞENİN ROLÜNDE PSİKOLOJİK İLAÇ GEÇMİŞİNİN ÖNEMİ

BAHİRE BÜŞRA TEMUR

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Anahtar Kelimeler: endişe, irkilme refleksi, psikiyatrik ilaç geçmişi, kesin olmayan tehdit beklentisi, anksiyete

Endişe, olumsuz yüklü "ya olursa" senaryolarını içeren, kontrol edilemeyen, ısrarcı bir düşünce kalıbıdır. Endişe, gelecekteki olaylara ilişkin artan beklenti olarak kavramsallaştırılmaktadır. Ancak, endişenin tehdit beklentisi ve belirsizlik karşısındaki işlevine ilişkin psikofizyolojik çalışmalar tutarsız bulgular ortaya koymuş ve sonuçları açıklayabilecek ek değişkenlerin incelenmesinin önemini artırmıştır. Bu çalışmada, sürekli endişe ile farklı derecelerdeki tehditlere karşı irkilme refleksleri arasındaki ilişkide psikiyatrik ilaç geçmişinin düzenleyici rolü araştırılmıştır. Bu çalışmada, üniversite öğrencileri (n = 65) kesin tehditler (%100 elektrik şoku ihtimali), belirsiz tehditler (%20 elektrik şoku ihtimali), ve güvenli durumlardan oluşan ve işitmeye dayalı irkilme reflekslerini ölçen Tehdit Olasılığı Görevini tamamladılar. Sürekli endişe, Penn State Endişe Ölçeği (PSWQ) kullanılarak ölçülmüş ve katılımcılardan psikiyatrik ilaç geçmişi öz bildirim yolu ile toplanmıştır. Çok düzeyli analiz sonucunda, tehdit durumlarının ana etkisini, psikiyatrik ilaç geçmişi ile tehdit durumları arasında iki yönlü etkileşimi ve sürekli endişe, tehdit durumları ve psikiyatrik aracılık geçmişi arasında üç yönlü etkileşim bulunmuştur. Daha yüksek endişe puanları, özellikle psikiyatrik ilaç geçmişi olan bireyler arasında belirsiz tehditlere karşı azalmış bir irkilme refleksi ile ilişkilidir, böylece psikiyatrik ilaç geçmişi olan yüksek endişeli katılımcılar artık belirsiz tehditlere karşı belirli tehditlerden daha fazla irkilmemiştir. Bulgularımız, endişe duyan bireylerin belirsizlikle başa çıkmakta güçlük çektiğini gösteren önceki çalışmalarla uyumludur. Bu çalışma, endişenin belirsiz tehdit beklentisi üzerindeki işlevi hakkındaki bilgilerimizi katılımcıların klinik özelliklerini de hesaba katarak genişletmiştir.

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To my loved ones
and people who suffer from chronic worry

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1. INTRODUCTION

Worry is a negative, future-oriented thinking pattern that everyone can experience in various live domains. Even though it involves unpleasant and stressful elements, worry is defined as an operation system of the brain to solve possible, uncertain, or threatening issues to keep organisms attentive by motivating individuals to act on the problems (Davey et al. 1996; Sweeny and Dooley 2016). However, its benefits for organisms disappear when it becomes pathological worry, which refers to uncontrollable, sustained chains of thoughts and images that cause discomfort and distress (Borkovec and Inz 1990). Pathological worry is one of the contributing elements of several anxiety disorders, particularly the hallmarks of generalized anxiety disorder (GAD). Pathological worriers always create what-if scenarios for their uncertain future and try to find several ways to solve those possible problems, even if the probability of those events happening is very low. Researchers have created several studies and models to capture the functional role of worry and how it contributes to the maintenance of anxious cycles in anxiety disorders using physiological and neurological tools such as skin conductance, heart rate variability, and electroencephalography. Due to the complex nature of worry, there are inconsistencies in their findings, which makes it hard to create necessary interventions for anxiety disorders. Therefore, the primary aim of this study is to expand our knowledge regarding worry using a more emotionally dynamic measure called the startle reflex. This measure allows us to capture the defensive motivational system through a task called the Threat Probability Task (TPT), which manipulates the occurrence dimension of uncertainty. In this way, we might capture how worry functions while anticipating different degrees of threat, considering the role of previous psychiatric mediation in this relationship. In other words, we investigated whether there is an association between worry and startle reflex measured by auditory probes while anticipating different threat types (certain, uncertain, safe) and how psychiatric medication history affects this relation. Hence, trait worry affects the response of individuals with medication histories to uncertain threat conditions.

1.1 History of Worry Studies

Worry is an active cognitive process derived from an old Germanic verb called wurgjan, meaning to strangle or choke in English, emphasizing its uncomfortable and suffocating nature (Crocq, 2015). Systematic studies of worry as a psychological phenomenon were not frequent due to the broader concept of anxiety until Breznitz's (1971) paper emphasized the importance of studying worry in understanding fear and anxiety. According to Breznitz, worry starts when an external threat with possible future outcomes contacts the anxiety-provoking incidents. Later, Borkovec and colleagues (1983) investigated the nature of worry and claimed that worry is a future-oriented, uncontrollable, and persistent chain of thoughts or images about various life domains that cause discomfort and distress. According to Borkovec and colleagues, worry is a cognitive aspect of anxiety, and it functions as an attempt to solve the problem regarding an issue with uncertain and threat-related outcomes.

1.2 Physiological Characteristics and Function of Worry

The role of worry in understanding anxiety and fear processing has gained interest in recent years. Earlier studies defined worry as a distinctive characteristic of generalized anxiety disorder (GAD), which is considered one of the least successfully treated anxiety disorders (Rodriguez et al. 2006). However, its significance extends beyond its role in GAD; studies also indicate that worry is a continuous dimension and cardinal feature of anxiety disorders, including social anxiety disorder, panic disorders, and panic disorders with agoraphobia (Ruscio et al. 2001; Starcevic et al. 2007). Given its broad influence, various studies have proposed models for the functions of worry on the development and maintenance of anxiety disorders, particularly GAD, as a persistent negative emotional state over time.

To understand how worry functions in the face of stressors and contributes to anxiety disorder, researchers have conducted varied studies using physiological measures such as heart rate, skin conductance, and the startle reflex. Earlier studies on the physiological characteristics of worry demonstrated that worry inductions lead to a decrease in peripheral physiology. In the first experimental study on the role of worry on emotional processing by Borkovec and Hu (1990), individuals with high speech anxiety who engaged in worry before performing a speech displayed decreased heart rate responses compared to those in relaxation or a neutral condition, even

though there was no cardiovascular response difference in the thinking period.

Moreover, Borkovec and colleagues (1983) found a negative correlation between the amount of time spent worrying in the face of fearful images and cardiac reactivity, indicating poor emotional processing in worriers, raising the possibility that worry might not be an efficient conceptual framework for the processing of emotional materials. Building upon these foundational investigations, Borkovec (1994) developed a well-known cognitive avoidance model. This model emphasizes the verbal nature of worry and describes its role as a cognitive avoidance or coping mechanism enabling individuals to direct their attention away from distressing uncertain situations or images, resulting in a short period of relief through dampening physiological arousal and negative affect to those stimuli. According to this model, when people are immersed in worry while processing affective materials, they are less likely to process emotions associated with those materials, which contributes to the maintenance of anxiety by hindering the emotional processing of feared materials. The basic idea behind the maintenance of anxiety is the entire emotional processing is necessary for the habituation and extinction of anxiety responses in the long term (Borkovec et al. 2004).

Earlier studies on the physiological characteristics of worry demonstrated a decrease in peripheral physiology, such as heart rate variability and skin conductance(Borkovec et al. 1993; Brosschot et al. 2007; Hoehn-Saric et al. 1989; Thayer et al. 1996). Besides, Hoehn-Saric et al. 's study (2004) found decreased skin conductance levels in chronic worriers in a daily monitoring study, suggesting that worry may indeed have a dampening impact on negative affective states (Hoehn-Saric et al. 2004).

Even though this model contributes to the understanding of the role of worry in the maintenance of anxiety disorders, later studies employing various physiological measures have concluded that worry does not dampen physiological arousal. It increases arousal in the the sympathetic nervous system by activating the defensive circuits and gives priority to cognitive and behavioral programs to deal with detected threats, rather than eliciting an autonomic, rigid response to stressors (Newman and Llera 2011; Steinfurth et al. 2017; Stapinski et al. 2010). Also, Davis and colleagues (2002) criticized the autonomic rigidity and decreased heart rate results of Borkovec and colleagues (1990), which found increased heart rates and no differences in high numbers of worry topics between high levels of worriers and low worriers. Put differently, participants who engaged in worry before exposing emotional stimuli showed elevated sympathetic nervous system activity such as heart rate, skin conductance, cortisol levels, and corrugator muscle activities. Simultaneously, they experience a

decrease in parasympathetic nervous system activity like heart rate variability and sinus arrhythmia. These studies have emphasized the importance of clarification between the mechanisms of worry, threat, and emotional processing.

To clarify the role of worry on emotional response, Newman and Llera (2010) conducted a study with chronic worriers and non-worriers in which researchers measured baseline levels of negative emotionality and induction of worry and exposed them to watching various emotional clips. They found that individuals with chronic worry already had high levels of negative emotionality rather than decreases in negative emotionality; they showed sustained negative emotionality throughout emotional processing, emphasizing the distinct role of worry in processing emotional materials rather than no processing of emotions.

In line with these results, Newman and Llera (2011) proposed a new framework for the worry function called the Contrast Avoidance Model (CAM), suggesting that worry functions as the avoidance of emotional shifts rather than emotional reactivity or experience. This model claims that individuals with high worry fear emotional shifts from positive to negative emotions, as they may be caught off guard and unprepared for possible threats. Therefore, they engage in chronic distress to prepare for the worst possible outcomes and maintain a state of hypervigilance for potential threats. CAM also suggests that worrying regarding potential threats increases physiological reactivity to a certain degree and hinders an additional increase in emotional reactivity in the face of stressors. Based on the cognitive psychology theory called affective contrast (Bacon et al. 1914), it suggests that the effect of emotional experiences is dependent on previous emotional experiences and how much contrast the emotions have. Therefore, if people experience unpleasant emotions after pleasant emotions, they experience these emotions as more unpleasant. Based on this theory, Newman and Llera (2011) suggest that individuals with chronic worry are overwhelmed by negative emotional contrasts and sustain their negative emotionality to avoid these contrasts. Recent studies have found supporting evidence for the contrast avoidance nature of worry, such that worry led to anxious activations in brain areas associated with emotional processing, along with potentiated startle responses and skin conductance, which are indicators of defensive activation and sustained activations in emotional brain areas (Steinfurth et al. 2016).

Although many studies use physiological measures to investigate the physiological correlates of worry induction in the face of imminent threats, these studies did not consider some essential elements. For instance, understanding human responses to emotional stimuli also necessitates investigating how chronic worry, defined as a sustained and generalized reaction to non-specific cues, alters the processing of phasic

threats (fear) and anxiety. Chronic worriers might engage in different strategies and defensive responses while processing contextual fear and anxiety, especially when the contextual fear is uncertain compared to realistic threats. Uncertainty refers to the probability of a particular outcome being unknown. Individuals can find anticipating those events intolerable and might be prone to worry (Dugas et al. 2004). Due to this close link between uncertainty and worry, studying chronic aversive anticipation of chronic worries in the face of different degrees of threats using an emotionally dynamic experimental setting and physiological measures might better capture its nature in threat processing.

1.3 Startle Reflex

The startle reflex is a contraction of eye muscles, an indicator of an early stage of defensive cascades in the autonomic nervous system when organisms encounter danger. It is an exceptional tool to investigate emotion processing, especially how humans engage with threats. The startle measures have several advantages, allowing researchers to rapidly monitor necessary information beforehand, during, and following the emotional processing, unlike electrodermal activity measures (Grillon 2002). Also, its neural circuitry is well-defined, enabling scientists to distinguish different patterns of activities and their associated pathways. While the startle reflex pathway is initiated by a loud acoustic probe (fear-potentiation) in the nucleus reticularis pontis caudalis and modulated by the central-medial amygdala, startle potentiation due to chronic stress or anxiety is found to be associated with another pathway called the bed nucleus of the stria terminalis by secretion of corticotropin-releasing hormone (Lee and David 1997; Liang et al. 1992). Studying startle reflexes in different emotional contexts has gained interest due to its link with a perception of cue and threat responding. This research area enables researchers to identify indicators of maladaptive threat responses in individuals to external or internal occurrences.

1.4 Modulation of Startle Reflex by Experimental Tasks

Due to the defensive nature of the startle reflex, which is modulated by a variety of sources such as darkness, emotional pictures, verbal threats, electric shocks, and auditory probes (Grillon and Bass 2003), experimenters designed their experimental tasks with great care to control confounding variables which might affect results.

Studies investigating threat-responding have focused on the manipulation of uncertainty (temporal predictability or occurrence of threat), defined as the inability to foresee the likelihood, intensity, or duration of future stimulus (Carleton 2012), which enables researchers to monitor maladaptive anticipation of potential uncertain threats and physiological responses (e.g., fight or flight).

One of the most popular tasks was the no-threat, predictable threat, and unpredictable threat (NPU task), which differentiates a predictable threat from an unpredictable threat by manipulating temporal predictability. This task consists of three types of trials: no-threat (safe from aversive stimuli), predictable threat (cues associated with aversive stimuli), and unpredictable threat (aversive stimuli can be delivered). Researchers have selected the aversive stimulus as electric shocks or developmentally and ethically appropriate stimulus types (air blast, female scream), depending on the study population (Schmitz and Grillon 2012). Increased startle reactivity in predictable threat conditions is called phasic fear and is hypothesized to be associated with fear-based psychopathologies, whereas elevated startle responses in unpredictable threat conditions are called sustained anxiety and are linked with anxiety-based psychopathologies.

Another task called the Threat Probability Task (TPT) manipulates the probability of the threat while holding other dimensions of uncertainty constant, enabling a smooth interpretation of the results (Bradford et al., 2014). TPT includes three conditions. A safe condition has 0% chance of aversive stimuli; an uncertain condition has a 20% chance to contain aversive stimuli within trials; and a certain condition has a 100% chance to deliver aversive stimuli. This task uses electric shocks as aversive stimuli. Studies investigating the threat response using these tasks indicated that uncertain threats elicit more defensive responses, suggesting that uncertainty is a necessary feature of threat anticipation (Bennet et al., 2018).

1.5 Worry and Startle Reflex to Threat

Few studies have investigated the potential link between worry and threat responses across various threat conditions. These studies yielded mixed results in both clinical and non-clinical samples. Some studies focused on GAD characterized by excessive worry, showed no effect of worry on startle responses to uncertain threats (Grillon et al. 2009; Gorka et al. 2017).

A study by Grillon and colleagues (2009) investigated the startle responses of indi-

viduals with GAD to threats. They found that individuals with GAD did not show heightened startle responses to uncertain threats delivered by air blasts to the neck of participants. They explained their findings with two explanations: individuals with GAD might be sensitive to uncertainty; however, aversive stimuli (air blast) might not be efficient for measuring their sensitivity to uncertain threats due to their high threshold for abnormal responding. Another explanation is that the nature of anxiety within the GAD might be different from other anxiety disorders due to its linguistic nature, enabling individuals to cope with anxiety-provoking situations. Likewise, Gorka and colleagues' study (2017) failed to find an association between GAD and startle response to uncertain threats, emphasizing the studying possible moderating factors for this relationship.

In contrast, a study by Grillon et al. (2017) compared the startle responses of different groups, such as individuals with GAD, social anxiety disorder (SAD), panic attacks (PA), and healthy controls. This study showed that individuals with GAD showed an elevated startle response in uncertain threat conditions compared to healthy controls, along with heightened baseline startle reactivity, reflecting the oversensitivity of the GAD sample to a perception of threats and exaggerated anticipatory anxiety in the threat-related context.

On the other hand, Rutherford et al. (2020)'s study investigated the role of chronic worry in startle reflex in individuals with and without anxiety disorder history and found that worry is associated with an attenuated startle response to uncertain threats, particularly among individuals with a history of anxiety disorder, emphasizing the importance of studying clinical diagnosis status in understanding the chronic worry and threat responses. Similarly, Nelson et al. (2015) investigated the effect of cognitive concerns, which is strongly linked to worry and GAD symptoms (Wheaton et al.2012), on threat response in the student population and demonstrated that cognitive concern is associated with decreased startle response in uncertain threat conditions. Thus, individuals with high levels of cognitive concern might engage in experiential avoidance (i.e., worry or rumination), defined as avoidance avoidance-orientated thinking patterns enabling individuals to refrain from aversive experiences and feelings, leading to a decrease in their anxiety regarding the anticipation of threat.

Research on non-clinical samples also yielded mixed results. Nelson and Sharmank's (2011) study showed that individual differences in trait worry levels are not associated with startle responses in uncertain conditions. Similarly, Bennett et al. (2018) found no association between worry levels and startle responses across threat conditions. In contrast, Carsten et al. (2023) found that trait-level worry is associated

with elevated startle responses in uncertain conditions compared to certain and safe threat conditions.

Therefore, clinical and subclinical studies on the association between worry and startle responses are inconsistent, raising the importance of further examination regarding the physiological correlates of worry. While previous studies have explored the relationship between worry and threat response, they have primarily sampled participants with no history of psychiatric medication and have not adequately addressed the possible role of previous psychiatric medication usage. However, the use of psychiatric medication might moderate the effect of peripheral physiology, resulting in heterogeneous study findings in the literature, especially in clinical studies. Psychiatric medication history, especially usage of serotonin reuptake inhibitors, might be closely linked to startle modulation. The serotonergic synapses are densely located in limbic regions like the amygdala and bed nucleus of the stria terminalis, which play essential roles in anxious responses (Davis 1998). When individuals startle to aversive stimuli, they also show activations in the amygdala and bed nucleus of the stria terminalis that are highly concentrated with serotonergic neurons. Therefore, participants who previously used serotonin-related medication might show distinct responses to aversive stimuli compared to individuals with no medication history.

1.6 Startle Reflex and Antidepressants

Serotonin is a monoamine neurotransmitter that has a significant role in the physiological function of the brain by sending afferents to stress-sensitive limbic structures like the hippocampus, which plays an essential role in anxiety disorders (Segi-Nishida 2017). The serotonin system is an essential structure that sends projections to different brain parts. The Deakin/Griffin hypothesis proposes that different aversive stimuli trigger serotonergic pathways. These serotonergic structures send unique projections to either the forebrain or brain stem structures to form adaptive responses to threatening occurrences (Deakin and Graeff 1991). For instance, serotonergic neurons in the dorsal raphe nucleus's dorsal parts project to the limbic structures of the forebrain that play roles in anxiety-related stress responses. Also, serotonergic neurons in the lateral parts of the dorsal raphe nucleus play a significant role in inhibitory control regarding fight or flight responses. Dysfunction in serotonergic systems leads to the development of anxiety disorders. Doctors have started to prescribe medications that affect serotonin, like serotonin reuptake inhibitors (SSRI), which have gained significant interest as anxiety and depression

treatments due to their fewer side effects compared to earlier antidepressant medications. A study in rodents found that SSRI usage increases the neurogenesis of hippocampal cells, which affects stress-related hormones like corticosterone and is sufficient to dampen acute stress-related anxiety (Hill et al. 2015). However, there is no effect of hippocampal cells' neurogenesis on hypothalamus-pituitary-adrenal regulation, which is associated with chronic stress reactions and anxiety (Herman et al. 2016). Also, studies on rodents showed that alterations in serotonin levels in the brain affect the startle response of the animals, like decreasing habituation —repeated exposure to the acoustic probes, and decreasing sustained fear responses in startle studies, corresponding to anxious responses (Davis et al. 2010; Koch, 1999; Nanry and Tilson 1998).

Studies on humans are scarce. These studies have mainly focused on current serotonin reuptake inhibitor treatments (SSRI) and measured using acoustic probes rather than mild levels of threats. Quednow et al. (2003) investigated the effect of SSRI and serotonin and norepinephrine reuptake inhibitors (SNRI) on startle modulation in individuals with depressive symptoms within the first two weeks of treatment. The findings showed that none of the medications affected startle modulation in individuals, even though they were associated with improvements in mood. Grillon et al.'s study (2007) investigated the impact of SSRI use on threat response across threat conditions with a healthy sample. The finding suggested that a single usage of SSRI heightened the startle magnitudes in uncertain and certain threat conditions in the healthy sample. They explained their findings that acute usage of SSRI affects the motivational system, especially cortical, behavioral, and physical responses to emotionally aversive stimuli.

Thus, existing literature on the relation between SSRI use and startle reflex primarily focused on current medication use during the experiment. To the best of our knowledge, no study has investigated the moderating effect of medication history on the relationship between worry and threat response.

1.7 Overview of Current Research

As stated before, in this study, we investigated the effect of trait worry on the startle reactivity to different degrees of threats, considering the role of previous psychiatric medication history. The importance of our study is as follows:

Even though worry is a significant structure in the maintenance of anxiety disorders

(Olatunji 2010), how worry functions in the face of threats and the physiological correlates of worry have inconsistent findings. Due to worry's complex nature, we decided to study worry, particularly chronic worry and threat perception. To gain a deeper understanding of the function of worry in the face of threats, we use the startle reflex as a measure to dynamically capture emotional sequences and the defensive motivational systems of humans while considering the previous psychiatric medication.

The startle reflex can be affected by numerous factors, including smoking habits, exercise, and darkness. Therefore, studying psychiatric medication history and SSRIs might be vital to understanding the association between trait worry and startle reactivity to threat types. In this way, we aimed to expand our knowledge regarding the role of worry in the maintenance of anxiety disorders, especially in the face of uncertain and threatening situations.

The primary aim of the present study was to investigate, for the first time, whether psychiatric mediation history moderates the association between trait worry and startle reflexes to threat types. We used the TPT to examine the association between trait worry and startle responses to uncertain vs. certain threats and whether there is a difference between individuals with a psychiatric medication history and individuals without a psychiatric medication history in this association. Based on the study by Grillon et al.(2007) on the administration of SSRIs and startle reflex, we hypothesized that startle responses under uncertain threats would be higher in individuals with a medication history when compared to individuals without a medication history. More importantly, based on the mixed findings in the worry literature, we predicted that medication history would moderate the association between worry and startle reactivity to uncertain and certain threats.

Also, we wanted to investigate additional variables, that are closely linked to worry, such as anxiety symptom severity (Beck Anxiety Inventory), probability bias (Judgment Bias), and emotional regulation strategies (Booth and Sharma 2021). Due to their close link, examining these variables might also expand our knowledge regarding the interplay between worry, startle modulation, and psychiatric medication history.

2. METHOD

2.1 Participants

We recruited an initial sample of 100 native Turkish-speaking students at Sabanci University. We asked participants to quit smoking 1.5 hours before the study, and we removed eight individuals given that they reported having a lifetime substance-related condition or a present psychiatric or neurological diagnosis rather than anxiety or depressive disorders. Regarding psychiatric medication history, we included participants who had previously used SSRIs such as fluoxetine, paroxetine, sertraline, and citalopram but omitted those who had used methylphenidate (n = 8). Please keep in mind that all information regarding medication history and current diagnosis was self-reported and not confirmed by medical reports. Non-responders with zero or absent responses for more than two-thirds of the startle reactions in baseline probes were also excluded (n = 21). In addition, we removed those with substantial artifacts from their electromyographic (EMG) data (n = 4). Lastly, we excluded two participants due to an experimenter error (i.e., forgetting to save data). The final sample consisted of 65 participants (40 identified as female). Participants were aged between 18 and 34 (M = 21.92, SD = 2.9). The Sabanci University Research Ethics Council approved the study. We collected informed consent before the study, and participants received course credits for their participation. Table B.1 shows the demographic and clinic characteristics of the participants.

2.2 Procedure

Participants received information about the study procedure and completed questionnaires that assessed trait worry levels, along with additional questionnaires including the Probability Bias Questionnaires, Beck Anxiety Inventory, and Positive

and Negative Affect Schedule. See Appendix for all measures. The study procedure included the TPT, demographic questions (i.e., psychiatric and medication history, smoking habits), and debriefing.

2.3 Measures

2.3.1 Penn State Worry Questionnaire (PSWQ)

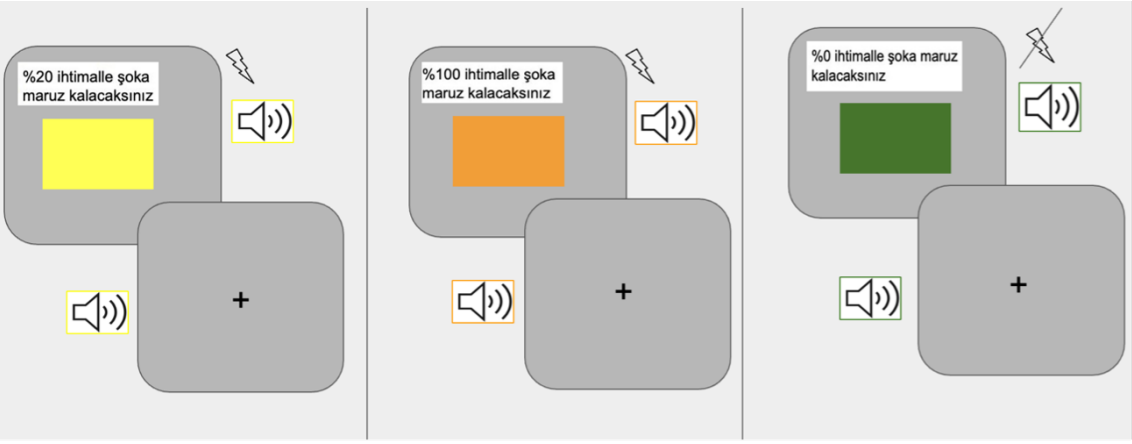
Trait levels of worry were measured using the PSWQ developed by Meyer et al. (1990). A self-reported questionnaire consists of 16 items about different aspects of worry, including excessiveness and uncontrollability. Each item is rated on 5 points Likert scale ranging from 1 (not at all typical) to 5 (very typical of me). The test-retest reliability of PSWQ is r = .90 and Cronbach alpha score is .91 (Meyer et al. 1990). In the present study, the Turkish adaptation of PSWQ, done by Yilmaz et al. (2008) was used with good test-retest reliability (r = .88) and Cronbach alpha ($\alpha = .91$). In the current sample, the PSWQ had excellent internal consistency ($\alpha = .93$)

2.3.2 Task and Stimuli

Participants were seated in front of a 24-inch LCD monitor (Philips 246V5, 1920 x 1080 pixels, 60-Hz refresh rate) at a viewing distance of approximately 60 cm. We utilized the Threat Probability Task (TPT) to assess participants' startle reflexes in the presence of varying threat probabilities. As a threat stimulus, participants may receive calibrated shocks on the forearm's median nerve via a constant-current stimulator (Digitimer, DS7A, Digitimer Ltd., Welwyn Garden City, United Kingdom). The TPT has three conditions: safety, uncertainty (20% of chance), and certainty (100 % of chance).

Threat signals were represented by colored squares (green for safety, orange for certainty, and yellow for uncertainty) that were displayed for 5 seconds, accompanied by written information suggesting the likelihood of an approaching shock. These stimuli were followed by inter-trial intervals (ITI) that ranged from 15 to 20 seconds. In uncertain and certain conditions, shocks were delivered for a millisecond after the 4.5-second presentation of the cues. The task consisted of six blocks. In the task, each condition was shown twice, for a total of 15 trials. Acoustic startle probes (50

Figure 2.1 Threat probability task



milliseconds of 100 dB white noise) were delivered via headphones. Startle probes are given 4 seconds into the cue presentations (8 of 15 trials) in each condition. Besides, startle probes were employed in four of the 15 ITI trials within 13-15 seconds to reduce predictability. However, startle probes in ITIs were not included in the analysis. Also, three startle probes were administered before the beginning of the main task to habituate startle responses, and these probes were not analyzed. We balanced the startle probes across conditions to control the effect of habituation and sensitization in line with the recommendations of Bradford and colleagues (2014).

2.3.3 Baseline Startle Reactivity Assessment

General startle reactivity was measured using a baseline task that included the same visual cues used in the main experiment. However, this task excluded threat- or uncertainty-related texts, as well as aversive stimuli (shocks). This task allowed us to evaluate participants' startle responses to acoustic probes generated by MATLAB software (sampling frequency: 44100 Hz, 0.5 millisecond duration). Acoustic probes were delivered using a headphone amplifier (Behringer MicroAmp HA400) to produce a loudness of 100 dB. Participants wore headphones (Philips SHM1900) while watching visual stimuli that consisted of nine trials with colored square cues and eight ITIs, totaling 17 trials. Startle probes were used for both cue presentations and ITIs.

2.3.4 Shock Calibration

Before beginning the threat probability task, participants underwent a shock calibration procedure. We administered the shocks to the skin above the median nerve of the left forearm, with a pulse length of 1000μs, a maximum current of 10mA, and a voltage of 300V. Due to individual variability in shock sensitivity, participants chose their shock levels, and calibration was accomplished by first delivering a shock with a low intensity of 0.5 mA and then increasing the voltage by 0.5 mA with the subjects' permission until they rated the shock as uncomfortable and unpleasant on a five-point scale ranging from 1- hardly felt, 2- barely noticeable, 3-acceptable, 4- uncomfortable and unpleasant, and 5-painful.

2.3.5 Startle Response Recording and Processing

We cleaned the skin around participants' left eyes and foreheads using water wipes and electrode abrading pads to reduce electrode impedance before attaching two 4 mm Ag/AgCl reusable electrodes underneath the left orbicularis oculi muscle, which enables measuring the EMG activity of eyeblinks, as well as one ground electrode on a small part of their foreheads. The EMG data were acquired using AcqKnowledge 5.0 software (Biopac Systems Inc.) at a sampling rate of 1000 Hz. We filtered the data with a FIR bandpass filter (28–500 Hz) to reduce electrical noise before rectifying it with a 20 ms window. We visually detected the peak startle blink response and measured the maximal peak activity (20-120 ms) after inserting the auditory probe. Also, we calculated eyeblink magnitude by subtracting the mean startle reactivity 50 ms before the acoustic probe from the peak startle response. Trials were visually evaluated for excessive activity between -50 ms and 20 ms during the pre-probe period, and those trials with excessive artifacts were excluded. We included trials with no startle responses in the analysis to calculate the average startle response (Blumenthal et al. 2005). However, participants with zero or missing activity on more than two-thirds of the 17 probes in the baseline task were called non-responders, and excluded from the data (Carsten et al. 2022; Kuhn et al. 2020).

2.3.6 Additional Materials for Exploratory Purposes

2.3.6.1 Judgement bias questionnaire

Probability bias was assessed using the version of the Judgment Bias Questionnaire based on the study of Booth and Sharma (2020). A self-report questionnaire is composed of 20 items, including ten negative and ten positive life events, and asks, "What is the probability of this happening to them?" via rating on a 7-point Likert scale ranging from 1 (would not happen to me) to 7 (would definitely happen to me). Booth and Sharma (2020) did not report formal psychometric testing but found good internal consistency and significant correlations between anxiety and depression, emphasizing that their questionnaire is valid. The probability score was calculated by subtracting the mean score of negative event probability ($\alpha = .76$) from the mean score of positive event probability ($\alpha = .83$).

2.3.6.2 Beck anxiety inventory (BAI)

Clinical-level anxiety was measured using the Beck Anxiety Inventory (BAI), developed by Beck and colleagues (1988). This self-reported questionnaire is composed of 21 items that measure cognitive and somatic symptoms of anxiety within a month via a 4-point Likert scale ranging from 0 (not at all) to 3 (severely—it bothered me a lot). This scale has excellent internal consistency ($\alpha = .93$) and good test-retest reliability (r =.84). We used the Turkish adaptation of BAI by Ulusoy et al. (1998) with excellent internal consistency ($\alpha = .93$). In the current sample, the BAI had excellent internal consistency ($\alpha = .90$)

2.3.6.3 Positive and negative affect schedule (PANAS)

Activations were measured using a positive and negative affect schedule (PANAS) formed by Watson et al. (1988). A self-reported questionnaire consists of 20 items, with ten positive activation items (i.e., attentive, inspired) and ten negative activations items (i.e., afraid, hostile). Participants rated each item on a 5-point Likert scale ranging from 1 (very slightly) to 5 (extremely). It is designed to measure activations in different time domains, including the general mood, year, month, week, day, or present moment, for measuring the state, dispositional, or trait activation of individuals. In this version of the PANAS, we asked participants to think about their last two weeks and rate the items. The test-retest reliability score of PANAS in

the original study was indicated as (r =.48) with a good internal consistency ranging from 85 to 88. This study used the Turkish adaptation of PANAS by Gencöz (2000) with good internal consistency ranging from 0.83 to 0.86 and a re-test reliability of 0.40 to 0.54. In the current sample, the PANAS' s internal consistency was .81 for negative activation and .83 for positive activation.

2.3.6.4 Emotion regulation

We decided to measure emotion regulation strategies of our participants employed during the experimental tasks. Since the TPT elicits aversive emotions, participants might use a variety of emotion regulation strategies to dampen their emotional states. Therefore, we developed an emotion regulation strategy questionnaire based on the inspiration of the State Emotion Regulation Inventory (Roth et al. 2009; trans. Gökdağ et al. 2022). The Original State Emotion Regulation Inventory consisted of integrative emotion regulation (emotional awareness and dealing with negative emotions effectively), suppressive emotion regulation (avoidance or minimizing experiencing negative emotions), and dysregulation emotion regulation (helpless style while dealing with negative emotions). Each subscale consisted of three or four items on the original scale. However, we selected the most suitable emotion regulation strategies for our experimental tasks and only created reappraisal, distraction, and acceptance subscales. The selection of suitable strategies solely depended on the previous visual task of startle modulations (Colezmann et al. 2015; Lissek et al. 2007; Zaehringer et al. 2018). Our scale consisted of three items per subscale, totaling nine items. In the analysis, we deleted some items for distraction and reappraisal due to poor internal consistency. In this study, all subscales—distraction (Cronbach's $\alpha = .87$), reappraisal (Cronbach's $\alpha = .84$), and acceptance (Cronbach's $\alpha = .81$)—have good internal consistency.

3. ANALYTIC STRATEGY

Our primary aim was to investigate how chronic worriers respond to anticipating a threat, a particularly uncertain threat, and whether psychiatric medication history could moderate their startle responses. To accomplish our aim, we analyzed the data using a multi-level modeling approach through R version 4.3.2 (R Core Team, 2023) and RStudio version 2023.12.1+402 (RStudio Team 2024). Multilevel regression models were estimated using lme4 version 1.1–34 (Bates et al. 2015), supported by lmerTest version 3.1-3 (Kuznetsova et al. 2017), reghelper version 1.1.2 (Hughes 2023), and jtools version 2.2.2 (Long 2022). The final model included experimental conditions, medication history, and PSWQ as predictors. Experimental conditions were 'simple' coded so that the uncertain threat condition was the reference level, and we compared the uncertain threat condition to both the safe (contrast 1) and certain threat (contrast 2) conditions. The PSWQ was grand-mean-centered and integrated into the model. We coded psychiatric medication history as effects-coded, with weights of -0.5 for no medication history and 0.5 for medication history. We standardized eyeblink magnitudes using the general startle reactivity of individuals at baseline and converted those to T-scores for analysis [T-scores = (Z-score $\times$ 10) + 50] (Lissek et al. 2008). Participants were allowed to have a random effect on the intercept. We estimated the model using REML, and Satterthwaite's method was used for degrees of freedom estimation.

4. RESULTS

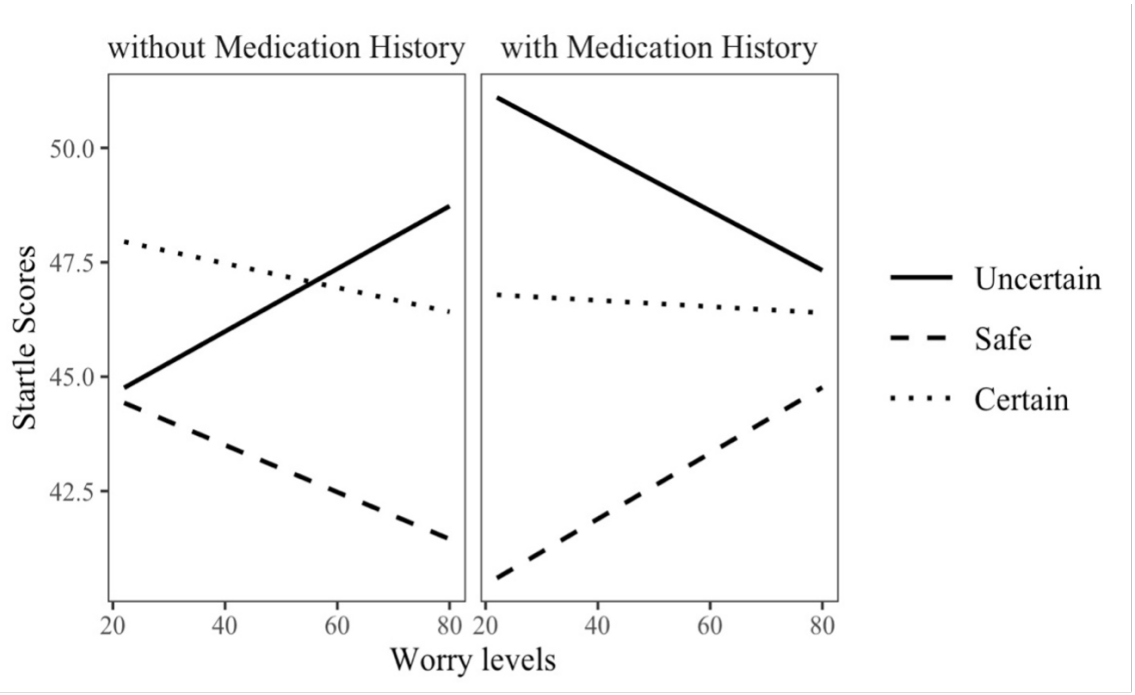
Sixteen out of 1541 trials displayed scaled residuals larger than three and were excluded, leaving 1525 trials for analysis. Parameter estimates are shown in Table 1. There was a significant main effect of condition (F (2, 1452.12) = 47.23, p <.001) such that startle responses in uncertain conditions were increased compared with both safe and certain threat conditions. Also, there was a significant interaction between condition and medication history, F (2, 1452.12) = 3.46, p =.03, indicating that participants with medication history showed heightened startle responses to uncertain conditions compared to certain conditions, B = 3.03, t (1452) = 2.99, p = .008. However, participants without medication history showed no difference in their startle responses to uncertain and certain conditions (B = -.31, t (1452) = -.41, p = .91).

The analysis also yielded a significant condition × PSWQ × medication history interaction, F (2, 1452.01) = 4.46, p = .01. The results suggested that when there was a unit increase in worry scores of individuals with medication histories under the uncertain threat condition, they showed a blunted startle response (B = -0.22).

To explore the effects of medication history on startle responses while accounting for worry levels, a simple slope analysis was conducted, focusing on threat types. The simple slopes of condition types of specifically uncertain vs certain threat conditions reached significance across both low and medium levels of worry only in participants with medication history. In other words, the differences between uncertain threat and certain threat conditions became significant only for people with medication history both in 1 SD below the mean worry levels (B = 4.26, 95% CL [1.35, 7.17], p = .004) and mean levels of worry (B = 3.01, 95% CL [1.02, 5.02], p = .003). However, this effect becomes nonsignificant 1 SD above the mean level of anxiety (B = 1.77, 95% CL [-.38, 3.92]).

Participants without medication history did not show larger startle responses in the uncertain threat condition than they did in the certain threat condition, at any level

Figure 4.1 Interaction between worry, condition, and medication history



of worry (1 SD below the mean, B = -1.81, 95% CL [1.03, -3.83], p = .09; mean, B = -0.31, 95% CI [0.76, -1.81], p = .68; 1 SD above the mean, B = 1.19, 95% CL [1.33, -1.42], p = .37). In other words, people with a medication history were found to consider uncertain threat conditions more stressful than other conditions if they had relatively low levels of worry. However, people with a medication history accompanied by relatively high levels of worry experienced uncertain and certain threat conditions in a similar degree of threat regardless of their possibility.

Participants without medication history did not show larger startle responses in the uncertain threat condition than they did in the certain threat condition, at any level of worry (1 SD below the mean, B = -1.81, 95 CL [1.03, -3.83], p = .09; mean, B = -0.31, 95 CL [0.76, -1.81], p = .68; 1 SD above the mean, B = 1.19, 95 CL [1.33, -1.42], p = .37). In other words, people with a medication history were found to consider uncertain threat conditions more stressful than other conditions if they had relatively low levels of worry. However, people with a medication history accompanied by relatively high levels of worry experienced uncertain and certain threat conditions in a similar degree of threat regardless of their probability. See Table 4.1 for details.

Table 4.1 Coefficient estimates from the linear mixed model

Model Term	**Estimate**	**95% CL**	**t**	**p**
Intercept	48.0	46.4, 49.70	56.80	$< .001$
Condition 1	5.87	4.62, 7.11	9.28	$< .001$
Condition 2	1.35	.11, 2.59	2.13	.03
Trait Worry	.004	-.13, .13	.06	.95
Medication History	1.59	-1.72, 4.88	.94	.35
Condition 1 × Trait Worry	.02	-.08, .11	.34	.73
Condition 2 × Trait Worry	.01	-.09, .11	.21	.84
Condition 1 × Medication History	1.93	-.61, 4.42	1.52	.13
Condition 2 × Medication History	3.33	.85, 5.81	2.62	.01
Trait Worry × Medication History	-.13	-.39, .12	-1.03	.31
Condition 1 × Trait Worry × Medication History	-.28	-.47, -.08	-2.83	.004
Condition 2 × Trait Worry × Medication History	-.22	-.41, -.03	-2.24	.03

Note. N = 65. Condition 1 corresponds to a comparison between the uncertain condition and the safe condition. Condition 2 corresponds to a comparison between the uncertain condition and the certain condition. Confidence intervals are estimated via bootstrapping, p-values are estimated with Satterthwaite's method.

4.1 Additional Analysis

We wanted to perform some additional analysis, especially for anxiety symptom severity and psychiatric mediation history, to gain a deeper understanding of the clinical characteristics of participants in threat anticipation studies. Furthermore, we looked at whether psychiatric medication history also had a moderating effect on the association between anxiety symptom severity and startle reflex to threats.

4.1.1 Threat Type × Anxiety Symptom Severity × Psychiatric Medication History

Seventeen out of 1557 trials had scaled residuals larger than three and were excluded, leaving 1540 trials for analysis. There was a significant main effect of condition ($F(2, 1467.08) = 40.68$, $p < .001$) such that startle responses in the uncertain condition were generally larger than those in the safe ($B = 5.75$, $t(1467.05) = 8.64$, $p < .001$) and certain threat conditions ($B = 1.38$, $t(1467.10) = 2.07$, $p = .04$). Also, there was a significant interaction between condition and anxiety symptom severity ($F(2,$

1467.14) = 8.34, p <.001), indicating that participants with high levels of anxiety showed blunted responses to uncertain conditions compared to certain conditions (B =-2.41, t (1467.16) = -3.51, p <.001). Furthermore, there is a significant interaction between anxiety symptom severity and medication history (F (2, 61.28) = 4.47, p =.040) indicating that participants with medication history also showed high levels of anxiety symptom severity (B = 3.66, t (61.29) = 2.11, p =.039).

Lastly, there is a significant three-way between condition, anxiety symptom severity, and psychiatric medication history, F (2, 1467.14) = 5.21, p =.001. The results suggested that when there was a unit increase in anxiety severity scores of individuals with medication histories under the uncertain threat condition, they showed a blunted startle response (B =-3.60, t (1467.16) =-2.62, p =.01).

To explore the effects of medication history on startle responses, a simple slope analysis was conducted. The simple slopes of condition types, particularly uncertain vs certain threat conditions reached significance across both low and medium levels of anxiety symptom severity only in participants with medication history. In other words, the differences between uncertain threat and certain threat conditions became significant only for people with medication history both in 1 SD below the mean anxiety severity levels (B = 7.05, 95% CL [3.85, 10.35], p < .001) and mean levels of anxiety severity (B = 2.84, 95% CL [0.72, 4.88], p = .007). However, this effect becomes nonsignificant 1 SD above the mean level of anxiety severity (B = -1.37, 95% CL [-4.23, 1.43], p = .34).

Participants without medication history did not show larger startle responses in the uncertain threat condition than they did in the certain threat condition, at any level of anxiety severity (1 SD below the mean, B = .54, 95% CL [-1.62, 2.64], p = .62; mean, B = -0.08, 95% CL [-1.61, 1.52], p = .92; 1 SD above the mean, B = -.68, 95% CL [-2.92, 1.61], p = .55).

In other words, people with a medication history were found to consider uncertain threat conditions more stressful than other conditions if they had relatively low levels of anxiety severity. However, people with a medication history accompanied by relatively high levels of anxiety severity experienced uncertain and certain threat conditions in a similar degree of threat regardless of their probability. These results are also in line with our primary findings. See Table B.2 for details.

We also conducted several correlational analyses, as presented in Table B.3. and B.4. Importantly, Spearman Rho's results showed a statistically significant positive relationship between PSWQ and distraction ($\rho(63)$ =.36, p =.003). Also, distraction has significant positive relationships with BAI (ρ=.28, p =.03) and probability bias

(ρ=.32, p =.01). We also found a positive correlation between trait worry and distraction only in participants with medication history (ρ=.61, p =.001). In other words, when worry levels of participants with medication histories increase, their usage of distraction as an emotion regulation strategy increases.

5. DISCUSSION

There are various studies investigating worry and its role in the formation and maintenance of anxiety disorders. However, there is a significant inconsistency in the literature regarding the physiological correlates of worry and how worry functions in the face of threat uncertainty. Understanding the nature of worry might be essential to creating interventions. Therefore, this study aimed to investigate the role of participants' clinical characteristics, specifically their previous psychiatric mediation history, on the association between trait worry and threat uncertainty. Consistent with our predictions, we found an interaction between trait worry, medication history, and threat uncertainty on startle reactivity. Among individuals with a psychiatric medication history, individuals with high levels of worry scores displayed blunted startle responses under the uncertain threat condition compared to the certain threat condition. However, participants with no psychiatric medication history did not show any differences across threat conditions.

Worry moderates the effect of threat levels on startle reactivity only among individuals with a medication history. The results indicated that participants with low and average levels of worry considered uncertain threat conditions more anxiety-provoking compared to certain and safe conditions. However, participants with excessive worry levels showed overall decreased responses in the uncertain condition and no differences in their startle responses in the uncertain vs. certain conditions, suggesting that they considered all threat types similarly regardless of threat probability. Our findings suggested some similarities with the results from Rutherford et al. (2020), who found an association between high levels of worry and blunted startle responses to uncertain threat conditions in individuals with history of anxiety disorders. However, our results extend prior knowledge regarding the effect of worry levels and threat levels on defensive responses by showing the importance of psychiatric medication history.

Given the avoidance function of worry in the face of threat (Borkovec et al. 1993), we can speculate that individuals with medication histories might be overly sensitive

to uncertain threats and might be prone to use worry as an emotion regulation strategy to avoid uncertainty. Theories on uncertainty and anxiety (Dugas et al. 1998) propose that uncertainty may overwhelm some individuals due to the maladaptive processing of aversive stimuli when faced with uncertainty. Those individuals subsequently engage in maladaptive emotion regulation activities, such as avoidance behaviors or verbal-linguistic thoughts like worry, to relieve stress and the physiological reactions of fearing consequences. In this approach, individuals reduce their physiological reactivity and feel relief in the short term. However, effectively processing fear-related information is critical to breaking the anxiety loop. Thus, individuals foster their anxious cycle due to a missed opportunity to properly process fear-related data (Borkovec et al. 2004). In line with avoidance model of worry, we might also explain our results based on the experiential avoidance model, which suggests putting purposeful efforts into reducing and escaping from negative, unwanted feelings and sensations. In this process, participants cannot tolerate their negative emotions and engage in short-term avoidance strategies to control their emotions. Even though experiential avoidance relieves stress symptoms, rigidly engaging in avoidance strategies to avoid uncomfortable feelings causes increased psychological distress and hinders the life activities of individuals (Kashdan et al. 2006). Therefore, in our study, participants with a medication history showed increased startle responses to uncertain threat conditions, and due to their increased physiological activities, they engaged in experiential avoidance strategies like worry to dampen their physiological arousal.

Only participants with a history of taking psychiatric medication showed heightened startle responses under uncertain threat. Anticipating uncertain aversive events affects the proper preparation for future events, mood, and physiological activity; however, individuals differ regarding responses to uncertainty and their decision to engage in efficient preparatory actions while dealing with uncertainty. The uncertainty and anticipation model of anxiety proposes that interrelated sets of neurological and psychological mechanisms are essential for adaptive anticipatory responding processes, and impairments in the process and neural mechanisms result in maladaptive reactions to uncertainty (Grupe and Nitschke 2013). According to this model, impairments in brain areas associated with emotional processing result in exaggerated emotional reactivity in the face of uncertainty. For instance, alterations in the anterior insula, defined as an interoceptive attention system responsible for tracking environmental and bodily changes, results in biased estimates of risk, while impairments in the orbitofrontal cortex lead to failures to learn from prediction errors. These maladaptive processes make it hard for individuals to estimate subjective feelings of threats and make cognitively accurate calculations of threats. Those

threat expectations lead to increased activation in the the bed nucleus of the stria terminalis, which plays a mediator role in emotional processing and responses to sustain fear and promotes the physiological and behavioral manifestations of anxiety disorders. Individuals with these maladaptive processes find uncertainty intolerable. Therefore, our results might be interpreted considering the model in terms of the oversensitivity of individuals with a psychiatric medication history to uncertainty. In other words, individuals with a psychiatric medication history might react strongly to uncertain situations, finding those events threatening even though the risk of harm is objectively low, and they may display elaborated startle reactivity as a defensive response to uncertain threats.

Furthermore, previous studies on clinical samples showed that individuals with a clinical diagnosis (i.e., post-traumatic stress disorder, panic disorder) show sensitivity to uncertain threat conditions compared to healthy controls (Grillon et al. 2008; Grillon et al. 2009). Therefore, those with a history of psychiatric medication might already be overly sensitive to uncertainty and have previously been prescribed medicine to alleviate their aversive, maladaptive response to anticipatory situations. One might think that when someone uses an antidepressant, their physiological reactivity may decrease due to the neurogenesis of hippocampal cells, which dampens physiological reactions to threats. However, our results suggested the opposite findings. We might explain our findings in light of Herman and colleagues' (2016) study. The findings demonstrated that increased hippocampal cells due to antidepressant usage do not affect the hypothalamic-pituitary-adrenal axis, which refers to responders to stress and regulators of adaptive responses to stress by the secretion of stress hormones. Inadequate or excessive activations of this system lead to psychopathologies. Therefore, we might capture their maladaptive anticipatory defensive responses by emotionally dynamic measures like the startle reflex even though they had a treatment.

Another possibility is that participants with a medication history might show relapse symptoms after the termination of medication treatment or psychotherapy. Studies have found one-fifth of individuals with emotional disorders (i.e., major depression, generalized anxiety disorder) had a relapse or recurrence after the follow-up period (Batelaan et al. 2017; Melfi et al. 1998). Thus, the oversensitivity of participants with medication histories to uncertainty might be partly attributable to their reappearing clinical symptoms. However, please keep in mind that we did not assess other factors that can affect relapse rates, such as discontinuation of medication or psychotherapy, duration of treatment, or perceived succeed of the treatment.

Although it is not the primary goal of this study, data allowed us to perform a

couple of additional analyses. First, we looked at the association between the anxiety symptom severity and startle responses under threats in individuals with and without psychiatric medication history. This finding supports our primary findings such that individuals with psychiatric medication history showed overall blunted responses to uncertain threat conditions when their anxiety symptom severity increases. In our correlation analysis, we found that high levels of worry, anxiety symptom severity, and probability bias are associated with distraction strategies employed during the experimental task. This additional analysis might also support that individuals with a psychiatric history consider uncertain situations as more anxiety-provoking and might employ avoidance strategies like a distraction or worry to dampen their physiological arousal.

5.1 Strengths and Limitations, and Future Directions

A strength of the current study was investigating the threat anticipation of participants through a laboratory task, the TPT, while measuring their startle responses to auditory probes within each threat condition. This approach allowed us to measure the emotional processing of threat and defensive responses in individuals with different clinical characteristics. This study adds to the growing literature on physiological correlates and the function of worry, especially chronic worry in the face of threat uncertainty, and demonstrates the importance of considering the clinical characteristics of participants while interpreting results. Also, we employed multilevel analysis for analyzing the data, which allows us to understand the condition- and individual-based variance in responses.

It is essential to acknowledge some limitations while interpreting the results. First, the sample size—of participants with a medication history in particular—was limited, which might decrease the power of the study. Second, we obtained our participants' medication history and clinical diagnosis information through the self-report method, which limited our conclusions. Our findings might only apply to unselected young adults from academic backgrounds. Different psychopathologies are associated with distinct results in the startle responses to threats, suggesting that the underlying mechanisms of each psychopathology show diverse functioning in the face of defensive responses towards threat types (Gorka et al. 2017). Therefore, future studies should examine the clinical diagnosis status, alongside their histories of using different types of psychiatric medications.

Besides, we focused on the effect of trait worry on defensive responses and extended

previous literature on the role of worry in peripheral physiology. However, we cannot draw whole conclusions regarding the effect of worrying (i.e., state worry) in physiology through self-reported measures of tendency to worry. Future studies should examine the association between active worrying and threat levels in the startle reflex to threats.

Lastly, even though we developed an emotion regulation scale for understanding the strategies employed during the experiment, future studies might use a more dynamic measure of capturing the emotion regulation strategies of individuals, particularly during the threat anticipation task, to increase our understanding of how worry and uncertainty interact, and which regulation strategies are employed.

6. CONCLUSION

In this study, we found that threat conditions, medication history, and worry are linked to startle response to unknown threats. This study is the first to demonstrate the moderator function of medication history in the link between worry and threat response through the threat anticipation task that manipulates the probability of occurrence. Thus, our investigation provided insight into the inconsistent findings about the role of worry in peripheral physiology. We hope that our research helps to explain the theoretical and practical applications of worry in therapeutic settings and interventions.

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APPENDIX A

A.1 Inform Consent

Sabancı Üniversitesi

Araştırma Katılım Formu

Çalışmanın Başlığı: Psikofizyolojik Tepkiler

Baş Araştırmacı: Robert W. Booth

Yardımcı Araştırmacı: Bahire Büşra Temur

Çalışmanın Amacı: Bu çalışma öğrencilerin laboratuvar ortamında oluşturulmuş belirli durumlara verdikleri fizyolojik tepki ve bu tepkilerin çeşitli psikolojik özelliklerle ilişkisini incelemeyi amaçlamaktadır. Çalışma toplamda 1 saat sürecektir. Bu çalışmanın ilk aşamasında sizlere hisleriniz hakkında sorular sorulacaktır ve anketleri doldurmanız yaklaşık 30 dakika sürecektir. Sonrasında da sizlerin laboratuvar ortamında oluşturulmuş durumlara tepkinizi ölçmek için fizyolojik bir ölçüm uygulanacaktır. Ayrıca sizlere çeşitli olayların gerçekleşme ihtimalleri de sorulacaktır. Lütfen çalışmanın sonunda sizden istenildiği şekilde bir ID oluşturmayı unutmayın. Bu ID verilerinizin güvenli ve anonim olarak saklanmasında kullanılacaktır. Bu araştırmada deney sırasında sizi rahatsız edebilecek şoklar ve yüksek desibelli sesler verilecektir ancak bu süreç bir saniyeden çok kısa bir sürede gerçekleşecektir, ayrıca medikal amaçlarla kullanılan şok cihazı sizin sağlığınızı hiçbir şekilde tehdit etmemektir. Ancak geçmiş kalp hastalığınız ve epilepsi nöbetleriniz bulunuyorsa bu deneye lütfen katılmayız. Bunun dışında, kulaklarınızda ve işitmenizde herhangi bir problem varsa lütfen çalışmaya katılmayınız. Ayrıca, bu deneyden rahatsız olacağınızı düşünüyorsanız lütfen çalışmaya katılmayınız. Çalışmaya katılımınız tamamıyla gönüllülük esasına dayanmaktadır. Bu çalışma sonucunda finansal bir kazanımınız olmayacaktır. Bize verdiğiniz bütün bilgiler gizli tutulacaktır. Size ait veri gizli tutulacaktır. Hiç kimse hangi verinin size ait olduğunu bilmeyecektir. Çalışmamızın sonuçlarını ve verilerini yayınlama hakkını tutmakla birlikte, herhangi bir kişisel bilgi ya da veri yayınlanmayacaktır. Veriler en az beş yıl arşivlerimizde saklı tutulacaktır. Çalışmadan istediğiniz anda geri çekilebilir ve istediğiniz zaman bizimle iletişime geçip size ait verinin silinmesini isteyebilirsiniz.

Eğer daha fazla açıklama yapılmasını isterseniz araştırmacılar ile iletişime geçebilirsiniz. Çalışmayı laboratuvarda tamamlarsanız, 2.5 Research Points alacaksanız. Sonuçlarınız ya da veriler yayınlanabilir ancak datalarınız kişisel verileri içeren bilgiler kesinlikle içermeyecektir. Verileri en az beş yıl süreyle arşivleyeceğiz. İstediğiniz zaman araştırmadan çekilebilir, istediğiniz zaman bizimle iletişime geçerek verilerinizi yok etmemizi isteyebilirsiniz. Tüm katılımcılar, daha fazla açıklama ve bilgi almak için araştırmaya dahil olan herhangi bir kişiyle iletişime geçebilir. Eğer çalışma süresince kendinizi rahatsız hissederseniz, LÜTFEN ÇALIŞMAYI DURDURUP ARAŞTIRMACIYI BİLGİLENDİRİNİZ. Bu durumu anlayışla karşılıyoruz ve durumunuzu kimseyle paylaşmayacağımızı temin ediyoruz. Lütfen böyle bir durumda bizimle robertbooth@sabanciuniv.edu,ya da busra.temur@sabanciuniv.edu adreslerinden iletişime geçin. Araştırmanın sonunda çalışmanın detaylarını açıklayan bir bilgilendirme formu alacaksınız.

Eğer haklarınızın herhangi bir şekilde ihlal edildiğini düşünüyorsanız, lütfen Sabancı Üniversitesi Araştırma Etik Kurulu Başkanı Prof. Dr. Mehmet Yıldız ile [(216) 300-1301, meyildiz@sabanciuniv.edu] iletişime geçiniz. Eğer yukarıda belirtilenlerin hepsini anladıysanız ve çalışmaya katılmak istiyorsanız, lütfen aşağıdaki bölümü imzalayın.

İmza:

Tarih:

A.2 Debriefing Statements

Bilgilendirme Formu

Araştırmamızı tamamladığınız için teşekkür ederiz. Katılımınız bizim için çok değerlidir.Size verdiğimiz testlerle anksiyete ve endişe seviyelerinizi, çeşitli olayların başınıza gelme ihtimallarını sorduk. Ayrıca, laboratuvar ortamında oluşturulmuş kesin veya belirsiz tehdit ve güvenli durumlara fizyolojik olarak tepkinizi ölçtük.

Öğrencilerin üniversite yıllarında çeşitli psikolojik sorunlar deneyimlediklerini biliyoruz. Bu çalışmada, öğrencilerin laboratuvar ortamında oluşturulan tehdit durumlarında verdikleri psikofizyolojik tepkileri ve bu tepkilerin endişe ve algılanan olasılık tahminleri ile ilişkisini incelemek istiyoruz.

Lütfen çalışmanın detaylarını ve hipotezlerini hiç kimseyle tartışmayın. Bu önemli nokta gelecekte toplayabileceğimiz verilerin kalitesini korumamıza yardım edecektir. Lütfen bütün verilerinizin gizli olduğunu unutmayınız- sizden başka hiç kimse hangi verinin size ait olduğunu bilmemektedir. Bununla birlikte, bize nedenini söylemek zorunda olmadan, istediğiniz zaman verilerinizi silmemizi isteyebilirsiniz.

Eğer haklarınızın herhangi bir şekilde ihlal edildiğini düşünüyorsanız, lütfen Sabancı Üniversitesi Araştırma Etik Kurulu Başkanı Prof. Dr. Mehmet Yıldız ile [(216) 300-1301,meyildiz@sabanciuniv.edu] iletişime geçiniz.

Başka genel sorularınız veya endişeleriniz için Sabancı Üniversitesi Sanat ve Sosyal Bilimler Fakültesi öğretim üyesi Doç.Dr. Rob Booth'a veya Büşra Temur'a başvurabilir veya mail atabilirsiniz: robertbooth@sabanciuniv.edu, busra.temur@sabanciuniv.edu Yardımınız için tekrar çok teşekkür ederiz!

Bu izin belgesini onaylayarak, verinizin bu çalışma ve akademik basımiçin kullanılabileceğine dair rıza gösterdiğinizi belirtiyorsunuz.

Araştırmacı: Dr. Robert W. Booth robertbooth@sabanciuniv.edu Bahire Büşra Temur busra.temur@sabanciuniv.edu İmza: Tarih:

A.3 Penn State Worry Questionnaire (Meyer et al., 1990) / Penn State Endişe Ölçeği

Her bir ifadenin sizi ne ölçüde tanımladığını, aşağıda verilen ölçekten yararlanarak değerlendiriniz. Sizin için uygun olan rakamı ilgili maddenin yanındaki boşluğa yazınız. Benim için hiçbir zaman doğru değil (1); Benim için bazen doğru (3); Benim için her zaman doğru (5).

1. Her şeye yetişebilecek kadar zamanım olmasa bile bunun için endişelenmem.

2. Endişelerim beni bunaltır.

3. Bir şeyler hakkında endişelenmeye eğilimli değilim.

4. Pek çok durum beni endişelendirir.

5. Bir şeyler hakkında endişelenmemem gerektiğini biliyorum; ancak kendime engel olamıyorum.

6. Baskı altında olduğumda çok fazla endişelenirim. 7. Her zaman bir şeyler hakkında endişeleniyorum.

8. Endişe veren düşünceleri aklımdan uzaklaştırmayı kolay bulurum.

9. Bir işi bitirir bitirmez, yapmak zorunda olduğum her şey için endişelenmeye başlarım.

10. Hiçbir şey için asla endişelenmem.

11. Bir sorun hakkında yapabileceğim daha fazla bir şey olmadığında o konu hakkında daha fazla endişelenmem.

12. Hayatım boyunca endişeli birisi oldum.

13. Birden bir şeylere endişelenmekte olduğumu fark ederim.

14. Bir kere endişelenmeye başladığımda durduramam.

15. Her zaman endişelenirim.

16. Tümüyle yapılıp bitirilinceye kadar planladığım işler hakkında endişelenmeye devam ederim.

A.4 Judgment Bias Questionnaire (Booth-Sharma, 2020)

Bu ankette, size bazı durumlar tasvir edilecektir. Lütfen uygun kutuyu işaretleyerek (1) her bir durumun sizin başınıza gelme olasılığını belirtmenizi rica ediyoruz. (1- Bana asla olmaz, 2 - Muhtemelen bana olmaz, 3 - Bana olmayabilir, 4 - Bana olabilir ya da olmayabilir, 5 - Bana olabilir, 6 - Muhtemelen bana olur, 7 - Bana kesinlikle olur).

1. Çok zengin olacaksınız.

2. Vahşice işlenmiş bir suçun kurbanı olacaksınız.

3. Bir sonraki tatil ya da seyahatinizden çok keyif alacaksınız.

4. Katılacağınız bir sonraki parti ya da sosyal olayda kendinizi rezil edeceksiniz.

5. Önümüzdeki beş sene içerisinde ciddi bir trafik kazası geçireceksiniz.

6. Arkadaşlarınız onlardan yardım istediğinizde yanınızda olacaklar.

7. Bir sonraki girişim ya da hedefinizde başarılı olacaksınız.

8. Önümüzdeki sene içerisinde cep telefonunuzu kaybedeceksiniz ya da telefonunuz ciddi anlamda zarar görecek.

9. Doğal bir afette ciddi anlamda yaralanacaksınız.

10. Önemli bir başarıdan dolayı tanınacaksınız.

11. Bir sonraki doktor kontrolünüzde, aile doktorunuz iyi fiziksel sağlığınız olduğunu söyleyecek.

12. Harika bir 90. yaş kutlamanız olacak.

13. Önümüzdeki ay içerisinde ailenizle ciddi bir tartışmaya gireceksiniz.

14. En iyi arkadaşınız sizden sıkılıp başka arkadaşlarıyla daha fazla zaman geçirmeye başlayacak.

15. Önümüzdeki sene içerisinde sevdiğiniz birini kaybedeceksiniz.

16. En iyi arkadaşınız sizden sıkılıp başka arkadaşlarıyla daha fazla zaman geçirmeye başlayacak.

17. Yarın sizin için harika bir gün olacak.

18. Düzenli olarak piyango bileti aldığınızda kazanacaksınız.

19. Otorite sahibi birisi tarafından size kötü davranılacak.

20. Size ciddi bir fiziksel hastalık teşhisi konacak.

A.5 Beck Anxiety Inventory (Beck et al. 1988) / Beck Anksiyete Ölçeği

Aşağıda insanların kaygılı ya da endişeli oldukları zamanlarda yaşadıkları bazı belirtiler verilmiştir. Lütfen her maddeyi dikkatle okuyunuz. Daha sonra, her maddedeki belirtinin BUGÜN DAHİL SON BİR (1) HAFTADIR sizi ne kadar rahatsız ettiğini yandakine uygun yere (x) işareti koyarak belirleyiniz. 0- Hiç, 1- Hafif düzeyde/ Beni pek etkilemedi, 2-Orta düzeyde/ Hoş değildi ama katlanabildim, 3- Ciddi düzeyde / Dayanmakta çok zorlandım

1. Bedeninizin herhangi bir yerinde uyuşma veya karıncalanma
2. Sıcak / ateş basmaları
3. Bacaklarda halsizlik / titreme
4. Gevşeyememe
5. Çok kötü şeyler olacak korkusu
6. Baş dönmesi veya sersemlik
7. Kalp çarpıntısı
8. Dengeyi kaybetme duygusu
9. Dehşete kapılma
10. Sinirlilik
11. Boğuluyormuş gibi olma duygusu
12. Ellerde titreme
13. Titreklik
14. Kontrolü kaybetme korkusu
15. Nefes almada güçlük
16. Ölüm korkusu
17. Korkuya kapılma
18. Midede hazımsızlık ya da rahatsızlık hissi
19. Baygınlık
20. Yüzün kızarması

21. Terleme (Sıcağa bağlı olmayan)

A.6 Positive and Negative Affect Scale (Watson et al. 1988) / Pozitif ve Negatif Duygu Ölçeği

Bu ölçek farklı duyguları tanımlayan birtakım sözcükler içermektedir. Her maddeyi, iki hafta nasıl hissettiğinizi düşünerek okuyunuz. Uygun cevabı her maddenin yanında ayrılan yere işaretleyiniz. Cevaplarınızı verirken aşağıdaki puanları kullanınız. 1-Çok az veya hiç, 2-Biraz 3-Ortalama, 4-Oldukça, 5-Çok fazla

1. İlgili
2. Sıkıntılı
3. Heyecanlı
4. Mutsuz
5. Güçlü
6. Suçlu
7. Ürkmüş
8. Düşmanca
9. Hevesli
10. Gururlu
11. Asabi
12. Uyanık
13. Utanmış
14. İlhamlı
15. Sinirli
16. Kararlı
17. Dikkatli
18. Tedirgin
19. Aktif
20. Korkmuş

A.7 Emotion Regulation / Duygu Düzenleme

Şoka maruz kaldığınız bloklarda, duygularınızı nasıl kontrol ettiğinize dair çeşitli sorular soracağız, lütfen ifadeleri 1 ile 7 arasındaki tuşlardan birine basarak cevaplayınız. (1-Hiç katılmıyorum, 4- Ne katılıyorum ne katılmıyorum, 7- Kesinlikle katılıyorum)

1. Başka şeyler düşünmeye çalıştım

2. Şok ile alakası olmayan başka konuları aklıma getirmeye çalıştım.

3. Ne kadar şok ihtimali beni endişelendirse de bu yaşadığım deneyim hakkında daha olumlu düşünmeye çalıştım.

4. Yaşadığım deneyimin ilginç ve her zaman yaşayamacağım bir şey olduğunu düşünerek beklemeye çalıştım.

5. Bu durumu kabul etmem gerektiğini düşündüm.

6. Bu durumun olacağını ve yapabileceğim bir şey olmadığını düşündüm.

7. Bu durum hakkında bir şey değiştiremeyeceğimi düşündüm

Distraction: 1,2

Reappraisal: 3,4

Acceptance: 5,6,7

A.8 Demographics/ Demografikler

1. **Yaşınız:**

2. **Cinsiyetiniz:**

(Kadın / Erkek / Other)

3. **Eğitim Düzeyiniz:**

(Hazırlık, 1. Sınıf (Lisans), 2. Sınıf (Lisans), 3.Sınıf (Lisans), Son Sınıf (Lisans), Yüksek Lisans Doktora).

4. **Gelir düzeyiniz:**

0-5500 TL

5501-8500 TL

8501- 12.000 TL

12001- 15.500 TL

15501-20.000 TL

20.001 ve üzeri

5. **Son zamanlarda teşhis edilen psikiyatrik, nörolojik ve/veya ruhsal sağlık probleminiz var mı?** (İstatistiki bilgi toplamak amacıyla sorulmuştur.)

Evet

Hayır

6. **Eğer *Evet* cevabınız verdiyseniz, lütfen sağlık probleminizi yazınız:**

.....

7. **Hayatınızın önceki bir aşamasında teşhis edilen psikiyatrik, nörolojik ve/veya ruhsal sağlık probleminiz var mıydı?** (İstatistiki bilgi toplamak amacıyla sorulmuştur.)

Evet

Hayır

8. **Eğer *Evet* cevabınız verdiyseniz, lütfen sağlık probleminizi yazınız:**

.....

9. **Daha önce psikolojik tedavi amaçlı bir ilaç kullandınız mı?**

Evet

Hayır

10. **Psikolojik tedavi amaçlı ilaç kullanım sürenizi lütfen belirtiniz**

Hiç

0-6 ay

6-12 ay

12 ay ve üzeri

11. **Sigara içiyor musunuz?**

Evet

Hayır

12. **Ne sıklıkla sigara içiyorsunuz?**

Hiç

Yılda birkaç kez

Ayda bir

Haftada bir

Her gün

APPENDIX B

B.1 Table for demographic characteristics

Table B.1 Demographic and clinical characteristics of participants in the study

	With psychiatric medication history	**Without medication history**
n	24	41
Gender (n women)	17	23
Age, M (SD)	21.96 (2.53)	21.90 (3.13)
PSWQ, M (SD)	55.29 (15.02)	48.12 (10.22)
n with Current Diagnosis	15	5

B.2 Tables for additional analyses

Table B.2 Coefficient estimates from the additional model

Model Term	**Estimate**	**95% CL**	**t**	**p**
Intercept	47.9	46.2, 49.5	56.6	$< .001$
Condition 1	5.8	4.5, 7.1	8.7	$< .001$
Condition 2	1.4	.04, 2.7	2.1	.039
BAI	1.2	-.5, 2.9	1.4	.17
Medication History	1.34	-2.0, 4.7	.8	.43
Condition 1 × BAI	.07	-1.3, 1.4	.1	.92
Condition 2 × BAI	-2.4	-3.7, -1.1	-3.5	.001
Condition 1 × Medication History	1.1	-1.6, 3.7	.79	.43
Condition 2 × Medication History	2.9	.34, 5.5	2.2	.03
BAI × Medication History	3.7,	.2, 7.04	2.1	.038
Condition 1 × BAI × Medication History	.50	-2.1, 3.1	.4	.72
Condition 2 × BAI × Medication History	-3.6	-3.6, -6.2	-2.6	.01

Note. N = 65. Condition 1 corresponds to a comparison between the uncertain condition and the safe condition. Condition 2 corresponds to a comparison between the uncertain condition and the certain condition. Confidence intervals are estimated via bootstrapping, p-values are estimated with Satterthwaite's method.

B.3 Tables for correlational analyses

Table B.3 Means, standard deviations and correlations

	M	*SD*	1	2	3	4	5	6	7
Trait Worry	50.8	12.6	-						
Anxiety Symptom Severity	17.3	10.8	.26*	-					
Negative Affect	22.5	6.96	.62***	.13	-				
Probability Bias	-1.13	1.26	.58***	.14	.57***	-			
Distraction	3.9	1.89	.36**	.28*	.12	.32**	-		
Reappraisal	4.8	1.69	-.01	-.04	-.14	-.14	.12	-	
Acceptance	5.66	1.18	.11	-.17	-.05	-.03	-.02	.09	-

Note: * $p < .05$, ** $p < .01$, ***$p < .001$, $N = 65$

Table B.4 Means, standard deviations and correlations across groups

	M	*SD*	1	2	3	4	5	6	7
Medication History Group									
Trait Worry	55.3	15.1	-						
Anxiety Symptom Severity	18.7	10.1	.25	-					
Negative Affect	24.1	7.4	.62***	-.01	-				
Probability Bias	-0.82	1.32	.44*	.12	.33	-			
Distraction	3.98	1.94	.61***	.41*	.50*	.50*	-		
Reappraisal	4.43	1.77	-.001	-.09	-.13	-.14	.05	-	
Acceptance	5.63	1.10	.36	-.13	.15	.14	.17	.32	-
No Medication History Group									
Trait Worry	48.1	10.2	-						
Anxiety Symptom Severity	16.5	11.2	.25	-					
Negative Affect	21.5	6.64	.61***	.21	-				
Probability Bias	-1.31	1.20	.68***	.15	.73***	-			
Distraction	3.84	1.88	.13	.19	.02	.03	-		
Reappraisal	5.01	1.62	-.0001	.01	-.12	-.12	.16	-	
Acceptance	5.67	1.25	.36	-.19	-.14	-.03	-.13	-.1	-

Note: * $p < .05$, ** $p < .01$, ***$p < .001$