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Unraveling Uncertainty:
Physiological Correlates of Uncertainty across Anxiety Symptom Dimensions

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Hannes Per Carsten
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Promotionsprüfungsausschuss

Vorsitzende:	Prof. Dr. Jenny Wagner
Erste Dissertationsgutachterin:	Prof. Dr. Anja Riesel
Zweite Dissertationsgutachterin:	Prof. Dr. Tina B. Lonsdorf
Erster Disputationsgutachter:	Prof. Dr. Lars Schwabe
Zweiter Disputationsgutachter:	Prof. Dr. Matthias J. Wieser

"[...] *fear is for things we're unsure of; certainties are merely awaited*".

Seneca (n.d.), Epistle 30 / 10[1]

[1] Translation from Romm, J. S. (Ed. & Trans.). (2018). How to Die: An Ancient Guide to the End of Life (Ancient Wisdom for Modern Readers) [Seneca]. Princeton University Press.

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Table of Contents

Danksagung 4
Table of Contents 6
Summary 9
1. Introduction 12
1.1 Defensive Responding 12
1.1.1 The Predatory Imminence Continuum Theory 13
1.1.2 Neural Underpinnings of Orienting and Defensive Responding 14
1.1.3 Defensive Responding Reflected in Reflex Physiology 17
1.2 The Modulatory Role of Uncertainty in Defensive Responding 17
1.2.1 Features of Threat Unpredictability 19
1.2.2 Electroencephalographic Correlates of Unpredictable Threat Anticipation 21
1.2.3 Errors as Endogenous Threats 23
1.3 Uncertainty in Anxiety-Related Psychopathology 24
1.3.1 Clinical Studies of Unpredictable Threat Anticipation 27
1.3.2 Dimensional Models of Anxiety-Related Psychopathology 28
1.3.3 Summary 29
2. Research Objectives 31
2.1 Research Aim 31
2.2 Research Questions 31
3. Summary of Studies 33
3.1 Study 1: Intolerance of Uncertainty in Unpredictable Threat Anticipation 33
3.2 Study 2: Testing the Influence of Uncertainty on the Error-Related Negativity 40
3.3 Study 3: Anxiety Dimensions in Threat Anticipation 47
3.4 Study 4: Transdiagnostic Physiological Correlates of Unpredictable Threat Anticipation 55
4. General Discussion 64
4.1 Summary of Findings 64
4.2 The Role of Unpredictability in Threat Anticipation Across Response Systems 65
4.3 Trait- and Symptom-based Modulation of Defensive Responding Under Uncertainty 68
4.4 The Uncertainty-Imminence Continuum Model of Defensive Responding 69
4.5 Strengths and Limitations 75
4.6 Methodological and Clinical Implications 78
4.7 Conclusion 82
References 83
Appendices 104
A Correlations of Psychophysiological Measures 104
Publications 107
Contributions and AI Statement 258
Materials 261
Declarations 263

List of Figures

Figure 1. *Central Models of Threat Anticipation* 19
Figure 2. *NPU-Threat Test* 21
Figure 3. *NPU-Threat Test Manipulating Threat Probability* 35
Figure 4. *Main Results of Study 1* 37
Figure 5. *Overview of the Procedure and Tasks in Study 2* 42
Figure 6. *Main Results of Study 2* 44
Figure 7. *Overview of the Sample and Procedure in Study 3* 50
Figure 8. *Main Results of Study 3* 52
Figure 9. *Main Results of Study 4* 58
Figure 10. *Exploratory Latent Profile Analysis* 60
Figure 11. *Clinical Correlates of Latent Profiles* 61
Figure 12. *Uncertainty-Imminence Continuum Model of Defensive Responding (UICM)* 72

List of Abbreviations

BNST	Bed nucleus of the stria terminalis
CGI	Clinical Global Impression Scale
CRN	Correct-related negativity
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EEG	Electroencephalography
EMG	Electromyography
ERN	Error-related negativity
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
GAF	Global Assessment of Functioning
HiTOP	Hierarchical Taxonomy of Psychopathology
HPA	Hypothalamic-pituitary-adrenal axis
ICD-11	International Classification of Diseases, Eleventh Revision
IU	Intolerance of uncertainty
IUS-12	12-item Intolerance of Uncertainty Scale
LPA	Latent profile analysis
LSAS	Liebowitz Social Anxiety Scale
MASQ-AA	Mood and Anxiety Symptom Questionnaire, Anxious Arousal subscale
NPU	Neutral, predictable, and unpredictable threat
OCD	Obsessive-compulsive disorder
PFC	Prefrontal cortex
PnC	Nucleus reticularis pontis caudalis
PSWQ	Penn State Worry Questionnaire
RDoC	Research Domain Criteria
SCID-5-CV	Structured Clinical Interview for DSM-5 Disorders, Clinician Version
SCR	Skin conductance response
UAMA	Uncertainty and Anticipation Model of Anxiety
UICM	Uncertainty-Imminence Continuum Model of Defensive Responding

Summary

Uncertainty is a pervasive feature of human experience. Potential threats are often insufficiently specified with regard to whether, when, and with what consequences they might occur. Under uncertainty, defensive responses serve an adaptive function by increasing vigilance, coordinating physiological mobilization, and preparing behavior for possible danger, which has been investigated in humans using the startle reflex, skin conductance response and event-related potentials such as probe-locked N1 and P3. Defensive responses may nevertheless become maladaptive when they are disproportionate to the actual threat, persist in relatively safe contexts, or cannot be flexibly regulated. Given that individuals differ in their ability to tolerate and adaptively respond to uncertainty, intolerance of uncertainty (IU) has been proposed as a transdiagnostic vulnerability factor for internalizing and anxiety-related psychopathology.

Drawing on four empirical studies using both cross-sectional and experimental designs, this dissertation examines how humans respond to unpredictable threat from multiple perspectives. To this end, different types of threat were considered, ranging from external aversive stimuli, such as auditory or electrotactile stimuli, to potential internal threat signals such as errors. Furthermore, uncertainty was operationalized in several ways, including direct comparisons between temporal unpredictability and threat occurrence probability, as well as the examination of a novel uncertainty symptom induction. Moreover, responses to uncertain threat were studied across different populations, including young adults and students, community samples, and clinical samples. Across these approaches, the dissertation examines which features of unpredictability are particularly relevant for individual differences, which physiological response systems are most sensitive to uncertainty, and whether altered responding is best understood in terms of diagnostic categories or transdiagnostic dimensional symptoms.

Study 1 examined differential effects of temporal unpredictability and threat occurrence probability within an adapted neutral, predictable, and unpredictable threat (NPU-threat) test in a preregistered sample of 90 students. Temporal unpredictability increased startle responding, probe-locked N1 amplitudes, and subjective anxiety ratings. Lower threat occurrence probability further increased startle responding, while subjective anxiety and P3 suppression were reduced. IU was selectively associated with enhanced startle responses under low occurrence probability, irrespective of the temporal predictability, suggesting that IU-related defensive responding may be particularly pronounced when threat occurrence probability is low, rendering the threatening situation uncertain.

Study 2 extended the investigation from externally signaled threat to errors as internal threat signals. Cross-sectional analyses in a combined sample of 355 nonclinical participants provided no evidence that IU or its subdimensions were associated with the error-related negativity (as a neural

index of performance monitoring). In a preregistered randomized controlled design, a subset of the sample (*N* = 60) underwent a newly developed uncertainty symptom induction, which increased subjective state uncertainty but did not alter the error-related negativity from pre to post symptom induction. These findings suggest that uncertainty-related alterations in defensive responding might not robustly extend to performance monitoring.

Study 3 examined whether the transdiagnostic anxiety dimensions anxious apprehension and anxious arousal were associated with physiological responses during predictable and unpredictable threat anticipation. To this end, 136 subclinical participants with particularly convergent or divergent profiles in these anxiety dimensions were drawn from a community sample. Employing the NPU-threat test, participants with anxious apprehension showed increased startle responding during unpredictable threat anticipation, whereas anxious arousal was associated with increased startle and N1 responses during unpredictable relative to predictable threat.

Study 4 extended this work to a clinical sample of 163 participants comprising equal numbers of patients with specific phobia, social anxiety disorder, and obsessive-compulsive disorder (OCD), as well as unaffected controls. Patients with OCD showed increased skin conductance responses during unpredictable threat anticipation. In addition, anxious apprehension was associated with stronger N1 modulation during unpredictable threat anticipation in patients with OCD. Exploratory latent profile analysis identified three multivariate physiological response profiles that cut across diagnostic categories. One threat-reactive profile was clinically enriched and characterized by stronger autonomic and early attentional engagement, higher representation of patients with social anxiety disorder and OCD, elevated anxious apprehension and social anxiety symptoms, and higher clinician-rated severity.

Taken together, across studies, unpredictable threat most consistently increased reflexive defensive responding and early attentional processing, whereas effects on later attentional allocation and performance monitoring were less robust. Importantly, uncertainty did not exert a uniform influence. Its effects depended on qualitative features of unpredictability, the physiological response system, and the individual difference factor examined. Clinical variation was likewise not captured by a single disorder-specific physiological signature but emerged in response-system-specific associations and heterogeneous multisystem response patterns. As a synthesis of the empirical findings and the broader theoretical literature, this dissertation proposes the uncertainty-imminence continuum model of defensive responding. The model conceptualizes defensive responding as arising from the interaction between situational threat architecture and individual differences across partially dissociable physiological systems, positioning uncertainty, alongside threat imminence, as a central organizing dimension relevant to anxiety-related psychopathology.

1. Introduction

"*The oldest and strongest emotion of mankind is fear, and the oldest and strongest kind of fear is fear of the unknown*" wrote H.P. Lovecraft in his 1927 essay "Supernatural Horror in Literature" (Lovecraft, 1927, as cited in Joshi & Schultz, 2001, p. 255). Fear of the unknown describes "an individual's propensity to experience fear caused by the perceived absence of information" (Carleton, 2016a, p. 5) and reflects the inextricable link between threat and uncertainty. This association captures a central challenge for psychological and neuroscientific models of anxiety. Humans and other animals rarely encounter threat under conditions of complete information; in the words of Arend (2024, p. 1), "uncertainty is elemental, everywhere, everything, and existentially connected to all human activity". Potential danger is often ambiguous, temporally unpredictable, probabilistic, and signaled indirectly (Dugas et al., 2026; Gu et al., 2020). This poses a challenge for adaptive responding, because responses are not only concerned with immediate danger but also with the anticipation of possible danger that is uncertain.

Against this background, the introduction begins by outlining normative defensive responding as the functional framework for understanding how uncertainty shapes responses to potential threat. This includes the organization of defensive behavior within the framework of the threat imminence continuum theory and the physiological systems through which defensive responding can be indexed. Next, the modulatory role of uncertainty in defensive responding is explored by considering uncertainty from both situational and individual difference perspectives. Finally, these processes are situated within categorical and dimensional models of anxiety-related psychopathology. Together, the following sections develop the theoretical and empirical background for the central research questions of this cumulative dissertation: How uncertainty shapes defensive responding, and how these responses may be related to individual differences and clinical expressions of anxiety-related psychopathology.

1.1 Defensive Responding

In order to survive, humans have always had to respond rapidly to impending threat. Quick responses to possibly dangerous situations were essential to survive under evolutionary pressure, i.e., under predation and environmental threat (Blanchard, 1997; Blanchard et al., 2011; Öhman & Mineka, 2001). This rapid discrimination of danger signals and safety signals was needed to recruit defensive mobilization and save resources (Nesse, 2005). Optimally, this evolutionarily conserved defensive system would generate many false alarms, because these false-positive errors would still have lower costs than one false-negative error (Nesse, 2005), a bias that has been rewarded through evolution (Abend, 2023). Consequently, humans frequently show defensive responses, which unfold across

psychological, physiological, and behavioral levels. At the psychological level, defensive responding includes changes in attention and subjective experience. As such, unexpected or biologically salient stimuli can elicit an orienting response that facilitates their detection and further processing (Nieuwenhuis et al., 2011; Öhman, 1979). At the physiological level, threat signals elicit sympathetic activation of the autonomic nervous system (Battaglia & Thayer, 2022; Roelofs & Dayan, 2022), and engage the hypothalamic-pituitary-adrenal (HPA) axis (McEwen, 2007). At the behavioral level, defensive responding includes reactions such as fight, flight, or freezing (Roelofs, 2017). Together, these multisystem responses coordinate threat detection, physiological mobilization, and adaptive action. The resulting pattern of defensive responding varies systematically with threat proximity (Abend, 2023; Fanselow et al., 2019).

1.1.1 The Predatory Imminence Continuum Theory

The predatory imminence continuum theory formalizes this variation by organizing defensive responding along a continuum of increasing threat imminence (Fanselow, 1994; Fanselow et al., 2019; Fanselow & Hoffman, 2024; Hoffman et al., 2022; Figure 1). According to this theory, defensive responding is dynamically organized into distinct modes that are recruited as a function of perceived threat proximity and expressed across psychological, physiological, and behavioral response levels. Psychological responses include attentional processing and subjective experience. In the pre-encounter phase, no predator is directly detected but the environment signals potential danger. Behavior is characterized by hypervigilant, cautious exploration and increased sensory sampling, reflecting anxiety-like states that bias attention toward possible danger while maintaining flexibility (e.g., walking through a forest known to contain wolves). Upon detection of a threat (e.g., spotting a wolf), the organism transitions into the post-encounter phase, behaviorally dominated by freezing and suppression of ongoing behavior and parasympathetically mediated bradycardia. This mode represents an active defensive strategy to promote survival by reducing detectability and preparing for rapid action, corresponding to an emotional state of fear. As threat imminence further escalates (e.g., when the wolf approaches and contact becomes likely), the organism enters the contact phase (or circa-strike phase; Abend, 2023). This mode is characterized by abrupt, high-intensity motor output, including explosive flight or defensive aggression, accompanied by strong sympathetic activation and maximal muscle recruitment. Behavior becomes rapid and less stereotyped, reflecting urgent, last-moment survival responses aimed at immediate escape or confrontation. Accordingly, each phase has a distinct adaptive value, functional specialization, and partially dissociable neural circuits (Fanselow & Hoffman, 2024; Hoffman et al., 2022; Tseng et al., 2023). This is mirrored in the terminology for affective states, in which anxiety describes the sustained

affective, anticipatory, pre-encounter to post-encounter state and fear describes the affective response to acute, imminent threat, i.e., post-encounter phase, with panic describing the affective response in the contact (circa-strike) phase (Abend, 2023; Hoffman et al., 2022). Neural responses underlying human defensive responding are likewise dissociable along the predatory imminence continuum.

1.1.2 Neural Underpinnings of Orienting and Defensive Responding

Establishing the basic mechanisms of normative defensive responding provides the functional and neurobiological reference framework for understanding how uncertainty modulates these systems and how such modulation may become maladaptive. At the neural level, distributed and interacting circuits spanning the extended amygdala, hypothalamus, midbrain, and cortical regions orchestrate defensive responding (Grogans et al., 2023). Recruitment within the central extended amygdala varies with threat imminence. Although the amygdala has traditionally been linked to phasic threat responses and the bed nucleus of the stria terminalis (BNST) to sustained anticipation of uncertain threat, recent evidence suggests substantial overlap, with both contributing across distal and imminent threat contexts (Cornwell et al., 2025). As threat becomes more imminent, the periaqueductal gray increasingly contributes to the coordination of defensive responses, including freezing and active defensive behavior (Fanselow, 1994; Fanselow & Hoffman, 2024; Perusini & Fanselow, 2015; Tovote et al., 2015). These subcortical systems interact with differentiated prefrontal regions that shape defensive responding according to current goals and contextual information (Grogans et al., 2023). Specifically, orbital and ventromedial prefrontal regions contribute to the integration of sensory and threat-value information, anterior cingulate and other medial prefrontal regions contribute to contextual threat appraisal and autonomic regulation, and lateral prefrontal regions support attentional control and goal-directed regulation (Kenwood et al., 2022). Within this distributed architecture, orienting responses are particularly relevant during the pre-encounter and early post-encounter phases, when potential threat still needs to be detected and evaluated. Classical accounts of threat-related orienting distinguished rapid subcortical processing from more elaborated cortical processing (LeDoux, 1995; LeDoux & Pine, 2016). Rapid visual threat processing may involve a subcortical pathway from the retina via the superior colliculus and pulvinar to the amygdala, enabling rapid threat-related processing without extensive cortical analysis (LeDoux, 1995; LeDoux & Pine, 2016). In contrast, cortical pathways allow more detailed sensory analysis and interact with attentional and prefrontal systems supporting contextual appraisal and flexible regulation of defensive responses (Carr, 2015; Pessoa & Adolphs, 2010). Contemporary accounts conceptualize threat processing less in terms of two strictly separate pathways but more as

recurrent interactions among subcortical, sensory, attentional, and prefrontal systems (Koller et al., 2019; Kragel et al., 2021; Pessoa & Adolphs, 2010).

Taken together, rapid and highly automated subcortical processing together with more elaborated cortical processing enable biologically salient stimuli to be detected quickly while permitting increasingly detailed and context-sensitive evaluation. These processes are part of broader defensive states that are expressed across psychological, physiological, and behavioral response systems. Specifically, the startle reflex, measured using electromyography (EMG), provides an index of reflexive defensive responding, whereas event-related potentials (ERPs), measured using electroencephalography (EEG), capture the temporal dynamics of sensory and attentional processing. Together, these measures form the operational basis for examining defensive responding in the empirical studies of this dissertation. An overview of these measures is provided in Box 1, with more detailed descriptions presented in the following sections.

Box 1. *Key Processes and their Psychophysiological Operationalizations*

Process	Operationalization
Reflexive defensive responding: Rapid activation of subcortical defensive systems that prepares the organism for protective action in response to potential threat as part of defensive responding.	**Startle eyeblink reflex** Electromyography of the m. orbicularis oculi following an acoustic startle probe. Potentiation of the response indexes increased defensive system activation (Blumenthal et al., 2005; Bradley et al., 2005; Hamm et al., 1993; Zheng & Schmid, 2023).
Early sensory processing: Rapid, largely automatic registration and gating of incoming sensory information facilitating enhanced processing of salient stimuli (Cuthbert et al., 1998).	**Probe-locked N1** Frontocentral negative event-related potential (ERP) component occurring approximately 100 ms after the acoustic startle probe reflecting early sensory processing in auditory cortical areas (Ford et al., 2016; Verkindt et al., 1995).
Later attentional allocation: Allocation and redistribution of attentional resources during more elaborated processing of incoming information (Polich, 2007, 2012).	**Probe-locked P3** Centroparietal positive ERP component approximately 300 ms after the startle probe. Its amplitude reflects the attentional resources allocated to the probe; suppression during threat anticipation suggests redirection of resources toward the threatening context (Ferry & Nelson, 2020; MacNamara & Barley, 2018).
Performance monitoring: Rapid evaluation of ongoing behavior and action outcomes that supports the detection of errors and the adaptive adjustment of subsequent behavior, here conceptualized to capture endogenous threat signals (Hajcak, 2012; Proudfit et al., 2013; Weinberg et al., 2012, 2016).	**Error-related negativity (ERN)** A frontocentral negative ERP component emerging within 100 ms after an erroneous response. Its amplitude indexes neural error processing and the demand to subsequently recruit cognitive control (Falkenstein et al., 1991; Gehring et al., 1993).

1.1.3 Defensive Responding Reflected in Reflex Physiology

The startle reflex provides a translational and quantifiable index of reflexive defensive responding, with increased startle magnitude reflecting greater defensive engagement (Blumenthal et al., 2005; Bradley et al., 2005; Hamm et al., 1993; Lang & Bradley, 2013; Zheng & Schmid, 2023). The primary acoustic startle response depends on a short-latency brainstem pathway involving the nucleus reticularis pontis caudalis (PnC), whereas affective modulation of startle magnitude is thought to rely on modulatory input from the centromedial amygdala to brainstem startle circuitry (Kuhn et al., 2020). Based primarily on rodent work, this modulatory pathway appears to involve projections from the central nucleus of the amygdala to the PnC, with additional modulation by interconnected regions such as the basolateral amygdala, bed nucleus of the stria terminalis, and periaqueductal gray (M. Davis, 2006; de Haan et al., 2018; Kuhn et al., 2020). The startle response is an adaptive (Landis & Hunt, 1939), cross-species translational measure (Fendt & Koch, 2013; Grillon & Baas, 2003; Haaker et al., 2019; Zheng & Schmid, 2023), providing insights into evolutionarily conserved aspects of defensive responding. In humans, the magnitude of the startle reflex is usually measured as EMG of the eye blink component (Blumenthal et al., 2005) and has been found to be potentiated during aversive states (Grillon & Baas, 2003) such as being placed in a dark room (Grillon et al., 1997, 1999) or anticipating aversive, electrotactile stimulation (Grillon & Ameli, 1998).

Taken together, normative defensive responding is dynamically organized along a continuum of threat imminence and expressed across coordinated psychological, physiological, and behavioral response levels. However, threat imminence represents only one situational dimension along which defensive responding may be organized.

1.2 The Modulatory Role of Uncertainty in Defensive Responding

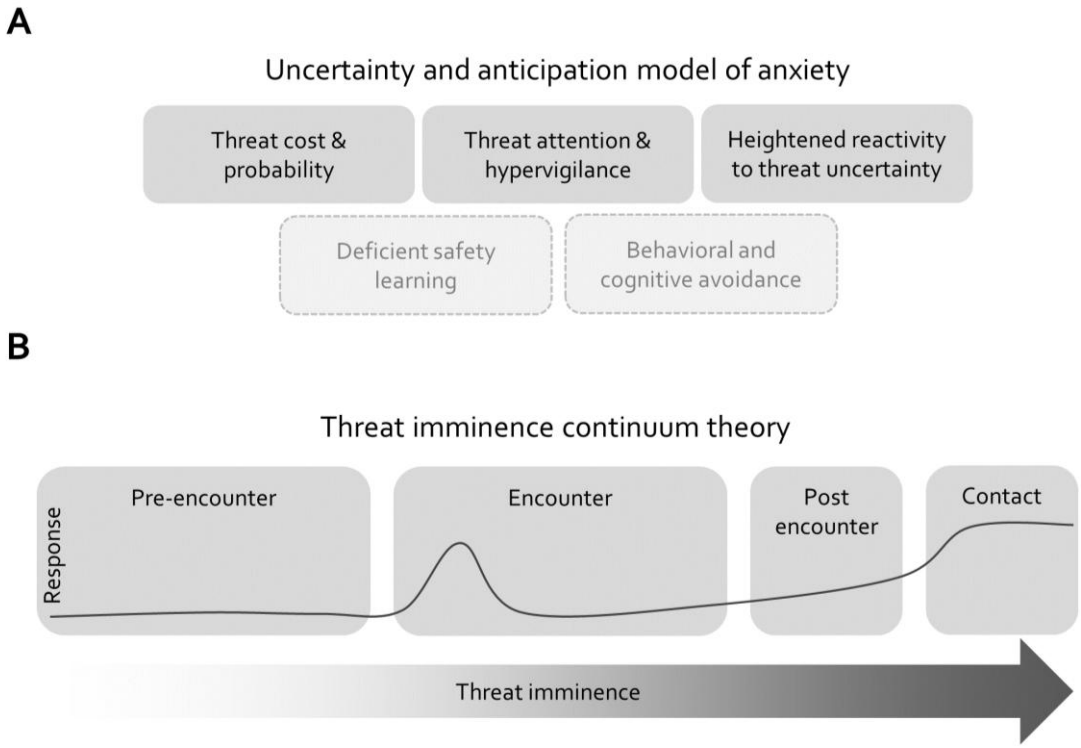
Real-world threats are rarely fully specified in advance. In natural environments, organisms seldom possess complete information about whether a threat will occur, when it will occur, or how severe its consequences will be. Thus, beyond threat imminence, potential danger is characterized by varying degrees and forms of uncertainty (Carleton, 2016a; Gu et al., 2020). From an evolutionary perspective, defensive systems likely evolved to operate under such epistemic constraints: survival did not require perfect prediction, but adaptive responding under incomplete information (Nesse, 2005). Uncertainty may therefore constitute a second situational dimension shaping defensive responding alongside threat imminence. Defensive activation in the pre-encounter phase of the threat imminence continuum theory is not triggered by direct predator contact, but by uncertain environmental cues that signal possible danger (Abend, 2023; Fanselow, 1994; Fanselow et al., 2019). Threat imminence and unpredictability can thus be conceptualized as partially independent

situational dimensions that jointly shape defensive engagement. In this dissertation, uncertainty and unpredictability are treated as related but distinct constructs. Unpredictability refers primarily to objective or experimentally defined features of a situation, such as variability in the timing, probability, or intensity of threat, whereas uncertainty refers more directly to the subjective state arising from incomplete information about potential outcomes (as differentiated by Grupe & Nitschke, 2013).

Anticipatory states such as anxiety can be understood as adaptive modes of functioning under incomplete information, biasing defensive responding toward potential harm to promote survival in contexts in which the costs of false-negative errors outweigh the cost of false-positive errors (V. M. Brown et al., 2023; Van den Bergh et al., 2021). Thus, defensive responses are considered normative insofar as they serve adaptive functions. As such, they facilitate the detection of potential danger, mobilize physiological resources, and prepare organisms for action (LeDoux, 1995; Öhman, 1979; Öhman & Mineka, 2001). However, the same mechanisms may become maladaptive when they are excessively engaged, insufficiently regulated, or persistent in contexts in which threat is absent or unlikely (V. M. Brown et al., 2023).

A prominent integrative framework for explaining how anticipatory responding under uncertainty may become maladaptive is the *Uncertainty and Anticipation Model of Anxiety* (UAMA; Grupe & Nitschke, 2013; Figure 1A). The UAMA integrates previous neuroscientific findings within a coherent neurobiological architecture of responding to unpredictable threat by organizing the findings into five essential processes for adaptive responses to unpredictable threat: 1) disrupted expected value calculation, 2) increased threat attention and hypervigilance, 3) deficient safety learning, 4) behavioral and cognitive avoidance, and 5) heightened reactivity to threat uncertainty (Grupe & Nitschke, 2013). The UAMA conceptualizes these five components as dynamically interacting processes embedded in distributed cortico-limbic-midbrain circuits (Grupe & Nitschke, 2013; Tanovic, Gee, et al., 2018). The UAMA thus represents a neurobiologically grounded framework that specifies mechanistic pathways through which normative anticipatory responding to unpredictable threat may transition into maladaptive states.

Figure 1. *Central Models of Threat Anticipation*



Note. Theoretical models of threat anticipation informative for the theoretical background of the present dissertation. **A**: Uncertainty and anticipation model of anxiety (Grupe & Nitschke, 2013) posing five central processes, of which three (in black font) are addressed experimentally. **B**: The threat imminence continuum theory (adapted from Abend, 2023 Figure 1; Fanselow, 1994), which conceptualizes responding to threat as a function of threat proximity.

However, uncertainty itself is not a unitary feature of threatening situations. The processes described by the UAMA may be engaged under different features and degrees of unpredictability, depending on what information about a potential threat is unavailable. To specify the situational conditions under which uncertainty shapes defensive responding, it is therefore necessary to distinguish different features of threat unpredictability.

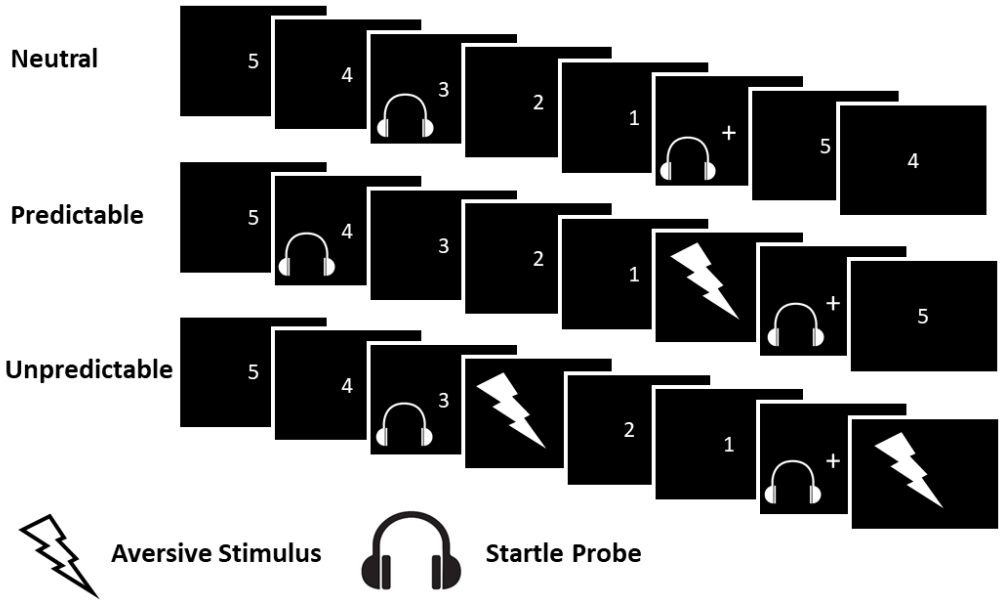
1.2.1 Features of Threat Unpredictability

Threats can vary along multiple features of unpredictability (Gu et al., 2020): Specifically, unpredictability may concern timing (when a threat will occur), threat occurrence probability (how often or whether a threat will occur), intensity or magnitude (how severe its consequences will be), and even valence (whether an outcome is aversive, neutral, or rewarding). In human experimental research, temporal unpredictability has been the most commonly manipulated feature of threat (Gorka, Lieberman, Shankman, et al., 2017a, 2017b; Grillon et al., 2008, 2009; Hoge et al., 2024;

Kreutzer & Gorka, 2021; MacNamara & Barley, 2018; Shankman et al., 2011), whereas fewer studies have directly varied threat occurrence probability (Bennett et al., 2018; Chin et al., 2016; Morriss, Bennett, et al., 2021; Tanovic, Pruessner, et al., 2018). Accordingly, both threat imminence and unpredictability represent key dimensions that shape defensive responding and can be systematically manipulated in laboratory settings.

The NPU-threat test is an instructed threat-of-shock paradigm for experimentally manipulating threat predictability (Schmitz & Grillon, 2012). The task comprises three conditions: a neutral (N) condition in which no aversive stimulus is delivered, a predictable (P) condition in which shocks are signaled by a discrete cue, and an unpredictable (U) condition, in which unsignaled aversive stimuli are delivered (Figure 2). The P and U conditions differ primarily by virtue of the temporal information available about the impending threat. While the P condition models temporally imminent and signaled threat, the U condition is thought to model sustained anticipatory responding under temporal unpredictability (Schmitz & Grillon, 2012). Abundant evidence indicates that startle responses are robustly potentiated during unpredictable threat anticipation relative to the neutral condition (Beatty et al., 2022; Ferry & Nelson, 2020; Nelson & Shankman, 2011; Papenfuss et al., 2021), demonstrating that the unpredictability of threat recruits sustained defensive activation. Of note, the effect of temporal unpredictability on startle magnitude seems specific to negative valence (Parisi et al., 2017). Thus, the NPU-threat test enables experimental dissociation of the effects of threat imminence and predictability on defensive responding. Beyond reflex potentiation, the modulation of defensive responding under unpredictable threat extends to neural indices of attentional processing.

Figure 2. *NPU-Threat Test*



Note. The depicted NPU-threat test is based on a version using the countdown as a threat cue (Nelson & Shankman, 2011) instead of a geometric symbol (Schmitz & Grillon, 2012) to increase the temporal predictability of the aversive stimulus in the predictable condition.

Consistent with the broader neurofunctional architecture of defensive responding outlined in Section 1.1.2, neuroimaging studies indicate that unpredictable threat anticipation recruits distributed cortical and subcortical circuitry, including regions implicated in salience processing, threat appraisal, and attentional control (Morriss, Bell, et al., 2022; Radoman et al., 2021; Robinson et al., 2012). Within the UAMA, the NPU-threat test is particularly suited to examine heightened reactivity to threat uncertainty, as unpredictable threat reliably elicits sustained defensive activation reflected in startle potentiation (Schmitz & Grillon, 2012). At the same time, the paradigm provides a context in which uncertainty-related changes in sensory and attentional processing can be examined, thereby addressing UAMA processes related to threat attention and hypervigilance. Assessing these processes requires measures with sufficient temporal resolution to distinguish early from later stages of information processing.

1.2.2 Electroencephalographic Correlates of Unpredictable Threat Anticipation

ERPs provide the temporal resolution required to distinguish early sensory processing from later attentional allocation during unpredictable threat anticipation (Box 1). Specifically, the N1 component is observed as a frontocentral negative deflection peaking approximately 100 ms following the onset of an auditory stimulus. When locked to acoustic startle probes, the N1 reflects early sensory processing (Cuthbert et al., 1998) in auditory cortical areas (Ford et al., 2016; Verkindt

et al., 1995) and is thought to capture an initial, automatic orienting response as part of a sensory gating mechanism of attention (Luck et al., 2000; Vogel & Luck, 2000). Sensory gating represents a pre-attentive filtering mechanism that enhances early sensory processing of threatening stimuli while inhibiting irrelevant competing input (Grunwald et al., 2003; Pessoa & Adolphs, 2010). Consistent with heightened vigilance under uncertainty, previous studies have found increased probe-locked N1 amplitudes during anticipation of unpredictable threat (Correa et al., 2022; Ferry & Nelson, 2020; Nelson, Hajcak, et al., 2015; Nelson & Hajcak, 2017b).

At a later stage of attentional processing, the P3 component is observable as a positive centroparietal deflection peaking around 300 ms post-stimulus and reflects the allocation of attentional resources associated with frontal temporo-parietal generators (Polich, 2007, 2012). During threat anticipation, probe-locked P3 amplitudes are typically suppressed, presumably reflecting a redistribution of attentional resources toward threat cues rather than the startle probe (Ferry & Nelson, 2020; MacNamara & Barley, 2018). Previous studies mainly found P3 suppression during the anticipation of threat irrespective of predictability (Correa et al., 2022; MacNamara & Barley, 2018; Nelson, Hajcak, et al., 2015; Nelson & Hajcak, 2017b). Although projections back to neural structures based on these findings warrant caution given the inverse problem and limited spatial precision of EEG source localization (Grech et al., 2008), results from the NPU-threat test nevertheless indicate that unpredictable threat alters early sensory processing and later attentional allocation during threat anticipation. To date, psychophysiological research on threat anticipation has predominantly focused on startle EMG, whereas ERP indices of sensory and attentional processing have garnered comparatively less attention. Taken together, startle EMG and probe-locked ERPs provide complementary indices of processes implicated in the UAMA. Startle EMG more directly captures heightened defensive reactivity to threat uncertainty, whereas modulation of N1 and P3 reflects changes in early sensory processing and later attentional allocation within an unpredictable threat context. Importantly, because the acoustic startle probes are not themselves the anticipated aversive stimulus, these ERP effects should be interpreted as contextual modulation of sensory and attentional processing rather than as direct measures of attentional bias towards threat (Box 1). The processes considered so far concern the anticipation of externally signaled threat. However, uncertainty-related processing may also extend to internally generated threat-relevant events. Errors provide a useful model of such endogenous signals, allowing the investigation of whether uncertainty also modulates neurocognitive processing beyond external threat anticipation.

1.2.3 Errors as Endogenous Threats

Threat-relevant events may originate externally from the environment or internally from one's own actions and their consequences. Errors represent such internally generated events. They are aversive and inherently unpredictable, signal a discrepancy between intended and actual outcomes, and may therefore be conceptualized as endogenous threat signals (Hajcak, 2012; Proudfit et al., 2013; Weinberg et al., 2012, 2016). Consistent with this interpretation, errors have been associated with startle potentiation, suggesting increased defensive engagement following erroneous responses (Hajcak & Foti, 2008; Riesel et al., 2013). Errors thus provide a means of extending the study of uncertainty from the anticipation of externally signaled threat to the processing of internally generated, potentially threatening events. This extension also entails a conceptual link to the UAMA. In particular, the UAMA process of inflated estimates of threat cost and probability includes altered updating of threat expectancies following aversive prediction errors, that is, discrepancies between predicted and actual outcomes (Grupe & Nitschke, 2013; Tanovic, Gee, et al., 2018). Although an error as a behavioral response is not itself equivalent to a prediction error, prominent accounts of performance monitoring propose that errors engage negative prediction error signals that support behavioral adaptation (Holroyd & Coles, 2002). This provides the theoretical basis for examining whether uncertainty also modulates neural responses to errors.

Detecting errors and adjusting subsequent behavior rely on performance monitoring processes, which constitute an adaptive component of cognitive control (Botvinick et al., 2001). Using EEG within response-conflict paradigms, the neural correlate of error monitoring can be studied, an ERP component coined the error-related negativity (ERN; Box 1; Gehring et al., 1993), initially termed error negativity (Falkenstein et al., 1991). The ERN has primarily been linked to activity in the anterior cingulate cortex, particularly its dorsal/anterior midcingulate region, with additional contributions from posterior cingulate and presupplementary motor regions (Debener et al., 2005; Grützmann et al., 2016; Manoach & Agam, 2013). Within the present framework, the ERN therefore provides a candidate neurophysiological measure for testing whether the modulatory effects of uncertainty extend from external threat anticipation to the processing of internally generated errors.

Taken together, unpredictability modulates multiple components of defensive responding, including reflexive defensive responding, autonomic arousal, and sensory and attentional processing, while conceptual links may extend to performance monitoring processes. The UAMA provides a framework for relating these processes to anticipatory responding under uncertainty (Grupe & Nitschke, 2013). Although such responses serve adaptive functions, individuals vary in the extent to which they are engaged, sustained, and regulated. Understanding this interindividual variability is

therefore important for determining when normative responding under uncertainty becomes clinically relevant.

1.3 Uncertainty in Anxiety-Related Psychopathology

Building on the normative models of defensive responding and uncertainty outlined above, the following section considers how these processes may translate to individual differences and clinical manifestations of anxiety-related psychopathology. Individual differences in defensive responding under uncertainty may provide a link between normative threat anticipation and anxiety-related psychopathology. From this perspective, anxiety-related psychopathology can be conceptualized as an exaggerated or dysregulated manifestation of otherwise normative defensive responses to potential threat (Abend, 2023; Kenwood et al., 2022; J. B. Rosen & Schulkin, 1998; Shuhama et al., 2019). In a similar vein, the UAMA suggests that clinical anxiety reflects exaggerated threat expectancy, increased threat attention and hypervigilance, and heightened reactivity to threat uncertainty (Grupe & Nitschke, 2013). A central question is therefore which individual difference factors contribute to such altered responding.

As such, individuals differ in how they cope with the experience of uncertainty (Birrell et al., 2011; Carleton et al., 2007; Freeston et al., 1994). This is reflected in the trait intolerance of uncertainty (IU; Carleton, 2016a, 2016b; Dugas et al., 2026), defined as "an individual's dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information, and sustained by the associated perception of uncertainty" (Carleton, 2016b, p. 31). Historically, IU was of interest in an attempt to explain pathologic worry and generalized anxiety disorder (Dugas et al., 1998; Freeston et al., 1994), but has since been described as a general psychological vulnerability factor for psychopathology (Dugas et al., 2026). This transdiagnostic conceptualization is supported by meta-analytic findings demonstrating robust associations between IU and internalizing psychopathology (Carleton, 2012; McEvoy et al., 2019; Shihata et al., 2016; Gentes & Ruscio, 2011). Primary studies have linked elevated IU to generalized anxiety and worry (T. A. Brown & Naragon-Gainey, 2013; Counsell et al., 2017; Koerner & Dugas, 2008), health anxiety and hypochondriasis (Deacon & Abramowitz, 2008), OCD and OCD symptoms (Holaway et al., 2006; Tolin et al., 2003), depressive symptoms and disorders (Jensen et al., 2016), social anxiety (Boelen & Reijntjes, 2009), panic and agoraphobic symptoms (Carleton et al., 2013; Mahoney & McEvoy, 2012), posttraumatic stress symptoms (Oglesby et al., 2015; Taylor et al., 2007), and psychosis-related symptoms (Fraser et al., 2006). Meta-analyses further support elevated IU in eating disorders (M. Brown et al., 2017) and associations between IU and psychotic symptoms (Morriss et al., 2025). Across disorders, IU shows the strongest correlations with symptoms of generalized

anxiety disorder (Akbari et al., 2026; Khawaja & McMahon, 2011; McEvoy et al., 2019). Consequently, IU represents a cross-sectional transdiagnostic marker (Knowles & Olatunji, 2023; Norr et al., 2013) that has also been implicated in the prediction of anxiety and distress, for example during the COVID-19 pandemic (Adamis et al., 2024; Akbari et al., 2024), or generally predicting the development of generalized anxiety disorder (Ryan et al., 2025), posttraumatic symptoms (Boelen, 2019; Oglesby et al., 2015) and potentially detrimental effects on treatment outcomes (Keefer et al., 2017; but see Laposa & Puccinelli, 2025). Behaviorally, IU has been shown to predict worry (Bruin et al., 2006; Groves et al., 2020), reassurance seeking, checking and avoidance behavior (Appel et al., 2026; Flores et al., 2018; Fourtounas & Thomas, 2016; Lind & Boschen, 2009; Sarawgi et al., 2013). Excessively executed, these maladaptive coping strategies may be conceptualized as maintaining factors that perpetuate anxiety-related psychopathology through negative reinforcement (Einstein, 2014; Flores et al., 2018; Mansell, 2005; Tolin et al., 2003).

In sum, IU captures a dispositional tendency to experience uncertainty as aversive and to manage this state via strategies that prioritize predictability (Carleton, 2016a; Einstein, 2014), hereby conferring vulnerability to internalizing psychopathology such as anxiety disorders (Ryan et al., 2025). Thus, IU as a personality trait dovetails with the UAMA's emphasis on heightened anticipatory processing (Grupe & Nitschke, 2013). If IU amplifies anticipatory responding, this vulnerability should also be observable in neurophysiological systems indexing defensive responding, including startle responses, sympathetic arousal, and the temporal dynamics of attentional allocation.

With respect to temporally unpredictable threat anticipation, individual differences in IU have been linked to startle responses (Nelson et al., 2016; Nelson & Shankman, 2011), while the direction of the effect was opposite in both studies. Specifically, Nelson et al. (2016) found that higher prospective IU was associated with increased startle, whereas Nelson and Shankman (2011) found decreased startle to unpredictable threat in individuals with higher IU. In line with this, increased IU has been linked to amygdala activity in the anticipation of potential threat (Greifenberger et al., 2025; Morriss et al., 2015; Oathes et al., 2015; Schienle et al., 2010; Somerville et al., 2013). Other studies did not find a link between IU and physiological outcomes during temporally unpredictable threat anticipation (Bennett et al., 2018; Lieberman et al., 2016; Morriss, Bradford, et al., 2022; Morriss et al., 2020; Papenfuss et al., 2021). With regard to threat probability (i.e., the occurrence probability of threat), Chin et al. (2016) found that IU was associated with increased startle responses during a lower reinforcement rate in a fear conditioning experiment. However, lowering the threat probability in another threat-of-shock experiment did not lead to effects of individual differences in IU (Bennett et al., 2018). This raises the question of which situational aspect of unpredictability individuals with higher IU are sensitive to. Since prior findings on effects of IU on temporal unpredictability and overall

threat probability are mixed (Bennett et al., 2018; Chin et al., 2016; Lieberman et al., 2016; Nelson et al., 2016; Nelson & Shankman, 2011; Papenfuss et al., 2021), empirical evidence is needed to pinpoint which experimental feature might be particularly relevant for eliciting heightened threat responding in individuals with higher IU.

Previous research linking IU to threat anticipation has primarily focused on ratings and startle responses, while attentional processes that are implicated in the UAMA (Fergus et al., 2013; Fergus & Carleton, 2016; Grupe & Nitschke, 2013) have received less attention. Compared to functional magnetic resonance imaging (fMRI) studies linking IU to activation in the limbic system, less empirical evidence is available for the neural underpinnings of attentional alterations in individuals with high IU (Bottesi, 2024; Greifenberger et al., 2025; Grupe & Nitschke, 2013; Tanovic, Gee, et al., 2018). Studies examining attentional processes during threat anticipation suggest decreased attentional processing during unpredictable threat anticipation to be linked to inhibitory IU (Correa et al., 2022), a subfactor of IU describing inhibited action in the face of uncertainty (Berenbaum et al., 2008; Birrell et al., 2011; Carleton et al., 2007). Conversely, parental prospective IU was associated with increased early attentional processing of startle probes in adolescents and young adults (Beatty et al., 2022). Further, attentional responding to unpredictable shocks was associated with individual differences in IU (Ferry & Nelson, 2021). Taken together, prior findings suggest that IU modulates multiple components of defensive responding, including reflexive defensive responding and attentional processing. However, the presence and direction of these associations vary across experimental contexts, features of unpredictability, and physiological measures. It therefore remains unclear under which conditions IU amplifies startle responding and how its effects unfold across the temporal course of attentional processing, from early sensory processing indexed by the probe-locked N1 to later attentional allocation indexed by the probe-locked P3.

Building on the conceptual link between uncertainty and performance monitoring outlined in Section 1.2.3, individual differences in IU may extend to neural responses to errors. Within the UAMA, inflated estimates of cost and altered updating following unexpected outcomes provide a theoretical rationale for such an association (Grupe & Nitschke, 2013; Tanovic, Gee, et al., 2018). Previous research linking individual differences in IU to the neural correlates of action monitoring is inconclusive: While an early study reported a bidirectional association between the subfactors of IU and the ERN (Jackson et al., 2016), later studies could not replicate this finding (Malbec et al., 2022; Ruchensky et al., 2020; Sandre & Weinberg, 2019), with the exception of Grabowska et al. (2024), who found tentative support for an association between inhibitory IU and the ERN. Thus, sufficiently powered studies are needed to clarify whether IU is reliably associated with the ERN. Performance

monitoring may likewise be sensitive not only to dispositional differences in IU but also to experimentally induced states of uncertainty.

Prior studies have examined performance monitoring under experimentally manipulated uncertainty using unpredictable tones (Jackson et al., 2015) or false feedback during a math task (White et al., 2018), as well as under threat of shock (Riesel et al., 2012). Unpredictable tones and threat of shock were associated with increased ERN amplitudes, whereas false feedback was associated with reduced ERN amplitudes. Since prior manipulations of predictability during error monitoring have relied on small samples (Jackson et al., 2015) and have not been independently replicated, it remains unclear whether situational uncertainty causally modulates performance monitoring. Across these lines of research, it remains largely unclear to what extent putative IU-related effects on threat anticipation, attention, and performance monitoring generalize to clinical populations. Accordingly, a key next step is to determine whether neurophysiological correlates associated with IU can also be observed in clinical populations, as this would help understand the mechanisms underlying psychopathology.

1.3.1 Clinical Studies of Unpredictable Threat Anticipation

Clinical studies employing the NPU-threat test provide evidence that anxiety-related psychopathology may be associated with heightened responding to unpredictable threat. In a sample of patients with mixed anxiety disorders, Hoge et al. (2024) reported increased startle potentiation during unpredictable threat anticipation. Heightened startle potentiation during unpredictable threat has also been reported in patients with panic disorder and PTSD (Grillon et al., 2008, 2009). Subsequent findings further suggested that panic attacks may constitute a particularly relevant clinical feature underlying increased responding to unpredictable threat in patients with generalized anxiety disorder and/or social anxiety disorder (Grillon et al., 2017). In addition, empirical evidence suggests startle potentiation to unpredictable threat in fear-based disorders, including specific phobia, suggesting that heightened responding to unpredictable threat may be particularly relevant in fear-based psychopathology (Gorka, Lieberman, Klumpp, et al., 2017; Gorka, Lieberman, Shankman, et al., 2017b).

However, findings across diagnostic groups remain heterogeneous. Although panic disorder has been associated with increased responding to unpredictable threat in some studies (Grillon et al., 2008; Shankman et al., 2013), this pattern has not emerged consistently (Gorka et al., 2014; Stevens et al., 2018). Greater PTSD symptom severity and comorbid panic disorder and PTSD have even been associated with blunted or reduced reactivity to unpredictable threat (Katz et al., 2018; Lieberman et al., 2020). Moreover, heightened reactivity has also been observed outside the internalizing

spectrum, including in alcohol use disorder (Gorka et al., 2020; Gorka & Shankman, 2017). Thus, altered responding to unpredictable threat anticipation does not appear to map straightforwardly onto individual diagnostic categories or onto the internalizing psychopathology spectrum as a whole. Although existing studies support the clinical relevance of unpredictable threat anticipation, the direction and diagnostic specificity of these alterations have remained elusive.

Several important research gaps further limit the interpretation of the clinical literature. First, previous research has not captured the full breadth of anxiety-related psychopathology, and patients with OCD remain underrepresented in clinical NPU research. Second, most clinical studies have focused on startle EMG, whereas substantially less is known about attentional processes during threat anticipation. Evidence from subclinical samples indicates that the probe-locked N1 (Box 1) is associated with anxiety-related symptom dimensions (Correa et al., 2022; Nelson, Hodges, et al., 2015; Stevens et al., 2018). Initial evidence for familial aggregation further suggests that enhanced N1 amplitudes may represent a potential endophenotypic marker of anxiety (Correa et al., 2022; Morriss et al., 2023). Probe-locked P3 amplitudes have likewise been associated with transdiagnostic symptom dimensions, including anxiety sensitivity and inhibitory IU (Correa et al., 2022; Nelson, Hodges, et al., 2015). Whether these dimensional associations generalize to patients with anxiety-related psychopathology remains to be established (Stevens et al., 2018). Third, prior clinical NPU studies have typically examined single outcome measures rather than integrating responses across physiological systems. It therefore remains unclear whether alterations in responses to unpredictable threat anticipation extend across reflexive defensive responding, early sensory processing, later attentional allocation, and autonomic arousal. Finally, most studies relied on comparisons between diagnostic groups and healthy controls. Given the heterogeneity and high comorbidity of anxiety-spectrum disorders (Essau et al., 2018), clinically meaningful variation in symptom severity and transdiagnostic traits may not be readily captured by categorical comparisons (Krueger & Markon, 2006). Dimensional approaches may therefore leverage continuous symptom variation to identify clinically relevant differences in defensive responding that may be obscured by diagnostic group comparisons alone.

Together, these gaps highlight the need for clinical approaches that integrate multiple physiological response systems and account for both diagnostic and dimensional variation in anxiety-related psychopathology.

1.3.2 Dimensional Models of Anxiety-Related Psychopathology

Two prominent frameworks that provide such a dimensional perspective are the Research Domain Criteria initiative (RDoC; Cuthbert, 2014) and the hierarchical taxonomy of psychopathology

(HiTOP; Kotov et al., 2017, 2021). The RDoC framework has helped spearhead a shift toward research that integrates fundamental biobehavioral findings to understand the mechanisms that underlie mental disorders (Cuthbert & Insel, 2013; Eaton et al., 2023). Within the RDoC framework, IU is categorized in the negative valence systems domain within the construct potential threat as a self-report unit of analysis. Importantly, the NPU-threat test is listed as a paradigm in this domain (National Institute of Mental Health, n.d.). Responses to unpredictable threat are therefore incorporated into the RDoC framework across units of analysis. This perspective extends beyond traditional nosological systems such as the DSM-5 (American Psychiatric Association, 2013) and ICD-11 (World Health Organization, 2020), by emphasizing transdiagnostic mechanisms of psychopathology rather than disorder-specific categories (Lilienfeld & Treadway, 2016).

Conceptually related to the RDoC framework and similarly motivated by the limitations of the ICD and DSM in accounting for heterogeneity within disorders and comorbidity across diagnostic categories, HiTOP provides a dimensional framework for psychopathology (Eaton et al., 2023; Kotov et al., 2017, 2021). HiTOP proposes a hierarchically graded, dimensional approach to modeling psychopathology that is rooted in empirical evidence rather than consensus-based expert decisions. Psychopathology is organized within broad spectra, which are further differentiated into narrower subfactors, syndromes or disorders, symptom components, and individual signs and symptoms (Kotov et al., 2017). Anxiety psychopathology and phobic fear are captured within the internalizing spectrum (Watson, Clark, et al., 2022; Watson, Levin-Aspenson, et al., 2022). Similarly, OCD is primarily placed on the internalizing spectrum (Watson, Levin-Aspenson, et al., 2022; L. Zhang & Takahashi, 2024), also loading on the thought disorder spectrum (Faure & Forbes, 2021; Sellbom et al., 2020). Together, RDoC and HiTOP provide complementary perspectives for linking dimensional psychopathology to underlying biobehavioral processes across units of analysis (C. N. Davis et al., 2025). This transdiagnostic and process-oriented view is aligned with the UAMA perspective on uncertainty in anxiety-related psychopathology.

1.3.3 Summary

Taken together, prior research indicates that defensive responding is organized not only by threat imminence but also by uncertainty. Normative defensive responses involve coordinated changes across reflexive, autonomic, and attentional systems that are adaptively recruited when threat is possible but insufficiently specified. Unpredictability can therefore be conceptualized as a central modulatory dimension of defensive responding that complements threat proximity in models of fear and anxiety (Abend, 2023; Fanselow et al., 2019; Grupe & Nitschke, 2013). These responses

may become maladaptive when they are excessively engaged, insufficiently regulated, or persist despite low objective threat (V. M. Brown et al., 2023).

Individual differences in IU may link these normative processes to internalizing psychopathology by shaping the extent to which uncertain situations elicit defensive mobilization and altered attentional processing (Dugas et al., 2026; Einstein, 2014; Shihata et al., 2016). However, prior findings linking IU to physiological responses to unpredictable threat remain mixed and appear to vary across features of unpredictability and physiological response systems (Bennett et al., 2018; Chin et al., 2016; Nelson et al., 2016; Nelson & Shankman, 2011; Tanovic, Gee, et al., 2018). It therefore remains unclear under which conditions IU amplifies reflexive defensive responding and how its effects unfold across early sensory processing, later attentional allocation, and performance monitoring (Correa et al., 2022; Jackson et al., 2016; Malbec et al., 2022; Tanovic, Pruessner, et al., 2018).

Clinical evidence is similarly heterogeneous, with studies reporting both heightened and attenuated responding to unpredictable threat across anxiety-related diagnostic groups (Gorka, Lieberman, Klumpp, et al., 2017; Gorka, Lieberman, Shankman, et al., 2017b; Grillon et al., 2008, 2009, 2017; Hoge et al., 2024; Katz et al., 2018; Lieberman et al., 2020). Moreover, previous clinical research has predominantly focused on startle potentiation and categorical comparisons between diagnostic groups and healthy controls, limiting conclusions about whether altered threat responding generalizes across physiological systems and reflects disorder-specific, dimension-specific, or transdiagnostic processes. Dimensional frameworks such as RDoC and HiTOP therefore provide a rationale for multisystem research linking physiological responses to transdiagnostic symptom dimensions (Cuthbert, 2014; Eaton et al., 2023; Kotov et al., 2021). The following section translates these gaps into the research questions of the present dissertation.

2. Research Objectives

2.1 Research Aim

The present cumulative dissertation aims to elucidate how uncertainty shapes defensive responding and related psychological and neurocognitive processes within the broader spectrum of internalizing and anxiety-related psychopathology. Building on experimental models of threat anticipation, the dissertation examines how threat predictability modulates defensive responding and attentional dynamics, and whether these responses vary systematically as a function of transdiagnostic symptom dimensions and clinical status. Across four studies, the dissertation links a normative neurobehavioral framework of defensive responding under uncertainty to clinically relevant individual differences in anxiety-related symptom dimensions.

Defensive responding is quantified using multimodal psychophysiological indices (mainly startle reflex and startle probe-locked ERPs indexing early sensory engagement, N1, and later attentional allocation, P3). In addition, the dissertation extends uncertainty research beyond externally signaled threat by testing whether uncertainty also modulates endogenous threat processing during performance monitoring, operationalized via the ERN. The overarching objectives are 1) to specify the role of IU in threat anticipation under different features of unpredictability (temporal vs. probabilistic unpredictability), 2) to determine which physiological processes are most sensitive to individual differences in IU and broader anxiety-related symptom dimensions, and 3) to examine how alterations in responses to unpredictable threat are expressed across diagnostic groups and dimensional symptom variation in anxiety-related psychopathology. Together, these objectives aim to clarify how unpredictable threat anticipation can be situated within neurobiological and clinical models of anxiety-related psychopathology.

2.2 Research Questions

The overarching aim of this dissertation is structured around three research questions that are addressed across four empirical studies. The corresponding hypotheses were formulated and preregistered per study.

Question 1 (Study 1):

Does IU selectively amplify defensive responding to unpredictable threat, and if so, under which feature of unpredictability?

Question 2 (Studies 1, 2, 3):

Which physiological processes—reflexive defensive responding, early sensory processing, later attentional allocation, autonomic arousal, and/or error monitoring—are most sensitive to individual differences in IU and broader anxiety-related symptom dimensions?

Question 3 (Studies 3, 4):

Are alterations in unpredictable threat anticipation best understood as disorder-specific signatures, as correlates of dimensional symptom variation, or as transdiagnostic response profiles cutting across anxiety-related psychopathology?

3. Summary of Studies

3.1 Study 1: Intolerance of Uncertainty in Unpredictable Threat Anticipation

Citation. Carsten, H. P., Härpfer, K., & Riesel, A. (2022). A rare scare: The role of intolerance of uncertainty in startle responses and event-related potentials in anticipation of unpredictable threat. *International Journal of Psychophysiology*, *179*, 56–66. https://doi.org/10.1016/j.ijpsycho.2022.06.018

3.1.1 Objective

The aim of Study 1 was to examine the role of different experimental features of unpredictability in threat anticipation. Unpredictability is a core feature and experimental operationalization of uncertainty and can arise from multiple situational characteristics, including temporal unpredictability and probabilistic unpredictability (Morriss, Bennett, et al., 2021; Morriss, Zuj, et al., 2021). Within experimental research on threat anticipation, the NPU-threat test has primarily been used to manipulate temporal predictability and has consistently demonstrated heightened defensive responding to temporally unpredictable threat (Gorka, Lieberman, Shankman, et al., 2017b; Nelson, Hajcak, et al., 2015; Nelson, Hodges, et al., 2015; Nelson & Shankman, 2011; Schmitz & Grillon, 2012). However, prior studies have varied threat occurrence probability unsystematically across predictable threat conditions, and only a limited number of studies have directly examined this probabilistic unpredictability (Bennett et al., 2018; Davies & Craske, 2015; Hefner & Curtin, 2012). Consequently, it remains unclear how temporal unpredictability and probabilistic unpredictability independently and jointly shape physiological responses during threat anticipation.

In addition to these experimental factors, individuals differ substantially in their responses to uncertainty, as reflected in the trait IU (Carleton et al., 2007; Freeston et al., 1994). Heightened IU has been identified as a transdiagnostic factor across internalizing psychopathology (Carleton, 2012; Gentes & Ruscio, 2011; Mahoney & McEvoy, 2012) and has consequently been imprinted into the RDoC matrix as part of the potential threat construct (Cuthbert & Insel, 2013). Theoretical models such as the UAMA imply that individuals with elevated IU show heightened threat expectancies and increased uncertainty-related arousal during unpredictable situations (Einstein, 2014; Grupe & Nitschke, 2013; Tanovic, Gee, et al., 2018). However, empirical findings linking IU to physiological responses during unpredictable threat anticipation are mixed, with studies reporting increased, decreased, or absent associations between IU and startle responding under conditions of temporal (Bennett et al., 2018; Lieberman et al., 2016; Morriss, Bradford, et al., 2022; Papenfuss et al., 2021) and probabilistic unpredictability (Bennett et al., 2018).

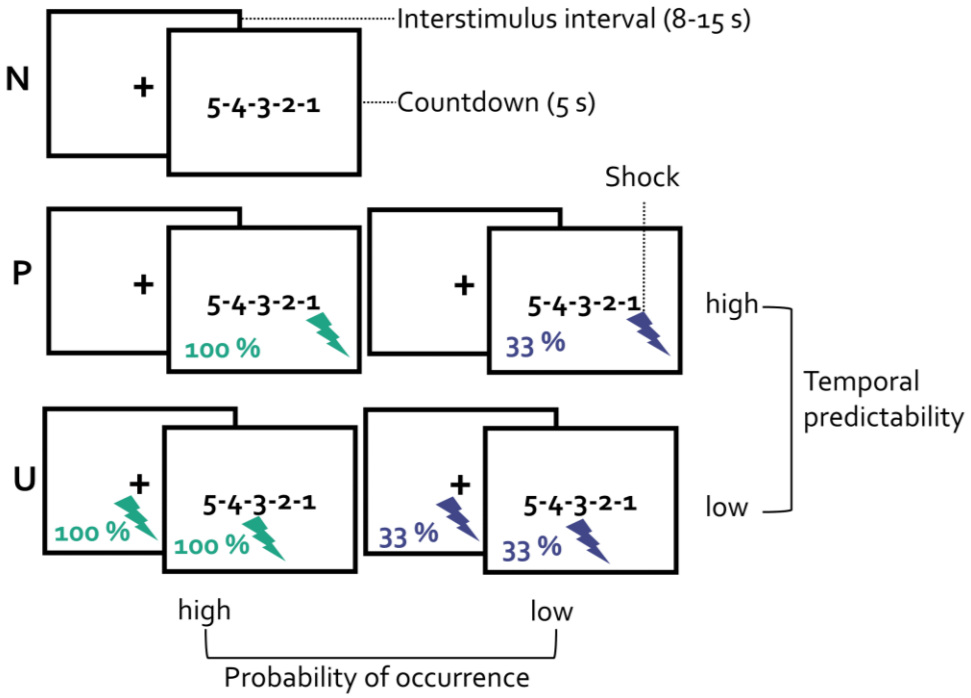
These inconsistencies suggest that IU may confer sensitivity to specific features of unpredictability rather than unpredictability per se (Shihata et al., 2016; Tanovic, Gee, et al., 2018). Accordingly, Study 1 aimed to systematically disentangle the effects of temporal predictability and threat occurrence probability on physiological indices of defensive responding. Here, startle EMG and startle probe-locked ERPs (N1, P3) were used to examine responses during threat anticipation across early sensory and later attentional processing stages. Study 1 focused on the question of whether individual differences in IU predict differential physiological responding in distinct features of unpredictability. The preregistered hypothesis predicted heightened physiological responding under lower threat occurrence probability in individuals with higher IU, reflected in a smaller difference in responses to high- and low-probability unpredictable threat and increased responding to low-probability predictable threat.

3.1.2 Method

The hypotheses and methods were preregistered prior to data collection (www.osf.io/fmt54) and the data are openly available (www.osf.io/sug8c). This study encompassed 90 students (73 % females) aged 18 to 30 (M = 23.52, SD = 3.22), based on an a priori power estimation to obtain .80 power at α = .05 to detect medium effect sizes of f^2 = 0.15. We excluded participants with lifetime substance-related disorders, bipolar disorder, schizophrenia spectrum disorder and neurological disorders, as well as intake of benzodiazepines and neuroleptics. IU was measured using the German translation of the short version of the Intolerance of Uncertainty Scale (IUS-12; Carleton et al., 2007; using the item translations of Gerlach et al., 2008), which showed good internal consistency (Cronbach's α = .87; validation study: α = .91; Carleton et al., 2007). After informed consent, the participants underwent an adapted version of the NPU-threat test (Schmitz & Grillon, 2012). Specifically, participants were presented with a countdown counting down from "5" to "1" (Nelson & Shankman, 2011) in three instructed conditions: In the no threat condition (N), no aversive stimulus was presented. In the predictable threat condition (P), participants received a shock to the back of the hand, every time the countdown reached "1". In the unpredictable threat condition (U), participants could receive a shock at any time during the countdown or the interstimulus interval (Figure 3). Two task blocks were presented in a randomized order. In one task block, shock probability was 100 % and in the other task block, the shock probability was lowered to 33 % (Figure 3). Thus, in addition to the established manipulation of temporal predictability, Study 1 introduced a systematic manipulation of threat occurrence probability (i.e., probabilistic unpredictability). The electric shock was calibrated to the intensity of a subjective rating of 7-8 (M = 3.46 mA, SD = 2.03, range 0.40 – 10.50) on a scale from 0 (not aversive) to 10 (extremely aversive, not endurable). Participants further

completed anxiety ratings after each task block (i.e., 100 % probability block and 33 % probability block) on visual analogue scales ranging from 0 to 100. Startle EMG and startle probe-locked ERPs (N1, P3) as well as startle probe-locked SCR were measured. Statistical analyses included multilevel models with random intercepts per participant to enable the analysis of single trial startle data.

Figure 3. *NPU-Threat Test Manipulating Threat Probability*



Note. Visualization of the NPU-threat test with high and low threat occurrence probability. N = Neutral, P = Predictable threat, U = Unpredictable Threat.

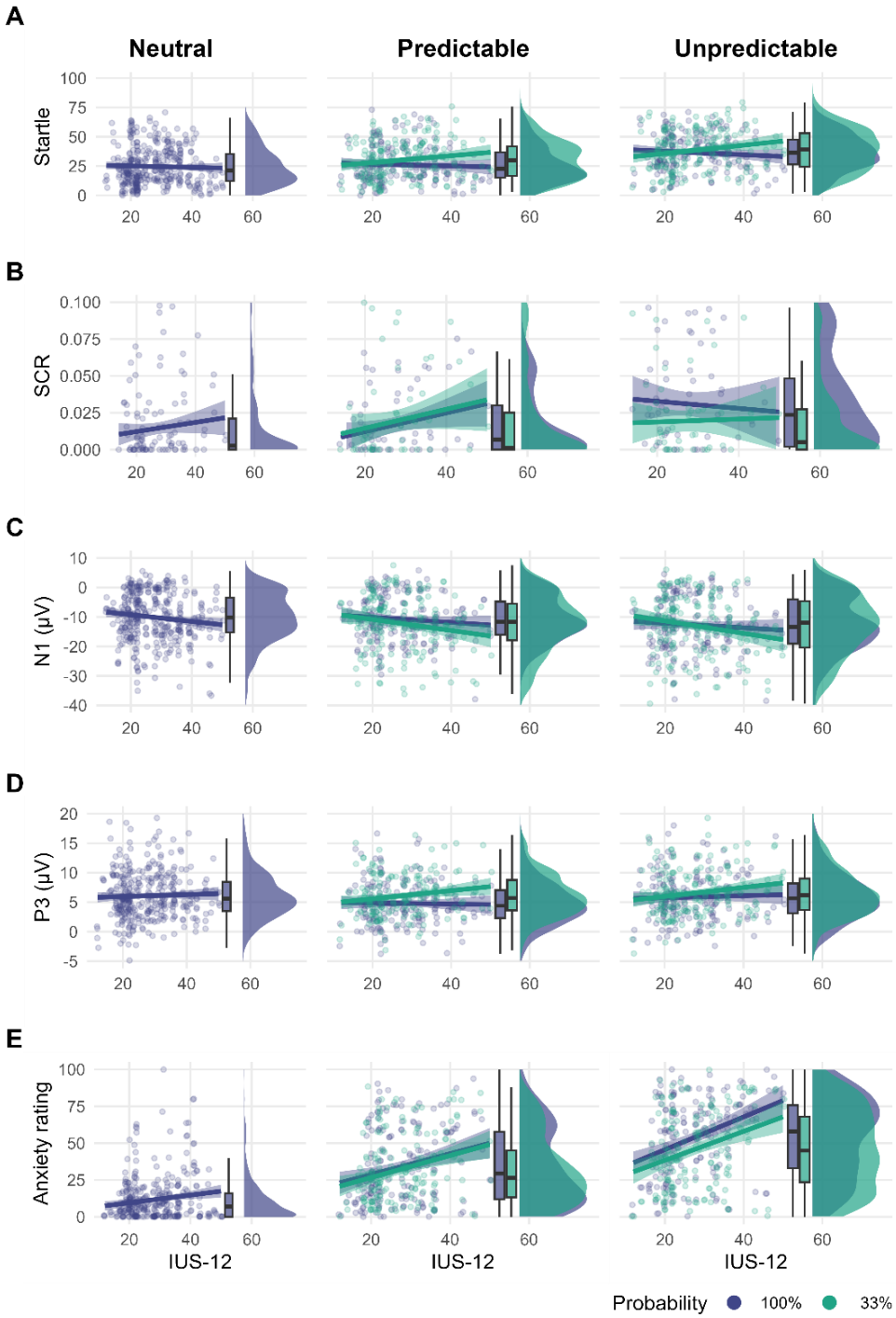
3.1.3 Results

Three main patterns of results emerged, concerning temporal unpredictability, threat occurrence probability, and individual differences in IU. First, across both threat occurrence probability blocks, the expected condition effects of the NPU-threat test were observed. Anxiety ratings increased stepwise from N to P to U. Startle responses were strongest during the U condition compared with both P and the N conditions, and probe-locked N1 amplitudes were likewise enhanced during U relative to P and N conditions. Probe-locked P3 amplitudes showed a different pattern, with stronger suppression during P compared with N and U conditions. Probe-locked SCR were elevated during U relative to N. Thus, temporal unpredictability was most consistently reflected in increased subjective anxiety, reflexive defensive responding, early sensory processing, and sympathetic arousal.

Second, lowering the threat occurrence probability from 100 % to 33 % further modulated responding, but these effects differed across outcomes. Startle responses were increased under low compared with high threat probability in both the P and U conditions. In contrast, anxiety ratings during U were lower under 33 % than 100 % threat probability. Probe-locked P_3 was generally more suppressed under high than low threat probability, whereas N1 amplitudes were not significantly affected by threat probability. SCR likewise showed no general effect of threat probability, although responses were larger during U than P under 100 % threat probability. Overall, participants responded to lower threat occurrence probability with increased startle, higher probe-locked P_3 (i.e., less suppression) and lower anxiety ratings.

Third, individual differences in IU selectively influenced these effects. Higher IU was associated with increased startle under low threat probability in both the P and U conditions, whereas no corresponding association emerged under high threat probability (Figure 4). Thus, the association between IU and defensive responding was linked to lower threat occurrence probability rather than specifically to temporal unpredictability. Higher IU was also associated with elevated anxiety ratings in the threat conditions, but this association did not vary as a function of threat probability. No significant associations with IU emerged for N1, P_3, or SCR. Exploratory analyses further suggested that the IU-related increase in startle under lower threat probability was primarily attributable to prospective rather than inhibitory IU.

Figure 4. *Main Results of Study 1*



Note. **A**: Range-corrected startle magnitude. **B**: Range-corrected, log-transformed startle probe-locked skin conductance responses. **C:** Startle probe-locked N1, FCz, area around the peak, ca. 120–180 ms. **D**: Startle probe-locked P3, Pz, mean activity 280–360 ms. **E**: Subjective anxiety ratings. Slopes across the Intolerance of Uncertainty Scale (IUS-12; Carleton et al., 2007), with shaded area indicating the standard error in temporally predictable and unpredictable shock conditions with 100 % and 33 % shock probability. Data are collapsed across cues for visualization (countdown, interstimulus interval). Adapted figure from Carsten et al. (2022).

3.1.4 Discussion

The results of Study 1 suggest that temporally unpredictable threat increases defensive responding as indexed by startle responses, and early attention, as indexed by N1, which is accompanied by subjective levels of anxiety, as indexed by ratings. Startle responses were increased for lower threat probability (33 %), irrespective of the temporal predictability, which suggests that the defensive responding was not proportional to the objective threat frequency (Bennett et al., 2018). This was further specified by a selective IU modulation of defensive responding, such that IU was associated with increased startle only under low threat probability (33 %) but not under high threat probability (100 %) in both temporally predictable and unpredictable threat anticipation. In other words, the IU associations in defensive responding to unpredictable threat anticipation were probability-driven rather than driven by temporal unpredictability. Notably, exploratory analyses indicated that this effect was attributable to prospective IU, consistent with theoretical accounts proposing that heightened anticipatory threat expectancy characterizes individuals high in IU. This may lead individuals to err on the side of caution (Van den Bergh et al., 2021) by maintaining heightened defensive mobilization even when the objective probability of threat is low. This mismatch between threat likelihood and defensive output aligns with models emphasizing inflated threat expectancy and uncertainty-related arousal in individuals with high IU (Einstein, 2014; Grupe & Nitschke, 2013). Thus, IU may amplify startle responses specifically under high uncertainty, even when those situations involve lower objective threat (Chin et al., 2016; Tanovic, Gee, et al., 2018). Consequently, for individuals high in IU, it may not be threat salience per se, but rather the salience introduced by uncertainty that is particularly aversive (Grupe & Nitschke, 2013; Tanovic, Gee, et al., 2018).

This effect was specific to startle and was not observed for N1, P3, or SCR, suggesting that the association with IU was selective for reflexive defensive responding rather than extending uniformly across early sensory processing, later attentional allocation, and autonomic arousal. Across threat probabilities, N1 was not significantly modulated by probability. Nevertheless, individual differences in condition-related N1 modulation covaried with startle modulation, particularly for contrasts involving unpredictable threat (Appendix A), suggesting partial convergence between early sensory and reflexive defensive responses despite their differential sensitivity to threat probability. In contrast, probe-locked P3 was generally suppressed under 100 % threat probability, indicating greater attentional engagement under higher task load, possibly due to increased proximity or frequency of aversive stimulation. In sum, probabilistic threat manipulations led to dissociable effects in early and later attentional processing stages. While early sensory processing of the startle probe

(N1) was unaffected by threat probability, later attentional allocation (P_3) was sensitive to threat probability, but not to individual differences in IU.

3.1.5 Conclusion

Study 1 contributes to the overarching research aims of this dissertation in three ways. First, with regard to Research Question 1, the findings indicate that IU does not uniformly amplify responding to unpredictability, but is associated with heightened reflexive defensive responding specifically under low threat occurrence probability rather than temporal unpredictability. By disentangling temporal and probabilistic unpredictability within the same paradigm, Study 1 therefore suggests that IU-related alterations in defensive responding may be more closely linked to uncertainty about whether a threat will occur than to uncertainty about when it will occur. Second, with regard to Research Question 2, this association was response-system-specific. IU was associated with increased startle responses under low threat probability but not with N1, P_3, or SCR, suggesting that reflexive defensive responding was more sensitive to individual differences in IU than early sensory processing, later attentional allocation, or sympathetic arousal. Third, Study 1 demonstrates the importance of differentiating features of unpredictability in experimental models of threat anticipation. The distinct effects of temporal unpredictability and threat occurrence probability indicate that unpredictability should not be treated as a unitary experimental construct and that its specific features may constitute important boundary conditions for individual difference associations. Importantly, Study 1 was conducted in a student sample, leaving open whether these associations generalize to broader and clinical populations.

3.2 Study 2: Testing the Influence of Uncertainty on the Error-Related Negativity

Citation. Carsten, H. P., Härpfer, K., Malbec, M., Wieser, M. J., & Riesel, A. (2025). Are errors more aversive in an uncertain world? Testing the influence of uncertainty on the error-related negativity in a randomized controlled trial. *International Journal of Psychophysiology*, *207*, 112480. https://doi.org/10.1016/j.ijpsycho.2024.112480

3.2.1 Objective

The aim of Study 2 was to examine whether uncertainty modulates performance monitoring, as indexed by the ERN, across dispositional and situational levels. Specifically, the study tested whether the ERN was associated with individual differences in IU and whether it was altered by experimentally induced state uncertainty.

Uncertainty has primarily been studied in the context of externally signaled threat, such as unpredictable aversive stimulation. However, uncertainty is not limited to environmental danger. Errors are inherently aversive, signal potentially negative consequences, and represent violations of expectations. From this perspective, they can be conceptualized as endogenous threat signals (Hajcak, 2012; Proudfit et al., 2013; Weinberg et al., 2012, 2016) and individuals display increased defensive responding following errors (Hajcak & Foti, 2008; Riesel et al., 2013). From a theoretical perspective, integrative models of anxiety such as the UAMA suggest inflated estimates of threat costs and disrupted prediction error signaling (Freeston & Komes, 2023; Greifenberger et al., 2025; Grupe & Nitschke, 2013; Tanovic, Gee, et al., 2018), that could be taken to suggest altered neural responses to errors in individuals who perceive uncertainty as aversive. Despite the theoretical plausibility of a link between error monitoring and uncertainty, and in contrast to the comparatively extensive startle literature using the NPU-threat paradigm, empirical evidence directly manipulating state uncertainty and assessing its impact on the ERN remains scarce. Prior studies have induced uncertainty during performance monitoring tasks through unpredictable tones (Jackson et al., 2015) or threat of shock (Riesel et al., 2012), both of which showed increases in ERN. Conversely, completing a math task with false feedback was associated with reduced ERN (White et al., 2018). Since prior manipulations of predictability during error monitoring include small sample sizes (Jackson et al., 2015) and have not been independently replicated, it remains unclear whether situational states of uncertainty causally modulate error monitoring processes.

Next to situational modulations of uncertainty, individual differences in IU have only inconsistently been linked to the ERN. While an early study reported a bidirectional association between the subfactors of IU and the ERN (Jackson et al., 2016), later studies could not replicate this finding (Malbec et al., 2022; Ruchensky et al., 2020; Sandre & Weinberg, 2019), with the exception of

Grabowska et al. (2024), who reported tentative support for an association of inhibitory IU and (principal component based quantification of the) ERN. Taken together, these findings on possible links between IU and performance monitoring are inconclusive, which motivated Study 2 to attempt a preregistered conceptual replication. To extend previous replication attempts (Malbec et al., 2022), Study 2 further involved a randomized controlled design, testing the influence of a novel uncertainty symptom induction on the ERN. Experimentally inducing uncertainty allowed us to test whether heightened IU serves as a process underlying altered error monitoring in internalizing psychopathology (Rosser, 2019; Shihata et al., 2016).

To induce states of uncertainty, a variety of experimental protocols have been reported in the literature (Deschenes et al., 2010; Faleer et al., 2017; Grenier & Ladouceur, 2004; Mosca et al., 2016; N. O. Rosen & Knäuper, 2009; Rosser, 2019; Tullett et al., 2014). Following Carleton's (2016a, 2016b) conceptualization of IU, the present, newly developed uncertainty induction was optimized for the salience of the symptom induction. A bidirectional effect of IU's subfactors on the ERN was expected, as well as an increased ERN attributable to the uncertainty symptom induction.

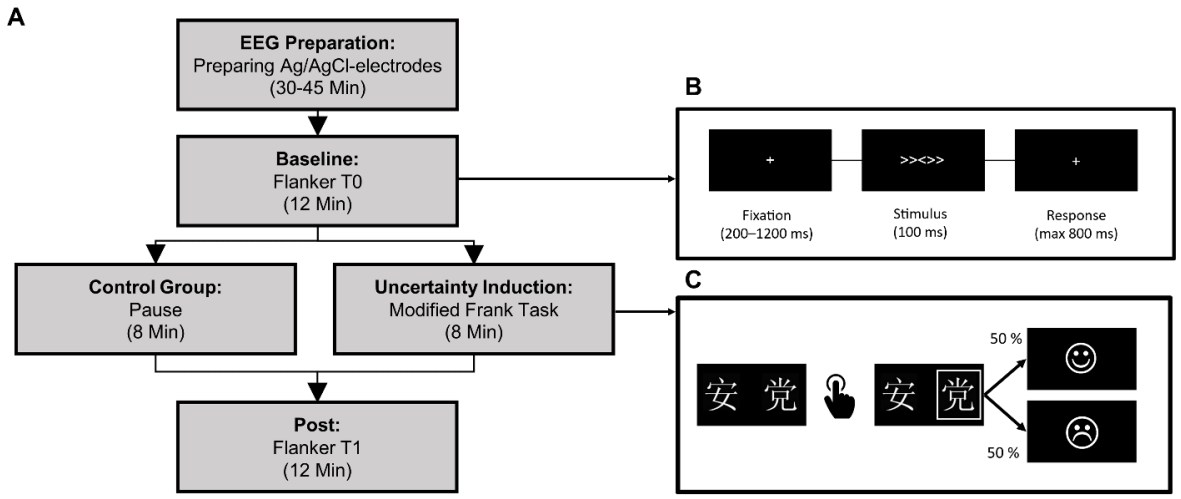
3.2.2 Method

The method and hypotheses were preregistered before the start of data collection (www.osf.io/7crds) and the data are openly available (www.osf.io/wh2an). The preregistered sample for the cross-sectional effects of IU on the ERN encompassed 118 participants after exclusion due to a priori defined exclusion criteria. Participants were aged 18-30 years (M = 23.00, SD = 3.03) and currently enrolled students. Exclusion criteria encompassed, as in Study 1, neurological disorders or substance-related disorders, schizophrenia spectrum disorder, bipolar disorder or needle phobia. For exploratory analyses, and to increase statistical power beyond the preregistered sample, the data were merged with two additional samples. First a sample examined at the University of Hamburg was included (N = 59). Second, data from Malbec et al. (2022) were included (N = 178) and preprocessed to be in accordance with the preprocessing pipeline of Study 2. Thus, data from 355 participants were available for cross-sectional analyses. To examine the effect of the uncertainty induction on the ERN, a subsample of the preregistered cohort was randomized to either an uncertainty induction group (n = 30) or a control group (n = 30; Figure 5A), with group size determined by an a priori power simulation based on effect sizes from previous uncertainty manipulations reporting medium to large effects (d = 0.87; White et al., 2018).

IU was measured using the short version of the Intolerance of Uncertainty Scale (IUS-12; Carleton et al., 2007; Gerlach et al., 2008). Participants were screened via phone, received written and verbal study information and provided informed consent. The participants then underwent a speeded

arrowhead version of the Eriksen-flanker task (Eriksen & Eriksen, 1974; Figure 5B), i.e., a baseline flanker task (To).

Figure 5. *Overview of the Procedure and Tasks in Study 2*



Note. **A:** Flowchart of the study procedure. The task duration is approximate. State ratings were conducted between baseline and induction procedures and between induction procedures and post measurement to assess momentary fluctuations in state uncertainty, worry, need for control, positive affect, and arousal. **B:** Eriksen-flanker task consisting of inter-trial interval with fixation cross, the presentation of congruent or incongruent stimuli and response window. The direction of the set of flanking arrows was pseudo-randomly congruent to the center arrow (<<<<< or >>>>>) or incongruent (<<><< or >><>>). **C:** Uncertainty symptom induction. Participants were presented with two signs and indicated their choice with a button press. Participants received probabilistic feedback, which was correct in 50 % of the choices.

Participants were then randomized to either an uncertainty induction or a time-matched control break, followed by a second flanker task (T1). Manipulation checks were administered after To and immediately before T1 using visual analogue scales (0-100; forced choice start at 50) assessing momentary uncertainty, worry, need for control, positive affect, and arousal. The uncertainty induction consisted of a learning task, in which participants selected "correct" signs while being told they were monitored and would receive performance feedback relative to their peers (Figure 5C). Feedback was in fact probabilistic (50 % correct and 50 % incorrect). To increase uncertainty, the experimenter provided scripted evaluative comments between blocks (e.g., claiming difficulty was reduced) and terminated the task after ca. 6 minutes, after which participants proceeded to the post-intervention flanker task (T1).

A 61-channel EEG was acquired, with a preregistered preprocessing pipeline including an early baseline (-500 to -300 ms relative to the response) and quantification of ERN as response-locked mean activity (0 - 100 ms). The data were analyzed using multilevel models, including complementary

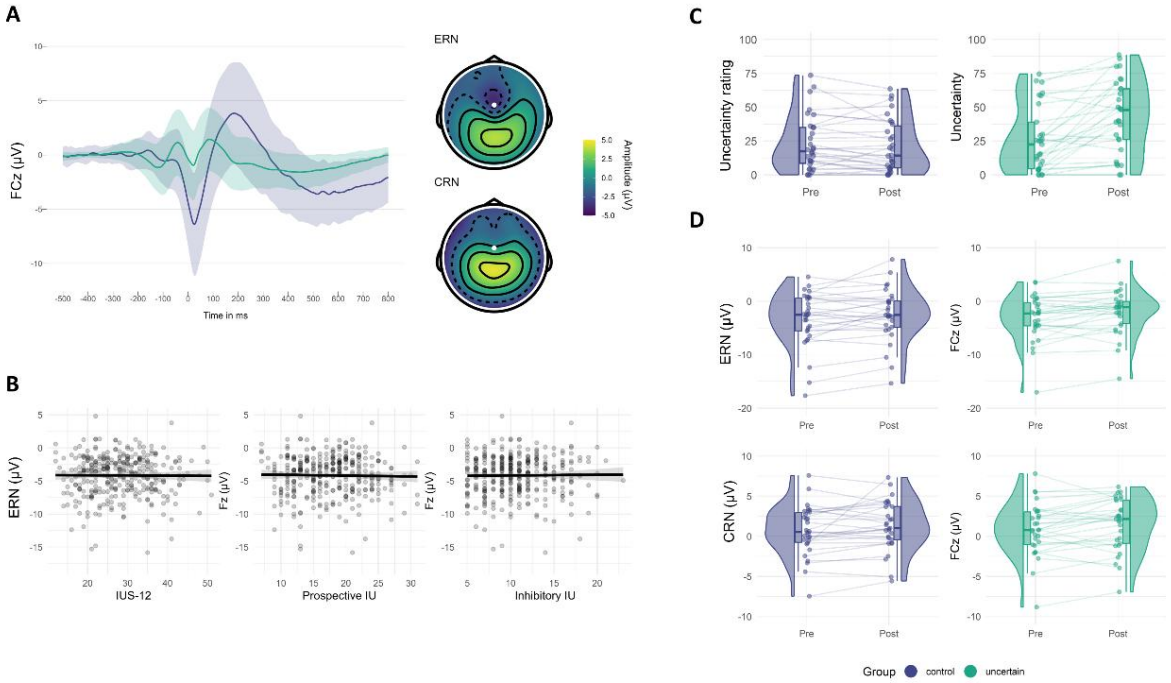
Bayesian multilevel analyses (Bürkner, 2017). Essentially, the analytical approach enabled modelling the repeated-measures structure of the ERP data and testing both categorical experimental effects and continuous individual difference effects and, via Bayesian analyses, quantifying evidence for the null hypothesis.

3.2.3 Results

For all included samples, significant differences between ERN and CRN amplitudes emerged (Figure 6A). Pertaining to individual differences, no cross-sectional effects emerged for IU or the respective subscales prospective IU or inhibitory IU on ERN or CRN amplitudes in the preregistered analyses (Figure 6B). For the exploratory analyses, two samples were added, including another sample from Hamburg (n = 59) and Rotterdam (n = 178), resulting in cross-sectional analyses for 355 participants. Together, the sample size was powered to detect even small effects of d = 0.14 (with 1 - β = .95) as indicated by sensitivity analyses. Complementary Bayesian analyses indicated strong evidence for null effects of overall IU, as well as the subfactors prospective IU and inhibitory IU on the ERN.

Testing the effect of the uncertainty induction, we found that the uncertainty induction increased ratings of state uncertainty from pre to post intervention (Figure 6C). However, this effect was not specific to uncertainty. The uncertainty induction also produced significant but smaller concurrent increases in worry, need for control and arousal in the induction group. Positive affect was not significantly affected by the intervention. Regarding ERPs, we found no significant effects of the uncertainty symptom induction on either ERN or CRN amplitudes (Figure 6D). Further, changes in ERN or CRN between To and T1 were not significantly modulated by trait individual differences in IU or the subfactors prospective and inhibitory IU.

Figure 6. *Main Results of Study 2*



Note. **A**: Grand averaged waveforms of error-related negativity (ERN) and correct-related negativity (CRN), scored at FCz (topography, white dot) with shaded area depicting the standard deviation at each ms in the preregistered sample (N = 118). **B**: Slopes of the IUS-12 and respective subscales for the ERN with shaded area depicting ± 95 % confidence interval in the combined sample (N = 355). **C**: Uncertainty ratings pre- and post uncertainty symptom induction in the induction group (n = 29) and control group (n = 29). **D**: ERN (top) and CRN (bottom) pre- and post uncertainty symptom induction per group. Figure adapted from Carsten et al. (2025).

3.2.4 Discussion

The results of Study 2 suggest that neither ERN nor CRN was cross-sectionally associated with individual differences in overall IU or on a subscale level in the examined student samples. The results from the randomized controlled design further suggest that the newly developed uncertainty symptom induction increased momentary states of uncertainty, but did not significantly affect ERN changes from pre to post symptom induction. Within the student samples examined here, these findings challenge a link between IU and the ERN by indicating that the ERN and CRN might be insensitive to individual differences in trait IU as well as momentary fluctuations of states of uncertainty.

Cross-sectional associations between IU and the ERN are suggested theoretically (Tanovic, Gee, et al., 2018) by frameworks conceptualizing errors as internal threat signals (Hajcak, 2012; Proudfit et al., 2013; Weinberg et al., 2012, 2016), a notion that is corroborated by empirical findings of increased defensive responding following errors (Hajcak & Foti, 2008; Riesel et al., 2013). The

previous empirical evidence is mixed, with reports of negative associations between inhibitory IU and the ERN in some studies (Grabowska et al., 2024; Jackson et al., 2016), but not consistently observed across studies (Malbec et al., 2022; Sandre & Weinberg, 2019). Conversely, prospective IU was reported to be associated with increased ERN in one study (Jackson et al., 2016) but not replicable in subsequent studies (Grabowska et al., 2024; Malbec et al., 2022; Sandre & Weinberg, 2019). The results of Study 2 extend these previous mixed findings in two ways. First, cross-sectional results add to the accumulating evidence suggesting no significant effects of IU or the respective subscales on the ERN (Malbec et al., 2022; Sandre & Weinberg, 2019). This previous evidence is corroborated by Bayesian analyses that indicate strong evidence against an effect of IU on a global or subscale level on the ERN. Second, previous cross-sectional literature is extended through results of Study 2's uncertainty symptom induction in a randomized controlled design, suggesting no significant changes in ERN pre-post symptom induction relative to the control group.

These findings hold implications for the broader scope of this dissertation. Empirical findings linked errors as endogenous threats (Proudfit et al., 2013; Weinberg et al., 2012, 2016) to reflexive defensive responding as indexed via increased startle (Hajcak & Foti, 2008; Riesel et al., 2013). However, error-related startle potentiation does not necessarily imply that neural indices of performance monitoring are associated with individual differences in IU or momentary fluctuations in uncertainty. As such, performance monitoring as indexed by the ERN and CRN might be integrated into broader cognitive control frameworks (Botvinick et al., 2001; Härpfer & Riesel, 2026; Holroyd et al., 2009; Holroyd & Coles, 2002; Moser et al., 2013; Yeung et al., 2004). Although the ERN shows cross-sectional associations with internalizing psychopathology (Moser et al., 2013; Pasion & Barbosa, 2019; Riesel, 2019; Riesel et al., 2025; Saunders & Inzlicht, 2020), i.e., with psychopathology implicated in models of uncertainty-related responding (Einstein, 2014; Grupe & Nitschke, 2013; Shihata et al., 2016; Van den Bergh et al., 2021), the way in which altered performance monitoring conveys vulnerability for internalizing and anxiety-related psychopathology (Härpfer & Riesel, 2026) might be less dependent on uncertainty-related information processing. In other words, errors might recruit cognitive control and defensive motivation circuitry independent of self-reported differences in state uncertainty or IU. Importantly, this notion does not preclude contextual influences on performance monitoring, as have been shown via unpredictable tones (Jackson et al., 2015) or punishment (Riesel et al., 2012, 2019). Taken together, the ERN may primarily reflect broader cognitive control and defensive motivation processes that operate partly independently of individual differences in IU or momentary uncertainty, while still remaining sensitive to contextual threat manipulations.

These theoretical implications of Study 2 should be interpreted against methodological limitations of the study. First, a comparatively young and academic sample was examined and participants with severe psychiatric disorders such as lifetime substance-related disorder, schizophrenia spectrum disorder, and bipolar disorder were excluded, limiting the clinical generalizability of these findings. However, n = 18 participants in our preregistered sample met the inclusion criteria of a lifetime internalizing disorder and the distribution of IUS-12 scores was comparable to the distribution reported in the validation study of the instrument (Carleton et al., 2007). Further, the symptom induction may have lacked specificity. Although it successfully increased state uncertainty, it also increased momentary states of worry, need for control, and arousal. Therefore, any effects of uncertainty on the ERN may have been confounded by these concurrent symptom changes. At the same time, the induction was intentionally designed to be highly salient, given the expected resilience of the young academic sample and prior studies asking for more salient symptom inductions (Härpfer et al., 2022).

3.2.5 Conclusion

Study 2 contributes to the overarching research aims of this dissertation in three ways. First, with regard to Research Question 2, the combined cross-sectional analyses provided no evidence that individual differences in overall IU or its subdimensions prospective and inhibitory IU were associated with performance monitoring as indexed by the ERN and CRN. Second, Study 2 extends the investigation of uncertainty from individual differences to experimentally induced states of uncertainty. Although the uncertainty induction successfully increased subjective state uncertainty, it did not alter ERN or CRN amplitudes. The randomized controlled design therefore provides no evidence that short-term increases in state uncertainty causally modulate error-related neural activity under the conditions examined here. Third, these findings delineate a boundary condition for the influence of uncertainty across neurophysiological processes. While errors can be conceptualized as endogenous, potentially threatening events, the present findings suggest that uncertainty-related alterations observed in other aspects of defensive responding do not necessarily extend to neural correlates of performance monitoring. Study 2 therefore constrains the interpretation of previous findings linking IU to the ERN and suggests that performance monitoring may be comparatively independent of both self-reported trait IU and short-term fluctuations in state uncertainty.

3.3 Study 3: Anxiety Dimensions in Threat Anticipation

Citation. Carsten, H. P., Härpfer, K., Nelson, B. D., Kathmann, N., & Riesel, A. (2023). Don't worry, it won't be fine. Contributions of worry and anxious arousal to startle responses and event-related potentials in threat anticipation. *Cognitive, Affective, & Behavioral Neuroscience*, *23*, 1141–1159. https://doi.org/10.3758/s13415-023-01094-4

3.3.1 Objective

The aim of Study 3 was to examine whether individual differences in anxious apprehension and anxious arousal were differentially associated with reflexive defensive responding and attentional processing during unpredictable threat anticipation. Building on the preceding studies, Study 3 shifts the focus from IU as a specific transdiagnostic vulnerability factor to broader anxiety symptom dimensions. Whereas Study 1 examined whether IU modulates defensive responding as a function of experimental features of unpredictability, Study 3 focuses on the research question of whether distinct phenotypic expressions of anxiety-related psychopathology are differentially reflected in psychophysiological responses during unpredictable threat anticipation. This question is central to dimensional models of anxiety, which propose that anxiety-related psychopathology cannot be fully understood by categorical diagnoses alone (Cuthbert, 2014; Cuthbert & Insel, 2013; Eaton et al., 2023; Insel, 2014; Insel et al., 2010; Kotov et al., 2017), but may instead be more precisely characterized by separable symptom dimensions that cut across diagnostic boundaries (Heller et al., 1997; Sharp et al., 2015; Snyder et al., 2023).

As such, a prominent dimensional framework distinguishes between anxious apprehension and anxious arousal (Heller et al., 1997; Sharp et al., 2015; Snyder et al., 2023), with anxious apprehension reflecting a tendency toward verbal, future-oriented rumination and worry, often accompanied by perceived difficulties in predicting, controlling, or coping with anticipated events (Barlow, 1991; Heller et al., 1997). In contrast, anxious arousal describes physiological hyperarousal, corresponding more closely to fear- and panic-related states (Clark & Watson, 1991; Sharp et al., 2015; Watson et al., 1995). These dimensions are related but distinguishable (Engels et al., 2007) and have been linked to partly distinct clinical phenotypes. While anxious apprehension is more pronounced in generalized anxiety and obsessive-compulsive symptomatology (Cox et al., 2010; Krueger, 1999), anxious arousal is more closely associated with focal fear (Lang et al., 2016). Since the pattern of results in previous studies comparing diagnostic groups with internalizing disorders to healthy controls in their threat anticipation has been mixed (Section 1.3.1) , e.g., in panic disorder (Gorka et al., 2014; Grillon et al., 2008; Shankman et al., 2013; Stevens et al., 2018), the anxiety dimension framework might provide an intermediate dimensional framework. Specifically,

diagnostic categories of anxiety disorders map onto the anxiety dimensions and the anxiety dimensions in turn might map onto differential threat anticipation response patterns.

Previous studies linking anxious apprehension to threat anticipation in the NPU-threat test provide tentative evidence for an association. Specifically, Nelson and Shankman (2011) found no significant association between anxious apprehension and startle responses in a nonclinical sample, while Rutherford et al. (2020) reported this association specifically in individuals with a history of anxiety disorders. As of yet, individual differences in self-reported anxious arousal have not been tested in the context of the NPU-threat test. Mapping physiological responses in predictable and unpredictable threat anticipation onto these diverging anxiety symptom dimensions therefore holds the potential to connect separate lines of research, i.e., bridging models of anxiety-related psychopathology rooted in the tripartite model proposing anxiety dimensions (Clark & Watson, 1991; Sharp et al., 2015; Snyder et al., 2023; Watson et al., 1995) and neuroscientifically grounded models highlighting altered responding to uncertainty in anxiety-related psychopathology (Dugas et al., 2026; Grupe & Nitschke, 2013; Rutherford et al., 2020).

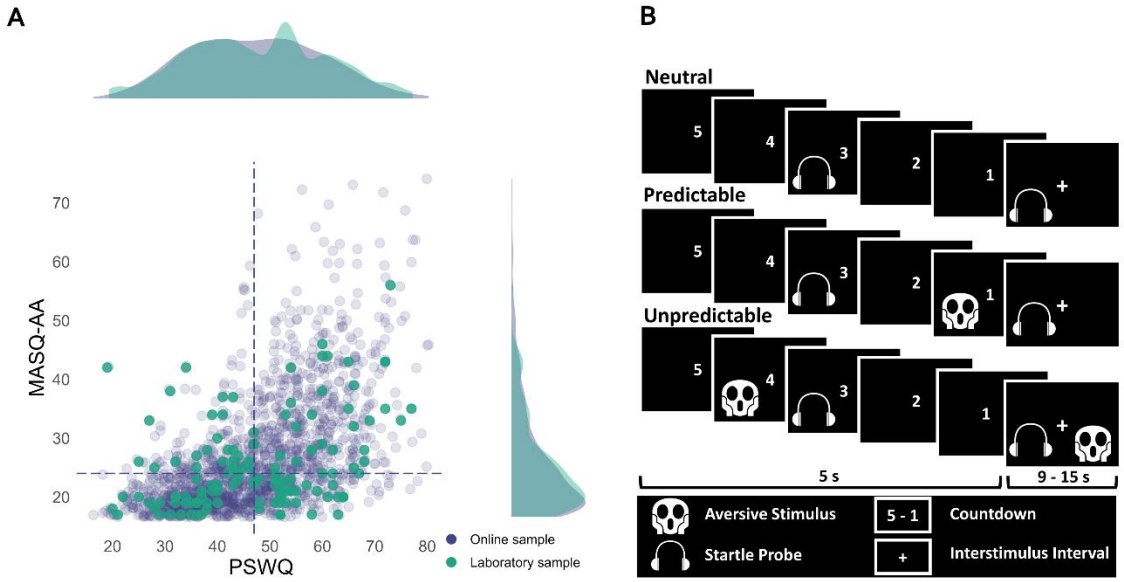
Against this background, Study 3 aimed to examine the unique and interactive contributions of anxious apprehension and anxious arousal to defensive responding during unpredictable threat anticipation. Participants were selected from a large community screening sample to obtain a broad distribution of converging and diverging profiles of anxious apprehension and anxious arousal. Using the NPU-threat test, Study 3 tested whether these anxiety dimensions were associated with altered startle responses, early sensory processing as indexed by the N1, and later attentional allocation as indexed by the P3 during predictable and unpredictable threat anticipation. By modeling anxious apprehension and anxious arousal simultaneously, the study sought to clarify whether distinct anxiety dimensions differentially shape the temporal dynamics of defensive responding and attentional processing.

3.3.2 Method

Study 3 was not preregistered and the data were collected prior to the start of the present dissertation project. Due to the scope of the informed consent obtained at the time of data collection, the participant-level data from Study 3 cannot be shared publicly. Participants were recruited in a two-step process (Figure 7A). First, an online screening sample completed the questionnaires that operationalized the anxiety dimensions anxious apprehension (Penn State Worry Questionnaire, PSWQ, $\alpha = 0.93$, Glöckner-Rist & Rist, 2014; Meyer et al., 1990) and anxious arousal (anxious arousal subscale of the Mood and Anxiety Symptoms Questionnaire, $\alpha = 0.90$, MASQ-AA, Watson & Clark, 1991). Second, participants were invited into the laboratory. The laboratory sample was oversampled

with participants in whom one anxiety dimension was more pronounced than the other, to optimize the variance distribution and facilitate disentangling possible interaction effects (Smith et al., 2016; Zambrano-Vazquez & Allen, 2014). In the laboratory, participants completed the NPU-threat test (Figure 7B). Similar to Study 1, this version of the NPU-threat test also presented a countdown in three instructed conditions (N, P, U), but differed in two aspects. First, only one task block was presented with a 100 % probability of occurrence of the aversive stimulus, so only the temporal predictability of threat was manipulated (not the probability of threat occurrence). Second, the aversive stimulus consisted of a female scream delivered through speakers in front of the participants (100 dB, duration of 1 s), paired with the picture of a fearful woman (NimStim image 01F; Tottenham et al., 2009). The outcomes included startle EMG and startle probe-locked ERPs (N1, P3). Startle responses were scored manually and the statistical approach included single trial multilevel models for startle and cue (i.e., countdown, interstimulus interval) and condition (N, P, U) aggregated models for ERP data.

Figure 7. *Overview of the Sample and Procedure in Study 3*



Note. **A** shows scatter plots and density distributions of the Penn State Worry Questionnaire (PSWQ), as well as the anxious arousal subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-AA). From the online screening sample (N = 1603), a total of N = 136 participants were invited to the laboratory to perform the NPU-threat test. To obtain equal sample sizes in each group of the median-based 2 (PSWQ: high vs. low) × 2 (MASQ-AA: high vs. low) design, we oversampled participants in whom one dimension was more pronounced than the other. **B** shows the NPU-threat test. In the neutral condition, the countdown was never followed by the aversive stimulus. In the predictable condition, the aversive stimulus occurred every time the countdown reached "1". In the unpredictable condition, the aversive stimulus could occur at any time during the countdown or the interstimulus interval. Figure adapted from Carsten et al. (2023).

3.3.3 Results

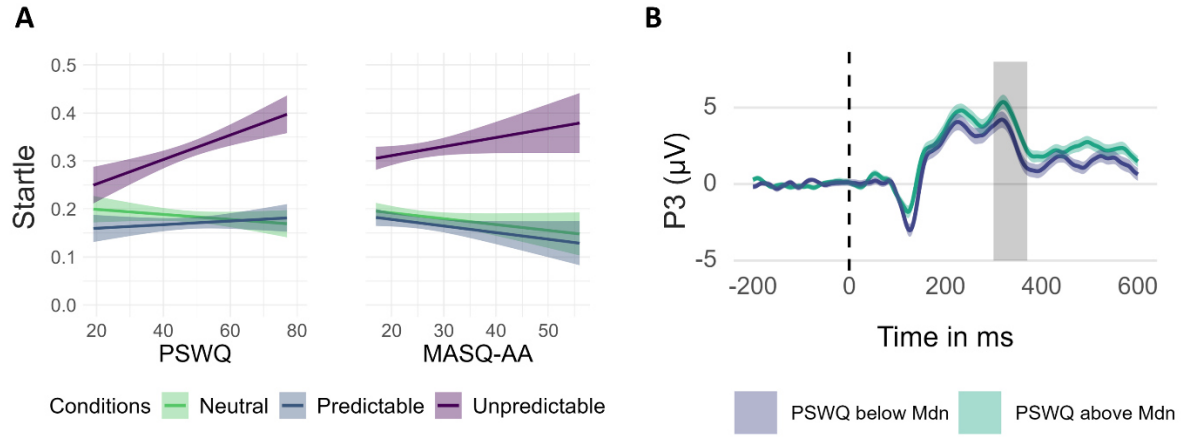
Three main result patterns emerged in Study 3, concerning task-level effects, differential associations with anxious apprehension and anxious arousal, and joint effects of the two anxiety dimensions. First, at the task level, participants showed increased startle responses in the U condition. Unexpectedly, startle responses were decreased in P compared to the N condition. This was mirrored in probe-locked N1, such that participants showed increased (i.e., more negative) N1 during the U condition and decreased N1 during the P condition. Probe-locked P3 was decreased in the P condition compared to the N and U conditions, indicating attentional resources to be focused on the task rather than the startle probe in the P condition.

Second, individual differences in the anxiety dimensions further qualified the startle reflex and attentional responding to the NPU-threat test. Specifically, higher PSWQ values (indexing anxious apprehension) were associated with increased startle responses during the U condition

compared with both the P and N conditions, indicating that individuals with increased anxious apprehension showed increased defensive responding specifically during unpredictable threat anticipation (Figure 8A). Further, participants with higher PSWQ showed increased probe-locked P3 in the P compared to the N condition, indicating that those with increased anxious apprehension allocated fewer attentional resources to temporally predictable threat (Figure 8B). Concerning anxious arousal, elevated MASQ-AA scores were associated with increased startle responses to the U condition in contrast to the P condition, whereas MASQ-AA slopes of startle responses did not differ significantly between the U and N conditions. This pattern of results was mirrored in probe-locked N1, in which MASQ-AA scores were also associated with increased N1 in the U compared to the P condition.

Third, the two anxiety dimensions also showed joint associations with physiological responding. Specifically, participants with increased PSWQ and MASQ-AA values showed increased overall startle responses, compared to participants with lower PSWQ and higher MASQ-AA values. This pattern was again mirrored in probe-locked N1, which was also increased in participants with both higher PSWQ and MASQ-AA values, suggesting that converging profiles in the anxiety dimensions might be associated with overall increased reflexive defensive responding and early attentional processing.

Figure 8. *Main Results of Study 3*



Note. **A**: Range-corrected startle slopes of the Penn State Worry Questionnaire (PSWQ) and the anxious arousal subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-AA) across experimental conditions of the NPU-threat test. Shaded area depicts 95% confidence interval of the estimated slope. **B**: Averages of P_3 in the predictable threat condition of the NPU-threat test for participants below and above the PSWQ median split (*Mdn* = 47). Shaded areas around the mean signal depict standard error at each ms. The shaded grey area depicts the time window for quantification of the P_3 (mean activity, 300-370 ms). Figure adapted from Carsten et al. (2023).

3.3.4 Discussion

The anxiety dimensions can be seen as a transdiagnostic coordinate system to map anxiety-related psychopathology. Therefore, links between psychophysiological responses during threat anticipation and the anxiety dimensions can be informative for clinical studies. Study 3 informs the overarching research aims of this dissertation in three aspects. First, on a task level, the modulatory effect of unpredictability in threat anticipation could be replicated across the converging outcomes startle and N1. In accordance with previous studies, participants overall showed increased startle responses and probe-locked N1 to the U condition (Ferry & Nelson, 2020; Gorka, Lieberman, Shankman, et al., 2017b; Nelson et al., 2016), reflecting sensitivity to unpredictable threat anticipation in defensive responding and early attentional processing. This underscores the stability of unpredictability-related effects on the task level of probe-locked N1, which has received less attention than startle responses in previous literature (Nelson, Hodges, et al., 2015).

Second, at the trait level, the findings demonstrated a dimensional contribution of anxious apprehension and anxious arousal to physiological responding during unpredictable threat anticipation. Startle responses to unpredictable threat anticipation were modulated by individual differences in anxious apprehension, which is a central symptom dimension in patients with

generalized anxiety disorder. Previous findings have suggested an empirical link between generalized anxiety disorder and startle to unpredictable threat (Grillon et al., 2017), a pattern which is inconsistent across previous empirical studies (Gorka, Lieberman, Shankman, et al., 2017b; Grillon et al., 2009). The findings of Study 3 may help contextualize these mixed results by indicating that startle responding to unpredictable threat varies as a function of anxious apprehension, although this finding warrants replication in a clinical sample.

Third, anxious arousal as measured via the MASQ-AA was associated with increased startle and N1 in the U compared with the P condition, suggesting a selective association with reflexive defensive responding and early sensory processing under temporally unpredictable threat. However, the fact that the contrast only emerged compared with predictable threat could also be taken to suggest less robust effects of anxious arousal, which is mirrored by comparably smaller effect sizes. Regarding general responding, the anxiety dimensions anxious apprehension and anxious arousal interacted in modulating startle and N1 such that increased values in both anxiety dimensions were associated with increased responding in both outcomes. This could be taken to suggest a quantitative influence of anxiety-related psychopathology. Participants scoring high in both anxiety dimensions might more closely resemble clinical populations, which may suggest heightened reactivity in defensive responding and early attention as a general feature in anxiety disorders, as suggested in previous studies (Kausche et al., 2022; Lang et al., 2016).

3.3.5 Conclusion

Study 3 contributes to the overarching research aims of this dissertation in three ways. First, with regard to Research Question 2, the findings indicate that reflexive defensive responding and early sensory processing, as indexed by startle and N1, were particularly sensitive to individual differences in the anxiety dimensions anxious apprehension and anxious arousal, whereas later attentional allocation showed a more selective association with anxious apprehension. Thus, Study 3 extends the individual differences focus from IU to the broader anxiety dimensions of anxious apprehension and anxious arousal and further supports a response-system-specific rather than uniform modulation of threat anticipation.

Second, with regard to Research Question 3, Study 3 provides evidence for a dimensional perspective by demonstrating that anxious apprehension and anxious arousal were associated with physiological responding across a community sample. These findings link experimentally induced temporal unpredictability to variation in clinically relevant anxiety dimensions. Third, Study 3 provides a bridge from dimensional associations in a community sample to their examination in clinical populations. Because clinical interviews were not conducted, it remains unclear whether the

observed associations extend to clinical manifestations of anxiety-related psychopathology, motivating the direct examination of these associations in clinical populations in Study 4.

3.4 Study 4: Transdiagnostic Physiological Correlates of Unpredictable Threat Anticipation

Citation. Carsten, H. P., Härpfer, K., Kausche, F. M., & Riesel, A. (under review). Transdiagnostic physiological correlates of unpredictable threat anticipation. Manuscript under review at *International Journal of Clinical and Health Psychology.*

3.4.1 Objective

The aim of Study 4 was to examine whether physiological responses to unpredictable threat differ across diagnostic groups and transdiagnostic anxiety-related symptom dimensions. In the preceding studies, especially Studies 1 and 3, the generalizability to clinical samples emerged as a limitation of the empirical findings. Study 4 sought to directly address this limitation and test the generalizability of effects to patients with anxiety-related psychopathology. Two theoretical notions mainly informed the research question and hypotheses. First, empirically derived models such as the UAMA (Grupe & Nitschke, 2013; Section 1.2) suggest hypervigilance and heightened reactivity to uncertain threat as central processes in anxiety-related psychopathology. This perspective is complemented by accounts proposing that uncertainty, particularly uncertainty about safety, biases information processing toward threat and sustains defensive preparedness (Freeston & Komes, 2023; Van den Bergh et al., 2021). Based on these models, increased responses to unpredictable threat in patients with anxiety-related psychopathology would be predicted. Empirically, some support for this can be derived from previous studies utilizing NPU-threat test designs. Specifically, increased startle responses to unpredictable threat anticipation have been reported in patients with panic disorder (Grillon et al., 2008; Shankman et al., 2013) and PTSD (Grillon et al., 2009) with findings emphasizing panic attacks as a particularly relevant transdiagnostic feature (Grillon et al., 2017). However, findings on panic disorder and panic attacks are mixed (Gorka et al., 2014; Stevens et al., 2018) and studies have mainly focused on startle responding and less on attentional mechanisms during unpredictable threat anticipation.

As a second rationale for Study 4, biodimensional analyses across anxiety disorders and OCD suggested a continuum from physiological hyperreactivity to hyporeactivity, corresponding to a symptomatic spectrum from circumscribed fear to generalized anxiety and anxious misery (Lang et al., 2016; McTeague & Lang, 2012). Physiological blunting as suggested by this spectrum in more generalized anxiety-related psychopathology has been reported in PTSD (Katz et al., 2018; Lieberman et al., 2020), with multiple trauma (McTeague et al., 2010), non-interpersonal trauma (Kreutzer & Gorka, 2021), and adverse childhood experiences (Ruge et al., 2024). Together, mixed previous findings of unpredictable threat anticipation in anxiety disorders (Section 1.3.1) and possible physiological blunting in more generalized anxiety psychopathology guided the hypothesis

expecting concurrent blunting across more generalized anxiety disorders but relative hypersensitivity to unpredictable threat. Beyond testing these theoretical patterns of results, Study 4 sought to address more practical research gaps. Specifically, previous empirical studies have seldom included direct disorder comparisons (Gorka, Lieberman, Shankman, et al., 2017b; Grillon et al., 2017; Katz et al., 2018; Shankman et al., 2013) by including two or more clinical groups. In this vein, no published NPU-threat study has examined unpredictable threat anticipation in a clinical group of patients with OCD. Further, while previous studies focused on startle responses, data across physiological processing domains including neural correlates of attentional processes are needed to capture the complexity of the multisystem response pattern of defensive responding.

3.4.2 Method

The hypotheses and methods of Study 4 were preregistered (https://osf.io/n9qxp) and the data are openly available (www.osf.io/gveky). Study 4 encompassed 163 participants who were recruited in four groups matched for age, gender, and years of education. The groups included patients with OCD, social anxiety disorder, specific phobia, and unaffected controls without the respective disorder. The sample size was determined by the broader project and a priori sensitivity simulations suggested that medium effect sizes of d = 0.50 would be detectable for the interaction of NPU condition × group, with a power of 95.30 % (95 % CI [93.80, 96.53]) for aggregated EEG data and 99.90 % (95 % CI [99.44, 100.00]) for single trial startle data. Participants were excluded if they had a neurological disorder, a lifetime substance-related or psychotic-spectrum disorder, a current manic episode, or were taking benzodiazepines or neuroleptic medication. Diagnoses were assessed via the Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5-CV; Beesdo-Baum et al., 2019). Questionnaires measuring transdiagnostic and symptom-specific constructs included the IUS-12 measuring IU (α = .90; Carleton et al., 2007), PSWQ to measure anxious apprehension (α = .94; Glöckner-Rist & Rist, 2014; Meyer et al., 1990), and MASQ-AA to measure anxious arousal (α = .88; Clark & Watson, 1991; Watson & Clark, 1991). The overall symptom severity was assessed via the clinician-rated Global Clinical Impression Scale (CGI; Guy, 1976), and overall functioning was assessed via the clinician-rated Global Assessment of Functioning (GAF; American Psychiatric Association, 2000). Similar to Study 3, the sample completed the NPU-threat test, which was presented with a countdown in three conditions with 100 % probability of the aversive stimulus. Thus, the temporal predictability was manipulated. The aversive stimulus consisted of an electric shock that was calibrated to an intensity of a subjective rating of 7-8 (M = 2.59 mA, SD = 1.48, range 0.30 – 13.00) on a scale from 0 (not aversive) to 10 (extremely aversive, not endurable). Outcome measures included startle EMG and startle probe-locked ERPs N1 and P3, as well as SCR and anxiety ratings assessed on

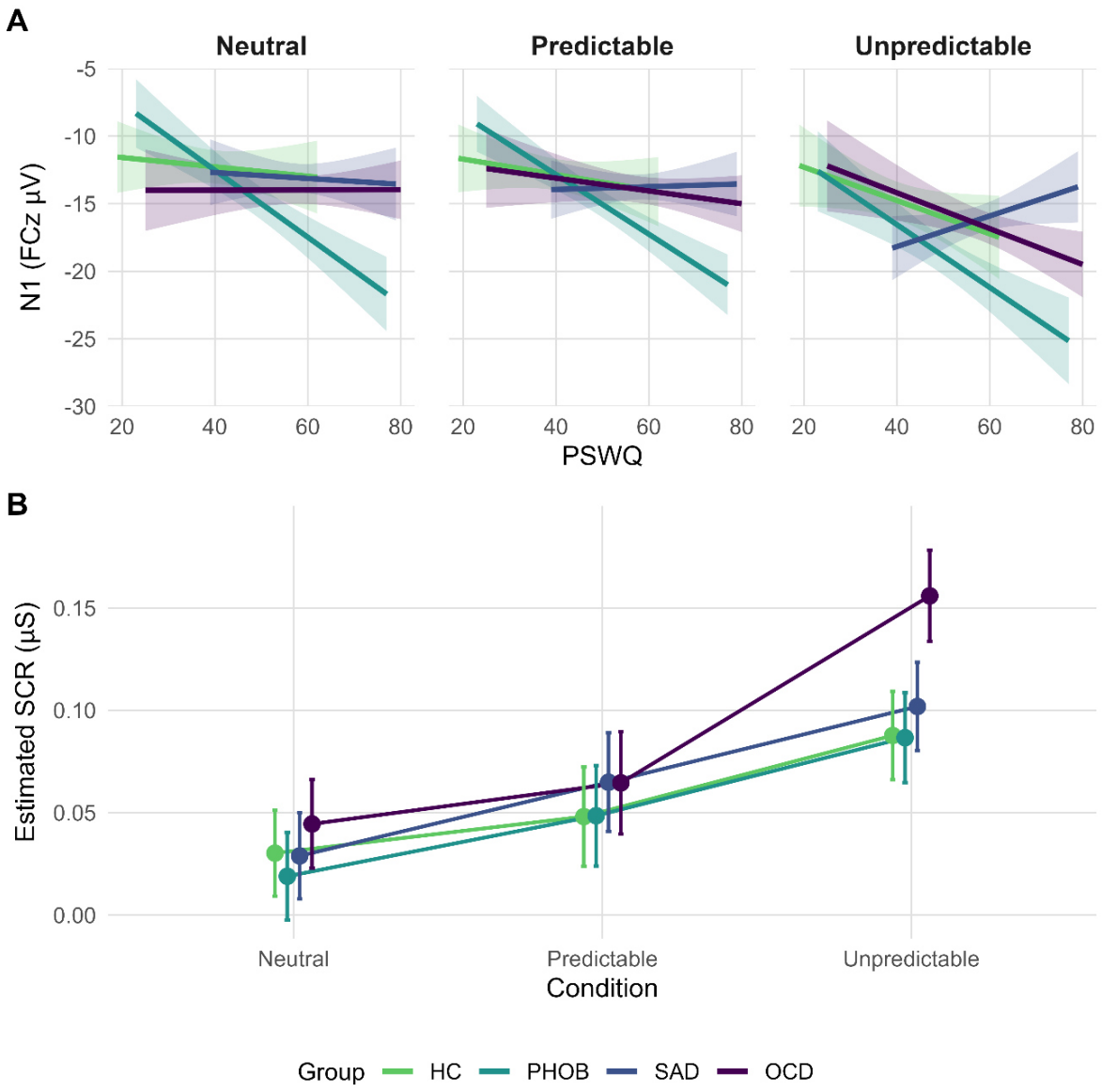
a 7-point Likert scale. The statistical approach included multilevel models and analyses per outcome measure, with single-trial analyses for startle responses and SCR. Complementing the outcome-specific statistical approach, exploratory latent profile analyses across psychophysiological outcome measures were performed in a reduced, complete-case sample (N = 143).

3.4.3 Results

Across participants, the NPU-threat test elicited the expected pattern of task effects. Specifically, ratings and startle responses showed graded increases from neutral to predictable to unpredictable threat anticipation (N < P < U), whereas probe-locked N1 was selectively enhanced during the U condition. Probe-locked P_3 amplitudes were suppressed during both P and U conditions.

The preregistered hypothesis regarding general physiological reactivity decreasing along a gradient from more circumscribed fear to generalized anxiety was not supported, due to the absence of main effects of group. Some support emerged for the hypothesis postulating hypersensitivity to unpredictable threat in anxiety-related psychopathology. Specifically, patients with OCD showed increased SCR during the U condition compared to patients with social anxiety disorder, specific phobia, and unaffected controls (Figure 9B). Dimensional analyses further specified the results. Specifically, PSWQ was associated with increased N1 in patients with OCD during the U relative to the N condition, indicating that patients with OCD and higher levels of anxious apprehension showed early hypervigilance to unpredictable threat (Figure 9A).

Figure 9. *Main Results of Study 4*

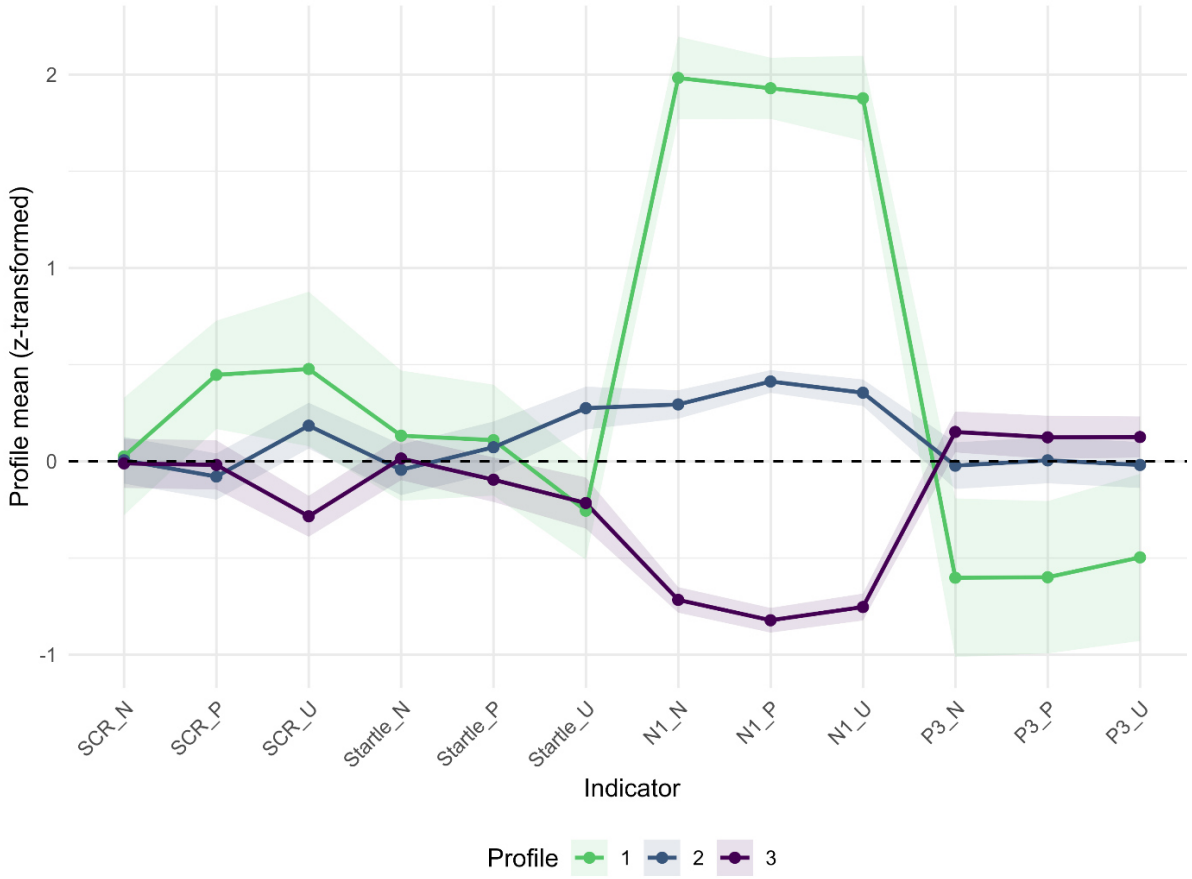


Note. **A**: Slopes of the Penn State Worry Questionnaire (PSWQ) and N1 across the conditions of the NPU-threat test and diagnostic groups. **B**: Estimated marginal means of skin conductance response (SCR) across conditions of the NPU-threat test and diagnostic groups. Error bars indicate 95 % CI around the estimated marginal mean. HC = unaffected controls; PHOB = patients with specific phobia; SAD = patients with social anxiety disorder; OCD = patients with obsessive-compulsive disorder. Figure adapted from Carsten et al. (under review).

To integrate physiological responding across systems, an exploratory latent profile analysis was conducted using condition-specific indicators of SCR, startle, N1, and P3. Based on model selection criteria, a three-profile solution was retained as the most parsimonious and interpretable solution, suggesting that the differences between the physiological profiles consisted primarily in broader multisystem response configurations rather than isolated sensitivity to unpredictable threat (Figure 10). Profile 1 was comparably small (n = 14) and characterized by pronounced early attention and sensory responding (N1). Profile 3 (n = 65) showed comparatively attenuated physiological responding, including reduced autonomic and defensive responding during unpredictable threat anticipation. Profile 2 (n = 64) reflected a more threat-reactive multisystem profile, with relatively stronger threat-related autonomic, reflexive, and attentional engagement compared with Profile 3 (Figure 10). The clinical relevance of these profiles was supported by differences in the diagnostic composition and symptom levels. Participants in the threat-reactive Profile 2 showed higher levels of anxious apprehension, social anxiety symptoms, and clinician-rated severity compared with Profile 3 (Figure 11A). On a diagnostic level, Profile 2 included a larger proportion of patients with social anxiety disorder and OCD, whereas unaffected controls and patients with specific phobia were more strongly represented in Profile 3 (Figure 11B). Thus, the latent profile analysis suggests that clinically meaningful variation in threat anticipation may be captured by multisystem physiological response profiles.

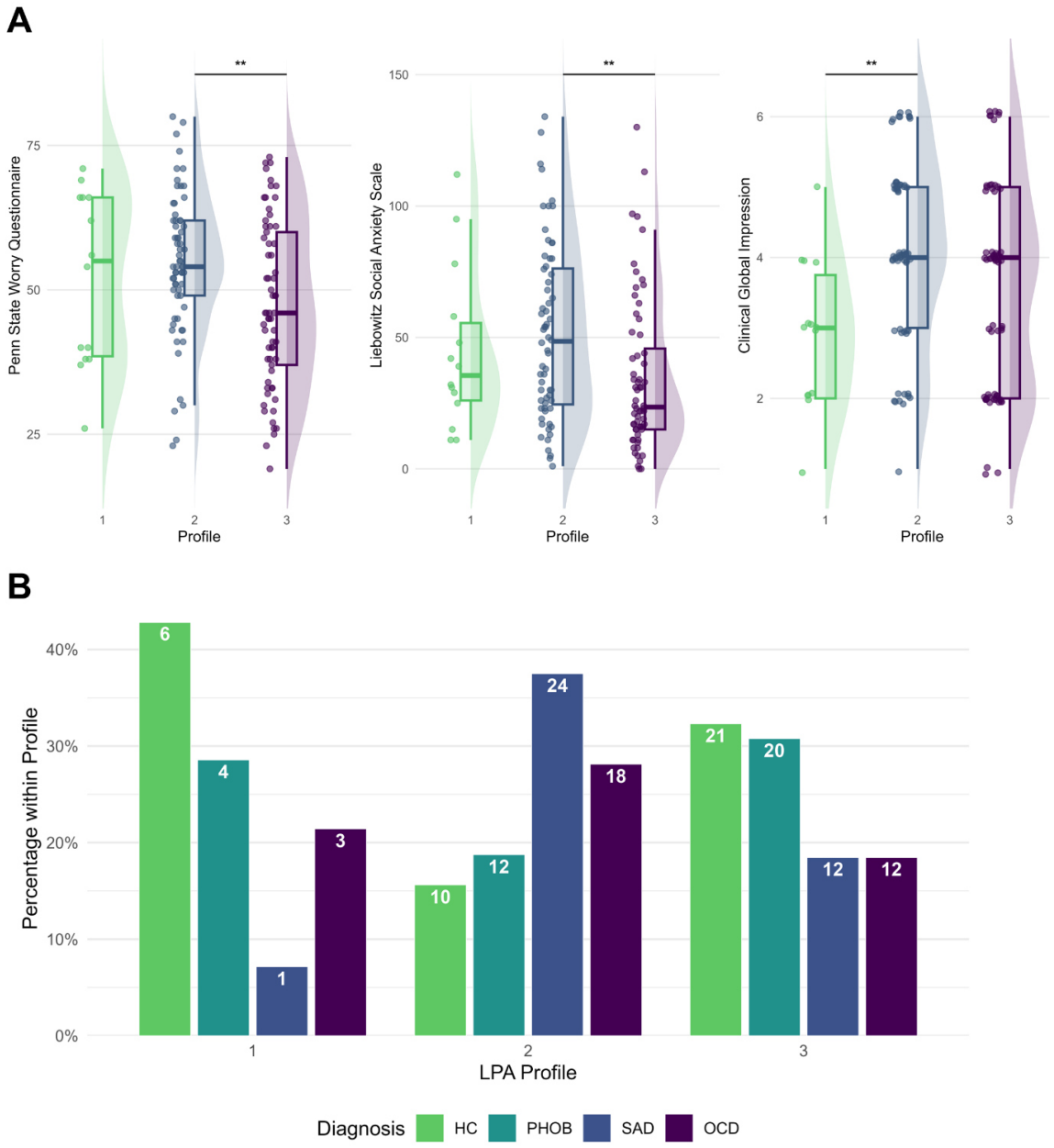
In summary, three main results emerged. First, anxious apprehension was associated with increased N1 amplitudes during unpredictable threat anticipation in patients with OCD. Second, the patients with OCD showed increased SCR during unpredictable threat anticipation. Third, physiological multisystem response patterns derived from an exploratory latent profile analysis suggested a threat-reactive profile with increased overall N1 and increased SCR and startle responses during unpredictable threat anticipation to be clinically enriched. Specifically, participants exhibiting this pattern showed elevated levels of anxious apprehension and social anxiety symptoms, while the profile also contained a higher proportion of patients with social anxiety disorder and OCD.

Figure 10. *Exploratory Latent Profile Analysis*



Note. Exploratory latent profile analysis of multisystem physiological responding during the NPU-threat test. Standardized physiological response profiles across skin conductance response (SCR), startle, probe-locked N1, and probe-locked P3 in the neutral (N), predictable threat (P), and unpredictable threat (U) conditions. Lines represent profile means and shaded areas indicate ±1 standard error. N1 and P3 were sign-reversed such that higher values indicate increased physiological responding. Profile 1: n = 14; Profile 2: n = 64; Profile 3: n = 65. Figure adapted from Carsten et al. (under review).

Figure 11. *Clinical Correlates of Latent Profiles*



Note. **A:** Clinical correlates of the retained profiles, comprising anxious apprehension measured with the Penn State Worry Questionnaire (PSWQ), social anxiety symptoms measured with the Liebowitz Social Anxiety Scale (LSAS), and clinician-rated symptom severity measured with the Clinical Global Impression Scale (CGI). Asterisks indicate significant pairwise profile differences. **B:** Diagnostic composition of the retained profiles. Bars indicate the percentage of each diagnostic group within the respective profile; white numbers indicate participant counts. Profile 1: n = 14; Profile 2: n = 64; Profile 3: n = 65. HC = unaffected controls; PHOB = specific phobia; SAD = social anxiety disorder; OCD = obsessive-compulsive disorder. Figure adapted from Carsten et al. (under review).

3.4.4 Discussion

The aims of Study 4 were to examine neural and peripheral physiological indicators of defensive responding across the spectrum of anxiety-related psychopathology and to test the generalizability of the findings of Studies 1 and 3 to clinical samples. Across the diagnostic groups, the NPU-threat test elicited the expected task effects, i.e., startle was generally potentiated during threat anticipation and further potentiated in temporally unpredictable threat anticipation. Further, N1 and SCR were particularly sensitive to temporally unpredictable threat anticipation, and P3 was generally suppressed during threat anticipation, irrespective of temporal predictability. This extends the pattern of results of increased startle and N1 observed in Studies 1 and 3 to a diagnostically heterogeneous clinical sample. Concerning clinical differences, the predicted linear decrease in general physiological reactivity from controls and specific phobia toward social anxiety disorder and OCD was not supported, thus the results do not clearly map onto the hyperreactivity to hyporeactivity spectrum suggested by Lang et al. (2016). Although patients with specific phobia showed overall increased startle while being overall less affected by symptom burden than the social anxiety disorder or OCD groups, no support emerged for diagnostic-group differences in general reactivity in N1, P3, or SCR.

The exploratory latent profile analysis does not show clear support for this spectrum either. Instead, a multisystem threat-reactive response pattern showed clinical enrichment on a diagnostic and dimensional level, suggesting that clinical burden may be reflected less in generalized physiological blunting than in specific multisystem patterns of threat responding. This absence of a common pattern of results of diagnostic groups across startle, SCR, N1, and P3 argues against a unitary physiological signature organized by the severity of anxiety-related psychopathology. Importantly, the circumscribed fear-anxious misery framework remains tenable despite these findings, because it was originally derived from disorder-specific imagery paradigms rather than a standardized, disorder-unspecific NPU-threat test (Lang et al., 2016; McTeague & Lang, 2012). However, patients with OCD displayed a diagnosis-specific response pattern that provides evidence relevant to two UAMA processes (Grupe & Nitschke, 2013). Specifically, patients with OCD showed selectively enhanced SCR in the U condition, indicating increased sympathetic arousal in an unpredictable threatening context, which corresponds to the UAMA process heightened reactivity to threat uncertainty (Grupe & Nitschke, 2013). Second, within the OCD group, higher anxious apprehension was associated with stronger N1 enhancement in the U relative to the N condition, corresponding to the UAMA process increased threat attention or hypervigilance (Grupe & Nitschke, 2013). The fact that these effects emerged in patients with OCD but not in patients with social anxiety disorder or specific phobia might reflect differences in clinical phenotype. Specifically, patients with

OCD show symptomatic overlap and high comorbidity with anxiety disorders (Cheng et al., 2025), but differ in cognitive aspects and symptom expression (American Psychiatric Association, 2013; Goodwin, 2015).

These findings were complemented by exploratory latent profile analysis which identified three profiles that cut across diagnostic categories. These multivariate physiological response profiles were more closely separated by general threat reactivity than isolated sensitivity to unpredictable threat. One of these profiles was relatively threat-reactive, characterized by stronger startle responding and early sensory processing, together with comparatively increased autonomic arousal during unpredictable threat anticipation. This profile was clinically enriched, containing more patients with social anxiety disorder and OCD and, on a dimensional level, showing increased levels of anxious apprehension, social anxiety symptoms and clinician-rated severity. However, the complementary profile with a similar size still contained a substantial proportion of patients, suggesting that patients with the same diagnosis can exhibit different physiological response patterns, while similar response patterns occurred across different diagnoses. This pattern raises the possibility that diagnostic categories may not represent the most meaningful level of abstraction for capturing the structure of physiological responding during threat anticipation. Importantly, this latent profile analysis is exploratory and, while it may be hypothesis-generating, it still warrants external replication and validation. Although the clinical enrichment may be interpreted as clinically meaningful variation being linked to multivariate physiological response patterns, these patterns should not be taken as a classification model or evidence for physiological subtypes at this point.

3.4.5 Conclusion

Study 4 contributes to the overarching research aims of this dissertation in three ways. First, this study extends the task-level effects of increased startle and N1 to unpredictable threat anticipation from student and community samples to clinical samples. Second, Study 4 shows that anxiety-related traits do not uniformly amplify physiological responses across measures, consistent with the selective associations observed in Studies 1 and 3. Instead, the results suggest that clinical alterations are response-system-specific rather than forming one diagnostic physiological signature in unpredictable threat anticipation. Third, more exploratorily, the results suggest that multivariate physiological response profiles may identify clinically relevant patterns of threat responding that cut across diagnostic categories. Taken together, the results from Study 4 suggest that alterations in unpredictable threat anticipation cannot be reduced to either diagnostic categories or symptom dimensions alone. Instead, they emerged from the interaction of clinical status, dimensional and transdiagnostic symptom variation, and partially dissociable physiological response systems.

4. General Discussion

Uncertainty is a central feature of threat anticipation and has been shown to modulate physiological indices of defensive responding to impending threat (e.g., Grillon et al., 2008). At the same time, uncertainty can take different forms, its effects may differ across physiological response systems, and individuals vary considerably in how they respond to uncertain situations. These individual differences are particularly relevant to anxiety-related psychopathology, for which altered anticipation of uncertain threat has been proposed as a candidate mechanism (Einstein, 2014; Grupe & Nitschke, 2013). This dissertation aimed to elucidate how uncertainty shapes defensive responding across psychological and physiological units of analysis and how these responses relate to transdiagnostic traits, symptom dimensions, and clinical manifestations of anxiety-related psychopathology. The General Discussion first summarizes the main findings across studies before deriving theoretical implications for unpredictability and individual differences in defensive responding and integrating them within an overarching model of defensive responding under uncertainty. The strengths and limitations of the dissertation are then considered to establish the evidential boundaries of this synthesis, followed by methodological and clinical implications and priorities for future research.

4.1 Summary of Findings

In Study 1 (Carsten et al., 2022), lower threat probability of temporally predictable and temporally unpredictable threat was associated with increased startle responding, while subjective ratings and attentional allocation (P_3 suppression) were decreased (Table 1). Trait IU was associated with startle responding selectively in the lower threat probability conditions, irrespective of temporal predictability, suggesting that lower threat probability might amplify or activate the influence of individual differences in IU during threat anticipation. In Study 2 (Carsten et al., 2025), the role of uncertainty in terms of internal, potentially threatening events (i.e., errors; Weinberg et al., 2016) was tested in a randomized controlled trial and using a novel uncertainty symptom induction. Although the symptom induction increased subjective uncertainty ratings, no significant effects of state uncertainty or trait IU on the neural index of performance monitoring (i.e., ERN) were observed. In Study 3 (Carsten et al., 2023), the effects of transdiagnostic anxiety symptom dimensions (anxious apprehension and anxious arousal) on defensive responding and attentional processes in unpredictable threat anticipation were tested in a community sample. Anxious apprehension was associated with increased startle responses to unpredictable threat and anxious arousal was associated with increased startle and N1 to unpredictable threat. Extending these findings to clinical populations, Study 4 (Carsten et al., under review) illustrated that patients with OCD showed

increased physiological arousal (i.e., SCR) during unpredictable threat anticipation, while in these patients with OCD, higher anxious apprehension was associated with enhanced probe-locked N1 during unpredictable threat anticipation. Exploratory latent profile analysis in Study 4 further revealed a multisystem threat-reactive response profile that was clinically enriched and included more severely affected individuals with social anxiety disorder and OCD. In other words, the results demonstrated that uncertainty-related threat responding:

- is particularly pronounced in defensive responding for lower threat probability (Study 1)
- is amplified by transdiagnostic anxiety-related traits such as IU, anxious apprehension, and anxious arousal (Studies 1, 3, and 4)
- does not robustly extend to internal potentially threatening events (i.e., errors) as indexed by performance monitoring via the ERN (Study 2)
- shows clinically meaningful associations both in individual physiological response systems, including increased SCR in OCD, and in multisystem response profiles associated with greater symptom severity (Study 4)

4.2 The Role of Unpredictability in Threat Anticipation Across Response Systems

The findings of this dissertation have two overarching theoretical implications for understanding the role of unpredictability in threat anticipation. First, they support and extend previous evidence that unpredictable threat reliably recruits reflexive defensive responding and early sensory processing. Second, they refine this account by showing that the effects of unpredictability differ across physiological response systems and can be distinguished from broader individual response styles. As such, Studies 1, 3, and 4 replicated the finding that temporal unpredictability as an anxiety-like state of sustained defensive preparedness (Schmitz & Grillon, 2012) led to increased startle responding. This pattern is consistent with previous findings in healthy adults (e.g., Nelson & Shankman, 2011; Papenfuss et al., 2021), adolescents (Beatty et al., 2022), and clinical samples (e.g., Grillon et al., 2017; Hoge et al., 2024). Further, unpredictability shaped early sensory processing as reflected in increased probe-locked N1 amplitudes in Studies 1, 3, and 4, indicating that experimental manipulations of unpredictability not only potentiated defensive reflexes but also recruited automatic sensory resources (Correa et al., 2022; MacNamara & Barley, 2018; Nelson, Hajcak, et al., 2015; Nelson & Hajcak, 2017b; Stevens et al., 2018).

However, the effects of unpredictability were not uniform across response systems. While startle responses and N1 showed relatively consistent sensitivity to unpredictable threat, P3 effects were less clearly tied to unpredictability (Table 1A). In Study 1, P3 suppression was most pronounced during predictable threat under high threat probability, whereas unpredictable threat did not reliably

suppress probe-locked P3 and this suppression was less pronounced under lower threat occurrence probability, indicating sensitivity of P3 suppression to higher threat probability and task load. Similarly, in Study 3, the probe-locked P3 was reduced during predictable threat anticipation but did not differ significantly between unpredictable threat anticipation and the neutral condition. In Study 4, the P3 was again suppressed during predictable threat anticipation but, in contrast to Studies 1 and 3, also during unpredictable threat anticipation. P3 suppression appears less tightly tethered to unpredictability than N1 enhancement, since these previous studies reported P3 suppression to both predictable and unpredictable threat anticipation (Beatty et al., 2022; Correa et al., 2022; MacNamara & Barley, 2018; Nelson, Hajcak, et al., 2015). This could be taken to suggest that probe-locked P3 may index attentional engagement with imminent or task-relevant threat with higher task load, rather than capturing variation in sensitivity to unpredictability itself.

This response-system-specific pattern is further corroborated by more robust correlations between startle and probe-locked N1 than between startle and probe-locked P3, suggesting that within the cascade of multisystem defensive responding, variance in early sensory responses might be more closely tied to reflexive defensive responding than to later and more elaborate attentional processing (Appendix A). Building on these findings, Study 4 examined whether interindividual differences in response styles across physiological outcomes reflect sensitivity to unpredictability or broader physiological response styles across threat contexts.

As such, the latent profile analysis in Study 4 suggests that unpredictability effects and individual response styles can be analytically distinguished. When profile membership was projected back onto task responding in the original NPU-threat test, robust condition effects were observed across response systems, but profile × condition interactions were limited. Only in SCR was a clear profile-specific condition modulation evident, whereas startle and probe-locked P3 showed largely parallel NPU effects across profiles and N1 mainly differed in overall amplitudes across response profiles. Thus, the profiles were better interpreted as broad multisystem response styles than as distinct forms of unpredictability sensitivity. Together, this suggests that temporal unpredictability reliably evokes defensive responding at the task level, but that individual differences in defensive responding may not be captured by unpredictability potentiation alone but might be better captured by general response patterns across physiological systems.

The differentiation between sensitivity to unpredictability and more general response styles is relevant for potential links to traits and symptoms, as physiological response systems that are particularly sensitive to threat unpredictability may also be more susceptible to individual-difference variation, as discussed in the following section.

Table 1. *Overview of Results across Studies*

	Startle	N1	P3	SCR	ERN	Ratings
A: Task level effects						
Temporal unpredictability *Studies 1,3,4*	↑ *S1, S3, S4*	↑ *S1, S3, S4*	↓ *S4*	↑ *S1, S4*	-	↑ *S1, S4*
Probabilistic unpredictability *Study 1*	↑	Ø	↑	Ø	-	↓
Experimentally induced state uncertainty *Study 2*	-	-	-	-	Ø	↑
B: Individual differences						
Intolerance of uncertainty *Studies 1,2,4*	↑† *S1*	Ø	Ø	Ø	Ø	↑†† *S1, S4*
Anxious apprehension *Studies 3, 4*	↑ *S3*	↑ *S4*	Ø	Ø	-	Ø
Anxious arousal *Studies 3, 4*	↑ *S3*	↑ *S3*	↓†† *S4*	↓ *S4*	-	↑†† *S4*
Diagnosis *Study 4*	Ø	Ø	Ø	↑ OCD	-	Ø

Note. **A**: Overview of task-level effects of uncertainty. **B**: trait-, symptom-, and diagnosis-based modulation across response systems.
↑ increased / positive association
↓ decreased / negative association
Ø assessed, but no significant association
- not assessed
For N1, ↑ refers to larger N1 amplitudes, i.e., more negative deflections. For P3, ↓ refers to reduced P3 amplitude, i.e., stronger P3 suppression.
ERN = error-related negativity; OCD = obsessive-compulsive disorder; S1-4 = Studies 1-4
† for low threat occurrence probability
†† overall effect, but not specific to unpredictable threat

4.3 Trait- and Symptom-based Modulation of Defensive Responding Under Uncertainty

A third overarching theoretical implication concerns the role of individual differences in defensive responding under uncertainty. The present findings refine accounts that conceptualize anxiety-related traits as general amplifiers of responding to uncertainty by suggesting that their effects depend on both the specific feature of unpredictability and the physiological response process examined. This selectivity was particularly evident for individual differences in IU. In Study 1, IU did not generally amplify responses to unpredictable threat. Instead, IU was selectively associated with increased startle responses under low threat probability, both in temporally predictable and temporally unpredictable threat conditions (Table 1B). Based on these findings, the effect of IU on defensive responding in unpredictable threat anticipation appears to be probability-driven rather than driven by temporal predictability, which is in line with prior empirical findings (Chin et al., 2016). Temporal unpredictability emerged as a robust within-person situational determinant of defensive responding across studies, whereas the clearest evidence for IU as a between-person moderator emerged under reduced threat occurrence probability in Study 1. Importantly, this modulation appeared to be specific to startle and did not extend to N1, P3, or SCR, indicating that IU primarily amplified reflexive defensive responding rather than early attentional responses, later attentional processing or sympathetic arousal. In Study 4, IU was associated with increased subjective threat ratings across conditions and showed a condition x group interaction for startle, but follow-up analyses did not indicate a robust IU-related increase in unpredictable-threat responding across clinical groups. Thus, the clearest evidence for IU-related physiological hyperreactivity emerged under lower threat probability in Study 1.

Broader anxiety symptom dimensions further modulated startle responses and N1 to unpredictable threat anticipation. Specifically, anxious apprehension and anxious arousal were associated with increased startle to unpredictable threat anticipation (Study 3) and increased N1, although this pattern did not emerge robustly across studies. These findings were observed for temporally unpredictable threat, suggesting that individual differences in broader anxiety dimensions are implicated in shaping early reflexive responding and early attentional processing. In Study 4, IU correlated with anxious arousal (r = .57) and anxious apprehension (r = .69), consistent with meta-analytic evidence suggesting a strong association between IU and anxious apprehension (Akbari et al., 2026). This raises the question of whether specific or shared aspects of the respective symptom dimension or trait are implicated in startle responses and probe-locked N1. Some evidence for specificity to IU emerged in Study 4, in which IU was retained in the final simultaneously entered dimensional models including anxious apprehension and anxious arousal, whereas in Study 3, IU was not assessed. In Study 1, the specificity of IU effects was tested by including trait anxiety (Spielberger

et al., 1983) in the models. This did not change the pattern of results, which can be taken to suggest some level of specificity of effects to IU.

Taken together, these findings suggest that unpredictability constitutes a central situational determinant of defensive responding. Across studies, temporal unpredictability reliably potentiated reflexive defensive responding and early sensory processing, whereas later attentional allocation was less consistently modulated and appeared more dependent on threat imminence or task load. At the same time, IU did not operate as a general amplifier of uncertainty-related responding but selectively intensified startle responding under lower threat probability. Thus, defensive responding was shaped not only by how imminent a threat was, but also by how unpredictable its occurrence and timing were.

4.4 The Uncertainty-Imminence Continuum Model of Defensive Responding

In the previous sections, the role of unpredictability in threat anticipation and its further modulation by anxiety-related traits and symptoms were discussed. The present section integrates these empirical findings at a higher level of abstraction. The theoretical background, which motivated the present dissertation, spans from individual difference factors (Carleton, 2016b; Dugas et al., 2026; Sharp et al., 2015), across neural processes and mechanisms (Grupe & Nitschke, 2013) to specific situational factors (Abend, 2023; Fanselow, 1994). These factors represent different functional layers, i.e., a more macro-level, trait-like layer that is theorized to influence a micro-level, situational layer. To capture this structure of macro to micro level dependency and facilitate a transtheoretical integration of findings across the broader theoretical background, I propose the *Uncertainty-Imminence Continuum Model of Defensive Responding* (UICM; Figure 12).

The UICM is an integrative model consisting of different layers: an individual differences layer capturing transdiagnostic traits, a mechanistic processing layer capturing psychophysiological processes implicated in anxiety-related psychopathology, and a situational layer capturing determinants of defensive responding, i.e., threat proximity and qualitative as well as quantitative features of uncertainty. As individual differences on a trait level, IU and the anxiety dimensions anxious apprehension and anxious arousal are included (Carleton, 2016b; Dugas et al., 2026; Sharp et al., 2015; Snyder et al., 2023). In this dissertation, these trait variables have displayed associations with startle responding (Studies 1 and 3) and N1 to unpredictable threat anticipation (Studies 3 and 4, Table 1). This is complemented by prior evidence suggesting a role of IU in startle responses during unpredictable threat anticipation (Nelson et al., 2016; Nelson & Shankman, 2011) and amygdala activity (Greifenberger et al., 2025; Morriss et al., 2015; Oathes et al., 2015; Schienle et al., 2010; Somerville et al., 2013). Regarding anxious apprehension, Rutherford et al. (2020) found a link to

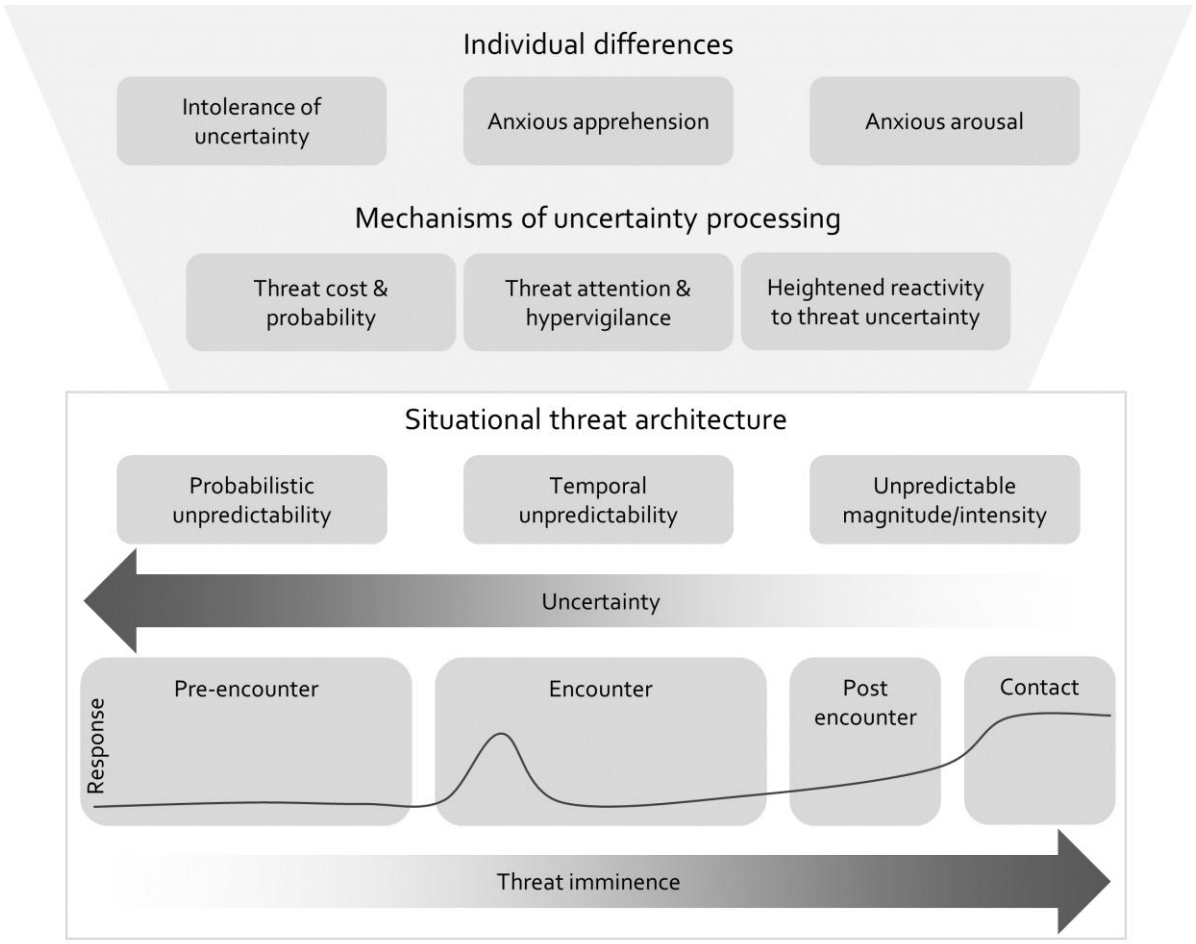
startle responses during unpredictable threat anticipation in participants with a history of anxiety disorders (but see Nelson & Shankman, 2011), which together with findings from Studies 3 and 4 empirically suggests a role of anxious apprehension in shaping defensive responding. This dispositional layer of the UICM might be extended to include further transdiagnostic symptom dimensions such as anxiety sensitivity (Nelson, Hodges, et al., 2015) that have been shown to be associated with defensive responding to unpredictable threat anticipation. These individual difference factors may influence defensive responding through mechanisms of uncertainty processing, which constitute the second layer of the UICM.

Specifically, the mechanisms of uncertainty processing layer includes five processes that shape anticipatory responses to future threat and are derived from the UAMA (Figure 1; Grupe & Nitschke, 2013). For brevity, Figure 12 focuses on three processes that were addressed in the studies of this cumulative dissertation. First, inflated threat cost and probability estimation concern how participants estimate the probability and cost of future negative events and how they update these estimates following prediction errors (Grupe & Nitschke, 2013). In Study 1, this process is captured through the manipulation of threat occurrence probability, which led to increased startle responding. Increased IU was associated with this enhanced defensive responding that was disproportionate to the lower objective threat probability, consistent with but not directly demonstrating inflated threat estimates. Second, threat attention and hypervigilance constitute a central process in the UAMA and UICM (Figure 12; Grupe & Nitschke, 2013). In the presented studies, probe-locked N1 provided an index of threat attention and hypervigilance and was consistently enhanced during unpredictable threat anticipation (Studies 1, 3, and 4) with additional modulation by individual differences in anxious arousal (Study 3) and anxious apprehension (Study 4). By contrast, the probe-locked P3 indexing later attentional allocation showed less consistent and less unpredictability-specific effects across studies (Table 1). Thus, threat attention and hypervigilance are captured through ERP components in this dissertation, with results implicating a role of early attention and sensory processing in unpredictable threat anticipation. Third, heightened reactivity to threat uncertainty as a UAMA component (Grupe & Nitschke, 2013) is more directly captured through the methodology of the present dissertation and thus implicated in the UICM. Operationalization of heightened reactivity to threat uncertainty across studies includes startle responses, SCR, and anxiety ratings. On the task level, SCR (Studies 1 and 4), startle responses (Studies 1, 3, and 4), and anxiety ratings (Studies 1 and 4) have shown consistent effects of the manipulation of temporal unpredictability (Table 1). Moreover, these measures indexing heightened reactivity to threat uncertainty have shown links to individual differences, e.g., through increased startle responses to unpredictable threat anticipation with increased levels of anxious apprehension and anxious arousal (Study 3). Taken together, the

studies most directly addressed heightened reactivity to threat uncertainty through startle, SCR, and anxiety ratings and addressed increased threat attention and hypervigilance through N1 and P3, as well as inflated threat cost and probability through threat occurrence probability manipulation. Accordingly, the UICM presents these processes as UAMA-derived interpretative mechanisms representing connecting links between individual differences on a trait level and defensive responding in specific situations.

In specific situations, defensive responding has been conceptualized to unfold along a continuum of threat imminence (Fanselow, 1994; Fanselow et al., 2019; Fanselow & Hoffman, 2024; Hoffman et al., 2022) that may be split into transient phases with distinct functional specialization and partially dissociable neural circuits (Fanselow & Hoffman, 2024; Hoffman et al., 2022; Tseng et al., 2023). This continuous and dimensional model provides a transition between the RDoC constructs of potential threat and acute threat (Insel et al., 2010), which are situated in the negative valence system domain. The predatory imminence continuum theory provides a framework for studying anxiety-related psychopathology in specifying normative and maladaptive responding along this continuum (Abend, 2023). Building on this framework and the findings of the present dissertation, the UICM extends the situational threat architecture of the threat imminence continuum by incorporating qualitative features of unpredictability and a quantitative uncertainty dimension (Figure 12).

Figure 12. *Uncertainty-Imminence Continuum Model of Defensive Responding (UICM)*



Note. The uncertainty-imminence continuum model of defensive responding (UICM). Disposition-situation model of defensive responding under uncertainty. Physiological responding to threatening situations can be organized along a threat imminence continuum (adapted from Abend, 2023 Figure 1; Fanselow, 1994) and on an uncertainty continuum made up of qualitative, situational features of unpredictability. Together, threat imminence and uncertainty shape defensive responding in specific situations. Trait-level individual differences moderate this situational responding. These moderators, as indexed via self-report, are connected to core processes of the uncertainty and anticipation model of anxiety (UAMA; Grupe & Nitschke, 2013).

The influence of qualitative features of unpredictability is experimentally grounded in the cumulative studies of this dissertation. Specifically, temporal unpredictability (*when* a threat will occur) was manipulated in Studies 1, 3, and 4 and has yielded robust increases across physiological outcomes (primarily startle, N1, and SCR) and subjective anxiety ratings. Moreover, probabilistic unpredictability (*if* a threat will occur) was tested in Study 1 and led to increased startle responding, suggesting an influence of probabilistic features of unpredictability in threat anticipation. Yet, there are more qualitative features of unpredictability that could be considered to influence threat

anticipation in a given situation. As such, unpredictable magnitude or intensity of the threat could be considered (Bradford et al., 2013; Dugas et al., 2026; Morriss, Bennett, et al., 2021; Shankman et al., 2011), a process that may have been tapped into through the uncertainty symptom induction of Study 2. Furthermore, unpredictable valence of a consequence could be considered, i.e., whether an outcome will be aversive or appetitive (Greenberg et al., 2015), as well as unpredictable duration (von Leupoldt et al., 2021), volatility/second-order uncertainty (Morriss, 2023; Sandhu et al., 2023), and uncertainty about safety (Morriss, Bennett, et al., 2021). Together, these more qualitative features of unpredictability may differentially map onto the threat imminence continuum. Probabilistic unpredictability might be more specific to the pre-encounter phase, as not knowing if a threat will occur includes the current absence or greater distance of threat. Temporal unpredictability in turn may modulate responses during the pre-encounter phase (Abend, 2023) and the encounter phase, as information of the precise temporal aspect of a threat might be lacking up to the post-encounter and contact phase, although arguably, the influence of temporal unpredictability might be most pronounced during the pre-encounter phase (Abend, 2023). Unpredictable magnitude and intensity (Figure 12) and unpredictable valence might shape defensive responding until the contact phase, in which information on these features is available. The UICM therefore extends the threat imminence continuum by specifying how probabilistic, temporal, and intensity/magnitude-related uncertainty may shape defensive responding in anticipation of threat.

Beyond these qualitative distinctions, unpredictability may also be conceptualized dimensionally. The qualitative aspects of unpredictability that have elicited robust associations with increased defensive responding (Table 1) may condense into an underlying situational uncertainty continuum. This situational uncertainty continuum could be influenced by more subtle situational features and experimental design choices, e.g., the inclusion of a countdown in the unpredictable threat anticipation phase (Nelson & Shankman, 2011) instead of geometric shapes (Schmitz & Grillon, 2012). In a specific situation involving the anticipation of threat, this quantitative uncertainty continuum may show the opposite direction of the threat imminence continuum (Figure 12). As such, dangerous real-life situations as well as experimental setups including impending threat may be characterized by a two-dimensional space modelling threat imminence and uncertainty. Although no established account explicitly proposes inverse continua of threat uncertainty and imminence, several theoretical models conceptualize uncertainty as a continuously varying property of threat representations. In particular, threat and safety computations have been proposed to depend jointly on imminence, value, and uncertainty, while computational accounts formalize uncertainty in terms of entropy, ambiguity, precision, or volatility (Bach & Dolan, 2012; Hirsh et al., 2012; Levy & Schiller, 2021; Tashjian et al., 2021). These accounts support representing threatening situations within a

multidimensional space. Within this space, uncertainty and imminence may often be negatively coupled, as approaching threat resolves uncertainty about its occurrence or timing, but they should be regarded as partially independent rather than necessarily inverse dimensions. This situational threat architecture may provide differential points of impact for dispositional factors such as individual differences in IU.

For example, a highly predictable and imminent threat in the post-encounter/contact phase might represent such a strong experimental situation in terms of task load that individual difference factors might be overshadowed by the strength of the experimental situation (Lissek et al., 2006). In contrast, in highly uncertain (in experimental terms unpredictable) situations with low threat imminence in the pre-encounter phase, IU may act as an amplifier of defensive responding. Aligned with this notion are theoretical frameworks that highlight altered safety inferences (Brosschot et al., 2017, 2018; Van den Bergh et al., 2021) and empirical findings from fear conditioning suggesting differences between clinical groups and healthy participants in response to the CS- in the acquisition phase, i.e., the stimulus never paired with an aversive unconditioned stimulus (Duits et al., 2015; Kausche et al., 2025). Against this background, the absence of evidence that IU modulates the ERN as a neural correlate of performance monitoring in Study 2 appears plausible. If errors are conceptualized as internal unpredictable and potentially threatening events (Jackson et al., 2016; Weinberg et al., 2012, 2016), the measurement of the ERN would be integrated in the contact phase of the predatory imminence continuum. Thus, mapping the ERN on the uncertainty/imminence continua suggests that performance monitoring may reflect a highly proximal, event-bound form of threat processing, in which individual differences in IU are less likely to exert modulatory effects in a student sample compared with more distal, uncertain threat anticipation. Similarly, contextual factors rendering the environment threatening such as punishment (Riesel et al., 2012) and inherently aversive startle probes (Hajcak & Foti, 2008; Riesel et al., 2013) or unpredictable tones (Jackson et al., 2015) may transiently alter ERN amplitudes in ways that the uncertainty induction in Study 2 could not capture, because the pre-post design in Study 2 assessed residual effects of the induction rather than uncertainty experienced concurrently with error processing. Nevertheless, the absence of evidence for the uncertainty symptom induction or IU influencing the ERN in Study 2 suggests that neural correlates of performance monitoring are less sensitive to trait IU or carry-over effects of state fluctuations in uncertainty than previous studies suggest. This may challenge the conceptualization of errors as internal threat signals (Jackson et al., 2016; Weinberg et al., 2012, 2016), as previously reported associations between IU and the ERN were not replicable (Jackson et al., 2016).

Taken together, uncertainty may be conceptualized not only in terms of distinct qualitative features, but also as a quantitative dimension that varies inversely with threat imminence in

anticipatory threat contexts. This two-dimensional architecture may suggest that dispositional individual difference factors such as IU exert their strongest influence when uncertainty is high and imminence is low, whereas highly imminent and predictable threat may constrain individual difference effects by imposing strong situational demands (Lissek et al., 2006). This conceptualization raises several open questions for future studies, particularly regarding the qualitative vs. quantitative effects of uncertainty and possible interactions with threat imminence in shaping defensive responding and providing grounds for susceptibility to anxiety-related psychopathology.

4.5 Strengths and Limitations

The research presented in this cumulative dissertation holds several strengths, but also several noteworthy limitations, which set evidential boundaries of the findings. The dissertation has a transdiagnostic scope by including underrepresented clinical phenotypes in threat anticipation research such as OCD. This transdiagnostic scope aligns with contemporary dimensional frameworks of psychopathology, including RDoC and HiTOP (Aftab et al., 2026; Kotov et al., 2017). By examining patients with OCD using the NPU-threat test, the dissertation provides an initial characterization of unpredictable-threat responding in this clinical group, relative to unaffected controls and patients with specific phobia and social anxiety disorder. Direct comparisons between diagnostic groups in the NPU-threat test are scarce and so far have included generalized anxiety disorder vs. social anxiety disorder (Gorka, Lieberman, Shankman, et al., 2017b; Grillon et al., 2017) vs. specific phobia (Gorka, Lieberman, Shankman, et al., 2017b) and panic disorder vs. PTSD (Katz et al., 2018) and panic disorder vs. depression (Shankman et al., 2013). By adding further direct comparisons, Study 4 of this dissertation broadens the scope of threat anticipation research in clinical populations. However, not the whole spectrum of anxiety-related psychopathology was covered. Specifically, diagnostic groups with panic disorder, agoraphobia, generalized anxiety disorder, separation anxiety, and selective mutism (American Psychiatric Association, 2013) were not included. To date, NPU-threat research has only indirectly addressed separation anxiety through symptom measures (Nelson & Hajcak, 2017a) or diagnostically heterogeneous pediatric samples (Mumper et al., 2022), while selective mutism has not been examined using the paradigm. While broader diagnostic coverage is needed to establish generalizability to the whole spectrum of anxiety disorders, theoretically informed group comparisons and transdiagnostic approaches as in Study 4 may still be informative for identifying processes that cut across diagnostic boundaries.

Another strength concerns the multisystem physiological assessment, comprising startle EMG, SCR, ERP components N1, P3, and ERN. This approach shows that uncertainty-related

responding is not a unitary physiological process but may be expressed differently across reflexive defensive responding, autonomic arousal, early sensory processing, later attentional allocation, and performance monitoring. Examining these physiological outcome measures within and across studies allowed both response-system-specific effects and convergence across outcome measures to be identified. Across studies, the most consistent effects of unpredictable threat emerged at earlier stages of responding, reflected in startle potentiation and N1 enhancement, whereas later attentional and performance monitoring measures showed less robust modulation. The replication of these findings across student, community, and clinical samples further substantiates their robustness across populations. A further methodological strength lies in the adherence to open and reproducible science principles, supporting scientific rigor and transparency across studies. Specifically, the hypotheses and methodology including psychophysiological preprocessing steps of Studies 1, 2, and 4 were preregistered. Study 2 additionally included a multi-center replication effort by combining the preregistered sample with independent datasets collected in Hamburg and Rotterdam. This resulted in a combined sample of 355 participants in Study 2 and enabled well-powered tests of small associations and Bayesian quantification of evidence for null effects. Studies 1, 2, and 4 likewise employed open sharing of data.

Further, the dissertation includes an integrative conceptual scope across uncertainty, defensive responding, and internalizing psychopathology. Within this dissertation, uncertainty is not treated as a narrow experimental manipulation, but as a broader organizing principle for defensive responding with relevance for anxiety-related psychopathology connecting basic processes of threat anticipation across response systems to clinically relevant traits and dimensions. Uncertainty was operationalized in several ways, but not exhaustively. The work covers temporal unpredictability (Studies 1, 3, and 4), probabilistic unpredictability (Study 1), and a state uncertainty induction (Study 2). However, other features—such as unpredictable intensity (Bradford et al., 2013; Dugas et al., 2026; Morriss, Bennett, et al., 2021; Shankman et al., 2011), unpredictable duration (von Leupoldt et al., 2021), unpredictable valence (Greenberg et al., 2015), volatility/second-order uncertainty (Morriss, 2023; Sandhu et al., 2023), and uncertainty about safety (Morriss, Bennett, et al., 2021)—were not systematically manipulated. Therefore, conclusions are restricted to the specific features of unpredictability tested in the present studies. A related limitation concerns the incomplete coverage of the UAMA processes in this dissertation (Grupe & Nitschke, 2013). The studies provided psychophysiological evidence relevant to three UAMA processes: threat cost and probability (occurrence probability manipulation in Study 1), threat attention and hypervigilance (ERPs indexing attentional processes in Studies 1, 3, and 4), and heightened reactivity to threat uncertainty (startle responses in Study 1, 3, and 4, SCR in Studies 1 and 4). Two central processes, namely deficient safety

learning and behavioral and cognitive avoidance were not covered (Figure 1; Grupe & Nitschke, 2013). The role of safety learning in anxiety-related psychopathology is subject to ongoing research as reflected in meta-scientific work (Kausche et al., 2025; Duits et al., 2015; Lissek et al., 2005). Behavioral and cognitive avoidance, including their experimental assessment, likewise constitute ongoing lines of research (reviewed in Arnaudova et al., 2017; Ball & Gunaydin, 2022). Incorporating these processes would have exceeded the scope of the present cumulative dissertation. Nevertheless, both processes are essential to an integrative account of threat anticipation under uncertainty, and their incorporation into models combining threat proximity and uncertainty represents an important direction for future research. Accordingly, the conclusions drawn here are restricted to the processes directly examined.

Further limiting the inferences from the present results, individual differences in IU were measured exclusively via self-report (Carleton et al., 2007; Gerlach et al., 2008). Mauss et al. (2024) meta-scientifically found weaker coherence between subjective experience (i.e., self-report) and physiology than between subjective experience and behavior, which they attribute to differences in the underlying processing systems. Subjective experience and behavior are relatively reflective and consciously controllable, whereas physiological responses are typically faster, more automatic, and less accessible to introspection. This could have impacted the strength of associations between individual differences in self-reported IU and physiological responses. However, across the studies of this dissertation, subjective ratings were not more consistently related to IU, despite both being assessed via self-report. More behavioral assessments of IU such as the beads task (as proposed in Jacoby et al., 2014, 2015) were not employed to assess individual differences in IU. However, in Study 2, we included a newly developed symptom induction procedure, which was used as an experimental manipulation, but not as an individual difference measure. Still, experiment-based behavioral assessments of IU simplify real-life uncertainty, which is often prolonged, ambiguous, socially embedded, and linked to avoidance, checking, reassurance seeking, or worry over time (Einstein, 2014). This constraint in ecological validity is a general limitation of experimental research on neural correlates of IU (Dugas et al., 2026). Possible bridges to real life scenarios consist of altering the experimental tasks to be dynamic, complex, unfolding scenarios rather than static tasks (Dugas et al., 2026), and employing ecological momentary assessment (e.g., Appel et al., 2024).

Beyond this limitation in ecological validity, a further methodological constraint concerns causal inference. Most associations between anxiety-related psychopathology and physiological responding in this dissertation are correlational. Although Study 2 employed a randomized controlled experimental symptom induction with pre-post physiological and self-report assessment, the associations of IU, anxious apprehension, and anxious arousal with physiological responding in

Studies 1, 3, and 4 were examined cross-sectionally. The findings therefore identify candidate physiological correlates and response profiles, particularly in Study 4, but do not establish their temporal or causal role. It thus remains to be seen whether these patterns represent correlates, vulnerability factors, compensatory adaptations, or consequences of anxiety-related psychopathology.

Taken together, this dissertation combines a transdiagnostic sampling approach, multisystem psychophysiological assessment, multiple operationalizations of uncertainty, and transparent research practices, supporting an integrative examination of the role of uncertainty in defensive responding. At the same time, the conclusions are constrained by incomplete coverage of the anxiety disorder spectrum and features of unpredictability, as well as reliance on self-reported IU in cross-sectional associations. The findings should therefore be understood as identifying candidate physiological correlates and response patterns rather than establishing a comprehensive or causal account of the psychophysiological underpinnings of uncertainty. These limitations provide the basis for the future research directions outlined in the following section.

4.6 Methodological and Clinical Implications

The findings of this dissertation suggest several methodological and clinical directions for future research. Methodologically, the present findings suggest four priorities for future research, concerning the experimental operationalization of uncertainty and threat imminence, the assessment and induction of uncertainty, multisystem psychophysiological measurement, and the integration of categorical and dimensional approaches. First, several features of the proposed UICM combining quantitative and qualitative aspects of uncertainty with threat imminence remain to be tested (Figure 12). Across the included studies in this dissertation, partially dissociable effects emerged for temporal and probabilistic unpredictability. As such, temporal unpredictability was associated with robust startle and N1 increases, as well as increased anxiety ratings (Table 1), while probabilistic unpredictability elicited a startle-specific potentiation at lower threat occurrence probability, especially in individuals with increased levels of IU. The consideration of different experimental features of unpredictability has been the subject of prior studies (Bennett et al., 2018; Morriss, Bennett, et al., 2021; Shankman et al., 2011) and clarifications have also been called for in literature reviews (Dugas et al., 2026; Morriss, Zuj, et al., 2021). Thus, future studies are required to further understand the interplay of different features of unpredictability, which could inform and refine the overall understanding of defensive responding under uncertainty in the context of the UICM (Figure 12). Threat of shock designs manipulating unpredictability should explicitly report, manipulate, and compare different dimensions of unpredictability rather than focusing singularly on

temporal unpredictability with high task load (Lissek et al., 2006). Methodologically, the UICM (Figure 12) implies that uncertainty should be operationalized both qualitatively and quantitatively. As such, complementing categorical manipulations with continuous indices such as entropy or inverse precision (Hirsh et al., 2012) could improve comparability across paradigms and help disentangle uncertainty from threat imminence. Future research should further extend the UICM by addressing alterations in safety learning and behavioral and cognitive avoidance, the two UAMA processes not examined in this dissertation (Grupe & Nitschke, 2013). Mapping these processes across different combinations of threat unpredictability and imminence could clarify when impaired safety learning and maladaptive avoidance emerge and how they sustain defensive responding in anxiety-related psychopathology (Arnaudova et al., 2017; Ball & Gunaydin, 2022; Duits et al., 2015; Kausche et al., 2025). Taken together, future studies should orthogonally manipulate threat imminence and uncertainty, systematically compare different features of unpredictability, and assess their effects across multiple physiological response systems. Such designs could test the central UICM prediction that dispositional factors such as IU exert their strongest influence under high uncertainty and low imminence, while also incorporating safety learning and avoidance as additional processes shaping defensive responding.

Additionally, the newly developed uncertainty symptom induction employed in Study 2 holds several methodological implications for future research. The uncertainty symptom induction was developed based on previous manipulations (Deschenes et al., 2010; Faleer et al., 2017; Grenier & Ladouceur, 2004; Mosca et al., 2016; N. O. Rosen & Knäuper, 2009; Rosser, 2019; Tullett et al., 2014) and optimized to focus on a specific situation, be sufficiently salient to invoke state changes in uncertainty, and enable standardization e.g., through a computerized task. Since Study 2 showed increases in other state symptoms next to state uncertainty, a logical implication is to uncover and refine the methodological components of the uncertainty induction to increase specificity to uncertainty. This might include a trade-off between specificity and salience of the symptom induction (Lissek et al., 2006). Further, measuring physiological responses during the symptom induction as opposed to pre-post measurements might help to elucidate variation in individual responses. As discussed in Malbec (2026), future research could benefit from multilevel assessment of IU including ecologically valid assessment methods and behavioral tasks (Jacoby et al., 2014, 2015), in which responses during symptom induction protocols might represent one level. Taken together, future research should refine uncertainty inductions while embedding them in multimodal and ecologically valid assessment frameworks that capture physiological responses during the induction and characterize individual responses with greater granularity.

A further priority is to determine whether physiological multisystem response profiles represent replicable and generalizable patterns of defensive responding. Studies 1, 3, and 4 employed startle EMG and EEG measuring the ERP components N1 and P3. Considering individual difference associations with psychophysiological measures (Table 1B), there was non-convergence within measures across studies and substantial non-convergence of effects across outcomes within studies. This underscores the importance of employing multimodal outcome measures, since single-outcome studies risk missing individual difference effects in reflexive defensive responding (e.g., IU association with startle in Study 1) and later attentional processes (e.g., anxious apprehension being associated with P3 but not N1 during predictable threat anticipation in Study 3). The implicated multisystem approaches spanning different aspects of defensive responses are conceptually in line with the dual-pathway model suggesting partial discernibility of cortical and subcortical pathways (Carr, 2015; Koller et al., 2019; LeDoux, 1995; Villa et al., 2025). In line with this, previous studies on attentional processing can be taken to suggest that alterations in the attentional dynamics for aversive stimuli in anxiety-related psychopathology are not uniform but might follow an early hypervigilance and later avoidance pattern (Kausche et al., 2022; Weinberg & Hajcak, 2011; Z.-M. Zhang et al., 2017). Future studies should therefore combine multiple physiological measures and model their temporal dynamics and interplay to determine whether putative clinically relevant individual differences emerge as replicable multisystem profiles rather than isolated effects in single outcomes.

Moreover, a related methodological implication concerns combining categorical diagnoses and dimensional symptom measures within the same analytical framework. Study 4 adopted such an approach by examining diagnostic group differences alongside transdiagnostic symptom dimensions. This strategy is consistent with the notion that dimensional models complement diagnoses by capturing symptom severity and heterogeneity within and across diagnostic categories (Ruggero et al., 2019). Empirical studies further indicate that dimensional measures can explain clinically relevant variance beyond categorical diagnoses (Martin et al., 2021; Shankman et al., 2017; Snyder et al., 2023). Applying both perspectives within the same dataset may therefore clarify whether variation in physiological responses is associated with diagnostic status, dimensional symptom variation, or their combination, thereby connecting otherwise partly separate lines of research. Exclusively categorical analyses may be less sensitive to dimensional individual differences because categorization inherently entails a loss of information and statistical power (MacCallum et al., 2002). At the same time, including multiple categorical and dimensional predictors expands the analytical space and may increase false-positive risk when hypotheses are not prespecified or multiplicity is not adequately controlled (Forstmeier et al., 2017; Simmons et al., 2011). Taken together, integrating categorical and dimensional analyses may improve sensitivity to clinically

meaningful physiological variation, provided that analytical flexibility is adequately constrained. Beyond these methodological considerations, the findings also raise questions about the clinical relevance of uncertainty in threat anticipation.

Two clinical and translational implications follow from the present findings. First, the multisystem response profiles identified in Study 4 highlight potentially clinically relevant heterogeneity that was not captured by diagnostic categories alone. Although the threat-reactive profile was clinically enriched, diagnostic groups were still substantially distributed across both more and less threat-reactive profiles, indicating that clinical status did not map uniformly onto a single physiological response pattern. These findings raise the possibility that multisystem physiological responses could complement diagnoses and dimensional symptom measures by identifying psychophysiologically distinct subgroups. However, the present profiles are exploratory and should not yet be interpreted as clinically applicable subgroups. As such, they require replication in independent clinical samples (Schmiege et al., 2018), as well as assessment of their temporal stability and prospective tests of whether profile membership predicts treatment response. At the level of individual NPU measures, initial longitudinal evidence supports the broader prognostic potential of responses elicited by the NPU-threat test. Startle responding during threat anticipation has prospectively predicted subsequent functional impairment beyond DSM diagnoses (Stevens et al., 2019). More recently, heightened startle potentiation to unpredictable threat predicted the later development of generalized anxiety disorder in adolescents (Jayakumar et al., 2025). If replicated and extended to multisystem response profiles, such findings raise the possibility that physiological responses to unpredictable threat could provide prognostic information beyond diagnostic categories and concurrent symptom severity. This may be particularly relevant in OCD, where heightened autonomic responding and anxious apprehension-related early sensory enhancement during unpredictable threat anticipation were present in Study 4. Such work could determine whether these response patterns normalize with treatment or characterize subgroups with different treatment trajectories.

Second, a central future direction following from the results presented in this dissertation concerns the potential sensitivity of psychophysiological markers of defensive responding to treatment-related change. Startle responding to unpredictable threat appears sufficiently stable in the absence of intervention while remaining modifiable by treatment: Gorka, Lieberman, Klumpp, et al. (2017) reported high temporal stability across 12 weeks in healthy controls, but reductions following cognitive behavioral therapy in patients with fear-based disorders that covaried with symptom improvement. Hoge et al. (2024) similarly found reductions in anxiety-potentiated startle following both escitalopram and mindfulness-based stress reduction in patients with anxiety

disorders. Future clinical trials could therefore distinguish whether baseline physiological responding predicts subsequent treatment outcome, whether changes in responding track or mediate symptom improvement, and whether baseline response patterns predict differential benefit from specific interventions. The latter would constitute an important prerequisite for ultimately using such measures for treatment stratification.

4.7 Conclusion

In conclusion, this cumulative dissertation drew on four empirical studies to elucidate how uncertainty shapes defensive responding and related psychological and neurocognitive processes across the broader spectrum of internalizing and anxiety-related psychopathology. Across studies, responding to unpredictable threat was most consistently expressed in reflexive defensive responding and early attentional processing, particularly during temporally unpredictable or low-probability threat. Importantly, uncertainty did not exert a uniform influence. Its effects depended on the specific feature of unpredictability, the physiological response system, and the individual difference factor examined. IU and anxiety symptom dimensions selectively modulated physiological responses, whereas neural correlates of error monitoring showed no robust association with trait IU or experimentally induced state uncertainty. In the clinical sample, physiological responses did not map onto a single diagnostic signature but emerged as heterogeneous multisystem response patterns, with some evidence of heightened unpredictable-threat responding in OCD.

These findings informed the development of the uncertainty-imminence continuum model of defensive responding, which integrates individual differences, central processes of anticipatory responding, and situational features including threat proximity and qualitative and quantitative dimensions of uncertainty. More broadly, the results underscore the importance of distinguishing qualitative features of unpredictability, assessing defensive responding across multiple physiological systems, and integrating categorical and dimensional perspectives on psychopathology. At the same time, the identified physiological correlates and response patterns should be understood as candidates rather than established causal mechanisms or clinically applicable biomarkers. Future research should therefore directly test the predictions of the uncertainty-imminence continuum model, replicate the multisystem response patterns identified here, and examine their temporal, prognostic, and treatment-related relevance. Overall, by beginning to unravel how uncertainty shapes defensive responding across situational features, physiological response systems, and individual differences, this dissertation positions uncertainty alongside threat imminence as a central organizing dimension of defensive responding, thereby anchoring uncertainty as a central component of threat anticipation.

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Appendices

A Correlations of Psychophysiological Measures

Table A1. *Correlations Between Psychophysiological Outcomes within NPU Conditions and Threat Probabilities in Study 1*

Probability / condition	Startle–N1	Startle–P3	Startle–SCR	N1–P3	N1–SCR	P3–SCR
100% N	.02	.24*	-.06	-.16	-.08	.10
100% P	.08	.12	-.05	-.01	-.15	.01
100% U	-.01	-.12	-.22	-.19	-.04	.15
33% N	-.10	.17	.13	-.17	-.01	-.09
33% P	-.24*	.20	.09	-.21*	.05	.04
33% U	-.41***	.14	.12	-.28*	-.12	.21

Note. Pearson correlation coefficients between participant-level mean physiological responses calculated separately per threat-probability and NPU condition. Startle responses are based on within-participant *t*-transformed amplitudes. Correlations not involving SCR were based on n = 90; correlations involving SCR were based on n = 66. N = neutral, P = predictable, U = unpredictable. SCR = range-corrected, log-transformed startle probe-locked skin conductance response.
* $p < .05$. ** $p < .005$. *** $p < .001$.

Table A2. *Correlations Between Psychophysiological Difference Scores in Study 1*

Probability / contrast	Startle–N1	Startle–P3	Startle–SCR	N1–P3	N1–SCR	P3–SCR
100% U – N	-.42***	.05	.19	-.13	-.07	.00
100% P – N	-.16	-.03	.06	.03	-.22	.01
100% U – P	-.33**	.07	.09	-.17	-.09	.20
33% U – N	-.36***	.04	.28*	-.03	-.26*	-.02
33% P – N	-.24*	.09	-.04	.01	.23	-.02
33% U – P	-.10	.11	.26*	-.09	.01	.13

Note. Values are Pearson correlation coefficients between participant-level mean physiological responses calculated separately within each threat-probability and NPU condition. Startle responses are based on within-participant *t*-transformed amplitudes. Correlations not involving SCR were based on n = 90; correlations involving SCR were based on n = 66.
N = neutral, P = predictable, U = unpredictable. N1 is retained in its original signed amplitude; more negative values indicate larger N1 responses. SCR = range-corrected, log-transformed startle probe-locked skin conductance response.
* $p < .05$. ** $p < .005$. *** $p < .001$.

Table A3. *Correlations Between Psychophysiological Outcomes within NPU Conditions Study 3*

Condition	Startle–N1	Startle–P3	N1–P3
N	-.13	-.02	-.26**
P	.11	.04	-.29***
U	-.32***	.20*	-.22*

Note. Values are Pearson correlation coefficients between participant-level mean physiological responses calculated separately within each NPU condition. Pairwise complete observations were used (n = 136). N = neutral, P = predictable, U = unpredictable. * p < .05. ** p < .005. *** p < .001.

Table A4. *Correlations Between Psychophysiological Difference Scores in Study 3*

Contrast	Startle–N1	Startle–P3	N1–P3
U – N	-.42***	.12	-.15
P – N	-.29***	.12	-.18*
U – P	-.53***	.27**	-.25**

Note. Values are Pearson correlation coefficients between participant-level mean physiological responses calculated separately within each NPU condition. Pairwise complete observations were used (n = 136). N = neutral, P = predictable, U = unpredictable. * p < .05. ** p < .005. *** p < .001.

Table A5. *Correlations Between Psychophysiological Outcomes within NPU Conditions Study 4*

Condition	Startle–N1	Startle–P3	Startle–SCR	N1–P3	N1–SCR	P3–SCR
N	-.11	.07	-.02	-.15	.02	.08
P	-.12	-.17*	.31***	-.11	-.15	-.08
U	-.14	-.15	.26**	-.11	-.18*	-.06

Note. Values are Pearson correlation coefficients between participant-level mean physiological responses calculated separately within each NPU condition. Startle responses are based on *t*-transformed amplitudes within participants. Pairwise complete observations were used. N = neutral, P = predictable, U = unpredictable. SCR = log-range-transformed skin conductance response. * $p < .05$. ** $p < .005$. *** $p < .001$.

Table A6. *Correlations Between Psychophysiological Difference Scores in Study 4*

Contrast	Startle–N1	Startle–P3	Startle–SCR	N1–P3	N1–SCR	P3–SCR
U – N	-.24**	-.06	.33***	.12	-.12	-.03
P – N	-.20*	-.19*	.20*	.29***	-.18*	-.12
U – P	-.34***	-.07	.37***	.15	-.21*	.05

Note. Values are Pearson correlation coefficients between participant-level mean physiological responses. N and U were averaged across ISI and countdown periods, whereas P used countdown responses. Startle responses are based on *t*-transformed amplitudes within participants. Pairwise complete observations were used. N = neutral, P = predictable, U = unpredictable. SCR = log-range-transformed skin conductance response. * $p < .05$. ** $p < .005$. *** $p < .001$.

Publications

This cumulative dissertation is based on four studies, for which articles have been published or are currently under review.

Study 1: Intolerance of Uncertainty in Unpredictable Threat Anticipation

Carsten, H. P., Härpfer, K., & Riesel, A. (2022). A rare scare: The role of intolerance of uncertainty in startle responses and event-related potentials in anticipation of unpredictable threat. *International Journal of Psychophysiology*, *179*, 56–66. https://doi.org/10.1016/j.ijpsycho.2022.06.018

Study 2: Testing the Influence of Uncertainty on the Error-Related Negativity

Carsten, H. P., Härpfer, K., Malbec, M., Wieser, M. J., & Riesel, A. (2025). Are errors more aversive in an uncertain world? Testing the influence of uncertainty on the error-related negativity in a randomized controlled trial. *International Journal of Psychophysiology*, *207*, 112480. https://doi.org/10.1016/j.ijpsycho.2024.112480

Study 3: Anxiety Dimensions in Threat Anticipation

Carsten, H. P., Härpfer, K., Nelson, B. D., Kathmann, N., & Riesel, A. (2023). Don't worry, it won't be fine. Contributions of worry and anxious arousal to startle responses and event-related potentials in threat anticipation. *Cognitive, Affective, & Behavioral Neuroscience*, *23*, 1141–1159. https://doi.org/10.3758/s13415-023-01094-4

Study 4: Transdiagnostic Physiological Correlates of Unpredictable Threat Anticipation

Carsten, H. P., Härpfer, K., Kausche, F. M., & Riesel, A. (under review). Transdiagnostic physiological correlates of unpredictable threat anticipation. Manuscript under review at *International Journal of Clinical and Health Psychology*.

Study 1

A Rare Scare: The Role of Intolerance of Uncertainty in Startle Responses and Event-Related Potentials in Anticipation of Unpredictable Threat

Hannes Per Carsten, Kai Härpfer, & Anja Riesel

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A rare scare: The role of intolerance of uncertainty in startle responses and event-related potentials in anticipation of unpredictable threat☆,☆☆

Hannes Per Carsten *, Kai Härpfer, Anja Riesel

Department of Psychology, University of Hamburg, Hamburg, Germany

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ABSTRACT

Intolerance of uncertainty (IU) represents a transdiagnostic risk factor for internalizing psychopathology. However, little is known regarding its psychophysiological correlates. IU is thought to render individuals hypersensitive to threatening events, even if the occurrence probability is low. To test this, we recruited 90 students who completed two NPU-threat tests separating temporal unpredictability from probabilistic unpredictability (i.e., probability of occurrence): First, a NPU version in which the timing of threat (i.e., shock) was either predictable or unpredictable but the shock probability was 100 % in each trial. Second, a probabilistic NPU version in which the timing of the shock was also either predictable or unpredictable, but the shock probability was 33 % in each trial. Startle reflex, event-related potentials N1 and P3 locked to auditory startle probes, and anxiety ratings were analyzed. As expected, temporally unpredictable threat modulated startle, N1, and anxiety ratings. IU predicted increased startle to lower shock probability, regardless of the temporal predictability. No evidence emerged for IU affecting N1 or P3. However, IU predicted anxiety ratings to threat conditions regardless of temporal or probabilistic predictability. Individual differences in IU shape startle responses to eventual threat: IU increases automatic defensive responding to unpredictable and potentially threatening situations if the threat probability is low. Individuals with higher IU may tend to "err on the side of caution" with a mismatch between physiological preparation and threat probability, such that the effects of IU are particularly observable in low threat probability conditions.

1. Introduction

1.1. Uncertainty and unpredictability

Uncertainty is engrained within the human experience. Uncertainty may occur within the past (*do I have this headache because of the wine last night?*), the future (*will I have a headache tomorrow if I drink this glass of wine?*), the mundane (*will I get a headache?*), or the fundamental (*could this headache be a brain tumor?*). The common element of these examples is the potential absence of information, and thus the unknown (Carleton, 2016b). The unknown can be broken down into further sub parameters of uncertainty and/or unpredictability (Morriss, Bennett, and Larson, 2021; Morriss, Zuj, et al., 2021). The unpredictability of an event includes different aspects: Probabilistic unpredictability (the unpredictability of occurrence), temporal unpredictability, unpredictable modality, intensity, frequency, and duration. Yet, how these aspects of unpredictability differentially influence the experience of uncertainty is unknown.

1.2. Predictability of threat in experimental manipulations

To experimentally test responses to unpredictability, Schmitz and Grillon (2012) developed the neutral, predictable threat, and unpredictable threat test (NPU-threat test). Here, the temporal predictability of threat is manipulated: In the predictable condition (P), participants receive a temporally predictable aversive stimulus (i.e., threat), which is signaled by a preceding cue. Previous studies used different cues to signal predictable threat such as geometric shapes (Schmitz and Grillon, 2012), a countdown (Nelson and Shankman, 2011), or loading bars (Bennett et al., 2018). In the unpredictable condition (U), participants receive a temporally unpredictable aversive stimulus. In the neutral condition (N), participants receive no aversive stimulus at all. While

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* Corresponding author at: Department of Psychology, Universität Hamburg, Von-Melle-Park 11, 20146 Hamburg, Germany.
E-mail address: hannes.carsten@uni-hamburg.de (H.P. Carsten).

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most studies using the NPU-threat test measured startle reflex (cf. Schmitz and Grillon, 2012), fewer studies also measured event-related potentials (e.g., Nelson et al., 2015) or skin conductance response (Morriss et al., 2020). The present study uses startle reflex and event-related potentials (N1, P3) to examine the dynamics of the neural processing of unpredictable threat anticipation.[1] In an aversive context, individuals usually display increased startle responses (Hamm et al., 1993; Schmitz and Grillon, 2012) indexing defensive responding. Further, an aversive context usually leads to increased startle probe locked N1 (for unpredictable threat; Nelson et al., 2015) and decreased startle probe locked P3 (Bradford et al., 2017; Ferry and Nelson, 2020; MacNamara and Barley, 2018; Nelson et al., 2015).

Most studies have used the NPU-threat test to manipulate the temporal predictability of threat and typically found increased startle responses to temporally unpredictable threat (e.g., Nelson et al., 2015). Only a few studies have systematically manipulated the probability of occurrence of threat: Davies and Craske (2015) lowered the threat probability to 50 % and found no evidence for increased physiological responding that is solely attributable to a lowered threat probability. Instead, defensive responding—as assessed by the startle reflex—was increased if the threat was temporally unpredictable and had a lower occurrence probability. These findings suggest sensitivity of defensive responding to shared aspects of unpredictability (i.e., temporal and probabilistic unpredictability). In contrast, Bennett et al. (2018) found increased defensive responding to lower threat probability (50 %), but temporal unpredictability more potently increased defensive responding, suggesting that a lower threat probability uniquely increases defensive responding. Hefner and Curtin (2012) found that threat probabilities of 60 % and 20 % increased defensive responding compared with a 100 % threat probability in temporally predictable threat anticipation. Together, these findings imply that temporal unpredictability leads to increased defensive responding which might further be potentiated by probabilistic unpredictability. Prior studies using the NPU-threat test have unsystematically varied the shock occurrence probability during the temporally predictable threat condition (e.g., 60 % in Radoman et al. (2021) or 100 % in Gorka et al. (2020)). Thus, within-subject data directly comparing the effect of threat probability is crucial to understand the consequence of this methodological heterogeneity between studies.

1.3. Individual differences in responding to unpredictability

Prior research has shown that individuals differ considerably in how they cope with the experience of unpredictability (i.e., uncertainty; Carleton et al., 2007; Freeston et al., 1994). This is reflected in the trait intolerance of uncertainty (IU; Carleton, 2016a,b). The initial conceptualization of IU (Dugas et al., 1998; Freeston et al., 1994) included the assumption that individuals with higher IU are intolerant of uncertain events, regardless of the probability of the event (Dugas et al., 2001) and regardless of the consequences of the event (Ladouceur et al., 2000; cf. Carleton, 2012).

Since this initial conceptualization, extensive research has demonstrated associations between self-reported IU and internalizing psychopathology (Carleton, 2012; Gentes and Ruscio, 2011; McEvoy et al., 2019; Shihata et al., 2016). Disorder categories with increased levels of IU include generalized anxiety disorder (e.g., T. A. Brown and Naragon-Gainey, 2013; Counsell et al., 2017; Koerner and Dugas, 2008), obsessive-compulsive disorder (e.g., Holaway et al., 2006; Tolin et al., 2003), depression (e.g., Jensen et al., 2016), social anxiety disorder (e.g., Boelen and Reijntjes, 2009), panic disorder and agoraphobia (e.g., Carleton et al., 2013; Mahoney and McEvoy, 2012a), posttraumatic stress disorder (e.g., Oglesby et al., 2015) and eating disorders (e.g., M. Brown et al., 2017). Consequently, IU has been postulated to be a central transdiagnostic feature of internalizing psychopathology.

Resulting from extensive research linking self-report IU to internalizing psychopathology, IU is listed in the Research Domain Criteria matrix (RDoC; Cuthbert and Insel, 2013; Insel et al., 2010) below the construct potential threat, which is part of the negative valence systems domain. The RDoC initiative promotes research that integrates empirical biobehavioral findings to understand the mechanisms underlying mental disorders (Cuthbert and Insel, 2013). Researchers are called to identify robust associations within a construct across different units of analysis, i.e., across genetic, molecular, cell, neural circuitry, and physiological levels as well as across behavioral measures, self-report, and paradigms. This follows the fundamental aim to improve diagnostic and treatment of mental disorders (Cuthbert and Insel, 2013) by identifying vulnerable individuals, developing individualized interventions, and predicting treatment trajectories.

In this context, IU is particularly interesting because it has emerged as a key transdiagnostic dimension relevant to internalizing psychopathology. Yet, to increase the clinical utility of IU, lines of research identifying neural correlates of IU are important to increase our understanding of the underlying cognitive and behavioral processes and offer interesting targets for individualized treatment (Wever et al., 2015). Individual differences in self-reported IU might manifest in differential responses to experimental manipulations of unpredictability. If IU predicts responses to unpredictable threat, this could result in increased external validity of the construct and advance the understanding of the role of IU as a transdiagnostic feature of internalizing psychopathology (Tanovic et al., 2018).

1.4. Intolerance of uncertainty predicting responses to unpredictable threat

From a theoretical perspective, IU may affect various aspects of responses to unpredictable events. Theoretical models (the uncertainty and anticipation model of anxiety, Grupe and Nitschke, 2013; the extended transdiagnostic model of IU, Einstein, 2014) predict individuals with increased IU to show inflated threat expectancies that lead to uncertainty arousal (i.e., the somatic and inhibitory component of IU). To prevent this arousal (Jacoby et al., 2014), individuals tend to display safety behaviors such as rumination, reassurance seeking, and compulsions, as well as avoidance (Flores et al., 2020; Jacoby et al., 2015; San Martín et al., 2020). The empirical evidence for these predictions is mixed: Individuals with higher IU previously displayed decreased (Nelson and Shankman, 2011) and increased (for prospective IU; Nelson, Liu, et al., 2016) startle responses during the anticipation of temporally unpredictable threat. Other studies did not corroborate a link between IU and startle responses in anticipation of temporally (Bennett et al., 2018; Lieberman et al., 2016; Morriss et al., 2020, 2022; Papenfuss et al., 2021) and probabilistic unpredictable threat (Bennett et al., 2018). In a fear condition experiment, Chin et al. (2016) reported that individuals with higher IU displayed increased defensive responding during a lower reinforcement rate (50 % vs. 75 %), suggesting a role of IU in probabilistic unpredictability. In addition, meta-analytic findings suggest that higher IU decreases safety learning in the extinction phase—a phase that is arguably closely related to probabilistic unpredictability (Morriss et al., 2021). Thus, in light of these mixed findings, further data are required to clarify the role of IU in responses to unpredictability (Shihata et al., 2016; Tanovic et al., 2018). Individuals with higher IU might be more sensitive to a specific aspect of unpredictability, which could explain the mixed previous evidence. This can be tested by directly comparing associations of IU and responses to different aspects of unpredictability. Further comparisons of IU and the neural processing of threat over time—automatic sensory processing and later processing stages that correspond to attentional processes—are limited in relation to NPU threat-based tasks (Ferry and Nelson, 2021), although have been examined in relation to other types of tasks (Bauer

[1] Note that also data on skin conductance responses were measured that are presented in Supplement S5.

et al., 2020; Ferry and Nelson, 2021; MacNamara, 2018; Nelson et al., 2014; Nelson, Kessel, et al., 2016). Accordingly, one major aim of the present study is to identify correlates of IU in the neural dynamics of threat anticipation, thereby broadening our understanding of IU across units of analysis. This represents a vital step in forming integrative, transdiagnostic theories modelling the etiology of internalizing psychopathology.

1.5. Hypotheses

The present preregistered study investigated how temporal unpredictability (when the threat occurs) and probabilistic unpredictability (if the threat occurs) influence peripheral (startle reflex) and electrophysiological markers (startle probe locked N1 and P3) of automatic defensive responding. To this end, we administered two NPU task blocks in which the threat (i.e., shock) was either just temporally unpredictable (i.e., timing of the shock) or additionally probabilistically unpredictable (i.e., occurrence of the shock). We examined whether individual differences in IU affect responses to different aspects of unpredictability to unravel physiological correlates of IU.

Hypotheses were informed by three aspects: First, Dugas et al. (2001) suggested that individuals with higher IU are intolerant of uncertain events, irrespective of the probability that the event may occur. Second, transdiagnostic (Einstein, 2014) and neurobiological models (Grupe and Nitschke, 2013) predict increased threat expectancies and increased physiological arousal to unpredictable situations in individuals with higher IU. Third, evidence from fear conditioning studies suggest a role of IU in probabilistic unpredictability (Chin et al., 2016; Morriss, Wake, et al., 2021). Against this background, we expected that individuals with higher IU are hypersensitive to threatening events with a lower probability of occurrence.[2] Specifically, we expected that individuals with higher IU would show (1) a smaller difference in physiological responses from high to low threat probability for temporally unpredictable threat indicating hypersensitivity to threat with lower probability of occurrence and (2) increased physiological responses in temporally predictable threat with lower probability. In other words, across outcomes, we expected higher IU leading to increased startle, and probe locked N1, and decreased P3 in lower threat probability compared with high threat probability.

2. Methods

The hypotheses and methods of this study were preregistered before the start of data collection (www.osf.io/fmt54). The methods of the study were confirmed by the local ethics committee as being in accordance with the Declaration of Helsinki (World Medical Association, 2013).

2.1. Participants

A total of 90 students (73 % identified as female) aged 18 to 30 years ($M = 23.52$, $SD = 3.22$) were recruited. Participants were mainly psychology undergraduates (71.10 %) and had $M = 12.36$ years of education ($SD = 0.61$). All participants reported German as their first language. Inclusion criteria—assessed in an online screening and subsequent telephone interview—encompassed the age range of 18–30, right-handedness, and the ability to give informed consent in German. Exclusion criteria encompassed having a lifetime substance-related disorder, bipolar disorder, or schizophrenia spectrum disorder, which were assessed by trained raters using the Structured Clinical Interview for DSM-5 Disorders-Clinical Version (SCID-5-CV; Beesdo-Baum et al., 2019). Further exclusion criteria included lifetime neurological disorders, intake of benzodiazepines (last week) and neuroleptics (last three months), needle-phobia, uncorrectable visual, hearing, or motor impairments, hairstyles interfering with the electroencephalography (EEG), and psoriasis or severe neurodermatitis. The subjects received either course credit or 10€ per hour for their participation. The sample size of 90 complete cases was based on an a priori power analysis of a linear regression to estimate an appropriate sample size for level 2 effects in multilevel regression models (Maas and Hox, 2005). The power analysis was carried out using G*Power 3.1.9.7 (Erdfelder et al., 2009; Faul et al., 2007) to obtain .80 power at threshold of $\alpha = .05$ to detect medium effect sizes of $f^2 = 0.15$ in a linear multiple regression with three predictors. This required a sample size of 77 participants. To detect even smaller effects, the target sample size was set to 90 complete data sets after exclusion in startle and EEG preprocessing. Four participants were excluded and replaced, as they terminated the experiment upon request ($n = 2$), due to technical failure ($n = 1$), or due to performance mistakes by the experimenter, e.g., forgetting to start the recording ($n = 1$).

2.2. Questionnaires

IU was measured using the German short version of the Intolerance of Uncertainty Scale (IUS-12; Carleton et al., 2007; Gerlach et al., 2008). The IUS-12 consists of 12 items rated on a five-point Likert scale ranging from 1 (“not characteristic of me”) to 5 (“entirely characteristic of me”). The participants showed comparable levels of IUS-12 to the large student samples used to validate the questionnaire ($M = 27.53$, $SD = 8.61$, range 12–50; cf. Carleton et al., 2007) and the distribution of IUS-12 is comparable to other non-clinical samples in the field (cf. Morriss, Wake, et al., 2021, Table S3). Further, the IUS-12 showed good internal consistency (Cronbach's $\alpha = .871$; validation study: $\alpha = .910$; Carleton et al., 2007).[3]

2.3. Task and stimuli

During the experiment, participants sat in a dimly lit, electromagnetically shielded and sound-attenuated cabin. Stimuli were presented using Presentation Software (Neurobehavioral Systems, Inc., Albany, California) at a viewing distance of approximately 24 in. on a 16 in. monitor with a resolution of 1920 × 1080 pixels and a refresh rate of 120 Hz. We used the countdown version of the NPU-threat test (Nelson and Shankman, 2011; Schmitz and Grillon, 2012). As the threat stimulus, participants could receive a shock delivered by an electrode at the dorsal surface of the right hand (Digitimer DS7A, Welwyn Garden City, UK). Before the experiment, we calibrated ideographic shock levels ($M = 3.46$ mA, $SD = 2.03$) using a staircase procedure (Lonsdorf et al., 2017) up to a subjective rating of unpleasant but tolerable (7 on a scale ranging from 0 = feeling nothing to 10 = not tolerable). Participants completed two NPU-threat task blocks in a randomized order: (1) One task block in which the shock probability in the threat conditions (predictable and unpredictable) was 100 % and (2) one task block in which the shock probability was lowered to 33 %. In the latter, participants were instructed that the shock probability was “very unlikely”. Four shocks occurred per threat condition in the 100 % shock probability task block (i.e., predictable $P_{100\%}$, and unpredictable $U_{100\%}$), and $M = 1.25$ shocks occurred per threat condition in the 33 % shock probability task block (i.e., temporally predictable $P_{33\%}$ and unpredictable $U_{33\%}$). During both NPU-threat tests, two alternating cues were presented: A black screen as the interstimulus interval (13 ± 2 s) and a numerical countdown counting from five to one as the threat cue (1 s per digit). Participants were instructed about the cue types before the task. Both NPU-threat test blocks included three conditions (N, P, U), which each included 8 cues (i.e., 4 interstimulus intervals and 4 countdowns)

[2] For a detailed overview of the hypotheses for each outcome measure see www.osf.io/fmt54.

[3] The broader project included a larger range of questionnaires. Here, we will only introduce those measures relevant to the current study.

and a black screen (10 s) separating the conditions. In the P conditions (i.e., $P_{100\%}$ and $P_{33\%}$), the shock occurred when the countdown reached "1. In the U conditions (i.e., $U_{100\%}$ and $U_{33\%}$) the shock could occur at any time during the interstimulus interval (M = 4.5 s, SD = 2.38) and countdown (M = 3.23 s, SD = 0.35). Each condition was presented twice, resulting in two orders (PNUPNU or UNPUNP) which were randomized across participants. Headphones delivered startle probes consisting of bursts of white noise with a duration of 50 ms (rise/fall time < 1 ms). Startle probe intensity was set to 95 dB to optimize the paradigm to reveal intraindividual differences between experimental conditions (Blumenthal et al., 2005), and to increase the difference in salience between the auditory and electrotactile stimulation. Startle probes were presented in each interstimulus interval (M = 7.46 s, SD = 2.30 relative to onset) and countdown (M = 2.96 s, SD = 0.55 relative to onset). Participants received 48 startle probes in each of the two NPU-threat tests. Prior to the experiment, participants received 16 startle probes to allow for initial startle habituation (Blumenthal et al., 2005).

2.4. Anxiety ratings

Participants rated their level of anxiousness in the experimental conditions (N, P, U) and cues (countdown, interstimulus interval) after each of the two task blocks (100 % shock probability and 33 % shock probability). The rating consisted of visual analogue scales ranging from 0 to 100 (forced choice with 50 as default) presented on a tablet PC. Participants were excluded from the rating analyses if the experimenter failed to deliver one of the ratings (n = 1).

2.5. Startle recording and processing

The eyeblink component of the startle reflex was measured with two 6 mm diameter Ag/AgCl electrodes below the eyelid of the right orbicularis oculi and a ground electrode on the right infraorbital triangle. Data were recorded using a BrainAmp ExG amplifier (Brain Products GmbH, Gilching, Germany) at a sampling rate of 1000 Hz. Brain Vision Analyzer 2.2 (Brain Products GmbH, Gilching, Germany) was used to process the physiological data. Startle data were filtered (28–500 Hz, 24 dB/octave roll-off), rectified, baseline corrected (baseline = 50 ms prior to startle probe onset), and integrated (9 ms moving average). Amplitudes to each cue within each condition within each task block were manually scored from onset to peak in a response latency window of 20 to 120 ms post startle probe onset. Undetectable reactions were scored as zero and included into the analyses. Voluntary or spontaneous blinks −50 to 20 ms relative to the startle probe onset were scored as missings and excluded from the analyses. To ensure the availability of sufficient startle reactions, participants were excluded from the startle analyses (n = 2) if they showed zeros or missings to >66 % of the startle probes, including the 16 startle trials presented in the initial startle habituation phase (cf. Kuhn et al., 2020). In the remaining data, 7.91 % of the reactions were zeros. The zeros differed between the conditions ($X^2(2, N = 687) = 31.5$, $p < .001$), with less zeros in U than in P or N ($ps < .001$). Meeting the exclusion criteria for one physiological outcome (startle, N1, P3) did not exclude participants' data from the analyses of the other outcomes. Internal consistency of the startle data was determined by calculating Cronbach's alpha based on single trials for each cue within each condition within each task block and ranged from α = .841 to α = .952.

2.6. Electroencephalography recording and processing

EEG data were acquired with two 32-channel BrainAmp amplifiers (Brain Products GmbH, Gilching, Germany) using 61 concentric and equidistant Ag/AgCl scalp electrodes (Easycap, Herrsching, Germany). The recording reference was located between the AF3 and Fz, the ground electrode between AF4 and Fz. Further electrodes were placed at the left infraorbital site and neck. Impedances were kept below 5 kΩ. Data were acquired at a sampling rate of 1000 Hz and recorded with a band-pass filter of 0.1 to 250 Hz. Raw data were band-pass filtered (0.1 to 30 Hz; 24 dB/octave roll-off) and notch-filtered (50 Hz). Semi-automatic independent component analysis (Jung et al., 2000) was applied to correct for eye movement artefacts. Data were re-referenced offline to a common average reference. Startle probe locked epochs for each cue within each condition within each task block of 1200 ms length were extracted (200 ms prestimulus to 1000 ms poststimulus), baseline-corrected (−200 ms relative to startle probe onset) and rejected if an absolute voltage-range exceeded 300 μV or if there was a voltage step between two data points > 50 μV or a voltage difference < 0.5 μV within a 100 ms interval.[4] Quantification of the event-related potentials was based on visual inspection of the grand-averaged waveforms and topographical distributions of the data. Area-around-the-peak quantification was used for the N1 component (scored at FCz where it was maximal between 110 and 180 ms). The P3 (scored at Pz) was quantified as mean amplitude between 280 and 360 ms (Fig. 3). No participant's N1 or P3 data were excluded due to <50 % usable segments per condition and cue after artefact correction. Split half reliability was determined by Spearman-Brown corrected correlations of odd and even trials for each condition in each task. For N1, these ranged from r = .87 to .93, for P3 from r = .72 to .76.

2.7. Data analysis

All analyses were performed in the statistical environment R, version 4.0.3 (R Core Team, 2020), and RStudio, version 1.3.1093 (RStudio Team, 2020). A p-value of .05 formed the significance threshold. First, separate multilevel regression models were calculated for each outcome (anxiety ratings, startle, N1, and P3) using the lme4 package (Bates et al., 2015). Fixed effects included *condition* (3 factor levels: N, P, and U), *probability* (2 factor levels: 100 % shock and 33 % shock), and *IUS-12* (continuous, grand-mean centered, and entered at level 2). Condition and probability were entered as fixed effects at level 1 and nested within participants. Second, if main effects or interactions involving condition emerged, *cue* (2 factor levels: countdown and interstimulus interval) was entered into the multilevel regression models. Factorial predictors were effect-coded. Interactions including the factorial predictors were followed up by Tukey-corrected pairwise comparisons of the estimated marginal means for each interacting factor level. Interactions including IUS-12 were followed up by Tukey-corrected pairwise comparisons of the estimated marginal means of linear trends of IUS-12 across the levels of the interacting predictor using the R package emmeans (Russell et al., 2021). A unique intercept was estimated per participant (i.e., random intercept) to model variance in intercepts due to unexplained differences between participants. An unstructured covariance matrix and Satterthwaite's method of estimating degrees of freedom were used. The multilevel regression models were based on maximum likelihood estimation. Intra-class correlation coefficients (ICC) were estimated from the null models.

Following deviations from the preregistration were made (www.osf.io/fmt54): As an additional outcome we included anxiety ratings. In the startle analyses, we used raw amplitudes instead of t-transformed amplitudes, because the multilevel regression model with t-transformed amplitudes resulted in a singular fit. The estimation of random intercepts account for individual differences in absolute startle magnitude (i.e., random variance in the data) that could have been accounted for by standardization. Instead of dummy-coding, we effect-coded the categorical predictor variables (i.e., sum-to-zero coding; West et al., 1996), because interpreting interactions requires meaningful values of predictors coded at 0. However, simple effects are presented as comparisons

[4] No trials were rejected based on these criteria. Note, that artefact rejection was based on individual channel mode. Thus, only channels relevant to the scoring of the N1 (FCz) or P3 (Pz) would have been rejected.

of estimated marginal means.

3. Results

3.1. Anxiety ratings

The analysis of anxiety ratings yielded main effects of condition and cue and a condition × cue interaction (Table 1; Supplement S3): Anxiety ratings of condition U were increased compared with N ($b = 42.38$, $SE = 1.58$, $t(968) = 26.78$, $p < .001$) and compared with P ($b = 19.94$, $SE = 1.58$, $t(968) = 12.60$, $p < .001$). Ratings of condition P were increased compared with N ($b = 22.44$, $SE = 1.58$, $t(968) = 14.18$, $p < .001$). No difference emerged between the interstimulus interval and countdown in conditions N or U ($ps > .560$), but participants rated increased anxiousness to the countdown in condition P ($b = 9.23$, $SE = 2.24$, $t(968) = 4.12$, $p = .002$). A main effect of probability emerged and a condition × probability interaction (Table 1): No differences in ratings were observed between $P_{100\%}$ and $P_{33\%}$ ($b = 1.86$, $SE = 1.60$, $t(970) = 1.16$, $p = .856$). Anxiety ratings of $U_{100\%}$ were increased compared with $U_{33\%}$ ($b = 8.32$, $SE = 1.60$, $t(970) = 5.12$, $p < .001$).

A main effect of IUS-12 and an IUS-12 × condition interaction emerged[5]: Across both task blocks, larger IUS-12 scores were associated with increased anxiety ratings in conditions U ($b = 0.78$, $SE = 0.13$, $t(968) = 5.90$, $p < .001$) and P ($b = 0.46$, $SE = 0.13$, $t(968) = 3.49$, $p = .002$) compared with N. We expected IU to predict differences in anxiety ratings as a function of shock probability. However, no evidence emerged for an IUS-12 × probability interaction or an IUS-12 × probability × condition interaction (Table 1, Fig. 1D).

3.2. Startle

As shown in Table 1 and Supplement S4, main effects emerged for condition and cue which were further specified by a condition × cue interaction. Overall, startle responses were increased in condition U compared with N ($b = 34.43$, $SE = 2.80$, $t(8096) = 12.31$, $p < .001$) and compared with P ($b = 28.04$, $SE = 2.79$, $t(8096) = 10.10$, $p < .001$). Across cues, no evidence emerged for increased startle to P compared with N ($b = 6.39$, $SE = 2.79$, $t(8096) = 2.29$, $p = .197$). On the cue level, participants showed increased startle to the countdown in P compared with the countdown in N ($b = 14.28$, $SE = 3.94$, $t(8096) = 3.62$, $p = .016$) and compared with the interstimulus interval in N ($b = 13.07$, $SE = 3.93$, $t(8096) = 3.33$, $p = .042$). A main effect of probability emerged, which was specified by a condition × probability interaction (Table 1): In both the U ($U_{33\%} > U_{100\%}$, $b = 14.04$, $SE = 2.79$, $t(8096) = 5.04$, $p < .001$) and P ($P_{33\%} > P_{100\%}$, $b = 12.91$, $SE = 2.78$, $t(8096) = 4.65$, $p < .001$) conditions, participants showed an increased startle to 33 % vs. 100 % probability, whereas the N condition without shock did not differ significantly between the task blocks, as expected ($b = -3.50$, $SE = 2.80$, $t(8096) = -1.25$, $p = .812$).

In terms of associations between IU and startle to temporally and probabilistically unpredictable threat, an IUS-12 × condition interaction emerged. This was further specified by an IUS-12 × probability interaction, as well as an IUS-12 × condition × probability interaction (Table 1, Figs. 1A, 2, Supplement S4).[6] Only during lower shock probability, IUS-12 predicted startle in both threat conditions. Specifically, IUS-12 predicted increased startle during $U_{33\%}$ compared with $U_{100\%}$ ($b = 2.04$, $SE = 0.32$, $t(8096) = 6.34$, $p < .001$). Of note, differences were observed for this effect depending on the order of tasks.[7] Similarly, IUS-12 predicted increased startle during $P_{33\%}$ compared with $P_{100\%}$ ($b = 1.22$, $SE = 0.32$, $t(8096) = 3.80$, $p = .002$). However, post-hoc contrasts of linear trends of IUS-12 showed no evidence for differences of the IUS-12 slopes in condition $U_{100\%}$ compared with the IUS-12 slopes in N ($b = 0.41$, $SE = 0.32$, $t(8096) = 1.27$, $p = .799$). In an exploratory analysis, effects of the subscales of the IUS-12 (i.e., prospective IU, inhibitory IU) were tested. No evidence emerged for inhibitory IU predicting differences between $P_{33\%}$ and $P_{100\%}$ or $U_{33\%}$ and $U_{100\%}$ ($ps > .636$). Prospective IU predicted increased startle to $P_{33\%}$ vs. $P_{100\%}$ ($b = 2.32$, $SE = 0.67$, $t(8074) = 3.45$, $p = .007$) and increased startle to $U_{33\%}$ vs. $U_{100\%}$ ($b = 2.28$, $SE = 0.67$, $t(8074) = 3.43$, $p = .008$). This suggests that the effect of IUS-12 predicting increased startle during improbable threat anticipation might be driven by prospective IU.

3.3. Event-related potentials

The startle probe locked N1 differed between the conditions as indicated by a main effect of condition (Table 2, Fig. 3A, Supplement S6). N1 was increased (more negative) during condition U compared with N ($b = -2.92$, $SE = 0.50$, $t(968) = -5.83$, $p < .001$) and compared with P ($b = -2.06$, $SE = 0.50$, $t(968) = -4.13$, $p < .001$). No differences were observed between N and P ($b = 0.85$, $SE = 0.50$, $t(968) = 1.71$, $p = .527$). In addition, a main effect of cue emerged: Overall, participants showed increased N1 to the countdown compared with the interstimulus interval ($b = -1.10$, $SE = 0.29$, $t(968) = -3.80$, $p < .001$). Furthermore, no effects of probability or IUS-12 and no interactions including these variables of interest reached significance (Table 2, Fig. 1B).

The analysis of startle probe locked P3 yielded a main effect of condition and a condition × cue interaction (Table 2, Supplement S7). Participants showed decreased P3 during the presentation of the interstimulus interval in condition P compared with the interstimulus interval in N ($b = -1.43$, $SE = 0.40$, $t(968) = -3.55$, $p = .021$). No evidence emerged for a difference between the countdowns in N and P ($b = 0.44$, $SE = 0.40$, $t(968) = 1.10$, $p = .995$; countdown vs. interstimulus interval in P: $b = 0.83$, $SE = 0.40$, $t(968) = 2.06$, $p = .653$). In contrast to previous studies, the P3 in condition U was not significantly decreased compared with N ($b = -0.03$, $SE = 0.28$, $t(968) = -0.11$, $p = .999$). In condition P, participants showed decreased P3 compared with U ($b = -0.91$, $SE = 0.28$, $t(968) = -3.19$, $p = .019$; Fig. 3B). A main effect of probability emerged: The P3 was generally decreased during 100 % shock probability ($b = -0.80$, $SE = 0.20$, $t(968) = -4.88$, $p < .001$; Fig. 3B), but this effect of probability was independent of the experimental conditions (Table 2). No further effects of the probability or IUS-12 emerged (Table 2).

4. Discussion

The present study tested the role of IU in the anticipation of unpredictable threat. Specifically, we varied the threat probability and the temporal predictability of threat and measured startle reflex, startle probe locked N1, P3, and anxiety ratings. Temporally unpredictable threat was associated with increased startle, N1, and anxiety ratings in both NPU task blocks. Moreover, the results show that individuals with

[5] To test specificity of this effect to IUS-12, we included trait anxiety (subscale of the State-Trait-Anxiety Inventory, STAI-T, 20 items, 4-point Likert scale, Spielberger et al., 1983) into the model, which did not change the pattern of results or the significance of the IUS-12 × condition interaction ($F(2, 968) = 17.59$, $p < .001$). For the full model controlling for STAI-T see Supplement S11).

[6] To test specificity of this effect to IUS-12, we included STAI-T into the model, which did not change the pattern of results or the significance of the IUS-12 × probability interaction ($F(1, 8097) = 60.71$, $p < .001$). For the full model controlling for STAI-T see Supplement S11).

[7] To test the robustness of this effect across the order of the task blocks (33 % shock probability first vs. 100 % shock probability first) the task block order was included into the model. The task block order interacted with IUS-12 in predicting increased startle in lower shock probability ($F(1, 8092) = 12.20$, $p < .001$). IUS-12 only predicted increased startle during $U_{33\%}$ when the 33 % shock probability task was presented first ($b = 1.75$, $SE = 0.41$, $t(8086) = 4.26$, $p = .001$) but not when the 100 % shock probability task was presented first ($b = 0.05$, $SE = 0.53$, $t(8095) = 0.08$, $p = .999$).

Table 1
Multilevel regression models predicting anxiety ratings and raw startle responses.

	Anxiety ratings			Startle		
	df	*F*	*p*	*df*	*F*	*p*
Fixed effects						
Condition	2, 968	585.00	**<.001**	2, 8096	216.06	**<.001**
Cue	1, 968	31.42	**<.001**	1, 8096	45.15	**<.001**
Probability	1, 973	14.08	**<.001**	1, 8096	40.33	**<.001**
IUS-12	1, 88	11.37	**.001**	1, 88	2.51	.117
Condition × Cue	2, 968	7.70	**<.001**	2, 8096	10.15	**<.001**
Condition × Probability	2, 968	7.08	**<.001**	2, 8096	4.31	**.013**
Cue × Probability	1, 968	0.13	.714	1, 8096	0.01	.929
Condition × IUS-12	2, 968	17.59	**<.001**	2, 8096	7.95	**<.001**
Probability × IUS-12	1, 983	1.02	.313	1, 8096	60.71	**<.001**
Condition × Cue × Probability	2, 968	0.13	.881	2, 8096	0.50	.604
Condition × Probability × IUS-12	2, 968	0.36	.701	2, 8096	2.53	.080
Random components						
σ^2	227.94			5308.62		
τ_{00}	245.98			4076.43		
ICC	.33			.42		
Marginal R^2	.392			.053		
Conditional R^2	.707			.464		

Note. F-values are estimated using Satterthwaite's degrees of freedom method. Cross level interactions involving cue are not shown here (see Supplement S3–S5). Conditions include neutral, predictable threat, and unpredictable threat. Cue includes countdown and interstimulus interval. Probability includes 100 % and 33 %. IUS-12 = Short version Intolerance of Uncertainty Scale (Carleton et al., 2007; Gerlach et al., 2008).
σ^2 = residual variance; τ_{00} = random intercept; ICC = intra class correlation.

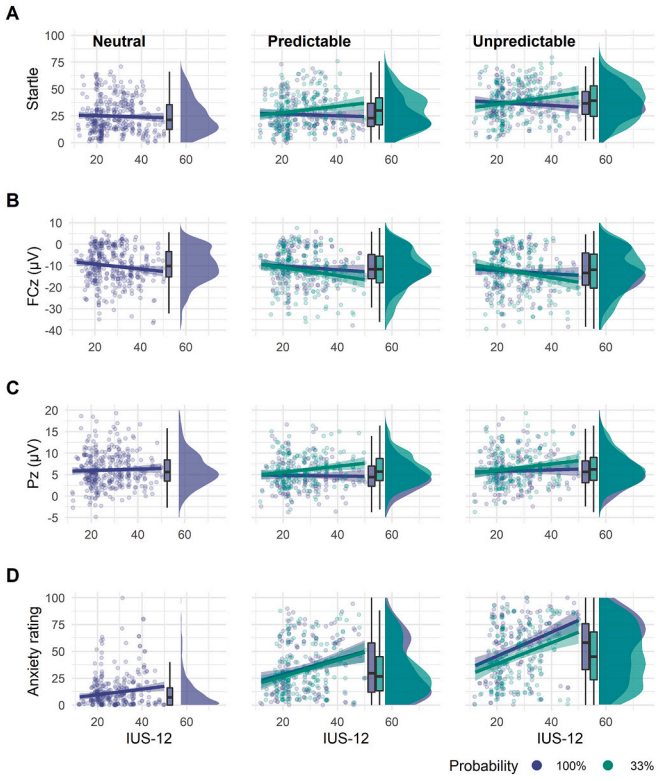


Fig. 1. Responses across the experimental conditions.
Note. **A**: Range-corrected startle magnitude. **B**: Startle probe locked N1, area-around the peak, ca. 120–180 ms. **C**: Startle probe locked P3, mean activity 280–360 ms. **D**: Subjective anxiety ratings. Slopes across the Intolerance of Uncertainty Scale (IUS-12; Carleton et al., 2007), with shaded area indicating the standard error in temporally predictable and unpredictable shock conditions with 100 % and 33 % shock probability. Data are collapsed across cues (countdown, interstimulus interval). For descriptive statistics for each outcome see Supplement S1–S2.

higher IU displayed increased startle responses in both threat conditions during lower threat probability (i.e., $P_{33\%}$ and $U_{33\%}$). These findings suggest that the link between IU and automatic defensive responding may be pronounced in situations with low threat probability.

4.1. Intolerance of uncertainty and probabilistic unpredictability

Prior research has demonstrated that the anticipation of unpredictable threat increases startle responses (Schmitz and Grillon, 2012), startle probe locked N1 (Nelson et al., 2015), and reduces P3 (Ferry and Nelson, 2020; MacNamara and Barley, 2018; Nelson et al., 2015). Mostly in line with this, temporally unpredictable threat increased anxiety ratings, startle, and N1, but did not decrease P3. An additive effect of probabilistic unpredictability was evident in startle responses, while no differences of probabilistic unpredictability emerged for N1 or P3 and decreased responses emerged in anxiety ratings. Higher IU led to increased startle responses in the conditions with 33 % shock probability (i.e., $U_{33\%}$ and $P_{33\%}$). However, no evidence emerged for IU affecting startle responses in the conditions with 100 % shock probability (i.e., $U_{100\%}$ and $P_{100\%}$). Together, our data indicate that regardless of the temporal predictability, probabilistic unpredictability may play a key role for IU. These effects were specific to startle responses, suggesting that automatic defensive responding rather than early (as reflected in N1) or later (as reflected in P3) attentional processes are modulated by individual differences in IU. These findings conceptually converge with Chin et al. (2016), who found a link between IU and defensive responding to lower threat probability. However, these findings diverge from Bennett et al. (2018), who did not find a link between IU and defensive responding to probabilistic or temporal predictability. In this respect, our findings warrant direct and conceptual replication.

In a previous fear conditioning experiment, IU affected defensive responding during 50 % threat probability but not during 75 % threat probability (Chin et al., 2016). The present study extends these findings by showing that IU predicts defensive responding to an even lower threat probability. Future studies could compare more gradual threat probabilities. This might clarify at which threat probability individual differences in IU influence defensive responding. Furthermore, this could shed light on the adaptivity of defensive responding during lower threat probability: Increased defensive responding could be considered adaptive during a 100 % threat probability, but might still be considered adaptive during 33 % threat probability depending on the aversiveness

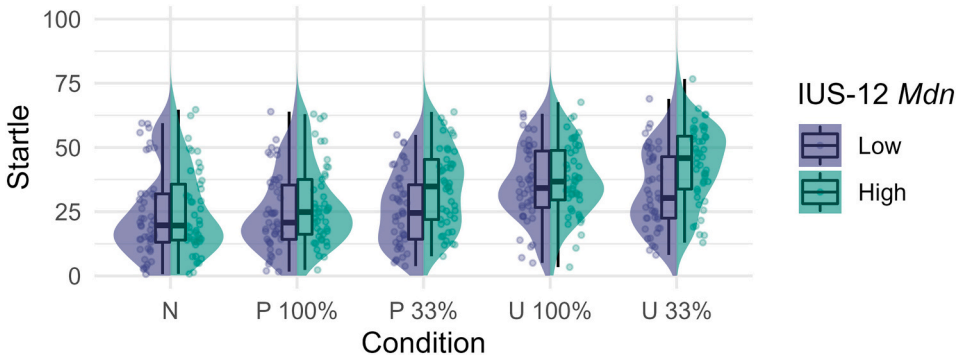


Fig. 2. Startle responses across experimental conditions and intolerance of uncertainty.
Note. For illustration, the startle magnitude data are range corrected within participants and aggregated per participant per experimental condition of the NPU-threat test (N = Neutral; P = Predictable threat; U = Unpredictable threat) in both task blocks (100 % and 33 % threat probability). Data are collapsed across cues (countdown, interstimulus interval). Color coding depicts the median split of the Intolerance of Uncertainty Scale (IUS-12; Carleton et al., 2007; *Mdn* = 25).

Table 2
Multilevel regression models predicting startle probe locked event-related potentials N1 and P3.

	N1			P3		
	df	*F*	*p*	*df*	*F*	*p*
Fixed effects						
Condition	2, 968	33.02	**<.001**	2, 968	7.52	**<.001**
Cue	1, 968	14.31	**<.001**	1, 968	1.11	.293
Probability	1, 968	2.23	.136	1, 968	23.61	**<.001**
IUS-12	1, 88	2.45	.121	1, 88	0.75	.390
Condition × Cue	2, 968	2.82	.060	2, 968	4.61	**.010**
Condition × Probability	2, 968	2.35	.096	2, 968	1.15	.317
Cue × Probability	1, 968	1.39	.239	1, 068	0.12	.725
Condition × IUS-12	2, 968	1.10	.335	2, 968	1.36	.258
Probability × IUS-12	1, 968	1.73	.189	1, 968	3.35	.068
Condition × Cue × Probability	2, 968	1.45	.236	2, 968	0.02	.976
Condition × Probability × IUS-12	2, 968	0.47	.625	2, 968	2.06	.128
Random components						
σ^2	22.53			7.27		
τ_{00}	57.31			8.59		
ICC	.70			.53		
Marginal R^2	.046			.033		
Conditional R^2	.731			.557		

Note. *F*-values are estimated using Satterthwaite's degrees of freedom method. Cross level interactions involving cue are not shown here (see Supplement S6–S7). Conditions include neutral, predictable threat, and unpredictable threat. Cue includes countdown and interstimulus interval. Probability includes 100 % and 33 %. IUS-12 = Short version Intolerance of Uncertainty Scale (Carleton et al., 2007; Gerlach et al., 2008).
σ^2 = residual variance; τ_{00} = random intercept; ICC = intra class correlation.

of threat. For individuals with higher IU, we expected a smaller difference in startle responses between threat probabilities of 100 % and 33 %, indicating hypersensitivity to threat with lower probability of occurrence. Surprisingly, we found overall increased startle responses during 33 % threat probability and further increased responses to 33 % threat probability in individuals with higher IU. Thus, instead of the absolute frequency of threat, the unpredictability of the threat and associated uncertainty could account for the aversiveness of a situation, especially in individuals with high IU. To date, there is no objective criterion when erring on the side of caution (i.e., increased responses to lower threat probability) becomes maladaptive (Carleton, 2016a). In fact, the adaptivity might depend on context factors. As such, we found that IU only increased defensive responding in temporally unpredictable threat during 33 % threat probability compared with 100 % threat probability, when the 33 % shock probability task block was presented first. This finding suggests that there may be a desensitization effect to shocks, startle probes, or to the NPU-threat test itself, and that individuals with higher IU might be sensitive to lower threat probability specifically in novel situations. Novel situations are especially characterized by unpredictability and might trigger uncertainty arousal (Einstein, 2014) leading to dysfunctional coping to mitigate the arousal, while familiarity with a situation may dampen the effects of IU. For clinicians treating patients with internalizing psychopathology, this could imply that individualized treatment (e.g., exposure therapy) should include contextual changes to increase flexibility and incorporate novelty, a call that has also been made previously based on experimental conditioning studies (Craske et al., 2014). However, more research is needed to better understand the role of IU across different contexts and translate these findings to clinical settings.

Exploratory analyses further revealed that increased defensive responding during lower threat probability might be driven by prospective IU rather than inhibitory IU. Prior studies found that prospective IU increased startle during temporally unpredictable threat (Nelson, Liu, et al., 2016) and found an association between inhibitory IU and smaller startle during temporally unpredictable threat anticipation (Nelson and Shankman, 2011). The exploratory results of the current study extend Nelson, Liu, et al.'s (2016) findings to probabilistic unpredictability, however, no evidence emerged for an effect of inhibitory IU (Nelson and Shankman, 2011). Future studies should try to clarify whether the subscales of IU demonstrate a bidirectional relationship with defensive responding during unpredictable threat anticipation.

4.2. *Intolerance of uncertainty and temporally unpredictable threat*

Across physiological outcome measures (i.e., startle, N1, and P3), we found no evidence for IU modulating responses to temporally unpredictable threat during high threat probability. Increased IU generally predicted increased anxiety ratings in threat conditions, but this effect was not specific to temporal unpredictability. Based on Nelson and

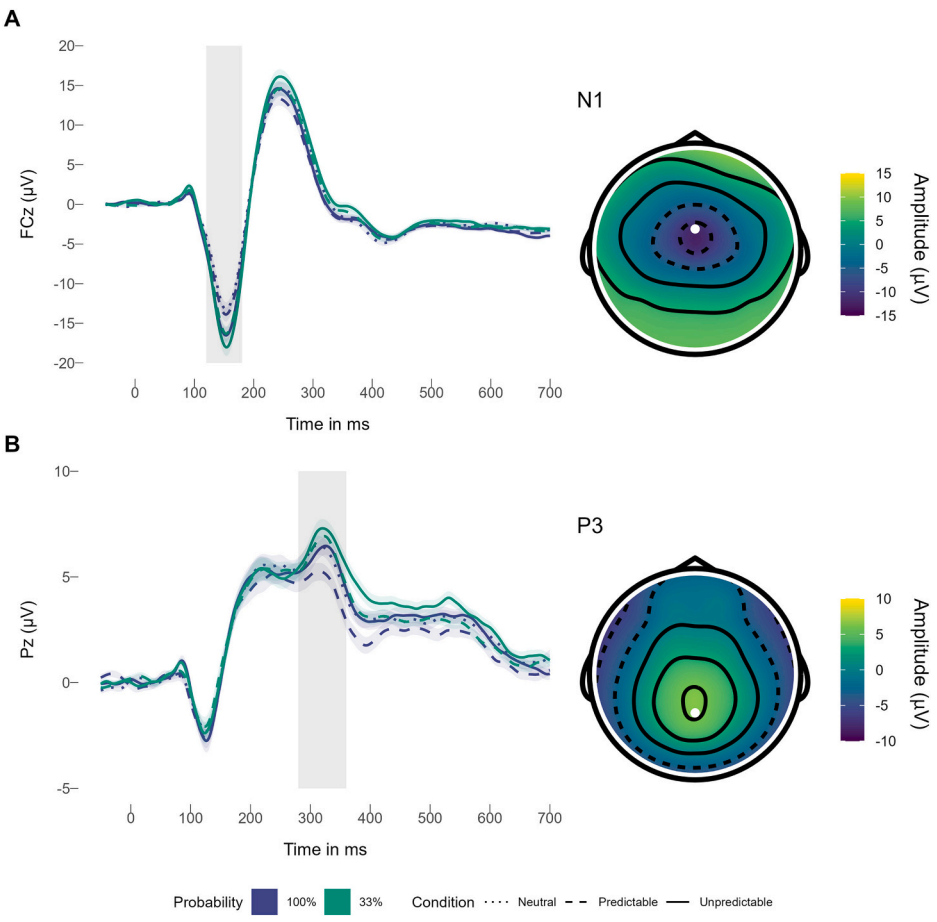


Fig. 3. Grand averages and head maps of the N1 (**A**) and P3 (**B**).
Note. The signal is locked to startle probes and is collapsed across cues (countdown, interstimulus interval) of the NPU-threat test. The time windows for quantification of N1 (**A**: ±25 ms area around the individual peak at FCz (white dot) ca. 120–180 ms) and P3 (**B**: mean activity 280–360 ms at Pz (white dot)) are indicated by shaded grey bars. The shaded area around the mean signal depicts ±1 SE of the distribution at each ms. For head maps per experimental condition see Supplement S8–S9.

Shankman (2011), we expected decreased startle during temporally unpredictable threat, although previous evidence is mixed with studies reporting decreased, increased (for prospective IU; Nelson, Liu, et al., 2016), or no effects (Bennett et al., 2018; Morriss et al., 2020; Papenfuss et al., 2021). Adding to these findings, our data pose three interpretations: First, an association between IU and responses to temporally unpredictable threat might not be as strong or robust as previous studies and theoretical models suggest. Second, methodological heterogeneity such as task variations might set experimental boundary conditions, i.e., latent mediating variables determining whether the effect is observable. Heterogeneity in data preprocessing and analysis (i.e., forking paths; Gelman and Loken, 2013) might further explain inconsistencies in this line of research. Third, rather than one specific aspect of unpredictability (e.g., temporal unpredictability or probabilistic unpredictability) that high IU individuals are sensitive to, an interplay of aspects that render a situation unpredictable could be required to establish the link between IU and defensive responding. To unravel physiological correlates of IU, future research could establish a relational map between different aspects of unpredictability, but data on this is scarce (Bennett et al., 2018; Bradford et al., 2014; Ferry and Nelson, 2020; Shankman et al., 2011) and mostly do not comprise self-reported IU. Relatedly, heightened physiological responses to unpredictability in high IU individuals might follow a dose-response effect driven by quantitative unpredictability rather than qualitative aspects of unpredictability. In the present study, the frequency of shocks was relatively high in the temporally unpredictable condition in the 100 % shock probability NPU-threat test (1 shock / 18.75 s). This might have introduced a ceiling effect in which individual differences in IU become unapparent as all individuals respond with increased defensive preparation. Lowering the threat probability might have added qualitatively and/or quantitatively to the unpredictability of the condition, so that individuals with higher IU showed greater defensive responding. Examining which aspects of unpredictability link to physiological correlates of IU represents an interesting avenue for future research. First, it may underscore the ecological validity of IU by delineating context factors in natural settings that high IU individuals are hypersensitive to. Second, it could improve the development of RDoC paradigms optimized to distinguish individuals based on the interplay of IU and hypersensitivity to unpredictable threat (cf. Wever et al., 2015). Importantly, this could extend diagnostic beyond self-report to identify individuals vulnerable to internalizing psychopathology and advance studying potential clinical correlates of IU such as treatment response across units of analysis.

Given the broad clinical correlates of IU (Carleton et al., 2012; Gentes and Ruscio, 2011; McEvoy et al., 2019; Shihata et al., 2016), inferences based on our data might furthermore inform transdiagnostic etiological models of internalizing psychopathology. Contrary to Dugas et al.'s (2001) conceptualization of IU, our data suggest that individuals with higher IU might be intolerant of uncertain events depending on the probability that the uncertain event may occur. This pattern of results is in accordance with predictions from transdiagnostic (Einstein, 2014) and neurobiologically informed models (Grupe and Nitschke, 2013), suggesting inflated threat expectancies and physiological arousal in unpredictable situations. However, these predictions also apply to temporal unpredictability, for which we did not find confirmatory evidence. Thus, more studies refining the association of IU and responding to unpredictable threat are needed.

4.3. Diverging findings across the temporal dynamic of threat processing

While most task effects during 100 % threat probability converged across outcome measures (i.e., increased responses to unpredictable threat in anxiety ratings, startle, and N1 and increased responses to predictable threat in ratings, startle, and decreased P3), the pattern of results was heterogeneous when examining the impact of IU. Specifically, we found no effects of IU in N1 and P3, i.e., in outcome measures that tap into different processes. As such, the startle probe locked P3 indexes attentional allocation to the startle probe. We found decreased P3 in anticipation of temporally predictable threat and generally decreased P3 in the task block with 100 % threat probability, suggesting sensitivity of startle probe locked P3 to task load or proximity of threat rather than aspects of unpredictability. The increased frequency of shocks during 100 % probability and the temporal proximity of shocks in condition P might bind attentional resources to the task and not the startle probe. Finding no effects of IU in N1 and P3 is in contrast to Correa et al. (2022), who found inhibitory IU to be associated with increased startle probe locked N1 and decreased P3 in unpredictable threat anticipation. We therefore exploratorily tested effects of the subscales of IU and were unable to replicate this effect, which could be due to methodological differences between studies (e.g., differences in sample size).

Nelson et al. (2015) found a small association between startle responses and N1 in threat conditions. Although we found evidence for IU predicting startle responses, no evidence emerged for IU predicting N1 in probabilistic threat anticipation. The N1 is thought to reflect automatic attentional allocation to the startle probe (Nelson et al., 2015), thus an effect of IU on defensive responding during probabilistic threat anticipation might be more specific to valence than attention. In summary, we found a unique relationship between IU and startle responses during lower threat probability, which might imply that IU specifically modulates defensive preparation rather than attentional allocation during the processing of unpredictable threat.

4.4. Limitations

The findings of the present study need to be interpreted in light of several limitations. First, participants were not instructed about the precise probability during the 33 % threat probability task block but were told that the threat probability was “very low”. This might have introduced another aspect of unpredictability, i.e., the unpredictable contingency. Contingency instructions have been shown to promote threat extinction in individuals with higher IU (Morriss and van Reekum, 2019) and alter threat reversal (Mertens and Morriss, 2021). Thus, our findings might be more comparable to findings from fear conditioning without explicit contingency instructions (Morriss, Wake, et al., 2021) but with known temporal contiguity. The subjects were fully instructed about the temporal predictability of threats, which might have rendered the $U_{100\%}$ condition less uncertain (cf. Morriss et al., 2022; Morriss, Zuj, et al., 2021). In addition, lowering the shock probability in the $P_{33\%}$ condition added uncertainty to this condition. Together, introducing 33 % threat probability conditions provided a more granular insight into the gradation of occurrence probability and allowed disentangling different aspects of uncertainty. Future studies should consider including vs. excluding explicit contingency instructions during lower threat probability to clarify whether the link between IU and defensive responding is solely attributable to decreased threat probability.

Second, we cannot rule out habituation or desensitization effects to the shocks and startle probes across the task blocks with 100 % and 33 % shock probability. We opted against recalibration of the shock between the task blocks to ensure comparability between the tasks. There were less zeros in startle responses in condition U than in condition P or N. Thus, a differential habituation between the conditions is possible. To experimentally control for habituation effects, we randomized the order of conditions (PNUPNU vs. UNPUNP) and the order of task blocks (33 % first vs. 100 % first) across participants. The order of task blocks was included as a control variable in the startle analyses to test the robustness of the effects.

Third, regarding our sample, the generalizability of the present findings might be limited to young adults with an academic background. Further, no data were collected on ethnicity or nationality. We recruited a rather homogenous sample to test the fundamental research question whether IU modulates physiological responses in varying threat probability. Still, the levels of IUS-12 were comparable to the validation sample of the questionnaire (Carleton et al., 2007) and to general population samples reported in the research field (Bennett et al., 2018; Morriss, Wake, et al., 2021; Nelson and Shankman, 2011). Although we did not exclude participants with internalizing disorders, future studies could aim to generalize our findings to clinical populations, as they typically report higher levels of IU (Khawaja and Yu, 2010; Mahoney and McEvoy, 2012b). This might allow comparing interaction effects between IU and clinical status in defensive responding to eventual threat.

Next to limitations, the methodology used in this study also comprises strengths: The methods and hypotheses were preregistered prior to data collection (www.osf.io/fmt54), which is consistent with the principles of open science. The application of multilevel modelling can account for random effects introduced by individual differences in responses to the task and absolute amplitudes of physiological responses, to avoid within person standardization. In addition, no data aggregation is necessary, which increases statistical power (Hox et al., 2017). Next, we tested the robustness and specificity of IU effects by including the order of blocks, the subscales of IU and STAI-T into the models. The order of blocks and the subscales of IU further specified the effects, while including STAI-T did not change the results, which implies specificity of the effects to IU over a broader measure of anxiety. Finally, we report multimodal outcome measures capturing defensive responding (startle), earlier (N1) and later attentional processes (P3), and subjective anxiety (ratings). This allows for more granular examination of the temporal dynamics of physiological correlates of IU. While converging evidence across outcome measures might imply robustness or a stronger evidence base, the differential pattern of our findings may also be informative. Based on the frequentist analysis, no assertion can be made regarding the evidence for the null hypothesis, but the specificity of the findings of IU associations with startle can be taken to suggest specificity to processes of earlier defensive preparation as opposed to later attentional processes or retrospective anxiety ratings.

4.5. Conclusion

In the present study, we examined the association of IU and multimodal physiological responses in anticipation of temporally and probabilistically unpredictable threat. We found that IU predicted increased automatic defensive responding during lower threat probability regardless of the temporal predictability. Accordingly, individuals with higher IU might display increased uncertainty arousal if the “if” of the threat is unpredictable. Yet, our results point to more fine-grained analyses of context factors such as novelty in studying physiological correlates of IU. Future studies should compare quantitative (e.g., gradual probability) and qualitative (e.g., modality, intensity, frequency, timing) manipulations of unpredictability to shed light on the neurofunctional basis of IU. Together with the present findings, this could translate to clinical utility by informing etiological models, prevention, diagnostic, and treatment of internalizing psychopathology, in which IU is a fundamental component.

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Appendix A. Supplementary data

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Supplementary Material to

"A Rare Scare: The Role of Intolerance of Uncertainty in Startle Responses and Event-Related Potentials in Anticipation of Unpredictable Threat"

Hannes Per Carsten[1*], Kai Härpfer[1], Anja Riesel[1]

[1]Department of Psychology, University of Hamburg, Hamburg, Germany

*Correspondence concerning this article should be addressed to Hannes Per Carsten, Department of Psychology, Universität Hamburg, Von-Melle-Park 11, 20146 Hamburg, Germany. E-Mail: hannes.carsten@uni-hamburg.de

Table of Contents:

Table S1: Descriptives of anxiety ratings, startle, and skin conductance responses……..……S1

Table S2: Descriptives of event-related potentials N1 and P3……..…….……S2

Table S3: Multilevel regression model anxiety ratings...……S3

Table S4: Multilevel regression model startle responses…….S4

S5: Preprocessing and results of multilevel regression model skin conductance responses……..….S5

Table S6: Multilevel regression model startle probe locked N1……...……..S7

Table S7: Multilevel regression model startle probe locked P3……...……...S8

Figure S1: Head maps of N1 across experimental conditions…….S9

Figure S2: Head maps of P3 across experimental conditions…….……...S10

Table S8: Multilevel regression model for startle responses including STAI-T……...S11

Table S1

Descriptives of anxiety ratings, startle, and skin conductance responses across experimental conditions

	Ratings (0-100)			Startle (µV)			SCR (µS)		
	M	*SD*	*Mdn*	*M*	*SD*	*Mdn*	*M*	*SD*	*Mdn*
Condition									
Neutral	11.62	16.00	5.00	67.31	73.72	45.27	0.029	0.085	0
Predictable 100%	34.02	25.89	29.50	75.41	80.17	52.10	0.023	0.085	0
Predictable 33%	32.40	22.93	26.50	88.08	88.76	62.17	0.037	0.137	0
Unpredictable 100%	53.93	27.12	58.00	102.72	96.87	75.42	0.047	0.120	0
Unpredictable 33%	45.9	26.61	45.00	117.45	147.96	84.12	0.044	0.131	0

Note. Skin conductance responses (SCR) are log-transformed and range-corrected within participants.

Table S2

Descriptives of event-related potentials N1 and P3 across experimental conditions

	N1 (µV)			P3 (µV)		
	M	*SD*	*Mdn*	*M*	*SD*	*Mdn*
Condition						
Neutral	-10.11	8.03	-10.74	5.83	4.11	5.41
Predictable 100%	-10.96	8.12	-11.73	4.89	3.94	4.41
Predictable 33%	-12.28	9.41	-11.66	6.02	3.67	5.68
Unpredictable 100%	-13.02	9.58	-13.47	5.80	4.16	5.60
Unpredictable 33%	-12.98	10.19	-11.92	6.54	4.00	6.20

Note.

Table S3

Effect-coded multilevel regression model predicting anxiety ratings

	b	*SE*	*CI* [95%]	*t*	*p*	R^2
Fixed effects						
(Intercept)	31.55	1.72	28.18 – 34.92	18.39	**<0.001**	
Cue[CD]	2.58	0.46	1.67 – 3.48	5.61	**<0.001**	.025
Condition[P]	1.65	0.65	0.38 – 2.93	2.55	**0.011**	.005
Probability[33%]	-1.75	0.47	-2.67 – -0.84	-3.75	**<0.001**	.012
IUS-12	0.68	0.20	0.28 – 1.08	3.37	**0.001**	.114
Condition[U]	18.37	0.65	17.09 – 19.64	28.27	**<0.001**	.393
Cue[CD] × Condition[P]	2.34	0.65	1.06 – 3.61	3.60	**<0.001**	.010
Cue[CD] × Probability[33%]	0.17	0.46	-0.73 – 1.07	0.37	0.714	.000
Condition[P] × Probability[33%]	0.82	0.65	-0.45 – 2.10	1.27	0.205	.001
Cue[CD] × IUS-12	0.00	0.05	-0.10 – 0.11	0.06	0.955	.000
Condition[P] × IUS-12	0.05	0.08	-0.10 – 0.20	0.62	0.533	.000
Probability[33%] × IUS-12	0.06	0.06	-0.05 – 0.17	1.01	0.313	.001
Cue[CD] × Condition[U]	-0.28	0.65	-1.56 – 0.99	-0.44	0.662	.000
Probability[33%] × Condition[U]	-2.41	0.65	-3.68 – -1.13	-3.70	**<0.001**	.011
Condition[U] × IUS-12	0.37	0.08	0.22 – 0.52	4.80	**<0.001**	.018
Cue[CD] × Condition[P] × Probability[33%]	0.13	0.65	-1.15 – 1.40	0.20	0.843	.000
Cue[CD] × Condition[P] × IUS-12	0.10	0.08	-0.05 – 0.25	1.32	0.187	.001
Cue[CD] × Probability[33%] × IUS-12	-0.03	0.05	-0.14 – 0.08	-0.54	0.588	.000
Condition[P] × Probability[33%] × IUS-12	0.02	0.08	-0.13 – 0.17	0.26	0.798	.000
Cue[CD] × Probability[33%] × Condition[U]	-0.32	0.65	-1.60 – 0.95	-0.50	0.618	.000
Cue[CD] × Condition[U] × IUS-12	-0.06	0.08	-0.21 – 0.09	-0.80	0.423	.001
Probability[33%] × Condition[U] × IUS-12	-0.06	0.08	-0.21 – 0.09	-0.82	0.410	.001
Cue[CD] × Condition[P] × Probability[33%] × IUS-12	-0.00	0.08	-0.15 – 0.15	-0.05	0.960	.000
Cue[CD] × Probability[33%] × Condition[U] × IUS-12	0.01	0.08	-0.14 – 0.16	0.15	0.880	.000
Random components						
σ^2, τ_{00}	227.94, 245.98					
ICC	.33					
Marginal R^2, Conditional R^2	.392, .707					
$N_{participants}$, $N_{observations}$	90, 1080					

Note. Factorial predictors are effect-coded (-1 for reference, 1 for the effect in square brackets, 0 for everything else). For cue (CD = countdown; ISI = interstimulus interval), ISI is the reference category. For condition (N = neutral, P = predictable, U = unpredictable threat) N is the reference category. For probability (33%; 100%) 100% is the reference category. IUS-12 (Short version Intolerance of Uncertainty Scale-12) values are grand-mean centered. Semi-partial R^2 indicates the partial effect sizes for each model parameter (Edwards et al., 2008; Jaeger, 2017).
σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation.

Table S4

Effect-coded multilevel regression model predicting startle responses

	b	*SE*	*CI* [95%]	*t*	*p*	R^2
Fixed effects						
(Intercept)	87.36	6.78	74.07 – 100.64	12.89	**<0.001**	
Cue[CD]	5.41	0.80	3.83 – 6.98	6.72	**<0.001**	.005
Condition[P]	-5.83	1.14	-8.05 – -3.60	-5.13	**<0.001**	.003
Probability[33%]	5.11	0.81	3.54 – 6.69	6.35	**<0.001**	.005
IUS-12	1.25	0.79	-0.30 – 2.79	1.58	0.113	.020
Condition[U]	22.79	1.14	20.56 – 25.02	20.03	**<0.001**	.044
Cue[CD] × Condition[P]	1.78	1.14	-0.45 – 4.00	1.57	0.117	.000
Cue[CD] × Probability[33%]	-0.07	0.80	-1.65 – 1.51	-0.09	0.929	.000
Condition[P] × Probability[33%]	1.37	1.14	-0.85 – 3.60	1.21	0.226	.000
Cue[CD] × IUS-12	0.09	0.09	-0.09 – 0.27	0.96	0.338	.000
Condition[P] × IUS-12	0.13	0.13	-0.13 – 0.38	0.96	0.335	.000
Probability[33%] × IUS-12	0.72	0.09	0.54 – 0.91	7.79	**<0.001**	.007
Cue[CD] × Condition[U]	3.29	1.14	1.06 – 5.52	2.89	**0.004**	.001
Probability[33%] × Condition[U]	1.96	1.14	-0.27 – 4.19	1.72	0.085	.000
Condition[U] × IUS-12	0.38	0.13	0.12 – 0.64	2.88	**0.004**	.001
Cue[CD] × Condition[P] × Probability[33%]	-0.03	1.14	-2.26 – 2.19	-0.03	0.977	.000
Cue[CD] × Condition[P] × IUS-12	0.15	0.13	-0.11 – 0.41	1.14	0.256	.000
Cue[CD] × Probability[33%] × IUS-12	0.02	0.09	-0.16 – 0.20	0.19	0.850	.000
Condition[P] × Probability[33%] × IUS-12	-0.12	0.13	-0.37 – 0.14	-0.88	0.377	.000
Cue[CD] × Probability[33%] × Condition[U]	-0.97	1.14	-3.20 – 1.26	-0.86	0.392	.000
Cue[CD] × Condition[U] × IUS-12	0.02	0.13	-0.24 – 0.27	0.13	0.897	.000
Probability[33%] × Condition[U] × IUS-12	0.29	0.13	0.04 – 0.55	2.23	**0.025**	.001
Cue[CD] × Condition[P] × Probability[33%] × IUS-12	0.04	0.13	-0.22 – 0.30	0.30	0.762	.000
Cue[CD] × Probability[33%] × Condition[U] × IUS-12	0.16	0.13	-0.09 – 0.42	1.25	0.210	.000
Random components						
σ^2, τ_{00}	5308.62, 4076.43					
ICC	.42					
Marginal R^2, Conditional R^2	.053, .464					
$N_{participants}$, $N_{observations}$	90, 8208					

Note. Factorial predictors are effect-coded (-1 for reference, 1 for the effect in square brackets, 0 for everything else). For cue (CD = countdown; ISI = interstimulus interval), ISI is the reference category. For condition (N = neutral, P = predictable, U = unpredictable threat) N is the reference category. For probability (33%; 100%) 100% is the reference category. IUS-12 (Short version Intolerance of Uncertainty Scale-12) values are grand-mean centered. Semi-partial R^2 indicates the partial effect sizes for each model parameter (Edwards et al., 2008; Jaeger, 2017).
σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation.

Skin conductance responses recording and processing

SCR was measured with two Ag/AgCl electrodes with 6 mm diameter at the intermediate phalanges of the second and third digits of the non-dominant hand. Electrodes were applied at least 5 min prior to measurement onset. A low constant-voltage of 0.5 V was passed through the electrodes. Data were down-sampled offline to 10 Hz. Phasic SCR to startle probes during the presentation of interstimulus intervals were scored manually from minimum to maximum 0.9 - 3.5 s relative to the startle probe onset. Manual raters were blinded to the experimental conditions and stimuli[1]. Undetectable reactions were scored as zeros and included into the analyses. SCRs were range corrected (individual SCR / participant's maximum SCR) and log-transformed (log(SCR+1)). Participants were excluded from the analyses (n = 22) if 66% or more SCRs to the presentation of the shocks did not meet the minimum amplitude criterion of 0.01 µS.

Skin conductance responses results

SCRs were locked to the startle probes during the presentation of the interstimulus interval. A main effect of condition and a condition × probability interaction emerged (Table S5): SCRs were increased in the $U_{100\%}$ condition compared with $P_{100\%}$ (b = 0.03, SE = 0.01, t(3239) = 3.97, p = .001), but no significant difference emerged between $U_{33\%}$ and $P_{33\%}$ (b = 0.01, SE = 0.01, t(3239) = 1.11, p = .876). Participants displayed increased SCR in U compared with N irrespective of shock probability (b = 0.02, SE = 0.01, t(3239) = 2.86, p = .048), while the N and P did not differ significantly (b = 0.01, SE = 0.01, t(3239) = 1.12, p = .875). No evidence emerged for IUS-12 predicting SCR (Table S5).

[1] The manual scoring was repeated by an independent blinded rater. To assess interrater reliability, the data were aggregated per stimulus in each experimental condition. Krippendorff's α was calculated using the R package "krippendorffsalpha" (Hughes, 2021). Between the raters, the reliability was near perfect (α = .963, 95% CI [.911, .992], Hughes, 2021).

Table S5

Effect-coded multilevel regression model predicting skin conductance responses

	b	*SE*	*CI* [95%]	*t*	*p*	R^2
Fixed effects						
(Intercept)	0.03	0.00	0.02 – 0.04	7.48	**<0.001**	
Condition[P]	-0.00	0.00	-0.01 – 0.00	-1.44	0.150	.001
Probability[33%]	0.00	0.00	-0.00 – 0.00	0.11	0.916	.000
IUS-12	0.00	0.00	-0.00 – 0.00	0.47	0.640	.001
Condition[U]	0.01	0.00	0.01 – 0.02	4.78	**<0.001**	.010
Condition[P] × Probability[33%]	0.01	0.00	0.00 – 0.01	2.70	**0.007**	.003
Condition[P] × IUS-12	0.00	0.00	-0.00 – 0.00	0.26	0.794	.000
Probability[33%] × IUS-12	-0.00	0.00	-0.00 – 0.00	-0.44	0.662	.000
Probability[33%] × Condition[U]	-0.00	0.00	-0.01 – 0.00	-0.78	0.435	.000
Condition[U] × IUS-12	-0.00	0.00	-0.00 – 0.00	-0.63	0.526	.000
Condition[P] × Probability[33%] × IUS-12	-0.00	0.00	-0.00 – 0.00	-0.82	0.411	.000
Condition[U] × Probability[33%] × IUS-12	0.00	0.00	-0.00 – 0.00	1.24	0.214	.001
Random components						
σ^2, τ_{00}	0.01, 0.00					
ICC	.10					
Marginal R^2, Conditional R^2	.010, .106					
$N_{participants}$, $N_{observations}$	72, 3320					

Note. Factorial predictors are effect-coded (-1 for reference, 1 for the effect in square brackets, 0 for everything else). For condition (N = neutral, P = predictable, U = unpredictable threat) N is the reference category. For probability (33%; 100%) 100% is the reference category. IUS-12 (Short version Intolerance of Uncertainty Scale-12) values are grand-mean centered. Semi-partial R^2 indicates the partial effect sizes for each model parameter (Edwards et al., 2008; Jaeger, 2017).
σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation.

Table S6

Effect-coded multilevel regression model predicting startle probe locked N1

	b	***SE***	***CI* [95%]**	***t***	***p***	R^2
Fixed effects						
(Intercept)	-11.56	0.81	-13.16 – -9.97	-14.26	**<0.001**	
Cue[CD]	-0.55	0.14	-0.83 – -0.26	-3.78	**<0.001**	.011
Condition[P]	-0.04	0.20	-0.44 – 0.36	-0.19	0.852	.000
Probability[33%]	-0.22	0.14	-0.50 – 0.07	-1.49	0.136	.002
IUS-12	-0.15	0.09	-0.33 – 0.04	-1.56	0.118	.055
Condition[U]	-1.42	0.20	-1.82 – -1.02	-6.94	**<0.001**	.035
Cue[CD] × Condition[P]	-0.35	0.20	-0.75 – 0.05	-1.70	0.089	.002
Cue[CD] × Probability[33%]	0.17	0.14	-0.11 – 0.45	1.18	0.239	.001
Condition[P] × Probability[33%]	-0.44	0.20	-0.84 – -0.04	-2.16	**0.031**	.004
Cue[CD] × IUS-12	-0.02	0.02	-0.05 – 0.02	-0.95	0.342	.001
Condition[P] × IUS-12	-0.01	0.02	-0.06 – 0.04	-0.46	0.647	.000
Probability[33%] × IUS-12	-0.02	0.02	-0.06 – 0.01	-1.32	0.189	.001
Cue[CD] × Condition[U]	-0.12	0.20	-0.52 – 0.28	-0.58	0.560	.000
Probability[33%] × Condition[U]	0.24	0.20	-0.16 – 0.64	1.18	0.237	.001
Condition[U] × IUS-12	-0.02	0.02	-0.07 – 0.02	-0.99	0.323	.001
Cue[CD] × Condition[P] × Probability[33%]	-0.12	0.20	-0.53 – 0.28	-0.61	0.541	.000
Cue[CD] × Condition[P] × IUS-12	-0.01	0.02	-0.06 – 0.03	-0.54	0.587	.000
Cue[CD] × Probability[33%] × IUS-12	-0.01	0.02	-0.05 – 0.02	-0.84	0.403	.001
Condition[P] × Probability[33%] × IUS-12	-0.01	0.02	-0.05 – 0.04	-0.25	0.806	.000
Cue[CD] × Probability[33%] × Condition[U]	0.34	0.20	-0.06 – 0.74	1.68	0.093	.002
Cue[CD] × Condition[U] × IUS-12	-0.01	0.02	-0.06 – 0.03	-0.59	0.555	.000
Probability[33%] × Condition[U] × IUS-12	-0.02	0.02	-0.06 – 0.03	-0.69	0.491	.000
Cue[CD] × Condition[P] × Probability[33%] × IUS-12	-0.01	0.02	-0.06 – 0.03	-0.50	0.616	.000
Cue[CD] × Probability[33%] × Condition[U] × IUS-12	0.01	0.02	-0.03 – 0.06	0.52	0.603	.000
Random components						
σ^2, τ_{00}	22.53, 57.31					
ICC	.70					
Marginal R^2, Conditional R^2	.046, .731					
$N_{participants}$, $N_{observations}$	90, 1080					

Note. Factorial predictors are effect-coded (-1 for reference, 1 for the effect in square brackets, 0 for everything else). For cue (CD = countdown; ISI = interstimulus interval), ISI is the reference category. For condition (N = neutral, P = predictable, U = unpredictable threat) N is the reference category. For probability (33%; 100%) 100% is the reference category. IUS-12 (Short version Intolerance of Uncertainty Scale-12) values are grand-mean centered. Semi-partial R^2 indicates the partial effect sizes for each model parameter (Edwards et al., 2008; Jaeger, 2017). σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation.

Table S7

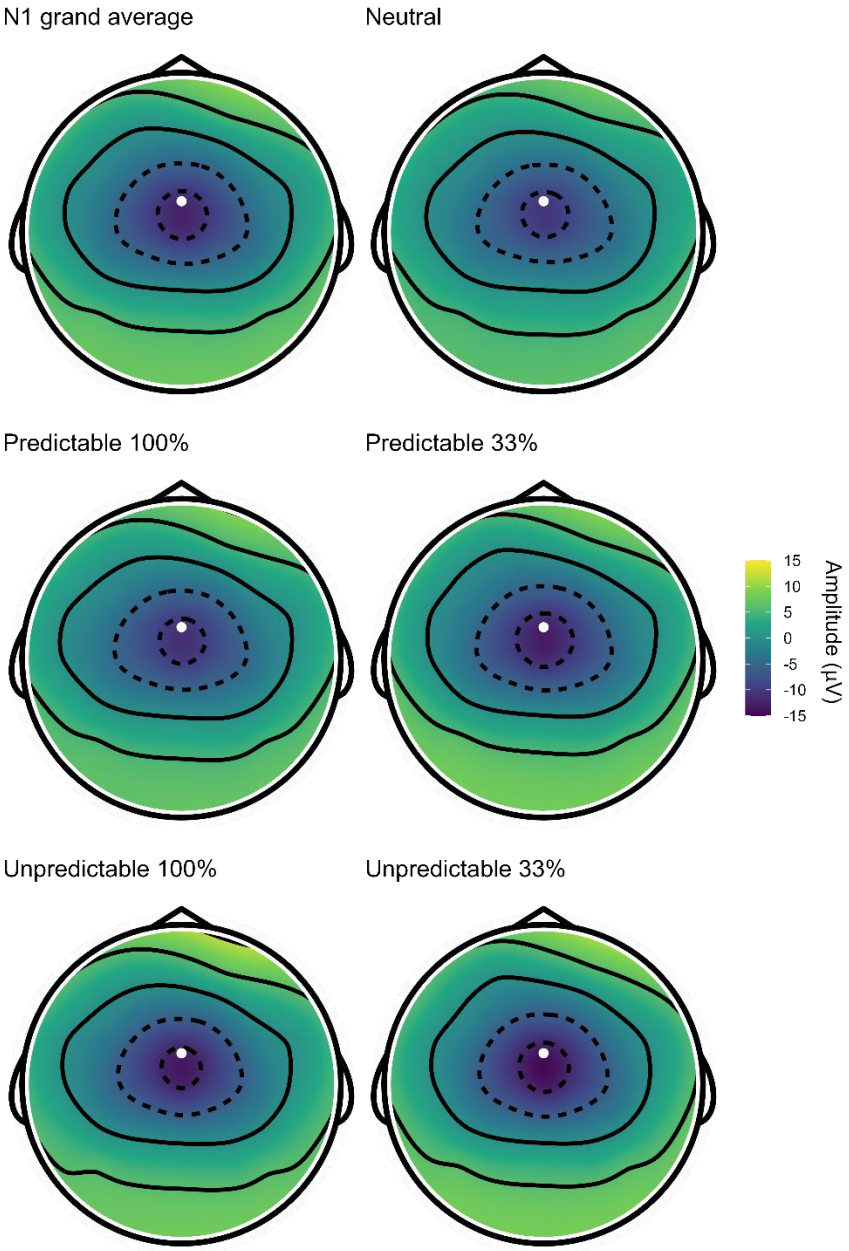
Effect-coded multilevel regression model predicting startle probe locked P3

	b	*SE*	*CI* [95%]	*t*	*p*	R^2
Fixed effects						
(Intercept)	5.90	0.32	5.27 – 6.53	18.46	**<0.001**	
Cue[CD]	0.09	0.08	-0.07 – 0.25	1.05	0.293	.001
Condition[P]	-0.45	0.12	-0.68 – -0.22	-3.86	**<0.001**	.012
Probability[33%]	0.40	0.08	0.24 – 0.56	4.86	**<0.001**	.019
IUS-12	0.03	0.04	-0.04 – 0.11	0.86	0.388	.009
Condition[U]	0.26	0.12	0.04 – 0.49	2.27	**0.023**	.004
Cue[CD] × Condition[P]	0.35	0.12	0.12 – 0.58	3.03	**0.003**	.007
Cue[CD] × Probability[33%]	0.03	0.08	-0.13 – 0.19	0.35	0.725	.000
Condition[P] × Probability[33%]	0.16	0.12	-0.06 – 0.39	1.42	0.157	.002
Cue[CD] × IUS-12	0.02	0.01	-0.00 – 0.03	1.63	0.104	.002
Condition[P] × IUS-12	0.00	0.01	-0.02 – 0.03	0.36	0.716	.000
Probability[33%] × IUS-12	0.02	0.01	-0.00 – 0.04	1.83	0.068	.003
Cue[CD] × Condition[U]	-0.20	0.12	-0.43 – 0.03	-1.72	0.087	.002
Probability[33%] × Condition[U]	-0.03	0.12	-0.26 – 0.20	-0.24	0.813	.000
Condition[U] × IUS-12	0.02	0.01	-0.01 – 0.04	1.21	0.227	.001
Cue[CD] × Condition[P] × Probability[33%]	-0.01	0.12	-0.23 – 0.22	-0.05	0.957	.000
Cue[CD] × Condition[P] × IUS-12	-0.01	0.01	-0.03 – 0.02	-0.42	0.677	.000
Cue[CD] × Probability[33%] × IUS-12	0.01	0.01	-0.01 – 0.03	0.87	0.383	.001
Condition[P] × Probability[33%] × IUS-12	0.02	0.01	-0.01 – 0.04	1.29	0.197	.001
Cue[CD] × Probability[33%] × Condition[U]	0.02	0.12	-0.20 – 0.25	0.21	0.833	.000
Cue[CD] × Condition[U] × IUS-12	0.02	0.01	-0.01 – 0.05	1.52	0.129	.002
Probability[33%] × Condition[U] × IUS-12	0.01	0.01	-0.02 – 0.04	0.71	0.479	.000
Cue[CD] × Condition[P] × Probability[33%] × IUS-12	0.01	0.01	-0.02 – 0.04	0.85	0.398	.001
Cue[CD] × Probability[33%] × Condition[U] × IUS-12	-0.02	0.01	-0.04 – 0.01	-1.35	0.177	.001
Random components						
σ^2, τ_{00}	7.27, 8.59					
ICC	.53					
Marginal R^2, Conditional R^2	.033, .557					
$N_{participants}$, $N_{observations}$	90, 1080					

Note. Factorial predictors are effect-coded (-1 for reference, 1 for the effect in square brackets, 0 for everything else). For cue (CD = countdown; ISI = interstimulus interval), ISI is the reference category. For condition (N = neutral, P = predictable, U = unpredictable threat) N is the reference category. For probability (33%; 100%) 100% is the reference category. IUS-12 (Short version Intolerance of Uncertainty Scale-12) values are grand-mean centered. Semi-partial R^2 indicates the partial effect sizes for each model parameter (Edwards et al., 2008; Jaeger, 2017). σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation.

Figure S1

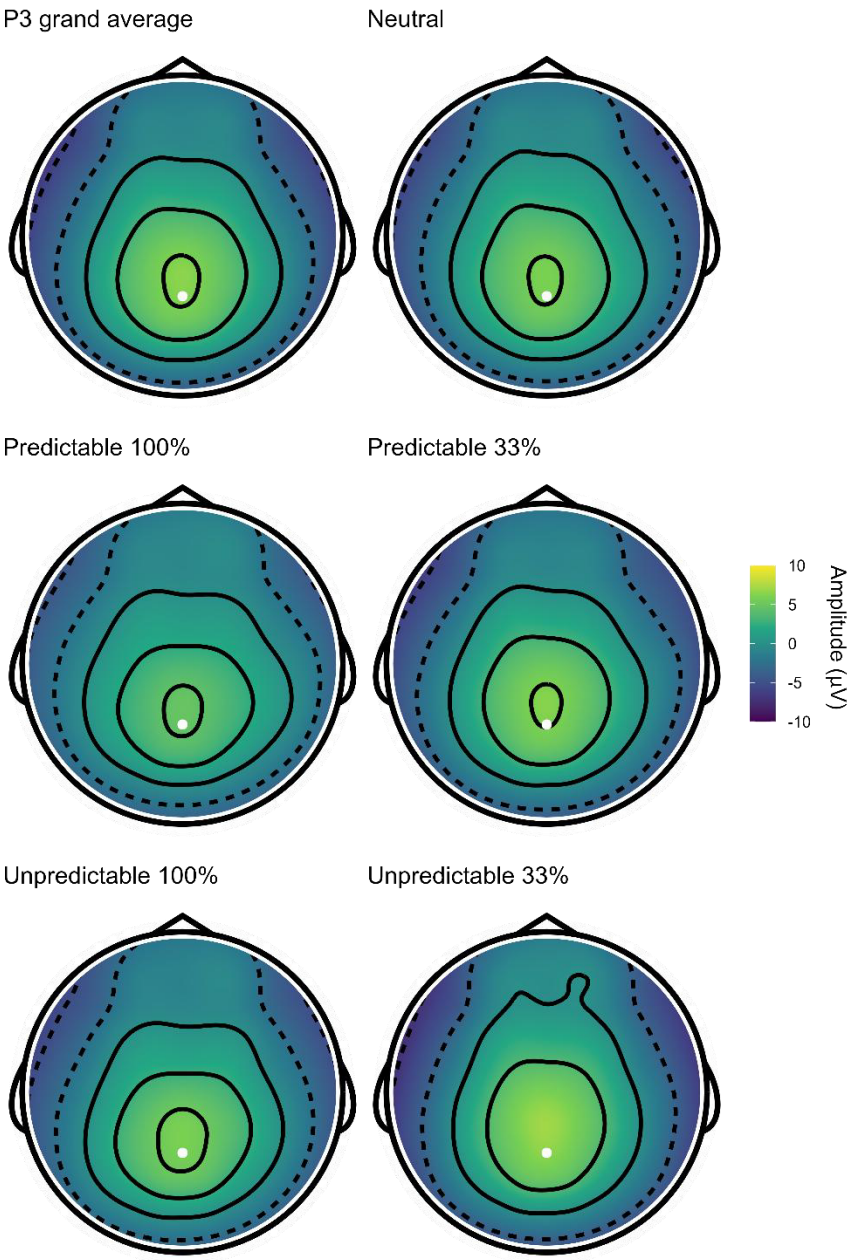
Grand averages and head maps of startle probe locked N1 across experimental conditions



Note. The signal is locked to startle probes. The N1 was quantified as ± 25 ms area around the individual peak (ca. 120-180 ms) at electrode FCz (white dot). The experimental conditions include neutral (i.e., no threat), predictable threat, and unpredictable threat in both threat probability tasks (100% and 33% threat probability). Data are collapsed across cues (countdown, interstimulus interval).

Figure S2

Grand averages and head maps of startle probe locked P3 across experimental conditions



Note. The signal is locked to startle probes. The P3 was quantified as mean activity 280 – 360 ms at electrode Pz (white dot). The experimental conditions include neutral (i.e., no threat), predictable threat, and unpredictable threat in both threat probability tasks (100% and 33% threat probability). Data are collapsed across cues (countdown, interstimulus interval).

Table S8

Multilevel regression model predicting anxiety ratings and raw startle responses controlling for STAI-T.

	Anxiety Ratings			Startle		
	df	*F*	*p*	*df*	*F*	*p*
Fixed effects						
Condition	2, 968	585.00	**<.001**	2, 8096	216.06	**<.001**
Cue	1, 968	31.42	**<.001**	1, 8096	45.15	**<.001**
Probability	1, 973	14.08	**<.001**	1, 8096	40.33	**<.001**
IUS-12	1, 87	2.94	.090	1, 87	1.91	.170
STAI-T	1, 87	2.43	.123	1, 87	0.05	.820
Condition × Cue	2, 968	7.70	**<.001**	2, 8096	10.15	**<.001**
Condition × Probability	2, 968	7.08	**<.001**	2, 8096	4.31	**.013**
Cue × Probability	1, 968	0.13	.714	1, 8096	0.01	.929
Condition × IUS-12	2, 968	17.59	**<.001**	2, 8096	7.95	**<.001**
Probability × IUS-12	1, 983	1.02	.313	1, 8097	60.71	**<.001**
Condition × Cue × Probability	2, 968	0.13	.881	2, 8096	0.50	.604
Condition × Probability × IUS-12	2, 968	0.36	.701	2, 8096	2.53	.080
Random components						
σ^2	227.94			5308.62		
τ_{00}	241.75			4121.48		
ICC	.33			.42		
Marginal R^2	.399			.053		
Conditional R^2	.708			.467		

Note. *F*-values are estimated using Satterthwaite's degrees of freedom method. Conditions include neutral, predictable threat, and unpredictable threat. Cue includes countdown and interstimulus interval. Probability includes 100% and 33%.
IUS-12 = Short version Intolerance of Uncertainty Scale (Carleton et al., 2007; Gerlach et al., 2008). STAI-T = Trait-Anxiety Inventory (Spielberger et al., 1983).
σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation.

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Study 2

Are Errors More Aversive in an Uncertain World? Testing the Influence of Uncertainty on the Error-Related Negativity in a Randomized Controlled Trial.

Hannes Per Carsten, Kai Härpfer, Marcelo Malbec, Matthias J. Wieser, & Anja Riesel

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Full Length Article



Are errors more aversive in an uncertain world? Testing the influence of uncertainty on the error-related negativity in a randomized controlled trial☆

Hannes Per Carsten [a,*], Kai Härpfer [a], Marcelo Malbec [b], Matthias J. Wieser [b], Anja Riesel [a]

[a] Department of Psychology, University of Hamburg, Germany
[b] Department of Psychology, Education and Child Studies, Erasmus University Rotterdam, the Netherlands

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ABSTRACT

Overactive error monitoring—as measured by the error-related negativity (ERN)—is a candidate transdiagnostic risk marker for internalizing psychopathology. Previous research reported associations of the ERN and individual differences in intolerance of uncertainty (IU). These findings imply associations between the subconstructs of IU (prospective and inhibitory IU) and the ERN, which we sought to replicate and extend by testing for causal influences that might elucidate specific mechanisms underlying this association. To test associations of uncertainty and the ERN, a preregistered, randomized-controlled design was employed. After measuring the baseline ERN of $N = 120$ university students, a subsample was randomly assigned to two groups: While an intervention group ($n = 30$) performed an unsolvable probabilistic "learning" task intended to induce state uncertainty, a passive control group ($n = 30$) rested. Subsequently, the ERN was assessed again. Self-reported uncertainty was assessed before and after the intervention. To further increase the statistical power of the replication attempt, we performed a correlation analysis (non-preregistered) by including data from two additional samples collected at different study sites. This analysis comprised psychophysiological data from a total of $N = 355$ participants. Cross-sectionally, no effects of IU on the ERN emerged. Regarding the state uncertainty induction, the intervention group displayed increased self-reported uncertainty after the intervention, but no evidence emerged for ERN alterations attributable to the intervention. The link between individual differences in IU and the ERN might be smaller and less robust than previous findings suggest, reflecting the understudied character of this association. The absence of evidence for mechanistic changes in the ERN due to a successful induction of state uncertainty further questions a link between IU and the ERN. In line with previous studies that linked increased ERN to anxiety, independent of current clinical status, the ERN seems unaffected by short-term changes such as symptom provocations in non-clinical populations.

1. Introduction

Errors are potentially harmful. If you slip while climbing stairs, you may have an immediate sense of threat, even though you are actually safe and can regain your balance on the stairs. If you slip while climbing a mountain, a misplaced foot could lead to mortal danger. Errors—like slipping—are inherently unpredictable. Committing an error is never an intentional action but includes an element of surprise. Errors can thus be conceptualized as inherently unpredictable endogenous threats that individuals wish to avoid in order to prevent danger (Proudfit et al., 2013; Weinberg et al., 2016).

1.1. Performance monitoring in anxiety

Avoiding errors requires performance monitoring (Botvinick et al., 2001), an adaptive process of cognitive control whose neural correlates

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* Corresponding author at: Department of Psychology, Universität Hamburg, Von-Melle-Park 11, 20146 Hamburg, Germany.
E-mail address: hannes.carsten@uni-hamburg.de (H.P. Carsten).

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can be studied using human electroencephalography (EEG). As such, the error-related negativity (ERN) is a frontocentral negative event-related potential component (ERP) occurring shortly after committing an error (Falkenstein et al., 1991; Gehring et al., 1993). A smaller but similar negativity after correct responses was labeled the correct-response negativity (CRN; Vidal et al., 2000, 2003). The ERN is linked to activity in the midcingulate cortex, more specifically the dorsal (Debener et al., 2005) and posterior region (Manoach and Agam, 2013), and the presupplementary motor area (Grützmann et al., 2016). While performance monitoring generally constitutes an adaptive process, alterations in performance monitoring can become maladaptive: An overactive performance monitoring might exhaust resources, especially if it is disproportional to a marginal likelihood of committing an error and if the potential consequences of an error are harmless. Conversely, an underactive performance monitoring and accompanying lack of adaptive behavior could impair goal attainment or even jeopardize an individual, if the consequences of errors are harmful. In line with these examples, accumulating evidence suggests altered performance monitoring in individuals with internalizing and externalizing psychopathology (Lutz et al., 2021a; Pasion and Barbosa, 2019; Riesel, 2019; Saunders and Inzlicht, 2020).

Following a categorical view on psychopathology, an increased ERN has most robustly been linked to obsessive-compulsive disorder (OCD) and obsessive-compulsive symptoms (Riesel, 2019). Further, an increased ERN has been found in patients with anxiety disorders such as generalized anxiety disorder (Weinberg et al., 2010) without comorbid depression (Weinberg et al., 2015), social anxiety disorder (Endrass et al., 2014), and health anxiety (Riesel et al., 2017), which is mirrored in meta-analytic evidence linking anxiety disorders and anxiety psychopathology across different anxiety disorder categories to increased ERN amplitudes (Moser et al., 2013; Pasion and Barbosa, 2019; Saunders and Inzlicht, 2020). Different internalizing symptom dimensions have been postulated to specify the relationship between internalizing psychopathology and an increased ERN; one prominent example of this is anxious apprehension, i.e., the tendency for future oriented trait-like worry (Moser et al., 2013). Meta-analyses on the link between worry and the ERN show small effects (Moser et al., 2013; Saunders and Inzlicht, 2020), which might not be present or smaller in subclinical populations (Härpfer et al., 2020; Saunders and Inzlicht, 2020) and might not be sensitive to variations in state-worry (Härpfer et al., 2022). This raises the question, whether worry is the prior symptom dimension or clinical phenotype responsible for altered performance monitoring in patients with anxiety disorders. Inconsistency in prior empirical findings could be due to the influence of alternative phenotypes of internalizing psychopathology (Härpfer et al., 2022; Riesel et al., 2023), which previous research did not sufficiently consider. While robust associations emerged between internalizing psychopathology and an increased ERN, the underlying symptom dimension or phenotype driving this association remains elusive. Next to worry as a candidate symptom dimension underlying the association between internalizing psychopathology and the ERN, other symptom dimensions such as checking (Weinberg et al., 2015) and uncertainty have been suggested (task-related uncertainty: Cavanagh et al., 2012; Cavanagh and Shackman, 2015; Jackson et al., 2015, trait-uncertainty: Grabowska et al., 2024; Jackson et al., 2016; Ruchensky et al., 2020, but see Malbec et al., 2022; Sandre and Weinberg, 2019).

Further understanding the associations of performance monitoring and internalizing psychopathology could shed light on the neurofunctional underpinnings of internalizing psychopathology and inform etiological models of mental disorders. Most of these conclusions rely on cross-sectional evidence (with few exceptions, e.g., Härpfer et al. (2022)). Thus, to strengthen empirical evidence and examine mechanistic links between symptoms and the ERN, further studies with pre-post designs using symptom inductions are required.

1.2. Intolerance of uncertainty: a phenotype of altered performance monitoring in anxiety?

As such, fundamental fears (Carleton, 2016b) for instance, the fear of the unknown (commonly conceptualized as intolerance of uncertainty, IU; Carleton, 2016a; Carleton et al., 2007), have rarely been focused in previous ERN research. IU describes "[…] an individual's dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information, and [is] sustained by the associated perception of uncertainty." (Carleton, 2016b, p.31). Subfactors of IU include prospective IU, a more cognitive dimension closely linked to anxious apprehension ("Unforeseen events upset me greatly") and inhibitory IU, a rather behavioral dimension describing behavioral inhibition when faced with uncertainty ("When it's time to act, uncertainty paralyses me"; Carleton, 2012; Carleton et al., 2007). IU varies in the general population (Carleton et al., 2007) and is transdiagnostically increased in individuals with internalizing psychopathology (Carleton, 2012; Gentes and Ruscio, 2011; McEvoy et al., 2019; Shihata et al., 2016). On a diagnostic level, IU is increased in patients with disorder categories also characterized by an increased ERN, e.g., in obsessive-compulsive disorder (Holaway et al., 2006; Tolin et al., 2003) and generalized anxiety disorder (Brown and Naragon-Gainey, 2013; Counsell et al., 2017; Koerner and Dugas, 2008). This partial co-occurrence may hint to a direct link between IU and the ERN.

A wealth of studies has linked IU to physiological response patterns (cf. Tanovic et al., 2018; Wever et al., 2015) such as increased defensive responses during contexts with lower threat probabilities compared with contexts in which the presence of a threat was more likely (Carsten et al., 2022; Chin et al., 2016, but see Bennett et al., 2018). Here, external threats (e.g., tactile shocks, auditory stimulation) were used, while so far, little attention has been directed to internal threatening events. Errors have been conceptualized as internal threatening events (Hajcak, 2012; Proudfit et al., 2013; Weinberg et al., 2016) and have been shown to increase defensive responding (Hajcak and Foti, 2008; Riesel et al., 2013). In a study by Jackson et al. (2015) the presentation of unpredictable tones during a flanker task led to an increased ERN, which has been interpreted as an environmental amplification of the neural processing of internal threats (i.e., errors). Later, Jackson et al. (2016) reported a bidirectional association between the subfactors of self-reported IU and the ERN. Specifically, prospective IU was associated with an increased (i.e., more negative) ERN and inhibitory IU was associated with a decreased (i.e., less negative) ERN, while overall IU was not significantly associated with the ERN. In a modified flanker task that included ambiguous trials, Sandre and Weinberg (2019) did not replicate this bidirectional association between the subfactors of IU and the ERN. Instead, both subfactors of IU were unidirectionally associated with an increased CRN. In a larger sample of 100 participants, Ruchensky et al. (2020) found no association between the subfactors of IU and the ERN but instead reported that depressive symptoms (as measured by the BDI-II, Beck et al., 1996) were linked to an increased ΔERN (i.e., ERN minus CRN), if overall IU was lower. This interaction of depressive symptoms and IU was interpreted to indicate the general role of the ERN as a risk marker for psychopathology. Grabowska et al. (2024) found a small association of inhibitory IU and the ERN, supporting Jackson et al.'s (2016) finding that inhibitory IU might be associated with decreased ERN. This effect emerged only in principal component based ERN quantification (Grabowska et al., 2024). In sum, these empirical findings on potential links between IU and the ERN are inconclusive, which motivated a preregistered replication attempt, which did not report confirmatory evidence for a link of the subfactors of IU and the ERN (Malbec et al., 2022). Here, Malbec et al. (2022) concluded that previous studies on the link between IU and the ERN might have been underpowered and thus previously reported effect sizes might have been exaggerated.

Next to the possibility of a non-existent or actually smaller true effect of IU (or the subscales of IU) on the ERN, two further reasons might

explain the mixed previous findings. First, a true effect of IU on the ERN might depend on experimental boundary conditions that have not yet been systematically varied. As such, previous studies investigating the influence of IU on the ERN used different adaptations and timings of the flanker task to elicit the ERN (Jackson et al., 2016; Malbec et al., 2022; Ruchensky et al., 2020; Sandre and Weinberg, 2019). Second, these studies examined IU on a trait level using self-report questionnaires. Considering the ERN, task variations inducing threat of shock (Riesel et al., 2012) or unpredictability through tone sequences (Jackson et al., 2015) reported ERN changes depending on the manipulation. Thus, the ERN might be sensitive to fluctuations in momentary states of uncertainty rather than self-reported and trait-like IU. Importantly—and in contrast to previous cross-sectional studies (Grabowska et al., 2024; Jackson et al., 2016; Malbec et al., 2022; Ruchensky et al., 2020; Sandre and Weinberg, 2019)—experimental manipulations inducing uncertainty could hint to causal links between IU and the ERN. In light of mixed previous evidence, and to increase the knowledge base on IU and the ERN, the present study sought to provide a well-powered replication attempt. Further, we sought to extend previous studies by testing the effect of an uncertainty symptom induction on the ERN to investigate IU as a mechanism underlying altered performance monitoring in internalizing psychopathology (Rosser, 2019; Shihata et al., 2016). Two previous studies tested effects of uncertainty manipulations on the ERN using different manipulations and found contrary results: Jackson et al. (2015) found that unpredictable tones increased the ERN. In contrast, White et al. (2018) found that a math test with false feedback (i.e., uncertain evaluative threat) reduced the ERN. Thus, the direction of effects of uncertainty manipulations on the ERN and the underlying determinants (e.g., complexity of the manipulation) are unclear, which highlights the need for further research.

1.3. Uncertainty symptom inductions

To induce emotional states of uncertainty, different induction protocols have been put forward (Deschenes et al., 2010; Faleer et al., 2017; Grenier and Ladouceur, 2004; Mosca et al., 2016; Rosen and Knäuper, 2009; Rosser, 2019; Tullett et al., 2014). Previous manipulations include linguistic manipulations with manipulated feedback (Faleer et al., 2017; Rosen and Knäuper, 2009), catastrophizing future life events (Mosca et al., 2016), or text vignettes (Britton and Davey, 2014). Further IU manipulations involved a personalized uncertain situation from the protagonist's perspective (Meeten et al., 2012), listening to a manipulative presentation (Deschenes et al., 2010), and a gambling task (Ladouceur et al., 2000). Following Carleton's (2016a, 2016b) conceptualization of IU as the fear of the unknown, we aimed at developing a symptom induction that would create a maximal “unknown” so that individuals with different levels of IU would respond to the unknown based on their IU. In a previous study from our group, we found no effect of a state worry induction on the ERN (Härpfer et al., 2022). The worry induction shared features with previously reported uncertainty inductions, i.e., a catastrophizing of an idiosyncratic life event (Mosca et al., 2016). In the current study, we aimed at increasing the salience of the uncertainty intervention and to include a variety of unknowns (Carleton, 2016b). This might increase the sensitivity of the study to unravel links between uncertainty and the ERN, while taking into account potential costs of specificity of the intervention to specific parameters of uncertainty.

1.4. The current study

In search of a transdiagnostic symptom dimension that reflects an increased performance monitoring, IU is a promising candidate phenotype. Yet, previous cross-sectional studies examining IU and the ERN found mixed results (Jackson et al., 2016; Malbec et al., 2022; Ruchensky et al., 2020; Sandre and Weinberg, 2019), with larger samples tending not to find effects of IU on the ERN (Malbec et al., 2022; Ruchensky et al., 2020). The current study has two aims: First, we aimed at conceptually replicating Jackson et al.'s (2016) cross-sectional findings of a bidirectional link between the subscales of trait-IU and the ERN. Second, we aimed at uncovering links of momentary state uncertainty and the ERN in an uncertainty symptom induction design. To this end, we developed an experimental state uncertainty induction.

As preregistered (https://osf.io/7crds), we expected to find a cross-sectional bidirectional association between the subfactors of IU and the ERN (Jackson et al., 2016), i.e., prospective IU to be associated with an increased ERN and inhibitory IU to be associated with a decreased ERN. We further expected that an induction of momentary emotional states of uncertainty (Jackson et al., 2015) would lead to an increased ERN. Further, we examined two exploratory research questions. For the cross-sectional analyses, to increase statistical power beyond our preregistered a priori power analysis, we collapsed our data with two additional samples. First, we included another sample examined at the University of Hamburg (Supplementary Sample 1 (Hamburg), $N = 59$). Second, we included data published by Malbec et al. (2022) applying our preregistered preprocessing steps (Supplementary Sample 2 (Rotterdam), $N = 178$). Second, we aimed at examining the influence of trait-IU on fluctuations in state uncertainty attributable to our intervention and possible links between trait-IU, state uncertainty fluctuations, and the ERN.

2. Methods

2.1. Participants

2.1.1. Cross-sectional study - preregistered sample

As preregistered, 120 participants were sampled to cross-sectionally test the influence of IU on the ERN. This sample size was based on power simulations in multilevel models (Arend and Schäfer, 2019; Green and Macleod, 2016). The standardized effect size of prospective IU regressed on the ERN ($\beta = 0.39$, retrieved from Jackson et al., 2016) informed our power simulation. The simulation yielded a power of 80.2 % (95 % CI [77.59, 82.63]). Thus, the likelihood to find a true effect of prospective IU on the ERN is 80.2 % given the sample size of 120 participants. Participants were excluded due to equipment failure ($n = 1$), low data quality (i.e., >25 % of all trials containing artifacts; $n = 3$) and <6 error trials ($n = 1$). Note, that $n = 3$ participants were replaced due to differences in the preregistrations within the larger project (cf. Härpfer et al., 2022). Of the remaining 118 participants, 86 identified as female, 31 as male and 1 as diverse, they were aged 18 to 30 years ($M = 23.46$, $SD = 3.03$, Table 1). Participants received course credit or monetary compensation for participating. Inclusion criteria encompassed age (18–30 years), normal or corrected-to-normal vision, and ability to provide written informed consent. Exclusion criteria encompassed lifetime substance-related disorder, schizophrenia spectrum disorder, bipolar disorder, or needle phobia assessed by trained personnel via the Structured Clinical Interview for DSM-5-clinical version (SCID-5-CV; Beesdo-Baum et al., 2019). In total, $n = 18$ participants had a current or lifetime diagnosis of $\geq$ one mental disorder, including a major depressive episode ($n = 7$), anxiety disorder ($n = 8$), somatoform disorder ($n = 2$), and eating disorder ($n = 5$). Note, that information on clinical status was missing for seven participants. Exclusion criteria further encompassed lifetime neurological disorders, use of benzodiazepines during the last week or neuroleptic medication during the last three months assessed via self-report. Participants in the preregistered sample were currently medicated with oral contraceptives ($n = 11$), antidepressants ($n = 4$), dermatological drugs against acne ($n = 3$), and thyroid hormones ($n = 2$). Further exclusion criteria consisted of hairstyles and skin conditions that preclude from EEG studies. Participants were parallelized across groups (i.e., uncertainty induction group and control group) based on their gender.

Table 1
Demographic and questionnaire data.

	Preregistered sample ($N = 118$)	Supplementary Sample 1 (Hamburg) ($N = 59$)	Supplementary Sample 2 (Rotterdam) ($N = 178$)	Control	Induction	Control vs. induction
Demographics						
Gender (f/m/d)	86/31/1	41/18/0	145/33/0	21/8/0	21/7/1	$\chi^2(2) = 1.07$, $p = .585$
Age	23.00 3.03)	22.86 (2.78)	21.24 (3.35)	23.40 (3.03)	24.00 (2.81)	$t(56) = -0.63$, $p = .531$
Education	12.28 (0.74)	12.32 (0.51)	–	12.30 (0.79)	12.2 (0.98)	$t(56) = 0.29$, $p = .769$
Clinical						
IUS	27.62 (8.36)	25.05 (6.84)	29.37 (7.84)	25.66 (6.17)	28.41 (8.78)	$t(56) = -1.39$, $p = .172$
PIU	17.18 (5.43)	15.75 (4.44)	18.24 (5.07)	15.93 (4.31)	17.69 (5.80)	$t(56) = -1.31$, $p = .195$
IIU	10.45 (3.88)	9.31 (3.35)	11.12 (3.63)	9.72 (3.21)	10.72 (4.44)	$t(56) = -0.98$, $p = .329$
PSWQ	46.08 (1.19)	43.46 (9.97)	45.19 (10.80)	43.83 (9.93)	46.90 (11.88)	$t(56) = -1.07$, $p = .291$
MASQ-AA	26.64 (7.91)	24.53 (8.55)	–	27.21 (8.62)	25.76 (7.42)	$t(56) = 0.69$, $p = .496$
STAI-T	38.73 (8.79)	36.39 (8.08)	45.41 (7.85)	37.72 (7.59)	39.07 (9.86)	$t(56) = -0.58$, $p = .563$
OCI-R	11.84 (8.42)	9.22 (6.84)	–	12.21 (8.05)	10.59 (9.61)	$t(56) = 0.70$, $p = .489$
BDI-II	5.72 (6.75)	4.03 (5.51)	5.84 (7.82)	6.59 (7.97)	5.76 (6.72)	$t(56) = 0.43$, $p = .671$
AUDIT	4.45 (3.37)	4.22 (3.60)	–	5.00 (3.36)	3.07 (2.86)	$t(56) = 2.35$, $p = .022$

Note. Gender (f = female, m = male, d = diverse); age and education in years. Abbreviations: AUDIT, alcohol use disorders identification test; BDI-II, Beck Depression Inventory II; EHI, Edinburgh Handedness Inventory (Modified); IUS, Intolerance of Uncertainty Scale-12; PIU, subscale prospective intolerance of uncertainty; IIU, subscale inhibitory intolerance of uncertainty; MASQ-AA, Mood and Anxiety Symptom Questionnaire (anxious arousal subscale); OCI-R, Obsessive-Compulsive Inventory; PSWQ, Penn State Worry Questionnaire; STAI-T, State-Trait-Anxiety Inventory (trait subscale). Note, that of the preregistered sample, a subsample was randomized to the control group and uncertainty induction group. For cross-sectional analyses, an additional sample from Hamburg ($n = 59$) and from Rotterdam ($n = 178$) was collapsed with the preregistered sample.

2.1.2. Cross-sectional study - supplementary samples

To increase statistical power beyond our preregistered a priori power analysis, the preregistered sample of 118 participants was merged with two additional samples. First, a sample examined at the University of Hamburg was included (Supplementary Sample 1 (Hamburg), $N = 59$). Second, data from Malbec et al. (2022) were included (Supplementary Sample 2 (Rotterdam), $N = 178$) and preprocessed using the current study's preprocessing pipeline (see Section 2.5), resulting in a total sample size of 355 participants for cross-sectional analysis (Table 1).

2.1.3. Uncertainty induction study

To test the influence of the uncertainty induction on the ERN, a preregistered subsample of 60 participants was randomized to either an uncertainty induction group ($n = 30$) or a control group ($n = 30$). This sample size was based on a previous manipulation of the ERN ($d = 0.87$; $\eta^2 = 0.159$; White et al., 2018). In the a priori power simulation, the sample size for the effect of the uncertainty induction on the ERN strongly depended on the random slope components in the model. If 60 participants were tested, assuming a medium random slope, the power was 64 % (95 % CI [60.94, 66.98]). Assuming a large random slope, the power was 97.20 % (95 % CI [95.98, 98.13]). The medium random slope assumes, that 68 % of the intra-individual slopes lie within 1 *SD* of 0.30 around the direct effect of time (i.e., pre vs. post intervention), while the large random slope assumes that 68 % of the intra-individual slopes of time lie within 1 *SD* of 0.50 around the direct effect of time (Arend and Schäfer, 2019).

2.2. Questionnaires (Table 1)

IU was measured using the German translation of the short version of the Intolerance of Uncertainty Scale (IUS-12, α = .87; Carleton et al., 2007; Gerlach et al., 2008). This includes 12 items measuring the subscales prospective IU and inhibitory IU. Each item can be rated on a five-point Likert scale ranging from 1 (“not at all characteristic of me”) to 5 (“entirely characteristic of me”). Further self-reported questionnaires included the Penn State Worry Questionnaire (PSWQ; 16 items, 5-point Likert scale 1–5; α = .93; Glöckner-Rist and Rist, 2014; Meyer et al., 1990), the anxious arousal subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-AA; 17 items, 5-point Likert scale 1–5; α = .86; Watson et al., 1995; Watson and Clark, 1991), the trait anxiety subscale of the State-Trait-Anxiety Inventory (STAI-T; 20 items, 4-point Likert scale 1–4; α = .90; Laux, 1981; Spielberger et al., 1983), the Obsessive-Compulsive Inventory Revised (OCI-R; 18 items, 5-point Likert scale 0–4; α = .86; Foa et al., 2002; Gönner et al., 2007), the Beck Depression Inventory (BDI-II; 21 items, 4-point Likert scale 0–3; α = .92; Beck et al., 1996; Hautzinger et al., 2006), and the Alcohol Use Disorder Identification Test (AUDIT; 10 items, 5-point Likert scale 0–4; α = .87; Babor et al., 2001). Correlations between the questionnaires are reported in Supplement B.

2.3. Task

Participants sat in a dimly lit, electrically shielded cabin at a viewing distance of approximately 24 in. in front of a 19-in. LCD monitor (Dell 1907FPV, resolution 1920 × 1080 pixels, refresh rate 120 Hz). A speeded arrowhead version of the Eriksen-flanker task (Eriksen and Eriksen, 1974) with a set of five horizontally aligned arrows (one target, four flankers) was displayed using Presentation Software (Neurobehavioral Systems, Inc., Albany, California). The set of arrows was approximately 6.2° in width and approximately 1.0° in height. The direction of the set of flanking arrows were pseudo-randomly congruent to the center arrow (<<<<< or >>>>>) or incongruent (<<><< or >><>>). Participants were instructed to indicate the direction of the center arrow by pressing a key with their respective left or right index finger as quickly and as accurately as possible. A total number of 400 trials were presented, separated into five blocks of 80 trials and preceded by 20 practice trials. After each block, participants received a performance feedback asking them to respond faster, irrespective of their actual response times, since group differences were shown to be pronounced under speed conditions (Riesel et al., 2019a). Each trial included fixation cross (200–1200 ms), flanker and target presentation (100 ms) and response (max. 800 ms). Accuracy was defined as the percentage of correct responses across all responses. Response times were defined as the time difference between the stimulus onset (i.e., arrows) and the respective correct or incorrect response. The post-error slowing (PES) was quantified using the robust measurement method (i.e., the average response time difference between the last correct trial before an error and the first correct trial after an error, Table 2, Dutilh et al., 2012).

Table 2
Descriptive statistics of flanker task behavioral data of the preregistered sample pre intervention.

	Preregistered sample ($N = 118$)	Supplementary Sample 1 (Hamburg) ($N = 59$)	Control group		Induction group		Control vs. induction
			T0	T1	T0	T1	
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	
Correct (*n*)	337.62 (38.92)	336.83 (33.30)	337.72 (46.31)	348.48 (42.79)	328.24 (40.48)	320.66 (77.00)	T0: $t(55) = 0.83$, $p = .410$, $d = 0.22$ T1: $t(55) = 1.70$, $p = .096$, $d = 0.45$
Error (*n*)	50.53 (29.96)	54.47 (29.17)	45.86 (32.57)	44.66 (40.14)	58.72 (30.09)	60.59 (45.08)	T0: $t(55) = -1.56$, $p = .124$, $d = -0.41$ T1: $t(55) = -1.42$, $p = .161$, $d = -0.37$
Missed (*n*)	11.85 (20.42)	8.71 (11.71)	16.41 (27.52)	6.86 (10.59)	13.03 (22.62)	18.76 (72.61)	T0: $t(55) = 0.51$, $p = .612$, $d = 0.13$ T1: $t(55) = -0.87$, $p = .390$, $d = -0.23$
Accuracy (%)	86.87 (8.01)	86.03 (7.61)	87.86 (8.86)	88.60 (10.28)	84.68 (8.21)	83.20 (12.21)	T0: $t(55) = 1.42$, $p = .161$, $d = 0.37$ T1: $t(55) = 1.82$, $p = .074$, $d = 0.48$
RT correct (ms)	425.85 (52.45)	420.72 (43.15)	435.53 (61.68)	416.70 (56.05)	416.92 (51.12)	394.05 (63.29)	T0: $t(55) = 1.25$, $p = .216$, $d = 0.33$ T1: $t(55) = 1.44$, $p = .155$, $d = 0.38$
RT error (ms)	366.27 (66.09)	365.15 (55.35)	379.33 (63.44)	367.50 (60.23)	358.97 (81.54)	358.22 (79.89)	T0: $t(55) = 1.06$, $p = .294$, $d = 0.28$ T1: $t(55) = 0.50$, $p = .620$, $d = 0.13$
PES	40.86 (24.65)	30.44 (22.35)	39.89 (28.29)	28.01 (30.01)	33.09 (20.94)	25.27 (26.19)	T0: $t(55) = 1.04$, $p = .303$, $d = 0.27$ T1: $t(55) = 0.37$, $p = .712$, $d = 0.10$

Note. Summary statistics of *n* and reaction times (RT) for the preregistered sample. Post-error slowing (PES) was quantified using the robust measurement method (i.e., the average response time difference between the last correct trial before an error and the first correct trial after an error).

2.4. Procedure

The hypotheses and methods of this study were preregistered before the start of data collection (https://osf.io/7crds). The methods of the study were confirmed by the local ethics committee as being in accordance with the Declaration of Helsinki (World Medical Association, 2013). Prior to the laboratory assessment, participants were screened for eligibility via a phone interview. Participants received verbal and written information about the objectives and methods of the study and provided written informed consent. After completing questionnaires, participants performed a flanker task (T0, Fig. 1). Next, the experimental group (i.e., uncertainty induction group) received an uncertainty induction, while the control group paused for an equivalent amount of time. Subsequently, the participants of the control group and uncertainty induction group performed another flanker task (T1). Manipulation checks (i.e., state ratings) were implemented after the baseline flanker task (T0) and before the post-intervention flanker task (T1, Fig. 1) in order to assess intraindividual state changes over time. To assess the effect of the uncertainty induction, visual analogue scales (VAS) were implemented ranging from 0 to 100 (forced choice starting at 50) capturing relevant symptom dimensions starting with "at this moment…". Two items were used to assess uncertainty ("…, how affected are you by feelings of uncertainty", "…, how uncertain do you feel?"). Additional symptom dimensions included worry ("…, how worried are you", "…, how much do you ruminate"), need for control ("…, how much do you feel the urge to check things", "…, how much do you feel the need to control things"), affect ("…, how many positive feelings do you feel [e.g., joyful, enthusiastic, active]?", "…, how many negative feelings do you feel [e.g., angry, sad, anxious]?", and arousal ("…, how aroused are you", "…, how tensed are you?" cf. Härpfer et al., 2022).

2.4.1. Uncertainty symptom induction

The uncertainty induction consisted of a difficult version of the Frank task (Frank et al., 2004; Fig. 2).

Participants in the uncertainty induction group were instructed to learn the correct signs by making choices and adapting to the feedback they received. Participants were instructed that most people learn the correct signs easily, that the experimenter would monitor their learning through a camera in the room, and that at the end of the experiment, participants would receive individual feedback on their learning performance compared with previous participants. The actual feedback during the task was random/probabilistic and correct in 50 % of the responses and incorrect in 50 % of the responses (Fig. 2). After every experimental block (ca. 150 s), the experimenter entered the room and stated that the difficulty of the task for the next trial block was decreased. After six minutes, the experimenter aborted the intervention by saying "There is no point in continuing this, we might try again later on in the experiment." After this uncertainty induction, the participants completed another flanker task (T1, Fig. 1).

2.5. Electroencephalography recording and processing

The EEG data from the preregistered sample and Supplementary Sample 1 (Hamburg) was acquired using 61 concentric and equidistant Ag/AgCl scalp electrodes (Easycap, Herrsching, Germany) and two 32-channel amplifiers. The recording reference was located between AF3 and Fz, the ground electrode was placed between the Fz and AF4. External electrodes were placed at the left infraorbital site for vertical eye movements and at the neck for the electrocardiogram. Impedances were kept below 5 kΩ. Data were acquired at a sampling rate of 1000 Hz and recorded with a band-pass filter of 0.01 Hz to 250 Hz. The EEG data from the Supplementary Sample 2 (Rotterdam) was recorded using a 32 + 2 Ag/AgCl electrodes cap with a 10/20 layout. To capture eye movements, two external electrodes were placed below and two above the left eye and one at the outer canthus of each eye. Data were recorded

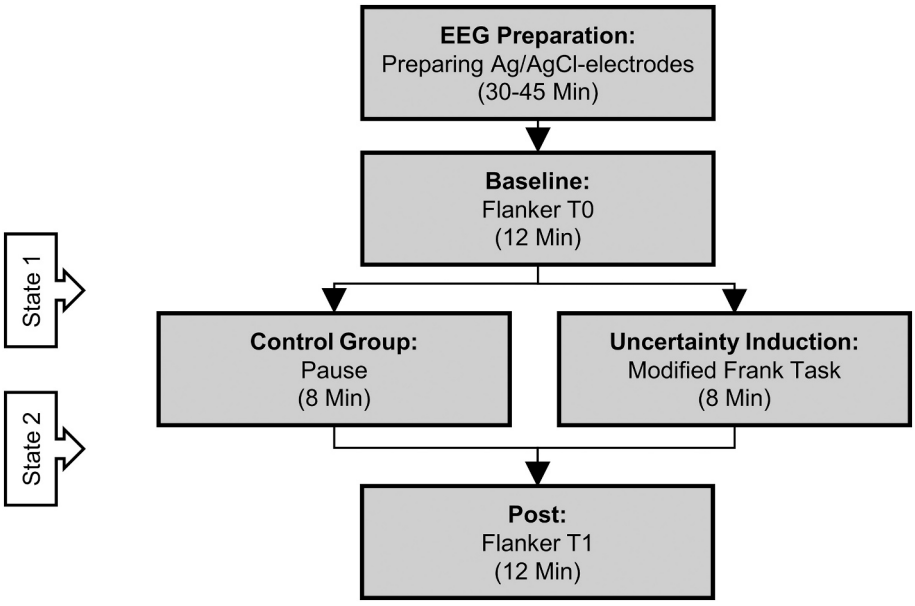


Fig. 1. Flowchart of the study procedure.
Note. Duration of each task is approximative. State ratings throughout the study ensured the tracking of momentary fluctuations in state uncertainty, state worry, state need for control, state positive affect, and arousal.

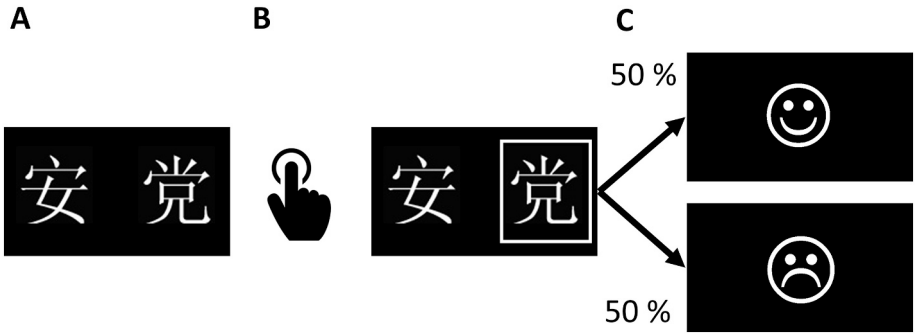


Fig. 2. Frank task.
Note. Illustration of the uncertainty induction. Individuals are presented with two signs (A) and indicate their choice with a button press (B). Participants then receive a probabilistic feedback (C) which is correct in 50 % of the choices.

using the Active-Two BioSemi system (BioSemi, Amsterdam, Netherlands), including two additional electrodes (Common Mode Sense and Driven Right Leg) for online reference and ground measurement. The data were recorded with 512 Hz sampling rate and 24-bit A/D conversion (Malbec et al., 2022).

Offline, the data were processed in Brain Vision Analyzer 2.3 (Brain Products GmbH, Gilching, Germany). Raw EEG data were band-pass filtered (0.1–30 Hz, 24 dB/octave roll-off) and notch-filtered (50 Hz), and corrected for ocular artifacts via a semi-automatic independent component analysis. Data were then re-referenced to a common average reference and baseline-corrected (−500 ms to −300 ms relative to responses). Next, data were segmented into response-locked epochs of 1500 ms (−500 ms pre-response to 1000 ms post-response). Segments containing artifacts were removed (i.e., absolute voltage range exceeding 200 μV, voltage step exceeding 50 μV between consecutive data points or maximum voltage difference of <0.5 μV within 100 ms intervals). In the preregistered sample, artifact rejection caused M = 0.78 % (SD = 3.95 %, Max = 13.00 %) data loss in the first flanker task (T0) and M = 0.53 % (SD = 1.25 %, Max = 10.40 %) in the second flanker task (T1). In the Supplementary Sample 1 (Hamburg), artifact rejection caused M = 0.83 % (SD = 1.43 %, Max = 7.20 %, n = 59) data loss. In the Supplementary Sample 2 (Rotterdam) artifact rejection caused M = 1.47 % (SD = 5.58 %, Max = 22.00 %, n = 178) data loss. Participants were excluded if >25 % of all trials contained artifacts (n = 3; Luck, 2014), or if less than six usable error segments were left for averaging for either T0 or T1 (n = 1; Olvet and Hajcak, 2009). As preregistered, ERN and CRN were quantified as mean activity 0–100 ms relative to responses at channel FCz based on grand-averaged waveforms of the data and topographical distribution (Fig. 4). For the exploratory analyses, including Supplementary Sample 1 (Hamburg) and Supplementary Sample 2 (Rotterdam), the signal from channel Fz was analyzed due to different electrode layouts in both labs (i.e., in the layout used by Malbec et al. (2022) no FCz electrode was included).

To determine split half reliability, we calculated Spearman-Brown corrected correlations of odd and even trials separately for ERN and CRN. Here, the ERPs demonstrated good split half reliability for the preregistered cross-sectional analyses at channel FCz (ERN: r_{T0} = .94, CRN: r_{T0} = .98) and for the uncertainty induction design (ERN: r_{T0} = .95, CRN: r_{T0} = .99, ERN: r_{T1} = .92, CRN: r_{T1} = .99). For the cross-sectional analyses including Supplementary Sample 1 (Hamburg) and Supplementary Sample 2 (Rotterdam), the ERPs demonstrated good split half reliability at channel Fz (ERN: $r_{\text{preregistered sample}}$ = .90, CRN: $r_{\text{preregistered sample}}$ = .94, ERN: $r_{\text{Supplementary Sample 1 (Hamburg)}}$ = .86, CRN: $r_{\text{Supplementary Sample 1 (Hamburg)}}$ = .98, ERN: $r_{\text{Supplementary Sample 2 (Rotterdam)}}$ = .85, CRN:

$r_{\text{Supplementary Sample 2 (Rotterdam)}} = .98$).

2.6. Data analysis

The data were analyzed using R version 4.3.2 (R Core Team, 2023) and RStudio version 2023.06.1 (RStudio Team, 2023). A *p*-value of .05 was defined as the significance threshold. Multilevel regression models (MLM) were used to test the hypotheses and were estimated using the lme4 package (Bates et al., 2015). MLMs included an unstructured covariance matrix (Volpert-Esmond et al., 2021). Degrees of freedom of the models were estimated using Satterthwaite's method (Kuznetsova et al., 2017). Mean amplitudes at each time point (level 1) were nested within individual subjects (level 2, random intercept). Continuous level 2 predictors (i.e., questionnaire data) were grand mean centered. Models included the predictors: Response type (factor with 2 levels correct vs. false, entered at level 1), time (factor with 2 levels T0 vs. T1, indexing the time-point before vs. after the intervention, entered at level 1), group (factor with 2 levels indicating whether the participant was randomized to the control group or the uncertainty induction group, entered at level 2), prospective IU (grand mean centered continuous predictor entered at level 2), inhibitory IU (grand mean centered continuous predictor, entered at level 2). Initially, a model with no predictors (null model) was run to estimate the variance in the dependent variable that can be attributed to within-individual variation (level 1) and between-person differences (level 2) and reported as the intraclass correlation coefficient (ICC). Factorial predictors were dummy coded for analyses. Semipartial R^2 indicates the partial effect sizes for each model parameter and was estimated using the package r2glmm (Edwards et al., 2008; Jaeger, 2017) Significant interactions were followed up by pairwise comparisons of the estimated marginal means (factorial predictors) or contrasts of the slopes (dimensional predictors) using the package emmeans (Russell et al., 2021). The confidence intervals and *p*-values of post-hoc tests were corrected for multiple comparisons using the Tukey method. To quantify the evidence for the respective nullhypothesis of each effect, complementary Bayesian multilevel models were estimated using the package brms (Bürkner, 2017) via STAN. Using the Hamiltonian Monte Carlo sampler algorithm, 3000 iterations were run with random initial values for each chain. Random intercepts and fixed effects were assigned default flat normal priors with a $M = 0$ and $SD = 10$. For the *SD*s of random effects and the residuals, Student-t priors with 3 *df*, $M = 0$ and a scale of 10 were used. For brevity, we reported BF_{10} for each effect. BF_{10} indicates the extent to which the data supports the inclusion of a given effect compared with the model without this effect. The evidence provided can be weak (BF_{10} of 1–3 or 1–0.33), moderate (BF_{10} of 3–20 or 0.33–0.05), strong (BF_{10} 20–150 or 0.05–0.0067), or very strong ($BF_{10} > 150$ or 0.0067–0) with $BF_{10} > 1$ indicating evidence for the inclusion of an effect while $BF_{10} < 1$ indicate evidence against the inclusion of an effect.

2.6.1. Preregistered cross-sectional analysis

The model depicted in Eq. (1) was used to test cross-sectional hypothesis stating that prospective IU would be associated with enhanced ERN amplitudes and inhibitory IU would be associated with reduced ERN amplitudes (Wilkinson Notation):

$$\text{Amplitude} \sim \text{Response type} \times \text{Prospective IU} \times \text{Inhibitory IU} + (1 \mid \text{Participant}) \quad (1)$$

In model 1, individual amplitudes (from T0) were predicted by the level 1 predictor response type, which tests if the ERN differs from the CRN. The intercept of amplitude could vary randomly per participant. Further predictors included fixed effects for prospective IU and inhibitory IU. Here, we expected a significant interaction of the fixed effects of response type × prospective IU, driven by enhanced amplitudes for individuals with increased prospective IU scores for false responses. Further, we expected a significant interaction of the fixed effects of response type × inhibitory IU, driven by enhanced amplitudes for individuals with decreased inhibitory IU for false responses. The three-way interaction of the fixed effects response type × prospective IU × inhibitory IU controlled for effects of overall IU beyond the subfactors.

2.6.2. Preregistered analysis of the pre-post design

To test the hypothesis stating that the uncertainty induction would lead to increased ERN compared with the control group, the following model was specified (Eq. (2)):

$$\text{Amplitude} \sim \text{Response type} \times \text{Time} \times \text{Group} + (1 \mid \text{Participant}) \quad (2)$$

In model 2, ERP amplitudes were predicted by the fixed predictors response type (CRN vs. ERN), time (indicating pre vs. post intervention) and group (indicating uncertainty induction vs. control group). ERN at each factor level of time was nested within the participant. We expected a significant time × group interaction driven by enhanced ERN from T0 to T1 in the uncertainty induction group relative to the control group.

2.6.3. Cross-sectional analyses including supplementary samples

As an exploratory test of the replicability of the bidirectional effect of the subscales of IU reported by (Jackson et al., 2016), we collapsed the cross-sectional data from the present study with two further samples (i.e., Supplementary Sample 1 (Hamburg), $n = 59$; Supplementary Sample 2 (Rotterdam), $n = 178$, Table 1). This was tested using Eq. (3) and by including a random effect of the laboratory (Lab, factor with 2 levels entered at level 2) and allowing for a random intercept per laboratory.

$$\text{Amplitude} \sim \text{Response type} \times \text{Prospective IU} \times \text{Inhibitory IU} + (1 \mid \text{Participant}) + (1 \mid \text{Lab}) \quad (3)$$

Further, we tested whether ERN changes due to the uncertainty induction depended on trait IU variations (Eq. (4)).

$$\text{ERN} \sim \text{Time} \times \text{Group} \times \text{Prospective IU} + \text{Time} \times \text{Group} \times \text{Inhibitory IU} + (1 \mid \text{Participant}) \quad (4)$$

Model 4 allowed the exploratory test whether individuals with higher levels of prospective IU or inhibitory IU demonstrate altered changes in the ERN attributable to the state uncertainty induction.

3. Results

3.1. Subjective ratings pre and post intervention

The influence of the uncertainty induction on ratings in visual analogue scales was tested using a multilevel model including the factors group (uncertainty induction vs. control condition) time (pre vs. post intervention), and dimension of the state ratings (i.e., uncertainty, worry, control, positive affect, arousal, Fig. 3). Here, no significant main effect of group ($b = 3.31$, $SE = 5.33$, $t(1138) = 0.62$, $p = .534$, $R^2 = .001$) emerged, but a significant main effect of time ($b = -6.60$, $SE = 3.36$, $t(1138) = -1.96$, $p = .050$, $R^2 = .004$), factor (ANOVA III output of the interaction: $F(4, 1103) = 18.25$, $p < .001$) as well as a group × time interaction ($b = 15.52$, $SE = 4.76$, $t(1138) = 3.26$, $p = .001$, $R^2 = .010$). The main effect of the group × time × factor interaction across all factors was not significant $F(4, 1103) = 1.65$, $p = .158$), which was due to mostly consistent pattern of increased ratings after the uncertainty induction, but not after the control condition: Posthoc contrasts of the estimated marginal means revealed that state uncertainty ratings increased in the uncertainty induction group from pre to post intervention ($b = 17.76$, $t(1103) = 5.30$, $SE = 3.35$, $p < .001$, $d = 0.98$), while they did not differ significantly in the control group from pre to post ($b = -2.07$, $t(1103) = -0.63$, $SE = 3.29$, $p = .531$, $d = -0.16$). However, this pattern of results was not specific to state uncertainty ratings. Specifically, there was also an increase in ratings of state worry (uncertainty group pre to post: $b = 13.36$, $t(1103) = 3.99$, $SE = 3.35$, $p <$

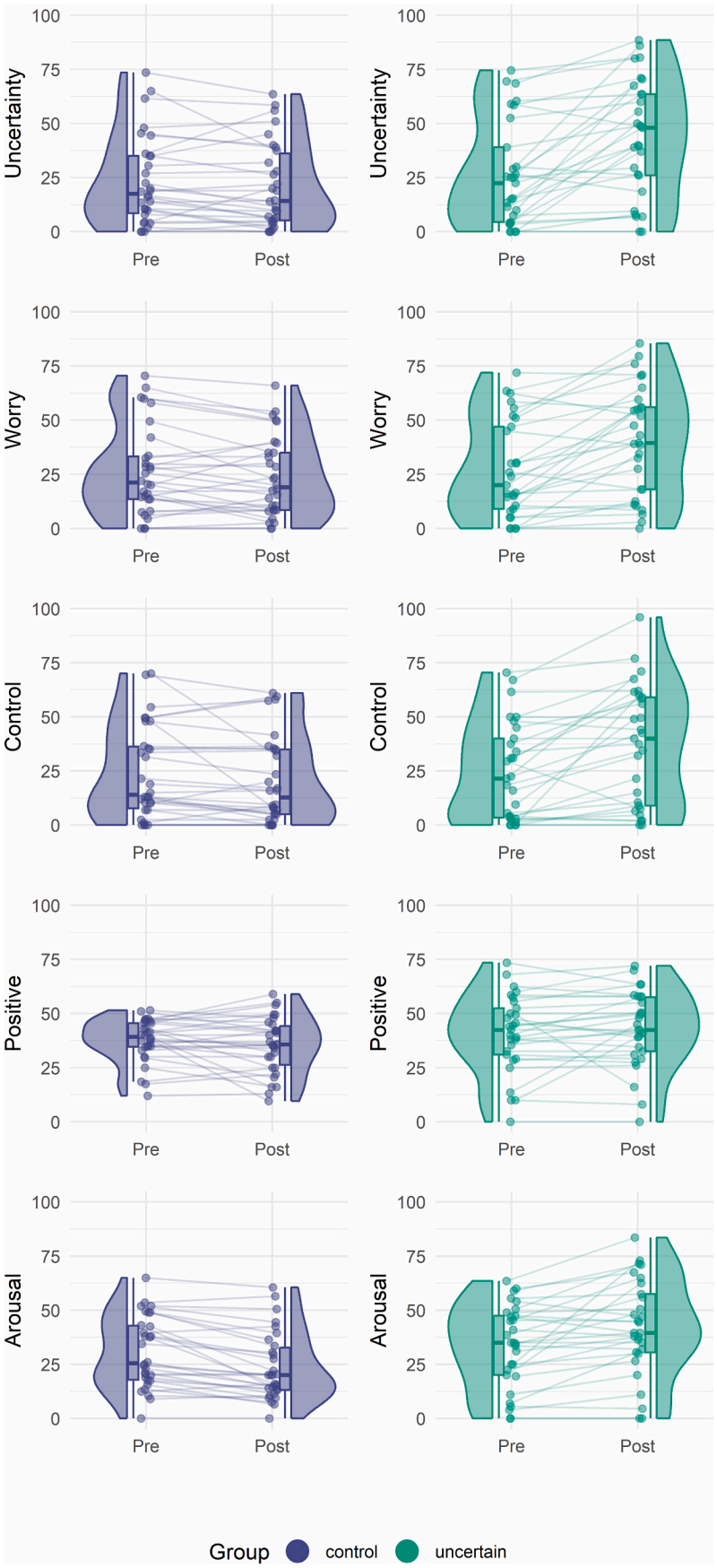


Fig. 3. Results of the subjective ratings pre and post the uncertainty induction and control condition.
Note. Subjective state ratings were captured via two items per dimension (uncertainty, worry, need for control, positive affect, arousal).

.001, $d = 0.74$, control group pre to post: $b = -2.70$, $t(1103) = 0.82$, $SE = 3.29$, $p = .413$, $d = -0.18$) and state need for control (uncertainty group pre to post: $b = 12.72$, $t(1103) = 3.80$, $SE = 3.35$, $p < .001$, $d = 0.70$, control group pre to post: $b = -3.68$, $t(1103) = 1.12$, $SE = 3.29$, $p = .264$, $d = -0.20$). Nonetheless, the largest effects were observed for changes in state uncertainty. Furthermore, both groups did not show significant differences in positive affect from pre to post intervention (uncertainty group pre to post: $b = -2.31$, $t(1103) = 0.69$, $SE = 3.35$, $p = .491$, $d = 0.13$, control group pre to post: $b = -2.27$, $t(1103) = -0.69$, $SE = 3.29$, $p = .492$, $d = -0.11$), while state arousal increased in the uncertainty induction group and decreased in the control group (uncertainty group pre to post: $b = 8.91$, $t(1103) = 2.66$, $SE = 3.35$, $p = .008$, $d = 0.49$, control group pre to post: $b = -6.92$, $t(1103) = -2.10$, $SE = 3.29$, $p = .036$, $d = -0.37$). In sum, the uncertainty induction increased state uncertainty in the intervention group relative to the control group. However, this effect was not specific to state uncertainty, as the uncertainty induction also led to increased state worry, state need for control, and state arousal in the intervention group compared with the control group, from T0 to T1, but to a lesser extent than state uncertainty (Fig. 3). The only dimension which was not significantly affected by the uncertainty induction was positive affect.

Exploratorily, we tested whether changes in the state dimensions were influenced by trait IU. Effects of trait IU were tested on an overall level, as well as on a subscale level (i.e., subscales prospective IU and inhibitory IU). Separate models were run per level of factor (i.e., state ratings of uncertainty, worry, control, positive affect, arousal) to avoid four level interactions. For the subscale models, both subscales were included in the models to statistically control for effects of overall IU. Taken together, changes in state measurements were not influenced by overall IU nor by the subscales of IU (Table 3).

3.2. Event-related potentials

Grand averaged response-locked ERPs at T0 and their corresponding scalp topographies for the preregistered sample are depicted in Fig. 4. Descriptive statistics of the ERN and CRN for the preregistered sample (per time point i.e., pre intervention vs. post intervention) and for the Supplementary Sample 1 (Hamburg) and Supplementary Sample 2 (Rotterdam) are shown in Table 4.

3.2.1. Cross-sectional results

The model including test statistics is depicted in Table 5. As expected, a main effect of response (i.e., errors vs. correct responses) emerged (Table 5), indicating that the ERN signal was increased (more negative) compared with the CRN. In the preregistered sample including 118 participants, no main effects of prospective IU or inhibitory IU, nor an interaction of the subscales with response emerged (Table 5, Fig. 5C).

To test the effect of overall IU, a model with overall IU was run without including the subscales prospective IU and inhibitory IU. The effect of overall IU was not significant ($b = -0.04$, $SE = 0.04$, $t(232) = -1.01$, $p = .315$, $R^2 = .006$), as was the response × IU interaction ($b = 0.02$, $SE = 0.03$, $t(232) = 0.58$, $p = .560$, $R^2 = .001$). Hence, we found no evidence for cross-sectional effects of IU on the ERN in this sample (Fig. 5C).

As an exploratory analysis, the data from the present study were collapsed with Supplementary Sample 1 (Hamburg, $n = 59$) and Supplementary Sample 2 (Rotterdam, $n = 178$, Malbec et al. (2022), including a fixed effect for the laboratory (i.e., Hamburg or Rotterdam). Note, that due to differences in the electrode layouts, data from channel Fz from each laboratory were used (Section 2.5) The model is depicted in Table 6. Here, the ERN was again increased compared with the CRN (Table 6). Further, a main effect of laboratory emerged ($b = 0.74$, $SE = 0.28$, $t(351) = 2.69$, $p = .008$, $R^2 = .015$, $BF_{10} = 1121.14$), indicating that participants the Hamburg lab (i.e., preregistered sample and Supplementary Sample 1 (Hamburg)) displayed smaller (i.e., more positive) amplitudes in ERN and CRN compared with participants in the Supplementary Sample 2 (Rotterdam). No significant effects or interactions including the subscales of IU (i.e., prospective IU and inhibitory IU) emerged (Table 6, Fig. 5A, Fig. 5B). To test for overall effect of IU, we ran a model with overall IU, dropping the subscales. Here, no significant effect of overall IU emerged ($b = -0.02$, $SE = 0.02$, $t(704) = -0.83$, $p = .409$, $R^2 = .001$, $BF_{10} = 2 \times 10^{-5}$.) and no significant response × IU interaction ($b = 0.02$, $SE = 0.01$, $t(704) = 1.51$, $p = .132$, $R^2 = .001$). We conducted a sensitivity analysis to assess the smallest effect size that could be detected with the collapsed sample of $N = 355$ participants in a cross-level interaction of response (i.e., ERN vs. CRN) and IU using simr version 1.0.5 (Green and Macleod, 2016). The simulation was based on 10,000 Monte Carlo simulations (Arend and Schäfer, 2019) and a significance threshold of $\alpha = .05$. According to the result of the power simulation, we could have detected effect sizes of $d = 0.11$ in the data with a likelihood of 82.40 % (95 % CI[81.64, 83.14]) and effect sizes of $d = 0.14$ in the data with a likelihood of 95.54 % (95 % CI[95.12, 95.94]).

3.2.2. Pre post design - uncertainty symptom induction

The statistics of the preregistered model are shown in Table 7. A main effect of response emerged with increased (i.e., more negative) amplitudes for ERN compared with CRN. No significant effects emerged regarding the research question whether an induction of state uncertainty, compared with a passive waiting (control) condition, would alter the ERN from T0 to T1. The relevant interaction effect response × time × group was not significant and the effect size estimate was $R^2 = .000$ (Fig. 6). Hence, no evidence could be quantified for the state uncertainty induction affecting ERN or CRN from T0 to T1 relative to the control condition.

Exploratory analyses encompassed testing whether changes in ERN from T0 to T1 per group would be modulated by differences in IU or the subscales of IU (i.e., prospective IU and inhibitory IU). Here, the overall pattern of results did not change. The relevant interaction for overall IU (time × group × IU) was not significant ($b = -0.01$, $SE = 0.08$, $t(102) = -0.08$, $p = .939$, $R^2 = .000$). Thus, ERN changes from T0 to T1 were not significantly influenced by trait IU. Further, no significant effect emerged for overall IU affecting the ERN irrespective of group, as indicated by the absence of a significant time × IU interaction ($b = -0.07$, $SE = 0.07$, $t(102) = -1.05$, $p = .297$, $R^2 = .002$). On a subscale level, the relevant interactions (time × group × prospective IU and time

Table 3
Exploratory analyses of intolerance of uncertainty and changes in state symptom ratings.

State dimension	group × time × IU						group × time × prospective IU						group × time × inhibitory IU					
	b	*SE*	*df*	*t*	*p*	R^2	*b*	*SE*	*df*	*t*	*p*	R^2	*b*	*SE*	*df*	*t*	*p*	R^2
Uncertainty	−0.23	0.40	222	−0.58	.560	.001	−0.53	0.63	218	−0.84	.401	.002	0.24	0.84	218	0.29	.772	.000
Worry	0.15	0.49	222	0.30	.766	.000	−0.18	0.79	218	−0.23	.815	.000	0.66	1.04	218	0.64	.525	.001
Need for control	−0.25	0.50	222	−0.49	.625	.001	0.50	0.80	218	0.63	.529	.001	−1.36	1.06	218	−1.28	.203	.004
Positive affect	−0.19	0.96	222	−0.20	.843	.000	−0.71	1.53	218	−0.46	.644	.001	0.54	2.03	218	0.27	.791	.000
Arousal	0.24	0.56	222	0.43	.665	.001	0.77	0.89	218	0.86	.390	.002	−0.52	1.19	218	−0.44	.660	.001

Note. Separate models were run per state dimension and for overall intolerance of uncertainty (IU) and on the subscale level (i.e., prospective IU and inhibitory IU). Group was a factor with two levels (uncertainty induction group, control group). Time was a factor with two levels (i.e., pre vs. post intervention).

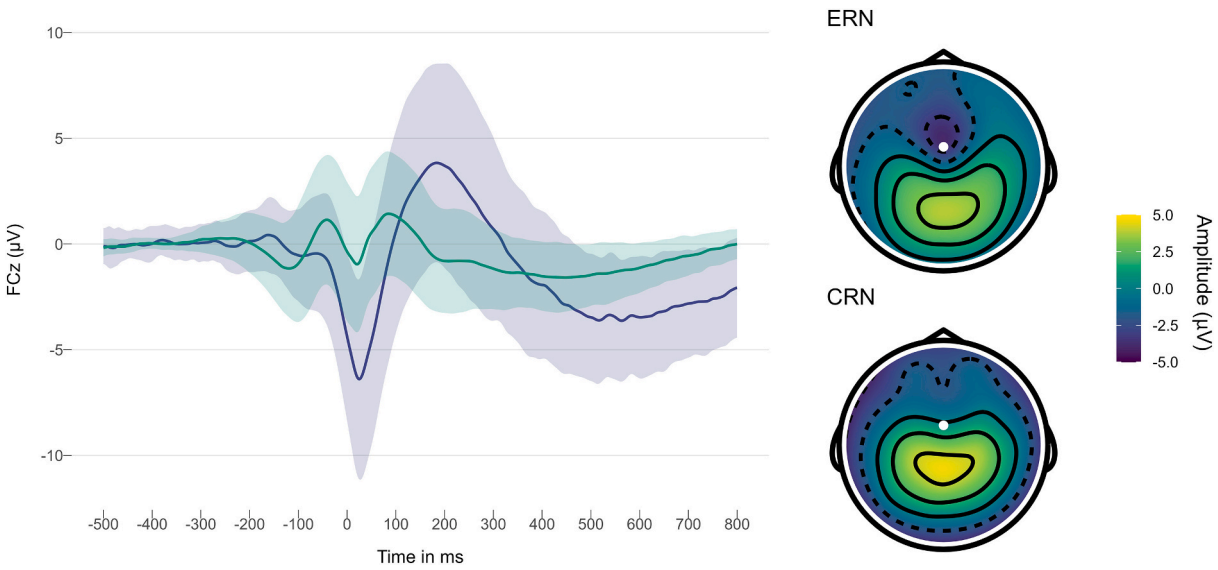


Fig. 4. Grand averages (left) of the Error-Related Negativity (ERN) and Correct-Related Negativity (CRN) and topographies (right) at T0.
Note. Quantification was mean amplitude 0–100 ms after a response at FCz (white dot). The shaded area depicts the standard deviation at each ms.

Table 4
Descriptive statistics of the error-related negativity and correct-related negativity per sample and time point.

Study part	Group	Response (channel)	Time point	*N*	Amplitude *M* (*SD*)
Cross-sectional	Preregistered	Correct (FCz)	T0	118	0.39 (2.96)
		Error (FCz)	T0	118	−3.78 (4.42)
	Supplementary Sample 1 (Hamburg)	Correct (Fz)	T0	59	−1.21 (2.22)
		Error (Fz)	T0	59	−3.89 (2.58)
Cross-sectional	Supplementary Sample 2 (Rotterdam)	Correct (Fz)		178	−2.13 (2.63)
		Error (Fz)		178	−4.45 (3.03)
Uncertainty induction study	Induction	Correct (FCz)	T0	29	0.84 (3.33)
		Error (FCz)	T0	29	−3.11 (4.28)
	Control	Correct (FCz)	T0	29	0.67 (3.13)
		Error (FCz)	T0	29	−3.46 (5.20)
	Induction	Correct (FCz)	T1	29	1.45 (3.28)
		Error (FCz)	T1	29	−1.99 (4.19)
	Control	Correct (FCz)	T1	29	1.30 (3.10)
		Error (FCz)	T1	29	−2.53 (5.00)

Note. For the Rotterdam sample, only Fz data are available due to different electrode layouts. For the Hamburg sample, data from channel FCz were preregistered.

× group × inhibitory IU) did not point to significant influences of the subscales of IU on ERN changes from T0 to T1. Specifically, no significant effects emerged for the time × group × prospective IU interaction ($b = 0.01$, $SE = 0.13$, $t(102) = 0.07$, $p = .942$, $R^2 = .000$) or time × prospective IU ($b = -0.02$, $SE = 0.10$, $t(102) = -0.22$, $p = .827$, $R^2 = .000$). No significant effects emerged for the time × group × inhibitory IU interaction ($b = -0.02$, $SE = 0.17$, $t(102) = -0.14$, $p = .829$, $R^2 = .000$) or time × inhibitory IU ($b = -0.14$, $SE = 0.14$, $t(102) = -1.05$, $p = .296$, $R^2 = .002$). In sum, no evidence emerged for IU (or the subscales) predicting variability in ERN changes from pre to post intervention or control condition.

4. Discussion

Previous studies suggested that associations between internalizing psychopathology and the ERN might be specified by an association of IU and the ERN (Grabowska et al., 2024; Jackson et al., 2016; Ruchensky et al., 2020; Sandre and Weinberg, 2019). The aim of this preregistered study was to test whether performance monitoring is affected by trait IU and state variations in the processing of uncertainty. Cross-sectionally, neither in an initial, preregistered sample ($N = 118$), nor in an exploratory combined sample ($N = 355$), evidence emerged for influences of IU on performance monitoring as indexed by ERN/CRN. In a pre-post design, effects of state uncertainty were tested in a subsample via an uncertainty symptom induction. Although self-reported state uncertainty was successfully increased as a result of the symptom induction, no differences in neural indices of performance monitoring were observed. Together, this preregistered, cross-sectional, well-powered, collaborative multi-site study challenges the notion of a link between trait IU and state uncertainty and the ERN.

Cross-sectional links between IU and performance monitoring have been suggested theoretically (Tanovic et al., 2018) and empirically (Grabowska et al., 2024; Jackson et al., 2016; Ruchensky et al., 2020; Sandre and Weinberg, 2019). More precisely, previous empirical studies pointed towards a negative association of inhibitory IU and the ERN (Grabowska et al., 2024; Jackson et al., 2016, but see Malbec et al., 2022; Sandre and Weinberg, 2019) while prospective IU seemed to be positively associated with the ERN (Jackson et al., 2016, but see Grabowska et al., 2024; Malbec et al., 2022; Sandre and Weinberg, 2019). Regarding the CRN, a positive association of both inhibitory IU and prospective IU was observed (Sandre and Weinberg, 2019). In the current study, we were not able to replicate any of the previously reported cross-sectional associations. Specifically, no evidence emerged for an association of prospective IU or inhibitory IU and the ERN or the CRN in our preregistered analysis, although the variability in IU and ERN/CRN was comparable to previous studies (Supplement A). Also, no evidence

Table 5
Multilevel model testing the cross-sectional effects of intolerance of uncertainty on the error-related negativity and the correct-related negativity.

Fixed effects	*b*	*SE*	95 % *CI*	*df*	*t*	*p*	R^2	BF_{10}
(Intercept)	0.33	0.40	−0.45, −1.11	228	0.84	.403		
Response	−3.95	0.32	−0.45, −3.32	228	−12.30	**<.001**	.223	3.86×10^{18}
PIU	−0.12	0.08	−0.27, 0.04	228	−1.44	.151	.012	7.27×10^{-10}
IIU	0.06	0.12	−0.18, 0.29	228	0.48	.631	.001	6.95×10^{-10}
Response × PIU	0.02	0.07	−0.10, 0.15	228	0.38	.704	.000	3.92×10^{-8}
Response × IIU	0.06	0.10	−0.13, 0.25	228	0.63	.526	.001	4.10×10^{-5}
PIU × IIU	0.00	0.02	−0.03, 0.03	228	0.30	.768	.001	5.92×10^{-6}
Response × PIU × IIU	−0.02	0.01	−0.04, 0.01	228	−1.04	.162	.004	4.10×10^{-3}
Random effects								
σ^2	4.70							
$\tau_{00\ id}$	9.53							
ICC	0.28							
$N_{\ id}$	118							
Observations	236							
Marginal R^2/conditional R^2	.245/.751							

Note. Correct-response negativity (CRN); error-related negativity (ERN); response (correct, incorrect); PIU, subscale prospective intolerance of uncertainty; IIU, subscale inhibitory intolerance of uncertainty. Quantification was mean amplitude (0–100 ms) at channel FCz with an early pre-response baseline of −500 to −300 ms; significant $p < .05$ printed in bold. $BF_{10} > 1$ indicates evidence for the inclusion of an effect while $BF_{10} < 1$ indicates evidence against the inclusion of an effect.

emerged for these associations in an exploratory, merged analysis with two supplementary samples including re-preprocessed data of the sample of Malbec et al. (2022). The absence of previously reported effects in our collaborative replication attempt suggests several possible explanations. First, previous literature might have overestimated cross-sectional effects. As theorized in Malbec et al. (2022), previous studies might have been underpowered and the effect sizes reported in previous studies might therefore have been exaggerated (Ioannidis, 2005). In the current study, the cross-sectional analysis with combined samples was powered with (1 - β) = .82 to detect effect sizes of $d = 0.11$, and .95 to detect effect sizes of $d = 0.14$. Thus, if true cross-sectional effects of IU on performance monitoring would be smaller than $d = 0.11$ or $d = 0.14$ respectively, they could not have been detected using our current, comparatively large sample. This raises the question whether smaller true effects would be of practical or clinical significance and further strengthens the argument of Malbec et al. (2022), that previous studies might have been underpowered to detect small effects of IU on performance monitoring. Further, the methods of most previous studies on IU and performance monitoring were not preregistered. In the current study, the methods including the EEG preprocessing pipeline were preregistered (https://osf.io/7crds) and applied to our confirmatory analyses as well as exploratory, merged, cross-sectional analyses. Next to preregistration and statistical power, another methodological reason that might limit the replicability of associations between IU and the ERN across studies could consist in methodological variability in the preprocessing pipelines of ERPs. At each decision node of a preprocessing pipeline, multiple defensible options are available, which introduce a multiverse of preprocessing forking paths (Clayson, 2024; Gelman and Loken, 2013). Thus, to detect the influence of these preprocessing forking paths on the processes under study, large scale collaborative projects are necessary (cf. Paul et al., 2022; Trübutschek et al., 2024).

Next to the absence of true effects or smaller true effects of IU on performance monitoring, another possible explanation could be that associations between IU and performance monitoring might only be present or increased in clinical samples. For instance, regarding the link between trait worry and the ERN, meta-analytical evidence points to clinical status as a moderator (Saunders and Inzlicht, 2020), while subclinical populations have been less consistently associated with an altered ERN (Clayson et al., 2020; Härpfer et al., 2020, 2022; Seow et al., 2020). Additionally, there is currently a scarcity of studies investigating clinical samples with a focus on transdiagnostic symptom dimensions (Riesel et al., 2023). Extending previous results on cross-sectional effects of IU on performance monitoring to clinical samples in future research might help to shed light on the possibility that cross-sectional effects of IU on performance monitoring might be specific to IU variations beyond a clinical threshold. In a similar vein, another possible explanation could be that cross-sectional effects might blur associations of broader constructs that have been shown to be associated with the ERN, such as anxious apprehension (Moser et al., 2013; Saunders and Inzlicht, 2020; Weinberg et al., 2010). While meta-analytical evidence points towards a small overall effect of trait worry on the ERN (Saunders and Inzlicht, 2020), more recent studies challenge this effect and point towards a specificity of these effects to clinical samples or a family history of internalizing psychopathology (Härpfer et al., 2020, 2022). This is in line with studies suggesting that the ERN is a more general phenotype of the internalizing/externalizing spectrum of psychopathology (Lutz et al., 2021a; Lutz et al., 2021b; Pasion and Barbosa, 2019; Riesel, 2019). Trait IU has been shown to display large correlations with trait worry (Buhr and Dugas, 2006). Given the previous evidence of anxious apprehension and the ERN, it is possible that earlier cross-sectional effects of IU and the ERN might actually be shadow correlations of true correlations between anxious apprehension and the ERN. However, none of the questionnaires that were included in the present study and capture broader constructs were significantly associated with the ERN (Supplement B). In an exploratory correlation matrix, small correlations arised between the CRN and the questionnaires PSWQ, MASQ-AA, STAI-T, and BDI-II (which in turn share variance, as indicated by the correlation matrix). Future studies could build on these effects and focus on CRN, which is underrepresented, especially in studies focusing on ΔERN (but see Riesel et al., 2023).

Alternatively, given the heterogeneous evidence on anxious apprehension and the ERN, these effects might be attributable to broader categories such as internalizing psychopathology (Pasion and Barbosa, 2019) or a family history of internalizing psychopathology (Carrasco et al., 2013; Riesel et al., 2011; Riesel et al., 2019c). Together, the absence of IU effects on performance monitoring in the current, well-powered sample raises the question whether effects of IU on the ERN have been overestimated. Although there are specific mechanisms which have been put forward (theoretically), the current study adds to the mixed empirical basis on these mechanisms. Against this background, the results of the current study can be taken to suggest that effects of IU on performance monitoring in the general population are smaller than previously observed or possibly even limited to clinical populations.

Next to testing cross-sectional effects of trait IU on the ERN and CRN, we aimed at testing specific mechanisms of possible links between state fluctuations in uncertainty and performance monitoring. The current study utilized a randomized-controlled pre-post design, in which a subsample of participants was randomized to an uncertainty symptom induction or a control condition. While the uncertainty symptom

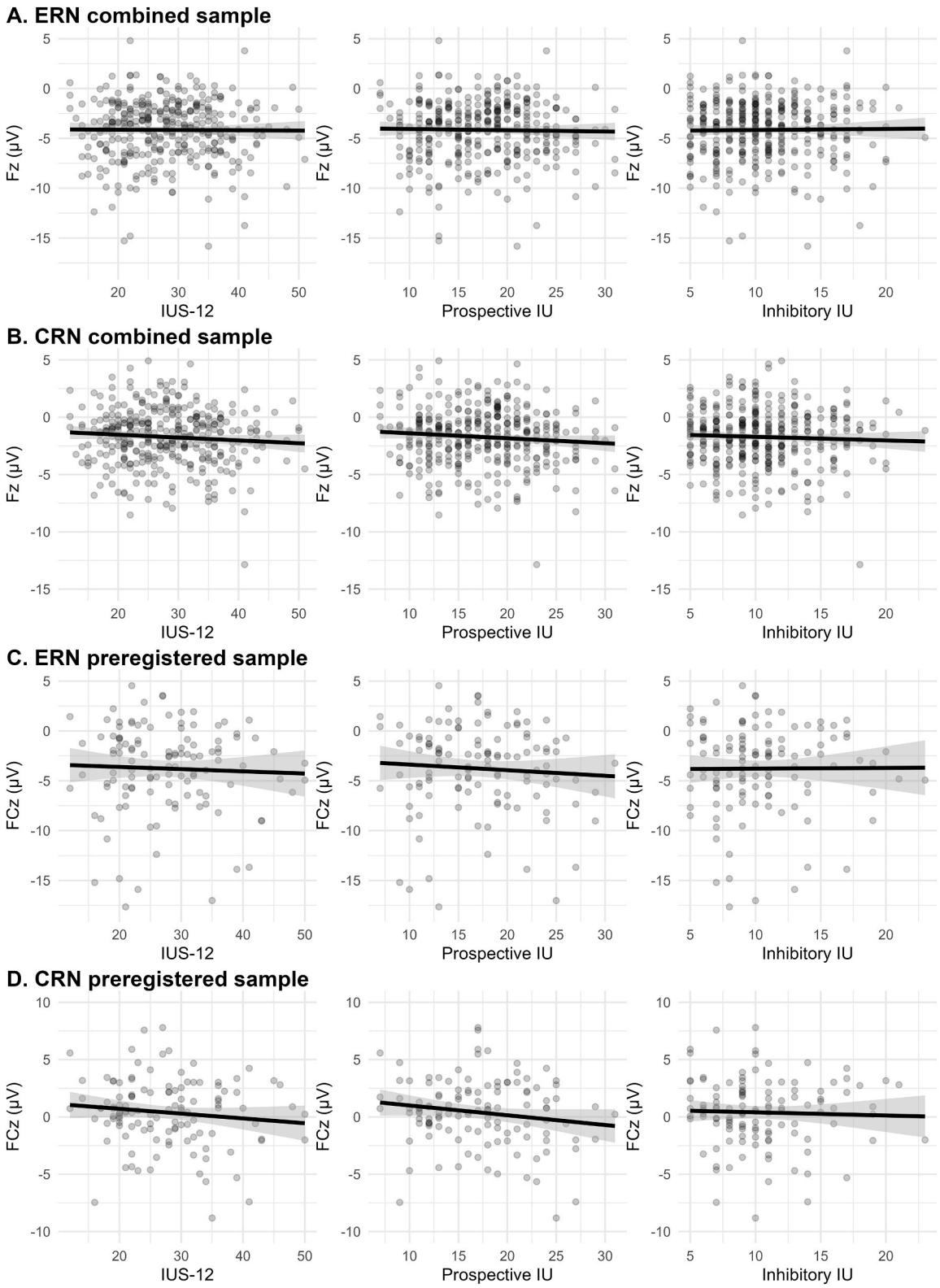


Fig. 5. Slopes of intolerance of uncertainty (IUS-12) and the subscales prospective IU and inhibitory IU for A: the error-related negativity (ERN) of the combined sample ($N = 355$), B: the correct-related negativity (CRN) of the combined sample, C: the ERN of the preregistered sample ($N = 118$), and D: the CRN of the preregistered sample.

Note. Quantification was mean amplitude 0–100 ms after a response at Fz for the combined sample and FCz for the preregistered sample. The shaded area around the slope depicts the 95 % confidence interval of the slope estimate.

Table 6
Multilevel model testing the cross-sectional effects of intolerance of uncertainty on the error-related negativity and the correct-related negativity with combined samples.

Fixed effects	*b*	*SE*	95 % *CI*	*df*	*t*	*p*	R^2	BF_{10}
(Intercept)	−1.23	0.23	−1.68, −0.79	700	−5.45	**<.001**		
Lab	−0.81	0.30	−1.39, −0.23	700	−2.74	**.006**	.015	1121.14
Response	−2.45	0.17	−2.78	700	−2.12	**<.001**	.107	1.21×10^{55}
PIU	−0.04	0.04	−0.11, 0.03	700	−1.17	.241	.003	2.31×10^{-10}
IIU	0.03	0.05	−0.07, 0.13	700	0.67	.504	.001	1.22×10^{-12}
Lab × Response	0.14	0.22	−0.29, 0.58	700	0.66	.511	.000	6.88
Response × PIU	0.02	0.03	−0.03, 0.07	700	0.68	.496	.000	2.20×10^{-8}
Response × IIU	0.03	0.04	−0.04, 0.14	700	0.81	.416	.000	6.14×10^{-8}
PIU × IIU	−0.01	0.01	−0.02, 0.01	700	−0.81	.421	.001	5.00×10^{-5}
Response × PIU × IIU	0.00	0.01	−0.01, 0.01	700	−0.76	.449	.000	1.30×10^{-8}
Random effects								
σ^2	2.09							
$\tau_{00\ id}$	5.50							
ICC	0.45							
N_{id}	355							
Observations	710							
Marginal R^2/conditional R^2	.180/.774							

Note. Correct-response negativity (CRN); error-related negativity (ERN); response (correct, incorrect); PIU, subscale prospective intolerance of uncertainty; IIU, subscale inhibitory intolerance of uncertainty. Quantification was mean amplitude (0–100 ms) at channel Fz with an early pre-response baseline of −500 to −300 ms; significant $p < .05$ printed in bold. $BF_{10} > 1$ indicates evidence for the inclusion of an effect while $BF_{10} < 1$ indicates evidence against the inclusion of an effect.

Table 7
Multilevel model testing the longitudinal effects of uncertainty on the error-related negativity and the correct-related negativity.

Fixed effects	*b*	*SE*	95 % *CI*	*df*	*t*	*p*	R^2
(Intercept)	0.67	0.75	−0.81, 2.14	222	0.89	.374	
Response	−4.13	0.53	−5.16, −3.09	222	−7.85	**<.001**	.129
Time	0.63	0.53	−0.41, 1.67	222	1.20	.231	.003
Group	0.17	1.06	−1.91, 2.25	222	0.16	.871	.000
Response × Time	0.30	0.74	−1.16, 1.77	222	0.40	.686	.000
Response × Group	0.18	0.74	−1.28, 1.65	222	0.25	.806	.000
Time × Group	−0.02	0.74	−1.48, 1.45	222	−0.02	.980	.000
Response × Time × Group	0.21	1.05	−1.86, 2.28	222	0.20	.843	.000
Random effects							
σ^2	4.01						
$\tau_{00\ id}$	12.15						
ICC	0.54						
N_{id}	58						
Observations	232						
Marginal R^2/conditional R^2	.195/.800						

Note. Correct-response negativity (CRN), error-related negativity (ERN), group (uncertainty induction, control), response (correct, incorrect), time (T0, T1); Quantification was m amplitude (0–100 ms) at electrode FCz with an early pre-response baseline of −500 to −300 ms; significant $p < .05$ printed in bold.

induction was successful in increasing ratings of state uncertainty in the intervention group but not in the control group, the effect of the uncertainty symptom induction in subjective ratings did not translate to significant changes in ERN/CRN from pre to post intervention. Further, exploratory analyses on more fine-grained associations of trait IU and ERN changes, and possible associations between variations in subjective uncertainty ratings and ERN changes did not unravel any further associations between uncertainty and the neural markers of performance monitoring. Another possible explanation of the absence of effects of state changes in uncertainty on post-intervention ERN/CRN could be that effects of state uncertainty on performance monitoring may only be apparent during (not after) an experimental symptom induction. In Jackson et al. (2015), the inclusion of unpredictable tones during a task to measure the ERN led to a significantly increased ERN in a sample of 23 participants. Further, state manipulations of other dimensions (e.g., punishment; Riesel et al., 2012) have been shown to increase the ERN. Thus, it is possible that experimental manipulations targeting the ERN are required to take place during the experimental task used to measure the ERN. In the current study, the ERN was measured before and after the uncertainty symptom induction vs. control condition (i.e., passive waiting). Symptom fluctuations might thus impact the ERN only momentarily without any carry-over effects. However, further experimental data is necessary to corroborate this idea.

Importantly, the experimental protocol to induce state uncertainty has been developed for the current, preregistered study and state symptom fluctuations attributable to the uncertainty symptom induction were not specific to subjective ratings of uncertainty. Rather, subjective ratings of state worry, need for control, and arousal were also significantly increased, while positive affect was not significantly affected by the uncertainty symptom induction. Nevertheless, this novel experimental protocol to induce state uncertainty via a modified Frank task (Frank et al., 2004) aligns with previous state uncertainty manipulations (Britton and Davey, 2014; Deschenes et al., 2010; Faleer et al., 2017; Grenier and Ladouceur, 2004; Ladouceur et al., 2000; Meeten et al., 2012; Mosca et al., 2016; Rosen and Knäuper, 2009; Tullett et al., 2014; for an overview of effect sizes see Rosser, 2019) and produced effect sizes of state uncertainty in subjective ratings that are within the range of previously reported manipulations.

Taken together, the aim of the randomized-controlled-design of the current study was to test links of uncertainty and performance monitoring via an uncertainty symptom induction. The underlying assumption was that by inducing state uncertainty (among other symptoms) a carry-over effect on neural indices of performance monitoring (i.e., ERN) would be observable. However, the ERN has previously been

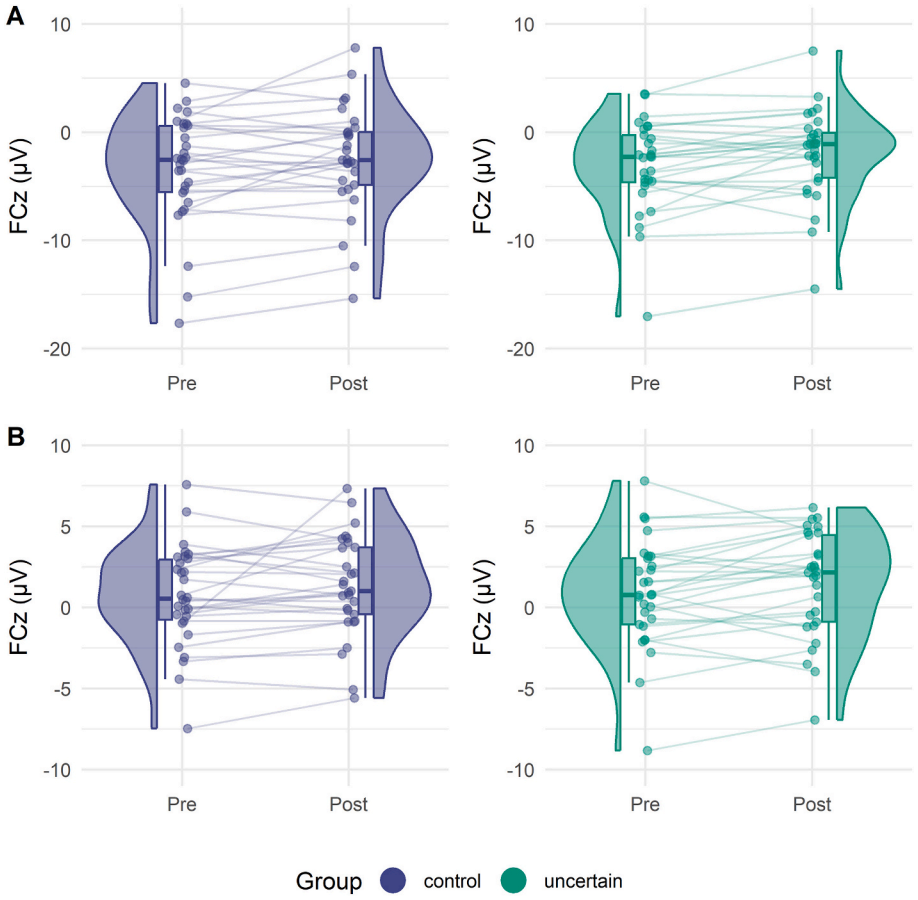


Fig. 6. Error-related negativity (A) and correct-related negativity (B) pre and post intervention for the experimental group (uncertainty induction) and control group (passive waiting).

conceptualized as a trait-like variable (e.g., Riesel et al., 2014, 2015). Also, IU is mostly conceptualized as a relatively stable personality trait (Carleton, 2016a, 2016b; Carleton et al., 2007), co-occurring with increased ERN in individuals with internalizing psychopathology, but in separate lines of research (Brown and Naragon-Gainey, 2013; Counsell et al., 2017; Gentes and Ruscio, 2011; Holaway et al., 2006; McEvoy et al., 2019; Shihata et al., 2016). The absence of effects in the pre-post design of the current study could thus be taken to suggest that the ERN might be less sensitive to short-term experimental manipulations.

The results of our study highlight several avenues for future research. First, future studies could extend knowledge on experimental symptom inductions—that have been shown to alter the ERN—by varying parameters that are more specific to one symptom dimension, e.g., by including or excluding an element of unpredictability (i.e., surprise to induce state-uncertainty) in a punishment flanker-task (Riesel et al., 2012; Riesel et al., 2019b). This would allow testing whether experimental protocols designed to alter the ERN can be augmented by the inclusion of specific state changes in symptom dimensions that represent candidate phenotypes of increased ERN. Second, more globally and in line with diathesis-stress models that focus on developmental trajectories of internalizing psychopathology (Meyer et al., 2017; Weinberg et al., 2022), observational studies that include population wide stressors could be conducted to test associations of uncertainty and the ERN. The ERN has been conceptualized as a state-independent vulnerability marker, which is corroborated by the absence of effects of the uncertainty symptom induction in the current experimental, randomized-controlled study and e.g., Härpfer et al. (2022). Therefore, population-wide stressors such as the COVID-19 pandemic might reflect global stressors with elements of unpredictability and uncertainty that are more salient and externally valid compared with experimental symptom induction protocols. In line with this, Riesel et al. (2021) found that pre-pandemic ERN was predictive of peri-pandemic internalizing symptoms in an indirect pathway mediated by peri-pandemic perceived risk and peri-pandemic stress. Together, future research could focus on disentangling the specificity of associations between symptom dimensions and the ERN by varying more specific experimental parameters and focus on longitudinal assessments of the ERN and psychopathology in naturalistic settings. This might broaden the knowledge base of the role of the ERN in developmental trajectories of internalizing psychopathology.

4.1. Limitations

The results of the present study have to be interpreted in light of several limitations. The uncertainty symptom induction might not have been potent enough to alter the ERN, i.e., to show carry-over effects on the ERN measured in the second flanker task. However, the uncertainty symptom induction led to increased ratings of state uncertainty with a large effect size of $d = 0.98$ in ratings that were conducted immediately after the symptom induction and immediately before the second flanker task. This effect size is at the upper bound the confidence interval of a meta-analytical synthesis of effect sizes in manipulations of state uncertainty ($g = 0.62$, 95 % CI[0.23, 1.00], Rosser (2019)). In this context, the uncertainty induction might not have been specific enough, since next to ratings of state uncertainty, the experimental uncertainty induction also led to increased ratings of state worry, state need for control, and arousal. Thus, any specific effects of state uncertainty on the ERN may have been confounded by concurrent increases in state worry, state need for control, and arousal, should these symptom changes influence the ERN. In developing the experimental protocol, we opted to

maximize the salience of the symptom induction for two reasons: First, we tested a young, academic sample, which might respond with more resilience to an experimental protocol aimed at increasing state uncertainty. Second, prior symptom inductions from our lab in a comparable randomized-controlled trial (Härpfer et al., 2022) did not show an impact on the ERN and the salience or potency of the symptom induction was identified as a possible limitation. Next to this, the control group was a passive waiting group and did not perform a task or intervention, while the uncertainty induction group underwent an intervention. Thereby, it is not discernible, which aspect of the uncertainty induction led to increased ratings in the state symptom dimensions uncertainty, state worry, state need for control, and arousal. Future studies could include an active control condition in which the probabilities in the Frank task and the feedback is not manipulated, to control for unspecific effects of the intervention.

Moreover, the generalizability of the results might be limited to a young, academic sample. In our preregistered sampling strategy, we only excluded participants with severe psychiatric disorders (lifetime substance-related disorder, schizophrenia spectrum disorder, bipolar disorder) to avoid confounding influences on the ERN due to underlying associations with the disorder and the ERN and potential influences of medication, or difficulties during the EEG preparation (needle phobia). Besides this exclusion, in total, $n = 18$ participants (15.25 %) of our preregistered final sample met criteria for a current or lifetime mental disorder, which suggests some degree of generalizability. However, we did not explicitly recruit a clinical sample, thus clinical inferences are limited. With respect to the experimental task, the present study employed a modified flanker task, in which participants received standardized speed feedback regardless of their actual performance. This aimed at enhancing interindividual differences, as previous research suggests that patients with internalizing psychopathology might not inherently exhibit larger ERN amplitudes, but rather show an inflexibility in downregulating their error monitoring systems under speed instructions (Riesel et al., 2019a). However, given that this study investigated an unselected sample and previous research suggests that faster response speeds can result in smaller ERN amplitudes (Falkenstein et al., 2000; Gehring et al., 1993), the standardized speed instructions used in our task may have contributed to floor effects, thereby reducing potential ERN variance in the preregistered sample. Notwithstanding these limitations, the present study holds several strengths. Cross-sectionally, we could extend the findings of Malbec et al. (2022) to show that in a student sample, effects of prospective IU and inhibitory IU could not be replicated (Jackson et al., 2016). Due to the preregistered randomized-controlled design, potential effects of state uncertainty on the ERN that might elucidate an underlying mechanistic link between IU and the ERN could be investigated. Further, by including two supplementary samples including the re-preprocessed data of Malbec et al. (2022), we could increase the sensitivity of our cross-sectional replication attempt to render effect sizes of $d = 0.14$ detectable with a likelihood of 95.54 % in $N = 355$ participants.

4.2. Conclusion

In summary, the present findings suggest that the ERN was cross-sectionally not significantly associated with individual differences in trait IU on a global or subscale level. Further, although state uncertainty could be induced via a novel state uncertainty symptom induction, these changes in state uncertainty were not significantly associated with pre-post changes in the ERN or CRN. This suggests that the ERN in subclinical participants might be insensitive both, to state changes in uncertainty and to individual differences in trait IU, thereby challenging the notion of a link between IU and the ERN. This further corroborates the role of the ERN as a trait-like neural risk marker and mirrors findings suggesting an insensitivity of the ERN to symptom changes (Riesel et al., 2014, 2015) and suggests that the link between IU and the ERN might be smaller or less robust than previous research has suggested.

CRediT authorship contribution statement

Hannes Per Carsten: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kai Härpfer:** Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Marcelo Malbec:** Writing – review & editing, Validation, Investigation, Data curation. **Matthias J. Wieser:** Writing – review & editing, Validation, Resources. **Anja Riesel:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpsycho.2024.112480.

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Supplementary Material to

"Are Errors More Aversive in an Uncertain World? Testing the Influence of Uncertainty on the Error-Related Negativity in a Randomized Controlled Trial."

Hannes Per Carsten[1*], Kai Härpfer[1], Marcelo Malbec[2], Matthias J. Wieser[2], & Anja Riesel[1]

[1]Department of Psychology, University of Hamburg, Germany

[2]Department of Psychology, Education and Child Studies, Erasmus University Rotterdam, the Netherlands

*Correspondence concerning this article should be addressed to Hannes Per Carsten, Department of Psychology, Universität Hamburg, Von-Melle-Park 11, 20146 Hamburg, Germany.

E-Mail: hannes.carsten@uni-hamburg.de

Table of Contents:

Supplement A: Comparison of variability in Error-Related Negativity (ERN) and Intolerance of Uncertainty across previous studies 3

Supplement B: Correlation matrix of error-related negativity, correct-related negativity and questionnaires 4

Supplement A: Comparison of variability in Error-Related Negativity (ERN) and Intolerance of Uncertainty across previous studies

Study	*N*	ERN (μV) *M* (*SD*)	CRN (μV) *M* (*SD*)	IUS-12 *M* (*SD*)	P-IU *M* (*SD*)	I-IU *M* (*SD*)
Jackson et al., 2016	61	0.81 (5.74)	6.83 (5.29)	27.25 (9.63)	17.19 (6.51)	9.75 (3.73)
Sandre & Weinberg, 2019	62	-0.97 (5.85)	7.38 (3.63)		20.40 (5.21)	12.13 (4.05)
Ruchensky et al., 2020	100	1.12 (6.64)	7.13 (6.88)	29.35 (7.98)		
Malbec et al., 2022	188	0.28 (3.69)	3.55 (2.56)	29.38 (7.93)	18.23 (5.14)	11.15 (3.65)
Grabowska, 2024*	130	-4.48 (3.93)			3.06 (0.81)	2.43 (1.00)
Preregistered sample	118	-3.78 (4.42)	0.39 (2.96)	27.62 (8.36)	17.18 (5.43)	10.45 (3.88)
Supplementary Sample 1 (Hamburg)	59	-3.89 (2.58)	-1.21 (2.22)	25.05 (6.84)	15.75 (4.44)	9.31 (3.35)
Supplementary Sample 2 (Rotterdam	178	-4.45 (3.03)	-2.13 (2.63)	29.37 (7.84)	18.24 (5.07)	11.12 (3.63)

Note. ERN, Error-Related Negativity; CRN, Correct-Related Negativity. IUS-12, Intolerance of Uncertainty Scale; P-IU, subscale prospective intolerance of uncertainty; I-IU, subscale inhibitory intolerance of uncertainty.

Jackson, F., Nelson, B. D., & Hajcak, G. (2016). The uncertainty of errors: Intolerance of uncertainty is associated with error-related brain activity. Biological Psychology, 113, 52–58. https://doi.org/10.1016/j.biopsycho.2015.11.007; Sandre, A., & Weinberg, A. (2019). Neither wrong nor right: Theta and delta power increase during performance monitoring under conditions of uncertainty. International Journal of Psychophysiology, 146, 225–239. https://doi.org/10.1016/j.ijpsycho.2019.09.015; Malbec, M., Hindmarsh, J. N., Jongerling, J., Franken, I. H., & Wieser, M. J. (2022). No intolerance of errors: The effect of intolerance of uncertainty on performance monitoring revisited. International Journal of Psychophysiology, 179, 77–88. https://doi.org/10.1016/j.ijpsycho.2022.07.001; Grabowska, A., Sondej, F., & Senderecka, M. (2024). A Machine Learning Study of Anxiety-related Symptoms and Error-related Brain Activity. Journal of Cognitive Neuroscience, 1–26. https://doi.org/10.1162/jocn_a_02126

*In this study P-IU and I-IU scores were divided by the number of items.

Supplement B: Correlation matrix of error-related negativity, correct-related negativity and questionnaires

Variable	1	2	3	4	5	6	7	8	9	10
1. ERN	-									
2. CRN	.72 ***	-								
3. IUS-12	-.04	-.12	-							
4. P-IU	-.07	-.16	.93***	-						
5. I-IU	.01	-.04	.85***	.60***	-					
6. PSWQ	-.09	-.21*	.55***	.49***	.50***	-				
7. MASQ-AA	-.14	-.21*	.31***	.24**	.34***	.49***	-			
8. STAI-T	-.13	-.23*	.66***	.55***	.65***	.80***	.49***	-		
9. OCI-R	-.01	-.14	.41***	.37***	.36***	.38***	.37***	.48***	-	
10. BDI-II	-.14	-.26**	.45***	.35***	.47***	.52***	.46***	.66***	.37***	-
11. AUDIT	-.08	-.08	.02	-.03	.09	.02	.21*	.09	.17	.08

Note. $N = 118$. Abbreviations: AUDIT, alcohol use disorders identification test; BDI-II, Beck Depression Inventory II; CRN: Correct-related negativity; ERN: Error-related negativity; IUS, Intolerance of Uncertainty Scale-12; PIU, subscale prospective intolerance of uncertainty; IIU, subscale inhibitory intolerance of uncertainty; MASQ-AA, Mood and Anxiety Symptom Questionnaire; OCI-R, Obsessive-Compulsive Inventory; PSWQ, Penn State Worry Questionnaire; STAI-T, State-Trait-Anxiety Inventory (Trait Subscale). * indicates $p < .05$, ** indicates $p < .01$, *** indicates $p < .001$

Study 3

Don't Worry, It Won't Be Fine. Contributions of Worry and Anxious Arousal to Startle Responses and Event-Related Potentials in Threat Anticipation.

Hannes Per Carsten, Kai Härpfer, Brady Nelson, Norbert Kathmann, & Anja Riesel

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RESEARCH ARTICLE

Don't worry, it won't be fine. Contributions of worry and anxious arousal to startle responses and event-related potentials in threat anticipation

Hannes Per Carsten[1] · Kai Härpfer[1] · Brady D. Nelson[2] · Norbert Kathmann[3] · Anja Riesel[1]

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Abstract

A widely shared framework suggests that anxiety maps onto two dimensions: anxious apprehension and anxious arousal. Previous research linked individual differences in these dimensions to differential neural response patterns in neuropsychological, imaging, and physiological studies. Differential effects of the anxiety dimensions might contribute to inconsistencies in prior studies that examined neural processes underlying anxiety, such as hypersensitivity to unpredictable threat. We investigated the association between trait worry (as a key component of anxious apprehension), anxious arousal, and the neural processing of anticipated threat. From a large online community sample ($N = 1{,}603$), we invited 136 participants with converging and diverging worry and anxious arousal profiles into the laboratory. Participants underwent the NPU-threat test with alternating phases of unpredictable threat, predictable threat, and safety, while physiological responses (startle reflex and startle probe locked event-related potential components N1 and P3) were recorded. Worry was associated with increased startle responses to unpredictable threat and increased attentional allocation (P3) to startle probes in predictable threat anticipation. Anxious arousal was associated with increased startle and N1 in unpredictable threat anticipation. These results suggest that trait variations in the anxiety dimensions shape the dynamics of neural processing of threat. Specifically, trait worry seems to simultaneously increase automatic defensive preparation during unpredictable threat and increase attentional responding to threat-irrelevant stimuli during predictable threat anticipation. The current study highlights the utility of anxiety dimensions to understand how physiological responses during threat anticipation are altered in anxiety and supports that worry is associated with hypersensitivity to unpredictable, aversive contexts.

Keywords Anxiety dimensions · Startle reflex · Event-related potentials · NPU-threat test · Anxious apprehension · Threat anticipation · Uncertainty · Unpredictability

Introduction

Anxiety disorders are prevalent (Baxter et al., 2013), highly comorbid (Kessler et al., 2005; Stein et al., 2017), and impose an immense burden of disease on the affected individuals (Baxter et al., 2014; Wittchen et al., 2011). This underscores the importance of studying the underlying mechanisms that contribute to the development and maintenance of anxiety disorders. Yet, shortcomings emerge from studies trying to identify these underlying mechanisms of anxiety by using categorical approaches (Lang et al., 2016; Marin et al., 2020). Comorbidity is often unattended to and findings are rarely disorder-specific (Lang et al., 2016). This calls for approaches that examine transdiagnostic symptom dimensions to study anxiety symptomatology, rather than categorical and disorder-specific analyses. Recent transdiagnostic research endeavors guided by the principles of the Research Domain Criteria (RDoC; Insel et al., 2010) have begun to illuminate the underlying mechanisms of more specific transdiagnostic phenotypic expressions of anxiety (Duits et al., 2015; Janiri et al., 2020; Lang et al., 2016; Sharp et al., 2015), such as hypersensitivity to unpredictable

✉ Hannes Per Carsten
hannes.carsten@uni-hamburg.de

[1] Department of Psychology, University of Hamburg, Von-Melle-Park 11, 20146 Hamburg, Germany

[2] Department of Psychology, Stony Brook University, Stony Brook, NY, USA

[3] Department of Psychology, Humboldt University of Berlin, Berlin, Germany

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threat (Gorka et al., 2017). However, how the underlying mechanisms of anxiety disorders manifest themselves across units of analysis (e.g., self-report and psychophysiology; Cuthbert, 2014) remains vague. Unraveling the interplay of the underlying mechanisms of anxiety across units of analysis could be used to tailor interventions to individual anxiety symptom profiles (Sharp et al., 2015). Ultimately, this could help to alleviate the burden of disease generated by anxiety disorders.

Among various frameworks modelling anxiety symptomatology, one largely shared decomposition of anxiety symptomatology proposes two psychologically and neurally distinct dimensions (Cox et al., 2010; Heller et al., 1997; Lang et al., 2016; Sharp et al., 2015). First, *anxious apprehension*—a trait that can condense into an emotional state of anxiety and symptoms of worry—describes the tendency for verbal, future-oriented rumination characterized by a perceived inability to predict, control, or cope with the anticipated events (Barlow, 1991; Heller et al., 1997). Second, the trait *anxious arousal*—corresponding to emotional states of panic and fear—captures the propensity to experience symptoms of physiological hyperarousal and somatic tension when faced with even mildly threatening stimuli (Clark and Watson, 1991; Sharp et al., 2015; Watson et al., 1995). Anxious apprehension and anxious arousal are distinguishable but not distinct dimensions (Engels et al., 2007). They co-occur (Sharp et al., 2015) but differ in their clinical manifestations. Anxious apprehension is phenotypically predominant in patients with obsessive-compulsive disorder and patients with generalized anxiety disorder (Cox et al., 2010; Krueger, 1999). Anxious arousal is more pronounced in focal fears (e.g., specific phobia; Lang et al., 2016). The anxiety dimensions of anxious apprehension and anxious arousal could provide a theoretical framework that maps different phenotypic expressions of anxiety disorders. Considering the anxiety dimensions as a theoretical framework in studies could aid with integrating heterogeneous findings across anxiety-disorder categories and facilitate to reveal the underlying mechanisms. Anxious apprehension and anxious arousal are primarily measured via self-report (Sharp et al., 2015). In the current study, we operationalized anxious apprehension via the central symptom component worry as a trait-variable (Glöckner-Rist and Rist, 2014; Meyer et al., 1990; Sharp et al., 2015). We aimed at testing the correlates of self-reported individual differences in worry and anxious arousal in peripheral physiology and neural processing (Sharp et al., 2015).

Therefore, we examined associations between worry, anxious arousal, and responses to the anticipation of predictable and unpredictable threat relative to safety by using the NPU-threat test (Grillon et al., 2004; Nelson and Shankman, 2011; Schmitz and Grillon, 2012). The NPU-threat test enables differentiating responses to temporally predictable threat from responses to temporally unpredictable threat. In the neutral condition, participants never receive an aversive stimulus. In contrast, in the predictable condition, the participants receive a temporally predictable aversive stimulus signaled by a cue. Responses in the predictable condition are closely linked to the emotional states of fear (i.e., phasic response to predictable imminent threat; Schmitz and Grillon, 2012). In the unpredictable condition, participants may receive an unsignaled, aversive stimulus at any time. Responses in the unpredictable condition are thought to reflect emotional states of anxiety and defensive preparedness (i.e., sustained tension due to the unpredictability of threat; Schmitz and Grillon, 2012). Thus, the NPU-threat test enables investigating possible links between worry and anxious arousal and the corresponding states of anxiety (unpredictable threat condition) and fear (predictable threat condition).

Previous studies using the NPU-threat test mostly measured the eyeblink component of the startle reflex (Lieberman, Stevens, et al., 2017b; Nelson and Shankman, 2011; Schmitz and Grillon, 2012). The startle reflex captures defensive responding (Blumenthal et al., 2005; Hamm et al., 1993), is initiated in the nucleus reticularis pontis caudalis, and is modulated by affective information from the centromedial amygdala (Kuhn et al., 2020). Compared with the neutral condition, startle responses in the unpredictable condition are usually increased (anxiety-potentiated). To a lesser extent, startle responses in the predictable condition are usually increased compared with the neutral condition (fear-potentiated; Bradford, Kaye, and Curtin, 2014; MacNamara and Barley, 2018; Schmitz and Grillon, 2012). Fear-potentiated startle might be sensitive to the modality of the aversive stimulus, as Ferry and Nelson (2020) found decreased startle in anticipation of predictable screams compared with shocks. To capture the temporal dynamics of the neural processing of threat stimuli, previous NPU-studies used the event-related potential (ERP) components N1 and P3 (Carsten et al., 2022; Ferry and Nelson, 2020; MacNamara and Barley, 2018; Nelson, Hajcak, et al., 2015a; Nelson, Hodges, et al., 2015b; Stevens et al., 2018). The N1 is observable as a frontocentral negative deflection approximately 100 ms after stimulus onset. Locked to acoustic startle probes (i.e., probe locked), the N1 likely reflects early sensory processing (Cuthbert et al., 1998) in auditory cortical areas (Ford et al., 2016; Verkindt et al., 1995). The P3 is observable as a positive centroparietal deflection approximately 300 ms after stimulus onset and likely reflects attentional allocation at a later stage of the information-processing cascade (Polich, 2012). Subcomponents of the P3 are theorized to originate from frontal lobe activation (P3a) and tempoparietal activation, respectively (P3b; Polich, 2007, 2012). Previous studies found elevated probe locked N1 specific to the unpredictable condition of the NPU-threat test (Ferry and Nelson, 2020; Nelson, Hajcak, et al., 2015a; Nelson and Hajcak, 2017;

but not in MacNamara and Barley, 2018). These studies also found evidence for a suppressed probe locked P3 in the unpredictable condition and predictable condition relative to the neutral condition, which presumably reflects attentional allocation to the task rather than to the startle probe (Ferry and Nelson, 2020; MacNamara and Barley, 2018; Nelson, Hajcak, et al., 2015a; Nelson and Hajcak, 2017; but see Stevens et al., 2018). Taken together, the probe locked N1 seems to be more closely linked to unpredictable threat anticipation, whereas the probe locked P3 might be insensitive to threat predictability (Nelson, Hajcak, et al., 2015a). In the present study, we included startle and probe locked N1 and P3 to elucidate different aspects and the temporal dynamics of threat processing and to examine their association to individual differences in trait worry and anxious arousal.

Previous research on possible connections between anxiety dimensions and the neural basis of threat processing is scarce. We derived indications from theoretical reasoning as well as from clinical and subclinical studies focusing on the anxiety dimensions. From a theoretical perspective, anxious apprehension is linked to states of worry (Sharp et al., 2015), which in turn is considered a coping strategy for unpredictability and uncertainty (Einstein, 2014; Sibrava and Borkovec, 2006). Thus, unpredictable situations might be more aversive for individuals with increased trait worry (Carleton, 2016b; Einstein, 2014). This increased aversion, in turn, could manifest itself in increased responses to unpredictable threat. In contrast, anxious arousal corresponds to physiological hyperreactivity (Sharp et al., 2015), which is associated with more focal fears (specific phobia; Lang et al., 2016). Based on this, increased physiological responses to predictable threat could be expected as a function of anxious arousal. A clinical study of anxiety disorders characterized by worry (generalized anxiety disorder; Cox et al., 2010; Goodwin et al., 2017; Krueger, 1999) found on a trend level elevated startle responses in the unpredictable condition (Grillon et al., 2017). In contrast, other studies did not find an effect of generalized anxiety disorder on startle responses (Gorka et al., 2017; Grillon et al., 2009). Regarding disorders predominantly characterized by anxious arousal, elevated startle responses to unpredictable but not predictable threat were found in patients with specific phobia (Gorka et al., 2017). This contradicts the above described theoretically derived assumption that anxious arousal might be insensitive to threat predictability. Dimensional studies following the RDoC principles (Insel et al., 2010) focus on individual differences in anxiety-related traits. Whereas Nelson and Shankman (2011) found no significant associations of worry and startle responses in the unpredictable condition in a nonclinical sample, Rutherford et al. (2020) found this association specifically in individuals with a history of anxiety disorders. Previous studies associated cognitive concerns—a trait that is linked to worry (Wheaton et al., 2012, but cf. Olthuis et al., 2014)—with attenuated startle responses in the unpredictable condition (Nelson, Hodges, et al., 2015b), but no evidence emerged for probe locked N1 or P3 (Stevens et al., 2018). To the best of our knowledge, individual differences in self-reported anxious arousal have not yet been tested in the context of the NPU-threat test. In summary, the delineated findings from clinical and subclinical studies are contradictory, thereby impede precise predictions, and thus highlight the need for further research. Furthermore, prior studies have not directly examined worry and anxious arousal simultaneously. Thus, the heterogeneity of findings in clinical studies might be attributable to individual differences in these transdiagnostic anxiety dimensions. Yet, we lack knowledge on the isolated effects and possible interactions of these dimensions. Because of the heterogeneity of theoretical predictions and mixed empirical findings, we did not formulate directional hypotheses regarding links of worry and anxious arousal to physiological responses in the NPU-threat test.

The present study used self-report measures of worry and anxious arousal, the NPU-threat test, and physiological outcome measures. This aims to elucidate whether worry and anxious arousal influence physiological responses (startle and ERP components N1 and P3) in the anticipation of threat. Examining both anxiety dimensions simultaneously allows us to test possible interaction effects of the anxiety dimensions on threat anticipation. This might advance our understanding of how anxious apprehension and anxious arousal, as central dimensions of anxiety, influence the temporal dynamics of the neural processing of aversive stimuli in the context of predictable and unpredictable threat.

Methods

Participants

An online screening sample (N = 1,603, 72.5% female, 27.5% male, aged 18-65, M = 29.06, SD = 9.29) was recruited via university mailing lists and social networks. The online screening sample only completed questionnaires capturing individual differences in the anxiety dimensions, i.e., the Penn State Worry Questionnaire (PSWQ; 16 items, 5-point Likert scale 1-5, “not at all typical of me” to “very typical of me”; N = 1,603; Glöckner-Rist and Rist, 2014; Meyer et al., 1990) to measure trait worry and the anxious arousal subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-AA; 17 items, 5-point Likert scale 1-5, N = 1,603; Watson and Clark, 1991). To perform the NPU-threat test, we invited 136 participants from the online screening sample into the laboratory (Fig. 1). These participants were selected from the online screening sample based on their PSWQ and MASQ-AA values. Specifically, we

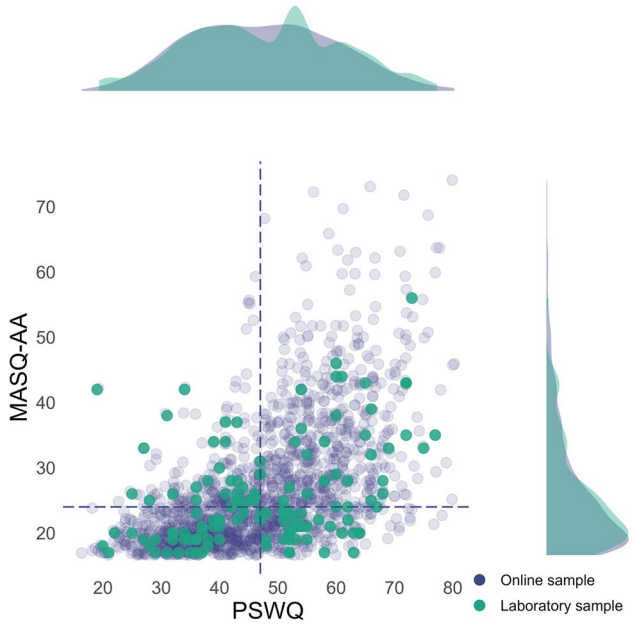


Fig. 1 Scatter plots and density distribution of PSWQ and MASQ-AA scores. *Note*. From an online screening sample (N = 1,603), we invited N = 136 participants to the laboratory to perform the NPU-threat test while we collected psychophysiological data. The recruitment was based on the median of the questionnaires operationalizing the anxiety dimensions, i.e., Penn State Worry Questionnaire (PSWQ, *Mdn* = 47, dashed vertical line) and the anxious arousal subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-AA, *Mdn* = 24, dashed horizontal line). To obtain equal sample sizes in each group of the median based 2 (PSWQ: high vs. low) × 2 (MASQ-AA: high vs. low) design, we oversampled participants in whom one dimension was more pronounced than the other

formed a 2 (PSWQ: high vs. low) × 2 (MASQ-AA: high vs. low) design based on median splits of the online screening sample (PSWQ *Mdn* = 47, MASQ-AA *Mdn* = 24; Härpfer et al., 2020; Kausche et al., 2022). During recruiting—to obtain equal sample sizes in each group of the median based 2×2 design—we oversampled participants from the online sample in whom one dimension was more pronounced than the other. This optimizes the variance distribution and facilitates disentangling possible interaction effects (Smith et al., 2016; Zambrano-Vazquez and Allen, 2014) but does not result in distinct groups (Fig. 1); therefore, we analyzed the data dimensionally. The sampling strategy lowered the correlation between PSWQ and MASQ-AA from $r = 0.56$ (online screening sample, $p < .001$) to $r = 0.36$ (laboratory sample, $p < .001$). The age of the 136 participants ranged from 18–62 years ($M = 28.78$, $SD = 9.50$), 63% of the participants identified as female and 37% identified as male.

Exclusion criteria encompassed lifetime neurological diseases, bipolar disorder, schizophrenia spectrum disorder, or substance-related disorder assessed via clinical screening (Wittchen et al., 1997). Participants were further excluded for the intake of benzodiazepines 1 week before testing or the intake of neuroleptics 3 months before testing, assessed via self-report. Participants gave written, informed consent before participation. The ethics committee of the Humboldt-Universität zu Berlin approved the study as being in accordance with the Declaration of Helsinki (World Medical Association, 2013).

Questionnaires

In the online sample, the PSWQ ($M = 47.10$, $SD = 12.46$, $N = 1{,}603$) showed good internal consistency ($\alpha = 0.93$), akin to the MASQ-AA ($M = 26.57$, $SD = 9.59$, $\alpha = 0.90$). In the laboratory sample, the PSWQ scores ranged from 19-77 ($M = 47.62$, $SD = 13.28$), the MASQ-AA scores ranged from 17–56 ($M = 25.79$, $SD = 8.12$; Fig. 1). In addition to the PSWQ and MASQ-AA, the laboratory sample completed the State-Trait-Anxiety Inventory measuring trait anxiety (STAI-T; $M = 38.70$, $SD = 9.25$, 20 items, 4-point Likert scale, 1-4, $\alpha = 0.92$, $N = 136$; Spielberger et al., 1983; Laux, 1981) and the Obsessive-Compulsive Inventory Revised measuring obsessive-compulsive symptoms (OCI-R; $M = 12.50$, $SD = 9.75$, 20 items, 5-point Likert scale 0-4, $\alpha = 0.88$, $N = 136$; Foa et al., 2002; Gönner et al., 2007). Furthermore, depressive symptoms were measured using the Beck Depression Inventory (BDI-II; $M = 7.71$, $SD = 7.15$, 21 items, 4-point Likert scale 0-3, $\alpha = 0.89$, $N = 136$; Beck et al., 1996; Hautzinger et al., 2006).

Task and stimuli

The participants completed the task in a dimly lit cabin, shielded from auditory and electromagnetic noise. Visual stimuli were presented on a 19-inch LCD monitor (Dell, 1907 FPV, 1,280 x 1,024 pixels, 60-Hz refresh rate) in a viewing distance of approximately 65 cm using Presentation Software version 20.2 (Neurobehavioral Systems, Inc., Albany, California). We used the countdown version of the NPU-threat test (Nelson and Shankman, 2011; Schmitz and Grillon, 2012; Fig. 2). Each condition (i.e., neutral, predictable, unpredictable) was presented twice, resulting in two orders (PNUPNU or UNPUNP) which were randomized across participants. A numerical countdown counting from five to one served as the threat cue (1 s per digit), and a black screen stating the current condition served as the interstimulus interval (i.e., cue offset to the onset of the subsequent cue, 12 ± 3 s). Each condition included 9 cues (i.e., 5 interstimulus intervals and 4 countdowns) and a black screen (10 s) separated the conditions. A female scream delivered through speakers in front of the participant (100 dB, 1 s) paired with the picture of the face of a fearful woman served as the aversive stimulus (NimStim image 01F; Tottenham et al., 2009). Four aversive stimuli occurred per condition

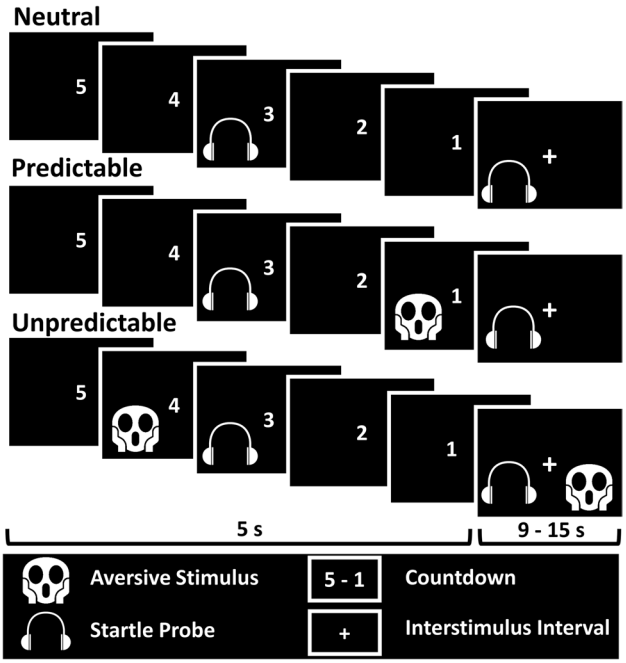


Fig. 2 NPU-threat test. *Note.* In the neutral condition, the countdown was never followed by the aversive stimulus (100 dB, auditory scream paired with the picture of a fearful face, image 01F from NimStim Tottenham et al. (2009)). In the predictable condition, the aversive stimulus occurred every time the countdown reached "1". In the unpredictable condition, the aversive stimulus could occur at any time during the countdown or the interstimulus interval

(i.e., predictable and unpredictable). In the predictable condition, the aversive stimulus occurred when the countdown reached "1" (in 100% of the presentations), but not during the presentation of the interstimulus interval. In the unpredictable condition, the aversive stimulus could occur at any time during the interstimulus interval (5.5 ± 2.5 s, in 40% of the presentations) and countdown (4.2 ± 0.5 s, in 50% of the presentations). Thus, the temporal predictability of the aversive stimulus was manipulated. Headphones delivered startle probes to elicit the startle reflex in 75% of the interstimulus intervals and countdowns. The startle probes consisted of 93 dB bursts of white noise with a duration of 50 ms (rise/fall time < 1 ms). Before the experiment, the participants received 6 acoustic startle probes to allow an initial startle habituation (Blumenthal et al., 2005).

Startle recording and processing

The eyeblink component of the startle response was recorded as electromyographic (EMG) signal measuring the contraction of the left orbicularis oculi muscle. Therefore, we attached one Ag/AgCl electrode (sensor Ø = 4 mm) vertically in line with the pupil, as close to the palpebrae inferior as possible and placed another electrode 1.5 cm laterally at the same horizontal level.

EMG data were recorded using BrainVision Recorder 2.1 and a 16-channel BrainAmp amplifier (Brain Products GmbH, Gilching, Germany) with a sampling rate of 1,000 Hz and an online band-pass filter (0.01–1,000 Hz). EMG data were preprocessed and scored offline by using BrainVision Analyzer 2.2 (Brain Products GmbH, Gilching, Germany). A band-pass filter (28–500 Hz, 24 dB/octave roll off) was applied before rectification and baseline-correction (50 ms interval before startle probe onset). Subsequently, a moving average of 9 ms integrated the data. Amplitudes of the startle EMG signal were scored manually from onset to peak in a response latency window of 20 to 120 ms after startle probe onset. The response onset was defined as a visually distinguishable difference from the baseline (−50 to 20 ms relative to the startle probe). If a response onset was detected, the peak was defined as the highest first peak in a peak window 25 to 150 ms relative to the startle probe. If no reaction emerged in the response latency window, the segment was scored as zero and was included into the analyses (M = 33.64%, SD = 27.18%; Blumenthal et al., 2005). If a voluntary or spontaneous blink occurred in the interval −50 ms to 20 ms relative to the startle probe onset, the reaction was scored as missing and excluded from the analyses (M = 6.78%, SD = 5.69%; Blumenthal 2005). The single trial startle responses were entered into the analyses without aggregation (participant's individual trials M = 33.66, Mdn = 34, SD = 2.00). Internal consistency of the startle responses was calculated by using Cronbach's alpha based on single trials for each cue within each condition and ranged from α = 0.868 to α = 0.942. An independent rater blinded to the experimental conditions repeated the manual scoring. To determine interrater reliability, the data were aggregated per cue (countdown, interstimulus interval) in each experimental condition (neutral, predictable, unpredictable). Krippendorff's α was calculated using the R package "krippendorffsalpha" (Hughes, 2021). Between the raters, the reliability was near perfect (α = 0.997, 95% confidence interval [CI] [0.996, 0.997]; Hughes, 2021).

Electroencephalography recording and processing

Electroencephalographical (EEG) activity was measured with 60 concentric and equidistant Ag/AgCl scalp electrodes (Easycap, Herrsching, Germany) with additional external electrodes placed at the nasion, the neck, and the left infraorbital site. The ground electrode was positioned on the right cheek. Electrode Cz was the recording reference. All impedances were kept <5 kΩ. Continuous EEG signals were digitized at a sampling rate of 1,000 Hz with two 32-channel BrainAmp amplifiers (Brain Products GmbH, Gilching, Germany) and recorded with a band-pass filter of 0.1 to 250 Hz.

Raw data were preprocessed using the software Brain Vision Analyzer 2.2 (Brain Products GmbH, Gilching, Germany) and were digitally filtered with low and high cutoffs of 0.1 and 30 Hz, respectively, and a notch filter of 50 Hz. A semiautomatic, independent component analysis (ICA) was used to correct for vertical and horizontal eye movement artifacts. Before segmentation, electrodes were re-referenced to a common average reference. Subsequently, epochs of 1,000 ms starting at −200 ms relative to the startle probe onset were extracted. The epochs were baseline corrected (−200 ms to startle probe onset) after artifact rejection. Artifacts were defined as an absolute voltage range in a segment exceeding 300 µV, or a voltage step between consecutive data points exceeding 50 µV, or a voltage difference of less than 0.5 µV within a 100-ms interval (Nelson, Hajcak, et al., 2015; Nelson and Hajcak, 2017). Additionally, we visually inspected the data to detect and reject remaining artifacts. Artifact rejection caused an average data loss of 0.11% (*SD* = 0.38), i.e., on average, less than 1 of 36 trials per participant was contaminated with artifacts, and no participant was excluded from the EEG data analyses due excessive artifacts or equipment failure. The exclusion criterion was less than 50% usable trials in at least one experimental condition (i.e., neutral, predictable or unpredictable; Nelson, Hajcak, et al., 2015a; Nelson and Hajcak, 2017). Next, the epochs were averaged per cue (interstimulus interval, countdown) separately for each condition (neutral, predictable, unpredictable) within each participant. This aggregation left 6 data points per participant per ERP component (i.e., N1 and P3).

We scored the ERPs based on grand-averaged waveforms and topographical distribution (Supplement H: Figure S2): The probe N1 was maximal at electrode FCz between 120–170 ms and was quantified as ±25 ms area around the individual peak. The probe P3 was maximal at the electrode Pz and was scored as mean activity 300–370 ms after startle probe onset. To determine split half reliability, we calculated Spearman-Brown corrected correlations of odd and even trials for each condition (i.e., neutral, predictable, and unpredictable). For N1, these ranged from $r = 0.88$ to 0.90. For P3 these ranged from $r = 0.61$ (predictable condition) to $r = 0.80$ (neutral and unpredictable condition).

Data analysis

We analyzed the data using R version 4.0.3 (R Core Team, 2020) and RStudio version 1.3.1093 (RStudio Team, 2020). A *p*-value of .05 formed the significance threshold. Multilevel regression models (MLM) were conducted for each outcome measure separately (startle, N1, P3) using the lme4 package (Bates et al., 2015). MLMs hold three advantages for the present data structure. First, the questionnaires (PSWQ and MASQ-AA) are analyzed continuously without forming artificial groups. Second, random effects can model individual differences in absolute amplitude. Raw EMG startle data require no standardization and variations in the within-person effects can be modelled using random effects (i.e., via random intercepts). Third, no data aggregation is necessary for the EMG data, which increases statistical power (Hox et al., 2017). Note, that data on ERPs were aggregated within each participant per cue per condition of the NPU-threat test because of low signal-to-noise ratio in single trial EEG data. The intraclass correlation (ICC) was estimated from the null models, which indicates the proportion of the total variance explained by the grouping structure in the population (Hox et al., 2017). The models were estimated by using maximum likelihood estimation and an unstructured covariance matrix. For the final models, the individual amplitudes of single trial startle and aggregated ERPs (level 1) to each cue and condition were nested within the respective participant (level 2). Fixed effects included the unweighted effect-coded level 1 (i.e., within participant) predictors condition (neutral, predictable, unpredictable) and cue (interstimulus interval, countdown). For condition, neutral was the reference category, for cue, interstimulus interval was the reference category. Individual PSWQ and MASQ-AA values were grand-mean centered and entered as level 2 (i.e., between participant) predictors. The predictors PSWQ and MASQ-AA were entered into the models together. Thus, any significant cross-level interaction involving PSWQ or MASQ-AA suggests specificity of that questionnaire relative to the other questionnaire. Semipartial R^2 indicates the partial effect sizes for each model parameter (Edwards et al., 2008; Jaeger, 2017). A maximal random approach was used to model random effects (Barr et al., 2013). The random effects included random intercepts for each individual participant, as models with random slopes for condition failed to converge. Significant cross-level interactions, including PSWQ or MASQ-AA, were followed up by pairwise comparisons of the PSWQ or MASQ-AA slopes for each level of the interacting factorial predictor (Russell et al., 2021). The confidence intervals and *p*-values were corrected for multiple comparisons by using the Tukey method. Equation 1 depicts the general model in Wilkinson notation.

$$\text{Amplitude} \sim \text{Condition} * \text{Cue} * \text{PSWQ} * \text{MASQ AA} + (1 \mid \text{Participant}) \quad (1)$$

Results

Startle

The statistical details of the results for startle responses are shown in Table 1 (for descriptive statistics see Supplement

Table 1 Multilevel regression models predicting raw startle responses to the NPU-threat test

Fixed effects	*b*	*SE*	95% CI	*df*	*t*	R^2
Intercept	32.36	4.03	24.46, 40.27	132	8.02	
Countdown	−0.63	0.59	−1.79, 0.52	4422	−1.07	.000
Predictable	−9.06	0.84	−10.70, −7.42	4422	−10.83	.026***
Unpredictable	16.15	0.93	14.52, 17.78	4422	19.37	.078***
PSWQ	0.26	0.32	−0.37, 0.88	132	0.81	.007
MASQ	−0.27	0.56	−1.36, 0.82	132	−0.49	.002
Countdown × Predictable	−2.44	0.84	−4.08, −0.80	4422	−2.92	.002**
Countdown × Unpredictable	−0.12	0.83	−1.76, 1.51	4422	−0.15	.000
Predictable × PSWQ	−0.15	0.07	−0.27, −0.02	4422	−2.21	.001*
Predictable × MASQ	−0.30	0.12	−0.52, −0.07	4422	−2.58	.001**
Unpredictable × PSWQ	0.36	0.07	0.26, 0.51	4422	5.90	.008***
Unpredictable × MASQ	0.25	0.11	0.03, 0.48	4422	2.22	.001*
PSWQ × MASQ	0.06	0.03	0.01, 0.12	132	2.15	.047*
Predictable × PSWQ × MASQ	0.00	0.00	−0.01, 0.01	4422	−0.13	.000
Unpredictable × PSWQ × MASQ	−0.01	0.01	−0.02, 0.01	4422	−1.08	.000
Random components						
σ^2	1417.55					
τ_{00}	1927.18					
ICC	.53					
Marginal R^2	.069					
Conditional R^2	.606					
$N_{participants}$	136					
Observations	4578					

Cross-level interactions involving cue were not significant (*p*s > .211, R^2s < .00). To reduce complexity, cross-level interactions involving cue are not shown here (but see Supplement B). For contrast coded conditions, neutral is the reference category, for contrast coded cues, interstimulus interval is the reference category. PSWQ = Penn-State Worry Questionnaire (grand-mean centered); MASQ = Mood and Anxiety Questionnaire (anxious arousal subscale, grand-mean centered); σ^2 = residual variance; τ_{00} = random intercept; ICC = intra-class correlation;

***$p < .001$; **$p < .01$; *$p < .05$;

See Supplement E-F for analyses of the *t*-transformed and range corrected startle data

A). Startle responses in the unpredictable condition were increased compared with the neutral condition, whereas startle responses in the predictable condition were decreased compared with the neutral condition. In the unpredictable condition, participants showed increased startle responses to the countdown and interstimulus interval (Table 1). However, in the predictable condition, startle responses were smaller during the countdown compared with the interstimulus interval (Table 1; Fig. 3).

Concerning the anxiety dimensions, the analysis yielded condition × PSWQ interactions for predictable and unpredictable threat (Table 1). Follow-up contrasts of the slopes of PSWQ revealed that higher PSWQ predicted increased startle to unpredictable threat compared with both other conditions (unpredictable vs. predictable threat: $b = 0.53$, $SE = 0.11$, $t(4422) = 4.68$, $p < .001$; unpredictable threat vs. neutral condition: $b = 0.62$, $SE = 0.11$, $t(4422) = 5.53$, $p < .001$). The PSWQ slopes in the predictable condition did not differ significantly from the neutral condition ($b = 0.09$, $SE = 0.11$, $t(4422) = 0.83$, $p = .682$). A condition × MASQ-AA interaction (Table 1) indicates that participants with increased MASQ-AA scores showed increased startle in the unpredictable compared with the predictable condition ($b = 0.55$, $SE = 0.20$, $t(4422) = 2.77$, $p = .016$). No evidence emerged for differences between the slopes in the unpredictable and neutral condition ($b = 0.21$, $SE = 0.20$, $t(4422) = 1.07$, $p = .535$) or the predictable and neutral condition respectively ($b = -0.34$, $SE = 0.20$, $t(4422) = -1.71$, $p = .201$). The PSWQ × MASQ-AA interaction (Table 1) entailed contrast of the MASQ-AA slopes centered at ± 1 *SD* of PSWQ. Participants with higher PSWQ and higher MASQ-AA showed increased overall startle compared with participants with lower PSWQ and higher MASQ-AA ($b = 1.70$, $SE = 0.79$, $t(132) = 2.15$, $p = .033$). In other words, overall startle was increased in participants with increased scores in both anxiety dimensions. The fixed effects in the model explained 6.90% of the variance in the data, combined with the random effects of the model, 60.60% of the variance

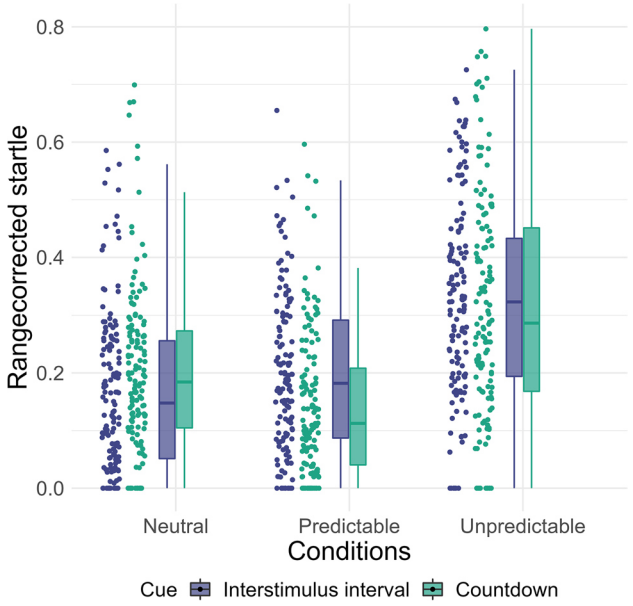


Fig. 3 Participant's mean startle responses across the conditions and cues. *Note*. Raw startle amplitudes were range corrected within participants to control for individual differences in absolute blink magnitude. Each amplitude was divided by the maximal amplitude of the participant, so that all amplitudes lie between 0 and 1

of the data were explained. To test the robustness of the effects against the pre-processing choice to use raw-startle magnitude in multilevel models (Carsten et al., 2022; Faunce et al., 2022), the analyses were repeated with *t*-transformed (Supplement E) and range corrected (Supplement F) startle amplitudes.[1]

Event-related potentials

N1

The statistical details of the results for startle probe locked N1 are shown in Table 2. The probe locked N1 was increased (i.e., more negative) during unpredictable threat anticipation, compared with the neutral condition. In contrast, the probe locked N1 was decreased (i.e., less negative) during predictable threat anticipation, compared with the neutral condition (Table 2; Fig. 5). No evidence emerged for differences between the cues (i.e., countdown, interstimulus interval), and no condition × cue interaction emerged (Table 2).

Regarding the anxiety dimensions, significant interactions between the threat conditions and MASQ-AA emerged, as well as a MASQ-AA × PSWQ interaction (Table 2). Follow-up contrasts of the slopes of MASQ-AA revealed that increased MASQ-AA values led to increased N1 in the unpredictable condition compared with the predictable condition ($b = -0.12$, $SE = 0.04$, $t(660) = -2.80$, $p = .015$), whereas no evidence emerged for differences between the slopes of the unpredictable vs. neutral ($b = -0.04$, $SE = 0.04$, $t(660) = -1.03$, $p = .559$) or predictable vs. neutral conditions ($b = 0.07$, $SE = 0.04$, $t(660) = 1.77$, $p = .181$). The PSWQ × MASQ-AA interaction (Table 2) was followed by contrasts of the MASQ-AA slopes centered at ±1 *SD* of PSWQ. Overall, participants with higher PSWQ and higher MASQ-AA showed increased (i.e., more negative) N1 compared with participants with lower PSWQ and higher MASQ-AA ($b = -0.21$, $SE = 0.10$, $t(132) = -2.02$, $p = .046$). Thus, overall N1 was increased in participants with increased scores in both anxiety dimensions. An ICC of 0.70 indicates small variability within and large variability between participants. Combined, the fixed and random effects in the model explained 77.10% of the variance in the N1 data, whereas the fixed effects explained 9.20% of the variance.

P3

The statistical details of the results for probe locked P3 are shown in Table 3. Note that increased (i.e., more positive) P3 could be interpreted as increased allocation of attentional resources to the startle probe and not the task-associated threat stimuli (Nelson, Hajcak, et al., 2015a). During predictable threat anticipation, the probe locked P3 was decreased compared with the neutral condition (Table 3; Fig. 6). During unpredictable threat anticipation, the P3 did not differ significantly from the neutral condition. In the predictable threat condition, the participants showed increased probe locked P3 during the countdown compared with the interstimulus interval (Table 3; contrast of the estimated marginal means: $b = 1.34$, $SE = 0.41$, $t(660) = 3.29$, $p = .013$). In the neutral condition the P3 during the countdown and interstimulus interval did not differ significantly ($b = 0.45$, $SE = 0.41$, $t(660) = 1.10$, $p = .881$).

Concerning the anxiety dimensions, a significant cross-level interaction between the predictable condition × PSWQ emerged (Table 3), which stems from increased P3 in participants with higher PSWQ in the predictable compared with the neutral condition (contrast of the slopes of PSWQ: $b = 0.05$, $SE = 0.02$, $t(660) = 1.96$, $p = .122$; Figure 7B). Notably, the significant interaction in the effect-coded model

[1] The effects of the NPU-threat test conditions converged across quantification approaches (i.e., increased startle for unpredictable threat and decreased startle during the predictable countdown). Increased startle in the unpredictable condition in participants with increased PSWQ (i.e., Unpredictable × PSWQ interaction, Table 1) also converged across quantifications. The Unpredictable × MASQ interaction only emerged for raw and range corrected startle. The Predictable × PSWQ, Predictable × MASQ, and PSWQ × MASQ interactions only emerged for raw startle.

Table 2 Multilevel regression models predicting probe locked N1 to the NPU-threat test

Fixed effects	*b*	*SE*	95% CI	*df*	*t*	R^2
Intercept	−10.75	0.53	−11.79, −9.71	790	−20.23	
Countdown	0.04	0.12	−0.20, −0.28	790	0.30	.000
Predictable	1.65	0.17	1.31, 1.99	790	9.53	.066***
Unpredictable	−2.18	0.17	−2.52, −1.84	790	−12.56	.109***
PSWQ	0.03	0.04	−0.06, 0.11	790	0.64	.006
MASQ	−0.03	0.07	−0.17, 0.11	790	−0.41	.002
Countdown × Predictable	0.27	0.17	−0.07, 0.61	790	1.56	.002
Countdown × Unpredictable	−0.05	0.17	−0.39, 0.29	790	−0.32	.000
Predictable × PSWQ	0.01	0.01	−0.02, 0.04	790	0.81	.001
Predictable × MASQ	0.06	0.02	0.02, 0.11	790	2.63	.005*
Unpredictable × PSWQ	−0.01	0.01	−0.04, 0.01	790	−0.92	.001
Unpredictable × MASQ	−0.05	0.02	−0.10, −0.01	790	−2.21	.004*
PSWQ × MASQ	−0.01	0.00	−0.02, −0.00	790	−2.02	.056*
Predictable × PSWQ × MASQ	0.00	0.00	−0.00, 0.00	790	0.28	.000
Unpredictable × PSWQ × MASQ	0.00	0.00	−0.00, 0.00	790	0.38	.000
Random components						
σ^2	10.93					
τ_{00}	32.38					
ICC	.70					
Marginal R^2	.092					
Conditional R^2	.771					
$N_{participants}$	136					
Observations	816					

Cross-level interactions involving cue are not shown (see Supplement C). For contrast coded conditions, neutral is the reference category, for contrast coded cues, interstimulus interval is the reference category. PSWQ = Penn-State Worry Questionnaire (grand-mean centered); MASQ = Mood and Anxiety Questionnaire (Anxious Arousal subscale, grand-mean centered); σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation;

***$p < .001$; **$p < .01$; *$p < .05$

(Table 3) did not survive the Tukey correction of the post-hoc tests. No evidence emerged for differences of the PSWQ slopes in the unpredictable and neutral condition ($b = 0.01$, $SE = 0.02$, $t(660) = 0.41$, $p = .912$) or predictable and unpredictable condition ($b = 0.04$, $SE = 0.03$, $t(660) = 1.56$, $p = .489$). PSWQ and MASQ-AA did not interact in predicting the P3 (Table 3). An ICC of .52 indicates large variability between participants. The fixed and random effects of the model combined accounted for 56.40% of the variance in the data.

Discussion

Anxiety maps onto the symptom dimensions anxious apprehension and anxious arousal, but the underlying neural mechanisms are unclear. This study was designed to examine whether individual differences in worry—as a key component of anxious apprehension—and anxious arousal predict state changes in the neural processing of aversive stimuli. Participants were recruited from a large, online, community sample to oversample individuals with converging and diverging profiles on the anxiety dimensions. This approach was taken to examine possible interactions between worry and anxious arousal that might modulate the dynamics of threat processing. Outcome measures included the startle reflex and startle probe locked ERP components N1 and P3. In line with previous studies, we found increased startle to unpredictable threat (Carsten et al., 2022; Ferry and Nelson, 2020; Gorka et al., 2017; Nelson et al., 2016), which was simultaneously mirrored in enhanced probe locked N1 reflecting increased early sensory processing. The probe locked P3 was decreased during predictable threat anticipation reflecting reduced attention allocation to the startle probe during the anticipation of predictable threat. Regarding the anxiety dimensions, we found three main results. First, worry was associated with increased startle to unpredictable threat. Second, worry was linked to increased probe locked P3 during predictable threat. Third, anxious arousal was associated

Table 3 Multilevel regression models predicting probe locked P3 to the NPU-threat test

Fixed effects	*b*	*SE*	95% CI	*df*	*t*	R^2
Intercept	4.75	0.33	4.10, 5.39	790	14.36	
Countdown	0.29	0.12	0.06, 0.52	790	2.48	.006*
Predictable	−0.98	0.17	−1.31, −0.66	790	−5.91	.030***
Unpredictable	0.07	0.17	−0.26, 0.39	790	0.41	.000
PSWQ	0.02	0.03	−0.03, 0.07	790	0.76	.004
MASQ	−0.06	0.05	−0.15, 0.03	790	−1.40	.014
Countdown × Predictable	0.38	0.17	0.05, 0.70	790	2.28	.005*
Countdown × Unpredictable	−0.31	0.17	−0.64, 0.02	790	−1.87	.003
Predictable × PSWQ	0.03	0.01	0.00, 0.05	790	2.03	.004*
Predictable × MASQ	−0.01	0.02	−0.06, 0.03	790	−0.54	.000
Unpredictable × PSWQ	−0.01	0.01	−0.03, 0.02	790	-0.66	.000
Unpredictable × MASQ	−0.02	0.02	−0.06, 0.03	790	-0.82	.001
PSWQ × MASQ	−0.00	0.00	−0.01, 0.00	790	-0.98	.007
Predictable × PSWQ × MASQ	0.00	0.00	−0.00, 0.00	790	1.12	.001
Unpredictable × PSWQ × MASQ	0.00	0.00	−0.00, 0.00	790	0.22	.000
Random components						
σ^2	10.02					
τ_{00}	11.57					
ICC	.52					
Marginal R^2	.061					
Conditional R^2	.564					
$N_{participants}$	136					
Observations	816					

Cross-level interactions involving cue are not shown here (see Supplement D). For contrast coded conditions, neutral is the reference category, for contrast coded cues, interstimulus interval is the reference category. PSWQ = Penn-State Worry Questionnaire (grand-mean centered); MASQ = Mood and Anxiety Questionnaire (anxious arousal subscale, grand-mean centered); σ^2 = residual variance; τ_{00} = random intercept; ICC = Intraclass correlation; ***$p < .001$; **$p < .01$; *$p < .05$

with increased startle and probe locked N1 during unpredictable threat compared with predictable threat. Together, these findings imply that individual differences in worry and anxious arousal alter the psychophysiological response patterns to threat anticipation.

Startle

Startle responses during temporally unpredictable threat anticipation were increased compared with the neutral condition, which is in line with task effects observed in previous studies (Nelson and Shankman, 2011; Schmitz and Grillon, 2012). During the anticipation of predictable threat, startle responses are usually increased (Bradford et al., 2014; Gorka, Nelson, and Shankman, 2013; Schmitz and Grillon, 2012). Contrary to our expectations, we found reduced startle responses during the countdown in the predictable compared with the neutral and unpredictable threat condition. This counterintuitive finding may indicate that individuals display decreased defensive preparedness in anticipation of temporally predictable and imminent aversive stimuli. But our finding could also be due to a combination and/or interaction of experimental factors, such as the choice of an auditory aversive stimulus, relatively low startle probe volume, and a visual countdown as the cue stimulus. Specifically, we used an auditory aversive stimulus, which might explain why startle responses during the presentation of the countdown in the predictable condition were reduced. Ferry and Nelson (2020) also found decreased startle in anticipation of predictable screams but not in anticipation of shocks. Thus, fear potentiated startle in the NPU-threat test might depend on the modality of the aversive stimulus. The inherent social component of the auditory scream might have triggered a response preparation, which has been shown to link to decreased startle (Löw et al., 2015). Another possible explanation consists in the comparably low volume of the startle probes. Here, the volume of startle probes was 93 dB. Other studies report volumes ranging from 95 dB (Carsten et al., 2022; Nelson and Shankman, 2011) to 103 dB (Ferry and Nelson, 2020; Gorka et al., 2013, 2017; Grillon et al., 2017; Lieberman, Gorka, et al., 2017a; Lieberman, Stevens, et al., 2017b; Morriss, Biagi, and Dodd, 2020a; Nelson et al.,

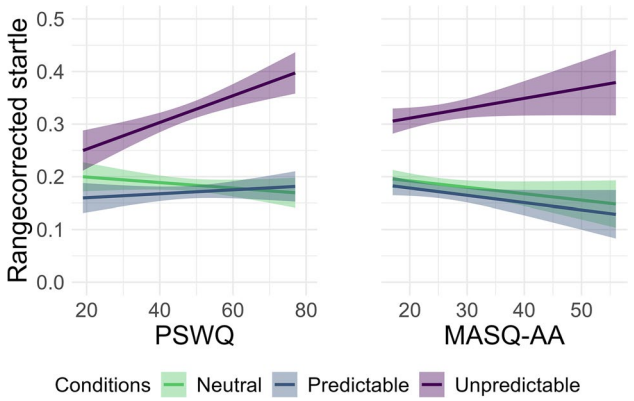


Fig. 4 Startle slopes of the Penn-State Worry Questionnaire (PSWQ) and the anxious arousal subscale of the Mood and Anxiety Symptom Questionnaire (MASQ-AA) across the experimental conditions of the NPU-threat test. *Note*. Data are collapsed across cues (interstimulus interval, countdown), because no modulation by cue was observed. The shaded area indicates a 95% confidence interval of the estimated slope. Raw startle amplitudes were range corrected within participants to control for individual differences in absolute blink magnitude. Each amplitude was divided by the maximal amplitude of the participants, so that all amplitudes lie between 0 and 1

2016; Nelson, Hajcak, et al., 2015a; Nelson, Hodges, et al., 2015b; Shankman et al., 2013). This may have intensified the difference in salience between the startle probe and aversive stimulus (100 dB) in our study. Together with a precisely predictable aversive stimulus in the predictable threat condition due to the use of a countdown as the preceding threat cue (as opposed to geometric shapes; MacNamara and Barley, 2018; Schmitz and Grillon, 2012; Shankman et al., 2013), this salience difference might have enabled the participants to block out the acoustic startle probes in the predictable condition compared with the unpredictable threat condition, in which startle responses were increased. In summary, reduced startle in anticipation of predictable threat might either point to decreased defensive preparation during temporally predictable threat or result from a high degree of threat predictability and threat imminence. Future studies could elucidate this question by extending previous findings that disentangle effects of variations in the experimental setup of the NPU-threat test (Ferry and Nelson, 2020).

Worry, as measured by the PSWQ, exerted a modulating effect on startle responses in anticipation of unpredictable

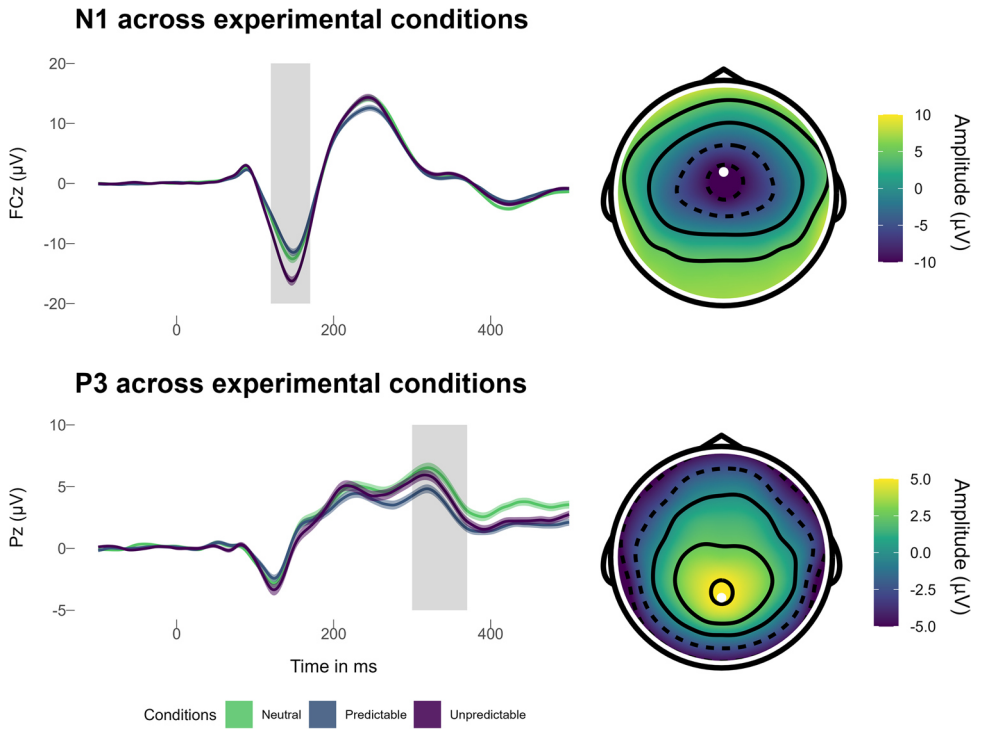


Fig. 5 Grand averages across experimental conditions (left) and head maps (right) of the event related potentials N1 (top) and P3 (bottom). *Note*. The signal is locked to startle probes and is collapsed for the grand averages (left) for illustration across cues of the NPU-threat test. The time windows for quantification of N1 (±25 ms area around the individual peak at FCz; white dot; ca. 120-170 ms) and P3 (mean activity 300–370 ms at Pz; white dot) are indicated by shaded grey bars. The shaded area around the mean signal depicts ± standard error of the distribution at each ms. The head maps (right) show the grand average signal collapsed across the conditions and cues of the NPU-Threat test

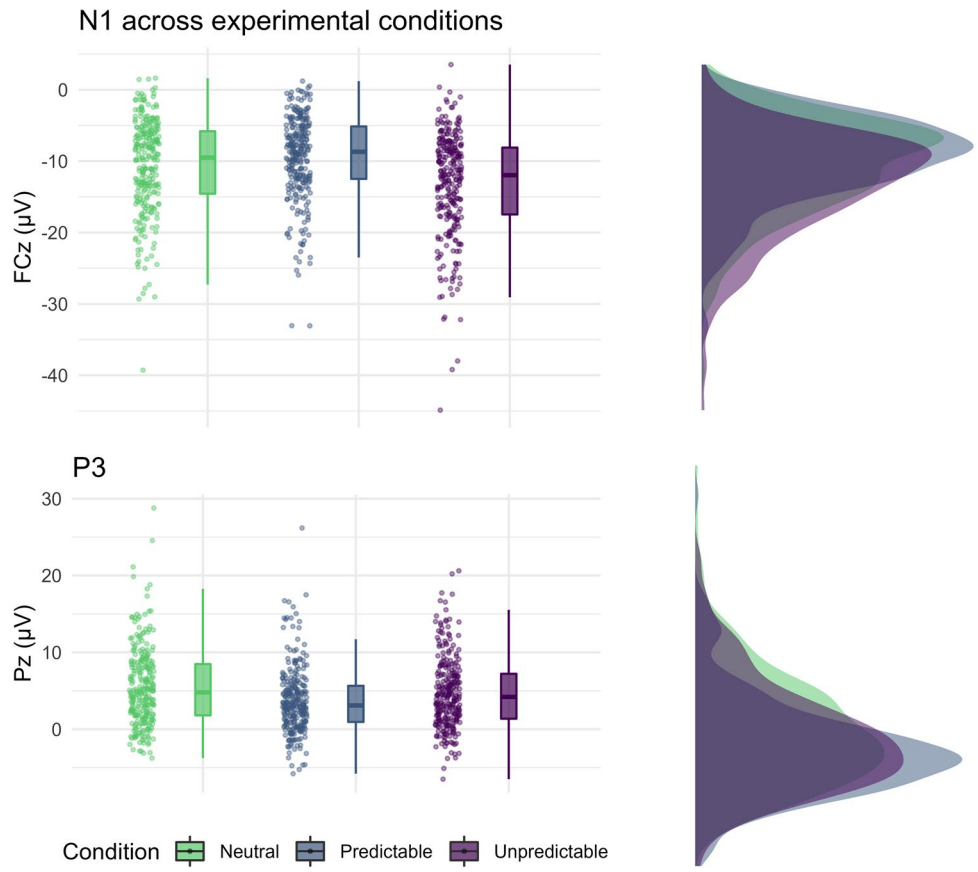


Fig. 6 Jitter plot, box plot and density plots of the N1 (top) and P3 (bottom) across the conditions of the NPU-threat test. *Note.* Data are collapsed across the cues (countdown and interstimulus interval)

threat: Increased PSWQ values led to increased startle during unpredictable threat anticipation compared with the neutral condition (Figure 4). This adds to previous but inconsistent studies investigating the role of worry and generalized anxiety disorder in the neural processing of threat (Gorka et al., 2017; Grillon et al., 2009, 2017; Nelson and Shankman, 2011; Rutherford et al., 2020). As such, our findings suggest that in subclinical individuals greater worry is associated with increased automatic defensive preparedness in unpredictable threatening contexts. Individuals who are hypersensitive to unpredictable contexts might habitually have adopted worrying to decrease the uncertainty arousal associated with unpredictable situations (Einstein, 2014; Sibrava and Borkovec, 2006). However, this finding is in contrast to results of Nelson and Shankman (2011), who found no evidence for PSWQ modulating startle in the NPU-threat test in a sample of introductory psychology students. Similarly, our findings are contrary to Rutherford et al. (2020), who even found decreased startle to unpredictable threat in participants with higher PSWQ values, but only if they had a history of anxiety disorders. Importantly, Rutherford et al. (2020) manipulated the occurrence probability of threat, whereas in the present study, the temporal predictability was manipulated. Previous studies suggest that associations between anxiety-related traits and threat anticipation might be sensitive to specifics aspects of predictability. As such, individual differences in intolerance of uncertainty (IU; Carleton, 2016a, 2016b) increased defensive responding to threat with unpredictable or lowered occurrence probability (Carsten et al., 2022; Chin et al., 2016, but see Bennett et al., 2018).

Together, a role of worry in defensive responding to unpredictable threat is likely. Yet, the direction of effects warrants further investigation, because there is inconsistency between studies finding decreased defensive responding to unpredictable threat (Rutherford et al., 2020) and increased anxiety potentiation (indicated by the present findings). This might help to integrate the mixed prior findings of clinical studies on generalized anxiety disorder (Gorka et al., 2017; Grillon et al., 2009, 2017). One possible explanation for the observed inconsistencies could be that patients with an anxiety disorder and/or with increased worry might display concurring overall attenuated physiological responses and an increased anxiety

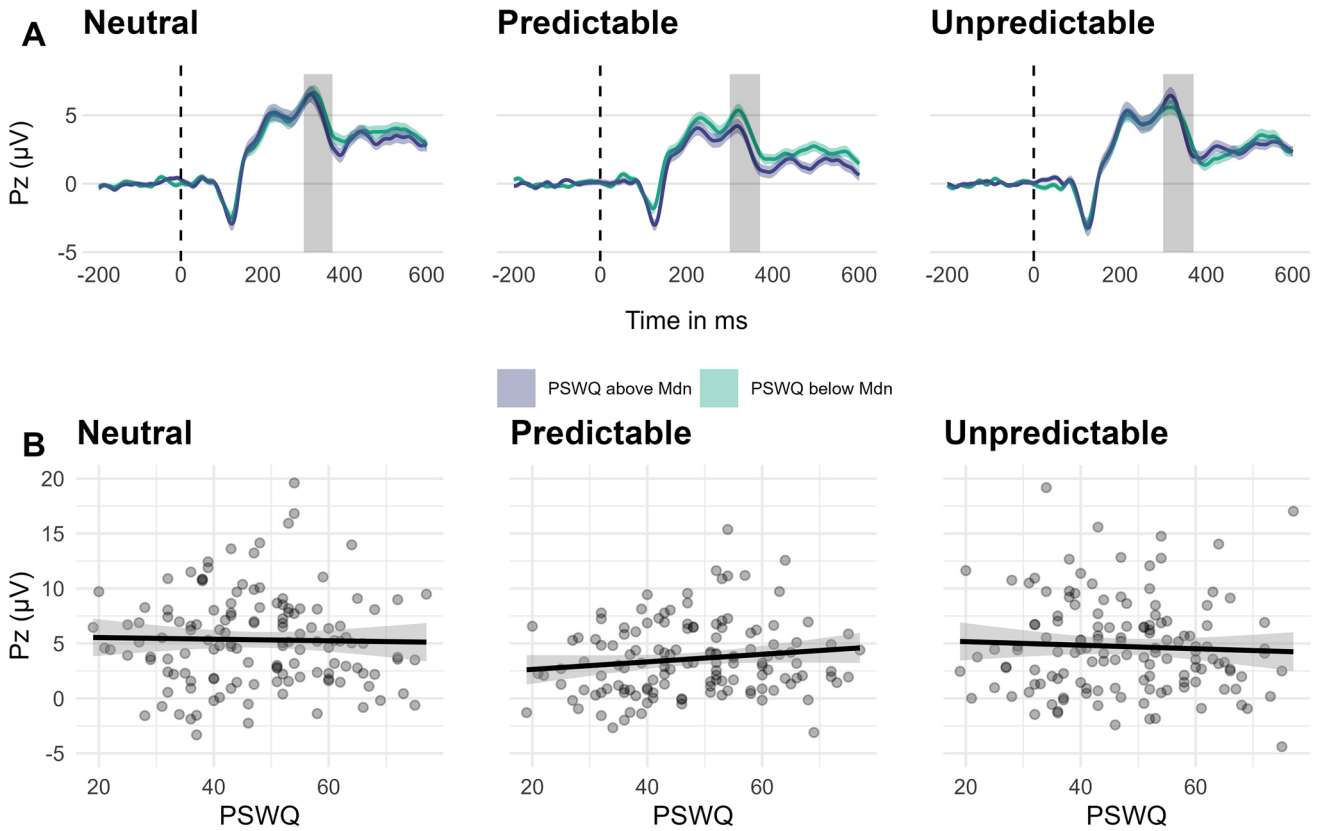


Fig. 7 Averages (**A**) and slopes (**B**) per condition of the NPU-threat test by PSWQ. *Note*. **A.** Averages of P3 across the conditions of the NPU-threat test for participants below and above the median split (47, color-coded) of the Penn-State Worry Questionnaire (PSWQ). Shaded areas around the signal depict the standard error at each ms; the shaded grey areas show the time window for quantification of the P3 (mean activity 300–370 ms). The dashed line indicates the onset of the startle probe. **B.** Slopes of the PSWQ and P3 across the experimental conditions of the NPU-threat test. The shaded area around the slope depicts the 95% confidence interval of the slope estimate. Data are collapsed across cues (countdown, interstimulus interval)

potentiation. In a clinical population, Lang et al. (2016) found evidence for decreased physiological responding as a function of distress/broad negative affectivity, the generalization of anxiety and functional impairment. Our results suggest that worry as a specific symptom dimension often accompanying negative affectivity might actually increase defensive responding to unpredictable threat in the subclinical spectrum of anxiety. Controlling for negative affect by means of BDI-II did not change this pattern of results, suggesting that it might be more specific to worry. Elevated levels of worry are present in more generalized anxiety with generalized anxiety disorder as the clinical phenotype and prototype (Cox et al., 2010; Krueger, 1999). Thus, future studies should focus on factors such as clinical status, functional impairment, and comorbidity, to broaden our understanding of the isolated effect of worry on unpredictable threat anticipation. Another avenue for future research is to extend the focus from anxiety-related traits to more fear-related traits (Corr, 2009) to understand how trait-fearfulness might translate to physiological response patterns (Panitz et al., 2018). This might help to understand which transdiagnostic symptom dimensions shape responses to threat in more focal fears (e.g., specific phobia) versus more generalized anxiety (e.g., generalized anxiety disorder).

As a more fear-related construct, in the current study, anxious arousal was associated with increased startle responses in unpredictable threat anticipation relative to predictable threat anticipation (as indicated by an Unpredictable × MASQ interaction). Hence, individuals, who report increased anxious arousal, might show increased defensive preparedness in unpredictable aversive contexts. This could be more specific to unpredictability than to the presence of threat. A similar pattern of results related to anxious arousal emerged in startle probe locked N1.

N1

Regarding general task effects and in line with previous findings, startle probe locked N1 was increased (i.e., more

negative) during unpredictable threat anticipation (Ferry and Nelson, 2020; Nelson, Hajcak, et al., 2015a; Nelson and Hajcak, 2017), which mirrors the effect observed in startle. In addition, we found a decreased auditory processing of startle probes during predictable threat anticipation as indicated by a reduced N1 in the predictable threat condition relative to the neutral condition. This finding converges with reduced startle responses during the predictable condition. Together, reduced startle and N1 during the predictable threat condition point to decreased defensive preparation during temporally predictable threat and could result from a high degree of threat predictability and threat imminence in our task.

Anxious arousal was associated with increased (i.e., more negative) probe locked N1 in unpredictable threat anticipation relative to predictable threat anticipation. In essence, MASQ-AA predicting both—increased startle and N1—in the unpredictable condition compared with the predictable condition could indicate that individuals with increased trait anxious arousal respond automatically to unpredictable aversive contexts. This conveys preliminary evidence for a signature of hyperreactivity to unpredictable threat across psychophysiological units of analysis in individuals with increased anxious arousal. Although this effect emerged for startle and N1 in conjunction, it should be interpreted as exploratory. There are no previous data or clear theoretical predictions pointing to this specific pattern of results, and the effect sizes were small (startle: $R^2 = .001$; N1: $R^2 = .004$). For startle, the effect was sensitive to pre-processing choices and was statistically significant for raw and range corrected startle but not for *t*-transformed startle. Furthermore, the MASQ-AA slopes in startle and N1 differed significantly only between unpredictable and predictable conditions, but not between the unpredictable and neutral condition. Future studies could try to replicate this effect and test whether it holds true or is actually increased in clinical populations.

P3

In line with previous studies, the startle probe locked P3 was decreased during predictable threat anticipation suggesting decreased attentional allocation (i.e., orienting response) to task-irrelevant threat stimuli (i.e., startle probe) when a threat is temporally predictable and imminent (Ferry and Nelson, 2020; MacNamara and Barley, 2018; Nelson, Hajcak, et al., 2015a; Nelson and Hajcak, 2017). Unexpectedly, the probe locked P3 in predictable threat anticipation was more decreased during the interstimulus interval compared with the countdown, indicating that this preparatory focus of attention on predictable threatening stimuli (i.e., blunted probe locked P3) might already be initiated by the instruction during the interstimulus interval.

Concerning the anxiety dimensions, we found evidence for an effect of worry on the attentional allocation to the startle probe during the anticipation of predictable threat: Increased PSWQ scores were associated with an increased P3 in the predictable condition. Previous research found decreased probe locked P3 during the anticipation of (predictable) threat (Ferry and Nelson, 2020; MacNamara and Barley, 2018; Nelson, Hajcak, et al., 2015a). This is considered to indicate that attentional resources are directed to the threat cue rather than the task-irrelevant startle probe, which might be an adaptive strategy in the face of predictable threat. Our results suggest that individuals with increased trait worry seem to have difficulty in this preparatory focus of attention (Forster et al., 2015; Morriss, Biagi, and van Reekum, 2020b). This indicates a decreased ability to distinguish between predictable and unpredictable situations in individuals with elevated worry, which could render predictable situations more uncertain and thus aversive. This attentional bias might result in a quantitative difference in experiences of uncertainty and could thereby contribute to the development and maintenance of anxiety and intolerance of uncertainty (Carleton, 2016b). But the reverse path also is possible, wherein anxious apprehension and worrying are conceptualized as a coping mechanism to reduce uncertainty (i.e., a consequence of intolerance of uncertainty; Einstein, 2014). The absence of evidence for PSWQ modulating earlier neural processing (N1) during the anticipation of predictable threat could be taken to suggest that worry mitigates threat responses in a predictable context primarily by means of attentional allocation.

Overall, our findings suggest that worry increases defensive responding in anticipation of unpredictable threat (as indexed by increased startle in the unpredictable condition) and increases attentional allocation to irrelevant stimuli during predictable threat anticipation (as indexed by increased P3 to startle probes in the predictable condition in participants with increased worry). Anxious arousal might be associated with increased defensive responding to unpredictable threat relative to predictable threat.

Limitations

Several limitations should be considered when interpreting the present findings. First, findings on predictable threat anticipation should be interpreted with caution, because the typical potentiation for predictable threat anticipation did not emerge in startle or N1. However, an expected task effect regarding predictable threat anticipation was evident in probe locked P3, which was decreased compared with the the neutral condition. Future studies might build on these findings and examine boundary effects of the NPU-threat test, e.g., by comparing the sensory modality (Ferry and Nelson, 2020) or intensity of the aversive stimuli. Along these lines, it might be helpful to remove sources of potential threat during the neutral condition, i.e., to exclude

potentially aversive startle probes that might render the neutral condition unsafe. Second, it remains unclear whether the role of the anxiety dimensions might be increased or different in clinical manifestations of anxiety symptomatology. Thus, the results of the present study allow inferences about trait worry, but the link to clinical manifestations of anxiety and hence inferences relating to the generalization of anxiety (Lang et al., 2016) remain indirect. Although participants were not screened for lifetime anxiety disorders, an inclusion of participants with prior or current anxiety disorders—but intact functional adaptability—is likely, because we oversampled participants with diverging anxiety dimension profiles and anxiety disorders are extensively prevalent in the general population (Baxter et al., 2013). Previous findings could be taken to suggest categorical differences between individuals with a lifetime anxiety disorder versus without (Rutherford et al., 2020). In the current study, we did not screen for current or prior anxiety disorders, which makes it impossible to identify a clinical threshold for the effects of interest. Instead, we followed the central ideas of the RDoC approach (Insel et al., 2010), proposing a continuum for psychopathology with close relations to underlying neurophysiological systems. In this vein, our dimensional analytic strategy conveyed no evidence for a bimodal distribution of startle to unpredictable threat anticipation that would suggest a clinical threshold of the effects (Sharp et al., 2015).

Third, no data were collected on ethnicity or nationality, which limits the interpretation of the generalizability of our results. However, the online screening was made available to the general population in Berlin, of which we included participants based on their trait worry and anxious arousal profiles. The participant's age ranged from 18 to 62 years ($M = 28.60$, $SD = 9.22$), with $M = 13.30$ ($SD = 2.06$) years of education. Thus, although data on ethnicity and nationality is missing, we recruited a community sample, which ensures a higher degree of generalizability compared with the frequently used samples of undergraduates. By operationalizing anxious apprehension by means of the PSWQ, we focused on a specific symptom dimension (i.e., worry) that characterizes anxious apprehension. Further aspects of anxious apprehension such as beliefs related to uncertainty and uncontrollability, i.e., intolerance of uncertainty, might further play a role in attentional and defensive responding to unpredictable threats (Carsten et al., 2022; Correa et al., 2022; Morriss, Biagi, and Dodd, 2020a). Lastly, the PSWQ and MASQ-AA were not readministered during the laboratory assessment. Consequently, we cannot rule out a change in trait levels of anxious apprehension and anxious arousal from the online screening to the laboratory assessment.

Next to these limitations, the present study comprises considerable strengths. Due to a comparably large sample size, the statistical analyses were powered to detect even small effects. This is especially true for the startle data, as no data aggregation, as compared with more traditional ANOVA approaches, was necessary. Moreover, employing MLMs enabled us to model individual differences in physiological response patterns with more granularity by accounting for the dimensional data structure of the questionnaires. Across outcome measures, the data exhibited significant clustering (as indicated by ICCs), which confirms the inclusion of random effects. Using these granular analytic approaches, we aimed at disentangling possible interaction effects of worry and anxious arousal specific to threat processing, which were not evident in the data. This further corroborates the separability of the anxiety dimensions (Sharp et al., 2015) and indicates that trait levels of worry and anxious arousal differentially translate to state changes across different units of analysis or that the interrelations between trait levels and state changes are too small to be detectable in the current, comparably large sample.

Conclusions

In consideration of these limitations and strengths, the present study conveys evidence for trait worry and anxious arousal as central anxiety dimensions that differentially modulate physiological and attentional aspects in threat processing. Particularly, trait variations of worry and anxious arousal allowed the prediction of state changes in psychophysiological responses to unpredictable threat anticipation. Participants with increased worry displayed increased startle in unpredictable threat anticipation compared with the predictable threat and neutral conditions. To a smaller degree, participants with increased anxious arousal displayed increased startle in unpredictable threat anticipation. Together, both anxiety dimensions explain unique variance in defensive preparedness to unpredictable aversive contexts. Individual differences in the anxiety dimensions might thus be reflected in altered physiological response patterns, such that individuals with elevated scores on either anxiety dimension—but more pronounced for worry—show amplified defensive preparedness in the face of uncertain threats. Furthermore, in a predictable, aversive context, worry might modulate the allocation of attentional resources to threat stimuli such that we observed a blunting in the preparatory focus of attention during predictable threat. Altogether, this suggests an essential role of trait worry in alterations of the sequential neural processing of threat stimuli and corroborates theoretical conceptualizations that highlight anxious apprehension as a central underlying symptom dimension in anxiety.

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Kai Härpfer: Methodology, Validation, Investigation, Data Curation, Writing - Review & Editing

Brady Nelson: Software, Writing - Review & Editing

Norbert Kathmann: Resources, Supervision

Anja Riesel: Conceptualization, Methodology, Validation, Resources, Writing - Review & Editing, Supervision, Project administration, Funding acquisition

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Supplementary Material to

"Don't worry, it won't be fine. Contributions of worry and anxious arousal to startle responses and event-related potentials in threat anticipation."

Hannes Per Carsten[1]*, Kai Härpfer[1], Brady Nelson[2], Norbert Kathmann[3], & Anja Riesel[1]

[1]Department of Psychology, University of Hamburg, Hamburg, Germany

[2]Department of Psychology, Stony Brook University, NY, USA

[3]Department of Psychology, Humboldt University of Berlin, Berlin, Germany

*Correspondence concerning this article should be addressed to Hannes Per Carsten, Department of Psychology, Universität Hamburg, Von-Melle-Park 11, 20146 Hamburg, Germany.

E-Mail: hannes.carsten@uni-hamburg.de

Table of Contents:

Supplement A: Multilevel model for startle including interaction terms with cue 2

Supplement B: Multilevel model for raw startle including interaction terms with cue .. 3

Supplement C: Full multilevel model for N1 5

Supplement D: Full multilevel model for P3 7

Supplement E: *t*-transformed startle analyses 9

Supplement F: Range-corrected startle analyses 11

Supplement G: Power Simulations 13

Supplement H: Grand averages 15

Supplement A: Multilevel model for startle including interaction terms with cue

Table S1

		Startle (μV)	**Startle (*t*)**	**N1 (μV)**	**P3 (μV)**
Condition	**Cue**	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Neutral	ISI	27.21 (45.83)	47.65 (7.41)	-10.39 (6.28)	5.23 (5.17)
	CD	31.07 (52.47)	49.01 (8.42)	-10.83 (6.97)	5.72 (4.93)
Predictable	ISI	29.44 (52.32)	48.79 (9.57)	-9.63 (5.74)	3.00 (3.79)
	CD	23.04 (40.68)	46.77 (7.06)	-9.23 (5.99)	4.44 (4.67)
Unpredictable	ISI	52.20 (75.36)	54.09 (11.89)	-13.38 (7.25)	4.74 (4.76)
	CD	50.94 (75.86)	53.66 (11.20)	-13.13 (7.45)	4.70 (4.59)

Note. ISI: Interstimulus interval. CD: Countdown

Supplement B: Multilevel model for raw startle including interaction terms with cue

Table S2

Multilevel model predicting range corrected startle responses to the NPU-Threat test. To calculate the range corrected amplitudes, each raw amplitude of a participant was divided by that participant's maximal amplitude and multiplied by 100 so that all amplitudes lie between 0 and 100.

Fixed Effects	***b***	***SE***	**95% *CI***	***df***	***t***	***R²***
Intercept	32.36	4.03	24.45, 40.27	132	8.02	***
Countdown	-0.63	0.59	-1.79, 0.52	4424	-1.07	.000
Predictable	-9.06	0.84	-10.70, -7.42	4424	-10.83	.025***
Unpredictable	16.15	0.83	14.51, 17.78	4424	19.37	.076***
PSWQ	0.26	0.32	-0.37, 0.88	132	0.81	.002
MASQ	-0.27	0.55	-1.36, 0.82	132	-0.49	.003
Countdown × Predictable	-2.44	0.84	-4.08, -0.80	4424	-2.92	.004**
Countdown × Unpredictable	-0.12	0.83	-1.76, 1.51	4424	-0.15	.000
Countdown × PSWQ	-0.04	0.05	-0.13, 0.05	4424	-0.78	.000
Countdown × MASQ	0.04	0.08	-0.12, 0.20	4424	0.51	.000
Predictable × PSWQ	-0.15	0.07	-0.27, -0.02	4424	-2.21	.000*
Predictable × MASQ	-0.30	0.12	-0.52, -0.07	4424	-2.58	.001*
Unpredictable × PSWQ	0.39	0.07	0.26, 0.51	4424	5.90	.003***
Unpredictable × MASQ	0.25	0.11	0.03, 0.48	4424	2.22	.001*
PSWQ × MASQ	0.06	0.03	0.01, 0.12	132	2.15	.006*
Predictable × PSWQ × MASQ	-0.00	0.01	-0.01, 0.01	4424	-0.13	.000
Unpredictable × PSWQ × MASQ	-0.08	0.11	-0.30, 0.14	4424	-0.69	.000
Countdown × Predictable × PSWQ	-0.01	0.07	-0.13, 0.12	4424	-0.09	.000
Countdown × Predictable × MASQ	-0.06	0.12	-0.29, 0.16	4424	-0.53	.000
Countdown × PSWQ × MASQ	0.00	0.00	-0.01, 0.01	4424	0.33	.000
Countdown × Unpredictable × PSWQ	0.07	0.07	-0.06, 0.20	4424	1.07	.001
Countdown × Unpredictable × MASQ	-0.08	0.11	-0.30, 0.14	4424	-0.69	.000
Countdown × Predictable × PSWQ × MASQ	-0.01	0.01	-0.02, 0.00	4424	-1.25	.000
Countdown × Unpredictable × PSWQ × MASQ	0.01	0.01	-0.00, 0.02	4424	1.31	.000
Random Components						

σ^2	1417.55
τ_{00}	1928.18
ICC	.58
Marginal R^2	.069
Conditional R^2	.606
$N_{participants}$	136
Observations	4578

Note. For contrast coded conditions, neutral is the reference category, for contrast coded cues, interstimulus interval is the reference category. PSWQ = Penn-State Worry Questionnaire (grand-mean centered); MASQ = Mood and Anxiety Questionnaire (Anxious Arousal subscale, grand-mean centered); σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation;
*** $p < .001$; ** $p < .01$; * $p < .05$

To test the specificity of the effects to PSWQ, we exploratorily included BDI-II into the model, which did not change the pattern of results regarding PSWQ. Specifically, the Unpredictable × PSWQ interaction remained significant ($b = 0.40$, $SE = 0.08$, $t(4422) = 5.14$, $R^2 = .006$). While the Predictable × MASQ interaction remained significant ($b = -0.27$, $SE = 0.13$, $t(4422) = -2.05$, $R^2 = .001$), the Unpredictable × MASQ interaction was no longer significant when including BDI-II into the model ($b = 0.18$, $SE = 0.13$, $t(4422) = 1.37$, $R^2 = .000$).

Supplement C: Full multilevel model for N1

Table S3

Multilevel model predicting startle probe locked N1 in μV to the NPU-Threat test.

Fixed Effects	***b***	***SE***	**95% *CI***	***df***	***t***	***R²***
Intercept	-10.75	0.53	-11.79, -9.71	132	-20.23	***
Countdown	0.04	0.12	-0.20, 0.28	660	0.30	.000
Predictable	1.65	0.17	1.31, 1.99	660	9.53	. 066***
Unpredictable	-2.18	0.17	-2.52, -1.84	660	-12.56	.109***
PSWQ	0.03	0.04	-0.06, 0.11	132	0.64	.006
MASQ	-0.03	0.07	-0.17, 0.11	132	-0.41	.002
Countdown × Predictable	0.27	0.17	-0.07, 0.61	660	1.56	.002
Countdown × Unpredictable	-0.05	0.17	-0.39, 0.29	660	-0.32	.000
Countdown × PSWQ	0.01	0.01	-0.01, 0.02	660	0.58	.000
Countdown × MASQ	-0.00	0.02	-0.03, 0.03	660	-0.10	.000
Predictable × PSWQ	0.01	0.01	-0.02, 0.04	660	0.81	.001
Predictable × MASQ	0.06	0.02	0.02, 0.11	660	2.63	.006**
Unpredictable × PSWQ	-0.01	0.01	-0.04, 0.01	660	-0.92	.001
Unpredictable × MASQ	-0.05	0.02	-0.10, -0.01	660	-2.21	.004*
PSWQ × MASQ	-0.01	0.00	-0.02, -0.00	132	-2.02	.056*
Predictable × PSWQ × MASQ	0.00	0.00	-0.00, 0.00	660	0.28	.000
Unpredictable × PSWQ × MASQ	0.00	0.00	-0.00, 0.00	660	0.38	.000
Countdown × Predictable × PSWQ	0.02	0.01	-0.01, 0.05	660	1.38	.001
Countdown × Predictable × MASQ	0.04	0.02	-0.01, 0.09	660	1.74	.002
Countdown × PSWQ × MASQ	-0.00	0.00	-0.00, 0.00	660	-0.07	.000
Countdown × Unpredictable × PSWQ	-0.00	0.01	-0.03, 0.02	660	-0.16	.000
Countdown × Unpredictable × MASQ	-0.03	0.02	-0.08, 0.02	660	-1.24	.001
Countdown × Predictable × PSWQ × MASQ	-0.00	0.00	-0.00, 0.00	660	-1.83	.003
Countdown × Unpredictable × PSWQ × MASQ	0.00	0.00	0.00, 0.01	660	2.52	.005*
Random Components						

σ^2	10.93
τ_{00}	32.38
ICC	.75
Marginal R^2	.092
Conditional R^2	.771
$N_{participants}$	136
Observations	816

Note. For contrast coded conditions, neutral is the reference category, for contrast coded cues, interstimulus interval is the reference category. PSWQ = Penn-State Worry Questionnaire (grand-mean centered); MASQ = Mood and Anxiety Questionnaire (Anxious Arousal subscale, grand-mean centered); σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation;
*** $p < .001$; ** $p < .01$; * $p < .05$

Supplement D: Full multilevel model for P3

Table S4

Multilevel model predicting startle probe locked P3 in μV to the NPU-Threat test.

Fixed Effects	***b***	***SE***	**95% *CI***	***df***	***t***	***R²***
Intercept	4.75	0.33	4.10, 5.39	132	14.36	***
Countdown	0.29	0.12	0.06, 0.52	660	2.48	.006*
Predictable	-0.98	0.17	-1.31, -0.66	660	-5.91	.030***
Unpredictable	0.07	0.17	-0.26, 0.39	660	0.41	.000
PSWQ	0.02	0.03	-0.03, 0.07	132	0.76	.004
MASQ	-0.06	0.05	-0.15, 0.03	132	-1.40	.014
Countdown × Predictable	0.38	0.17	0.05, 0.70	660	2.28	.005*
Countdown × Unpredictable	-0.31	0.17	-0.64, 0.02	660	-1.87	.003
Countdown × PSWQ	0.01	0.01	-0.01, 0.03	660	1.12	.001
Countdown × MASQ	-0.02	0.02	-0.06, 0.01	660	-1.48	.002
Predictable × PSWQ	0.03	0.01	0.00, 0.05	660	2.03	.004*
Predictable × MASQ	-0.01	0.02	-0.06, 0.03	660	-0.54	.000
Unpredictable × PSWQ	-0.01	0.01	-0.03, 0.02	660	-0.66	.000
Unpredictable × MASQ	-0.02	0.02	-0.06, 0.03	660	-0.82	.001
PSWQ × MASQ	-0.00	0.00	-0.01, 0.00	132	-0.98	.007
Predictable × PSWQ × MASQ	0.00	0.00	-0.00, 0.00	660	1.12	.001
Unpredictable × PSWQ × MASQ	0.00	0.00	-0.00, 0.00	660	0.22	.000
Countdown × Predictable × PSWQ	-0.00	0.01	-0.03, 0.02	660	-0.35	.000
Countdown × Predictable × MASQ	-0.03	0.02	-0.07, 0.01	660	-1.31	.002
Countdown × PSWQ × MASQ	0.00	0.00	-0.00, 0.00	660	0.61	.000
Countdown × Unpredictable × PSWQ	-0.02	0.01	-0.04, 0.01	660	-1.32	.002
Countdown × Unpredictable × MASQ	0.06	0.02	0.02, 0.11	660	2.81	.007*
Countdown × Predictable × PSWQ × MASQ	0.00	0.00	-0.00, 0.00	660	0.54	.000
Countdown × Unpredictable × PSWQ × MASQ	-0.00	0.00	-0.00, 0.00	660	-0.51	.000

Random Components	
σ^2	10.02
τ_{00}	11.57
ICC	.54
Marginal R^2	.061
Conditional R^2	.564
$N_{participants}$	136
Observations	816

Note. For contrast coded conditions, neutral is the reference category, for contrast coded cues, interstimulus interval is the reference category. PSWQ = Penn-State Worry Questionnaire (grand-mean centered); MASQ = Mood and Anxiety Questionnaire (Anxious Arousal subscale, grand-mean centered); σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation;
*** $p < .001$; ** $p < .01$; * $p < .05$

To test the specificity of this effect to PSWQ we exploratorily included BDI-II into the model, which did not change the pattern of results. Specifically, the interaction (Predictable × PSWQ) remained significant (b = -0.03, SE = 0.01, $t(789)$ = 2.03, p = .042).

Supplement E: *t*-transformed startle analyses

Of note, the random-intercept model failed to converge with *t*-transformed startle amplitudes. The data were *t*-transformed within each individual, so the mean value for each participant was 50 (*SD* = 10). Hence, the *t*-transformation decreased the random variance in the data and thus a generalized linear model was estimated.

Table S5

Generalized linear regression models predicting t-transformed startle responses to the NPU-Threat test.

Fixed Effects	***b***	***SE***	**95% *CI***	***t***	***p***
Intercept	49.99	0.15	49.79, 50.28	339.02	<.001
Countdown	-0.15	0.15	-0.43, 0.14	-0.99	.323
Predictable	-2.21	0.21	-2.62, -1.80	-10.58	<.001
Unpredictable	3.95	0.21	3.54, 4.36	18.97	<.001
PSWQ	0.00	0.01	-0.02, 0.02	0.06	.955
MASQ	-0.00	0.02	-0.04, 0.04	-0.03	.974
Countdown × Predictable	-0.84	0.21	-1.25, -0.43	-4.00	.001
Countdown × Unpredictable	0.01	0.21	-0.40, 0.42	0.04	.970
Countdown × PSWQ	0.01	0.01	-0.01, 0.04	1.07	.283
Countdown × MASQ	-0.00	0.02	-0.04, 0.04	-0.17	.866
Predictable × PSWQ	-0.00	0.02	-0.04, 0.03	-0.21	.833
Predictable × MASQ	-0.05	0.03	-0.10, 0.01	-1.62	.106
Unpredictable × PSWQ	0.06	0.02	0.03, 0.09	3.62	.003
Unpredictable × MASQ	0.06	0.03	-0.00, 0.11	1.93	.053
PSWQ × MASQ	0.00	0.00	-0.00, 0.00	0.02	.981
Predictable × PSWQ × MASQ	-0.00	0.00	-0.00, 0.00	-0.03	.978
Unpredictable × PSWQ × MASQ	-0.00	0.00	-0.00, 0.00	-0.94	.348
Countdown × Predictable × PSWQ	-0.00	0.02	-0.04, 0.03	-0.24	.813
Countdown × Predictable × MASQ	-0.01	0.03	-0.07, 0.04	-0.45	.656
Countdown × PSWQ × MASQ	-0.00	0.00	-0.00, 0.00	-0.77	.440
Countdown × Unpredictable × PSWQ	0.04	0.02	0.01, 0.07	2.43	.015

Countdown × Unpredictable × MASQ	-0.01	0.03	-0.06, 0.05	-0.28	.781
Countdown × Predictable × PSWQ × MASQ	0.00	0.00	-0.00, 0.00	0.16	.872
Countdown × Unpredictable × PSWQ × MASQ	-0.00	0.00	-0.00, 0.00	-0.56	.574

Model fit	R^2	F	df	p
	.091	19.9	23, 4577	<.001

Note. For contrast coded conditions, neutral is the reference category, for contrast coded cues, interstimulus interval is the reference category. PSWQ = Penn-State Worry Questionnaire (grand-mean centered); MASQ = Mood and Anxiety Questionnaire (Anxious Arousal subscale, grand-mean centered);

Supplement F: Range-corrected startle analyses

Table S6

Multilevel model predicting range-corrected startle responses to the NPU-Threat test. To calculate the range-corrected amplitudes, each raw amplitude of a participant was divided by that participant's maximal amplitude and multiplied by 100 so that all amplitudes lie between 0 and 100.

Fixed Effects	***b***	***SE***	**95% *CI***	***df***	***t***	***R²***
Intercept	21.95	1.14	19.72, 24.17	132	19.32	***
Countdown	-0.41	0.38	-1.14, 0.33	4424	-1.09	.000
Predictable	-5.51	0.53	-6.56, -4.47	4424	-10.37	.025***
Unpredictable	9.87	0.53	8.83, 10.91	4424	18.62	.076***
PSWQ	0.09	0.09	-0.09, 0.26	132	0.95	.002
MASQ	-0.18	0.16	-0.49, 0.12	132	-1.18	.003
Countdown × Predictable	-2.19	0.53	-3.23, -1.15	4424	-4.11	.004***
Countdown × Unpredictable	0.09	0.53	-0.95, 1.13	4424	0.17	.000
Countdown × PSWQ	0.03	0.03	-0.03, 0.09	4424	0.95	.000
Countdown × MASQ	-0.01	0.05	-0.11, 0.09	4424	-0.18	.000
Predictable × PSWQ	-0.02	0.04	-0.10, 0.06	4424	-0.50	.000
Predictable × MASQ	-0.11	0.07	-0.25, 0.03	4424	-1.48	.001
Unpredictable × PSWQ	0.16	0.04	0.07, 0.24	4424	3.74	.003***
Unpredictable × MASQ	0.14	0.07	0.00, 0.29	4424	1.99	.001*
PSWQ × MASQ	0.01	0.01	-0.00, 0.03	132	1.62	.006
Predictable × PSWQ × MASQ	0.00	0.00	-0.01, 0.01	4424	0.09	.000
Unpredictable × PSWQ × MASQ	-0.01	0.01	-0.02, 0.01	4424	-1.08	.000
Countdown × Predictable × PSWQ	-0.01	0.04	-0.10, 0.07	4424	-0.34	.000
Countdown × Predictable × MASQ	-0.03	0.07	-0.17, 0.12	4424	-0.36	.000
Countdown × PSWQ × MASQ	-0.00	0.00	-0.01, 0.00	4424	-0.62	.000
Countdown × Unpredictable × PSWQ	0.10	0.04	0.02, 0.18	4424	2.37	.001*
Countdown × Unpredictable × MASQ	-0.02	0.07	-0.16, 0.12	4424	-0.26	.000
Countdown × Predictable × PSWQ × MASQ	0.00	0.00	-0.01, 0.01	4424	0.38	.000
Countdown × Unpredictable × PSWQ × MASQ	-0.00	0.00	-0.01, 0.00	4424	-0.85	.000
Random Components						

σ^2	572.69
τ_{00}	139.29
ICC	.20
Marginal R^2	.078
Conditional R^2	.258
$N_{participants}$	136
Observations	4578

Note. For contrast coded conditions, neutral is the reference category, for contrast coded cues, interstimulus interval is the reference category. PSWQ = Penn-State Worry Questionnaire (grand-mean centered); MASQ = Mood and Anxiety Questionnaire (Anxious Arousal subscale, grand-mean centered); σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation;
*** $p < .001$; ** $p < .01$; * $p < .05$;

Supplement G: Power Simulations

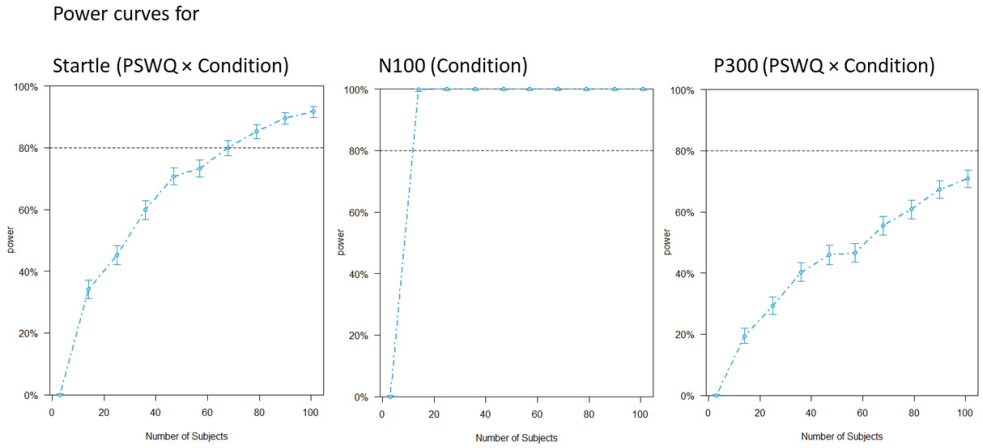
The power analysis was computed using simr version 1.0.5 (Green & Macleod, 2016). Each analysis is based on 1,000 Monte Carlo simulations (Arend & Schäfer, 2019). For each outcome (i.e., startle, N1, P3), we simulated the power of the consistent highest order effect along the sample size. The resulting power estimates and power curves (Figure S1) indicate the likelihood of finding comparable true effects in the data given the sample size of n = 101.

In the startle data, the consistent effect across analytical approaches was the cross-level interaction PSWQ × condition. According to the result of the power simulation, we could have detected comparable effects in the data with a likelihood of 90.10 % (95 % CI [88.08, 91.88]).

For N100, we simulated the level 1 effect of condition, as this was the only emergent effect in the data. The simulation result suggests that the power for finding comparable level 1 effects in the N100 data was 100 % (95 % CI [99.63, 100.0]).

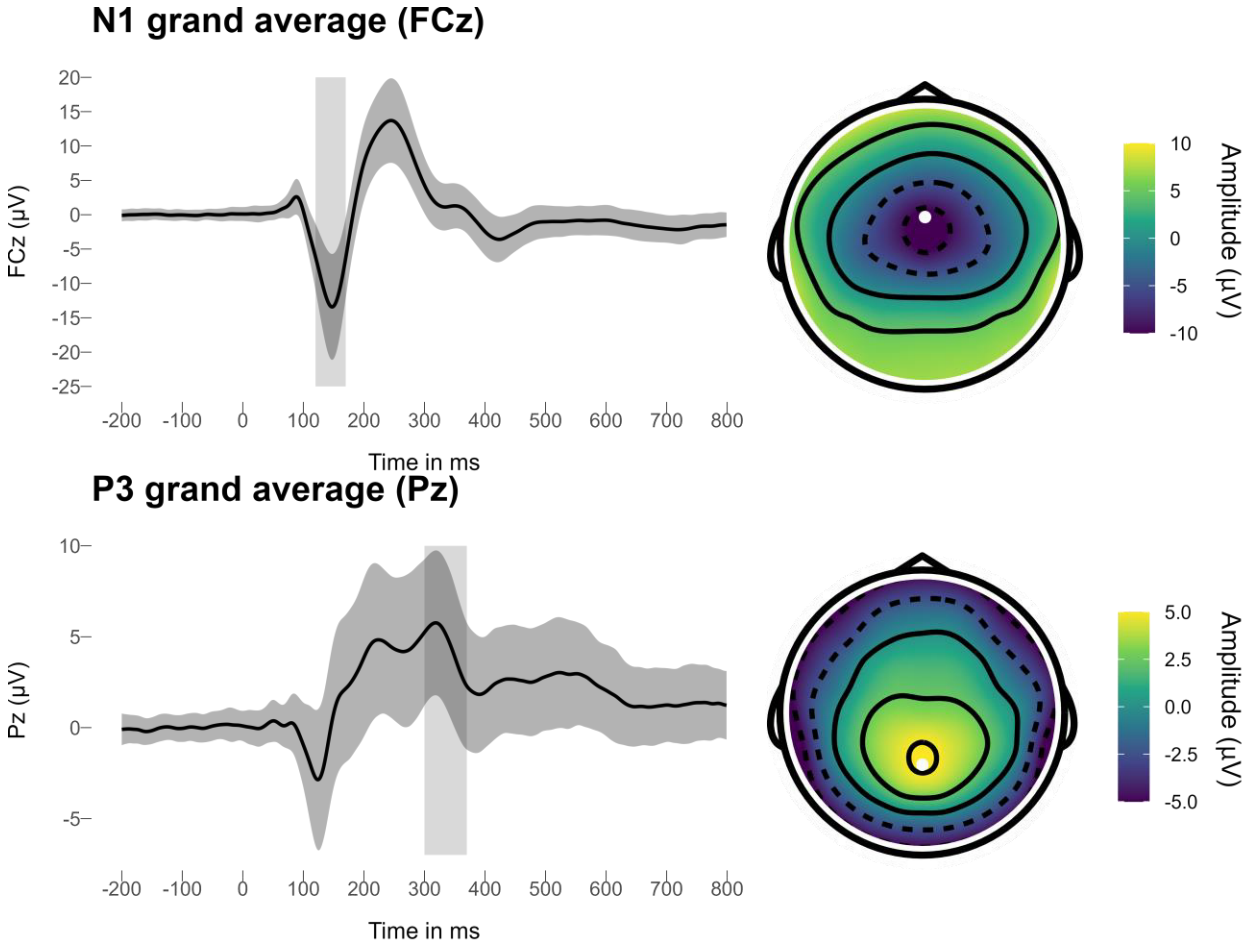
For P300, we simulated the cross-level interaction of PSWQ × condition. The result indicates that comparable interaction effects in the P300 data could have been found with a probability of 70.10 % (95 % CI [67.16, 72.92]).

Figure S1 Power curves using 1,000 Monte Carlo simulations for the relevant effects of each outcome. Error bars depict the 95 % CI.



Supplement H: Grand averages

Figure S2 Grand averages and topographical depictions of the event-related potentials N1 and P3 collapsed across experimental conditions



Note. The signal is locked to startle probes and is collapsed across conditions and cues of the NPU-Threat test. The time windows for quantification of N1 (± 25 ms area around the individual peak at FCz; white dot; ca. 120-170 ms) and P3 (mean activity 300 – 370 ms at Pz; white dot) are indicated by shaded grey bars. The shaded area around the mean signal depicts ± 1 standard deviation of the distribution at each ms.

Study 4

Transdiagnostic Physiological Correlates of Unpredictable Threat Anticipation.

Hannes Per Carsten, Kai Härpfer, Franziska Magdalena Kausche, & Anja Riesel

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Transdiagnostic Physiological Correlates of Unpredictable Threat Anticipation

Hannes Per Carsten[1*], Kai Härpfer[1], Franziska Magdalena Kausche[1], Anja Riesel[1]

[1]Department of Psychology, University of Hamburg, Hamburg, Germany

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*Correspondence concerning this article should be addressed to Hannes Per Carsten, Department of Psychology, Universität Hamburg, Von-Melle-Park 11, 20146 Hamburg, Germany. E-Mail: hannes.carsten@uni-hamburg.de

Abstract

Responses to unpredictable threat have been proposed as a candidate mechanism in anxiety-related psychopathology, but clinical findings remain heterogeneous and often rely on single physiological outcomes. The present study examined whether physiological responses during threat anticipation map onto categorical and dimensional conceptualizations of psychopathology across the anxiety and obsessive-compulsive spectrum. In a transdiagnostic sample of $N = 163$ participants, patients with specific phobia, social anxiety disorder (SAD), and obsessive-compulsive disorder (OCD), as well as unaffected controls completed the NPU-threat test in order to measure responses to predictable and unpredictable threat. Physiological responding was assessed using startle reflex, skin conductance responses (SCR), and event-related potentials indexing early sensory processing (N1) and later attentional allocation (P3). Results indicated a group-based effect for SCR, such that patients with OCD showed enhanced autonomic responding during unpredictable threat anticipation. Dimensionally, anxious arousal was associated with reduced SCR during unpredictable threat and lower P3 amplitudes across conditions. Intolerance of uncertainty modulated startle particularly in controls, and anxious apprehension was associated with increased N1 amplitudes in OCD. Exploratory latent profile analysis identified three multisystem physiological response profiles. A threat-reactive profile characterized by increased N1 and both increased SCR and startle to unpredictable threat was particularly clinically enriched, showing higher clinical severity, greater representation of SAD and OCD, and elevated anxious apprehension and social anxiety symptoms. Together, findings suggest that threat anticipation in anxiety-related psychopathology is best understood as a multisystem and partly transdiagnostic process rather than as a single physiological marker of diagnostic status or unpredictable-threat sensitivity.

Keywords: anxiety, obsessive compulsive disorder, uncertainty, anticipatory anxiety, unpredictable threat, latent profile analysis

Introduction

Anxiety disorders are highly prevalent (Baxter et al., 2013), debilitating, and account for a substantial share of the disease burden attributable to mental disorders, as measured by disability-adjusted life years (Baxter et al., 2014; Murray et al., 2012). At the same time, anxiety disorders are highly heterogeneous, with patients differing in symptom expression, severity, chronicity, comorbidity, and functional impairment (American Psychiatric Association, 2013). This heterogeneity complicates efforts to identify the neural and psychophysiological processes underlying different phenotypic expressions of anxiety and to translate these insights into targeted interventions (Cuthbert & Insel, 2013). Responses to unpredictable threat represent one candidate process implicated in anxiety-related psychopathology (Abend, 2023; Grupe & Nitschke, 2013; Rosen & Schulkin, 1998). The present study therefore examined how unpredictable threat anticipation varies across patients with different anxiety disorders and obsessive-compulsive disorder (OCD).

Neurobiologically informed models suggest that uncertainty plays a central role in the formation and maintenance of anxiety-related psychopathology. Specifically, anxiety-related psychopathology has been linked to elevated threat expectancies (Grupe & Nitschke, 2013), impaired safety inference in ambiguous contexts (Brosschot et al., 2017, 2018), and a bias towards threat-based responding under uncertainty (Freeston & Komes, 2023; Van den Bergh et al., 2021). In addition, elevated levels of self-reported trait intolerance of uncertainty have been consistently observed in anxiety-related psychopathology (Boelen & Reijntjes, 2009; Carleton et al., 2013; Gentes & Ruscio, 2011; Holaway et al., 2006; Mahoney & McEvoy, 2012; McEvoy et al., 2019; Tolin et al., 2003).

Experimental approaches have operationalized uncertainty by varying the predictability of aversive events, most prominently in the NPU-threat test, an instructed threat-of-shock paradigm developed by Schmitz & Grillon (2012). Here, the degree of predictability varies directly, which distinguishes responses to predictable from responses to unpredictable threat. Specifically, in the predictable condition (P), participants receive a highly predictable aversive stimulus whose occurrence is signaled by a cue. In contrast, participants receive unsignaled aversive stimuli in the unpredictable condition (U), whereas in the

neutral condition (N), participants never receive an aversive stimulus (Schmitz & Grillon, 2012). The increase in responding from neutral to unpredictable threat is typically interpreted as anxiety potentiation, whereas increased responding to predictable threat is interpreted as fear potentiation. Previous studies have used the startle reflex to assess defensive responding (Blumenthal et al., 2005) in the NPU-threat test (Carsten et al., 2022, 2023; Gorka et al., 2017; Grillon et al., 2017; Hoge et al., 2024; Nelson et al., 2016; Nelson & Shankman, 2011; Schmitz & Grillon, 2012). Complementary electroencephalography enables studying the attentional dynamics during threat anticipation. Specifically, the event-related potential component N1 locked to acoustic startle probes indexes early sensory processing of the probes, whereas the P3 component reflects later attentional allocation. In a more aversive context, a general neural response pattern involves increased startle (Schmitz & Grillon, 2012), increased probe-locked N1 (Carsten et al., 2023; Nelson, Hajcak, et al., 2015) and decreased probe-locked P3 (Ferry & Nelson, 2020; MacNamara & Barley, 2018; Nelson, Hajcak, et al., 2015). Here, a less positive (i.e., suppressed) P3 is interpreted as the allocation of attentional resources to the threat cue rather than to the startle probe.

Clinical studies using the NPU-threat test suggest that anxiety-related psychopathology might be associated with alterations in unpredictable threat anticipation, but the pattern of findings across diagnostic groups is inconsistent. In a sample of patients with mixed anxiety disorders, increased startle during unpredictable but not predictable threat was found (Hoge et al., 2024). Heightened startle potentiation during unpredictable threat anticipation has been reported in patients with panic disorder and posttraumatic stress disorder (PTSD; Grillon et al., 2008, 2009) with subsequent findings implicating that panic attacks might be particularly relevant for increased responding to unpredictable threat in patients with generalized anxiety disorder (GAD) and/or social anxiety disorder (SAD; Grillon et al., 2017). However, other studies challenge this association of heightened unpredictable-threat responding in GAD in combination with panic attacks. For instance, Gorka et al. (2017) found elevated startle potentiation to unpredictable threat in more fear-based disorders, including specific phobia. Next, while some studies linked panic disorder to increased responses to unpredictable threat (Grillon et al., 2008; Shankman et al., 2013), other studies found contradictory response patterns (Gorka et al., 2014; Stevens et al., 2018). Additionally, heightened

reactivity to unpredictable threat has also been observed in externalizing psychopathology such as alcohol use disorder (Gorka et al., 2020; Gorka & Shankman, 2017), whereas blunted or reduced reactivity has been reported in relation to greater PTSD symptom severity (Lieberman et al., 2020) and comorbid panic disorder/PTSD (Katz et al., 2018). Further, previous research has not covered the breadth of the internalizing spectrum with patients with OCD being underrepresented in this field. Thus, although clinical studies using the NPU-threat test support the relevance of unpredictable threat anticipation for anxiety-related psychopathology, the inconsistent result pattern across diagnostic groups suggests substantial variability in effects. As outlined above, prior clinical NPU studies have typically relied on single outcome measures, most commonly startle potentiation, and on comparing responses to unpredictable threat anticipation in diagnostic groups with healthy controls. Thus, it remains unclear whether alterations in unpredictable threat anticipation generalize across response systems, including defensive reflex modulation, early sensory processing, and attentional allocation. Moreover, because anxiety disorders are heterogeneous and highly comorbid, diagnostic group comparisons may obscure clinically meaningful variation in symptom severity and dimensional traits (Cuthbert, 2015; Cuthbert & Insel, 2013; Krueger & Markon, 2006).

To map anxiety-related psychopathology, two integrative frameworks informed the research question of the present study, the framework of anxiety dimensions (Sharp et al., 2015; Snyder et al., 2022) and the spectrum from circumscribed fear to anxious misery (Lang et al., 2016). First, the dimensional and commonly shared decomposition of anxiety proposes two anxiety dimensions, which are considered phenomenologically and neurally distinguishable (Cox et al., 2010; Heller et al., 1997; Sharp et al., 2015; Snyder et al., 2022). Anxious apprehension grasps the tendency for verbal, future-oriented rumination and worry. Anxious arousal captures the propensity to experience symptoms of physiological hyperarousal when confronted with mild stressors (Clark & Watson, 1991; Sharp et al., 2015; Watson et al., 1995). While the evidence for anxious apprehension modulating responses to temporally unpredictable threat is scarce and inconsistent (Nelson & Shankman, 2011; Carsten et al., 2023; Rutherford et al., 2020), self-report anxious arousal has not yet been empirically linked to threat anticipation in clinical samples (Carsten et al.,

2023). Prior studies on dimensional traits have linked intolerance of uncertainty to defensive responding in anticipation of temporally unpredictable threat (Nelson et al., 2016; Nelson & Shankman, 2011), although the evidence is mixed (Bennett et al., 2018; Lieberman et al., 2016; Morriss et al., 2020, 2022; Papenfuss et al., 2021) and findings might be specific to lower probability of threat (Carsten et al., 2022; Chin et al., 2016). Taken together, these findings suggest that individual difference constructs are promising candidates for explaining variance in threat anticipation, but existing evidence remains limited, inconsistent, and largely based on few clinical samples and single-outcome studies. Second, beyond symptom-level dimensions, anxiety disorder categories themselves may also be organized along a broader clinical spectrum from circumscribed fear to anxious misery. As such, Lang et al. (2016) mapped anxiety disorders along a gradient from circumscribed fear, such as specific phobia, through more generalized psychopathology, such as SAD, to "anxious misery", including OCD and GAD. Movement toward the anxious misery pole was characterized by greater comorbidity, chronicity, functional impairment, and physiological hyporeactivity. These data were derived from disorder-specific aversive imagery paradigms (McTeague & Lang, 2012), in which threat predictability was not directly manipulated. Thus, it remains unclear whether the circumscribed fear–anxious misery spectrum also maps onto responses to predictable and unpredictable threat.

Taken together, prior research suggests that responses to unpredictable threat are relevant to anxiety-related psychopathology, but the multimodal physiological underpinnings as well as the clinical and potentially transdiagnostic pattern of this association remain unclear due to mixed prior findings. On the one hand, the spectrum from circumscribed fear to anxious misery suggests that anxiety disorder categories may differ in general physiological reactivity, with circumscribed fear characterized by heightened defensive responding and anxious misery by blunted responding (Lang et al., 2016). On the other hand, neurobiologically informed models of uncertainty and clinical NPU findings suggest that more generalized, impairing, and comorbid psychopathology may be associated with heightened sensitivity to unpredictable threat (Freeston & Komes, 2023; Grillon et al., 2008; Grupe & Nitschke, 2013; Hoge et al., 2024; Van den Bergh et al., 2021). These two patterns are not mutually exclusive: individuals closer to the

anxious-misery pole may show reduced overall physiological reactivity while still displaying stronger condition-specific modulation by unpredictable threat. The present study therefore examined whether diagnostic groups ordered along the circumscribed fear–anxious misery spectrum differ in both general physiological reactivity and sensitivity to unpredictable threat across startle, SCR, N1, and P3 responses. In addition, we tested whether dimensional constructs of anxiety-related psychopathology can explain variation in responding to threat anticipation beyond the categorical diagnosis. Specifically, we examined self-reported intolerance of uncertainty, anxious apprehension, anxious arousal, and negative affect as predictors of physiological reactivity and sensitivity to unpredictable-threat. We preregistered three hypotheses (https://osf.io/n9qxp): First, we expected general physiological reactivity to decrease with proximity to the anxious-misery pole, such that responses would be strongest in unaffected controls, followed by specific phobia, SAD, and OCD (H1: unaffected controls > specific phobia > SAD = OCD). Second, we expected sensitivity to unpredictable threat to increase along the same spectrum (H2: unaffected controls < specific phobia < SAD = OCD). Third, we expected dimensional constructs of anxiety-related psychopathology to account for individual differences in physiological reactivity and unpredictable-threat sensitivity beyond diagnostic categories (H3).

Methods

Participants

We recruited 163 participants in four groups matched for age, gender, and years of education. The recruited clinical groups included patients with specific phobia, SAD, OCD, and unaffected controls without the respective mental disorders. Participants' age ranged between 18 to 63 (Table 1). Five participants were excluded due to premature termination of the experiment (n = 3) and hardware or software errors (n = 2), leaving a total sample of N = 158 participants. The sample size was determined by a power analysis for a different research question within the broader project (Härpfer et al., 2025). An a priori sensitivity analysis was conducted using Monte Carlo simulations to estimate the smallest detectable standardized effects in a two-level regression model given the planned sample size of N = 160 (Arend &

Schäfer, 2019; Green & Macleod, 2016). For the effects of diagnostic group, and the interaction of NPU condition × group, default medium effect sizes of $d = 0.50$ were assumed. Following this power simulation for the aggregated EEG data (i.e., 6 observations per subject), the likelihood to detect the interaction was 95.30% (95% CI [93.80, 96.53]), for the startle data (in single trial analyses i.e., 48 observations per subject) the likelihood to detect the interaction was 99.90% (95% CI [99.44, 100.00], https://osf.io/n9qxp).

Patients were recruited via the outpatient units of the University of Hamburg, student recruiting systems of the university, advertisement on the campus and social media, and platforms for part-time jobs. Participants received course credit or monetary compensation for the time of their participation. Inclusion criteria encompassed age (18-65 years), normal or corrected-to-normal vision, and the ability to give informed consent (assessed via self-report). Exclusion criteria were assessed via self-report and included a history of any neurological disorder, use of benzodiazepines (within the last week), neuroleptic medication (within the last three months). Exclusion criteria were assessed via the Structured Clinical Interview for DSM-5 Disorders–Clinical Version (SCID-5-CV; Beesdo-Baum et al., 2019) and included substance-related disorder (lifetime), schizophrenia spectrum and other psychotic disorders (lifetime), and manic episode (current). For the unaffected control group, exclusion criteria further encompassed lifetime diagnoses of disorders specifying the other groups, i.e., specific phobia, SAD, and OCD. Table 1 shows demographic and clinical characteristics of the full sample and groups.

Table 1 Demographic and clinical characteristics of the total sample and subgroups

	Full Sample (N = 158) Mean (SD)	**Control** (n = 42) Mean (SD)	**PHOB** (n = 40) Mean (SD)	**SAD** (n = 39) Mean (SD)	**OCD** (n = 37) Mean (SD)	**Group differences** F- or χ^2- Statistic
Demographics						
Age	28.63 (8.32)	29.19 (8.22)	27.73 (9.73)	28.72 (7.68)	28.92 (7.64)	$F(3, 154) = 0.23$, $p = .872$
Gender %	74.05 f 25.95 m	71.43 f 28.57 m	77.50 f 22.50 m	74.36 f 25.64 m	72.97 f 27.03 m	$\chi^2(3) = 0.42$, $p = .936$
Education	12.20 (1.02)	12.21 (0.93)	12.18 (1.01)	12.26 (1.12)	12.16 (1.07)	$F(3, 154) = 0.07$, $p = .978$
% Psychotropic Medication	10.78	0	5.26	18.18	32.14	$\chi^2(3) = 14.41$, $p = .002$
Clinical						
Diagnoses	1.83 (1.63)	0.19 (0.46)	1.88 (1.29)	2.69 (1.47)	2.73 (1.58)	$F(3, 154) = 36.10$, $p < .001$ Control < PHOB < SAD = OCD
CGI	3.71 (1.40)	1.98 (0.61)	3.8 (0.99)	4.58 (1.03)	4.62 (0.89)	$F(3, 152) = 76.45$, $p < .001$ Control < PHOB < SAD = OCD
GAF	69.55 (17.37)	86.39 (14.68)	75.4 (11.41)	58.34 (11.44)	55.62 (9.26)	$F(3, 153) = 58.93$, $p < .001$ Control > PHOB > SAD = OCD
IUS-12	31.10 (10.34)	24.93 (7.71)	28.45 (10.15)	38.69 (7.62)	32.97 (10.37)	$F(3, 154) = 17.47$, $p < .001$ Control = PHOB < OCD < SAD
PSWQ	50.82 (13.67)	40.24 (11.20)	48.68 (13.73)	57.77 (9.05)	57.81 (11.96)	$F(3, 154) = 21.22$, $p < .001$ Control < PHOB < SAD = OCD
MASQ	25.87 (8.37)	21.86 (5.76)	24.55 (8.11)	28.13 (7.93)	29.46 (9.54)	$F(3, 154) = 7.62$, $p < .001$ Control = PHOB = SAD = OCD. Control < SAD/OCD
STAI-T	44.93 (13.06)	35.57 (8.33)	40.05 (12.36)	53.36 (10.04)	51.95 (11.69)	$F(3, 154) = 26.98$, $p < .001$ Control = PHOB < SAD = OCD
STAI-S	39.24 (11.52)	32.66 (6.10)	35.00 (9.12)	45.53 (10.37)	44.68 (13.72)	$F(3, 152) = 16.66$, $p < .001$ Control = PHOB < SAD = OCD
LSAS	42.44 (31.79)	20.98 (16.99)	31.59 (23.93)	71.46 (28.76)	47.65 (31.13)	$F(3, 153) = 29.51$, $p < .001$ Control = PHOB < OCD < SAD
SMSP	6.30 (7.51)	1.95 (3.73)	8.64 (7.81)	6.54 (7.39)	8.41 (8.56)	$F(3, 152) = 7.72$, $p < .001$ Control < PHOB = SAD = OCD

OCI-R	13.43 (12.50)	5.98 (5.42)	9.13 (10.00)	11.54 (8.86)	28.54 (11.43)	$F(3, 154) = 46.84$, $p < .001$ Control = PHOB = SAD < OCD
AUDIT	4.04 (3.14)	3.74 (3.10)	4.45 (2.90)	3.67 (2.82)	4.35 (3.80)	$F(3, 154) = 0.66$, $p = .579$ Control = PHOB = SAD = OCD
BDI-II	11.32 (11.58)	4.27 (5.27)	7.88 (9.53)	16.97 (12.51)	17.08 (12.23)	$F(3, 154) = 16.17$, $p < .001$ Control = PHOB < SAD = OCD

Note. Control = control group; PHOB = specific phobia group; SAD = social anxiety disorder group; OCD = obsessive-compulsive disorder group; CGI = Clinical Global Impression Scale – Severity; GAF = Global Assessment of Functioning; AUDIT = Alcohol Use Disorders Identification Test; BDI-II = Beck Depression Inventory–II; IUS-12 = Intolerance of Uncertainty Scale–12; LSAS-SR = Liebowitz Social Anxiety Scale – Self-Report; MASQ = Mood and Anxiety Symptom Questionnaire–Anxious Arousal; OCI-R = Obsessive-Compulsive Inventory–Revised; PSWQ = Penn State Worry Questionnaire; SMSP = Severity Measure for Specific Phobia; STAI-S = State–Trait Anxiety Inventory – State; STAI-T = State–Trait Anxiety Inventory – Trait.

Clinical measures

On the day of the laboratory assessment, participants completed the following questionnaires: Intolerance of uncertainty was measured using the short form of the Intolerance of Uncertainty Scale (IUS; 12 items, 5-point Likert scale 1-5; α = .90; Carleton et al., 2007). Worry was measured by the Penn State Worry Questionnaire (PSWQ; 16 items, 5-point Likert scale 1-5; α = .94; Glöckner-Rist & Rist, 2014; Meyer et al., 1990). Anxious arousal was measured by the respective subscale of the Mood and Anxiety Symptom Questionnaire (MASQ; 17 items, 5-point Likert scale 1-5; α = .88; Clark & Watson, 1991; Watson et al., 1995). Depressive Symptoms and negative affect were measured using the Beck Depression Inventory (BDI-II; 21 items, 4-point Likert scale 0-3; α = .95; Beck et al., 1996; Hautzinger et al., 2006). Further questionnaire data were acquired in order to describe the symptomatology of the sample. These questionnaires are not part of the confirmatory hypothesis testing but are included in exploratory analyses. State and trait anxiety were measured using the respective subscales of the State-Trait-Anxiety Inventory (STAI-T (α = .95) and STAI-S (α = .95); each 20 items; 4-point Likert scale 1-4; Laux, 1981; Spielberger et al., 1983). Social phobia symptoms were measured using the self-report version of the Liebowitz Social Anxiety Scale (LSAS; 24 items, 4-point Likert scale 0-3; α = .98; Liebowitz, 1987; Stangier & Heidenreich, 2003). Specific phobia symptoms were measured using the Severity Measure for Specific Phobia (SMSP; 10 items, 5-point Likert scale 0-4; α = .86; Craske et al., 2013). Obsessive-compulsive symptoms were measured using the Obsessive-Compulsive Inventory Revised (OCI-R; 18 items, 5-point Likert scale 0-4; α = .91; Foa et al., 2002; Gönner et al., 2007). Alcohol consumption was measured using the Alcohol Use Disorder Identification Test (AUDIT; 10 items, 5-point Likert scale 0-4; α = .66; Babor et al., 2001). Trained psychologists performed the diagnostics using the Structured Clinical Interview for DSM-5 Disorders – Clinical Version (SCID-5-CV; Beesdo-Baum et al., 2019). The overall severity was assessed via the Global Clinical Impression Scale (GCI; Guy, 1976), and overall functioning was assessed via the global assessment of functioning (American Psychiatric Association, 2000).

Procedure

The local ethics committee at the University of Hamburg approved the study procedure (AZ: 2021_351) to be in accordance with the declaration of Helsinki (World Medical Association, 2013). Prior to the laboratory assessment, participants were screened for eligibility in a phone interview. Upon arrival in the laboratory, participants received verbal and written information of the objectives and methods of the study and gave written informed consent. After completing questionnaires, participants were prepared for the psychophysiological measurement and performed the NPU-threat test as a part of larger project.

Task and Stimuli

Participants were seated in a dimly lit, electrically shielded cabin at a viewing distance of approx. 60 cm in front of a 19-inch monitor with a resolution 1920 × 1080 pixels and a refresh rate of 120 Hz. To assess responses during unpredictable threat anticipation, a countdown version of the NPU-threat test (Nelson & Shankman, 2011; Schmitz & Grillon, 2012) was used. In the P condition, participants received a highly predictable, aversive electrotactile stimulation signaled by a cue (the "1" of a countdown). In contrast, participants received unsignaled electrotactile stimulation U condition, whereas in the N condition, participants never received an aversive stimulus. Each condition occurred twice, resulting in two possible orders (PNUPNU or UNPUNP) that was counterbalanced across participants. A black screen stating the current condition served as the interstimulus interval (12 ± 3 s) and a numerical countdown counting from five to one served as threat cue (1 s per digit). Each condition included nine cues (i.e., five interstimulus intervals and four countdowns) and a black screen (10 s) that separates the conditions. Four aversive stimuli occurred per condition (i.e., P and U). In the P condition, the aversive stimulus occurred when the countdown reached "1", in the U condition the aversive stimulus could occur at any time during the countdown (4.2 ± 0.5 s) and interstimulus interval (5.5 ± 2.5 s). Startle probes were delivered via headphones (Sony MDR-ZX110) to elicit the startle reflex in 100% of the interstimulus intervals and countdowns. The startle probes consisted of 95 dB bursts of white noise with a duration of 50 ms (rise/fall time < 1 ms). Prior to the experiment, participants received 16 acoustic startle probes to allow an initial

startle habituation (Blumenthal et al., 2005). A total of 64 startle probes were delivered per participant. The aversive stimulus consisted of an individually calibrated electrotactile stimulation. The calibration followed a staircase procedure (Lonsdorf et al., 2017), in which the participant subjectively rated the stimulus from 0 (not aversive) to 10 (extremely aversive, not endurable). The intensity of the aversive stimulus was increased stepwise to a subjective rating of 7-8 (M = 2.59 mA, SD = 1.48, range 0.30 – 13.00). During the calibration procedure, a minimum of 10 electrotactile stimuli were presented, to decrease habituation effects during the task.

Startle recording and processing

Two Ag/AgCl electrodes with a sensor diameter of 6 mm were placed below the right eyelid to measure the surface electromyography of the eyeblink component of the startle reflex. A ground electrode was placed on the right infraorbital triangle. Data were recorded with a sampling rate of 1,000 Hz. Preprocessing involved a band pass filter on raw signal (28 - 500 Hz, 24 dB/octave roll-off), rectification, baseline correction (50 ms prior to startle probe onset), signal integration (9 ms moving average) and segmentation (-500 to 250 ms relative to startle probe). Data were then automatically scored using a custom-made algorithm in Brain Vision Analyzer 2.3. This involved the identification of missings, i.e., segments with spontaneous blinks in the baseline period (-50 to 20 ms relative to startle probe). If the data in this segment deviated by 4 SD from one of two 200 ms baseline periods (-500 to -300 ms and/or -300 to -100 ms relative to startle probe), the segment was scored as missing (M = 13.50%, SD = 7.98%). We implemented two baseline periods to decrease the probability that spontaneous blinks were included in one baseline period and thus missings in the refractory time window (i.e., -50 to 20 ms relative to startle probe) would not be detected based on the 4 SD deviation criterion. In segments without missings, startle blink amplitudes were scored using the EMG Onset Search solution implemented in Brain Vision Analyzer 2.3. As preregistered, the onset of a startle response was scored if there was a 3 SD deviation from the -50 to 20 ms baseline in a 20 – 120 ms onset window relative to the startle probe. A subsequent peak was scored if it occurred within 25 – 150 ms relative to the startle probe. If the response threshold of 3 SD was not met, the

segment was scored as a nonresponse and included in the analysis (M = 5.11%, SD = 9.68%). To calculate the interrater reliability of this automatic scoring, we compared it with a manual scoring of an experienced rater blinded to the experimental conditions (cf. Carsten et al., 2023). Intraclass correlations were calculated between the automatic scoring and manual scoring on trial level using the "irr" package (Gamer et al., 2019). Trial-level agreement was near perfect as indicated by a two-way absolute-agreement single-measure intraclass correlation (ICC = .989, 95% CI [.988, .990]). N = 3 participants were excluded from the startle analysis because they showed nonresponses or missings to more than 66 % of the startle probes, including the initial startle habituation phase. The single trial startle responses were entered into the analyses without aggregation (participant's individual trials M = 41.90, Mdn = 42, SD = 4.40) and without standardization, due to multilevel modelling using random effects to account for interindividual differences in absolute startle magnitude. Internal consistency of the startle responses was estimated using Cronbach's alpha across single trials separately for each cue within each condition and ranged from α = .892 to α = .975 (N interstimulus interval: α = .918; N countdown: α = .896; P interstimulus interval: α = .892; P countdown: α = .975; U interstimulus interval: α = .914; U countdown: α = .894).

Electroencephalogram recording and processing

EEG data were acquired via 61 Ag/AgCl-electrodes mounted on a cap with equidistant electrode sites (Easycap, Herrsching, Germany) and two 32-channel BrainAmp amplifiers (Brain Products GmbH, Gilching, Germany). EEG signals were recorded with a band-pass filter of 0.01 to 250 Hz and digitized continuously at a sampling rate of 1,000 Hz. The recording reference was located between AF3 and Fz, the ground electrode between AF4 and Fz. An external electrode was placed at the left infraorbital site for vertical eye movements. Processing of the EEG data was performed in Brain Vision Analyzer version 2.3 (Brain Products GmbH, Gilching, Germany). The data were band-pass filtered with a low cut-off of 0.1 Hz and a high cut-off of 30 Hz (24 dB/oct roll-off) as well as a notch filtered (50 Hz). To detect and correct for ocular artifacts, an independent component analysis (ICA; Jung et al., 2000) was used, in which relevant components were semi automatically identified and manually checked by visual inspection of the scalp

topography, the component activation, and the inspection of the corrected EEG signal. The continuous data were then re-referenced to the average of all scalp electrodes and segmented into startle probe-locked epochs (-200 ms to 800 ms relative to the startle probe). Segments containing artifacts (i.e., absolute voltage range exceeding 200 μV, voltage step exceeding 50 μV between consecutive data points, or maximum voltage difference of less than 0.5 μV within 100 ms intervals) were removed. Segments were then baseline corrected (i.e., -200 ms to 0 ms relative to the startle probe). No participant was excluded based on the predefined exclusion criterion (i.e., >50 % segments at any cue (i.e., interstimulus interval or countdown) in any condition (i.e., N, P, or U) after artifact rejection). The quantification of ERPs was based on visual inspection of the grand-averaged waveforms and topographical distributions: The probe N1 (scored at FCz) was quantified as the ± 25 ms area around the most negative peak (approx. between 60 ms and 170 ms). The probe P3 (scored at Pz) was quantified as mean activity 250 - 350 ms (Polich, 2007). To determine split-half reliability, we calculated Spearman-Brown corrected correlations of odd and even trials separately for the conditions (i.e., N, P, U). For N1, reliabilities were high across conditions, with $r = .92$ in the N and $r = .88$ in both the P and U conditions. For P3, reliabilities were $r = .79$ in the N condition, $r = .83$ in the P condition, and $r = .84$ in the U condition.

Skin conductance recording and processing

SCRs were measured using two Ag/AgCl electrodes with 12 mm sensor diameter placed at the distal and proximal hypothenar eminence of the non-dominant hand. Electrodes were applied five minutes prior to measurement onset. A low constant-voltage of 0.5 V was passed through the electrodes. Preprocessing of SCR involved down sampling to 10 Hz, a continuous decomposition analysis using Ledalab (Benedek & Kaernbach, 2010) running in Matlab R2025b (Mathworks®, Natick, Massachusetts, USA). The data were optimized using the "optimize" function implemented in Ledalab. SCRs were automatically scored in a response onset window of 0.9 s to 3.5 s after stimulus onset. For this, the amplitudes were required to exceed a minimum amplitude threshold of 0.01 μS. SCRs were scored in

response to the interstimulus intervals in conditions N and U and the "5" of the countdown in conditions N, P, and U, in trials without a preceding electrotactile stimulation in the time window of 2.6 s before the onset of the countdown. Participants with no discernible responses to more than 66% of aversive stimuli were excluded from SCR analyses (n = 13).

Ratings

Participants were asked to rate how anxious they were at the presentation of each cue (i.e., interstimulus interval and countdown) in each condition (i.e., N, P, and U) on a 7-point Likert scale from "not at all anxious" to "extremely anxious".

Statistical analyses

The analyses were performed in R version 4.5.2 and RStudio version 2026.1.1.403. Multilevel models were estimated using the packages "lme4"(Bates et al., 2015), the package "emmeans" (Russell et al., 2021) and "lmerTest" (Kuznetsova et al., 2017). Separate models were fitted for each outcome: startle, N1, P3, SCR, and ratings. Trial-level data were analyzed for startle and SCR, whereas EEG data for the N1 and P3 were aggregated per cue and condition. Physiological responses were nested within participants. Continuous questionnaire predictors were grand-mean centered. Confirmatory models included condition, diagnostic group, and their interaction:

$$Y \sim condition \times group + (1 + condition \mid participant)$$

To test dimensional predictors, we fitted models including intolerance of uncertainty, anxious apprehension, anxious arousal, and depressive symptoms, operationalized by the IUS, PSWQ, MASQ, and BDI-II:

Y ~ condition × IUS + condition × PSWQ + condition × MASQ + condition × BDI + (1 + condition | participant)

To compare categorical and dimensional predictors, significant dimensional predictors were subsequently entered together with diagnostic group in combined models. Where preregistered, combined models were simplified by backward elimination of fixed effects, beginning with the highest-order interactions while retaining lower-order terms involved in significant interactions. Random-effects structures included random intercepts and condition slopes by participant whenever supported by model convergence. In case of non-convergence, the random-effects structure was simplified. Fixed effects were evaluated using Satterthwaite-approximated degrees of freedom. Significant interactions involving categorical predictors were followed up with Tukey-corrected pairwise comparisons of estimated marginal means. Interactions involving continuous predictors were followed up with comparisons of estimated slopes across factor levels. The significance threshold was set to $\alpha = .05$.

Results

See Supplement A for descriptive statistics of the all outcomes (i.e., ratings, startle, SCR, N1, and P3).

Ratings

The final model for ratings after the preregistered model selection was

Rating ~ MASQ + IUS + condition × group × BDI + (1 + condition | participant)

The analysis of the anxiety ratings yielded significant main effects of condition, BDI, IUS, and MASQ (for the full model results see Supplement B). Participants rated the conditions as anxiety inducing U > P > N (Supplement B). Overall, higher IUS scores were associated with higher anxiety ratings in all conditions ($b = 0.03$, $SE = 0.01$, $t(921) = 3.07$, $p = .002$, $R^2 = .044$). Similarly higher MASQ scores were

associated with higher anxiety ratings in all conditions (b = 0.03, SE = 0.01, t(921) = 2.08, p = .038, R^2 = .021). Further, a condition × group × BDI interaction emerged (F(6, 151) = 2.49, p = .025, R^2 = .028). Follow-up analyses indicated that in the predictable threat condition, BDI scores were negatively associated with ratings in the control group (b = −0.086, SE = 0.037, 95% CI [−0.159, −0.014], p = .020), whereas the corresponding slopes were not significant in the OCD, PHOB, or SAD groups. However, Tukey-adjusted contrasts of BDI slopes between groups did not reach the significance threshold. Together, this indicates that intolerance of uncertainty and anxious arousal were associated with increased ratings across all conditions and groups.

Skin conductance responses

The final model for SCR after the preregistered stepwise model reduction was

SCR ~ condition × group + condition × MASQ + (1 | participant)

The model yielded main effects of condition (F(2, 5916) = 179.08, p < .001, R^2 = .006) and group (F(3, 146) = 2.66, p = .050, R^2 = .002), which were qualified by a significant condition × group interaction, (F(6, 5916) = 5.31, p < .001, R^2 = .008, see Supplement C). Group contrasts within each condition indicated that groups did not differ in N or P (all ps ≥ .346). In U, however, the OCD group showed larger SCRs than controls (b = 0.07, SE = 0.016, t = 4.34, p < .001), PHOB (b = 0.07, SE = 0.016, t = 4.38, p < .001), and SAD (b = 0.05, SE = 0.016, t = 3.44, p = .003), whereas no other group contrasts reached significance. Thus, the interaction was driven by selectively enhanced SCRs during unpredictable threat anticipation in OCD.

Concerning dimensional effects, the model yielded a condition × MASQ interaction (F(2, 5914) = 6.72, p = .001 R^2 = .002). Follow-up analyses showed that MASQ was not significantly related to SCRs in the N condition (b = 0.00009, SE = 0.00069, t(194) = 0.13, p = .899) and in the P condition (b = -0.00078, SE = 0.00079, t(338) = -0.98, p = .329), but was negatively associated with SCRs in the U condition (b = -0.00185, SE = 0.00071, t(215) = -2.61, p = .010). Correspondingly, the MASQ slope differed significantly between U and N, (Δslope = 0.00193, SE = 0.00053, t(5913) = 3.67, p < .001), whereas the contrasts

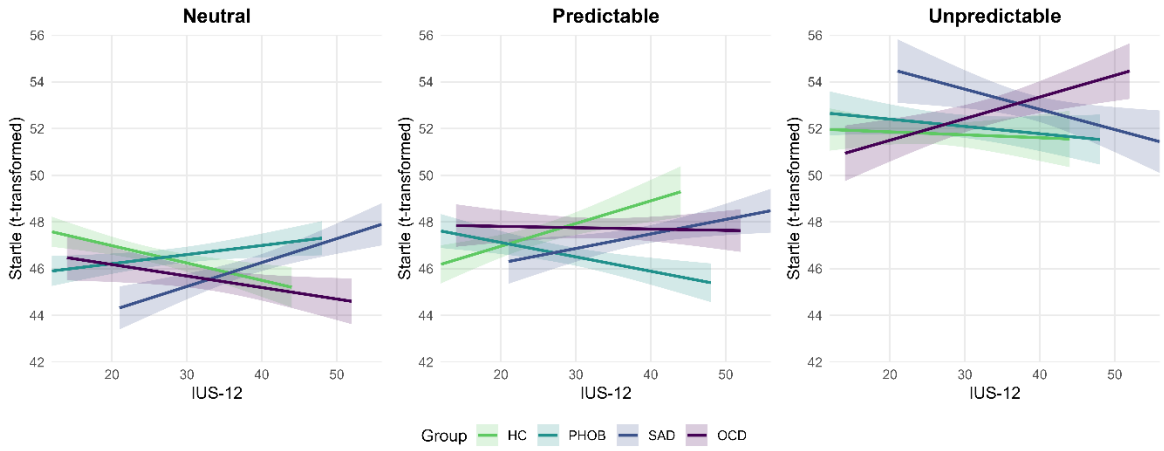
between N and P were not significant (p = .366, P and U, p = .234). Thus, higher anxious arousal was associated with reduced SCRs specifically during unpredictable threat anticipation. There was no significant condition × group × MASQ interaction (F(6, 5900) = 0.44, p = .850).

Startle

The final model for startle after the preregistered stepwise model reduction was *Startle ~ condition × group × IUS + (1 | participant)*. The pattern of task effects was as expected from previous studies (U > P > N, see Supplement D).

Concerning individual difference effects, the model yielded a trendwise significant condition × group interaction (F(6, 6289) = 2.07, p = .053, R^2 = .002) which was further specified by a significant condition × group × IUS interaction (F(6, 6289) = 2.60, p = .016, R^2 = .003). Tukey-corrected contrasts of the slopes of IUS per level of condition and group lead to one significant difference of the slopes in the control group between conditions N and P (Δslope[N–P] = -2.31, SE = 0.68, t(6289) = -3.42, p = .031), indicating that participants from the control group displayed increased startle responses in the P condition compared with the N condition if they had increased IU scores (Figure 1). All other contrast did not reach the predefined significance threshold after Tukey correction (p's > .459). Following the condition × group interaction with contrast of the estimated marginal means between groups per level of condition, we found that the control group showed increased startle in the P condition compared with participants from the PHOB group (b = 90.32, SE = 30.5, t(154) = 2.96, p = .019). However, this effect might not be specific to the P condition, as it was also observable, yet not significant in the U condition (b = 78.06, SE = 30.50, t(153) = 2.56, p = .055), and, to a lesser extent, in the N condition (b = 65.92, SE = 30.50, t(154) = 2.16, p = .139) and might thus reflect a main effect of group. No further significant contrasts emerged between groups. Overall, startle responses varied by condition, group, and intolerance of uncertainty, with higher intolerance of uncertainty associated with greater P vs. N startle differentiation in the control group, and controls showing generally higher startle responses than the PHOB group.

Figure 1



Note. Associations between intolerance of uncertainty (IUS-12) and startle magnitude across experimental conditions. Groups include unaffected controls (HC), specific phobia (PHOB), social anxiety disorder (SAD), and obsessive-compulsive disorder (OCD). Solid lines represent fitted linear trends based on the observed data, shaded bands indicate ±1 standard error.

N1

The final model for N1 after stepwise model reduction was

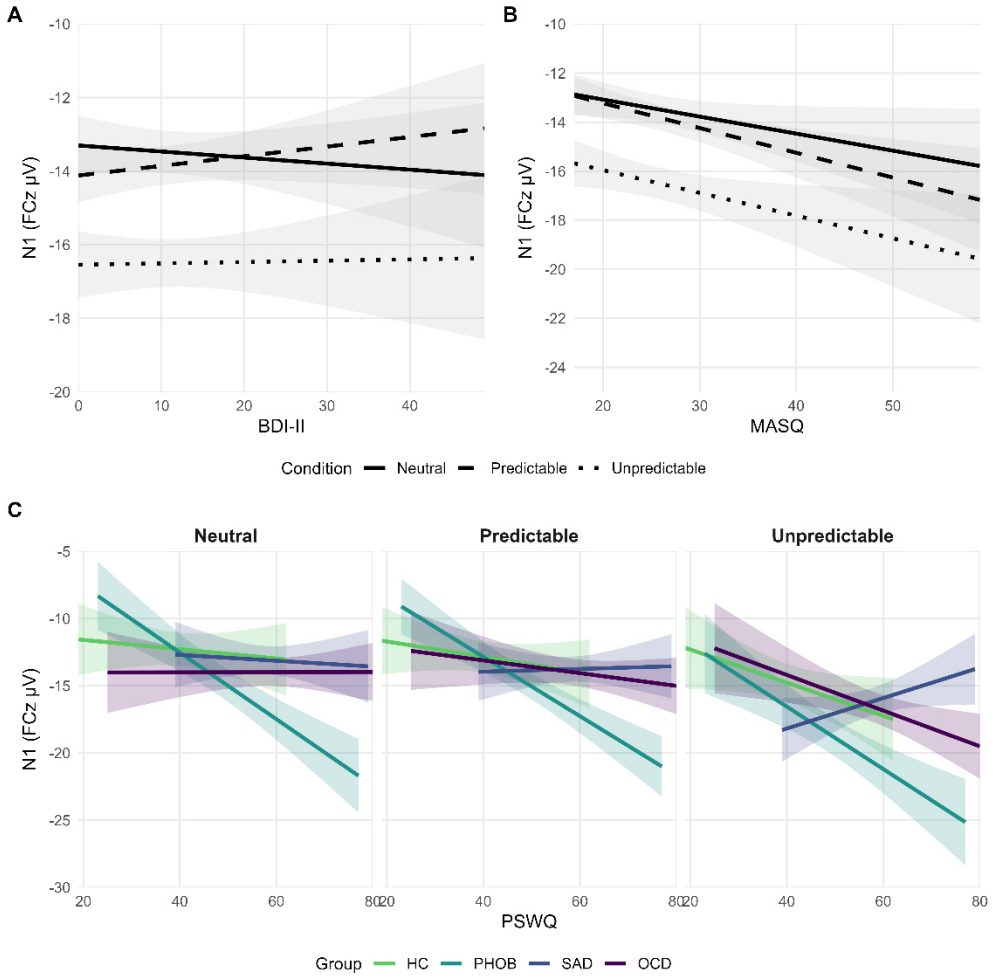
N1 ~ condition × MASQ + condition × BDI + condition × group × PSWQ + (1 | participant)

Across participants, N1 showed a U > P = N pattern (see Supplement E).

Regarding individual difference effects, a condition × group × PSWQ interaction emerged (F(6, 770) = 2.24, p = .038, R^2 = .009). Contrasts of the PSWQ slopes within groups yielded a significant difference between the U and N condition (b = 0.17, SE = 0.06, t(770) = 2.79, p = .015), indicating a stronger PSWQ-related increase in N1 in the U vs. N in patients with OCD. Other contrast did not reach significance after Tukey correction (p's > .171). The PHOB group showed a consistently negative PSWQ-N1 association across all three conditions (b = -0.25, SE = 0.08, t(148) = -3.02, p = .003), indicating that higher PSWQ scores were associated with a more negative (i.e., increased) N1. Further, a condition × BDI interaction emerged (F(2, 770) = 5.04, p = .007, R^2 = .007). BDI was positively associated with N1 in the P condition (b = 0.19, SE = 0.08, t(182) = 2.51, p = .013), whereas the corresponding slopes were not significant in N

(b = 0.06, SE = 0.08, t(182) = 0.79, p = .429) and or U (b = 0.14, SE = 0.08, t(182) = 1.79, p = .075). The BDI slopes differed significantly between P and N (Δslope[N–P] = −0.13, SE = 0.04, t(770) = −3.16, p = .005), while differences between N and U (p = .160) and between P and U (p = .379) did not reach significance. This pattern of results indicates that higher BDI scores are associated with a reduced N1 during predictable threat anticipation. In addition, a condition × MASQ interaction emerged. (F(2, 770) = 3.04, p = .048, R^2 = .004). This was driven by a significant difference of MASQ slopes between N and P (b = 0.13, SE = 0.05, t(770) = 2.36, p = .049), whereas differences between N and U (p = .849) and P and U (p = .167) did not reach significance. Overall, N1 was enhanced during unpredictable threat anticipation, with modulation by individual differences. Worry was associated with stronger unpredictable N1 responses in patients with OCD and across conditions in the PHOB group, depressive symptoms were associated with blunted N1 during predictable threat, and anxious arousal was associated with increased N1 during predictable threat relative to safety (Figure 2).

Figure 2



Note. **A.** Association between Beck Depression Inventory-II (BDI-II) scores and probe-locked N1 amplitude. **B.** Association between Mood and Anxiety Symptom Questionnaire Anxious Arousal subscale (MASQ) scores and probe-locked N1 amplitude. **C.** Association between Penn State Worry Questionnaire (PSWQ) scores and probe-locked N1 shown per group. Groups include unaffected controls (HC), specific phobia (PHOB), social anxiety disorder (SAD), and obsessive-compulsive disorder (OCD). Shaded bands indicate ±1 standard error.

P3

The final model for the probe-locked P3 after preregistered stepwise model reduction was

P3 ~ condition + MASQ + (1 + condition | participant)

Generally, the P3 was suppressed in threat conditions (U = P < N, see Supplement F). Concerning individual differences, the model further yielded a main effect of MASQ ($F(1, 156) = 9.48$, $p = .002$, $R^2 = .106$). Higher anxious arousal was associated with lower P3 amplitudes across conditions ($b = -0.12$, $SE = 0.04$, $t(156) = -2.71$, $p = .008$). The condition × MASQ interaction was not significant ($F(2, 156) = 0.16$, $p = .854$).

Exploratory latent profile analysis

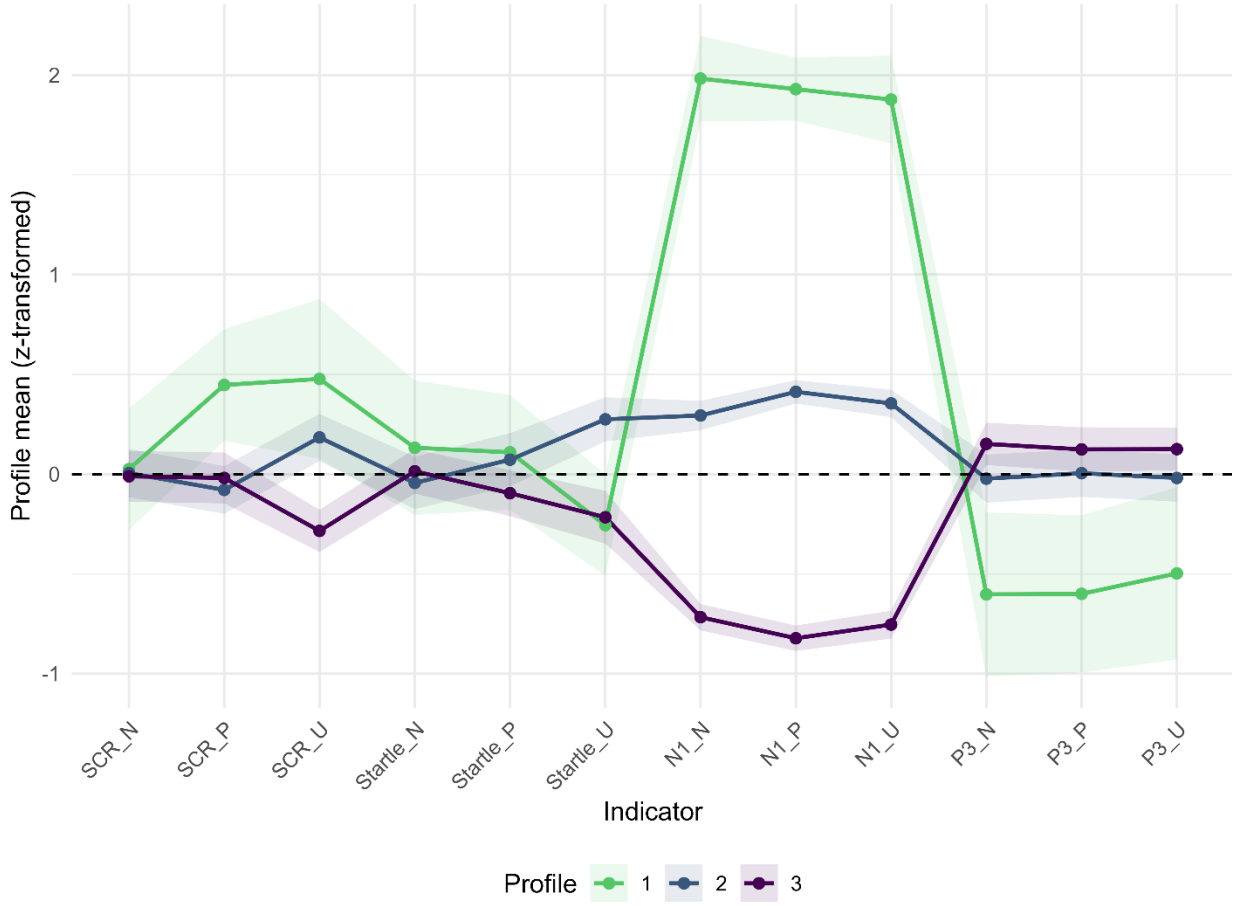
Latent profile analysis was conducted as an exploratory person-centered analysis to identify participants with similar multimodal response patterns in threat anticipation and to integrate results across outcomes. The latent profile analysis was based on z-standardized, condition-averaged physiological indicators (startle, SCR, N1, P3) across the three conditions (N, P, U) in the complete-case sample without missing data in any outcome ($N = 143$). One to five profile Gaussian mixture models with freely estimated profile means, equal indicator variances, and zero within-profile covariances were compared using information criteria, entropy, minimum class size, posterior classification probabilities, and substantive interpretability. Fit improved markedly from one to three profile solution with significant BLRTs supporting the addition of profiles up to three classes (Supplement G). Although four and five profile solutions yielded marginal additional improvement in *BIC*, they produced smaller and less clearly differentiated profiles. The three-profile solution was therefore retained as the most parsimonious and interpretable solution with adequate classification quality (*BIC* = 4802.11, entropy = .85, minimum class assignment probability = .91).

Retained solutions were interpreted based on their multisystem response patterns, and modal profile membership was then merged back into the full dataset to examine external validity in relation to diagnostic group and clinical variables using omnibus ANOVAs and chi-square/Fisher tests, followed by corrected post hoc comparisons. As such, the retained profiles differed more clearly in their multisystem response configuration than in purely condition specific response to unpredictable threat (Figure 3, Figure S2 Supplement H). Profile 1 ($n = 14$; 9.79% of the sample) was characterized by pronounced early sensory

processing (N1) across all conditions together with relatively elevated response pattern with increased N1, average P3 suppression, and both SCR and startle increases to unpredictable threat. Profile 2 appeared to capture a defensive/autonomic unpredictable threat-reactive response style. Profile 3 (n = 65; 45.45%) was characterized by comparatively attenuated neural and peripheral responding including less negative N1 indicating less automatic early sensory processing of stimuli regardless of condition, slightly lower P3, and both lower startle and SCR during unpredictable threat compared with Profile 2. Profile 3 suggests generalized physiological dampening particularly under unpredictable threat, consistent with relatively hyporeactive defensive responding.

To clarify whether the retained physiological profiles reflected general response style or differential sensitivity to the NPU conditions, modal profile membership from the retained three-profile solution was projected back onto the original data and separate mixed models were fit for SCR, startle, N1, and P3. This back-projection was used to determine in which physiological systems the retained profiles actually differed across the N, P, and U conditions (Supplement H). Taken together, the back-projected models indicated that the retained latent profiles are better characterized as broad multisystem response styles rather than distinct forms of condition-specific NPU sensitivity. Only SCR showed a clear profile × condition interaction, suggesting that autonomic responding differentiated the profiles in their sensitivity to threat anticipation, especially under unpredictable threat. In contrast, N1 showed strong profile differences in overall level with only trend-level evidence for differential NPU modulation, while P3 and startle showed largely parallel condition effects across profiles (Supplement H, Figure S2).

Figure 3



Note. Profiles retained from latent profile analysis. Shaded error bars represent +/- 1 standard error. For visualization, N1 and P3 were recoded such that higher *z*-values (i.e., $z > 0$) represent increased sensitivity to threat. Conditions include neutral (N), predictable threat (P), and unpredictable threat (U).

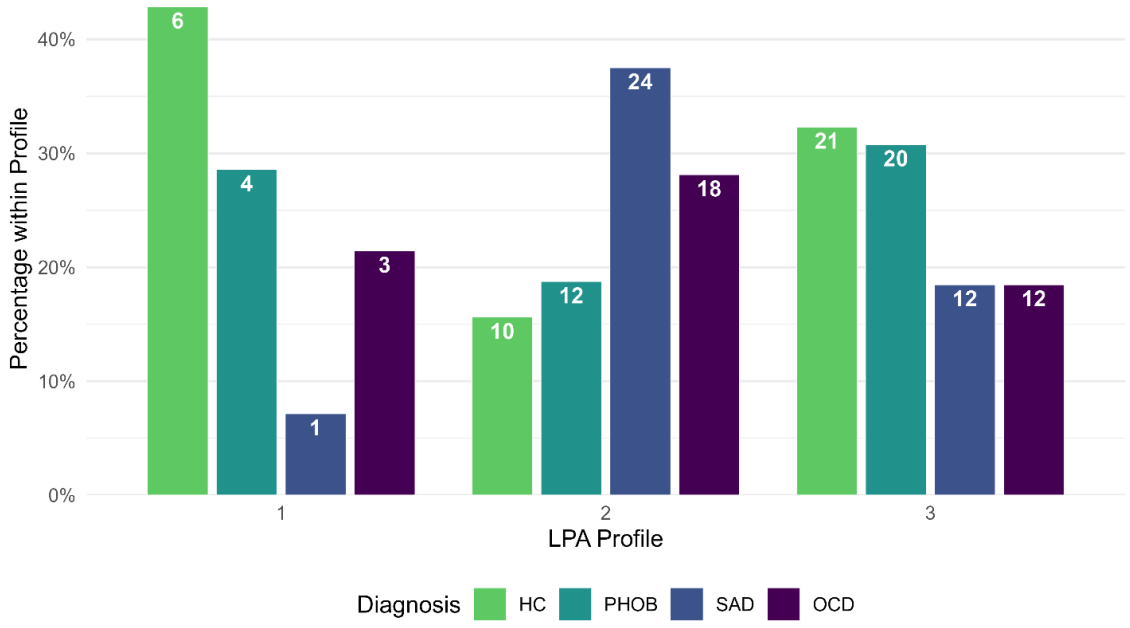
Clinical correlates of latent profiles

To examine the clinical relevance of the physiological profiles, modal profile membership was related to clinical status and diagnostic group composition. Clinical status differed descriptively across profiles (Supplement I, Figure S3), with the highest proportion of clinically affected participants in Profile 2 (56/64; 87.50%) compared with Profile 1 (10/14; 71.43%) and Profile 3 (46/65; 70.77%). The omnibus association was not significant using Pearson's χ^2 test ($\chi^2(2, N = 143) = 5.75$, $p = .056$, Cramér's $V = .20$), but reached significance using Fisher's exact test ($p = .049$). Pairwise comparisons suggested that this pattern was mainly driven by a higher clinical proportion in Profile 2 compared to Profile 3, although this

contrast did not survive Holm correction (raw p = .034, Holm-adjusted p = .102). Accordingly, profile membership showed only modest discrimination of clinical status in a logistic ROC analysis (AUC = .622, 95% CI [.524, .719]; Supplement I, Figure S4).

Notably, diagnostic composition differed significantly across profiles, ($\chi^2(6, N = 143) = 15.07$, p = .020, Fisher's exact p = .016, Cramer's V = .23). Descriptively, Profile 2 contained the largest proportion of patients with SAD and OCD whereas controls were comparatively underrepresented. In contrast, Profile 3 contained relatively larger proportions of unaffected controls and patients with specific phobia, consistent with a less clinically burdened or more circumscribed fear composition. Profile 1 was small and should be interpreted cautiously, but was composed primarily of unaffected controls and patients with specific phobia, with few patients with SAD (Figure 4). Cellwise residuals indicated that SAD participants were overrepresented in Profile 2 and underrepresented in Profile 3 descriptively, although these cellwise effects did not clearly survive correction for multiple comparisons (Supplement I, Table S9).

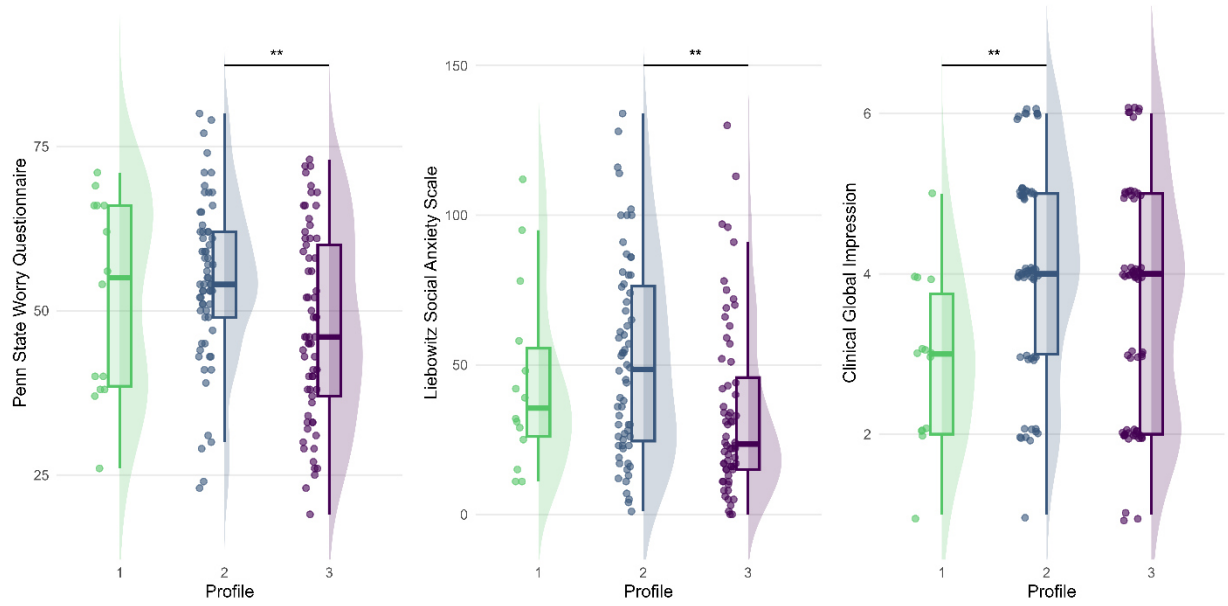
Figure 4



Note. Clinical composition of latent profiles. LPA = latent profile analysis; HC = unaffected controls; PHOB = specific phobia; SAD = social anxiety disorder; OCD = obsessive-compulsive disorder. White digits show the count of participants within each profile.

The group differences of the physiological profiles were further underscored by dimensional differences emerging for worry, social anxiety symptoms and clinician-rated severity (Figure 5). Specifically, PSWQ differed across profiles ($F(2, 140) = 4.48$, $p = .013$) with increased PSWQ scores in Profile 2 than Profile 3 ($b = 7.10$, $SE = 2.38$, $t(140) = 2.98$, $p = .010$) whereas Profile 1 did not differ in PSWQ from either profile ($ps > .479$). A similar pattern emerged for social anxiety disorder symptoms, ($F(2, 139) = 4.85$, $p = .009$), with Profile 2 showing higher LSAS scores than Profile 3 ($b = 17.17$, $SE = 9.23$, $t(139) = 3.11$, $p = .006$) and Profile 1 not differing significantly from Profiles 2 and 3 ($ps > .504$). Clinician-rated severity (i.e., CGI) also differed across Profiles, $F(2, 138) = 5.29$, $p = .006$, with Profile 2 showing greater severity than Profile 1 ($b = 1.17$, $SE = 0.40$, $t(138) = 2.93$, $p = .011$). The difference in CGI between Profiles 2 and Profile 3 was in the same direction but did not survive correction ($b = 0.53$, $SE = 0.24$, $t(138) = 2.23$, $p = .070$), while no significant difference emerged between Profiles 1 and 3 ($p = .251$).

Figure 5



Note. Clinical correlates of the physiological latent profiles. Profile 1 ($n = 14$) contains a smaller sample size than Profiles 2 ($n = 64$) and 3 ($n = 65$). ** = $p < .01$

Discussion

The present study examined whether physiological responses to predictable and unpredictable threat anticipation map onto categorical and dimensional variation across the anxiety and obsessive-compulsive spectrum. Two main findings emerged. First, diagnostic categories did not map onto threat-anticipation physiology in the linear manner predicted by the circumscribed fear–anxious misery framework, and sensitivity to unpredictable threat did not increase uniformly from controls to specific phobia, SAD, and OCD. Instead, diagnostic and dimensional effects were response-system specific. The clearest group-based effect emerged for SCR, in which patients with OCD showed enhanced autonomic responding during unpredictable threat anticipation. Dimensional predictors explained additional variance, but in partly distinct ways across physiological systems: anxious arousal was associated with reduced SCRs during unpredictable threat and lower P3 amplitudes across conditions, intolerance of uncertainty was associated with heightened startle to predictable threat in controls, and worry/anxious apprehension was related to stronger N1 modulation during unpredictable threat anticipation in patients with OCD. Second, exploratory latent profile analysis revealed three multimodal physiological response profiles that cut partly across diagnostic categories. These profiles reflected broad multisystem response styles rather than purely condition-specific NPU sensitivity, with one threat-reactive and clinically enriched profile showing greater diagnostic burden, higher representation of SAD and OCD, elevated worry and social anxiety symptoms, and greater clinician-rated severity. Together, these findings suggest that threat anticipation in anxiety-related psychopathology is best understood as a multisystem and transdiagnostic process rather than as a single marker of diagnostic status or unpredictable-threat sensitivity.

The diagnostic categories did not clearly map onto threat-anticipation physiology in the linear manner expectable by the circumscribed fear–anxious misery framework (Lang et al., 2016). We expected that general physiological reactivity would decrease with more generalized anxiety psychopathology. Evidence for this would have been conveyed by main effects of group. Consistent with this hypothesis in a limited sense, unaffected controls showed higher startle responses than patients with specific phobia.

However, this effect did not follow the expected clinical severity gradient, as the PHOB group was psychopathologically less affected than the SAD and OCD groups across dimensional measures. Apart from this finding, no support for physiological hyporeactivity emerged in group-based analyses across SCR, N1, and P3. At the dimensional level, some findings were compatible with physiological blunting in participants with higher symptom burden, although this pattern did not converge across outcomes. Specifically, increased BDI-II scores were associated with decreased startle-probe locked N1 in predictable threat anticipation, which could be taken to suggest that early attention to predictable threatening contexts might be decreased as a function of depressive symptoms. In contrast to a prior study (Carsten et al., 2023), higher MASQ scores were associated with greater P3 suppression across experimental conditions, which may reflect increased allocation of later attentional resources to threat-relevant stimuli in participants with higher anxious arousal (MacNamara & Barley, 2018; Nelson, Hajcak, et al., 2015). Simultaneously, increased anxious arousal was also associated with decreased SCR, especially in unpredictable threat anticipation, indicating less sympathetic activation. Thus, self-reported anxious arousal showed divergent associations across physiological systems, relating to hypervigilance at the level of P3 but reduced autonomic responding at the level of SCR.

The second hypothesis proposed increased sensitivity to unpredictable threat anticipation in groups closer to the "anxious misery" pole of anxiety-related psychopathology. At the group level, this prediction received limited support: Patients with OCD showed enhanced SCRs specifically during unpredictable threat anticipation. Extending these findings at the level of early sensory processing, PSWQ was associated with stronger N1 during unpredictable threat anticipation in OCD patients. Group-based differences for unpredictable threat anticipation emerged specifically in patients with OCD, which raises the question whether this pattern of results represents an effect of broad anxiety-related psychopathology or symptoms more specific to OCD. Although anxiety disorders and OCD share symptomatic overlap, are highly comorbid (Cheng et al., 2025), and are commonly conceptualized within the broader internalizing spectrum (Kotov et al., 2017, 2022), they differ with respect to cognitive aspects and symptom expression (American Psychiatric Association, 2013; Goodwin, 2015). As such, OCD might not represent the stereotypical

expression of “anxious misery” (Lang et al., 2016). Future studies should therefore include patients with GAD to disentangle whether the observed effects are more closely linked to generalized anxiety-related psychopathology or specific to OCD, for which the present findings provide tentative evidence.

Taken together, the confirmatory analyses provided only limited support for the preregistered hypotheses. Neither diagnostic categories nor individual symptom dimensions fully captured the heterogeneity of physiological responding. This raises the possibility that clinically meaningful variation may be organized less by diagnostic group membership alone but rather by broader configurations of physiological responses across systems. To address this possibility, we used exploratory latent profile analysis to examine whether multimodal physiological indicators formed distinct response profiles in a data driven analysis and related those to diagnoses and symptom dimensions.

In the latent profile analysis, three profiles emerged that differed primarily in their overall level of physiological responding across systems. To determine whether the retained physiological profiles captured general patterns of responding or differential modulation by NPU condition, profile membership was projected back onto the original data. This back-projection revealed main effects of condition across all outcomes, main effects of profile across outcomes except startle, and profile × condition interaction only for SCR. Thus, the data-driven profiles appeared to distinguish participants primarily by general response levels across physiological systems, rather than by differential sensitivity to unpredictable threat per se. However, for SCR (and descriptively for N1) profile-specific threat anticipation response patterns were evident. Profile 2 showed increased SCR to unpredictable threat and somewhat more graded threat-related potentiation of N1 amplitudes than Profile 3. At the same time, Profile 2 included more participants with a diagnosis (87.50%) than Profile 3 (70.77%) and Profile 1 (71.43%), which was further underscored by a larger proportion of patients SAD and OCD in Profile 2, as well as higher PSWQ scores and LSAS scores and clinician-rated severity. Thus, Profile 2, which encompassed nearly half of the sample, was both more threat-reactive and clinically enriched. This may suggest that a moderately threat-reactive multimodal physiological response pattern, as evident in Profile 2, characterized the more severely affected, worrying, and socially anxious patients in the sample. In contrast, the low-reactivity profile (i.e., Profile 3), despite

comprising a similarly sized group, was associated with lower clinician-rated severity and comparably lower SCR in unpredictable threat anticipation, a pattern mirrored descriptively in startle responses, as well as an attenuated early sensory processing (N1). Together, these data-driven profiles do not lend support to the idea of a general physiological blunting with increasing severity (Lang et al., 2016; McTeague & Lang, 2012), as has empirically been shown for survivors of noninterpersonal trauma (Kreutzer & Gorka, 2021; Lieberman et al., 2020). Rather, these results suggest that combining multimodal physiological indices during the NPU-threat test might hold incremental value in tracking clinically meaningful differences than considering outcomes one by one. Specifically, Profile 2 may reflect a response style in which unpredictable threat engages both sympathetic responding and early sensory processing, as indicated by stronger SCR increases and more pronounced N1 threat modulation relative to Profile 3. Clinically, this pattern may be relevant because such multisystem threat engagement could make ambiguous or uncertain contexts more salient and physiologically demanding (Brosschot et al., 2017, 2018; Van den Bergh et al., 2021), whereas the lower-reactivity pattern in Profile 3 may reflect comparatively buffered responding that is associated with lower clinical burden. This interpretation aligns with the uncertainty and anticipation model of anxiety, in which uncertain future threat is thought to promote maladaptive anticipatory responding through heightened threat expectancies, biased threat attention, reduced use of safety information, and exaggerated physiological reactivity to uncertainty (Grupe & Nitschke, 2013). At the same time, the association of Profile 2 with SAD/OCD and greater clinical severity extends the circumscribed fear–anxious misery framework (Lang et al., 2016; McTeague & Lang, 2012) by suggesting that clinical burden may be reflected less in generalized physiological blunting than in specific multisystem patterns of threat-context engagement.

As shown earlier, clinical effects in the NPU-paradigm have been heterogeneous across studies (Gorka et al., 2014; Grillon et al., 2017; Hoge et al., 2024; Katz et al., 2018; Stevens et al., 2018). Through the lens of these prior heterogenous findings, the present results provide three insights and avenues for future research. First, the present study provides direct comparisons of threat anticipation between disorder categories. Previous NPU studies with two or more clinical groups have usually not shown uniform

increases in unpredictable threat anticipation in startle responses (Gorka et al., 2017; Grillon et al., 2017; Katz et al., 2018; Shankman et al., 2013). Rather, the direct comparisons between disorder categories allowed for more nuanced differentiation of diagnostic groups. The present findings provide data for direct disorder comparisons across startle, SCR, N1, and P3, which can facilitate meta-scientific endeavors, especially network meta-analysis. This is highly needed, because there is no meta-analytic effect integration across NPU-threat test studies available yet. Second, the present study adds to the limited knowledge on how dimensional conceptualizations of psychopathology can provide incremental insight into the clinical correlates of physiological responses during unpredictable threat anticipation, an approach that is closely aligned with the Research Domain Criteria framework (Cuthbert, 2015, 2020). While subclinical studies often include associations with questionnaire data (e.g., Carsten et al., 2022, 2023; Morriss et al., 2020; Nelson et al., 2016; Nelson, Hodges, et al., 2015; Papenfuss et al., 2021; Rutherford et al., 2020), reports of dimensional effects in clinical studies are scarce. To connect and integrate subclinical findings and estimate their generalizability to clinical samples, questionnaire-physiology associations in clinical samples are necessary, which the present study provide. Third, the same strategies that help address clinical heterogeneity can also increase analytic complexity. Specifically, including direct disorder comparisons, broadening the spectrum of physiological outcomes, and adding dimensional effects can complicate interpretability of the results. Thus, data-driven approaches to integrate multivariate response patterns are warranted, such as the performed exploratory latent profile analysis. Importantly, the level of complexity could be reduced at each of the factors that produce complexity. As such, dimensional reductions such as factor analysis on questionnaire data would also be feasible. Together, these points suggest that progress in clinical NPU research may depend less on identifying a single robust marker of unpredictable-threat sensitivity and more on systematically characterizing how diagnostic status, symptom dimensions, and physiological systems jointly structure anticipatory responding to impending threat. At the same time, data-driven approaches that integrate response patterns across outcomes can reduce complexity but, as a cost, might limit generalizability and provide insights that are specific to the sample under study.

Limitations

The exploratory latent profile analysis should be interpreted with caution. Although the retained profiles showed clinically meaningful correlates, the external validity of physiological response levels and thus their generalizability remain to be tested. In particular, the clinically enriched threat-reactive Profile 2 warrants validation in an independent sample. Because the profiles were based on z-standardized physiological indicators, they describe relative response configurations within the present sample rather than absolute physiological thresholds. Accordingly, the resulting profiles are dependent on the distribution and reliability of the physiological indicators in this specific sample. In addition, the latent profile analysis was based on complete cases and downstream analyses relied on modal profile assignment, which does not fully account for classification uncertainty. Thus, the latent profile analysis should be regarded as an exploratory, hypothesis-generating extension of the preregistered confirmatory analyses rather than as evidence for established clinical subtypes. A related limitation concerns the clinical composition of the sample. The groups examined here did not cover the full anxiety disorder spectrum, which may have reduced the ability to detect the expected gradient from circumscribed fear to anxious misery (Lang et al., 2016; McTeague & Lang, 2012). In particular, future studies should include patients with generalized anxiety disorder, panic disorder, agoraphobia, and separation anxiety to determine whether the observed effects are linked to broad anxiety-related psychopathology or to more disorder-specific processes. A further, partly related limitation concerns psychotropic medication use, which differed across groups, with the highest proportion observed in the OCD group. Medication may have influenced physiological responding and therefore complicates disorder-specific interpretation. At the same time, excluding medicated patients would have reduced the clinical representativeness of the sample. Thus, future studies should test whether the present effects replicate in larger samples that allow medication status to be modeled more directly.

Finally, the definition of the control group may have affected the size and interpretation of clinical contrasts. The controls were screened to exclude the target disorders (i.e., specific phobia, SAD, and OCD) but were not necessarily free of any psychopathology. This increases the ecological validity of the control

group and may better approximate the general population, in which lifetime psychopathology is common (Caspi et al., 2020). At the same time, it may have reduced differences between controls and clinical groups, thereby increasing the likelihood of false-negative findings for effects of general psychopathology. Consequently, the present design may have been relatively conservative for detecting broad clinical effects, while being more informative for identifying effects specific to the disorders under study.

Conclusion

In conclusion, the present findings provide only limited support for the idea that physiological threat anticipation follows a simple gradient from circumscribed fear to anxious misery. Instead, effects differed across physiological systems, with the clearest group difference emerging for SCRs during unpredictable threat anticipation in OCD. The exploratory latent profile analysis further suggested that broader multisystem response patterns may capture clinically meaningful differences that are not fully explained by diagnostic categories alone. A clinically informative pattern emerged in the form of a threat-reactive profile characterized by stronger autonomic and early sensory engagement particularly during unpredictable threat, a higher proportion of patients with SAD and OCD, and elevated worry, social anxiety symptoms, and clinician-rated severity. Overall, threat anticipation in anxiety-related psychopathology appears to be better understood as a multimodal and partly transdiagnostic process than as a single physiological marker of diagnostic status or unpredictable-threat sensitivity.

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Hannes Per Carsten: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Project administration.

Kai Härpfer: Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing – Review & Editing, Project administration.

Franziska Magdalena Kausche: Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing – Review & Editing, Project administration.

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Supplementary Material to

Transdiagnostic Physiological Correlates of Unpredictable Threat Anticipation

Table of Contents:

Supplement A: Descriptive statistics 2

Supplement B: Multilevel model for ratings 4

Supplement C: Multilevel model for skin conductance responses 6

Supplement D: Multilevel model for startle 8

Supplement E: Multilevel model for N1 10

Supplement F: Multilevel model for P3 12

Supplement G: Latent profile analysis model indices 13

Supplement H: Physiological differences in latent profiles 15

Supplement I: Clinical correlates of latent profiles 18

Supplement A: Descriptive statistics

Table S1

Outcome	Condition, Cue	**Full Sample** (*N* = 158) *M* (*SD*)	**Control** (*n* = 42	**PHOB** (*n* = 40)	**SAD** (*n* = 39)	**OCD** (*n* = 37)
Ratings	N-ISI	1.97 (1.40)	1.83 (1.50)	1.93 (1.35)	1.95 (1.15)	2.18 (1.59)
	N-CD	1.96 (1.16)	1.81 (1.25)	1.90 (1.13)	1.82 (0.91)	2.32 (1.28)
	P-ISI	2.87 (1.28)	2.83 (1.51)	2.90 (1.32)	3.03 (1.11)	2.71 (1.14)
	P-CD	3.40 (1.43)	3.17 (1.55)	3.33 (1.46)	3.72 (1.34)	3.40 (1.37)
	U-ISI	4.29 (1.64)	3.95 (2.02)	4.10 (1.13)	4.44 (1.33)	4.71 (1.75)
	U-CD	4.60 (1.67)	4.02 (1.93)	4.73 (1.45)	4.97 (1.33)	4.68 (1.77)
Startle (*t*)	N-ISI	46.40 (6.94)	46.36 (6.99)	46.72 (7.01)	46.57 (7.21)	45.85 (6.33)
	N-CD	46.09 (7.50)	46.76 (7.78)	46.24 (7.11)	45.85 (7.50)	45.42 (7.58)
	P-ISI	45.79 (7.26)	46.25 (7.19)	45.36 (7.82)	45.93 (6.55)	45.71 (7.47)
	P-CD	48.74 (8.69)	48.67 (8.64)	47.80 (8.16)	48.92 (8.47)	49.75 (9.55)
	U-ISI	50.04 (9.88)	49.68 (10.35)	49.93 (9.51)	50.41 (9.92)	50.22 (9.67)
	U-CD	54.59 (11.23)	54.01 (11.31)	54.20 (11.46)	55.49 (11.26)	54.64 (10.83)
SCR (µS)	N-ISI	0.03 (0.07)	0.03 (0.04)	0.02 (0.01)	0.03 (0.04)	0.05 (0.05)
	N-CD	0.03 (0.08)	0.03 (0.05)	0.02 (0.02)	0.03 (0.04)	0.04 (0.05)
	P-ISI	n.a.	n.a.	n.a.	n.a.	n.a.
	P-CD	0.06 (0.18)	0.05 (0.06)	0.05 (0.05)	0.06 (0.12)	0.07 (0.07)
	U-ISI	0.10 (0.17)	0.07 (0.06)	0.08 (0.05)	0.10 (0.05)	0.14 (0.13)
	U-CD	0.13 (0.24)	0.12 (0.12)	0.10 (0.08)	0.11 (0.11)	0.20 (0.20)
N1 (µV)	N-ISI	-13.00 (7.62)	-11.69 (8.25)	-14.38 (8.24)	-12.64 (6.70)	-13.38 (7.10)
	N-CD	-13.97 (7.33)	-12.88 (8.03)	-14.98 (8.39)	-13.53 (6.80)	-14.59 (5.74)
	P-ISI	-12.60 (6.99)	-11.57 (7.94)	-13.90 (7.45)	-12.55 (5.95)	-12.41 (6.36)
	P-CD	-15.04 (6.79)	-14.15 (8.15)	-15.62 (6.43)	-14.98 (6.10)	-15.50 (6.45)
	U-ISI	-15.29 (8.88)	-13.18 (9.52)	-18.16 (10.44)	-15.25 (5.88)	-14.64 (8.43)
	U-CD	-17.71 (8.22)	-16.42 (9.10)	-18.98 (8.50)	-17.07 (7.56)	-18.48 (7.56)
P3 (µV)	N-ISI	7.11 (4.90)	7.20 (5.72)	7.40 (5.36)	7.19 (4.29)	6.61 (4.06)
	N-CD	7.19 (5.04)	7.41 (5.47)	7.04 (5.34)	7.40 (4.91)	6.88 (4.51)
	P-ISI	6.08 (5.08)	6.69 (5.81)	6.03 (5.27)	5.44 (4.18)	6.11 (4.98)
	P-CD	5.12 (5.04)	5.79 (5.03)	5.42 (5.42)	5.01 (4.22)	4.13 (3.37)
	U-ISI	6.03 (5.39)	5.84 (5.62)	6.46 (6.03)	6.41 (4.94)	5.39 (4.97)
	U-CD	5.30 (5.21)	5.72 (5.44)	5.61 (5.40)	4.93 (4.81)	4.88 (5.28)

Note. Data from the NPU-threat test per outcome and group. Conditions include neutral (N), predictable threat (P), and unpredictable threat (U). Cues include the inter-stimulus interval (ISI) and countdown (CD). Groups include the control group, patients with specific phobia (PHOB), social anxiety disorder (SAD) and obsessive-compulsive disorder (OCD).

Supplement B: Multilevel model for ratings

Table S2

Fixed Effects	***b***	***SE***	**95% *CI***	***df***	***t***	***p***
Intercept	1.97	0.29	1.40 – 2.54	921	6.89	<.001
Predictable	0.73	0.35	0.05 – 1.41	921	2.10	.036
Unpredictable	1.73	0.40	0.96 - 2.51	921	4.38	<.001
PHOB	0.02	0.35	-0.66 - 0.70	921	0.06	.952
SAD	-0.35	0.36	-1.05 – 0.36	921	-0.97	.334
OCD	0.41	0.35	-0.29 – 1.10	921	1.15	.250
BDI	-0.02	0.03	-0.09 – 0.04	921	-0.69	.492
IUS	0.03	0.01	0.01 – 0.05	921	3.07	.002
MASQ	0.03	0.01	0.00 – 0.05	921	2.08	.038
Predictable × PHOB	0.43	0.41	-0.38 - 1.24	921	1.04	.299
Unpredictable ×PHOB	0.64	0.47	-0.29 – 1.57	921	1.35	.177
Predictable × SAD	0.72	0.42	-0.11 – 1.54	921	1.71	.087
Unpredictable × SAD	1.03	0.48	0.09 – 1.97	921	2.15	.032
Predictable × OCD	-0.29	0.42	1.12 – 0.53	921	-0.70	.487
Unpredictable × OCD	0.39	0.48	-0.55 – 1.43	921	0.81	.416
Predictable × BDI	-0.06	0.04	-0.14 – 0.01	921	-1.60	.110
Unpredictable × BDI	-0.06	0.05	-0.15 – 0.03	921	-1.35	.177
PHOB × BDI	0.01	0.04	-0.07 – 0.08	921	0.24	.808
SAD × BDI	0.02	0.04	-0.06 – 0.09	921	0.44	.659
OCD × BDI	-0.03	0.04	-0.10 – 0.05	921	-0.71	.479
Predictable × PHOB × BDI	0.05	0.05	-0.04 – 0.14	921	1.14	.256
Unpredictable × PHOB × BDI	0.02	0.05	-0.08 – 0.13	921	0.47	.636
Predictable × SAD × BDI	0.07	0.04	-0.01 – 0.15	921	1.63	.103
Unpredictable × SAD × BDI	0.07	0.05	-0.03 – 0.17	921	1.45	.149
Predictable × OCD × BDI	0.13	0.04	0.04 – 0.21	921	2.91	.004
Unpredictable × OCD × BDI	0.12	0.05	0.02 – 0.21	921	2.43	.019
Random Components						
σ^2		0.58				
τ_{00}		0.95				
$\tau_{11\ \text{Predictable}}$		1.19				
$\tau_{11\ \text{Unpredictable}}$		1.73				
ICC		.70				
Marginal R^2		.390				
Conditional R^2		.819				
$N_{\text{participants}}$		158				
Observations		948				

Note. Groups include the unaffected control group, patients with specific phobia (PHOB), social anxiety disorder (SAD), and obsessive-compulsive disorder (OCD). Questionnaires include Beck Depression Inventory II (BDI), Intolerance of Uncertainty Scale-12 (IUS), and the Anxious Arousal subscale of the Mood and Anxiety Symptoms questionnaire (MASQ).
σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation;

Overall, participants showed increased ratings to predictable threat vs. no threat (b = 0.89, SE = 0.15, $t(143) = 6.17$, $p < .001$) and to unpredictable vs. no threat (b = 2.18, SE = 0.17, $t(143) = 13.19$, $p < .001$). Anxiety ratings to unpredictable threat were increased compared with predictable threat (b = 1.28, SE = 0.12, $t(143) = 10.37$, $p < .001$).

Supplement C: Multilevel model for skin conductance responses

Table S3

Fixed Effects	***b***	***SE***	**95% *CI***	***df***	***t***	***p***
Intercept	0.03	0.01	0.01 – 0.05	6051	2.76	.006
Predictable	0.01	0.01	-0.01 – 0.03	6051	1.34	.180
Unpredictable	0.05	0.01	0.03 – 0.07	6051	5.72	< .001
PHOB	-0.01	0.02	-0.04 – 0.02	6051	-0.75	.451
SAD	-0.00	0.02	-0.03 – 0.03	6051	-0.12	.902
OCD	0.01	0.02	-0.02 – 0.05	6051	0.83	.409
MASQ	0.00	0.00	-0.00 – 0.00	6051	0.13	.899
Predictable × PHOB	0.01	0.01	-0.01 – 0.04	6051	1.03	.304
Unpredictable × PHOB	0.02	0.01	-0.01 – 0.04	6051	1.43	.152
Predictable × SAD	0.02	0.01	-0.00 – 0.05	6051	1.65	.100
Unpredictable × SAD	0.03	0.01	0.01 – 0.05	6051	2.40	.016
Predictable × OCD	0.01	0.02	-0.02 – 0.04	6051	0.62	.533
Unpredictable × OCD	0.07	0.01	0.05 – 0.09	6051	5.63	< .001
Random Components						
σ^2		.02				
τ_{00}		0.00				
ICC		.13				
Marginal R^2		.064				
Conditional R^2		0.187				
$N_{participants}$		145				
Observations		6068				

Note. Groups include the unaffected control group, patients with specific phobia (PHOB), social anxiety disorder (SAD), and obsessive-compulsive disorder (OCD). Questionnaires include the Anxious Arousal subscale of the Mood and Anxiety Symptoms questionnaire (MASQ).
σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation;

Follow-up contrasts across groups indicated that all groups showed larger SCRs in U than in N (b = 0.08, SE = 0.004, $t(5916)$ = 18.82, $p < .001$). Follow-up contrasts by group showed that controls displayed larger SCRs in U than in P (b = 0.04, SE = 0.010, t = 3.88, $p < .001$), whereas P did not differ significantly from N (b = 0.02, SE = 0.010, t = 1.81, p = .168). Similarly, the OCD group showed larger SCR in U than in P (b = 0.09, SE = 0.011, t = 8.71, $p < .001$), while P did not

differ from N (b = 0.02, SE = 0.010, t = 1.97, p = .120). By contrast, both the PHOB and SAD groups showed graded increases across all three conditions. In PHOB, SCRs were larger in P than in N (b = 0.03, SE = 0.010, t = 2.95, p = .009), in U than in N (b = 0.07, SE = 0.008, t = 8.18, p < .001), and in U than in P (b = 0.04, SE = 0.010, t = 3.69, p < .001). The same pattern emerged in SAD, with larger SCRs in P than in N (b = 0.04, SE = 0.010, t = 3.66, p < .001), in U than in N (b = 0.07, SE = 0.008, t = 8.98, p < .001), and in U than in P (b = 0.04, SE = 0.010, t = 3.65, p < .001).

The exploratory analysis including cue into the model yielded a main effect of cue (F(1, 4726) = 15.75, p < .001) and a condition × cue interaction (F(1, 4724) = 20.69, p < .001). Neither the cue × group interaction, (F(3, 4726) = 1.49, p = .214) nor the condition × cue × group interaction (F(3, 4724) = 1.28, p = .281) reached significance. Follow-up contrasts indicated that cue effects depended on condition: in the N condition, SCRs did not differ between ISI and CD (b = 0.002, SE = 0.005, t(4725) = 0.44, p = .659), whereas in the U condition, SCRs were larger during CD than ISI (b = 0.034, SE = 0.006, t(4725) = 5.64, p < .001).

Supplement D: Multilevel model for startle

Table S4

Fixed Effects	***b***	***SE***	**95% *CI***	***df***	***t***	***p***
Intercept	121.88	23.41	75.99 – 167.76	6433	5.21	<.001
Predictable	20.02	6.59	7.10 – 32.95	6433	3.04	.002
Unpredictable	37.92	6.50	25.18 – 50.67	6433	5.83	<.001
PHOB	-65.57	30.31	-124.98 – 6.16	6433	-2.16	.031
SAD	-66.28	35.44	-135.76 – 3.19	6433	-1.87	.061
OCD	-39.13	31.10	-100.10– 21.83	6433	-1.26	.208
IUS	3.19	2.24	-1.55 – 7.93	6433	1.32	.187
Predictable × PHOB	-23.99	8.59	-40.83 - -7.15	6433	-2.79	.005
Unpredictable × PHOB	-11.96	8.50	-28.62 – 4.70	6433	-1.41	.159
Predictable × SAD	-11.52	10.01	-31.13 – 8.10	6433	-1.15	.250
Unpredictable × SAD	-4.60	9.98	-24.16 – 14.96	6433	-0.46	.645
Predictable × OCD	-5.50	8.84	-22.82 – 11.82	6433	-0.62	.534
Unpredictable × OCD	8.35	8.79	-8.88 – 25.59	6433	0.95	.342
Predictable × IUS	2.31	0.69	0.99 – 3.64	6433	3.42	.001
Unpredictable × IUS	1.53	0.67	0.21 – 2.85	6433	2.27	.023
PHOB × IUS	-2.58	3.05	-8.56 – 3.40	6433	-0.85	.397
SAD × IUS	-3.19	3.48	-10.01 – 3.62	6433	-0.92	.359
OCD × IUS	-4.02	3.13	-10.16 – 2.12	6433	-1.28	.200
Predictable × PHOB × IUS	-3.06	0.86	-4.74 - -1.38	6433	-3.57	< .001
Unpredictable × PHOB × IUS	-1.37	0.85	-3.05 – 0.30	6433	-1.61	.108
Predictable × SAD × IUS	-2.73	0.97	-4.62 - -0.83	6433	-2.82	.005
Unpredictable × SAD × IUS	-2.16	0.97	-4.05 - -0.26	6433	-2.23	.026
Predictable × OCD × IUS	-2.08	0.89	-3.81 - -0.34	6433	-2.34	.019
Unpredictable × OCD × IUS	-0.95	0.89	-2.69 – 0.79	6433	-1.07	.286
Random Components						
σ^2	7691.57					
τ_{00}	13242.39					
ICC	.63					
Marginal R^2	.048					
Conditional R^2	.650					
$N_{participants}$	154					
Observations	6459					

Note. Groups include the unaffected control group, patients with specific phobia (PHOB), social anxiety disorder (SAD), and obsessive-compulsive disorder (OCD). The questionnaire included in the final model is the Intolerance of Uncertainty Scale-12 (IUS),
σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation;

Concerning task effects, the model yielded a main effect of condition ($F(2, 6289) = 66.97$, $p < .001$). Startle responses during condition U were increased compared with N ($b = 35.93$, $SE = 3.20$, $t(6289) = 11.21$, $p < .001$), and also compared with P (U>P, $b = 26.11$, $SE = 3.20$, $t(6289) = 8.15$, $p < .001$). Startle responses in condition P were increased compared with N ($b = 9.82$, $SE = 3.21$, $t(6289) = 3.06$, $p = .006$). Including a condition × cue interaction (i.e., countdown, interstimulus interval) into the model further specified task effects ($F(2, 6286) = 15.54$, $p < .001$). Specifically, startle responses in the interstimulus interval were significantly decreased compared with the countdown in conditions P ($b = -20.68$, $SE = 3.78$, $t(6286) = -5.48$, $p < .001$) and U ($b = -20.00$, $SE = 3.76$, $t(6286) = -5.32$, $p < .001$) but not in N ($b = 5.41$, $SE = 3.77$, $t(6286) = 1.43$, $p = .152$).

Supplement E: Multilevel model for N1

Table S5

Fixed Effects	***b***	***SE***	**95% *CI***	***df***	***t***	***p***
Intercept	-12.42	1.54	-15.43 - -9.40	916	-8.08	<.001
Predictable	-0.36	0.84	-2.00 – 1.28	916	-0.43	.669
Unpredictable	-3.16	0.48	-4.81 - -1.52	916	-3.78	<.001
PHOB	-2.64	1.89	-6.35 – 1.07	916	-1.40	.163
SAD	-0.61	2.12	-4.77 – 3.56	916	-0.29	.775
OCD	-1.62	2.06	-5.65 – 2.42	916	-0.79	.432
BDI	0.06	0.08	-0.09 – 0.21	916	0.79	.429
MASQ	-0.02	0.10	-0.21 – 0.17	916	-0.21	.832
PSWQ	-0.04	0.10	-0.25 – 0.16	916	-0.44	.664
Predictable × BDI	0.13	0.04	0.05 – 0.21	916	3.16	.002
Unpredictable × BDI	0.08	0.04	-0.01 – 0.16	916	1.83	.067
Predictable × MASQ	-0.13	0.05	-0.23 - -0.02	916	-2.35	.019
Unpredictable × MASQ	-0.03	0.05	-0.13 – 0.08	916	-0.55	.585
Predictable × PSWQ	-0.02	0.06	-0.13 – 0.09	916	-0.33	.742
Unpredictable × PSWQ	-0.10	0.06	-0.21 – 0.01	916	-1.80	.072
Predictable × PHOB	0.61	1.03	-1.40 – 2.63	916	0.60	.550
Unpredictable × PHOB	-0.50	1.03	-2.52 – 1.51	916	-0.49	.624
Predictable × SAD	-0.70	1.15	-2.97 – 1.56	916	-0.61	.543
Unpredictable × SAD	-0.96	1.15	-3.23 – 1.30	916	-0.84	.404
Predictable × OCD	0.62	1.12	-1.58 – 2.81	916	0.55	.583
Unpredictable × OCD	1.47	1.12	-0.73 – 3.66	916	1.31	.190
Predictable × PHOB × PSWQ	0.04	0.07	-0.09 – 0.18	916	0.62	.535
Unpredictable × PHOB × PSWQ	0.10	0.07	-0.04 – 0.24	916	1.43	.154
Predictable × SAD × PSWQ	0.01	0.09	-0.17 – 0.18	916	0.09	.931
Unpredictable × SAD × PSWQ	0.20	0.09	0.03 – 0.37	916	2.26	.024
Predictable × OCD × PSWQ	-0.06	0.08	-0.21 – 0.10	916	-0.73	.467
Unpredictable × OCD × PSWQ	-0.07	0.08	-0.22 – 0.08	916	-0.92	.356
Random Components						
σ^2		14.82				
τ_{00}		42.66				
ICC		.74				
Marginal R^2		.109				
Conditional R^2		.770				
$N_{participants}$		158				
Observations		948				

Note. Groups include the unaffected control group, patients with specific phobia (PHOB), social anxiety disorder (SAD), and obsessive-compulsive disorder (OCD). Questionnaires include Beck Depression Inventory II (BDI), the Anxious Arousal subscale of the Mood and Anxiety Symptoms questionnaire (MASQ), and the Penn State Worry Questionnaire (PSWQ).
σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation;

Concerning task effects, a main effect of condition emerged ($F(2, 770) = 44.64$, $p < .001$). The probe-locked N1 was increased (i.e., more negative) in the U condition relative to N ($b = -3.17$, $SE = 0.37$, $t(770) = -8.47$, $p < .001$) and in the U condition relative to the P condition ($b = -2.94$, $SE = 0.37$, $t(770) = -7.86$, $p < .001$). The N1 did not differ significantly in the N and P condition ($b = 0.23$, $SE = 0.37$, $t(770) = 0.60$, $p = .818$). Including the factor cue into the model led to a condition × cue interaction ($F(2, 767) = 4.13$, $p = .016$). While the probe-locked N1 was increased during the countdown compared to the interstimulus interval ($b = -1.94$, $SE = 0.24$, $t(767) = -8.12$, $p < .001$), the cue-related enhancement was smaller in the N condition (countdown vs. interstimulus interval $b = -0.97$, $SE = 0.41$, $t(767) = -2.34$, $p = .020$), than in P ($b = -2.44$, $SE = 0.41$, $t(767) = -5.90$, $p < .001$) or U ($b = -2.41$, $SE = 0.41$, $t(767) = -5.83$, $p < .001$).

Supplement F: Multilevel model for P3

Table S6

Multilevel model predicting startle probe locked P3 in μV to the NPU-Threat test.

Fixed Effects	***b***	***SE***	**95% *CI***	***df***	***t***	***p***
Intercept	7.15	0.37	6.42 – 7.87	156	19.29	<.001
Predictable	-1.55	0.21	-1.97 - -1.14	157	-7.34	<.001
Unpredictable	-1.48	0.23	-1.94 – 1.02	157	-6.32	<.001
MASQ	-0.12	0.04	-0.21 – -0.03	156	-2.71	.007
Random Components						
σ^2	5.25					
τ_{00}	19.08					
ICC	.79					
Marginal R^2	.064					
Conditional R^2	.799					
$N_{participants}$	158					
Observations	948					

Note. Mood and Anxiety Symptoms questionnaire (MASQ).
σ^2 = residual variance; τ_{00} = random intercept; ICC = Intra class correlation.

Concerning task effects, the model yielded a main effect of condition, $F(2, 156) = 30.78$, $p < .001$. Relative to the neutral condition, P3 amplitudes were reduced in the predictable condition ($b = -1.55$, $SE = 0.21$, $t(156) = -7.32$, $p < .001$) and in the unpredictable condition ($b = -1.48$, $SE = 0.24$, $t(156) = -6.31$, $p < .001$).

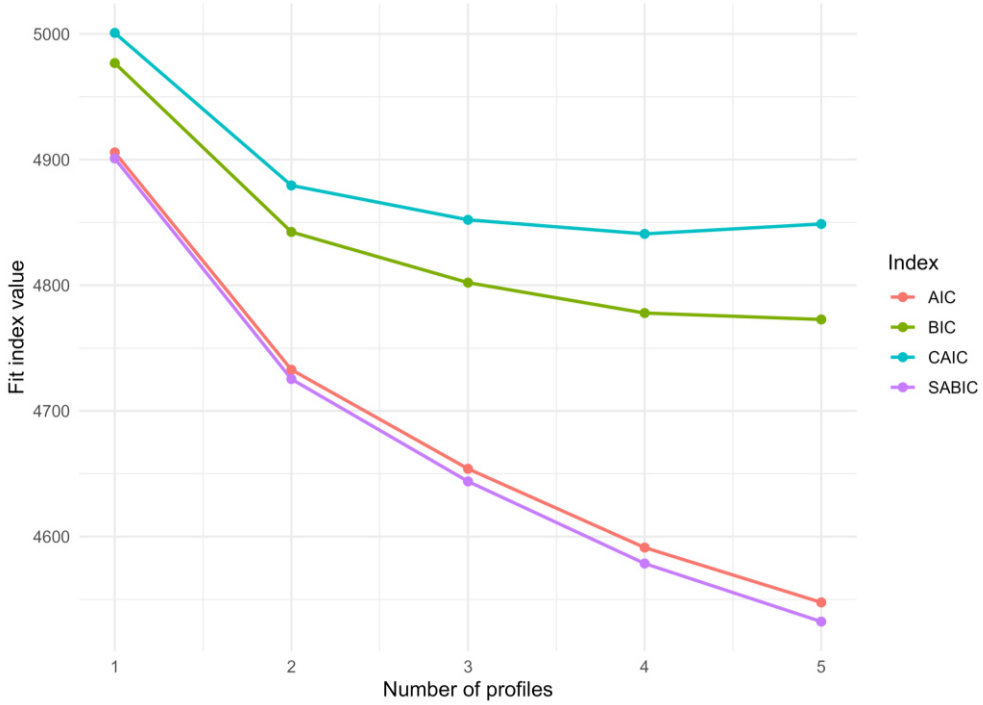
Supplement G: Latent profile analysis model indices

Table S7

Classes	LogLik	parameters	AIC	BIC	CAIC	SABIC	Entropy	prob_min	prob_max	n_min	n_max	BLRT_val	BLRT_p
1	-2428.87	24	4905.76	4976.86	5000.86	4900.92	1	1	1	1	1		
2	-2329.40	37	4732.82	4842.44	4879.44	4725.37	0.86	0.95	0.97	0.33	0.67	198.94	0.01
3	-2276.98	50	4653.96	4802.11	4852.10	4643.90	0.85	0.91	0.98	0.10	0.46	104.86	0.01
4	-2232.62	63	4591.26	4777.91	4840.91	4578.57	0.86	0.88	0.98	0.08	0.43	88.71	0.01
5	-2197.80	76	4547.61	4772.78	4848.78	4532.31	0.90	0.92	0.98	0.11	0.46	69.65	0.01

Note. LogLik = log-likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; CAIC = consistent Akaike information criterion; SABIC = sample-size adjusted Bayesian information criterion; BLRT = bootstrapped likelihood ratio test; prob_min = lowest average posterior class probability; prob_max = highest average posterior class probability; n_min = smallest class proportion; n_max = largest class proportion.

Figure S1 Elbow plot for the latent profile analysis



Note. AIC = Akaike Information Criterion BIC = Bayesian Information Criterion CAIC = Consistent Akaike Information Criterion SABIC = Sample-Size Adjusted Bayesian Information Criterion

Supplement H: Physiological differences in latent profiles

Table S8

Omnibus tests from the profile × condition back-projection models.

Outcome	Condition	Profile	Profile × Condition
N1	$F(2, 280) = 25.71$, $p < .001$	$F(2, 140) = 234.43$, $p < .001$	$F(4, 280) = 2.14$, $p = .076$
P3	$F(2, 280) = 24.73$, $p < .001$	$F(2, 140) = 3.38$, $p = .037$	$F(4, 280) = 0.14$, $p = .966$
SCR	$F(2, 280) = 150.98$, $p < .001$	$F(2, 140) = 2.68$, $p = .072$	$F(4, 280) = 4.34$, $p = .002$
Startle	$F(2, 420) = 77.72$, $p < .001$	$F(2, 420) = 2.27$, $p = .104$	$F(4, 420) = 1.49$, $p = .205$

Note. Skin conductance response (SCR).

N1

For the probe-locked N1, the model yielded a main effect of condition, $F(2, 280) = 25.71$, $p < .001$, and a strong main effect of profile, $F(2, 140) = 234.43$, $p < .001$, whereas the Profile × Condition interaction did not reach significance, $F(4, 280) = 2.14$, $p = .076$. Thus, the retained classes differed markedly in overall N1 amplitude, but not significantly in their NPU-specific modulation. Follow-up contrasts indicated that Class 1 showed a more negative N1 in U than in N ($b = -3.88$, $SE = 1.16$, $p = .003$) and P ($b = -3.62$, $SE = 1.16$, $p = .004$), with no difference between N and P ($p = .817$). Class 2 showed a graded pattern with increasingly negative amplitudes from N to P to U (all ps $\leq .004$). Class 3 also showed a more negative N1 in U than in N ($b = -2.17$, SE = 0.54, $p < .001$), whereas differences between P and the other two conditions were smaller and did not remain clearly significant after correction (ps $\geq .067$). Overall, the N1 pattern suggests quantitative differences in early sensory processing across classes rather than qualitatively distinct forms of condition sensitivity.

P3

For the probe-locked P3, there was a main effect of condition, $F(2, 280) = 24.73$, $p < .001$, and a main effect of class, $F(2, 140) = 3.38$, $p = .037$, but no Profile × Condition interaction, $F(4, 280) = 0.14$, $p = .966$. Accordingly, all profiles showed lower P3 amplitudes in threat conditions than in N. In profile 1, both P and U were lower than N (ps ≤ .039), but P and U did not differ significantly ($p = .592$). The same pattern emerged in profiles 2 and 3, where P and U were both reduced relative to N (all ps < .001), and only profile 2 showed a modest difference between the two threat conditions, with slightly lower P3 amplitudes in P than in U ($b = 0.79$, $SE = 0.39$, $p = .046$). Thus, P3 suppression primarily tracked threat condition similarly across all classes.

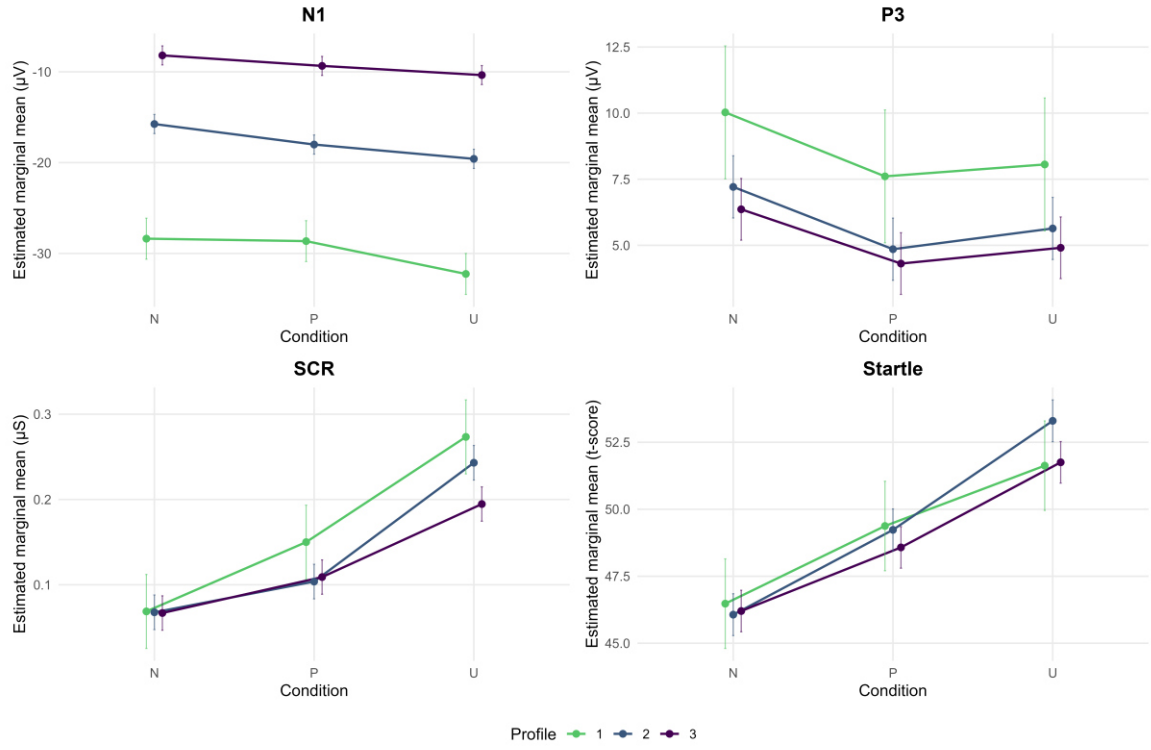
Skin conductance responses

For SCR, the model yielded a main effect of condition, $F(2, 280) = 150.98$, $p < .001$, whereas the main effect of profile was not significant, $F(2, 140) = 2.68$, $p = .072$. The profile × condition interaction was significant, $F(4, 280) = 4.34$, $p = .002$, indicating that the profiles differed in autonomic condition sensitivity. All three profiles showed the same ordinal pattern of N < P < U, with significant increases from N to P, N to U, and P to U within each profile (all ps ≤ .002). However, the magnitude of this increase differed across profiles. The increase from N to U was largest in profile 1 (Δ = .205) and profile 2 (Δ = .175), but smaller in profile 3 (Δ = .128), suggesting attenuated autonomic increase under threat, particularly unpredictable threat, in profile 3. Thus, SCR was the clearest physiological system in which the retained profiles differed in NPU modulation itself, not merely in overall response level.

Startle

For startle, there was a main effect of condition, $F(2, 420) = 77.72$, $p < .001$, but neither a main effect of profile, $F(2, 420) = 2.27$, $p = .104$, nor a Profile × Condition interaction, $F(4, 420) = 1.49$, $p = .205$. Across profiles, startle amplitudes were increased in U relative to N (all ps $< .001$) and in P relative to N (all ps $\leq .033$). Differentiation between U and P was somewhat weaker in profile 1 ($b = 2.25$, $SE = 1.20$, $p = .062$) but clear in profiles 2 and 3 (both ps $< .001$). Thus, startle potentiation primarily reflected the NPU manipulation itself and showed little evidence of profile-specific modulation.

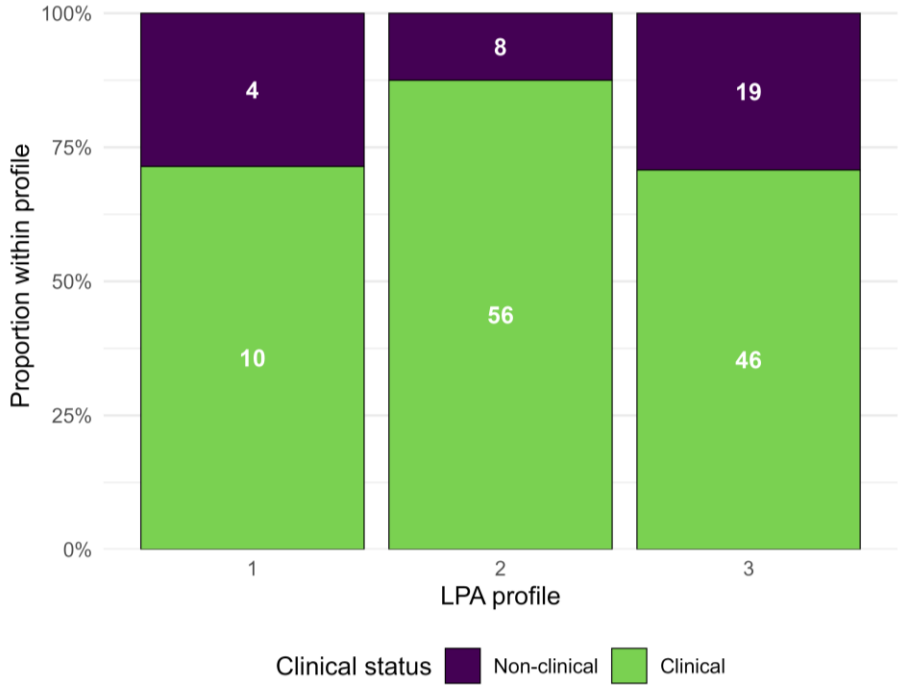
Figure S2 Estimated marginal means for profile × condition back-projection models



Note. Error bars represent +/- 1 standard error.

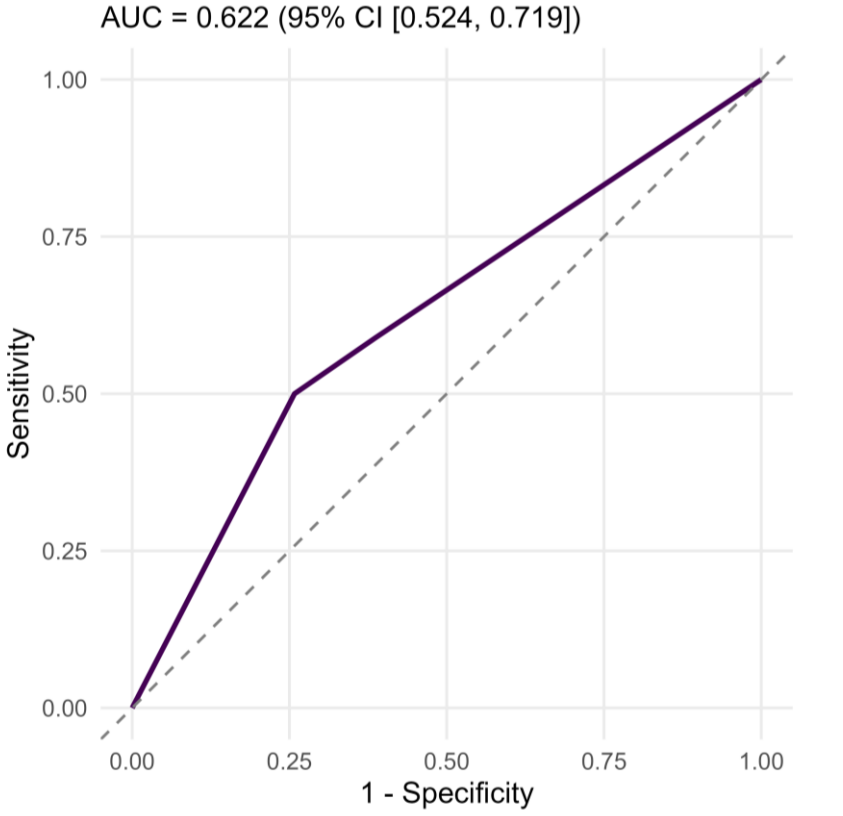
Supplement I: Clinical correlates of latent profiles

Figure S3 Clinical status across main latent profiles



Note. Latent profile analysis (LPA) and counts of participants with any diagnosis within physiologically derived profiles.

Figure S4 Receiver operating characteristic for clinical status by physiological latent profile



Note.

Table S9

Cellwise residual tests for diagnostic group by physiological profile

LPA profile	Group	Observed	Expected	Std. resid.	*p* (raw)	*p* (Holm)	Direction
2	SAD	24	16.56	2.86	.004	.051	overrepresented
2	HC	10	16.56	-2.52	.012	.129	underrepresented
3	SAD	12	16.82	-1.85	.065	.646	underrepresented
1	SAD	1	3.62	-1.69	.092	.828	underrepresented
1	HC	6	3.62	1.53	.127	.870	overrepresented
3	HC	21	16.82	1.60	.109	.870	overrepresented
2	PHOB	12	16.11	-1.59	.111	.870	underrepresented
3	PHOB	20	16.36	1.41	.159	.870	overrepresented
2	OCD	18	14.77	1.29	.197	.870	overrepresented
3	OCD	12	15.00	-1.11	.232	.870	underrepresented
1	PHOB	4	3.52	0.31	.758	.999	overrepresented
1	OCD	3	3.23	-0.15	.878	.999	underrepresented

Note. HC = unaffected controls; PHOB = specific phobia; SAD = social anxiety disorder; OCD = obsessive-compulsive disorder; LPA = latent profile analysis.

Contributions and AI Statement

Study 1

For Study 1, I contributed to the project from its planning through publication. Specifically, I contributed during the planning of this project by shaping the initial research idea and formulating the research question (conceptualization). I designed the reduced-threat-probability task (resources) and wrote the first draft of the preregistration (methodology). Together with the co-authors, I supported the verification of procedures and ensured the experiment's reproducibility. I played a central role in recruitment and data collection, including participant screening/interviews and conducting laboratory experiments (investigation). I supervised undergraduate students and research assistants during data acquisition and the scoring of psychophysiological measures (supervision; project administration). For data processing and analysis, I preprocessed EEG, EMG, and SCR data and conducted the statistical analyses (formal analysis). I created the figures for the manuscript (visualization) and wrote the initial manuscript draft, revising and editing it in response to co-author feedback and reviewer comments (writing—original draft; writing—review & editing).

Study 2

For Study 2 I was involved from planning through publication. During the planning phase, together with my co-authors Prof. Dr. Anja Riesel and Dr. Kai Härpfer, I formulated the research questions and hypotheses and supported the development of the randomized controlled pre-post design and its preregistration (conceptualization; methodology). I implemented and adapted the experimental tasks and procedures, including adapting the Frank task for the uncertainty induction (software) and developing the scripted protocol for the uncertainty induction (methodology; validation). During data collection, I was strongly involved in participant recruitment and screening, and I conducted laboratory experiments (investigation). I coordinated study logistics and supervised research assistants involved in data acquisition (project administration; supervision). I ensured secure storage and organization of study materials and data (data curation). For data processing and analysis, I preprocessed the EEG data and conducted the preregistered frequentist analyses (formal analysis). In addition, I preprocessed and harmonized the Rotterdam EEG dataset from Malbec et al. (2022) to align with the study's preprocessing pipeline for the supplementary pooled frequentist and Bayesian analyses (data curation; formal analysis). I created the figures and tables (visualization) and wrote the first draft of the manuscript, revising it based on co-author feedback and reviewer comments (writing—original draft; writing—review & editing).

Study 3

Study 3 was embedded in a larger project funded by the German Research Foundation (DFG) with grants awarded to Prof. Dr. Anja Riesel. I was not involved in the initial funding proposal, and the study design and procedures had been defined prior to my involvement. When I started my PhD, data collection had already been completed.

My primary responsibilities therefore centered on post-collection processing and reporting. I prepared, organized, and preprocessed the datasets (EEG, EMG, and ratings) and implemented quality-control procedures, including defining and applying inclusion/exclusion criteria to ensure analyses were conducted on reliable data (data curation; software; validation). Building on the predefined design, I planned and executed the complete statistical analysis pipeline and generated all figures for the manuscript (methodology; software; formal analysis; visualization). Finally, I wrote the initial manuscript draft and revised it in response to co-author feedback and reviewer comments (writing—original draft; writing—review & editing).

Study 4

Study 4 was embedded in a larger project funded by the German Research Foundation through grants awarded to Prof. Dr. Anja Riesel. Although I was not involved in the initial funding proposal, I made substantial contributions from the early project phase onward. I helped shape the research idea and refined the study's objectives and research questions (conceptualization). While the overarching design had been specified in the proposal, I further developed the research aims and expanded the assessment battery by adding questionnaire and peripheral physiological measures (conceptualization; methodology). Together with the research team, I formulated the hypotheses and wrote the first draft of the preregistration (methodology). I was responsible for implementing the peripheral physiology setup in the laboratory (resources; methodology) and, together with the team, contributed to piloting, refinement, and ensuring reproducibility of the experimental procedures (validation). During data collection, I recruited participants and conducted standardized clinical interviews and was involved as an experimenter in conducting the laboratory sessions (investigation). I supervised undergraduate students and research assistants to ensure consistent and high-quality data acquisition (supervision), and I supported study coordination as well as secure storage and organization of the data (project administration; data curation). For data processing and analysis, I preprocessed EEG, EMG, SCR, and rating data and ran the full statistical analysis pipeline (formal analysis, software). I produced the figures for the manuscript (visualization). Finally, I wrote the initial manuscript draft and revised it in response to co-author feedback and reviewer comments (writing—original draft; writing—review & editing).

AI Statement

Generative artificial intelligence (AI) was used in the process of this dissertation. AI was not used in the generation of ideas or the creation of scientific content presented. In the preparation of this dissertation, I used the following generative AI system:

- ChatGPT/UHHGPT (GPT-5.4 nano) was used for generation and editing of program code and language editing for the improvement of readability.

I declare that I familiarized myself with the capabilities and limitations of the above-mentioned generative AI system, verified that the content generated by the above-mentioned AI system and incorporated by me is factually correct and am aware that, as the author of this dissertation, I bear full responsibility for the statements and information presented in it.

Hamburg, 20.08.2026



Materials

Hardware

BrainAmp DC Amplifiers (Brain Products GmbH) were used to record continuous EEG data in all four studies.

BrainCap (EASYCAP GmbH) 64 channels with equidistant electrode layout was used to record continuous EEG data in all four studies.

Dell Monitor (Dell, Inc.) 19-inch LCD was used to display the NPU-threat test in Studies 1, 3, and 4 and the Flanker task in Study 2.

Digitimer High Voltage Stimulator model DS7A (Digitimer Ltd.) was used for electrotactile stimulation in Studies 1 and 4.

Multitrode electrodes (EASYCAP GmbH) sintered Ag/AgCl electrodes were used as ground for startle electromyography. For startle electromyography recording, lens electrodes (D-shaped, sensor Ø 6 mm) were used in Studies 1, 3, and 4. For skin conductance responses, lens electrodes (sensor Ø 12 mm) were used in Studies 1 and 4.

Sony MDR-ZX110 On Ear Headphones (Sony Corporation) were used for startle probe presentation in Studies 1, 3, and 4.

Software

BrainVisionRecorder (Brain Products GmbH) version 1.22 was used to record continuous EEG data in studies 1, 2, and 4 (for Study 3, version number is unknown).

BrainVision Analyzer (Brain Products GmbH), versions 2.2 and 2.3 were used to transform and preprocess continuous EEG data to stimulus- and response-locked event-related potentials in all four studies, as well as to preprocess startle electromyography and skin conductance data.

LimeSurvey (LimeSurvey GmbH), version 2, was used for administering questionnaires in Studies 1, 2, and 4.

Microsoft Word (Microsoft, Inc.) version 2016 was used for drafting the manuscripts for all four studies, as well as this dissertation.

Microsoft PowerPoint (Microsoft, Inc.) version 2016 was used for creating figures in all four studies, as well as in this dissertation.

Presentation (Neurobehavioral Systems, Inc.) version 22.1 was used to display the NPU-threat test in Studies 1, 3, and 4, and the Flanker task in Study 2 (for Study 3, version number is unknown).

PsychoEQ (psychoWare Software GmbH) version 21.01 was used for administering questionnaires in Study 4.

R (R Core Team, 2023) version 4.3.2 for Study 1, version 4.4.2 for Study 2, and version 4.5.0 for Studies 3 and 4 was used for statistical analyses and figure creation.

R Studio (RStudio Team, 2023) version 2023.06.1 for Study 1, version 2024.04.2 for Study 2, and version 2025.05.1 for Studies 3 and 4 was used as an integrated development environment for R.

Zotero (Corporation for Digital Scholarship) version 7.0 was used for reference management in all four studies.

Declarations

Erklärung gemäß § 5 (4d) der Promotionsordnung des Instituts für Psychologie der Universität Hamburg vom 20.08.2003

Eidesstattliche Erklärung nach § 9 (1c und 1d) der Promotionsordnung des Instituts für Psychologie der Universität Hamburg vom 20.08.2003

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BEWEGUNGSWISSENSCHAFT
Institut für Bewegungswissenschaft
Institut für Psychologie

Erklärung gemäß *(bitte Zutreffendes ankreuzen)*

☐ **§ 4 (1c) der Promotionsordnung des Instituts für Bewegungswissenschaft der Universität Hamburg vom 18.08.2010**

☒ **§ 5 (4d) der Promotionsordnung des Instituts für Psychologie der Universität Hamburg vom 20.08.2003**

Hiermit erkläre ich,

Hannes Per Carsten _____ (Vorname, Nachname),

dass ich mich an einer anderen Universität oder Fakultät noch keiner Doktorprüfung unterzogen oder mich um Zulassung zu einer Doktorprüfung bemüht habe.

Hamburg, 20.08.2026 _____

Ort, Datum



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Institut für Bewegungswissenschaft
Institut für Psychologie

Eidesstattliche Erklärung nach *(bitte Zutreffendes ankreuzen)*

☐ **§ 7 (4) der Promotionsordnung des Instituts für Bewegungswissenschaft der Universität Hamburg vom 18.08.2010**

☒ **§ 9 (1c und 1d) der Promotionsordnung des Instituts für Psychologie der Universität Hamburg vom 20.08.2003**

Hiermit erkläre ich an Eides statt,

1. dass die von mir vorgelegte Dissertation nicht Gegenstand eines anderen Prüfungsverfahrens gewesen oder in einem solchen Verfahren als ungenügend beurteilt worden ist.
2. dass ich die von mir vorgelegte Dissertation selbst verfasst, keine anderen als die angegebenen Quellen und Hilfsmittel benutzt und keine kommerzielle Promotionsberatung in Anspruch genommen habe. Die wörtlich oder inhaltlich übernommenen Stellen habe ich als solche kenntlich gemacht.

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